22 June 2017
EMA/12767/2018

Withdrawal Assessment Report

Invented name: OPDIVO

International non-proprietary name:nivolumab

Procedure No.EMEA/H/C/003985/II/0030

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

Marketing authorisation holder (MAH): Bristol-Myers Squibb Pharma EEIG

Rapporteur(s) and type of application	
CHMP Rapporteur:	Jorge Camarero
CHMP Co-Rapporteur	Paula van Hennik
PRAC Rapporteur:	Brigitte Keller-Stanislawski

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our websitewww.ema.europa.eu/contact

Assessment Timetable

Timetable	Planned dates
Start of procedure:	24 December 2016
CHMP Rapporteur Assessment Report	17 February 2017
CHMP Co-Rapporteur Assessment Report	17 February 2017
PRAC Rapporteur Assessment Report	24 February 2017
PRAC members comments	1 March 2017
Updated PRAC Rapporteur Assessment Report	2 March 2017
PRAC Outcome	9 March 2017
CHMP members comments	13 March 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 March 2017
Request for supplementary information	23 March 2017
Submission of MAH's responses	21 April 2017
Restart of the procedure	24 April 2017
CHMP Rapporteur Assessment Report	26 May 2017
PRAC Rapporteur Assessment Report	26 May 2017
PRAC members comments	31 May 2017
Updated PRAC Rapporteur Assessment Report	1 June 2017
PRAC Outcome	9 June 2017
CHMP members comments	12 June 2017
Updated CHMP Rapporteur Assessment Report	15 June 2017
Request for supplementary information	22 June 2017
Request for clock stop extension	7 July 2017
Oncology Scientific Advisory Group	21 November 2017
Submission of MAH's responses	13 October 2017
Restart of the procedure	16 October 2017
CHMP Rapporteur Assessment Report	24 November 2017
CHMP members comments	4 December 2017
Updated CHMP Rapporteur Assessment Report	8 December 2017
Planned opinion	12 December 2017
Withdrawal request	13 December 2017

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List of abbreviations

5-FU	5-Fluorouracil
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BOR	Best overall response
CI95	95% Confidence interval
CR	Complete response
(m)CRC	(metastatic) Colorectal cancer
CRF	Case report form
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DBL	Database lock
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern cooperative oncology group
ESMO	European society for medical oncology
FPFT	First patient first treatment
GCP	Good clinical practice
HR-QoL	Health related quality of life
ICF	Informed consent form
IEC	Independent ethics committee
IHC	Immunohistochemistry
IMAE	Immune-mediated AE
Iri	Irinotecan
IRRC	Independent radiology review committee
IRB	Institutional review board
IV	Intravenous
LLN	Lower limit of normal
LPLV	Last patient last visit
dMMR	deficient Mismatch repair
pMMR	proficient Mismatch repair
NA	Not applicable/available
NCCN	National comprehensive cancer network
NSCLC	Non-small cell lung cancer
MSI-H	Microsatellite instability high
MSI-L	Microsatellite instability low
MSS	Microsatellite stable
OESI	Other events of special interest
ORR	Objective response rate
OS	Overall survival
Oxa	Oxaliplatin
PD	Progressive disease
PD-1	Programmed death-1
PD-L1/2	Programmed death ligand-1/2
PFS	Progression-free survival
PR	Partial response

PRO	Patient reported outcomes
PS	Performance status
PT	Preferred term
Q2W	Every 2 weeks
QLQ-C30	Quality of life questionnaire- 30 item core
RECIST	Response evaluation criteria in solid tumours
SAE	Serious AE
SD	Stable disease
SOC	System organ class
cStage	combination Stage
mStage	monotherapy Stage
TSH	Thyroid-stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
UTD	Unable to determine

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 6 December 2016 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine based therapy for OPDIVO.
As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add the new indication and update the safety information. The Package Leaflet is updated in accordance.
RMP version 9.0 is submitted with this application

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0064/2014 on the agreement of a paediatric investigation plan (PIP) and on the granting of a deferral and on the granting of a waiver for nivolumab.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Derogation(s) of market exclusivity

N/A

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

Additional expert consultation

The CHMP considers a **SAG-Oncology** should be convened to provide scientific expertise on the following aspects:

1. No historical data are available for the subset of patients with dMMR mCRC, which makes it difficult to put the results of the study in context. Furthermore, contrary to the early stage CRC setting where dMMR is a known marker of good prognostic and poor response to 5-FU based adjuvant chemotherapy, the actual prognostic and/or predictive role of this biomarker in the

metastatic setting remains to be elucidated, which further complicates interpretation of the benefit with a lack of control data. Therefore, the SAG-O is invited to discuss on the prognostic/predictive value of dMMR/MSI-H in the metastatic setting of CRC.

2. The SAG-O is invited to discuss the strength of evidence for the clinical benefit of nivolumab in 2nd line of mCRC in patients with presence of dMMR/MSI-H, where well established treatment options are available, as well as in later lines of therapy, where treatment options are less well documented and presumably less effective.

2. Scientific discussion

2.1. Introduction

Mechanism of action

Nivolumab (Opdivo®, BMS-936558, MDX-1106, ONO-4538) binds to the programmed death-1 (PD-1) T-cell membrane receptor and thereby blocks its interaction with PD ligand 1 (PD-L1) and PD ligand 2 (PD-L2). PD-1 functions as an immune checkpoint and is a negative regulator of T cell activity which has been shown to control T cell immune response. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T cell proliferation and cytokine secretion. Nivolumab, by blocking binding of PD-L1 and PD-L2 to PD-1 receptor, potentiates T cell responses, including anti-tumour response, in a proportion of patients (

Figure 1).

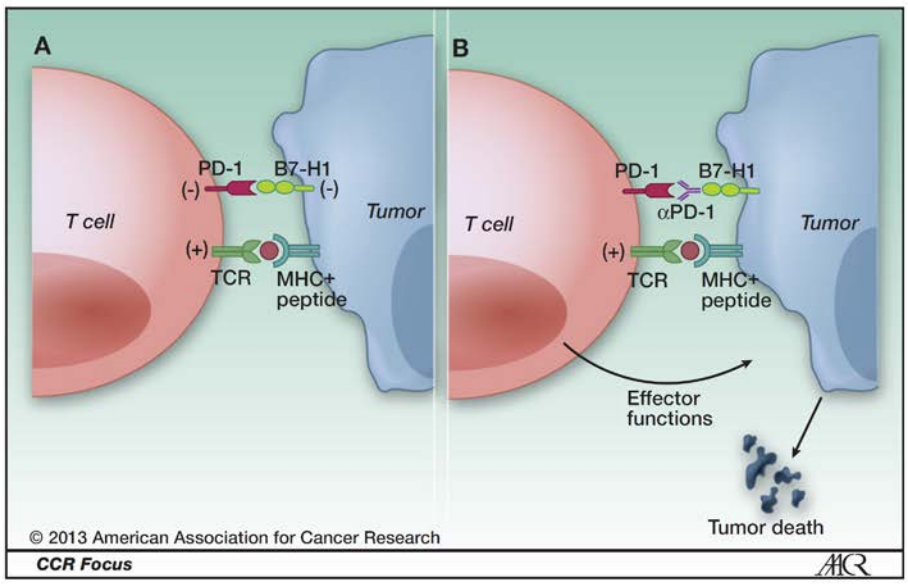


Figure 1. PD-1 and cancer. A, ligation of T-cell PD-1 by tumor B7-H1 results in the downregulation of T-cell effector functions that destroy tumor tissue. B, blockade of this pathway by anti-PD-1 antibodies prevents this downregulation, and allows T cells to maintain their antitumor functionality and ability to mediate tumor cell death.

B7-H1 = PD-L1

Figure 1. Mechanism of action of nivolumab

Colorectal cancer and microsatellite instability

Worldwide, CRC is the third most common form of cancer in men, with 746,298 cases (10.1% of the total) and second most common in women, with 614,304 cases (9.2% of the total) per year. Each year, there are about 608,000 deaths from colon cancer, which is approximately 8% of all cancer deaths, making colon cancer the fourth most common cause of cancer death. A small proportion of tumours including CRC have dMMR, which results in MSI-H.

CRC is the third most common cancer in the US, and will be responsible for an estimated 49,000 deaths in 2016. Although the prevalence of MSI-H/dMMR in early stage CRC is 15%, an estimated 5% of mCRC cases are MSI-H/dMMR.

Emerging evidence points to MSI-H/dMMRmCRC as a biomarker-defined, distinct population with an unmet need for effective therapy as compared to the mismatch repair system (MMR) proficient mCRC population. A pooled analysis of 4 Phase 3 studies in the 1L treatment of mCRC (CAIRO, CAIRO2, COIN, and FOCUS) has shown PFS and OS to be significantly worse (PFS: 6.2 vs 7.6 months, respectively; hazard ratio [HR], 1.33; 95% confidence interval [CI]: 1.12, 1.57; and OS: 13.6 vs 16.8 months, respectively; HR, 1.35; 95% CI: 1.13, 1.61, respectively; P = 0.001 for both) and lower ORR in the CAIRO trial (25% vs 31%)for patients with MSI-H/dMMRvs patients with microsatellite instability stable (MSS).MSI-H/dMMRmCRC has lower ORR, PFS, and OS compared with MMR proficient tumours. The poor prognosis may in part be conferred by the high rate of BRAF mutations associated with sporadic MSI-H/dMMR CRC,as approximately 30% of patients with MSI-H/dMMR CRC carry BRAF V600E mutations.

Standard Treatments for Unresectable/MetastaticColorectal Cancer

1Ltreatment options for subjects with mCRC are predominantly 5FU- or capecitabine-containing regimens in combination with either oxaliplatin or irinotecan (FOLFOX® or FOLFIRI®, respectively) with a biologic agent such as bevacizumab. The EGFR-targeting agents, panitumumab and cetuximab, are also options in 1L if extended-RAS and BRAF status are non-mutated.FOLFOX or FOLFIRI regimens are considered to be equivalent with a 1L median PFS(mPFS) of 8.5 months for FOLFIRI and 8 months for FOLFOX. FOLFIRI is associated with a 62.5% incidence of Grade 3 or higher toxicity even in recent trials, including predominantly gastrointestinal (GI) events and asthenic conditions. FOLFOX has a similar rate of toxicity overall to FOLFIRI, but is associated with significantly higher neurologic toxicity.

In second line (2L), for those subjects who received 1L therapy with FOLFOX or another 5FU-based therapy, the mPFS for subjects receiving FOLFIRI is approximately 4.5 months; there is an ORR of 15% with FOLFOX 2L (95% CI: 7%, 23%) vs 4% with FOLFIRI 2L (95% CI: 0%, 9%; P = 0.05).The VEGF-targeting agents, bevacizumab,ziv-aflibercept, and ramucirumab, have indications for 2L treatment in combination with chemotherapy and have demonstrated improvement in median OS (mOS), but for these biologic agents the improvement in mOS was less than 2 months (agent vs placebo group, respectively): 21.3 vs 19.9 months for bevacizumab,13.50 vs.12.06 months for ziv-aflibercept (Van Cutsem E et al 2012), and 13.3 vs 11.7 months for ramucirumab.PFS is similarly limited, at 5.7 months in the most recent 2L trial for VEGF-targeting agents, FOLFIRI with ramucirumab, which resulted in an ORR of 13.4% (without an independent central review).Panitumumab and cetuximab are also options in 2L, if extended-RAS and BRAF status are non-mutated.In combination with chemotherapy, these agents have demonstrated ORR of 35% for panitumumab in the 2L with a PFS of 5.9 months, and for cetuximab, an ORR of 12.8% and an mPFS of 3.7 months.

For subjects with mCRC who have received prior 5FU-Oxa-Iri, treatment options include regorafenib, which has demonstrated an improvement in mOS of less than 2 months, 6.4 vs 5.0 months when compared to BSC.mPFS was 1.9 months in the regorafenib group and 1.7 months in the BSC group. There

was an ORR of only 1% reported for regorafenib in this Phase 3 trial.76% of subjects required dose modifications due to toxicity, and Grade 3 or 4 treatment-related adverse events (AEs) occurred in 54% of subjects, including hand-foot skin reaction, fatigue, diarrhea, hypertension, and rash or desquamation.

Another treatment option is tipiracil/trifluoridine (TAS-102), which demonstrated an improvement in mOS from 5.3 months with placebo to 7.1 months, with an ORR of 1.6%.The mPFS was 2.0 months in the tipiracil/trifluoridine group and 1.7 months in the placebo group. Neutropenia was the most frequently observed clinically meaningful AE (Grade 3 or 4), occurring in 38% of subjects treated with tipiracil/trifluoridine. 53% had a delay of 4 days or more in beginning their next cycle owing to toxicity.

Although the EGFR agents are generally recommended in combination with chemotherapy in an earlier line of therapy, older data exists in the 3L setting for subjects not yet treated with an EGFR-targeting agent. In the 3L setting, cetuximab demonstrated an improvement in mOS of less than 2 months, ORR of 19.8%, and median DOR (mDOR) of 5.4 months (95% CI: 3.8, 5.5)in patients who have previously received chemotherapy; and an mOS of 6.1 vs 4.6 months, when compared to BSC. Grade 3 or higher rash was reported in 11.8% of subjects. Compared to BSC, panitumumab significantly prolonged PFS by 8 weeks (95% CI: 7.9, 8.4),and there is a 17% ORR in WT RAS patients. However, toxicities characteristic of these agents include dermatitis acneiform reported in 62% of subjects and12% Grade 3 dermatologic toxicities overall. In an open-label Phase 3 trial, the mDOR was 3.8 months (95% CI: 3.7, 4.8) in the panitumumab group and 5.4 months (95% CI:3.8, 5.5) in the cetuximab group. Recent efforts have focused on introducing EGFR-targeting agents earlier in the course of therapy in combination with 5FU-based chemotherapy: either 2Lor 1L, so the EGFR-naive RAS- and BRAF-WT patient population that has received prior 5FU-based chemotherapy may be less significant than when these trials were conducted.

MSI-H/dMMRmCRC is currently treated with standard of care therapy for mCRC although recent guidelines acknowledge the possibility of activity of PD-1 inhibitors. In modern chemotherapy trials, MSI-H/dMMRmCRC has a lower ORR, PFS, and OS compared with proficient MMR tumour. Venderbosch et al found significant differences in PFS and OS; Koopman et al found that the difference in PFS reached statistical significance at 4.0 vs 8.3 months (P = 0.02) and DCRs were also significantly worse in dMMR tumours at 56% vs 83% (P = 0.008).

Thus, subjects with mCRC that progress on chemotherapy have a high unmet need, and patients with MSI-H/dMMRmCRC represent a subset with less robust response to current therapies, even in the 1L setting.

Table 1 provides a summary of the efficacy of available agents in unresectable/mCRC.

Table 1: Agents Recommended in US and EU for the Treatment of Unresectable/Metastatic CRC

Setting	Population	Standard of Care	Response Rate (%)	DOR	PFS (months)	OS (months)
1L	KRAS and BRAF WT	FOLFOX or FOLFIRI + panitumumab[i] or cetuximab[ii]	40-60	NA	8.5-10	16.4-23.9
	KRAS or BRAF mut	FOLFOX or FOLFIRI+ bevacizumab[iii]	38-44	9-10 months	9.4-10.6	20.3-21.3
2L	KRAS and BRAF WT	FOLFOX or FOLFIRI + bevacizumab[iv,v] or ramucirumab or panitumumab	11-22	NA	6-7	12.9-14.5
	KRAS or BRAF mut	FOLFOX or FOLFIRI + or ramucirumab	11-22	NA	6-7	12.9-13.5

Table 1: Agents Recommended in US and EU for the Treatment of Unresectable / Metastatic CRC

Setting	Population	Standard of Care	Response Rate (%)	DOR	PFS (months)	OS (months)
3L	KRAS and BRAF WT, no prior EGFR inhibitor	single-agent panitumumabor cetuximab	22	median: 17 weeks;3.8-5.4 months	8.4	10
3L/4L	KRAS/BRAF mut/WT	regorafenib	1	NA	1.9	6.4
		LONSURF (trifluoridine/tipiracilHCl [TAS-102])	1.6	>200 days (1 responder)	2.0	7.1

Abbreviations: 1L = first line; 2L = second line; 3L = third line; 4L = fourth line; DOR = duration of response; HCl = hydrochloric acid; mut = mutation; NA = not available; OS = overall survival; PFS = progression-free survival; WT = wild type.

Unmet Medical Need

The benefit of current therapies for the sub-population of MSI-H/dMMR mCRC is not fully elucidated, but recent evidence suggests both poorer prognosis and abrogated response to cytotoxic chemotherapy in this group. Despite the numerous treatment options for mCRC, the benefit of these therapies after 1L therapy is modest, toxicity is significant, and complete radiographic responses are rare, thus highlighting the unmet medical need for more effective therapies in this population.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity / environmental risk assessment

The active substance, nivolumab is a protein and therefore no environmental risk assessment studies have been submitted, in line with guidelines.

2.2.2. Discussion and conclusion on non-clinical aspects

The new/extended indication does not lead to a significant increase in environmental exposure further to the use of nivolumab.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

According to the MAH, Study CA209142 was conducted in accordance with the principles of Good Clinical Practice as defined by the International Conference on Harmonisation and was conducted to meet the ethical requirement of European Directive 2001/20/EC. The protocol, amendments, administrative letters, and subject informed consent form received IRB/IEC approval prior to implementation. Compliance audits were performed as part of implementing quality assurance, and audit certificates are

provided as applicable in the study report. The quality of data collected and analyzed was monitored according to BMS standard operating procedures.

2.3.2. Pharmacokinetics

No new clinical pharmacology studies are included in this submission. The results of the PPK analysis conducted using data from multiple studies including mCRC subjects are provided in the following sections.

2.3.3. Pharmacodynamics

No new clinical pharmacology studies are included in this submission. The results of the PPK analysis conducted using data from multiple studies including mCRC subjects are provided in the following sections.

2.3.4. PK/PD modelling

Introduction

This document summarizes the nivolumab population pharmacokinetics (PPK) in subjects whose unresectable or metastatic colorectal cancer (mCRC) tumours have defects in mismatch repair (dMMR) resulting in a high level of microsatellite instability (MSI-H) from the monotherapy cohort of the Phase 2 Study CA209142. This analysis supports the clinical pharmacology profile of nivolumab in mCRC, and supports justification of the recommended nivolumab dose. A previously developed nivolumab PPK model was updated to assess the potential effects of mCRC tumour type on nivolumab PK. Exposure-response analyses were not conducted in this mCRC population as only single dose data was available. Additionally, the incidence and effect of immunogenicity on the safety and efficacy of nivolumab was assessed in CA209142. The effect of anti-drug antibodies on nivolumab CL was previously assessed in a previous PPK analysis and was not clinically relevant. The immunogenicity of nivolumab assessed from study CA209142 was also integrated with the overall immunogenicity across tumour types to assess the incidence and potential effect of immunogenicity on the safety profile of nivolumab.

The recommended nivolumab dose and schedule for mCRC is the same as that initially approved for non-small cell lung carcinoma (NSCLC), renal cell carcinoma (RCC), melanoma, and classical Hodgkin's lymphoma (cHL): nivolumab 3 mg/kg intravenously (IV) every 2 weeks (Q2W).

- Methods

The nivolumab clinical pharmacology profile, including single- and multiple-dose pharmacokinetics (PK), drug-drug interaction potential, QT prolongation potential, dose selection for phase 2/3 studies, and exposure-response (E-R) relationships with safety and efficacy across multiple tumour types have been characterized and described in previously submitted clinical pharmacology packages. The clinical pharmacology data in this application support the use of nivolumab as monotherapy for the treatment of subjects with dMMR or MSI-H, mCRC.

PPK analyses have previously been performed using serum concentration data from several Phase 1, 2, and 3 studies evaluating nivolumab treatment in solid tumours, including NSCLC, melanoma, RCC, squamous cell carcinoma of the head and neck (SCCHN), and urothelial carcinoma (UC). Collectively, these analyses indicated that age, gender, race, baseline lactate dehydrogenase (LDH), hepatic impairment, PD-L1 expression, immunogenicity, manufacturing process, and tumour type had no effect on nivolumab clearance. Baseline glomerular filtration rate, ECOG performance status, and body weight had minor, non-clinically meaningful effects on nivolumab clearance. Results of a post hoc analysis indicated that baseline serum albumin appeared to have an effect on nivolumab clearance, although the effect was not considered to be clinically meaningful because the EE-R relationships for both efficacy and safety were relatively flat in the NSCLC population

- Overview of Nivolumab Population Pharmacokinetics in mCRC

The PPK analysis included in this submission was performed to compare nivolumab PK in subjects with mCRC to that of subjects with NSCLC treated with nivolumab as 2nd line or greater (NSCLC 2L+) for which PK has been well established. This analysis included the effects of mCRC tumour type on nivolumab PK. Results of the analysis demonstrated nivolumab concentration-time data were well described by a previously-developed zero-order input intravenous infusion model with time-varying clearance. Overall, nivolumab CL in mCRC subjects was similar to that in NSCLC 2L+ and was consistent with previous results in the nivolumab development program in other tumour types. Baseline nivolumab CL was similar in subjects with mCRCvs NSCLC 2L+. The magnitude of change in CL over time was similar in mCRC subjects compared to those with NSCLC 2L+ (~34% vs 30%). CRC tumour type did not have an effect on

nivolumab exposure: subjects with mCRC have comparable exposures to those of subjects with NSCLC 2L+ (geometric mean differences < 10%).

- Overview of Nivolumab Immunogenicity

Of the 52 mCRC subjects with evaluable ADA data from Study CA209142 treated with nivolumab 3 mg/kg Q2W, 8 (15.4%) subjects were ADA positive. Of the 8 subjects, 1 subject (1.9% of the total) was persistent positive for ADA and 1 (1.9%) subject was neutralizing antibody (NAb) positive. Additionally, there did not appear to be a causal relationship between the onset of ADA and efficacy. Out of the 8 subjects that were ADA positive, 5 subjects had a BOR of PR, and 1 subject had a BOR of SD per IRRC. Thus, 62.5% of the ADA positive subjects had a response of CR and PR, which is generally consistent with the overall response observed in the all-treated subjects group in this study. Thus, the incidence of ADA did not appear to have an effect on the efficacy of nivolumab.

Of the nivolumab monotherapy treated subjects who were evaluable for ADA, 1 ADA negative and 1 ADA positive subject experienced select AEs in the hypersensitivity/infusion reaction category suggesting a lack of effect of ADA on safety.

Overall, immunogenicity in subjects with mCRC and other tumours was not clinically meaningful, given that there was no evidence of altered safety and efficacy profiles.

Population Pharmacokinetic Analysis

The PPK analysis serves to characterize nivolumab PK in subjects with mCRC, based on a previously established nivolumab PPK model using time-varying CL.2 The objective of the present analysis was to characterize the PK of nivolumab in subjects with mCRC, and to determine the effect of tumour type on nivolumab PK and exposure. The effect of tumour type on nivolumab CL and Emax was assessed relative to NSCLC 2L+ subjects in the full model along with several other covariates.

The PPK analysis was performed using data from 1084 subjects with multiple tumour types including mCRC. The analysis population consisted of all subjects enrolled who received nivolumab, and for whom nivolumab concentration values were available following nivolumab monotherapy from: 2 Phase 1 studies (MDX-1106-01 and MDX-1106-03), 2 Phase 2 studies (CA209063 and CA209142), and 3 Phase 3 studies (CA209017, CA209057, and CA209143).

These studies were selected either because they had intensive PK samples collected to allow characterization of nivolumab PK (MDX-1106-01 and MDX-1106-03) or because they were used as a reference tumour type in the PPK analysis (NSCLC 2L+ subjects from studies CA209063, CA209017, and CA209057). Study MDX-1106-03 also enrolled mCRC subjects which contributed to the CRC tumour type assessment. Data from study CA209142 allowed assessment of nivolumab PK in subjects with MSI-H CRC. Data from Study CA209143 was included to allow assessment of nivolumab PK in subjects with glioblastoma multiforme (GBM) to support an upcoming supplement.

- PPK Model

The PPK model was developed using a previously developed final model and included the effect of tumour type (CRC, GBM, NSCLC 2L+, or Other) on CL and tumour type on Emax. Base model development consisted of re-estimation of the previous final model parameters using data from the studies described previously. This approach leveraged the previously-determined structural, interindividual variability, residual error, and covariate effect components of the nivolumab PPK model. The full model was used to assess the temporal change of CL and to obtain summary measures of exposures for each subject. The full model was intended to assess the tumour type effects on various PK parameters. However, when the three tumour type effects (CRC, GBM or Others relative to NSCLC 2L+) were added onto the four PK parameters of interest (CL, VC, EMAX and T50) in the base model, the model became unstable. The model

was then simplified. For the purpose of this analysis, the estimation of the CRC and GBM effects vs NSCLC 2L+/Others were selected. Finally, the data did not appear to support further assessment of the tumour effects on VC when the model convergence and the condition numbers were inspected.

The full model was a 2-compartment model with zero-order IV infusion input and time-varying CL according to a sigmoidal Emax function and a proportional residual error model. The full PPK model included effects of baseline body weight (BBWT), eGFR, sex, PS, and race (African American or Asian) on CL, baseline WT and sex on VC, and tumour type on Emax.

The full model was as follows:

$$CL_{TV,i,t} = CL_{REF} * \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} * \left(\frac{BGFR_i}{BGFR_{REF}}\right)^{CL_{BGFR}} * (e^{CL_{SEX}})^{ISEX_i} * (e^{CL_{PS}})^{IPS_i} * (e^{CL_{RAAA}})^{IRAAA_i} * (e^{CL_{RAAS}})^{IRAAS_i} * (e^{CL_{CRC}})^{ICRC_i} * (e^{CL_{GBM}})^{IGBM_i} * (e^{CL_{OTH}})^{IOTH_i} * EXP\left(\frac{EMAX_{TV,i} * t^{HILL}}{T50^{HILL} + t^{HILL}}\right)$$

$$VC_{TV,i} = VC_{REF} * \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}} * (e^{VC_{SEX}})^{ISEX_i}¶$$

The effects of CRC and GBM tumour types relative to the Emax parameter value of a reference subject (tumour type category of NSCLC_2L) were given by the following expression:

$$EMAX_{TV,i} = EMAX_{REF} * (e^{EMAX_{CRC}})^{ICRC_i} * (e^{EMAX_{GBM}})^{IGBM_i}$$

where EMAXREF is the value of the parameter for the reference subject (NSCLC_2L); EMAXCRC is the estimated model parameter for the effect of CRC tumour type; ICRCi is the indicator variable for the CRC tumour type of subject i, respectively (1 = yes, and 0 = no); EMAXGBM is the estimated model parameter for the effect of GBM tumour type; IGBMi is the indicator variable for the GBM tumour type of subject i, respectively (1 = yes, and 0 = no).

Parameter estimates from the full PPK model are provided in Table 2

The PPK model parameters were estimated with good precision and the model evaluation demonstrated that there was good agreement between model predictions and observations.

Table 2: PPK Model Parameter Estimates (Full Model)

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
CL [L/h]	θ_1	0.0113	5.32E-04 (4.71)	0.0102 - 0.0126
VC [L]	θ_2	4.19	0.0649 (1.55)	4.06 - 4.30
Q [L/h]	θ_3	0.0311	0.00380 (12.2)	0.0256 - 0.0441
VP [L]	θ_4	2.90	0.160 (5.52)	2.56 - 3.27
PERR [-]	θ_6	0.233	0.0107 (4.59)	0.214 - 0.255
CL_{BBWT}	θ_7	0.561	0.0653 (11.6)	0.428 - 0.682
CL_{BGFR}	θ_9	0.157	0.0508 (32.4)	0.0609 - 0.257
CL_{SEX}	θ_{12}	-0.154	0.0326 (21.2)	-0.224 - -0.0921
CL_{PS}	θ_{13}	0.117	0.0290 (24.8)	0.0640 - 0.179
VC_{BBWT}	θ_{14}	0.758	0.0544 (7.18)	0.641 - 0.864
VC_{SEX}	θ_{15}	-0.129	0.0297 (23.0)	-0.186 - -0.0714
CL_{EMAX}	θ_{16}	-0.354	0.0692 (19.5)	-0.502 - -0.190
CL_{T50}	θ_{17}	1.50E+03	246 (16.4)	954 - 2130
CL_{HILL}	θ_{18}	1.96	0.614 (31.3)	1.23 - 12.3
CL_{RAA}	θ_{19}	0.00409	0.0486 (1.19E+03)	-0.0972 - 0.107
CL_{RAAS}	θ_{20}	-0.127	0.0787 (62.0)	-0.299 - 0.0176
CL_{CRC}	θ_{22}	0.0342	0.0615 (180)	-0.116 - 0.151
CL_{GBM}	θ_{23}	-0.598	0.0501 (8.38)	-0.689 - -0.500
CL_{OTH}	θ_{24}	0.0669	0.0455 (68.0)	-0.0251 - 0.165
$EMAX_{CRC}$	θ_{27}	0.164	0.248 (151)	-0.427 - 0.641
$EMAX_{GBM}$	θ_{28}	-1.39	0.864 (62.2)	-17.5 - 0.420
Random Effects[f,g]				
$\omega^2 CL$ [-]	$\omega_{1,1}$	0.113 (0.336)	0.0108 (9.56)	0.0911 - 0.140
$\omega^2 VC$ [-]	$\omega_{2,2}$	0.103 (0.321)	0.0182 (17.7)	0.0691 - 0.138
$\omega^2 VP$ [-]	$\omega_{5,3}$	0.261 (0.511)	0.0390 (14.9)	0.191 - 0.349
$\omega^2 EMAX$ [h]	$\omega_{4,4}$	0.0988 (0.314)	0.0344 (34.8)	0.0472 - 0.172
$\omega^2 CL$: $\omega^2 VC$	$\omega_{1,2}$	0.0543 (0.503)	0.00886 (16.3)	0.0360 - 0.0712

[a] Parameters with fixed values (not estimated) are denoted with a superscript 'f' after the names, with the fixed value given in the Estimate column

The PPK model was used to obtain summary measures of exposure for each subject in the analysis dataset. In addition, a graphical assessment of the effect of tumour type on nivolumab exposure was conducted.

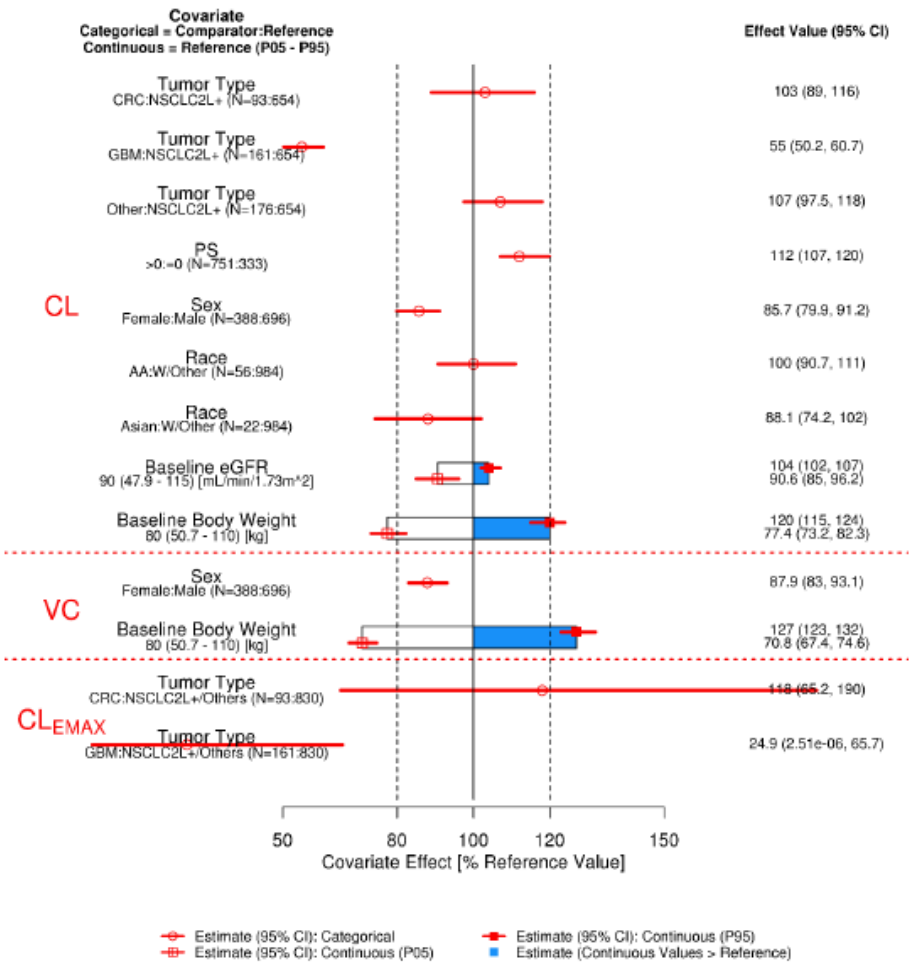
- Analyses of Covariate Effects

The effect of categorical and continuous covariates on the typical value of the structural model parameters of CL and VC and the estimated covariate effects (and 95% confidence intervals) are presented in Figure 2.

The magnitude of the effect of PS, body weight, sex and BGFR on CL, and the effect of sex and body weight on central volume of distribution in this population with CRC subjects is comparable to what was previously reported in the nivolumab comprehensive PPK analysis that included more tumour types. The

effect (point estimate) of CRC tumour type relative to NSCLC 2L+ on CL was close to zero. Accounting for uncertainty, the effect of CRC tumour type on CL is within [illegible] Figure 2 boundaries as shown.
The population mean CL of mCRC subjects, calculated as [exp(CLCRC)-1]*100, is 3.48% greater relative to that of NSCLC 2L+ subjects. Based on the full model, over time the population mean CL of the mCRC subjects decreased by 34.1%, calculated as [1-exp(CLEMAX*exp(EMAXCRC))]*100, from baseline CL compared to ~30% in subjects with tumour type of either NSCLC 2L+ or Others.

Overall, the effects of covariates including baseline body weight, baseline ALB, baseline GFR, PS, sex, and race were consistent with previous analyses.



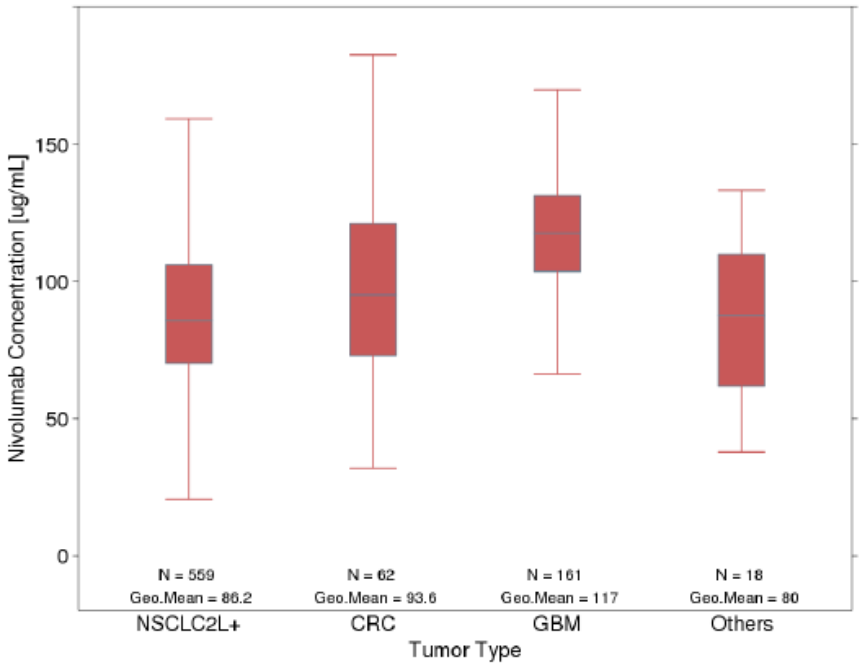
Analysis Directory: /global/pkms/data/CA/209/C19/prd/ppk/final
Program Source: Analysis Directory/R/scripts/cov-eff-plot-full_v5.3-model.r
Source: Analysis Directory/R/plots/cov-eff-plot-full_5.3.png

Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal red lines).
Note 2: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by the end of horizontal boxes (horizontal red lines). Open/Blue area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Figure 2 Covariate Effects on PK Model Parameters (Full PPK Model)

Assessment of Tumour Type on Nivolumab Exposure

Nivolumab Cavgss for CRC subjects, who received 3 mg/kg Q2W, appeared to be similar to subjects with NSCLC2L+ as presented below inFigure 3. The largest difference was observed in geometric mean Cminsswhich was 45% higher in CRC compared to NSCLC2L+ subjects as presented in Table 3.



Analysis Directory: /global/pkms/data/CA/209/C19/prd/ppk/final
Program Source: Analysis Directory/R/scripts/summarize-model-application.r
Source: Analysis Directory/R/plots/Cavgss-3mgkg-ttypef2.png
Note: The boxes represent the 25th, 50th, and 75th percentiles of the distribution. The whiskers extend to 1.5 times the interquartile range

Figure 3: Distribution of Nivolumab CAVGSS Estimates Between Tumour Types (3 mg/kg Q2Q)

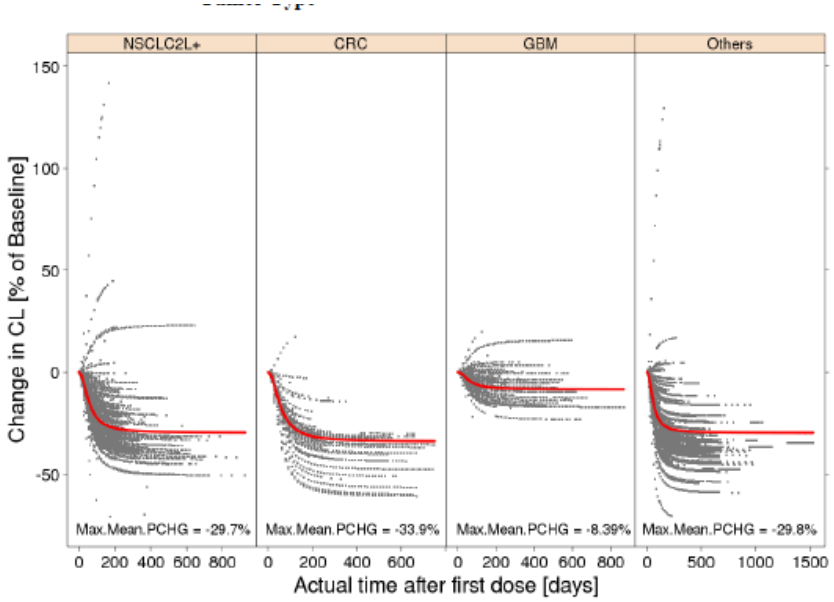
Table 3: Exposure Comparison 3mg/kg Q2Q0 Between Tumour Types

Exposure Parameter	Geometric Mean (CV%)		GM Diff Percent(%)[a]
	NSCLC 2L+ (N=559)	CRC (N=62)	CRC vs NSCLC2L+
Cmin1 (µg/mL)	17.2(28.9)	17(27.8)	-1.16
Cmax1 (µg/mL)	61.7(59.2)	60.3(15.3)	-2.27
Cavg1 (µg/mL)	27.1(23.2)	26.9(21.8)	-0.738
Cminss (µg/mL)	66.9(79.4)	73.9(48.3)	10.5
Cmaxss (µg/mL)	131(56)	137(32.6)	4.58
Cavgss (µg/mL)	86.2(65)	93.6(41.5)	8.58

[a] GM Diff Percent is the geometric mean difference in percentage, calculated as [(Test Tumor Type - NSCLC 2L+) / NSCLC 2L+] * 100
Analysis Directory: /global/pkms/data/CA/209/C19/prd/ppk/final
Program Source: Analysis Directory/R/scripts/summarize-model-application.r
Source: Analysis Directory/R/export/compare.exp.3mgkg.csv

- Assessment of Temporal Changes in Nivolumab CL

The model estimated (typical value) of Emax (-0.354) indicated that nivolumab CL decreased with time, and that the maximal decrease was approximately 30% [calculated as: 1 −exp(Emax)], as shown in Figure 4. The change in CL is estimated to occur soon after initiation of treatment, with the half-maximal change estimated to occur at approximately 2 months (T50 = 1500 h). The geometric mean CL for CRC patients of 11.7 mL/hr (after the first dose) reaches a steady-state value of 7.71 mL/hr.



%Change in CL = 100 * ((CL_t - $CL_{t=0}$)/$CL_{t=0}$)
Max.Mean.PCHG is the population mean percentage change of CL from baseline at the maximal observation time for each tumor type. It was calculated as follows:
(exp(EMAX*exp($EMAX_{TUMOR}$)*max.observed.time**HILL/(T50**HILL+max.observed.time**HILL)) -1) * 100
where $EMAX_{TUMOR}$ is the tumor type effects on EMAX, max.observed.time is the maximal observation time for each tumor type, EMAX, T50 and HILL are the model estimated time-varying CL parameters from the full model.
Analysis Directory: /global/pkms/data/CA/209/C19/prd/ppk/final
Program Source: Analysis Directory/R/scripts/summarize-model-application.r
Source: Analysis Directory/R/plots/CL.PCHG-vs-time.png

Figure 4: Model-Estimated Change in Clearance versus Time (Full Model) by Tumour Type

- Estimates of Individual Pharmacokinetic Parameters and Exposure Measures

A summary of the individual PK parameter estimates obtained from the full PPK model (with all studies) is provided in Table 4.

Table 4: Summary Statistics of Individual PK Parameters (n=1084)

Parameter	Mean	Geometric Mean	Median (Min, Max)	SD	CV(%)
Baseline CL (L/h)	0.0111	0.0103	0.0105(0.00208,0.0397)	0.00452	40.8
CLSS (L/h)	0.00825	0.00752	0.00743(0.000517,0.105)	0.0047	57
VC (L)	3.96	3.77	3.85(0.212,9.99)	1.21	30.4
VP (L)	3.04	2.9	2.9(0.783,21.2)	1.18	38.7
VSS (L)[a]	7	6.8	6.79(2.2,24.8)	1.77	25.2
T-HALF$_\alpha$ (hr)	34.3	33.5	34.1(4.3,74.2)	7.48	21.8
T-HALF$_\beta$ (day)	21.6	20.5	19.5(6.53,137)	9.05	41.9

[a] VSS = VC + VP
Analysis Directory: /global/pkms/data/CA/209/C19/prd/ppk/final
Program Source: Analysis Directory/R/scripts/ summarize-model-application.r
Source: Analysis Directory/R/export/stats.para.csv

Exposure-Response

E-R analyses for safety and efficacy in subjects with MSI-H CRC from study CA209142 were not conducted, as data were available from only one dose level.

E-R analyses for efficacy and safety following treatment with nivolumab have previously been conducted in treatment refractory SQ and NSQ NSCLC, advanced melanoma, and advanced RCC subjects.7,12,13

The E-R of efficacy for each of these tumour types was characterized with respect to overall survival, and in each of these analyses nivolumab exposure (Cavgss, time-averaged steady-state concentration) was not a significant predictor of overall survival, indicating that the E-R of nivolumab is relatively flat for these indications. These analyses included estimation of the effect of CL as well as Cavgss, as the overall survival of cancer patients has been reported to be associated with the clearance of monoclonal antibodies.14 This association has also been observed for nivolumab in previous analyses.7,12,13 In these analyses, it was possible to estimate the effects of both CL and Cavgss in the same model, as Cavgss values were available for more than one dose level.

Furthermore, experience from the nivolumab E-R analysis of efficacy in RCC found that the results may be misleading if the effect of CL is not taken into account. In the initial E-R analysis of OS conducted in subjects with RCC (including data from a single phase 3 study which investigated a single dose level of nivolumab 3 mg/kg only), nivolumab exposure was found to be a significant predictor of OS. This was because the data from a single dose level was insufficient to resolve the potential confounding effect of CL on Cavgss. However, when data from subjects with RCC treated with additional dose levels were added to the RCC analysis, the confounding effect of CL on Cavgss was resolved, and nivolumab exposure was not a predictor for OS.

Since the data from study CA209142 was only from a single nivolumab dose level (3 mg/kg Q2W), it is expected that similar to the case described for the RCC analysis, where CL had a confounding effect on the ability to assess the Cavgss on efficacy, E-R analysis of the CRC data would not be interpretable. Therefore, E-R analysis for efficacy was not conducted for subjects with CRC from study CA209142.

E-R analysis of safety (Grade 3+ drug related adverse events [DR-AEs] and adverse events leading to discontinuation or death [AE-DC/D]) was previously performed in subjects with treatment refractory SQ and NSQ NSCLC, advanced melanoma, and advanced RCC subjects.7,12,13 In each of these analyses, the nivolumab exposure (Cavgss) produced by doses of 1 to 10 mg/kg did not appear to have a significant effect on the risk of Grade 3+ DR-AEs or AE-DC/D. Thus, an E-R analysis of safety was not conducted for CRC subjects from study CA209142 as nivolumab 3 mg/kg Q2W has been shown to be safe and well-tolerated in multiple tumour types. Furthermore, no clinically relevant differences in select AEs between the CA209142 population and the pooled nivolumab monotherapy population across other tumour types were observed.

Justification of Recommended Nivolumab Dose

The selected dosing regimen for Study CA209142 (3 mg/kg Q2W) was based upon the collective clinical experience of nivolumab monotherapy across multiple tumour types. The analysis of safety, efficacy, and exposure-response data from the Phase 1 study CA209003, as well as the favourable risk-benefit ratio observed in multiple tumour types including melanoma, NSCLC, and RCC, cHL, UC, and SCCHN had demonstrated that nivolumab 3 mg/kg Q2W is active across multiple tumour types. Clinical observations and E-R analyses in melanoma, NSCLC, and RCC showed that the probability of a tumour response approached a plateau for nivolumab trough concentrations achieved following administration of 3 mg/kg and 10 mg/kg Q2W. In an E-R analysis of the relationship between nivolumab exposure (Cavgss) and OS over the 1 mg/kg Q2W to 10 mg/kg Q2W dose range, which included 3 mg/kg Q2W, nivolumab Cavgss was not a significant predictor of hazard of death in NSCLC, melanoma and RCC, indicating that over this dose range there is a flat E-R relationship. Based upon the totality of experience across immunogenic and non-immunogenic tumour types, 3 mg/kg Q2W was selected as the dose anticipated to achieve an appropriate balance of benefit and risk in Study CA209142.

Results from CA209142 demonstrated that mCRC subjects treated with nivolumab 3 mg/kg Q2W had an acceptable safety profile and a clinically meaningful response, with an ORR of 27% by IRRC assessment

in the monotherapy cohort and 24% in subjects with prior 5FU OXa-Iri. Collectively, these results support the recommended dose of nivolumab 3 mg/kg Q2W in the treatment of mCRC.

OTHER ASSESSMENTS

Immunogenicity of Nivolumab

The immunogenicity following the administration of nivolumab 3 mg/kg Q2W monotherapy has been well characterized in the nivolumab development program across multiple tumour types. This section provides updated immunogenicity analysis with data from Study CA209142.

Immunogenicity Analysis

During the clinical development of nivolumab, three assays were used to detect the presence of nivolumab ADA.15 The CA209142 study used in this submission and all of the studies included in the integrated summary of immunogenicity used the current sensitive and drug tolerant assay (ICDIM 140) for immunogenicity analysis. A summary of immunogenicity results from Study CA209142 is presented in Section 4.1.2.

The following definitions were applied to evaluate the immunogenicity of nivolumab:

-Evaluable Subjects: All treated subjects with baseline and at least 1 post-baseline immunogenicity assessment.

-Baseline ADA-Positive Sample: ADA was detected in the last sample before initiation of treatment.

-ADA-Positive Sample: After initiation of treatment, (1) ADA detected (positive seroconversion) in a sample in a subject for whom ADA was not detected at baseline or (2) an ADA-positive sample with ADA titer at least 4-fold or greater (≥) than baseline positive titer.

-Neutralizing ADA Positive Sample: A confirmed ADA-positive sample with neutralizing antibodies detected.

-ADA-Negative Sample: After initiation of treatment, ADA-not positive sample relative to baseline.

-Baseline ADA-Positive Subject: A subject with baseline ADA-positive sample.

-ADA-Positive-Subject: A subject with at least 1 ADA-positive sample at any time after initiation of treatment. The following are specific categories of ADA-positive subjects:

-Persistent Positive: A subject with ADA-positive samples at 2 or more consecutive time points, where the first and last ADA positive samples were at least 16 weeks apart.

-Not Persistent Positive - Last Sample Positive: Not persistent positive with ADA-positive sample at the last sampling time point. (Previously, this was termed Only Last Sample Positive.)

-Other Positive: Not persistent positive with ADA negative sample in the last sampling time point.

-Neutralizing ADA Positive Subject: A subject with at least one ADA positive sample with neutralizing antibodies detected.

ADA-Negative Subject: A subject with no ADA-positive sample after the initiation of treatment.

Immunogenicity Results from Study CA209142

A summary of the ADA assessments for subjects on Study CA209142 who had evaluable ADAdata at baseline and on treatment is presented in Table 5

Table 5: Summary of ADA Assessments in Study CA209142-Nivolumab Treated Subjects with Baseline and at Least one Post-Baseline Assessment

	Number of Subjects (%)[a]
	CA209142 (N=52)
Baseline ADA Positive	1 (1.9)
ADA Positive	8 (15.4)
Persistent Positive	1 (1.9)
Not PP - Last Sample Positive	3 (5.8)
Other Positive	4 (7.7)
Neutralizing ADA Positive[b]	1 (1.9)
ADA Negative	44 (84.6)

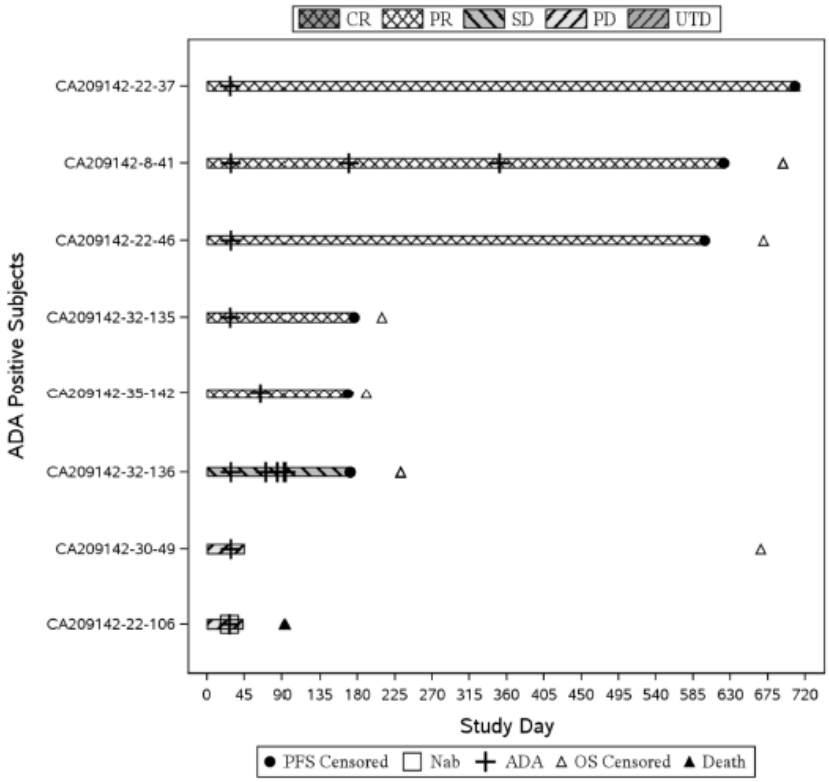
[a] MSI-H/dMMR CRC subjects per local lab

[b] For a narrative of the neutralizing ADA positive subject summarizing efficacy and safety data refer to Appendix 7.4A of the CA209142 CSR.

Baseline ADA Positive Subject: A subject with Baseline ADA positive sample; ADA Positive Subject: A subject with at least one ADA positive sample relative to baseline at any time after initiation of treatment; Persistent Positive Subject: ADA positive sample at 2 or more consecutive timepoints, with first and last ADA positive samples at least 16 weeks apart; Not PP - Last Sample Positive : Not persistent but ADA positive sample in the last sampling timepoint; Other Positive: Not persistent but some ADA positive samples with the last sample being negative; Neutralizing ADA Positive: At least one ADA positive sample with neutralizing antibodies detected post baseline; ADA Negative: A subject with no ADA positive sample after the initiation of treatment. Post-baseline assessments are assessments reported after initiation of treatment.
Source: Table S.7.10 of the CA209142 CSR

Of the 52 subjects with evaluable ADA, 8 subjects (15.4%) were ADA positive. Of the 8 subjects, 1 (1.9%) subject was persistent positive and 1 subject was neutralizing antibody (NAb) positive. The highest titer value observed in ADA positive subjects was 32, which occurred in 1 subject who had ADA status of Not PP - Last Sample Positive. All other ADA positive subjects had titer values of 16 or less.11 The incidence of nivolumab ADA in Study CA209142 was similar to what has been observed across other tumour types.3 Of the nivolumab monotherapy treated subjects who were evaluable for ADA, 1 ADA negative and 1 ADA positive subject experienced select AEs in the hypersensitivity/infusion reaction category, suggesting a lack of effect of ADA on safety.

The effect of ADA and NAb occurrence in relation to PFS and BOR per IRRC in all nivolumab monotherapy treated subjects who were ADA positive is presented in Figure 4.1.2-1. The results show a lack of direct causal relationship between the detection of ADA positive samples and BOR, the duration of PFS, or OS. Several subjects have a single positive ADA sample at the first time point (2 weeks after the first dose), but they have PFS values that ranged from day 45 to day 720 indicating that a lack of causal relationship exists. Further, of the 8 subjects that were ADA positive, 5 subjects had a BOR of PR, and 1 subject had a BOR of SD per IRRC. Thus, 62.5% of the ADA positive subjects had a response of CR or PR. While this overall response rate is numerically greater in this small subset relative to all nivolumab monotherapy treated subjects, ADA does not negatively affect the response to nivolumab. Thus, the incidence of ADA did not appear to have negative effects on the efficacy of nivolumab in this population. Overall, based on the above data, the incidence of nivolumab ADA did not appear to negatively effect the safety and efficacy of nivolumab in the monotherapy treated subjects with mCRC in study CA209142.



Bar indicates progression free survival
Horizontal axis origin corresponds to first dose date
Source: Figure S.8.2A of the CA209142 CSR

Figure 5: ADA and Nab Occurrence in Relation to PFS and BOR as Assessed in IRRC –All Nivolumab Monotherapy Treated Subjects with positive ADA Status

2.3.5. Discussion on clinical pharmacology

No dose finding study was conducted for nivolumab monotherapy for treatment of mCRC. The recommended dose and schedule of nivolumab monotherapy for treatment of mCRC is the same as that approved for melanoma, NSCLC, and renal cell carcinoma monotherapy: 3 mg/kg IV infusion over 60 minutes Q2W.

Sparse pharmacokinetic data were collected in study CA209142. An updated popPK analysis, including a clearance of nivolumab that varied in time,was presented. The popPK model described the PK data of subjects with mCRC reasonably well and overall, the popPK analysis indicated that there are no major differences in pharmacokinetics of nivolumab in mCRC compared to other solid tumour types. There is a large inter-subject variability in the change in clearance over time. There are insufficient data for mCRC to demonstrate a relationship between response and decrease in clearance over time.

The absence of exposure response analysis for efficacy and safety for subjects with mCRC has been sufficiently justified. Previous exposure-response relationships had shown that Cavg,ss was not a significant predictor of hazard of death after accounting for nivolumab CL. As in mCRC only one nivolumab dose was administered, relationships with Cavg,ss are confounded by nivolumab CL. Nivolumab 3 mg/kg Q2W has been shown to be safe and well tolerated in several other tumour types and previous analyses in advanced melanoma, NSCLC, and RCC patients have shown that AE-DC/D does not increase with Cavg,ss produced by nivolumab doses of 1 to 10 mg/kg Q2W.

The development of antibodies against nivolumab in study CA209142 in subjects with mCRC are in agreement with previously incidence of antibodies. Nivolumab has low immunogenic potential; pooled

analysis of all tumour types showed that approximately 10% of subjects who were treated with nivolumab 3 mg/kg every 2 weeks (Q2W) monotherapy tested positive for treatment-emergent anti-nivolumab antibody.Of those who were anti-nivolumab antibody positive, <1% is persistent positive and <1% has neutralizing antibodies. There is no indication that the safety profiles of persistent positive or neutralizing antibody positive subjects were different than those in other subjects. There was no evidence of loss of efficacy in subjects with neutralizing antibodies.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics of nivolumab has been sufficiently investigated for the extension of the indication of nivolumab 3 mg/kg every 2 weeks for treatment of mCRC. New analyses presented do not change current knowledge on PK/PD and immunogenicity for Opdivo.

2.4. Clinical efficacy

CA209142 is an open-label, multi-center, 2-stage Simon design study of nivolumab monotherapy (mStage) or in combination with ipilimumab (cStage) to estimate the response rate in MSI-H/dMMR CRC and mismatch repair proficient (pMMR)/non-MSI-H CRC. Mismatch repair (MMR)/microsatellite instability (MSI) status in potential subjects, detected by an accredited laboratory per local regulations, was determined prior to screening as part of standard diagnostic testing by investigators. Samples with instability in 2 or more of mononucleotide or dinucleotide markers, regardless of the panel of markers utilized, were defined as MSI-High. The study included subjects regardless of their PD-L1 status.

The current application for mCRC is based on data from the nivolumab monotherapy cohort (mStage1 and mStage2) from CA209142. Data in the combination cohort (nivolumab + ipilimumab) are not presented.

Table 6: Summary of CA209142 Study Design

Number of Subjects	**MSI-H/dMMR CRC per Local Lab, All Subjects:** N = 74 **MSI-H/dMMR CRC per Local Lab, Heavily-pretreated Efficacy Population (subjects with 5FU, oxaliplatin, and irinotecan as prior therapy):** N = 53
Nivolumab Regimen	Nivolumab montherapy, 3 mg/kg Q2W by IV infusion
Primary Objectives	To evaluate the investigator-assessed ORR of nivolumab monotherapy in dMMR/ MSI-H mCRC.
Secondary Objectives	To evaluate the IRRC-assessed ORR of nivolumab monotherapy in dMMR/MSI-H mCRC.
Key Exploratory Objectives	• To determine the safety and tolerability (defined as toxicity rates [worst CTC grade per subject] of AEs and specific laboratory tests) of nivolumab monotherapy (mStage 1 and 2) in subjects with mCRC. • To estimate PFS and OS for subjects with metastatic CRC who have received nivolumab monotherapy (mStage 1 and 2). • To evaluate health related quality of life using a validated instrument in the European Organisation for Research and Treatment of Care General Cancer Module (QLQ-C30). • To evaluate patient reported general health status as assessed by the five item EQ-5D
Study Status	Completed primary endpoint based on a 19-Sep-2016 DBL. Additional follow-up ongoing (analysis at a minimum of approximately 6 months follow-up). An interim CSR is available. The study is ongoing.

Abbreviations: CRC, colorectal cancer; DBL, database lock; dMMR, mismatch repair deficient system; IRRC, Independent Radiologic Review Committee; MSI-H, high-level microsatellite instability; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

2.4.1. Dose response study(ies)

No dedicated dose response studies have been conducted. The selected dosing regimen for Study CA209142 (3 mg/kg Q2W) was based upon the collective clinical experience of nivolumab monotherapy across multiple tumour types. According to the MAH, the analysis of safety, efficacy, and exposure-response data from the Phase 1 study CA209003, as well as the favourable risk-benefit ratio observed in multiple tumour types including melanoma, NSCLC, and RCC, cHL, UC, and SCCHN had demonstrated that nivolumab 3 mg/kg Q2W is active across multiple tumour types. Clinical observations and E-R analyses in melanoma, NSCLC, and RCC showed that the probability of a tumour response approached a plateau for nivolumab trough concentrations achieved following administration of 3 mg/kg and 10 mg/kg Q2W. In an E-R analysis of the relationship between nivolumab exposure (Cavgss) and OS over the 1 mg/kg Q2W to 10 mg/kg Q2W dose range, which included 3 mg/kg Q2W, nivolumab Cavgss was not a significant predictor of hazard of death in NSCLC, melanoma and RCC, indicating that over this dose range there is a flat E-R relationship. Based upon the totality of experience across immunogenic and non-immunogenic tumour types, 3 mg/kg Q2W was selected as the dose anticipated to achieve an appropriate balance of benefit and risk in Study CA209142.

Results from exploration of exposure-response relationships (exploratory endpoint) are not reported in the CSR.

2.4.2. Main study

CA209142 is a Phase 2 open-label, multi-centre, 2-stage Simon design stage trial of nivolumab (BMS-936558) monotherapy (mStage) or in combination with ipilimumab (cStage) in adults (> 18 years) with recurrent or metastatic CRC.

The current application for mCRC is based on data from the nivolumab monotherapy cohort (mStage1 and mStage2) from CA209142.

Methods

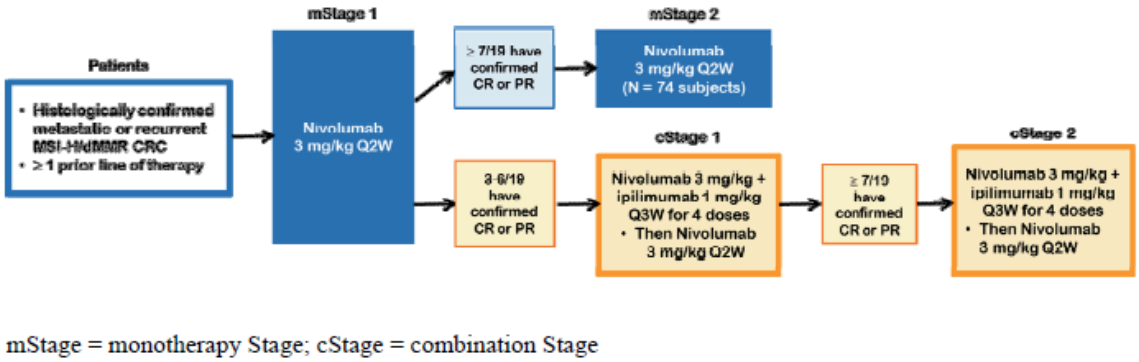
CA209142 is a Phase 2 open-label, multi-centre, 2-stage Simon design stage trial of nivolumab (BMS-936558) monotherapy (mStage) or in combination with ipilimumab (cStage) in adults (> 18 years) with recurrent or metastatic CRC.

This study consisted of 3 phases: screening, treatment and follow up. Tumour responses were assessed using RECIST v1.1 criteria beginning 6 weeks after first dose, and continuing every 6 weeks (+/- 1 week) for the first 24 weeks, then every 12 weeks (+/- 1 week) until disease progression. Subjects were treated until progression, unacceptable toxicity, or other protocol-defined reasons. Treatment beyond initial investigator-assessed progression was permitted if the subject had an investigator-assessed clinical benefit and was tolerating study drug. The investigator-assessed tumour response based on RECIST 1.1 criteria was used to guide the stage 1 decision and for the primary analysis of the ORR. In addition, an IRRC performed central review of the imaging per RECIST 1.1 criteria. Subjects were followed for OS every 3 months (for up to 3 years) until death, lost to follow-up, or withdrawal of study consent.

A total of 74 subjects were enrolled in the monotherapy treatment period, 53 of whom had received prior treatment with 5FU-Oxa-Iri. A total of 31 sites in 8 countries enrolled subjects. The last subject's first treatment occurred on 16-Mar-2016 and the LPLV was 10-Aug-2016, leading to a minimum follow-up of approximately 6 months (71 out of 74 subjects with at least 6 months follow-up and 3 subjects with 5 months follow-up) in this DBL (19-Sep-2016).

This interim CSR presents the results of the subjects with MSI-H/dMMR CRC in the monotherapy (mStage1 and mStage2) cohort (all nivolumab monotherapy treated) and a subset of subject those who

had received prior 5FU+ oxaliplatin + irinotecan (5FU-Oxa-Iri) (at any time during prior therapy) based on the 19-Sep-2016 clinical database lock (DBL).



mStage = monotherapy Stage; cStage = combination Stage

Figure 6 CA209142 Study Design Schema

Both Arms (nivolumab monotherapy) and (nivolumab + ipilimumab) followed a two-stage design to test whether nivolumab monotherapy or nivolumab combined with ipilimumab yields an ORR that is of clinical interest in MSI-H mCRC. On-treatment stages that meet an ORR threshold were to proceed from Stage 1 to Stage 2 (same for both m and cStage).

For mStage 1, if 7/19 or more subjects with MSI-H mCRC have a confirmed PR or CR, mStage 2 would open to enroll an additional 29 subjects. If there are more than 2 but less than 7 responses in the first 19 subjects, accrual to the mStage1 arm would be stopped, and the cStage1 arm would be opened for accrual. Additionally, if 2 or fewer of the first 19 subjects in mStage 1 have a confirmed CR or PR, the trial would close. CA209142 also contained a safety cohort of subjects with non-MSI-H mCRC to assess the safety and tolerability of nivolumab in combination with ipilimumab in subjects with non-MSI-H mCRC and to provide the starting dose for cStage 1. If 7/19 or more subjects in cStage 1 with MSI-H mCRC have a confirmed PR or CR, cStage 2 would open to enroll an additional 29 subjects. If 6 or fewer of the first 19 subjects with MSI-H mCRC have a confirmed PR or CR, cStage 1 would close and the trial would end. The determination of response rate was based on investigator-assessed tumour response per RECIST 1.1 criteria.

- **Study participants**

The study population included adults (≥ 18 years) with recurrent or metastatic MSI-H/dMMR CRC who had disease progression during, after, or had been intolerant to therapy with 5FU-based chemotherapy. Subjects were excluded with: active brain metastases or leptomeningeal metastases; active, known, or suspected autoimmune disease; or a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration.

Given the rarity of the MSI-H/dMMR population, subjects with different lines of prior therapy were allowed. For this target population, inclusion criteria included:

1) Histologically confirmed CRC,
2) metastatic or recurrent CRC,
3) Microsatellite instability expression or dMMR detected by an accredited laboratory per local regulations,
4) Prior treatment:

   a) For subjects with recurrent or metastatic MSI-H/dMMR CRC:

i) Progression during, after, or have been intolerant to ≥ 1 line treatment(s) for their metastatic disease, which must include at least

(1). A fluoropyrimidine, and

(2). oxaliplatin or irinotecan,

a. Subjects who received oxaliplatin in an adjuvant setting should have progressed during or within 6 months of completion of adjuvant therapy in order for oxaliplatin to count as a prior therapy needed for entry.

OR

ii) Subject actively refuses chemotherapy for the treatment of metastatic (Stage IV) or locally advanced disease considered as standard treatment for this disease stage, despite being informed by the investigator about the treatment options. The subject's refusal must be thoroughly documented. The investigator will discuss each individual subject refusing chemotherapy with the sponsor's medical monitor to confirm eligibility.

Additional inclusion and exclusion criteria are provided in the protocol.

Microsatellite instability

MSI expression detected by an accredited laboratory per local regulations and the procedure manual was the criteria used to enrol subjects. MSI-H in tumours refers to changes in 2 or more of the 5 National Cancer Institute-recommended panels of microsatellite markers in tumour tissue. The original (1997) Bethesda guidelines proposed a panel of 5 microsatellite markers for the uniform analysis of MSI in HNPCC. This panel, which is referred to as the Bethesda panel, included 2 mononucleotide (BAT-25 and BAT-26) and 3 dinucleotide (D5S346, D2S123, and D17S250) repeats. Individual testing sites may have utilized a slightly different panel of markers incorporating alternative mononucleotide or dinucleotide markers. Regardless of the panel of markers, samples with instability in 2 or more of these markers were defined as MSI-H, whereas those with one unstable marker were designated as MSI-Low (MSI-L). Samples with no detectable alterations are MSI-S (MSS).

For both the MSI-H and the non-MSI-H cohorts, a PCR test was utilized for central (repeat) testing. IHC was done locally per local standards. Additional tumour samples were requested to be sent to BMS for confirmatory testing.

- **Treatments**

Nivolumab 3 mg/kg was administered as a 60-minute intravenous (IV) infusion every 2 weeks (Q2W) until either RECIST 1.1 progression, unacceptable toxicity, or other protocol-defined reasons. Nivolumab was supplied as a solution for injection in 10-mL vials. Each vial contained a concentrated solution with the equivalent of 100 mg of nivolumab (10 mg/mL).

- **Objectives**

Primary objective:

To evaluate the investigator-assessed objective response rate (ORR) of nivolumab monotherapy in subjects with metastatic MSI-H CRC.

Secondary objective:

To evaluate the independent radiology review committee (IRRC)-assessed ORR of nivolumab monotherapy in subjects with metastatic MSI-H CRC.

Exploratory Objectives

- To determine the safety and tolerability (defined as toxicity rates [worst CTC grade per subject] of adverse events and specific laboratory tests) of nivolumab monotherapy (mStage 1 and 2) in subject with metastatic MSI-H CRC.
- To estimate PFS and OS for subjects with metastatic MSI-H CRC.
- To characterize the pharmacokinetics (PK) of nivolumab monotherapy, and to explore exposure-response relationships.
- To characterize the immunogenicity of nivolumab monotherapy.
- To evaluate the pharmacodynamic activity of nivolumab monotherapy in the peripheral blood and tumour tissue as measured by flow cytometry, immunohistochemistry, soluble factor analysis, and gene expression (microarray technology, quantitative RT-PCR).
- To investigate the association between biomarkers in the peripheral blood and tumour tissue, such as PD-L1 expression, with safety and efficacy for subjects with advanced or metastatic tumours treated with nivolumab monotherapy.
- To characterize the discordance rate between repeat MSI testing and prior MSI testing in subjects.
- To evaluate health related quality of life using a validated instrument in the European Organisation for Research and Treatment of Care General Cancer Module (QLQ-C30).
- To evaluate patient reported general health status as assessed by the 5 item EQ-5D.

- **Outcomes / endpoints**

Primary endpoint: The primary endpoint of this study is ORR which is based on tumour assessments at baseline and then at 6 weeks from first dose and which continue every 6 weeks for the first 24 weeks and every 12 weeks thereafter until disease progression (investigator-assessed RECIST 1.1-defined progression) or treatment discontinuation, whichever occurs later. ORR was further characterized by the duration of response (DOR) and rate of complete response (CR).

Secondary endpoints: independent central review committee (IRRC) assessed ORR, progression-free survival (PFS) based on investigator and IRRC assessments, and overall survival (OS) were examined as exploratory endpoints. Safety assessments were based on frequency of deaths, serious adverse events (SAEs), adverse events (AEs), leading to discontinuation or dose modification, overall AEs, clinical laboratory assessments (hematology, serum chemistry, liver, and thyroid function tests), and vital sign measurements. Immunogenicity was assessed by serum anti-drug antibody (ADA) and neutralizing ADA response to nivolumab. Patient-reported Outcomes: disease-specific and general health-related quality of life were assessed using valid and reliable patient-reported outcomes instruments, the European Organisation for Research and Treatment of Care General Cancer Module (EORTC QLQ-C30) and EuroQol EQ-5D, respectively.

- **Sample size**

This study consisted of 3 cohorts: non-MSI-H cohort, MSI-H cohort, and cohort C3 (MSI-H subjects who have not had prior therapy for their metastatic disease). It is expected to treat up to approximately 96 central-pathology-lab confirmed subjects (up to 29 non-MSI-H and up to 67 MSI H) for the initial non-MSI-H and MSI-H cohorts. It is expected to treat approximately 30 central-pathology-lab confirmed subjects in cohort C3.

The MSI-H cohort will include subjects who are defined as MSI-H based on standard diagnostic testing documented in the subject's medical history and prospectively confirmed in the current study by repeat testing using a polymerase chain reaction (PCR) test.

For the MSI-H cohort, a Simon optimal two-stage design will be used to test the null hypothesis that the true ORR is ≤30% (not considered clinically compelling) with either nivolumab monotherapy or the combination of nivolumab/ipilimumab. In the first stage (mStage 1), 19 subjects will be treated with nivolumab monotherapy. If there are 2 or fewer responses in these first 19 treated subjects, the protocol will be closed to further enrolment. If there are more than 2 but less than 7 responses in the first 19 treated subjects, accrual to the monotherapy arm will be stopped, and the combination arm will be opened for accrual. Otherwise, if there are 7 or more responses in the first 19 treated subjects, approximately 29 additional subjects will be accrued to the monotherapy arm (mStage 2) to target a total of 48 treated subjects.

If accrual to the combination arm is opened to the MSI-H cohort as specified above, stage I of the Simon two-stage design will be initiated in the combination arm with 19 treated subjects (cStage 1). If there are 6 or fewer responses in these first 19 treated subjects, accrual to the combination arm will be stopped. Otherwise, approximately 29 additional subjects will be accrued to the combination arm (cStage 2) to target a total of 48 subjects treated with combination therapy.

Subjects whose repeat testing does not confirm MSI-H status will be replaced in order to obtain the required number of subjects in each stage of the Simon design.

The null hypothesis will be rejected if 20 or more responses are observed in 48 treated subjects in the remaining open arm (nivolumab monotherapy or nivolumab/ipilimumab combination). Within a given treatment arm, this design yields a one-sided type I error rate of 5% and power of 90% when the true response rate is 52%

- **Randomisation**

NA

- **Blinding (masking)**

NA

- **Statistical methods**

CA209142 was originally designed using a Simon optimal two-stage design. For the monotherapy arm, under the null hypothesis that the true ORR is ≤ 30%, the first stage will treat19 subjects. If there are 7 or more responses in the first 19 treated subjects, approximately 29 additional subjects will be accrued to treat a target of 48 treated subjects. If 6 or less responses observed, the accrual to the monotherapy arm will be stopped and the stage 1 of the combination therapy will be opened for accrual.

The monotherapy arm of subjects had the first patient first treatment (FPFT) on 01-May-2014. The number of confirmed responses based on central confirmed MSI-H subjects was evaluated. Among the first 19 central confirmed MSI-H subjects, the number of confirmed responders was 4; 2 additional subjects developed best response of stable disease. Following this, it was evaluated that the maximum number of confirmed responders would not exceed 6among the first 19 central confirmed MSI-H subjects. Per study design, the combination arm was opened for enrolment to stage 1. Later evaluation revealed 7 confirmed responders in the monotherapy arm and therefore the original criteria for progressing to monotherapy stage 2 reached. As such, the monotherapy arm was resumed to accrual stage 2 subjects on 30-Oct-2015 when the enrolment to combination stage 1 was completed. During the stage 1review, approximately 34% of subjects who enrolled to monotherapy with MSI-H per local testing did not have confirmed central MSI H. Therefore, the stage 2 accrual for monotherapy enrolled additional subjects to ensure at least 48 centrally-confirmed MSI-H subjects. As such, the monotherapy actually enrolled and treated 74 subjects with local MSI-H.

Because of the divergence from the original primary analysis population of centrally confirmed MSI-H to the just per local MSI-H testing, a more conservative approach was used for the estimation of the 95% CI for the primary analysis on ORR. The Clopper-Pearson method was used, instead of the originally proposed Atkinson and Brown method. The investigator-assessed ORR was summarized for the monotherapy MSI-H cohort and a corresponding two-sided 95% exact CI was provided. ORR was further characterized by the DOR. DOR was summarized for MSI-H subjects who achieved confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with two-sided 95% CI (based on the log-log transformation), were also calculated. ORR based on IRRC assessment was summarized similarly and was characterized by DOR based on IRRC assessment similarly as above.

Safety was summarized for nivolumab monotherapy treated subjects with MSI-H-CRC. The safety profile was assessed through summaries of deaths, SAEs, AEs leading to discontinuation, AEs leading to dose delay of study therapy, overall AEs, select AEs, and laboratory abnormalities. In addition the percentage of subjects who received immune-modulating concomitant medications for management of AEs was reported. The total duration of all Immunomodulating medications (excluding overlaps) given for select AE management was reported.

PD-L1 expression was defined as the percent of tumour cells with membrane staining in a minimum of 100 evaluable tumour cells per Dako PD-L1 IHC assay. This is referred as quantifiable PD-L1 expression. Non-quantifiable PD-L1 expression could exist due to the biology of the tumour tissue sample, improper sample preparation or handling, or simply no sample. PD-L1 status is a dichotomized variable by 1% or 5% cut off for quantifiable PD-L1 expression. Values above or equal to the cut off were referred to as PD-L1 positive and negative respectively.

Patient-reported outcomes were analyzed for all nivolumab monotherapy treated subjects with a baseline assessment and at least 1 subsequent assessment. EORTC QLQ C-30 baseline and on-treatment measures as well as change from baseline were summarized using descriptive statistics. Completion rates were summarized for each assessment time point. Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point were summarized using descriptive statistics.

Immunogenicity analyses included all nivolumab-treated subjects with a baseline and at least 1 post-baseline assessment for ADA.

Results

Participant flow

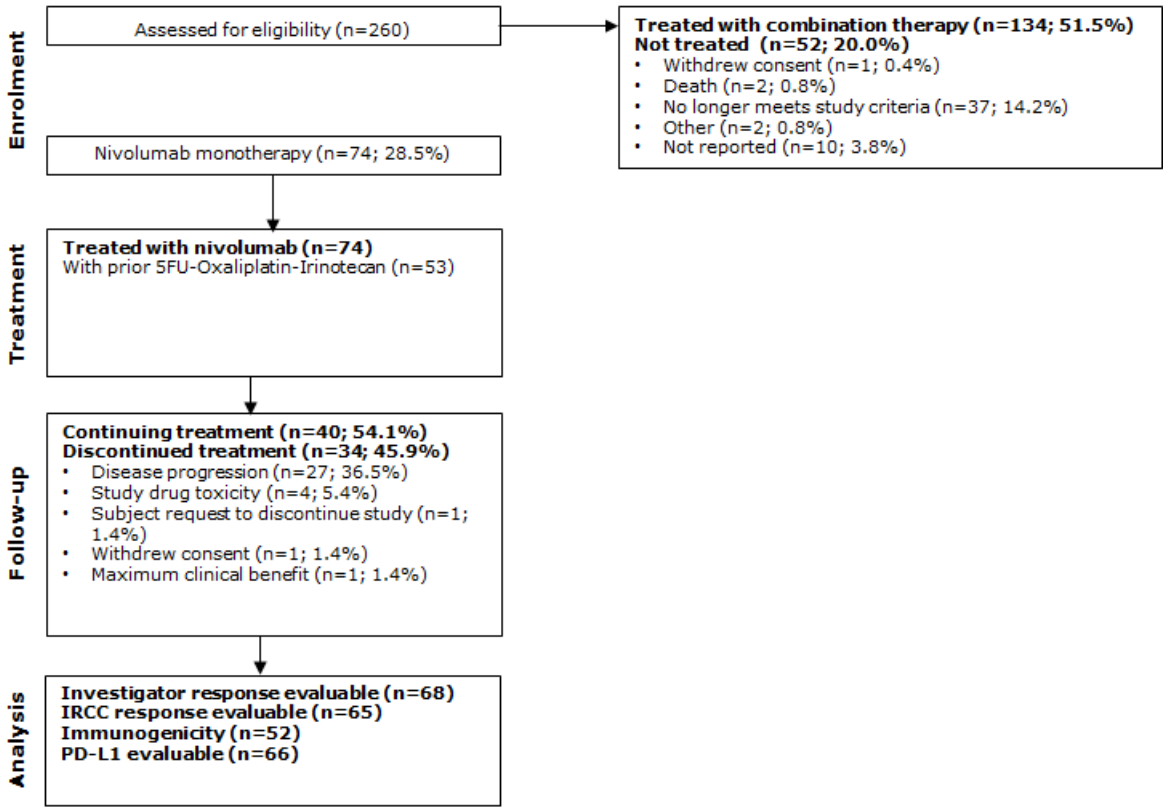


Figure 7 Participant flow

- **Recruitment**

The enrolment period into the monotherapy arm lasted approximately 2 years (Mar-2014 to Mar-2016). A total of 31 sites in 8 countries enrolled subjects (Australia 4 (5.4%), EU 39 (52.7%), USA 30 (40,5%), and Canada 1 (1.4%). The last subject's first treatment occurred on 16-Mar-2016 and the LPLV was 10-Aug-2016, leading to a minimum follow-up of approximately 6 months (71 out of 74 subjects with at least 6 months follow-up and 3 subjects with 5 months follow-up) in this DBL (19-Sep-2016).A total of 74 subjects were enrolled in the monotherapy treatment period, 53 of whom had received prior treatment with 5FU-Oxa-Iri.

- **Conduct of the study**

Relevant protocol deviations (significant protocol deviations that were programmable and could potentially affect the interpretability of study results) were reported in 4.1% of all subjects and 5.7% of subjects with prior 5FU-Oxa-Iri. Relevant protocol deviation at study entry included no measureable disease at baseline, and baseline ECOG > 1. The only relevant protocol deviation during the treatment period was prohibited anti-cancer therapy (Table 7). One subject received intraocular topical bevacizumab on 2 occasions to treat an eye condition (non-cancer indication)

Table 7: Relevant Protocol Deviations

	Number of Subjects (%)	
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
SUBJECTS WITH AT LEAST ONE DEVIATION	3 (4.1)	3 (5.7)
AT ENTRANCE		
WRONG CANCER DIAGNOSIS	0	0
NO MEASURABLE DISEASE AT BASELINE	1 (1.4)	1 (1.9)
BASELINE ECOG > 1	1 (1.4)	1 (1.9)
PROHIBITED PRIOR ANTI-CANCER THERAPY	0	0
ON-TREATMENT DEVIATIONS		
PROHIBITED ANTI-CANCER THERAPY	1 (1.4)	1 (1.9)

Changes in the Conduct of the Study

The original protocol for this study was dated 18-Nov-2013. Three global amendments and1 country-specific amendment was issued for this study. In addition 3 administrative letters were issued; errors on the title and document history pages were corrected, an exception regarding tumour tissue sample requirements was added (if a subject's tumour sample, after collection, was found tobe inadequate, the site may send in an archive sample that was obtained prior to the last systemic chemotherapy received), and a change in the Medical Monitor for the study was reported.

Table 8: Summary of Changes to Protocol CA209142

Document (Sites)	Date	Summary of Change
Amendment 01 (All)	06-Feb-2014	Based on a request from health authorities, subject eligibility criteria were revised to specify a washout period from prior therapy and which baseline toxicities from prior chemotherapy are allowed. Additional exclusion criteria were added to address this request. Other minor details were modified to increase comprehensibility.
Amendment 02 (FR)	01-Apr-2014	Based on a request from the French health authority, a urinalysis per local standard of care (including testing for proteinurea and evaluation of urine sediment by urine test strip) was added to the time and events schedule prior to first dose of study drug. In addition, Appendix 01 of the protocol was replaced with the most current version of Adverse Event Management Algorithms.
Amendment 03 (All)	23-Apr-2014	This global amendment was written primarily to be consistent with other protocols within the nivolumab program regarding Adverse Event Management Algorithms. Accordingly, the existing Appendix 01 of the protocol was replaced with the most up-to-date management algorithms. Other minor details were modified to increase comprehensibility.
Amendment 04 (All)	10-Jun-2015	A biomarker collection schedule that was aligned with the combination of nivolumab plus ipilimumab dosing for subjects dosed with the combination was added. An appendix regarding MSI testing panel descriptions (PCR and IHC), classification of MSI status, and sample prioritization was added. Other minor details were modified to increase comprehensibility.

Amendments are generally aimed to improve clarity and consistency in the conduct of the study.

- **Baseline data**

Baseline demographics, disease characteristics, tumour assessments, and prior cancer therapies were consistent with an expected population of metastatic CRC patients. Demographics and disease characteristics were generally similar between all nivolumab monotherapy treated subjects and subjects with prior 5FU-Oxa-Iri; which is not unexpected considering that this subgroup accounts for up to 72% of the total nivolumab monotherapy cohort.

Table 9: Baseline Demographic Characteristics – All Nivolumab Monotherapy Treated Subjects

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
AGE		
N	74	53
MEAN	52.3	52.3
MEDIAN	52.5	53.0
MIN , MAX	26 , 79	26 , 79
STANDARD DEVIATION	14.38	13.68
AGE CATEGORIZATION (%)		
< 65	57 (77.0)	42 (79.2)
>= 65 AND < 75	13 (17.6)	8 (15.1)
>= 75	4 (5.4)	3 (5.7)
>= 65	17 (23.0)	11 (20.8)
GENDER (%)		
MALE	44 (59.5)	30 (56.6)
FEMALE	30 (40.5)	23 (43.4)
RACE (%)		
WHITE	65 (87.8)	45 (84.9)
BLACK OR AFRICAN AMERICAN	7 (9.5)	6 (11.3)
ASIAN	1 (1.4)	1 (1.9)
AMERICAN INDIAN OR ALASKA NATIVE	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0
OTHER	1 (1.4)	1 (1.9)
ETHNICITY (%)		
HISPANIC OR LATINO	3 (4.1)	1 (1.9)
NOT HISPANIC OR LATINO	34 (45.9)	26 (49.1)
NOT REPORTED	37 (50.0)	26 (49.1)

Table 10: Baseline Disease Characteristics – All Nivolumab Monotherapy Treated Subjects

	Number of Subjects (%)	
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Ir N = 53
PERFORMANCE STATUS (ECOG) [%]		
0	32 (43.2)	21 (39.6)
1	41 (55.4)	31 (58.5)
3(A)	1 (1.4)	1 (1.9)
SMOKING STATUS		
CURRENT/FORMER	33 (44.6)	23 (43.4)
NEVER SMOKER	41 (55.4)	30 (56.6)
UNKNOWN	0	0
REGION		
US/CANADA	31 (41.9)	24 (45.3)
EUROPE	39 (52.7)	26 (49.1)
REST OF THE WORLD	4 (5.4)	3 (5.7)
DISEASE STAGE AT INITIAL DIAGNOSIS		
STAGE I	2 (2.7)	2 (3.8)
STAGE II	13 (17.6)	10 (18.9)
STAGE III	26 (35.1)	19 (35.8)
STAGE IV	33 (44.6)	22 (41.5)
BRAF/KRAS MUTATION STATUS		
KRAS/BRAF WILD-TYPE	28 (37.8)	19 (35.8)
BRAF MUTATION	12 (16.2)	6 (11.3)
KRAS MUTATION	26 (35.1)	22 (41.5)
UNKNOWN	8 (10.8)	6 (11.3)
LYNCH SYNDROME (B)		
YES	23 (31.1)	17 (32.1)
NO	26 (35.1)	14 (26.4)
UNKNOWN	25 (33.8)	22 (41.5)
LOCAL MICROSATELLITE INSTABILITY METHOD		
PCR	22 (29.7)	17 (32.1)
IHC	40 (54.1)	25 (47.2)
PCR/IHC	12 (16.2)	11 (20.8)
UNKNOWN	0	0

LOCAL MICROSATELLITE INSTABILITY RESULT		
MSI-H	73 (98.6)	52 (98.1)
MSI-H/MSI-S (C)	1 (1.4)	1 (1.9)
MSI-L	0	0
MSI-S	0	0
CENTRAL MICROSATELLITE INSTABILITY RESULT		
MSI-H	53 (71.6)	40 (75.5)
MSI-L	2 (2.7)	2 (3.8)
MSI-S	12 (16.2)	6 (11.3)
NOT REPORTED	7 (9.5)	5 (9.4)
TIME FROM INITIAL DIAGNOSIS TO FIRST DOSE		
N	74	53
MEDIAN (MIN - MAX)	1.89 (0.4 - 21.7)	2.02 (0.4 - 21.7)
< 1 YEAR	10 (13.5)	3 (5.7)
1- < 2 YEARS	29 (39.2)	23 (43.4)
2- < 3 YEARS	11 (14.9)	8 (15.1)
3- < 4 YEARS	11 (14.9)	8 (15.1)
4- < 5 YEARS	6 (8.1)	5 (9.4)
>= 5 YEARS	7 (9.5)	6 (11.3)

(A) One subject (CA209142-13-36) had an ECOG status of 3 on the day of the first dose of study drug. ECOG status at screening was
(B) History of Lynch syndrome testing and results obtained from Medical History, excluding Italy
(C) For analysis purpose, Subject in this category will be considered MSI-H per local laboratory.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; MSI-H = microsatellite instability - high; MSI-L = microsatellite instability - low; MSI-S = microsatellite stable (MSS); PCR = polymerase chain reaction

Table 11: Pre-Treatment Tumour Assessments - All Nivolumab Monotherapy Treated Subjects

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
PER INVESTIGATOR		
SUBJECTS WITH AT LEAST ONE LESION (%)	74 (100.0)	53 (100.0)
SITE OF LESION (A) (B) (%)		
ASCITES	2 (2.7)	1 (1.9)
BONE WITH SOFT TISSUE COMPONENT	1 (1.4)	1 (1.9)
CHEST WALL	3 (4.1)	3 (5.7)
EFFUSION	2 (2.7)	1 (1.9)
INTESTINE	7 (9.5)	4 (7.5)
KIDNEY	1 (1.4)	1 (1.9)
LIVER	40 (54.1)	29 (54.7)
LUNG	25 (33.8)	19 (35.8)
LYMPH NODE	35 (47.3)	27 (50.9)
MEDIASTINUM	2 (2.7)	1 (1.9)
OTHER	14 (18.9)	11 (20.8)
PANCREAS	3 (4.1)	1 (1.9)
PELVIS	9 (12.2)	7 (13.2)
PERITONEUM	19 (25.7)	12 (22.6)
PLEURA	2 (2.7)	2 (3.8)
SKIN/SOFT TISSUE	7 (9.5)	7 (13.2)
SPLEEN	6 (8.1)	5 (9.4)
VISCERAL, ADRENAL	2 (2.7)	2 (3.8)
VISCERAL, OTHER	5 (6.8)	3 (5.7)
NUMBER OF SITES WITH AT LEAST ONE LESION (B) (%)		
1	17 (23.0)	11 (20.8)
2	25 (33.8)	17 (32.1)
3	14 (18.9)	11 (20.8)
4	14 (18.9)	11 (20.8)
>=5	4 (5.4)	3 (5.7)
SUBJECTS WITH AT LEAST ONE TARGET LESION (%)	73 (98.6)	52 (98.1)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)		
N	73	52
MEDIAN (MIN - MAX)	100.0 (22 - 341)	111.5 (22 - 341)

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
PER IRRC		
SUBJECTS WITH AT LEAST ONE LESION (%)	73 (98.6)	52 (98.1)
SITE OF LESION (A) (B) (%)		
ABDOMINAL LYMPH NODE	13 (17.6)	10 (18.9)
ABDOMINAL WALL	10 (13.5)	10 (18.9)
ADRENAL GLAND	2 (2.7)	2 (3.8)
AXILLARY LYMPH NODE	2 (2.7)	2 (3.8)
BACK	1 (1.4)	1 (1.9)
BONE	4 (5.4)	3 (5.7)
COLON	2 (2.7)	1 (1.9)
COMMON ILIAC LYMPH NODE	6 (8.1)	5 (9.4)
DIAPHRAGM	1 (1.4)	0
EXTERNAL ILIAC LYMPH NODE	6 (8.1)	5 (9.4)
HILAR LYMPH NODE	4 (5.4)	3 (5.7)
INGUINAL LYMPH NODE	4 (5.4)	4 (7.5)
LIVER	39 (52.7)	26 (49.1)
LUNG	21 (28.4)	15 (28.3)
LYMPH NODE	3 (4.1)	3 (5.7)
MEDIASTINAL LYMPH NODE	8 (10.8)	7 (13.2)
MEDIASTINUM	1 (1.4)	0
MESENTERIC LYMPH NODE	12 (16.2)	7 (13.2)
MESENTERY	3 (4.1)	1 (1.9)
MUSCLE	1 (1.4)	1 (1.9)
OTHER	1 (1.4)	1 (1.9)
PARA-AORTIC LYMPH NODE	12 (16.2)	9 (17.0)
PELVIC LYMPH NODE	5 (6.8)	4 (7.5)
PELVIS	10 (13.5)	8 (15.1)
PERITONEUM	20 (27.0)	14 (26.4)
PLEURA	1 (1.4)	1 (1.9)
PUBIC BONE	1 (1.4)	0
RECTUM	1 (1.4)	1 (1.9)
RETROCRURAL LYMPH NODE	1 (1.4)	1 (1.9)
RETROPERITONEAL LYMPH NODE	15 (20.3)	9 (17.0)
RETROPERITONEUM	3 (4.1)	1 (1.9)
SOFT TISSUE	1 (1.4)	0
SPLEEN	4 (5.4)	3 (5.7)
SUBCUTIS	3 (4.1)	3 (5.7)
SUPRACLAVICULAR LYMPH NODE	1 (1.4)	1 (1.9)
THORACIC LYMPH NODE	2 (2.7)	2 (3.8)

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
NUMBER OF SITES WITH AT LEAST ONE LESION (B) (%)		
1	14 (18.9)	9 (17.0)
2	17 (23.0)	12 (22.6)
3	18 (24.3)	13 (24.5)
4	6 (8.1)	5 (9.4)
>=5	18 (24.3)	13 (24.5)
SUBJECTS WITH AT LEAST ONE TARGET LESION (%)	71 (95.9)	51 (96.2)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)		
N	71	51
MEDIAN (MIN - MAX)	85.0 (16 - 351)	102.0 (32 - 351)

(A) Subjects may have lesions at more than one site
(B) Includes both target and non-target lesions
Source: Table S.3.7A and Table S.3.7B

Mismatch Repair/Microsatellite Instability Testing:

Local laboratory methodology for defining MSI/dMMR predominantly used IHC (54.1% for IHC only and 16.2% were IHC/PCR). All subjects were evaluated as MSI-H by local laboratory methodology (1 subject was MSI-H/MSI-S).

Central testing was required for confirmation of MSI status. Central testing was not achieved in 7/74 subjects due to inadequate amount of tumour tissue and/or no viable tumour in the sample to be centrally tested. Concordance was noted in 79.1% (53/67) of the evaluated subjects.

MSI according to central laboratory (performed using PCR methodology) evaluated 53 (71.6%) of all nivolumab monotherapy treated subjects (40, 75.5% of subjects with prior 5FU-Oxa-Iri) as MSI-H. 16.2% and 2.7% were evaluated as microsatellite stable (MSS) or MSI-L (11.3% and 3.8% in the subjects with prior 5FU-Oxa-Iri) and 9.5% of the subjects had missing evaluation.

Among the subjects evaluated as MSI-H per local laboratory testing, Subject CA209142-3-54 initially presented with synchronous colon cancers (sigmoid and splenic flexure) at diagnosis.

The sigmoid tumour resection specimen was tested locally and was determined to be MSI-H/dMMR by IHC and PCR. These results were used to determine eligibility for protocol. Per protocol, tumour tissue was submitted for central testing. This tissue came from a metastatic site. Central testing by PCR demonstrated non-MSI-H. This subject initially had a confirmed PR to therapy, and then developed PD.

Baseline Tumour Burden/Characteristics:

Per investigator, all subjects had at least 1 lesion and the most common lesions involved the liver (54.1%), lymph node (47.3%), and lung (33.8%). 98.6% of subjects had at least one target lesion. The median sum of reference diameters of target lesions was 100.0 mm in allnivolumab monotherapy treated subjects and 111.5 mm in subjects with prior 5FU-Oxa-Iri.

Per IRRC, most subjects had at least one lesion (98.6%) and the most common lesionsinvolved the liver (52.7%), lung (28.4%), and peritoneum (27.0%). 95.9% of subjects had at least one target lesion. The median sum of reference diameters of target lesions was 85.0 mmin all nivolumab monotherapy treated subjects and 102.0 mm in subjects with prior5FU-Oxa-Iri.

Previous treatment

In order to be included in the MSI-H/dMMR CRC nivolumab monotherapy cohort, subjects were required to have progressed or have been intolerant to ≥ 1 line of treatment(s), including at least afluoropyrimidine and oxaliplatin or irinotecan, unless the subject actively refused chemotherapy.

The majority of subjects, among both all nivolumab monotherapy treated subjects (83.8%) as well as those subjects receiving prior 5FU-Oxa-Iri (98.1%), received 2 or more prior lines or regimens of systemic cancer therapy (Table 11Table 12). The most frequent prior systemic cancer therapies among all treated subjects were fluorouracil (98.6%), oxaliplatin (95.9%), bevacizumab or otherVEGF-inhibitors (77.0%), and irinotecan (74.3%). Over a third of subjects (36.5%)received prior radiation.

The time from completion of most recent prior therapy regimen to treatment was < 3months for48 (64.9%) and 37 (69.8%) nivolumab monotherapy treated subjects and subjects with prior5FU-Oxa-Iri, respectively (Table 12).

Table 12: Prior Cancer Therapy Summary - All Nivolumab Monotherapy Treated Subjects

	Number of Subjects (%)	
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
REGIMEN SETTING (A)		
ADJUVANT THERAPY	40 (54.1)	31 (58.5)
METASTATIC DISEASE	69 (93.2)	53 (100.0)
NEO-ADJUVANT THERAPY	5 (6.8)	5 (9.4)
NUMBER OF PRIOR REGIMEN RECEIVED		
0	1 (1.4) (B)	0
1	11 (14.9)	1 (1.9)
2	22 (29.7)	15 (28.3)
3	22 (29.7)	19 (35.8)
>=4	18 (24.3)	18 (34.0)
TYPE OF PRIOR THERAPY RECEIVED (A)		
OXALIPLATIN	71 (95.9)	53 (100.0)
IRINOTECAN	55 (74.3)	53 (100.0)
5FU (FLUOROURACIL, CAPECITABINE)	73 (98.6)	53 (100.0)
VEGF-INHIBITORS (BEVACIZUMAB, AFLIBERCEPT, RAMUCIRUMAB)	57 (77.0)	45 (84.9)
EGFR INHIBITORS (CETUXIMAB, PANITUMUMAB)	31 (41.9)	27 (50.9)
REGORAFENIB	12 (16.2)	12 (22.6)
TAS-102	0	0
IMMUNOTHERAPY	0	0
OTHER -EXPERIMENTAL DRUGS	6 (8.1)	5 (9.4)
OTHER -CHEMOTHERAPY	5 (6.8)	4 (7.5)
SUBJECT WITH PRIOR 5FU + OXALIPLATIN + IRINOTECAN	53 (71.6)	53 (100.0)
TIME FROM COMPLETION OF MOST RECENT PRIOR THERAPY REGIMEN TO TREATMENT		
< 3 MONTHS	48 (64.9)	37 (69.8)
3-6 MONTHS	8 (10.8)	5 (9.4)
> 6 MONTHS	17 (23.0)	11 (20.8)
NOT REPORTED	1 (1.4)	0
PRIOR SURGERY RELATED TO CANCER (C)		
YES	74 (100.0)	53 (100.0)
NO	0	0
PRIOR RADIOTHERAPY		
YES	27 (36.5)	23 (43.4)
NO	47 (63.5)	30 (56.6)

Among all subjects treated with nivolumab monotherapy:

-53 (71.6%) had received prior therapy with 5FU-Oxa-Iri. Regardless of the type of therapy received, 75.7% had progressed within 6 months of their most recent regimen, with 64.9%progressing within 3 months

-Of the 53 subjects with prior 5FU-Oxa-Iri, 79.2% had progressed within 6 months of their most recent regimen, with 69.8% progressing within 3 months

-The majority of subjects, among both all nivolumab monotherapy treated subjects (83.8%) as well as those subjects receiving prior 5FU-Oxa-Iri (98.1%), received 2 or more prior lines or regimens of systemic cancer therapy. 14.9%, 29.7%, 29.7%, and 24.3% of all nivolumab monotherapy treated subjects received 1, 2, 3, or > 4 prior lines of systemic cancer therapy.

-The most frequent prior systemic cancer therapies among all nivolumab monotherapy treated subjects were fluorouracil (98.6%), oxaliplatin (95.9%), bevacizumab or other VEGF inhibitors (77.0%), and irinotecan (74.3%). Over a third of subjects (36.5%) received prior radiation.

- **Numbers analysed**

Table 13 Analysis Populations

Population	Total N
All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.	260[a]
All Nivolumab Monotherapy Subjects, Including Treatment Failure (Not Treated) Subjects	126[b]
All Nivolumab Monotherapy Treated Subjects: All subjects who received at least one dose of study medication.	74
All Subjects with Prior 5FU-Oxaliplatin-Irinotecan: A subset population of All Nivolumab Monotherapy Treated Subjects who have received prior 5FU-Oxa-Iri	53
All IRRC Response Evaluable Subjects: All Nivolumab Monotherapy Treated Subjects who have baseline and at least one on-study evaluable tumor measurement per IRRC.	65
All Investigator Response Evaluable Subjects: All Nivolumab Monotherapy Treated Subjects who have baseline and at least one on-study evaluable tumor measurement per investigator.	68
All Immunogenicity Subjects: All Nivolumab Monotherapy Treated Subjects with baseline and at least one post-baseline assessment for ADA.	52
All PD-L1 Evaluable Subjects: All Nivolumab Monotherapy Treated Subjects with quantifiable baseline PD-L1 expression.	66

[a] Includes subjects enrolled in either nivolumab monotherapy (mStage) or nivolumab in combination with ipilimumab (cStage) cohorts. This CSR presents data from nivolumab monotherapy treated subjects only (including the subset of subjects with prior 5FU-Oxa-Iri).

[b] Includes 74 nivolumab monotherapy treated subjects and 52 treatment failure (not treated subjects).

A total of 86.5% of treated subjects received ≥ 90% of the planned dose intensity. The KM median duration of therapy for all nivolumab monotherapy treated subjects was 20.44 months (95% CI: 5.09, N.A.); this median was not reached for subjects with prior 5FU-Oxa-Iri.

- **Outcomes and estimation**

Primary endpoint- Investigator-assessed ORR

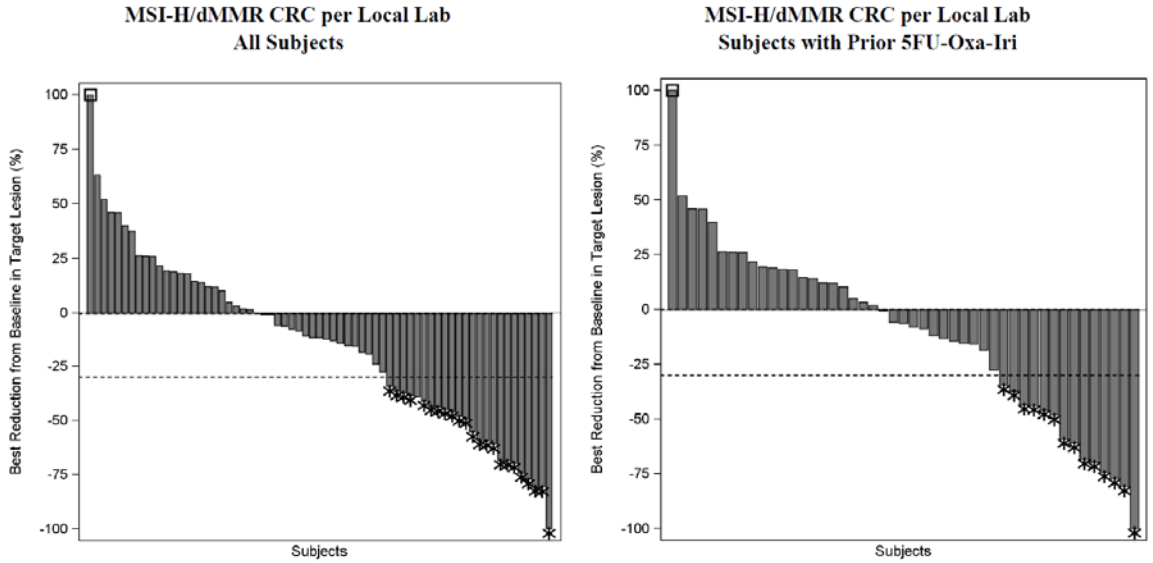
The primary endpoint of investigator-assessed ORR required confirmation of response at least 4 weeks after the first scan showing response in accordance with RECIST 1.1. The investigator-assessed ORR using RECIST 1.1 was 31.1% (23/74) in all nivolumab monotherapy treated subjects and 26.4% (14/53)

in subjects with prior 5FU-Oxa-Iri; with all responders achieving a PR (Table 14). The investigator-assessed disease control rate (DCR) was 68.9% in all nivolumab monotherapy treated subjects and 62.3% in subjects with prior 5FU-Oxa-Iri (Table 14). The waterfall plot of tumour response per investigator is depicted in Figure 8.

Table 14 Best overall response per investigator assessment

	Number of Subjects (%)	
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
BEST OVERALL RESPONSE (A):		
COMPLETE RESPONSE (CR) (95% CI)	0 (0.0, 4.9)	0 (0.0, 6.7)
PARTIAL RESPONSE (PR) (95% CI)	23 (31.1) (20.8, 42.9)	14 (26.4) (15.3, 40.3)
STABLE DISEASE (SD)	29 (39.2) (B)	20 (37.7) (B)
PROGRESSIVE DISEASE (PD)	18 (24.3)	15 (28.3)
UNABLE TO DETERMINE (UTD)	4 (5.4)	4 (7.5)
OBJECTIVE RESPONSE RATE (C) (95% CI)	23/74 (31.1%) (20.8, 42.9)	14/53 (26.4%) (15.3, 40.3)
DISEASE CONTROL RATE (D) (95% CI)	51/74 (68.9%) (57.1, 79.2)	33/53 (62.3%) (47.9, 75.2)

(A) Per RECIST 1.1 criteria
(B) Includes Subject GA209142-25-130 who had an investigator best response of SD when it should have been PD as he presented with a PD at S01. This subject was not counted in the number of subjects used to define Disease Control Rate as the SD was not for at least 12 weeks from study drug start date.
(C) CR+PR
(D) CR+PR+SD (for at least 12 weeks)
Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination



Subjects with target lesion at baseline and at least one on-treatment tumor assessment.
Negative/positive value means maximum tumor reduction /minimum tumor increase.
Best reduction is based on evaluable target lesion measurements up to progression or start of subsequent therapy.
Horizontal reference line indicates the 30% reduction consistent with a response per RECIST 1.1 criteria.
* indicates subject with confirmed PR or CR
Source: Figure S.5.1.3B

Figure 8: Waterfall plot of best reduction from baseline in sum of diameters of target lesions per investigator

Additional sensitivity analyses for all nivolumab monotherapy treated subjects were performed:

– Sensitivity analysis 1: Best overall unconfirmed response per investigator (up to start of subsequent therapy), shown in Table 15 and the results were in line with the primary analysis;

– Sensitivity analysis 2: Best overall response per investigator (response evaluable subjects), shown in Table 16 and the results were in line with the primary analysis.

Table 15 Best overall unconfirmed response per investigator

	Number of Subjects (%)	
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
BEST OVERALL RESPONSE (A):		
COMPLETE RESPONSE (CR) (95% CI)	0 (0.0, 4.9)	0 (0.0, 6.7)
PARTIAL RESPONSE (PR) (95% CI)	23 (31.1) (20.8, 42.9)	14 (26.4) (15.3, 40.3)
STABLE DISEASE (SD)	28 (37.8)	19 (35.8)
PROGRESSIVE DISEASE (PD)	17 (23.0)	15 (28.3)
UNABLE TO DETERMINE (UTD)	3 (4.1)	2 (3.8)
NOT REPORTED	3 (4.1)	3 (5.7)
OBJECTIVE RESPONSE RATE (B) (95% CI)	23/74 (31.1%) (20.8, 42.9)	14/53 (26.4%) (15.3, 40.3)
DISEASE CONTROL RATE (C) (95% CI)	51/74 (68.9%) (57.1, 79.2)	33/53 (62.3%) (47.9, 75.2)

(A) Per RECIST 1.1 criteria, confirmation of response not required
(B) CR+PR
(C) CR+PR+SD (for at least 12 weeks)
Unconfirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination
Program Source: /projects/bms218374/stats/csr/prog/tables/rt-ef-bor.sas 13OCT2016:10:35:25

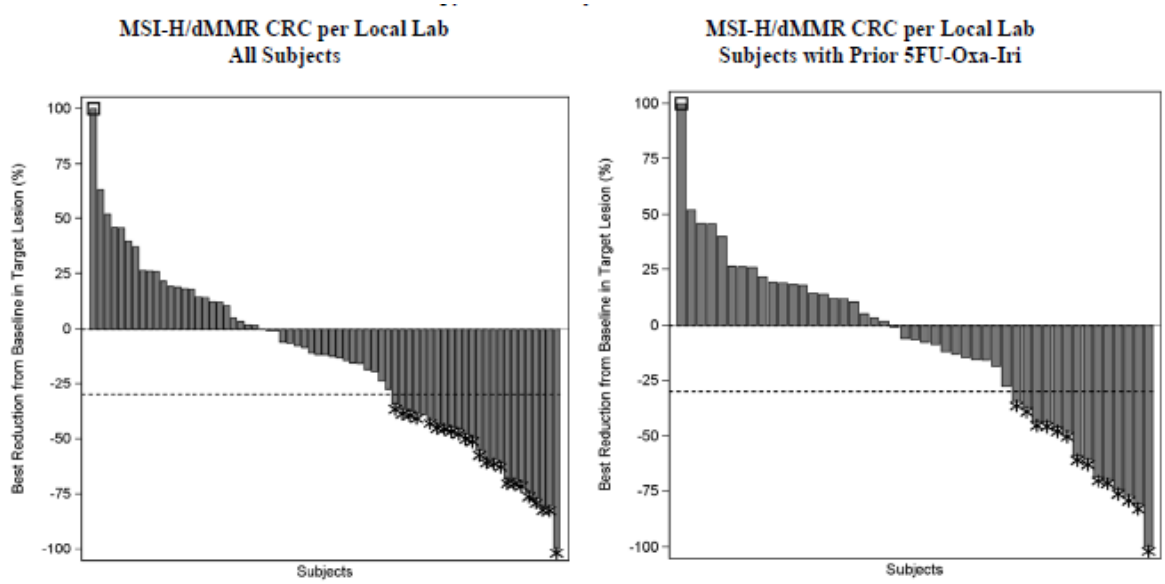
Table 16 Best overall response per investigator (response evaluable patients)

	Number of Subjects (%)	
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 68	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 47
BEST OVERALL RESPONSE (A):		
COMPLETE RESPONSE (CR) (95% CI)	0 (0.0, 5.3)	0 (0.0, 7.5)
PARTIAL RESPONSE (PR) (95% CI)	23 (33.8) (22.8, 46.3)	14 (29.8) (17.3, 44.9)
STABLE DISEASE (SD)	28 (41.2)	19 (40.4)
PROGRESSIVE DISEASE (PD)	17 (25.0)	14 (29.8)
UNABLE TO DETERMINE (UTD)	0	0
OBJECTIVE RESPONSE RATE (B) (95% CI)	23/68 (33.8%) (22.8, 46.3)	14/47 (29.8%) (17.3, 44.9)
DISEASE CONTROL RATE (C) (95% CI)	50/68 (73.5%) (61.4, 83.5)	32/47 (68.1%) (52.9, 80.9)

(A) Per RECIST 1.1 criteria, confirmation of response required
(B) CR+PR
(C) CR+PR+SD (for at least 12 weeks)
Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination
Program Source: /projects/bms218374/stats/csr/prog/tables/rt-ef-bor.sas 13OCT2016:10:35:28

The investigator-assessed ORR using RECIST 1.1 was comparable across baseline subgroups(age, region, gender, race, lynch syndrome, KRAS/BRAF mutation status, baseline ECOG performance status, time

from initial diagnosis to first dose, number of prior systemic regimens received, and time from completion of most recent prior therapy regimen to treatment) tumour



Subjects with target lesion at baseline and at least one on-treatment tumor assessment.
Negative/positive value means maximum tumor reduction /minimum tumor increase.
Best reduction is based on evaluable target lesion measurements up to progression or start of subsequent therapy.
Horizontal reference line indicates the 30% reduction consistent with a response per RECIST 1.1 criteria.
* indicates subject with confirmed PR or CR
Program Source: /projects/bms218374/stats/csr/prog/figures
Program Name: rg-ef-waterfall.sas 13OCT2016:10:31:55

Figure 9: Waterfall plot of best reduction from baseline in sum of diameters of target lesions per investigator - All Nivolumab Monotherapy Treated Subjects

The investigator-assessed ORR using RECIST 1.1 was comparable across baseline subgroups (age, region, gender, race, lynch syndrome, KRAS/BRAF mutation status, baseline ECOG performance status, time from initial diagnosis to first dose, number of prior systemic regimens received, and time from completion of most recent prior therapy regimen to treatment)

Table 17: ORR per Investigator by Subgroups - All Nivolumab Monotherapy Treated Subjects

	Objective Response Rate (%) (A) 95% CI	
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
AGE CATEGORISATION		
< 65 YEARS	19/57 (33.3%) (21.4, 47.1)	13/42 (31.0%) (17.6, 47.1)
>= 65 YEARS	4/17 (23.5%) (6.8, 49.9)	1/11 (9.1%) (0.2, 41.3)
>= 65 AND < 75 YEARS	2/13 (15.4%) (1.9, 45.4)	0/8 (0.0, 36.9)
REGION		
US/CANADA	11/31 (35.5%) (19.2, 54.6)	7/24 (29.2%) (12.6, 51.1)
EUROPE	12/39 (30.8%) (17.0, 47.6)	7/26 (26.9%) (11.6, 47.8)
GENDER		
MALE	16/44 (36.4%) (22.4, 52.2)	10/30 (33.3%) (17.3, 52.8)
FEMALE	7/30 (23.3%) (9.9, 42.3)	4/23 (17.4%) (5.0, 38.8)
RACE		
WHITE	19/65 (29.2%) (18.6, 41.8)	11/45 (24.4%) (12.9, 39.5)
BLACK OR AFRICAN AMERICAN	3/7 (42.9%) **(9.9, 81.6)**	2/6 (33.3%) **(4.3, 77.7)**
LYNCH SYNDROME		
YES	8/23 (34.8%) (16.4, 57.3)	6/17 (35.3%) (14.2, 61.7)
NO	8/26 (30.8%) (14.3, 51.8)	1/14 (7.1%) (0.2, 33.9)
UNKNOWN	7/25 (28.0%) (12.1, 49.4)	7/22 (31.8%) (13.9, 54.9)
KRAS/BRAF MUTATION STATUS		
KRAS/BRAF WILD-TYPE	12/28 (42.9%) (24.5, 62.8)	8/19 (42.1%) (20.3, 66.5)
BRAF MUTATION	3/12 (25.0%) (5.5, 57.2)	0/6 (0.0, 45.9)
KRAS MUTATION	7/26 (26.9%) (11.6, 47.8)	6/22 (27.3%) (10.7, 50.2)
UNKNOWN	1/8 (12.5%) (0.3, 52.7)	0/6 (0.0, 45.9)
BASELINE ECOG PERFORMANCE STATUS		
0	12/32 (37.5%) (21.1, 56.3)	5/21 (23.8%) (8.2, 47.2)
>= 1	11/42 (26.2%) (13.9, 42.0)	9/32 (28.1%) (13.7, 46.7)
NUMBER OF PRIOR SYSTEMIC REGIMEN RECEIVED (B)		
1	6/11 (54.5%) (23.4, 83.3)	0/1 (0.0, 97.5)
2	8/22 (36.4%) (17.2, 59.3)	7/15 (46.7%) (21.3, 73.4)
3	5/22 (22.7%) (7.8, 45.4)	4/19 (21.1%) (6.1, 45.6)
>= 4	3/18 (16.7%) (3.6, 41.4)	3/18 (16.7%) (3.6, 41.4)
TIME FROM COMPLETION OF MOST RECENT PRIOR THERAPY REGIMEN TO TREATMENT		
< 3 MONTHS	13/48 (27.1%) (15.3, 41.8)	10/37 (27.0%) (13.8, 44.1)
3 - 6 MONTHS	3/8 (37.5%) (8.5, 75.5)	0/5 (0.0, 52.2)
> 6 MONTHS	6/17 (35.3%) (14.2, 61.7)	4/11 (36.4%) (10.9, 69.2)

(A) Confidence interval based on the Clopper and Pearson method
(B) Does not include Subject CA209142-6-126 with no prior systemic regimen received and who achieved a partial response.
Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination
Source: Refer to Table 8.5.1.5B of the Interim CA209142 CSR

IRRC-assessed ORR - Secondary Endpoint

The secondary endpoint of IRRC-assessed ORR required confirmation of response at least 4 weeks after the first scan showing response in accordance with RECIST 1.1.The IRRC-assessed ORR using RECIST 1.1 was 27.0% (20/74) in all nivolumab monotherapy treated subjects and 22.6% (12/53) in subjects with prior 5FU-Oxa-Iri. 2 (2.7%) of the all nivolumab monotherapy treated subjects and 1 (1.9%) subject with prior 5FU-Oxa-Iri achieved CR, respectively. 18 (24.3%) of the all nivolumab monotherapy treated subjects and 11 (20.8%) of subjects with prior 5FU-Oxa-Iri achieved PR, respectively. The waterfall plot of tumour response per IRRC is depicted in Figure 10.The IRRC-assessed DCR was 62.2% in all nivolumab monotherapy treated subjects and 56.6% in subjects with prior 5FU-Oxa-Iri.

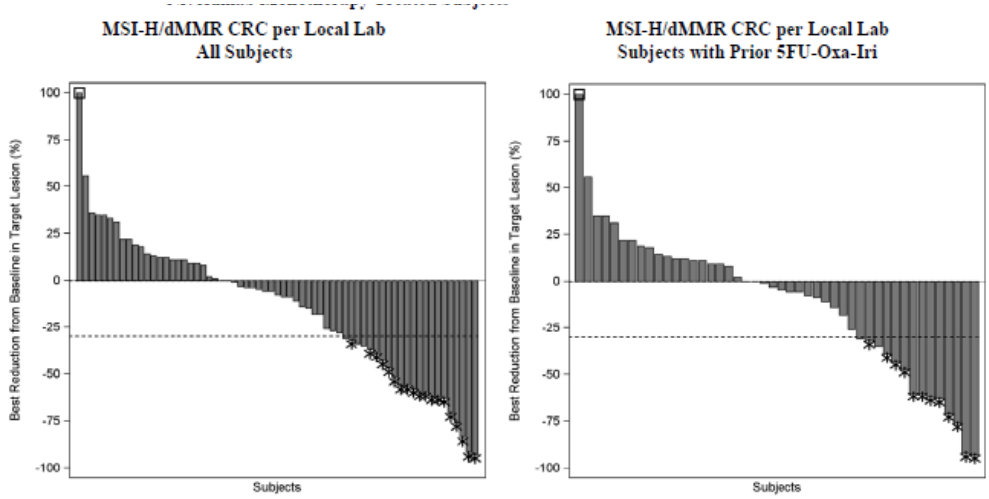


Figure 10: Waterfall plot of best reduction from baseline in sum of diameters of target lesions per IRRC - All Nivolumab Monotherapy Treated Subjects

The IRRC-assessed ORR using RECIST 1.1 was comparable across baseline subgroups (age, region, gender, race, lynch syndrome, KRAS/BRAF mutation status, baseline ECOG performance status, time from initial diagnosis to first dose, number of prior systemic regimens received, and time from completion of most recent prior therapy regimen to treatment).

Table 18: ORR per IRRC by Subgroups - All Nivolumab Monotherapy Treated Subjects

	Objective Response Rate (%) (A) 95% CI	
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
AGE CATEGORIZATION		
< 65 YEARS	16/57 (28.1%) (17.0, 41.5)	10/42 (23.8%) (12.1, 39.5)
>= 65 YEARS	4/17 (23.5%) (6.8, 49.9)	2/11 (18.2%) (2.3, 51.8)
>= 65 AND < 75 YEARS	2/13 (15.4%) (1.9, 45.4)	0/8 (0.0, 36.9)
REGION		
US/CANADA	11/31 (35.5%) (19.2, 54.6)	6/24 (25.0%) (9.8, 46.7)
EUROPE	9/39 (23.1%) (11.1, 39.3)	6/26 (23.1%) (9.0, 43.6)
GENDER		
MALE	12/44 (27.3%) (15.0, 42.8)	8/30 (26.7%) (12.3, 45.9)
FEMALE	8/30 (26.7%) (12.3, 45.9)	4/23 (17.4%) (5.0, 38.8)
RACE		
WHITE	17/65 (26.2%) (16.0, 38.5)	10/45 (22.2%) (11.2, 37.1)
BLACK OR AFRICAN AMERICAN	2/7 (28.6%) (3.7, 71.0)	1/6 (16.7%) (0.4, 64.1)
LYNCH SYNDROME		
YES	8/23 (34.8%) (16.4, 57.3)	5/17 (29.4%) (10.3, 56.0)
NO	6/26 (23.1%) (9.0, 43.6)	1/14 (7.1%) (0.2, 33.9)
UNKNOWN	6/25 (24.0%) (9.4, 45.1)	6/22 (27.3%) (10.7, 50.2)
KRAS/BRAF MUTATION STATUS		
KRAS/BRAF WILD-TYPE	9/28 (32.1%) (15.9, 52.4)	6/19 (31.6%) (12.6, 56.6)
BRAF MUTATION	2/12 (16.7%) (2.1, 48.4)	0/6 (0.0, 45.9)
KRAS MUTATION	6/26 (23.1%) (9.0, 43.6)	5/22 (22.7%) (7.8, 45.4)
UNKNOWN	3/8 (37.5%) (8.5, 75.5)	1/6 (16.7%) (0.4, 64.1)
BASELINE ECOG PERFORMANCE STATUS		
0	11/32 (34.4%) (18.6, 53.2)	4/21 (19.0%) (5.4, 41.9)
>= 1	9/42 (21.4%) (10.3, 36.8)	8/32 (25.0%) (11.5, 43.4)
NUMBER OF PRIOR SYSTEMIC REGIMEN RECEIVED (B)		
1	4/11 (36.4%) (10.9, 69.2)	0/1 (0.0, 97.5)
2	5/22 (22.7%) (7.8, 45.4)	4/15 (26.7%) (7.8, 55.1)
3	7/22 (31.8%) (13.9, 54.9)	5/19 (26.3%) (9.1, 51.2)
>= 4	3/18 (16.7%) (3.6, 41.4)	3/18 (16.7%) (3.6, 41.4)
TIME FROM COMPLETION OF MOST RECENT PRIOR THERAPY REGIMEN TO TREATMENT		
< 3 MONTHS	10/48 (20.8%) (10.5, 35.0)	7/37 (18.9%) (8.0, 35.2)
3 - 6 MONTHS	2/8 (25.0%) (3.2, 65.1)	0/5 (0.0, 52.2)
> 6 MONTHS	7/17 (41.2%) (18.4, 67.1)	5/11 (45.5%) (16.7, 76.6)

(A) Confidence interval based on the Clopper and Pearson method
(B) Does not include Subject CA209142-6-126 with no prior systemic regimen received and who achieved a partial response.
Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination
Source: Refer to Table 8.5.1.5A of the Interim CA209142 CSR

Concordance Between Investigator and IRRC Assessments

Investigator and IRRC assessments for responders, non-responders, and unable to determine were highly concordant; 90.4% in all nivolumab monotherapy treated subjects and 92.3% in subjects with prior 5FU-Oxa-Iri.

Time to and Duration of Response (TTR and DOR)

Investigator-assessed TTR and DOR

Median TTR per investigator was 2.76 months for all nivolumab monotherapy treated subjects and 2.81 months for subjects with prior 5FU-Oxa-Iri (Table 19). Median DOR per investigator was not reached in either subject population. The majority of responders had ongoing response at the clinical cut-off date.

Table 19: Time to Objective Response and Duration of Response per Investigator - All Nivolumab Monotherapy Treated Subjects

	MSI-H/dMMR CRC per Local Lab All Subjects N = 23	MSI-H/dMMR CRC per Local Lab Subjects with Prior 5FU-Oxa-Iri N = 14
TIME TO RESPONSE (MONTHS)		
NUMBER OF RESPONDERS	23	14
MEAN	3.54	4.35
MEDIAN	2.76	2.81
MIN, MAX	1.2, 16.1	1.2, 16.1
Q1, Q3	1.38, 3.15	1.48, 4.34
STANDARD DEVIATION	3.718	4.588
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.0+, 22.0+	1.0+, 17.9+
MEDIAN (95% CI) (B)	N.A. (6.83, N.A.)	N.A.
N EVENT/N RESP (%)	2/23 (8.7)	0/14
SUBJECTS WITH ONGOING RESPONSE (C)	19 (82.6)	13 (92.9)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)		
3 MONTHS	16 (69.6)	9 (64.3)
6 MONTHS	9 (39.1)	5 (35.7)
12 MONTHS	5 (21.7)	3 (21.4)

(A) Symbol + indicates a censored value
(B) Median computed using Kaplan-Meier method
(C) Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis and excludes responders censored prior to 8 weeks of the clinical data cutoff date if a patient is still in the first 24 weeks follow-up period, otherwise, the window is 14 weeks.
Source: Refer to Table 8.5.1.7B of the Interim CA209142 CSR

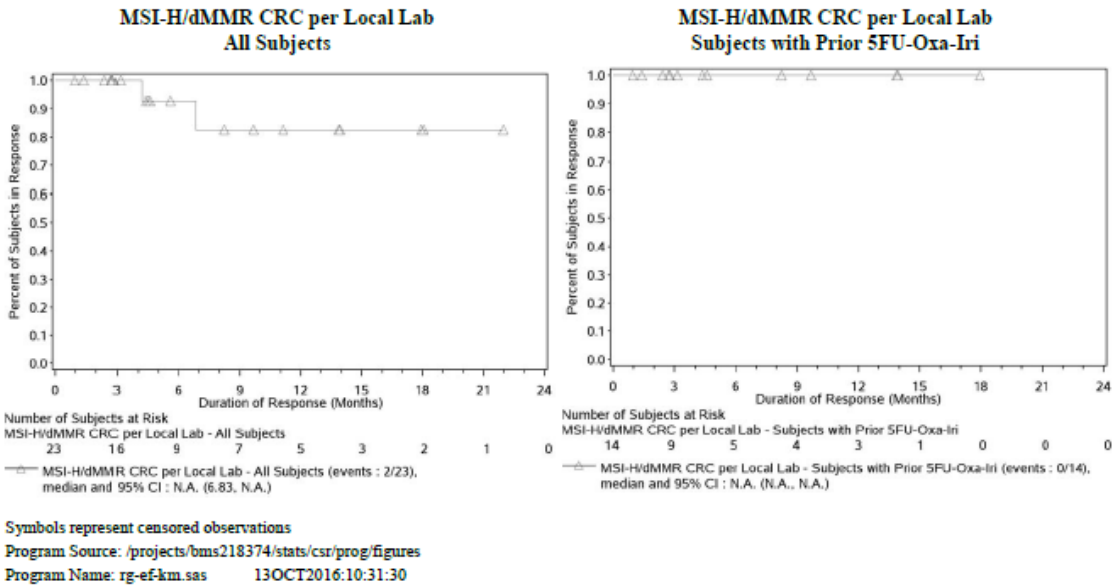


Figure 11 Kaplan-Meier Plot of Duration of Responses per investigator – All nivolumab monotheraphy treated subjects –MSI-H/dMMR CRC per LocalLab – All subjects

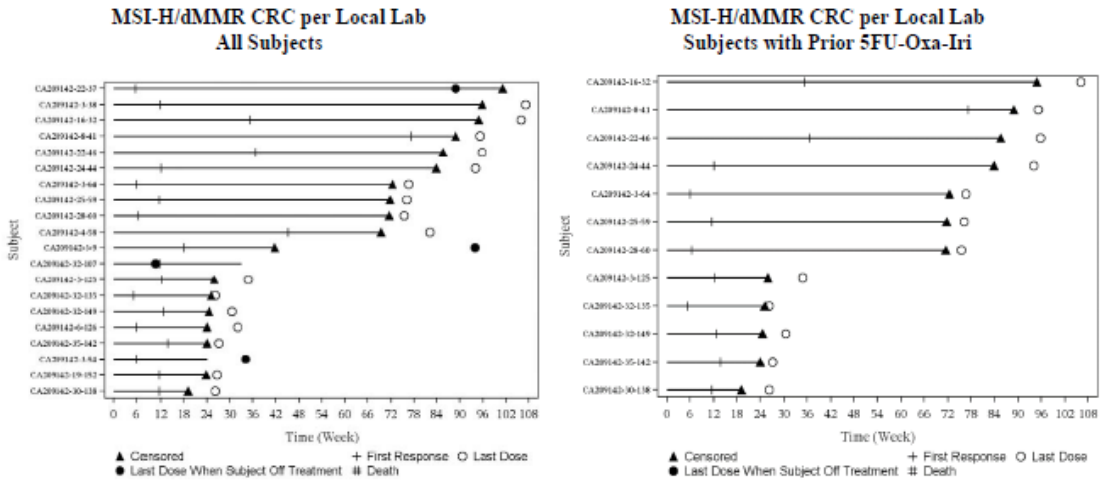
IRRC-assessed TTR and DOR

Median TTR per IRRC was 2.71 months for all nivolumab monotherapy treated subjects and 2.79 months for subjects with prior 5FU-Oxa-Iri (Table 20). Median DOR was not reached in either subject population. The majority of responders had ongoing response at the clinical cut-off date.

Table 20 Time to Objective Response Duration of Response per IRRC- All Nivolumab Monotherapy treated Subjects

	MSI-H/dMMR CRC per Local Lab All Subjects N = 20	MSI-H/dMMR CRC per Local Lab Subjects with Prior 5FU-Oxa-Iri N = 12
TIME TO RESPONSE (MONTHS)		
NUMBER OF RESPONDERS	20	12
MEAN	4.10	4.61
MEDIAN	2.71	2.79
MIN, MAX	1.2, 17.7	1.2, 17.7
Q1, Q3	1.43, 3.66	2.07, 5.63
STANDARD DEVIATION	4.114	4.772
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.8+, 22.0+	1.8+, 16.6+
MEDIAN (95% CI) (B)	N.A.	N.A.
N EVENT/N RESP (%)	2/20 (10.0)	0/12
SUBJECTS WITH ONGOING RESPONSE (C)	17 (85.0)	12 (100.0)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)		
3 MONTHS	15 (75.0)	8 (66.7)
6 MONTHS	8 (40.0)	6 (50.0)
12 MONTHS	7 (35.0)	5 (41.7)

(A) Symbol + indicates a censored value
(B) Median computed using Kaplan-Meier method
(C) Ongoing Response include responders who had neither progressed nor initiated subsequent therapy at the time of analysis and excludes responders censored prior to 8 weeks of the clinical data cutoff date if a patient is still in the first 24 weeks follow-up period, otherwise, the window is 14 weeks.
Source: Refer to Table 8.5.1.7A of the Interim CA209142 CSR



Bar indicates progression-free survival.
RECIST 1.1 Response Criteria. Horizontal axis origin corresponds to first dose date.

Figure 12: Event chart for tumour response and tumour progression per BIRC, duration of therapy and death, responders as assessed by BIRC – All nivolumab monotherapy treated subjects

Progression Free Survival (PFS) - Exploratory Endpoint

Investigator-assessed PFS

The median PFS per investigator was 9.6 months (95% CI: 4.3, NA) in all nivolumab monotherapy treated subjects and 8.6 months (95% CI: 1.5, NA) in subjects with prior 5FU-Oxa-Iri (Table 3.2-1 and Figure 3.2.5.1-1). For all nivolumab monotherapy treated subjects the 6-month and 12-month PFS rates per investigator were 58.5% and 48.4%, respectively. Similar rates were observed for subjects with prior 5FU-Oxa-Iri (54.8% and 46.1%, respectively). 41 (55.4 %) all nivolumab monotherapy treated subjects and 27 (50.9%) subjects with prior 5FU-Oxa-Iri were censored. 38 (51.4%) and 25 (47.2%) subjects had their PFS time censored on the date of last on-study tumour assessment, respectively. The most common reason for censoring among these subjects was 'still on treatment'.

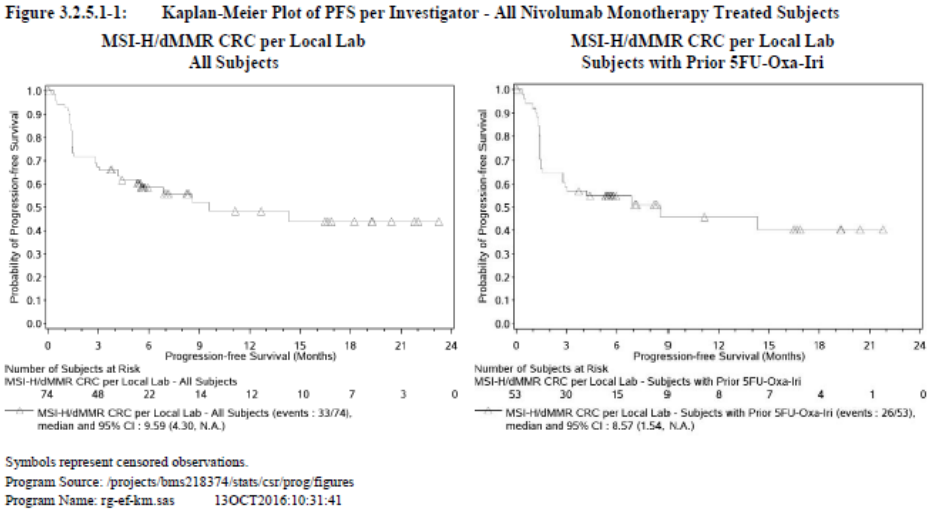


Figure 13

IRRC-assessed PFS

The median PFS per investigator was 7.6 months (95% CI: 3.0, NA) in all nivolumab monotherapy treated subjects and 4.9 months (95% CI: 1.5, NA) in subjects with prior 5FU-Oxa-Iri. For all nivolumab monotherapy treated subjects the 6-month and 12-month PFS rates per IRRC were 51.5% and 45.6%, respectively. Similar rates were observed for subjects with prior 5FU-Oxa-Iri (47.5% and 43.2%, respectively). 39 (52.7 %) nivolumab monotherapy treated subjects and 26 (49.1%) subjects with prior 5FU-Oxa-Iri were censored. 35 (47.3%) and 23 (43.4%) subjects had their PFS time censored on the date of last on-study tumour assessment, respectively. The most common reason for censoring among these subjects was 'still on treatment'.

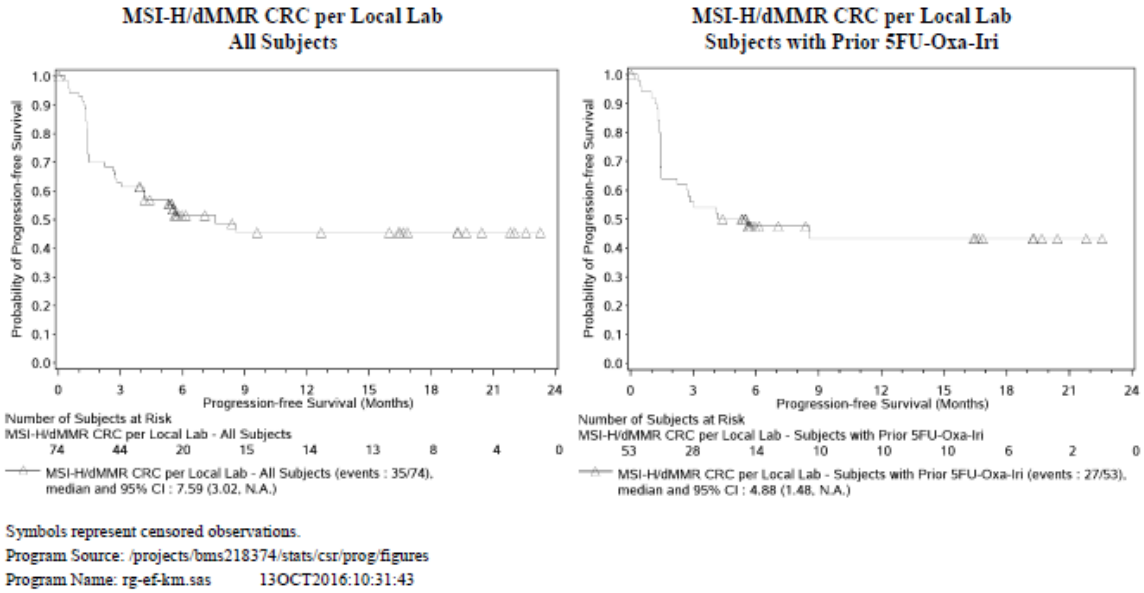


Figure 14: Kaplan-Meier plot of PFS per BIRC - All nivolumab monotherapy treated subjects

Overall Survival - Exploratory Endpoint

Median OS for all nivolumab monotherapy treated subjects or subjects with prior 5FU-Oxa-Irihas not yet been reached; 19 of 74 (25.7%) events have occurred (95% CI for median, 17.12, N.A) and 15 of 53 (28.3%) events occurred (95% CI for median, 16.33, N.A), respectively. At the time of the DBL, among all nivolumab monotherapy treated subjects, 55 (74.3 %) were censored. Among those censored, 40

(54.1%) subjects were still on treatment (35 [47.3%] subjects had not progressed), 12 [16.2%] subjects were in follow up, and 3 [4.1%] subjects were off study. In subjects with prior 5FUOxa-Iri, 38 (71.7%) subjects were censored. Among those censored, 30 (56.6%) were still on treatment (25 [47.2%] subjects had not progressed), 5 [9.4%] subjects were in follow-up, and 3 [5.7%] subjects were off-study.

Follow-up for OS

Median follow-up for OS (time between first dose date and last known date alive or death) was 7.41 months (range: 0.3 to 25.3 months) among all nivolumab monotherapy treated subjects and 7.23 months (range: 0.3 to 24.8 months) in subjects with prior 5FU-Oxa-Iri.Follow-up for OS was current for the majority of subjects; 57 (77.0%) all nivolumab monotherapy treated subjects and 41 (77.4%) subjects with prior 5FU-Oxa-Iri either died or had a last known alive date on or after the last patient last visit date.

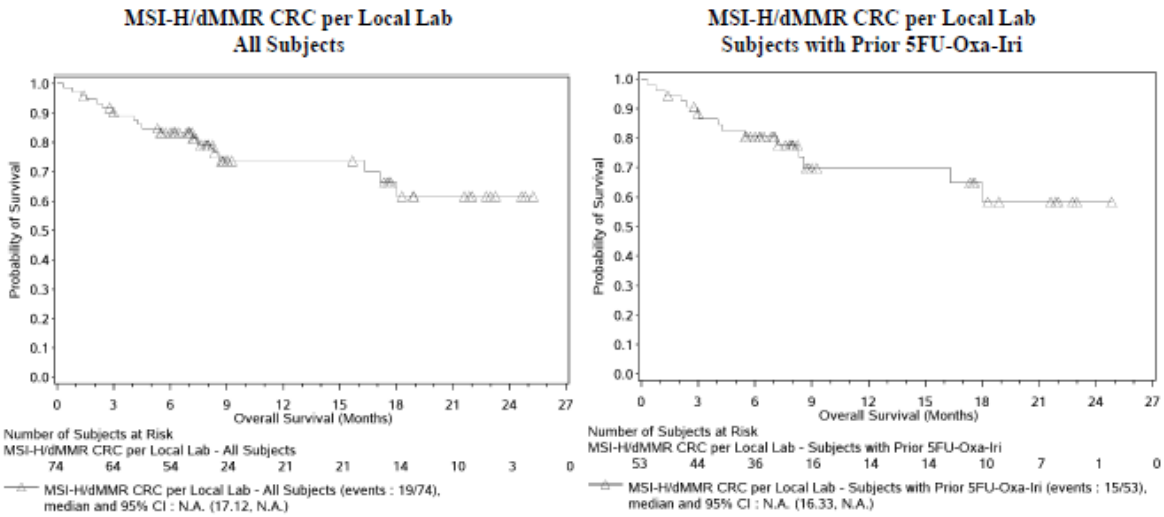


Figure 15: Kaplan-Meier plot of overall survival - All nivolumab monotherapy treated subjects

Table 21: Overall survival rates - All nivolumab monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
# EVENTS / # SUBJECTS (%)	19/74 (25.7)	15/53 (28.3)
MEDIAN OS (MONTHS) (95% CI)	N.A. (17.1, N.A.)	N.A. (16.3, N.A.)
3 MONTHS		
N AT RISK	64	44
OS RATE (95% CI)	90.4 (81.0, 95.3)	88.5 (76.2, 94.7)
6 MONTHS		
N AT RISK	54	36
OS RATE (95% CI)	83.4 (72.5, 90.2)	80.5 (66.7, 89.0)
9 MONTHS		
N AT RISK	24	16
OS RATE (95% CI)	73.8 (59.8, 83.5)	69.8 (52.4, 81.9)
12 MONTHS		
N AT RISK	21	14
OS RATE (95% CI)	73.8 (59.8, 83.5)	69.8 (52.4, 81.9)
18 MONTHS		
N AT RISK	14	10
OS RATE (95% CI)	66.4 (49.9, 78.5)	64.9 (45.7, 78.7)
24 MONTHS		
N AT RISK	3	1
OS RATE (95% CI)	61.6 (43.7, 75.4)	58.4 (37.1, 74.7)

Median computed using Kaplan-Meier method
N.A.: Not Available
Source: Refer to Table 8.5.3.1 of the Interim CA209142 CSR

Efficacy Update

Responses to questions in this RSI are referencing updated efficacy data with a clinical cut-off of 02-Jan-2017 (database lock [DBL] 06-Feb-2017). In this updated analysis, all 74 patients were analysed for efficacy as well as the 53 patients who received prior 5-FU-Oxa-Iri. This update provides an additional 5 months of follow-up (minimum follow-up of 11 months) since the time of the DBL used to support the filing. Since the initial analysis, 4 additional responders were reported. Responses continue to be observed across all subgroups of patients, including BRAF MT, Lynch, and non-Lynch patients. The added follow-up allows for better characterization of longer term OS (Table 22).

Table 22 Summary of Efficacy results (CA209142)

	Nivolumab (n=74) BICR	Nivolumab (n=74) Investigator
Confirmed objective response, n	24 (32.4)	23 (31.1)
(95% CI)	(22.0, 44.3)	(20.8, 42.9)
Complete response (CR), n (%)	2 (2.7)	0
Partial response (PR), n (%)	22 (29.7)	23 (31.1)
Stable disease (SD), n (%)	25 (33.8)	28 (37.8)
Median duration of response		
Months (range)[a, b]	Not reached (1.4+, 26.5+)	Not reached (3.9+, 26.5+)
Median time to response		
Months (range)	2.79 (1.2, 22.6)	2.76 (1.2, 16.1)
Disease control rate[a,] n (%)	47 (63.5)	51 (68.9%)
(95% CI)	(51.5, 74.4)	(57.1, 79.2)
Progression-free survival		
Events	39	36
Median (months) (95% CI)	8.3 (3.0, N.A.)	14.3 (4.3, NE)
Overall survival		
Events		23
Median (months) (95% CI)		N.A. (18.0, N.A.)
6-month rate (%) (95% CI)		83.4 (72.6, 90.2)
12-month rate (%) (95% CI)		73.4 (61.5, 82.1)

[a] Symbol + indicates a censored value

[b] Median computed using Kaplan-Meier method.

Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination.

Abbreviation: N.A.= not available

Source: Table S.5.1.1A (BOR per IRRC), Table S.5.1.1B (BOR per inv), Table S.5.1.7A (time to OR and DOR per IRRC), Table S.5.1.7B (time to OR and DOR per inv), Table S.5.2.1A (PFS per IRRC), Table S.5.2.1B (PFS per inv), Table S.5.3.1 (OS) of Appendix 1

- **Ancillary analyses**

Baseline PD-L1 Expression and Efficacy - Exploratory Endpoint

- Tumour Tissue Disposition Frequency of PD-L1 Expression

Subjects were enrolled regardless of tumour PD-L1 expression status; however, pre-study (baseline) tumour tissue specimens were systematically collected in order to conduct pre-planned analyses of efficacy and safety according to tumour PD-L1 expression status. Subjects were required to submit an archived tumour sample or, if not available, a pre-treatment fresh biopsy sample. Tumour tissue must have been obtained from an unresectable site of disease or from a site of metastatic disease.

The presence of a biopsy specimen was an inclusion criterion and hence a prerequisite for full eligibility of a subject. Tumour tissue samples were tested for tumour PD-L1 expression using the Dako PD-L1 IHC 28-8 pharmDxtest.PD-L1 was not used as stratification factor in Study CA209142.

- PD-L1 Expression and Efficacy

ORR

Objective responses were observed in all nivolumab monotherapy treated subjects regardless of tumour PD-L1 expression. ORR results in subjects with 5% cut-off baseline PD-L1 expression were similar to those with either ≥ 1% or < 1% baseline PD-L1 expression.

--ORR per investigator:

-In subjects with ≥1% baseline PD-L1 expression (n = 21), the ORR was 28.6% (95% CI: 11.3, 52.2); 6 (28.6%) had a PR.

-In subjects with < 1% baseline PD-L1 expression (n = 45), the ORR was 28.9% (95% CI:16.4, 44.3); 13 (28.9%) had a PR.

--ORR per IRRC:

-In subjects with ≥ 1% baseline PD-L1 expression (n = 21), 7 (33.3%) had a PR and the ORR was 33.3% (95% CI: 14.6, 57.0).

-In subjects with < 1% baseline PD-L1 expression (n = 45), 11 (24.4%) had a PR and the ORR was 24.4% (95% CI: 12.9, 39.5).

PFS

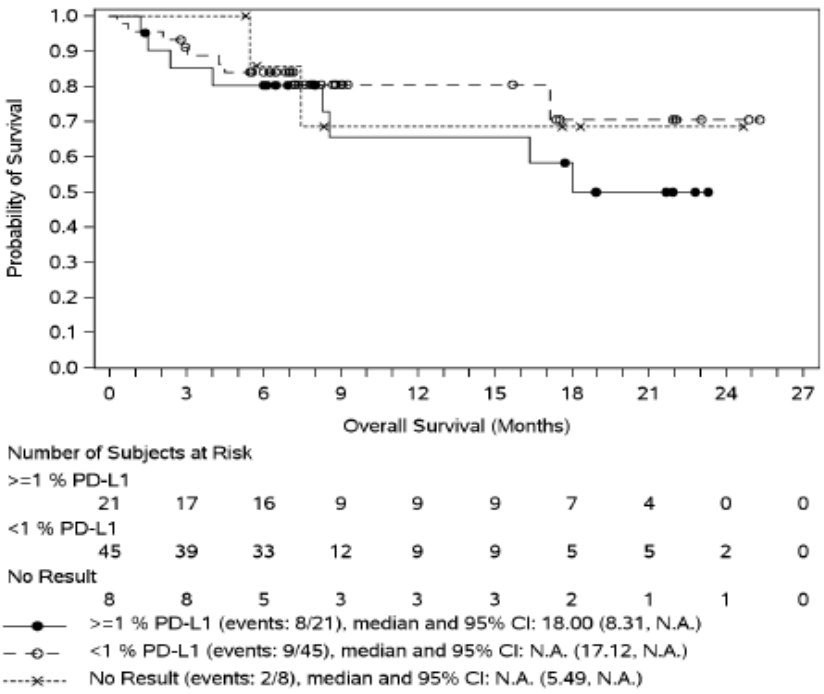
--Median PFS per investigator was 2.79 months (95% CI: 1.38, NA) in subjects with ≥ 1% baseline PD-L1 expression (n = 21) and 9.59 months (95% CI: 4.30, NA) in subjects with < 1% baseline PD-L1 expression (n = 45).

--Median PFS per IRRC was 4.17 months (95% CI: 1.38, NA) in subjects with ≥1% baseline PD-L1 expression (n = 21) and 7.59 months (95% CI: 2.76, NA) in subjects with < 1% baseline PD-L1 expression (n = 45).

PFS results in subjects with 5% cut-off baseline PD-L1 expression were similar to those with either ≥1% or < 1% baseline PD-L1 expression.

OS

Median OS was 18.00 months (95% CI: 8.31, NA) in the PD-L1 ≥ 1% cohort and not reached (95%CI: 17.12, NA) in the PD-L1 < 1% cohort (Figure 3.2.7.2-1). Median OS results in subjects with 5% cut off baseline PD-L1 expression were similar to those with either ≥ 1% or < 1% baseline PD-L1 expression.



Symbols represent censored observations
Program Source: /projects/bms218374/stats/csr/prog/figures
Program Name: rg-bm-km-pdl1.sas 13OCT2016:10:30:17

Figure 16: Kaplan-Meier plot of OS by baseline PD-L1 expression (1% expression level) – All nivolumab monotherapy treated subjects

- Concordance Between Local MSI Testing and Central MSI Testing

A summary of the concordance between local and central testing outcomes of the 74 nivolumab monotherapy treated subjects included in the current analysis population for Study CA209142 is provided below. All 74 subjects had a local laboratory result confirming that a tumour sample was MSI-H or dMMR. Out of the 74 subjects, 53 had confirmed MSI-H by a central test. An additional 7 subjects had missing central testing data due to inadequate amount of tumour tissue and/or no viable tumour in the sample to be centrally tested. The remaining 14 subjects had central test results that did not match the local testing.

Table 23 Concordance Between Local MSI Testing and Central MSI Testing – All nivolumab Monotherapy treated subjects

	Number of Subjects (%)		
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74		
	CENTRAL MSI ASESSMENT		
	MSI-H	NON MSI-H	NOT REPORTED
LOCAL MSI ASSESSMENT			
MSI-H	53 (71.6)	14 (18.9)	7 (9.5)
NON MSI-H	0	0	0
CONCORDANCE RATE OF RESPONDERS (A):		79.1 %	
REASON FOR MISSING CENTRAL MSI EVALUATION			
H&E PROCESSING			
NO TUMOR IDENTIFIED		1 (1.4)	
NO VIABLE TUMOR IDENTIFIED		1 (1.4)	
PCR PROCESSING			
TUMOR & NORMAL CONTROL DNA LOW/NO PCR AMPLIFICATION		3 (4.1)	
TUMOR DNA LOW/NO PCR AMPLIFICATION		2 (2.7)	
NUMBER OF CONCORDANT SUBJECTS		53 (71.6)	
LOCAL MSI METHOD FOR CONCORDANT SUBJECTS (B)			
IHC ONLY		27 (50.9)	
PCR ONLY		17 (32.1)	
IHC AND PCR		9 (17.0)	
NUMBER OF DISCORDANT SUBJECTS		14 (18.9)	
LOCAL MSI METHOD FOR DISCORDANT SUBJECTS (C)			
IHC ONLY		10 (71.4)	
PCR ONLY		2 (14.3)	
IHC AND PCR		2 (14.3)	

(A) Quantifies the frequency agreed on classification of a subject as MSI-H as a proportion of the total number of subjects assessed by both Local and Central Laboratory
(B) Percentages based on concordant subjects
(C) Percentages based on discordant subjects
Source: Refer to Table 8.3.4 of the Interim CA209142 CSR

There have been several studies carried out to assess the correlation between IHC and MSI testing, and the overall results seem to suggest that firstly neither test is 100% accurate in the detection of MSI-H tumours and secondly, there is actually a high level of concordance between both technologies. The largest study to date was performed by Cicek et al in 2011, when almost 6,000 tumours from patients in the Colorectal Cancer Family Registry were analyzed. The group showed a 90%-95% concordance between those cases identified as dMMR by MSI and those detected by IHC.

The discordance between local and central MSI testing observed in Study CA209142 in 14 subjects out of 74 (discounting the 7 subjects with missing central tests) was approximately 19%. Given the small sample size this discordance rate is comparable to the 5%-10% discordance identified by Cicek et al. The discordant cases were not limited to patients whose tumours were tested by IHC locally, and were also observed in tumours that were evaluated by PCR locally. In Study CA209142, 6 subjects that had MSI-H positive tumours by local testing but non-MSI-H by central testing, responded to nivolumab monotherapy. 2 subjects had a PR and 4 subjects had SD. Of note, one of these subjects had been identified as Lynch; and the others were not Lynch or Unknown.

Overall, based on evaluations of MSI-H/dMMR status by way of local testing, nivolumab demonstrated an overall benefit in the 74 subjects evaluated (investigator-assessed ORR of 31.1% and IRRC-assessed ORR of 27.0%). Of the subjects with MSI-H status confirmed by central testing, ORRs of the same magnitude in the population based on local testing were also observed: 35.8% for investigator-assessed ORR and 32.1% for IRR-assessed ORR.

- **Exploratory analyses**

Health-related Quality of Life - Exploratory Endpoint

--EORTC General Cancer Module (QLQ-C30)

The EORTC QLQ-C3014 is the most commonly used quality-of-life instrument in oncology trials. The instrument's 30 items are divided among 5 functional scales (physical, role, cognitive, emotional, and social), 9 scales measuring symptoms or concerns common to cancer patients (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health/quality-of-life scale. With the exception of 2 items included in the global health/quality-of-life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher values indicate better functioning or quality of life or a higher level of symptoms. A clinically meaningful change in score may be regarded as 10 points for each of the questionnaire's scales.

The EORTC QLQ-C30 questionnaire completion rate was 94.6% (70/74) among nivolumab monotherapy-treated subjects at baseline. Calculated as a percentage of subjects on study, completion rates remained at or above 70% through Week 79 after which fewer than 10 subjects were eligible for on-treatment patient-reported outcomes assessment. Accordingly, descriptive interpretations of EORTC QLQ-C30 findings are limited to the first 79 weeks of on-treatment follow-up.

As early as 13 weeks after initiating treatment, subjects exhibited meaningful improvements (ie, mean change $\geq$ 10 points) in emotional, role, and social functioning, with improvements remaining fairly consistent over time. Meaningful improvements in symptoms of fatigue, pain, insomnia, appetite loss, constipation, and diarrhea, as well as financial difficulties, were also observed. Moreover, a clinically relevant improvement in overall health status was observed by Week 13 and, with the exception of one time point, was maintained through Week 37. However, no meaningful improvements in physical functioning, nausea/vomiting, or dyspnea were observed, and clinically relevant worsening in cognitive functioning was observed at a single time point. The majority of subjects ($\geq$ 50%) did not experience any meaningful deterioration in functioning, symptoms, or overall health status during follow-up.

-Patient-reported General Health Status (EQ-5D) - Exploratory Endpoint

The EQ-5D-3L16 is a generic multi-attribute health-state classification system by which health is described in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is evaluated using 3 levels: no problems, some problems, and severe problems. Responses to these 5 dimensions are converted into 1 of 243 unique EQ-5D health state descriptions, which range between no problems on all 5 dimensions (11111) to severe/extreme problems on all 5 dimensions (33333). Using country-specific value weighting algorithms, a respondent's self-described health state can be converted into a utility representing the societal desirability of his/her own health. In addition, the EQ-5D includes a visual analogue scale (VAS) allowing a respondent to rate his/her health on a scale ranging from 0–100 with 0 being the worst health state imaginable and 100 being the best health state imaginable.

Questionnaire completion rates were not calculated for the EQ-5D-3L. However, the baseline completion rate for the EQ-5D VAS was 87.8%, and baseline completion rates for the components of the EQ-5D descriptive system ranged from 87.8% (mobility) to 89.2% (all other dimensions). Given patterns of item response during follow-up were similar to those observed for the EORTC QLQ-C30, descriptive interpretations of EQ-5D findings were limited to the first 79 weeks of on-treatment follow-up. At baseline, the percentage of subjects reporting health problems, as measured by the EQ-5D, ranged from 13.6% (self-care) to 68.2% (pain). As early as 13 weeks after treatment initiation, notable (>10%) reductions in health problems were observed for all dimensions with reductions being most pronounced

and consistent over time for usual activities, pain/discomfort, and anxiety/depression. The baseline mean (SD) EQ-5D VAS score was 50.6 (33.7). By week 7, the mean score for subjects on treatment had increased by more than 10 points, and mean scores for subjects who continued on treatment increased further over time. Mean VAS scores observed at or after week 19 exceeded normative values derived for numerous countries, including Belgium, France, Italy, and the US.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24: Summary of efficacy results for study CA209142

Title: A phase 2 clinical trial of nivolumab in recurrent or metastatic microsatellite instability high (MSI-H) colorectal cancer (updated with clinical cut-off Jan 2017)			
Study identifier	CA209142		
Design	Phase 2, open-label, multi-centre, 2-stage Simon design trial of nivolumab monotherapy (mStage) or in combination with ipilimumab (cStage) in adult patients with recurrent or metastatic MSI-H CRC. Only results for monotherapy are reported.		
	Duration of main phase:		Ongoing; FPFV 12 Mar 2014, LPLV interim analysis 03 Jan 2017
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Treatment with nivolumab monotherapy will have clinical activity in subjects with recurrent or metastatic MSI-H CRC.		
Treatments groups	Nivolumab monotherapy		3 mg/kg as 60 min IV infusion Q2W
Endpoints and definitions	Primary endpoint	Investigator-assessed BOR, ORR, DOR	• **BOR**: Best response designation recorded between date of first dose and date of initial objectively documented progression per RECIST v1.1 or date of subsequent therapy, whichever occurred first. For subjects without documented progression or subsequent therapy, all available response designations contributed to the BOR determination. For purposes of analysis, if a subject received one dose and discontinued the study without assessment or receives subsequent therapy prior to assessment, this subject was counted in the denominator (as non-respondent). • **ORR**: Number of MSI-H subjects with BOR of CR or PR, according to RECIST1.1 criteria, divided by the number of treated MSI-H subjects. **DOR**: Time from first confirmed response (CR or PR)to date of the first documented tumour progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurred first. For subjects who neither progressed nor died, the DOR censoring was the same as PFS censoring (see below).
	Secondary endpoint	IRRC-assessed BOR, ORR, DOR	Similar analyses as primary endpoint (see above).

	Exploratory endpoint	PFS	Time from first dosing date to date of first documented progression per RECIST 1.1, or death due to any cause, whichever occurred first. Subjects who died without reported prior progression and initiation of anti-cancer therapy were considered to have progressed on date of their death. Subjects who did not progress or died were censored on the date of their last evaluable tumour assessment. Subjects who did not have baseline on study tumour imaging assessments were censored on the first dosing date. Subjects who started any subsequent anticancer therapy without prior reported progression were censored at last evaluable tumour assessment prior to initiation of subsequent anti-cancer therapy.
	Exploratory endpoint	OS	Time from first dosing date to date of death. A subject who had not died was censored at their last known date alive.
Database lock	06 Feb 2017		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	All nivolumab monotherapy treated patients		
Descriptive statistics and estimate variability	Treatment group	All nivolumab monotherapy treated patients	Patients with prior 5FU-Oxa-Iri
	Number of subjects	74	53
	BOR by investigator • CR • PR • SD • PD • Unable to determine • Not reported	 0.0% 31.1% 37.8% 25.7% 5.4% 0%	 0.0% 26.4% 35.8% 30.2% 7.5% 0%
	ORR investigator (CI95)	31.1% (20.8-42.9)	26.4% (15.3-40.3)
	DOR investigator median Min, max	N.A. months 3.9+, 26.5+	N.A. months 3.9+, 23.5+
	BOR IRCC • CR • PR • SD • PD • Unable to determine • Not reported	 2.7% 29.7% 33.8% 28.4% 5.4% 0%	 1.9% 26.4% 30.2% 34.0% 7.5% 0%
	ORR IRRC (CI95)	32.4% (22.0–44.3)	28.3% (16.8-42.3)
	DOR IRRC median Min, max	N.A. months 1.4+, 26.5+	N.A. months 2.8+, 22.1+
	PFS investigator median (95% CI)	14.3 months (4.3-N.A.)	8.6 months (1.5-N.A.)
	PFS IRCC median (CI95)	8.3 months (3.0-N.A.)	4.9 months (1.5-N.A.)
	OS median (CI95)	N.A. months (18.0-N.A)	N.A. months (16.3-N.A.)
Descriptive statistics and estimate variability for PD-L1 ≥1% and <1% at baseline	Treatment group	PD-L1 ≥1	PD-L1 <1%
	Number of subjects	21	47
	ORR investigator (CI95)	28.6% (11.3-52.2)	27.7% (15.6-42.6)
	ORR IRRC (CI95)	33.3% (14.6-57.0)	27.7% (15.6-42.6)

	PFS investigator median (95% CI)	4.17 months (1.41-N.A.)	9.59 months (4.30-N.A.)
	PFS IRCC median (CI95)	4.17 months (1.38-N.A.)	8.31 months (2.83-N.A.)
	OS median (CI95)	19.61 months (8.57-N.A.)	N.A. months (17.12-N.A.)

2.5. Clinical studies in special populations

Table 25

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	0	0	0
Non Controlled trials **CT209142**	13/74 (17.6)	4/74 (5.4)	0/74

2.6. Analysis performed across trials (pooled analyses AND meta-analysis)

Not applicable, considering that only 1 CT is presented in support of this variation

2.7. Supportive study(ies)

No additional studies are presented in support of the current variation

2.8. Discussion on clinical efficacy

Design and conduct of clinical studies

The new claimed indication for OPDIVO is for the treatment of adults with dMMR or MSI-H mCRC after prior fluoropyrimidine-based therapy. The evidence presented to support the indication is limited to results of the nivolumab monotherapy cohort (mStage1 and mStage2) from Study CA209142. This is an open-label, multi-center, 2-stage design study of nivolumab monotherapy (mStage) or in combination with ipilimumab (cStage) to estimate the response rate in MSI-H/dMMR CRC and mismatch repair proficient (pMMR)/non-MSI-H CRC. Nivolumab 3 mg/kg was administered as a 60-minute intravenous (IV) infusion every 2 weeks (Q2W) until either RECIST 1.1 progression, unacceptable toxicity, or other protocol-defined reasons.

Study design: The trial started with monotherapy treatment and depending on the observed effect, the trial would either be stopped, the monotherapy cohort would be expanded or the combination therapy arm would be opened. After starting the first phase with 19 centrally-confirmed MSI-H patients, only 4 patients responded. According to design the monotherapy arm was stopped and the combination therapy cohort was opened. During recruitment for the combination therapy, 7 confirmed responses in the monotherapy arm were found and it was decided that the monotherapy cohort was reopened for enrolment. Instead of the predefined extra inclusion of 29 patients in the second phase, the sample size was increased to ensure at least 48 centrally-confirmed MSI-H patients were included as only a low number of MSI-H patients could be confirmed by central testing. The reasons for the unplanned opening

and closing of the trial have been presented, though uncertainties remain on the consequences for the internal validity of the trial.

A total of 74 subjects were enrolled in the monotherapy treatment period, 53 of whom had received prior treatment with 5FU-Oxa-Iri. This interim CSR presents the results of the subjects with MSI-H/dMMR CRC in the monotherapy (mStage1 and mStage2) cohort (all nivolumab monotherapy treated) and a subset of subject those who had received prior 5FU + oxaliplatin + irinotecan (5FU-Oxa-Iri) (at any time during prior therapy) based on the 19-Sep-2016 clinical database lock (DBL). An update with a clinical data cut-off as of 2 Jan 2017, with +5 months additional follow-up, has been presented during the procedure.

CA209142 is a single arm clinical trial without a comparative treatment, making the data difficult to interpret. Only 4% of mCRC is dMMR, but due to the high incidence of mCRC, there are approximately 225,000 dMMR CRC cases per year worldwide (11). Therefore, a randomised controlled trial would have been feasible with standard of care as a control treatment. Feasibility of a phase 3 trial is confirmed by the currently ongoing study comparing pembrolizumab with chemotherapy in MSI-H or dMMR stage IV CRC (NCT02563002; https://clinicaltrials.gov). Also no historical data are presented to compare the efficacy of nivolumab to the standard of care in the dMMR subpopulation of mCRC. Using historical data can be justifiable in situations where dramatic treatment effects are seen and the usual course of disease is highly predictable (CPMP/ICH/364/96). Although the use of historical data as control has its known limitations and bring about uncertainties, e.g. whether the study populations and historical control group are comparable and whether the outcome of the used control group is representative for what is seen for the target population in clinical practice, historical data would have helped to put the outcomes of the trial into context and to determine the B/R.

Main selection criteria include: adults with recurrent or metastatic MSI-H/dMMR CRC who had disease progression during, after, or had been intolerant to therapy with 5FU-based chemotherapy. Subjects were excluded with: active brain metastases or leptomeningeal metastases; active, known, or suspected autoimmune disease; or a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration. Baseline demographic and disease characteristics were representative for dMMR mCRC. To clarify, all patients had metastatic disease at the time of study entry, as all subjects had at least one site of metastatic disease at study entry. Patients were included after prior therapy with a fluorpyrimidine combined with oxaliplatin and/or irinotecan. Thus, the Sponsor agrees to adjust the indication as follows: OPDIVO is indicated for the treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based combination therapy.

Primary endpoint: Primary objective was to evaluate the investigator-assessed objective response rate (ORR) of nivolumab monotherapy in subjects with metastatic MSI-H CRC. The PEP is thus ORR which is based on tumour assessments at baseline and then at 6 weeks from first dose and which continue every 6 weeks for the first 24 weeks and every 12 weeks thereafter until disease progression (investigator-assessed RECIST 1.1-defined progression) or treatment discontinuation, whichever occurs later. Secondary endpoints include the independent radiology review committee (IRRC)-assessed ORR, progression-free survival (PFS) based on investigator and IRRC assessments, overall survival (OS), safety assessments: frequency of deaths, SAEs, AEs leading to discontinuation or dose modification, overall AEs, clinical laboratory and vital sign measurements, immunogenicity by ADA and neutralizing ADA response to nivolumab, and PRO.

A literature-based review, evaluating the correlation of both PFS and ORR with OS in the second-line treatment of mCRC with targeted therapies, analysed 20 trials with more than 7,500 patients. PFS and ORR showed moderate (R=0.734, R2=0.5387, p=0.0002) and poor correlation (R=0.1693, R2=0.029, p=0.48) with OS, respectively. OS is therefore still the preferred primary endpoint in trials for mCRC(12).

Given the uncontrolled studyand the lack of (historical) data on the natural course of dMMR/MSI-H CRC, the interpretation of OS of CA209142 will however be difficult.

A total of 31 sites in 8 countries enrolled subjects (Australia 4 (5.4%), EU 39 (52.7%), USA 30 (40,5%), and Canada 1 (1.4%). The last subject's first treatment occurred on 16-Mar-2016 and the LPLV was 10-Aug-2016, leading to a minimum follow-up of approximately 6 months (71 out of 74 subjects with at least 6 months follow-up and 3 subjects with 5 months follow-up) in this DBL (19-Sep-2016). A total of 74 subjects were enrolled in the monotherapy treatment period, 53 of whom had received prior treatment with 5FU-Oxa-Iri.

Study population: Among all nivolumab monotherapy treated subjects, the median age was 52.5 (range: 26 to 79) years, with 77% of patients <65 years and 5.4% >75 years. The majority were male (59.5%) and white (87.8%). The low median age is consistent with a mCRC population enriched for patients with Lynch syndrome. The disease stage at initial diagnosis was Stage IV for 44.6% and Stage III for 35.1% of All nivolumab monotherapy treated subjects. Baseline ECOG PS was 0 (32 subjects, 43.2%) or 1 (41 subjects, 55.4%). 37.8% of all nivolumab monotherapy treated subjects were KRAS/BRAF wild-type, 35.1%carried a KRAS mutation, and BRAF mutation was present in 16.2%.31.1% of all nivolumab monotherapy treated subjects had a history of Lynch syndrome, no history of Lynch syndrome for 35.1%, and history of Lynch syndrome was unknown for 33.8%.As of the DBL, the majority (98.6%) of subjects had PD-L1 tested at baseline and of these, most (90.4%) had quantifiable tumour PD-L1 expression at baseline. Of the 66 subjects with quantifiable tumour PD-L1 expression at baseline, 21 (31.8%) subjects had > 1% baseline PD-L1 expression and 45 (68.2%) had < 1% baseline PD-L1expression.

RAS and BRAF mutational status was not known for all patients. The frequency of KRAS mutations was 35.1% and 16.2% had a BRAF mutation. The frequencies of BRAF and KRAS mutations in MSI-H CRCs have been reported to be 16%-52% and 12%-20% in Western countries, respectively (13). Both RAS and BRAF mutational status are negative prognostic and predictive biomarkers, for example for efficacy of anti-EGFR therapy in the metastatic setting (1). Moreover, BRAF mutations are associated with immune escape in CRCs and using immunotherapy in BRAF mutated patients has therefore the potential hazard of selecting for tumour cells with more immune-evading capabilities (14). Despite the relevance of the status of these biomarkers in mCRC, NRAS was not determined and there are missing data for the two others. Further information will need to be provided.

From the all monotherapy treated group, 68 patients were response-evaluable by investigator assessment and 65 by IRRC. For the investigator assessments, in 4 patients responses were 'unable to be determined' having no on-study evaluations because of early discontinuation or death. IRRC assessment could not determine responses in 5 patients (3 had no on-study evaluation because of early discontinuation or death; 2 were censored for subsequent radiotherapy) and response was not reported for 1 patient (no scan sent to IRRC). First of all, this decreases the already small sample size and secondly, not all missing evaluations are accounted for.

Microsatellite instability was high (MSI-H) in 73 out of 74 patients (98.6%) of patients and one patients was classified as MSI-L or MSI-S according to local testing (52 MSI-H in the subgroup receiving prior 5FU+Oxa+Iri). Local results were mostly based on IHC (54.1%) and PRC/ICH (16.2%) assays. However, these results were not confirmed by central review (performed using PCR methodology) in a substantial number of patients, for which only 53 (71.6%) patients were classified as MSI-H in the monotherapy cohort (40, 75.5% of subjects with prior 5FU-Oxa-Iri), whilst 16.2% and 2.7% were evaluated as microsatellite stable (MSI-S) or MSI-L (11.3% and 3.8% in the subjects with prior 5FU-Oxa-Iri) and 9.5% of the subjects had missing evaluation.The level of concordance between local and central results for the presence of MSI is considered too high and a proper characterization of the studied population is critical considering the limited number of patients included in the only study presented to support the intended target population (any patients with MSI-H/dMMR mCRC ≥2L). In fact, PCR is the recommended method

for the assessment of MSI by some clinical guidelines whilst IHC is recommended for the assessment of MMR proteins expression. Local practice seems quite divergent, but in general access to IHC is higher than to PCR among centers. Thus, most patients were included based on the detection of loss of MMR proteins expression according to local practice. However, one would expect a high level of concordance given that MSI is the biologic footprint of the mismatch repair proteins deficiency. It is considered that the technique used may explain these differences given that within the discrepant cases, the vast majority corresponds to patients whose tumours were tested by IHC locally. The concern is mostly related to the 14 out of 67 samples with central testing for which discordant local vs central results were observed. It is argued that this discordance rate (which is 21%, and not 19% as reported by the MAH) is in line with that reported in the literature (5-10%) if the variability of the limited sample size is accounted for. Formally, in this trial the discordance rate is double than that expected, but the potential contribution of the low sample size cannot be omitted and no alternative explanation is provided. Higher response rates are seen in the subset of patients with central PCR confirmation (ORR by BICR: 35.8% in 53/74 with central confirmation, 21.4% in 14/74 with discordant results, and 28.6% in 7/74 with missing central testing), but given the low number of patients in the different subsets these results should be taken with caution.

The majority of subjects, among both all nivolumab monotherapy treated subjects (83.8%) as well as those subjects receiving prior 5FU-Oxa-Iri (98.1%), received 2 or more prior lines or regimens of systemic cancer therapy, while 54% of patients had received 3 or more prior lines (70% in the subgroup of subjects receiving prior 5RU-oxa-iri). The most frequent prior systemic cancer therapies among all treated subjects were fluorouracil (98.6%), oxaliplatin (95.9%), bevacizumab or other VEGF-inhibitors (77.0%), and irinotecan (74.3%), EGFR inhibitors 42%, regorafenib 16%. Over a third of subjects (36.5%) received prior radiation. Among all subjects treated with nivolumab monotherapy 53 (71.6%) had received prior therapy with 5FU-Oxa-Iri.

Regardless of the type of therapy received, 75.7% had progressed within 6 months of their most recent regimen, with 64.9% progressing within 3 months. Considering the protocol inclusion criteria, which require mCRC progression during, after, or intolerance to ≥ 1 line treatment(s) for their metastatic disease, one would expect that nearly 100% of patients would have progressed within 6 months (an even within 3 months) of their most recent regimen. This speaks in favour of a rather benign mCRC population. The Applicant has clarified that the actual data provided correspond to the time from completion of most recent prior therapy regimen to treatment that according to the MAH is independent of progression date on most recent prior therapy. However, no information has been presented on the actual time from progression on most recent prior therapy to nivolumab treatment. This should be provided. Moreover, these numbers suggest selection bias of a study population with a rather good prognosis compared to the overall population of mCRC patients. Around 25% of patients completed their most recent prior therapy >6 months ago and progression after start of first-line therapy is more than 40 months.

Statistical assessment: Statistical analyses methods used by the Applicant are commonly used and acceptable. Type I error control and sample size was only planned in case ORR would be >30% (for one-sided testing at 0.05), however the result of this test has not been reported. Also since the number of patients included in the second stage of the study was increased in comparison to that originally planned, proper inference after Simons 2-stage design (e.g. Koyama & Chen, stat in med 2007) should be applied, including adjusted confidence intervals for the ORR, instead of the pure descriptive CI95. The Applicant's post-hoc change from a Atkinsons & Brown method to a Clopper-Pearson method of calculation the CI does not solve this, unless the Applicant demonstrates that the actual type I error control of the latter is below or at a level properly adjusted for the two stage design with unplanned increase of stage 2.

In addition, the analysis population was changed (from those centrally MSI tested to those locally MSI tested) from stage 2 onwards which makes the design so adaptive that the impact on type I error of ORR is unclear.

No type I error control (and no planning for sufficient power) was planned for more clinically relevant endpoints, notably PFS and OS. The uncertainties regarding type I error control on ORR and more importantly PFS and OS due to deviation of the original plan (over-enrolment in stage 2 and opening up two studies) remain, and render the results more exploratory than confirmative evidence.

Efficacy data and additional analyses

Primary endpoint: **ORRs** per investigator and per IRRC in subjects with recurrent or metastatic MSI-H/dMMR CRC who had progression during, after, or have been intolerant to ≥ 1 line of treatment(s) for their metastatic disease were 31% (20.8%, 42.9%, 95%CI, all 23 PR) and 27% (142 CR + 18 PR), respectively. In the subgroup of patients receiving prior treatment with 5FU+oxa+iri, response rates were slightly lower: 26.4% (14 PR) and 22.6% ORR (1CR + 11 PR) per investigator and per IRRC, respectively. Disease control rate according to the investigator was 68.9% in the overall study population and 62.3% in the subgroup of patients previously treated with 5FU+oxa+iri. Disease control rate according to the IRRC were 62% and 56.6% for the overall and the subgroup≥3L population. Time to response was around 2.8 months, consistent in the relevant subgroup and both by investigator or IRRC assessment. Median duration of responses has not yet been reached. Although still premature, with a minimum FU of 6 months in all patients, antitumour activity results sounds promising. An update is requested.

Updated results (clinical cut-off 2 Jan 2017):Updated study results (cut-off Jan 2017) with +5 months additional follow up (minimum FU in all patients 11 months) are presented during the procedure, which are consistent to those initially submitted: ORR by IRRC 32.4% (2.7%CR, 29.7% PR, 33.8% SD), mDoR not reached, and DCR 63.5%.

In general, subgroup analysis presented show rather consistent results, with some exceptions noted, i.e. the lower rates of response in the elderly population and in patients with native KRAS/BRAF. The Applicant should clarify. In response to the questions raised, the MAH has presented an update of previous results, which show quite consistent response rates across the relevant subgroups identified, i.e. age, Lynch syndrome, BRAF/KRAS mutations, which is reassuring. The ORR, per BICR, for subjects < and ≥ 65 years of age are 33.3% (19/57) and 29.4%(5/17), respectively. The ORRs, per BICR, for subjects with and without Lynch Syndrome are 29.6% (8/27) and 35.7% (10/28), respectively. The ORRs, per BICR, for subjects with wild type KRAS and BRAF, mutant KRAS, and mutant BRAF are 31.0% (9/29), 30.8% (8/26), and 33.3 (4/12) respectively. Nevertheless, the limited number of patients, lack of mature OS/PFS data and the lack of external supportive evidence preclude firm conclusions at this stage. Further confirmatory data in these relevant subgroups of patients will need to be provided at post-marketing.

PFS and OS results are still immature. For PFS, 33 events in 74 patients have been reported by investigators, which show a median PFS of 9.6 months (95%CI, 4.3, NA) in the overall population, vs median PFS of 8.6 months (95%CI 1.5, NA) in the subgroup receiving 5FU+oxa+iri. By IRRC, median PFS was 7.6 months (95%CI 3.0, NA) and 4.9months (95%CI 1.5, NA) for the overall and the subgroup receiving 5FU+oxa+iri, respectively. The limited number of patients may well explain the differences in the response rates between investigator and IRRC, given that only 1 additional event of PFS was considered by IRRC vs investigators in both the overall and the subgroup highly treated population. For OS, events are limited to 26% (19/74) in the overall population and 28% (15/53) in the highly pretreated subgroup: OS rate at 6 months was 83.4%, 74% at 12 months for the overall population, vs 80.5% OS at 6 months and 70% at 12 months for the highly pretreated subgroup. Although promising, these results are very immature and should be taken with caution. An update with longer follow up of patients should

be provided. Updated PFS results with the new DBL of 06-Feb-2017 are reported and result in an additional follow-up of 5 months. Investigator-assessed median PFS increased from 9.59 to 14.29 months, for IRRC-assessed PFS this was from 7.59 to 8.31 months. Also an analysis of time to treatment failure was presented using the following as events: progression, treatment discontinuation, initiation of subsequent anti-cancer therapy, or death. Using IRRC assessment, 62.2% of patients had treatment failure after a median of 5.21 months. Using investigator assessment, failure percentage was 56.8% with a median of 8.02 months. TTF2 and PFS2 data were not collected and could therefore not be provided. With a total of 39 death events out of 74 patients, according to the IRRC, the median PFS is 8.3 months, 95%CI (3.0, NA). OS data are still immature and median is not yet reached: 23 events out of 74 patients, OS rate at 6 months 83.4%, OS rate at 12 months 73.4%.

Analyses are also presented **by PD-L1 expression**, which is based on tumour cell expression. 45 patients were classified as PD-L1<1% vs 21 were PD-L1 ≥1%. ORR results were rather consistent between the two subgroups, except a lower rate of ORR in patients with low expression based on IRRC assessment (33% high vs 24% low expression). However, given the limited number of patients in each subgroup, minor absolute numerical changes may influence relative numbers. By contrary, for PFS and OS, a trend for better results is shown in patients with low PD-L1 expression. Given the immaturity of these results, this should be taken cautiously. An update of study results based on PD-L1 tumour expression is presented, which show consistent results based either on a 1% or 5% cut-off. The majority of the studied population are <1% (63.5%) or <5% (77%), whilst information is missing for a small number of patients, i.e. 6 patients (8.1%) of the study population, results in this group should be taken with caution.
Post-hoc analysis for PD-L1 expression in tumour-associated immune cells (TAICs) was performed using a non-validated, qualitative assay with one pathologist defining expression as rare, intermediate of numerous without using numerical cut-off points. IRRC-assessed ORR was 21% in patients with rare PD-L1 expression in TAICs, 23.8% in the intermediate group, and higher in the numerous group, namely 43.5%. Results were given for 68 patients and the two patients with CR were not in the analysed group. In the Kaplan-Meier plot for survival, data showed that, although the numbers are low, rare expression is correlated with the best survival, which is contradicting the hypothesis of PD-1 inhibition in MSI-H mCRC (see Annex II for graphs). The MAH states that understanding the role for TAICs is an area of active exploratory investigation in ongoing trials, but also for CA209142 more efforts should be taken to investigate PD-L1 expression in both tumour and immune cells with a validated assay, especially because of the rationale of using anti-PD1 therapy in these tumours. The MAH should commit to continue investigating the role of PD-L1 expression in tumour cells and TAICs in their clinical program, including the population of MSI-H mCRC.

Assessment of paediatric data on clinical efficacy

Not applicable

Conclusions on the clinical efficacy

The evidence presented in support of the claimed indication seems encouraging in comparison to the expected outcomes in the general mCRC with available treatment options. However, due to the uncertainties on the actual predictive and/or prognostic value of the presence of dMMR in the metastatic setting and to the lack of control, either concurrent or historical, it is difficult to interpret the current study results. The CHMP has decided to convene a SAG-Oncology to discuss these aspects.

It is argued that patients with MSI have a worse prognosis and that response to therapy is lower that non-MSI patients. However, current knowledge in the field is limited and no sound evidence has been provided to substantiate that this general statement is true across the different lines of treatment. In this context and in the absence of comparative data over current SOC for these patients, it is difficult to judge

the relevance of nivolumab ORR study results for the intended target population, in particular when treatment options are available with well-established efficacy and safety (particularly in early lines of treatment). Further, the discrepant central vs local outcomes for selecting patients with MSI-H or MMRd add further uncertainties.

In addition, although available data look promising, the evidence provided is too limited and immature to reach sound conclusions on the clinical relevance of the study results, at present limited to ORR in a highly heterogeneous population. However median values have not been reached for the duration of tumour responses and for the relevant clinical endpoint, i.e.OS. The SAG-Oncology is also invited to discuss the strength of evidence for the clinical benefit of nivolumab in mCRC with presence of dMMR/MSI-H.

In conclusion, the provided data suggests anti-tumour activity of nivolumab in adults with dMMR/MSI-H mCRC after fluoropyrimidine-based combination therapy based on ORR, but placebo-controlled data reflecting the natural course of patients with dMMR/MSI-H mCRC are lacking. The clinically more important outcome of OS is immature. Co-Rapp: Also, uncertainties in defining the MSI status have remain. In conclusion, at present time efficacy results cannot be interpreted based on one single trial, since 1) control data are lacking and 2) ORR is not considered a valid surrogate endpoint in dMMR or MSI-H mCRC. Co-Rapp: 3) the internal validity of the data is questioned due to possible selection bias of a study population with a more favourable prognosis, proper definition of the study population by MSI status, and uncertainties regarding type I error control on clinical endpoints caused by deviating of the original study design (over-enrolment in stage 2 and opening up two studies), that render the results more exploratory than confirmative evidence.

2.9. Clinical safety

Introduction

The safety data for this variation is focused on the safety experience in study CA209142, a Phase 2, open-label, multi-center, 2-stage Simon design stage trial of nivolumab (BMS-936558) as monotherapy (mStage) or in combination with ipilimumab (cStage). This study supports the use of nivolumab at the proposed dose and schedule of 3 mg/kg administered as an intravenous (IV) infusion over 1 hour every 2 weeks (Q2W) for the treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC) previously treated at any time with fluoropyrimidine+oxaliplatin- or fluoropyrimidine+irinotecan-based chemotherapy. Safety analyses were conducted in all 74 treated subjects who received at least 1 dose of study drug.

Patient exposure

The enrolment period into the monotherapy arm lasted approximately 2 years (Mar-2014 to Mar-2016). A total of 31 sites in 8 countries enrolled subjects. The last subject's first treatment occurred on 16-Mar-2016 and the last subject's last visit was 10-Aug-2016, leading to a minimum follow-up of approximately 6 months (71 out of 74 subjects with at least 6 months follow-up and 3 subjects with $\geq$ 5 months follow-up) in this DBL (19-Sep-2016).

A total of 74 subjects were enrolled in the monotherapy treatment period, 53 of whom had received prior treatment with 5-fluorouracil (5-FU) combined with oxaliplatin (Oxa) or irinotecan (Iri) (hereafter, 5FU-Oxa-Iri).

Table 26 Subject Status Summary – All enrolled and treated subjects

	Total
SUBJECTS ENROLLED	260 (A)
SUBJECTS ENTERING MONOTHERAPY TREATMENT PERIOD (%)	74 (28.5)
SUBJECTS ENTERING COMBINATION TREATMENT PERIOD (%)	134 (51.5)
SUBJECTS NOT ENTERING THE TREATMENT PERIOD (%)	52 (20.0)
REASON FOR NOT ENTERING TREATMENT PERIOD (%)	
SUBJECT WITHDREW CONSENT	1 (0.4)
DEATH	2 (0.8)
SUBJECT NO LONGER MEETS STUDY CRITERIA	37 (14.2)
OTHER	2 (0.8)
NOT REPORTED	10 (3.8)

	MSI-H/dMMR CRC per Local Lab - All Subjects	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri
SUBJECTS	74	53
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	40 (54.1)	30 (56.6)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	34 (45.9)	23 (43.4)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)		
DISEASE PROGRESSION	27 (36.5)	20 (37.7)
STUDY DRUG TOXICITY	4 (5.4)	2 (3.8)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	1 (1.4)	0
SUBJECT WITHDREW CONSENT	1 (1.4)	1 (1.9)
MAXIMUM CLINICAL BENEFIT	1 (1.4)	0
SUBJECTS CONTINUING IN THE STUDY (%)	68 (91.9)	47 (88.7)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	6 (8.1)	6 (11.3)

(A) Includes subjects enrolled in either nivolumab monotherapy (mStage) or nivolumab in combination with (cStage) cohorts.
Percentages based on subjects enrolled or entering treatment period

Source: CA209142 Interim CSR[1] Table S.2.4 and Table S.2.5

A total of 86.5% of treated subjects received ≥ 90% of the planned dose intensity. The median duration of therapy for all nivolumab monotherapy treated subjects was 20.44 months (95% confidence interval: 5.09, not available); this median was not reached for subjects with prior 5FU-Oxa-Iri.

Table 27: Cumulative Dose and Relative Dose Intensity Summary – All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
NUMBER OF DOSES RECEIVED		
MEAN (SD)	17.1 (15.04)	16.8 (15.55)
MEDIAN (MIN - MAX)	13.0 (1 - 54)	13.0 (1 - 54)
CUMULATIVE DOSE (MG/KG)		
MEAN (SD)	50.83 (44.277)	49.54 (45.549)
MEDIAN (MIN - MAX)	38.77 (2.9 - 165.8)	38.70 (3.0 - 158.6)
RELATIVE DOSE INTENSITY		
>= 110%	0	0
90% TO < 110%	64 (86.5)	45 (84.9)
70% TO < 90%	7 (9.5)	6 (11.3)
50% TO < 70%	3 (4.1)	2 (3.8)
< 50%	0	0

Program Source: /projects/bms218374/stats/csr/prog/tables/rt-ex-rdi.sas 13OCT2016:10:36:13

Most subjects received all doses of study medication without an infusion interruption, infusion rate reduction, or dose delay. Reasons for infusion interruption, infusion rate reduction, or dose delay are provided in Table 28

Infusion interruption: 9.5% of subjects had an infusion interruption. Of these subjects, all had only 1 infusion interrupted.

Infusion rate reductions: 1 (1.4%) subject had 2 infusion rate reductions.

Dose delays: 25.7% of subjects experienced 1 dose delay. 21.6% of subjects experienced 2 or more dose delays.

Table 28: Infusion interruptions, Rate reductions and Dose Delays of Study Therapy - All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
SUBJECTS WITH AT LEAST ONE INFUSION INTERRUPTED (%)	7 (9.5)	4 (7.5)
NUMBER OF INFUSION INTERRUPTED PER SUBJECT (%)		
0	67 (90.5)	49 (92.5)
1	7 (9.5)	4 (7.5)
2	0	0
3	0	0
>= 4	0	0
TOTAL NUMBER DOSE INTERRUPTED/TOTAL NUMBER DOSE RECEIVED	7/1269 (0.6)	4/888 (0.5)
REASON FOR INFUSION INTERRUPTION (A)		
HYPERSENSITIVITY REACTION	2 (28.6)	1 (25.0)
INFUSION ADMIN ISSUES	0	0
OTHER	5 (71.4)	3 (75.0)
SUBJECTS WITH AT LEAST ONE INFUSION WITH IV RATE REDUCED (%)	1 (1.4)	0
NUMBER OF INFUSIONS WITH IV RATE REDUCTION PER SUBJECT (%)		
0	73 (98.6)	53 (100.0)
1	0	0
2	1 (1.4)	0
3	0	0
>= 4	0	0
TOTAL NUMBER IV RATE REDUCED/TOTAL NUMBER DOSE RECEIVED	2/1269 (0.2)	0/888
REASON FOR IV RATE REDUCTION (B)		
HYPERSENSITIVITY REACTION	0	0
INFUSION ADMIN ISSUES	0	0
OTHER	2 (100.0)	0
SUBJECTS WITH AT LEAST ONE DOSE DELAYED (%)	35 (47.3)	26 (49.1)
NUMBER OF DOSE DELAY PER SUBJECT		
0	39 (52.7)	27 (50.9)
1	19 (25.7)	13 (24.5)
2	4 (5.4)	4 (7.5)
3	9 (12.2)	9 (17.0)
>= 4	3 (4.1)	0
TOTAL NUMBER DOSE DELAYED/TOTAL NUMBER DOSE RECEIVED (C)	67/1195 (5.6)	48/835 (5.7)
REASON FOR DOSE DELAY (D)		
ADVERSE EVENT	38 (56.7)	27 (56.3)
OTHER	18 (26.9)	13 (27.1)
NOT REPORTED	11 (16.4)	8 (16.7)
LENGTH OF DELAY (D)		
4 - < 8 DAYS	35 (52.2)	23 (47.9)
8 - < 15 DAYS	18 (26.9)	16 (33.3)
15 - < 42 DAYS	12 (17.9)	9 (18.8)
>= 42 DAYS	2 (3.0)	0

(A) Percentages are computed out of the total number of dose interrupted
(B) Percentages are computed out of the total number of infusions with IV rate reduction
(C) TOTAL NUMBER DOSE RECEIVED is excluding first dose
(D) Percentages are computed out of the total number of dose delayed
A dose was considered as actually delayed if the delay is exceeding 3 days

Source: CA209142 Interim CSR[1] Table S.4.2, Table S.4.3, Table S.4.4

Adverse events

Common Adverse Events

The majority of nivolumab monotherapy treated subjects experienced at least 1 AE, regardless of causality, during treatment or within 30 days of last nivolumab dose (Table 29).

Among all nivolumab monotherapy treated subjects, the most frequently reported AEs were diarrhea (43.2%), fatigue (41.9%), anemia (36.5%), and nausea (33.8%).

Grade 3-4 AEs (regardless of causality) were reported in 48.6% of all nivolumab monotherapy-treated subjects. The most frequently reported Grade 3-4 AEs were lipase increased (9.5%), and anemia (8.1%).

When incidence rates were exposure-adjusted, the AE rate was 2064.4 per 100 person-years among all treated subjects (5% cut-off). Increased exposure did not appear to lead to an increased rate of AEs.

The overall frequency of AEs (regardless of causality) leading to a dose delay or reduction was 31.1% among all treated subjects.

Table 29: Adverse events by worst CTC grade reported in ≥ 10% of subjects - All nivolumab monotherapy treated subjects (DBL: 9-Feb-2017)

System Organ Class (%) / Preferred Term (%)	MSI-H/dMMR CRC per Local Lab – All Subjects N = 74		
	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	71 (95.9)	36 (48.6)	5 (6.8) (A) (B)
GASTROINTESTINAL DISORDERS	56 (75.7)	14 (18.9)	0
DIARRHOEA	32 (43.2)	2 (2.7)	0
NAUSEA	25 (33.8)	1 (1.4)	0
VOMITING	21 (28.4)	3 (4.1)	0
ABDOMINAL PAIN	19 (25.7)	2 (2.7)	0
CONSTIPATION	15 (20.3)	0	0
DYSPEPSIA	8 (10.8)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	53 (71.6)	7 (9.5)	1 (1.4) (A)
FATIGUE	31 (41.9)	3 (4.1)	0
PYREXIA	18 (24.3)	0	0
ASTHENIA	11 (14.9)	1 (1.4)	0
INVESTIGATIONS	35 (47.3)	16 (21.6)	0
ASPARTATE AMINOTRANSFERASE INCREASED	12 (16.2)	1 (1.4)	0
LIPASE INCREASED	11 (14.9)	7 (9.5)	0
ALANINE AMINOTRANSFERASE INCREASED	10 (13.5)	2 (2.7)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	9 (12.2)	1 (1.4)	0
INFECTIONS AND INFESTATIONS	33 (44.6)	7 (9.5)	0
UPPER RESPIRATORY TRACT INFECTION	10 (13.5)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	32 (43.2)	2 (2.7)	0
COUGH	19 (25.7)	0	0
METABOLISM AND NUTRITION DISORDERS	31 (41.9)	5 (6.8)	0
HYPERGLYCAEMIA	14 (18.9)	2 (2.7)	0
DECREASED APPETITE	10 (13.5)	1 (1.4)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	30 (40.5)	1 (1.4)	0
ARTHRALGIA	14 (18.9)	0	0
BACK PAIN	11 (14.9)	1 (1.4)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	30 (40.5)	1 (1.4)	0
PRURITUS	14 (18.9)	0	0
RASH	10 (13.5)	0	0
RASH MACULO-PAPULAR	8 (10.8)	1 (1.4)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	29 (39.2)	9 (12.2)	0
ANAEMIA	27 (36.5)	6 (8.1)	0
NERVOUS SYSTEM DISORDERS	24 (32.4)	2 (2.7)	0
HEADACHE	12 (16.2)	0	0
DIZZINESS	9 (12.2)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
(A) Includes 1 subject reported with Grade 5 sudden death.
(B) Includes 4 subjects reported with Grade 5 malignant neoplasm progression.

Source: CA209142 Interim CSR[1] Table S.6.2a

Drug-related Adverse Events

Any-grade drug-related AEs were reported in 68.9% of all nivolumab monotherapy treated subjects (Table 30). The most frequently reported drug-related AEs were fatigue (23.0%), diarrhea (21.6%), pruritus (13.5%), lipase increased (12.2 %), and rash (10.8%).

Grade 3-4 drug-related AEs were reported in 20.3% of all nivolumab monotherapy treated subjects. Among all nivolumab monotherapy treated subjects, the most frequently reported Grade 3-4 drug-related AEs were lipase increased (8.1%) and amylase increased (2.7%).

Table 30 Drug related Adverse Events by Worst CTC Grade Reported in ≥ 5% of subjects - All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74		
System Organ Class (%) Preferred Term (%)	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	51 (68.9)	15 (20.3)	1 (1.4) (A)
GASTROINTESTINAL DISORDERS	25 (33.8)	4 (5.4)	0
DIARRHOEA	16 (21.6)	1 (1.4)	0
NAUSEA	7 (9.5)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	25 (33.8)	1 (1.4)	1 (1.4) (A)
FATIGUE	17 (23.0)	1 (1.4)	0
ASTHENIA	5 (6.8)	0	0
INVESTIGATIONS	18 (24.3)	10 (13.5)	0
LIPASE INCREASED	9 (12.2)	6 (8.1)	0
ASPARTATE AMINOTRANSFERASE INCREASED	5 (6.8)	0	0
ALANINE AMINOTRANSFERASE INCREASED	4 (5.4)	1 (1.4)	0
AMYLASE INCREASED	4 (5.4)	2 (2.7)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	18 (24.3)	1 (1.4)	0
PRURITUS	10 (13.5)	0	0
RASH	8 (10.8)	0	0
RASH MACULO-PAPULAR	5 (6.8)	1 (1.4)	0
DRY SKIN	4 (5.4)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
(A) 1 subject with Grade 5 sudden death.

Source: CA209142 Interim CSR[1] Table S.6.3a

Serious adverse event / deaths / other significant events

Serious Adverse Events

SAEs were reported in 41.9% of nivolumab monotherapy treated subjects (Table 31). Grade 3-4 SAEs were reported in 29.7% of subjects.

The most frequently reported SAEs were malignant neoplasm progression (8.1%), abdominal pain, intestinal obstruction, and vomiting (4.1 % each), and diarrhea, small intestinal obstruction, and pyrexia (2.7% each).

An SAE of sudden death was reported for 1 subject.

Drug-related SAEs were reported in 10.8% of nivolumab monotherapy treated subjects (Table 2.3-2). Grade 3-4 drug-related SAEs were reported in 9.5% nivolumab monotherapy treated subjects. Drug-related SAEs consisted mainly of events in the SOC of Gastrointestinal (GI) Disorders.

There were no drug-related SAEs within the same PT reported in ≥ 2 subjects.

Table 31 SAEs by Worst CTC Grade reported in ≥ 1% of Subjects - All nivolumab Monotherapy treated subjects

System Organ Class (%) Preferred Term (%)	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74 Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	31 (41.9)	22 (29.7)	5 (6.8)
GASTROINTESTINAL DISORDERS	14 (18.9)	12 (16.2)	0
ABDOMINAL PAIN	3 (4.1)	0	0
INTESTINAL OBSTRUCTION	3 (4.1)	3 (4.1)	0
VOMITING	3 (4.1)	1 (1.4)	0
DIARRHOEA	2 (2.7)	2 (2.7)	0
SMALL INTESTINAL OBSTRUCTION	2 (2.7)	2 (2.7)	0
ASCITES	1 (1.4)	1 (1.4)	0
COLITIS	1 (1.4)	1 (1.4)	0
CONSTIPATION	1 (1.4)	0	0
GASTRITIS	1 (1.4)	1 (1.4)	0
HAEMATEMESIS	1 (1.4)	1 (1.4)	0
NAUSEA	1 (1.4)	1 (1.4)	0
PROCTALGIA	1 (1.4)	1 (1.4)	0
STOMATITIS	1 (1.4)	1 (1.4)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (10.8)	5 (6.8)	1 (1.4)
PYREXIA	2 (2.7)	0	0
ASTHENIA	1 (1.4)	1 (1.4)	0
INCARCERATED HERNIA	1 (1.4)	1 (1.4)	0
LOCAL SWELLING	1 (1.4)	1 (1.4)	0
PAIN	1 (1.4)	1 (1.4)	0
SUDDEN DEATH	1 (1.4)	0	1 (1.4)
SUPRAPUBIC PAIN	1 (1.4)	1 (1.4)	0
INFECTIONS AND INFESTATIONS	8 (10.8)	6 (8.1)	0
ABDOMINAL ABSCESS	1 (1.4)	1 (1.4)	0
ABDOMINAL WALL ABSCESS	1 (1.4)	1 (1.4)	0
CELLULITIS	1 (1.4)	0	0
DEVICE RELATED INFECTION	1 (1.4)	1 (1.4)	0
GASTROENTERITIS	1 (1.4)	1 (1.4)	0
KLEBSIELLA SEPSIS	1 (1.4)	0	0
PELVIC INFECTION	1 (1.4)	1 (1.4)	0
PNEUMONIA KLEBSIELLA	1 (1.4)	0	0
SEPTIC SHOCK	1 (1.4)	1 (1.4)	0
TOOTH INFECTION	1 (1.4)	0	0
WOUND INFECTION	1 (1.4)	1 (1.4)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	6 (8.1)	2 (2.7)	4 (5.4)
MALIGNANT NEOPLASM PROGRESSION	6 (8.1)	2 (2.7)	4 (5.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (2.7)	2 (2.7)	0
FEBRILE NEUTROPENIA	1 (1.4)	1 (1.4)	0
NEUTROPENIA	1 (1.4)	1 (1.4)	0
HEPATOBILIARY DISORDERS	2 (2.7)	2 (2.7)	0
BILE DUCT OBSTRUCTION	1 (1.4)	1 (1.4)	0
CHOLESTASIS	1 (1.4)	1 (1.4)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.7)	2 (2.7)	0
DYSPNOEA	1 (1.4)	1 (1.4)	0
PULMONARY EMBOLISM	1 (1.4)	1 (1.4)	0
ENDOCRINE DISORDERS	1 (1.4)	1 (1.4)	0
ADRENAL INSUFFICIENCY	1 (1.4)	1 (1.4)	0
INVESTIGATIONS	1 (1.4)	1 (1.4)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (1.4)	1 (1.4)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.4)	0	0
MUSCULOSKELETAL PAIN	1 (1.4)	0	0
NERVOUS SYSTEM DISORDERS	1 (1.4)	1 (1.4)	0
SPINAL CORD COMPRESSION	1 (1.4)	1 (1.4)	0
RENAL AND URINARY DISORDERS	1 (1.4)	1 (1.4)	0
ACUTE KIDNEY INJURY	1 (1.4)	1 (1.4)	0
VASCULAR DISORDERS	1 (1.4)	1 (1.4)	0
HYPOTENSION	1 (1.4)	1 (1.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Source: CA209142 Interim CSR Table S.6.18a[1]

Table 32 Drug related SAEs - All nivolumab Monotherapy treated subjects

System Organ Class (%) Preferred Term (%)	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74		
	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	8 (10.8)	7 (9.5)	1 (1.4)
GASTROINTESTINAL DISORDERS	4 (5.4)	4 (5.4)	0
COLITIS	1 (1.4)	1 (1.4)	0
DIARRHOEA	1 (1.4)	1 (1.4)	0
GASTRITIS	1 (1.4)	1 (1.4)	0
STOMATITIS	1 (1.4)	1 (1.4)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (2.7)	1 (1.4)	1 (1.4)
FALL	1 (1.4)	1 (1.4)	0
SUDDEN DEATH	1 (1.4)	0	1 (1.4)
ENDOCRINE DISORDERS	1 (1.4)	1 (1.4)	0
ADRENAL INSUFFICIENCY	1 (1.4)	1 (1.4)	0
INVESTIGATIONS	1 (1.4)	1 (1.4)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (1.4)	1 (1.4)	0
RENAL AND URINARY DISORDERS	1 (1.4)	1 (1.4)	0
ACUTE KIDNEY INJURY	1 (1.4)	1 (1.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: CA209142 Interim CSR[1] Table S.6.19a

Deaths

A total of 19 subjects had died as of the 19-Sep-2016 DBL (Table 2.2-1). Disease progression was the most common cause of death, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose.

Table 33 Death Summary - All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74
NUMBER OF SUBJECTS WHO DIED (%)	19 (25.7)
PRIMARY REASON FOR DEATH (%)	
DISEASE	17 (23.0)
STUDY DRUG TOXICITY	0
UNKNOWN	2 (2.7)
OTHER	0
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	4 (5.4)
PRIMARY REASON FOR DEATH (%)	
DISEASE	3 (4.1)
STUDY DRUG TOXICITY	0
UNKNOWN	1 (1.4)
OTHER	0
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	11 (14.9)
PRIMARY REASON FOR DEATH (%)	
DISEASE	10 (13.5)
STUDY DRUG TOXICITY	0
UNKNOWN	1 (1.4)
OTHER	0

Program Source: /projects/bms218374/stats/csr/prog/tables/rt-dt.sas 13OCT2016:10:35:13

No deaths were attributed to study drug toxicity by the investigator. There were no deaths attributed to "other" reasons.

Two subjects died due to "unknown" reasons, 1 within 100 days of their last nivolumab dose.

- Subject CA209142-3-8, who had an ileostomy in place with a baseline of 2-3 stools/day, had previously presented with Grade 3 diarrhea/colitis attributed as related to study drug by the investigator. The subject was treated with methylprednisolone and nivolumab was discontinued. The subject by report improved and was planned for discharge from the hospital, but was found unresponsive and subsequently pronounced dead. Autopsy results for the subject's sudden death were reported as "unknown cause."
- Subject CA209142-3-7 died 182 days from their last dose of study drug, and cause of death was reported as "unknown". The subject had disease progression on their first scheduled restaging scan at 6 weeks. On Day 82, he was hospitalized with a partial bowel obstruction (clinical database). A scan done on Day 86 confirmed progression of disease. The subject's last follow up was on Day 192 with no residual toxicity reported from therapy. He died of unknown cause on Day 254; no further information is available.

Selected AEs

In order to characterize AEs of special clinical interest that are potentially associated with the use of nivolumab, the Applicant identified select AEs based on the following 4 guiding principles:

- AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies
- AEs that may require immunosuppression (eg, corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity
- AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization

Based on these guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash are currently considered to be select AEs. Multiple event terms that may describe each

of these were grouped into endocrine, GI, hepatic, pulmonary, renal, and skin select AE categories, respectively.

Across select AE categories, the majority of events were manageable, with resolution occurring when immune-modulating medications (mostly systemic corticosteroids) were administered.

Some endocrine select AEs were not considered resolved due to the continuing need for hormone replacement therapy.

The majority of reported select AEs were Grade 1-2, with some higher grade Grade 3 events.

There were no Grade 4 or Grade 5 select AEs reported.

Most endocrine and all hypersensitivity/infusion reaction select AEs were considered drug-related by the investigator. A lower proportion of select AEs were reported as drug-related in the GI, hepatic, renal, and skin categories. There were no pulmonary select AEs considered drug-related by the investigator. The most frequently reported any-grade drug-related select AE categories were GI (24.3%) and skin (21.6%).

Table 34 Summary of Selected AEs Reported up to 30 days after last Dose - All nivolumab treated MSI-H/dMMR Subjects in CA209142

	MSI-H/dMMR CRC per Local Lab - All Subjects (N = 74)	
	Any Grade	Grade 3-4
ALL-CAUSALITY SELECT AES, BY CATEGORY		
ENDOCRINE	7 (9.5)	1 (1.4)
GASTROINTESTINAL	34 (45.9)	3 (4.1)
HEPATIC	17 (23.0)	4 (5.4)
PULMONARY	2 (2.7)	0
RENAL	8 (10.8)	2 (2.7)
SKIN	24 (32.4)	1 (1.4)
HYPERSENSITIVITY/INFUSION REACTIONS	3 (4.1)	0
DRUG-RELATED SELECT AES, BY CATEGORY		
ENDOCRINE	6 (8.1)	1 (1.4)
GASTROINTESTINAL	18 (24.3)	2 (2.7)
HEPATIC	6 (8.1)	2 (2.7)
PULMONARY	0	0
RENAL	3 (4.1)	2 (2.7)
SKIN	16 (21.6)	1 (1.4)
HYPERSENSITIVITY/INFUSION REACTIONS	3 (4.1)	0

MedDRA version 19.0; CTC version 4.0.
All events are within 30 days of the last dose of study drug.
Source: Table 1-1 of the SCS, Module 2.7.4

Table 35 Onset, Management, and Resolution of Drug-related Select AEs - All Nivolumab Monotherapy Treated Subjects in CA209142

Category	Overall % Select Event	Drug Related Select AEs (%)	Median Time to Onset (range), weeks	Select AE Treatment	Nivolumab DC due to Select AE	Resolution of Drug-related Events
Endocrine	9.5	8.1	7.07 (2.1 - 39.7)	No subjects treated with IMM	None	Event resolved: 2/6 subjects Median TTR: not evaluable (range: 0.4 - 73.0+weeks)
GI	45.9	24.3	2.21 (0.3 - 65.0)	1/18 subjects treated with high-dose corticosteroids (duration of 0.6 weeks); event not resolved as of DBL	1 subject	Event resolved: 13/18 subjects Median TTR: 6.14 (range: 0.1 - 69.1 weeks) TTR with IMM: 0.9+weeks
Hepatic	23.0	8.1	8.64 (2.0 - 50.4)	1/6 subjects treated with high-dose corticosteroids (duration of 24.3 weeks); 1 subject event resolved	1 subject	Event resolved: 3/6 subjects Median TTR: 6.14 weeks (range: 4.1+ - 29.3+) TTR with IMM: 6.1 weeks
Pulmonary	2.7	0	NA	NA	NA	NA
Renal	10.8	4.1	8.00 (2.1 - 27.4)	2/3 subjects treated with IMM; 1/3 subjects treated with high-dose corticosteroids (duration of 2.6 weeks); 1 subject event resolved	1 subject	Event resolved: 2/3 subjects Median TTR: 16.86 weeks (range: 2.6 - 21.1+) Median TTR with IMM: not evaluable (range: 2.6 - 21.1+ weeks)
Skin	32.4	21.6	7.43 (0.3 - 64.0)	5/16 subjects treated with IMM; 1/16 subjects treated with high-dose corticosteroids (duration of 8.6 weeks); 3 subject events resolved	None	Event resolved: 10/16 subjects Median TTR: 10.00 weeks (range: 0.3 - 94.3+) Median TTR with IMM: 22.50 weeks (range: 1.9 - 94.3+)
Hypersensitivity / Infusion Reactions	4.1	4.1	2.14 (2.1 - 2.1)	1/3 subjects treated with IMM; no subjects treated with high-dose corticosteroids (duration of 0.14 weeks); 1 subject event resolved	None	Event resolved: 3/3 subjects Median TTR: 0.14 weeks (range: 0.1 - 6.1) TTR with IMM: 0.1 week

Source: Refer to Section 2.5.1 of the SCS, Module 2.7.4 and Table S.6.114 of the CA209142 Interim CSR (Endocrine); Section 2.5.2 of the SCS, Module 2.7.4 (GI); Section 2.5.3 of the SCS, Module 2.7.4 (Hepatic); Section 2.5.4 of the SCS, Module 2.7.4 (Pulmonary); Section 2.5.5 of the SCS, Module 2.7.4 (Renal);Section 2.5.6 of the SCS, Module 2.7.4 (Skin); and Section 2.5.7 of the SCS, Module 2.7.4 (Hypersensitivity/Infusion Reactions)

Abbreviations: AE = adverse event; DBL = database lock;DC = discontinuation; GI = gastrointestinal; IMM = immune-modulating medication;NA = not applicable; TTR = time to resolution.

- **Endocrine Events**

Endocrine select AEs (all-causality, any grade) were reported in 7 (9.5%) nivolumab monotherapy treated subjects.

Among all treated subjects, 6 (8.1%) subjects had endocrine select AEs that were considered to be drug related by the investigator (Table 5.3.1-1Table 9). The most commonly reported drug-related events were hyperthyroidism and hypothyroidism. The majority of the drug-related endocrine events were Grade 1-2. There was 1 Grade 3-4 drug-related endocrine event of adrenal insufficiency. This event did not lead to permanent discontinuation of nivolumab and resolved at the time of DBL.

The median time to onset of drug-related endocrine select AEs was 7.07 weeks. No subjects were treated with immune-modulating medication. Overall, 2 of the 6 subjects with drug-related endocrine select AEs had resolution of their events at the time of DBL; median time to resolution was not evaluable.

Table 36 Summary of Drug – related Endocrine Select Adverse events reported up to 30 days after last Dose - All nivolumab Monotherapy treated subjects

Sub Category (%) / Preferred Term (%)	MSI-H/dMMR CRC per Local Lab – All Subjects N = 74		
	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	6 (8.1)	1 (1.4)	0
THYROID DISORDER	5 (6.8)	0	0
HYPERTHYROIDISM	3 (4.1)	0	0
HYPOTHYROIDISM	3 (4.1)	0	0
BLOOD THYROID STIMULATING HORMONE INCREASED	1 (1.4)	0	0
ADRENAL DISORDER	1 (1.4)	1 (1.4)	0
ADRENAL INSUFFICIENCY	1 (1.4)	1 (1.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: CA209142 Interim CSR[1] Table 8.6.107

- **Gastrointestinal Events**

GI select AEs (all-causality, any grade) were reported in 34 (45.9%) nivolumab monotherapy-treated subjects. Among all treated subjects, 18 (24.3%) subjects had GI select AEs that were considered to be drug-related by the investigator. One subject had a Grade 3 event of colitis that led to permanent discontinuation of nivolumab.

The median time to onset of drug-related GI select AEs was 2.21 weeks. 1 subject was treated with immune-modulating medication (high dose corticosteroid) for a median duration of 0.57 weeks, and did not have resolution of their event at the time of DBL. Overall, 13 of the 18 subjects with drug-related GI select AEs had resolution of their events, with a median time to resolution of 6.14 weeks.

Table 37 Summary of Drug – related Gastrointestinal Select Adverse events reported up to 30 days after last Dose - All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab – All Subjects N = 74		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	18 (24.3)	2 (2.7)	0
DIARRHOEA	16 (21.6)	1 (1.4)	0
COLITIS	1 (1.4)	1 (1.4)	0
FREQUENT BOWEL MOVEMENTS	1 (1.4)	0	0

Source: CA209142 Interim CSR[1] Table S.6.103

- **Hepatic Events**

Hepatic select AEs (all-causality, any grade) were reported in 17 (23.0%) nivolumab monotherapy treated subjects.

Among all treated subjects, 6 (8.1%) subjects had hepatic select AEs that were considered to be drug-related by the investigator. Two subjects had a Grade 3-4 event and 1 of the events (ALT increased) led to permanent discontinuation of nivolumab.

The median time to onset of drug-related hepatic select AEs was 8.64 weeks (Table 2.5.3-2).

One subject was treated with immune-modulating medication (high-dose corticosteroid) for a duration of 24.29 weeks, and had resolution of their event at the time of DBL. Overall, 3 of the 6 subjects with drug-related hepatic select AEs had resolution of their events; median time to resolution was 6.14 weeks.

Table 38 Summary of Drug-related Hepatic Select Adverse events reported up to 30 days after last Dose - All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab – All Subjects N = 74		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	6 (8.1)	2 (2.7)	0
ASPARTATE AMINOTRANSFERASE INCREASED	5 (6.8)	0	0
ALANINE AMINOTRANSFERASE INCREASED	4 (5.4)	1 (1.4)	0
BLOOD ALKALINE PHOSPHATASE INCREASED	2 (2.7)	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	1 (1.4)	1 (1.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: CA209142 Interim CSR[1] Table S.6.103

- **Pulmonary Events**

Pulmonary select AEs (all-causality, any grade) were reported in 2 (2.7%) treated subjects; neither event was considered drug-related.

- **Renal Events**

Renal select AEs (all-causality, any grade) were reported in 8 (10.8%) treated subjects.

Among all treated subjects, 3 (4.1%) subjects had renal select AEs that were considered to be drug-related by the investigator (Table 2.5.5-1). One Grade 3-4 event (acute kidney injury) led to permanent discontinuation of nivolumab.

The median time to onset of drug-related renal select AEs was 8.00 weeks (Table 2.5.5-2).

Two subjects were treated with immune-modulating medication, 2 subjects were treated with immune-modulating medication for a median duration of 3.29 weeks, and 1 subject was treated with high-dose corticosteroids for duration of 2.57 weeks. 1 subject did not have resolution of the event at the time of DBL. Overall, 2 of the 3 subjects with drug-related renal select AEs had resolution of their events, with a median time to resolution of 16.86 weeks.

Table 39 Summary of Drug-related Renal Select Adverse events reported up to 30 days after last Dose - All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab – All Subjects N = 74		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (4.1)	2 (2.7)	0
BLOOD CREATININE INCREASED	2 (2.7)	1 (1.4)	0
ACUTE KIDNEY INJURY	1 (1.4)	1 (1.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: CA209142 Interim CSR[1] Table S.6.103

- **Skin Events**

Skin select AEs (all-causality, any grade) were reported in 24 (32.4%) treated subjects. Among all treated subjects, 16 (21.6%) subjects had skin select AEs that were considered to be drug-related by the investigator. The most frequently reported drug-related events were pruritus, rash, and rash maculo-papular. There was no event of toxic epidermal necrolysis reported. The majority of drug-related events were Grade 1-2 and none led to permanent discontinuation of nivolumab. The median time to onset of drug-related skin select AEs was 7.43 weeks.

Five subjects were treated with immune-modulating medication for a median duration of 14.14 weeks (1 subject was treated with immune-modulating medication [high dose corticosteroid] for a duration of 8.57 weeks), and 3 subjects had resolution of their events at the time of DBL.

Overall, 10 of the 16 subjects with drug-related skin select AEs had resolution of their events, with a median time to resolution of 10.00 weeks.

Table 40 Summary of Drug-related Skin Select Adverse events reported up to 30 days after last Dose - All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab – All Subjects N = 74		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	16 (21.6)	1 (1.4)	0
PRURITUS	10 (13.5)	0	0
RASH	8 (10.8)	0	0
RASH MACULO-PAPULAR	5 (6.8)	1 (1.4)	0
DERMATITIS	1 (1.4)	0	0
ECZEMA	1 (1.4)	0	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	1 (1.4)	0	0
RASH ERYTHEMATOUS	1 (1.4)	0	0
RASH GENERALISED	1 (1.4)	0	0
SKIN EXFOLIATION	1 (1.4)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: CA209142 Interim CSR[1] Table S.6.103

- **Hypersensitivity / Infusion Reactions**

Hypersensitivity/infusion reactions (all-causality, any grade) were reported in 3 (4.1%) treated subjects. Among all treated subjects, 3 (4.1%) subjects had hypersensitivity/infusion reaction events that were considered to be drug related by the investigator. All of the events were Grade 1-2 and none led to permanent discontinuation of nivolumab.

The median time to onset of drug-related hypersensitivity/infusion reactions was 2.14 weeks. One subject was treated with immune-modulating medication for a duration of 0.14 weeks, and this subject had resolution of their event at the time of DBL. All 3 subjects with drug-related hypersensitivity/infusion reactions select AEs had resolution of their events, with a median time to resolution of 0.14 weeks.

Table 41 Summary of Drug-related Hypersensitivity / infusion Reactions Select Adverse events reported up to 30 days after last Dose - All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab – All Subjects N = 74		
Preferred Term (%)	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	3 (4.1)	0	0
HYPERSENSITIVITY	2 (2.7)	0	0
INFUSION RELATED REACTION	1 (1.4)	0	0

MedDRA Version: 19.0
CTC Version 4.0
Endocrine Adverse Events are not included in this table.
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: CA209142 Interim CSR[1] Table S.6.103

- **Other Events of Special Interest**

OESIs included the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis, pancreatitis, rhabdomyolysis, and uveitis. One OESI (Grade 2 pancreatitis) was reported between first dose and 100 days after last dose of study therapy (extended follow-up) in one nivolumab monotherapy treated subject. The event was considered drug-related by the investigator, and drug was not interrupted or permanently discontinued. The

pancreatitis event time to onset was 4.71 weeks. The subject was not treated with immune-modulating medication for the event. The event resolved 28.14 weeks later.

There were no events in the following OESI categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis, rhabdomyolysis, and uveitis.

Immunogenicity

Of the nivolumab monotherapy treated subjects who were evaluable for ADA, 1 ADA negative and 1 ADA positive subject experienced select AEs in the hypersensitivity/infusion reaction category. Thus, the presence of ADA was not associated with the occurrence of hypersensitivityand/or infusion-related reactions.

Laboratory findings
Hematology

Abnormalities in hematology tests that occurred during treatment or within 30 days of last dose of study drug were primarily Grade 1-2 in nivolumab monotherapy treated subjects.

Grade 3-4 hematologic abnormalities reported in ≥5% of subjects were anemia (7.0% Grade 3) and lymphocytopenia (7.1% [5.7% Grade 3, 1.4% Grade 4]).

Serum Chemistry

Liver Tests

Among all treated subjects, abnormalities in hepatic parameters (all increases) that occurred during treatment or within 30 days of last dose of study drug were primarily Grade 1-2.The only Grade 3-4 liver test abnormality reported in ≥5% of subjects was alkaline phosphatase(8.5% Grade 3).

Three (4.2%) subjects had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within 1 day, and 3 (4.2%) subjects had concurrent ALT or AST elevation > 3 xULN with total bilirubin > 2 x ULN within 30 days of last dose of study therapy .

Table 42 Summary of on-treatment laboratory Abnormalities in Specific Liver tests (SI Units)- All nivolumab Monotherapy treated subjects

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74
	N = 71
ALT OR AST > 3XULN	8 (11.3)
ALT OR AST > 5XULN	2 (2.8)
ALT OR AST > 10XULN	0
ALT OR AST > 20XULN	0
	N = 71
TOTAL BILIRUBIN > 2XULN	5 (7.0)
	N = 71
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	3 (4.2)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	3 (4.2)

Denominator corresponds to subjects with at least one on-treatment measurement of the corresponding laboratory parameter.
Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.

Source: CA209142 Interim CSR[1] Table 8.7.6-8I

Kidney Function Tests

Among all nivolumab monotherapy treated subjects, all reported creatinine abnormalities during treatment or within 30 days of last dose of study drug were Grade 1-2.

Thyroid Function Tests

The majority of subjects had normal TSH levels at baseline and throughout the treatment period (Table 43).

Table 43 Summary of on-treatment laboratory Abnormalities in Specific Thyroid Tests - (SI Units)- Nivolumab Monotherapy treated subjects with at Least one on-treatment TSH

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 70
TSH > ULN	20 (28.6)
TSH > ULN	
WITH TSH <= ULN AT BASELINE	12 (17.1)
TSH > ULN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	11 (15.7)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	7 (10.0)
WITH FT3/FT4 TEST MISSING (A) (B)	2 (2.9)
TSH < LLN	11 (15.7)
TSH < LLN	
WITH TSH >= LLN AT BASELINE	10 (14.3)
TSH < LLN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	3 (4.3)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	7 (10.0)
WITH FT3/FT4 TEST MISSING (A) (B)	1 (1.4)

Includes laboratory results reported after the first dose and within 30 days of last dose of study therapy.
(A) Within a 2-week window after the abnormal TSH test date
(B) Includes subjects with TSH abnormality and with no FT3/FT4 test values in the 2-week window or with non-abnormal value(s) from only one of the two tests and no value from the other test.
Source: CA209142 Interim CSR[1] Table 8.7.6-8I

Electrolytes

Among all nivolumab monotherapy treated subjects, most had normal electrolyte levels at baseline and during the treatment period. Abnormalities in electrolytes during treatment were primarily Grade 1 to 2 in severity.

No Grade 3-4 electrolyte abnormalities were reported in ≥5% of subjects.

Safety in special populations

Intrinsic and Extrinsic Factors

The frequencies of all-causality and drug-related AEs among all nivolumab monotherapy treated subjects for subgroups of gender, race, age, and region were similar to the AE frequencies in the overall treated population. Small numerical differences in frequencies of AEs were observed in the following subgroups:

- Any-grade and Grade 3-4 drug-related AEs for male (72.7% and 18.2%) vs female (63.3% and 23.3%). There were 44 male treated subjects and 30 female treated subjects.
- Any-grade and Grade 3-4 drug-related AEs for white (66.2% and 21.5%) vs black or African American (85.7% and 14.3%). There were 65 white and 7 black or African American treated subjects.
- Any grade and Grade 3-4 drug-related AEs for subjects < 65 (71.9%, 15.8%) vs> 65 (58.8% and 35.3%) years of age. There were 57 treated subjects < 65 years of age and 17 treated subjects > 65 years of age.
- Higher frequencies of any grade and Grade 3-4 drug-related AEs were reported in US/Canada subjects (87.1% and 29.0%, respectively) versus Europe (59.0% and 15.4%,respectively) or Rest of World (25.0% [any grade]). There were 31 treated subjects in US/Canada, 39 treated subjects in Europe, and 4 treated subjects in Rest of World.

These differences are of limited interpretability due to low sample sizes and event rates, and do not alter the overall safety profile of nivolumab in these subgroups.

Age Groups

In CA209142, the frequency of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term/Standardized MedDRA Query/SOC by age group are presented in Table 5.1.1-1. Interpretation is limited by the small number of subjects in the 75 to 84 years of age subgroup (N = 4), and that there were no subjects ≥85 years of age.

Table 44 Summary of on-treatment Adverse events by age group - treated subjects

	Age Group (Years)				
MedDRA Terms (%)	< 65 N = 57	65-74 N = 13	75-84 N = 4	>=85 N = 0	Total N = 74
TOTAL SUBJECTS WITH AN EVENT	54 (94.7)	13 (100.0)	4 (100.0)	0	71 (95.9)
SERIOUS AE - TOTAL	22 (38.6)	7 (53.8)	2 (50.0)	0	31 (41.9)
FATAL (DEATH)	6 (10.5)	1 (7.7)	0	0	7 (9.5)
HOSPITALIZATION/PROLONGATION	21 (36.8)	6 (46.2)	2 (50.0)	0	29 (39.2)
LIFE THREATENING	0	1 (7.7)	0	0	1 (1.4)
CANCER	0	0	0	0	0
DISABILITY/INCAPACITY	0	0	0	0	0
IMPORTANT MEDICAL EVENT	1 (1.8)	0	0	0	1 (1.4)
AE LEADING TO DISCONTINUATION	4 (7.0)	1 (7.7)	1 (25.0)	0	6 (8.1)
PSYCHIATRIC DISORDERS	7 (12.3)	4 (30.8)	1 (25.0)	0	12 (16.2)
NERVOUS SYSTEM DISORDERS	18 (31.6)	6 (46.2)	0	0	24 (32.4)
ACCIDENT AND INJURIES	5 (8.8)	1 (7.7)	1 (25.0)	0	7 (9.5)
CARDIAC DISORDERS	1 (1.8)	2 (15.4)	0	0	3 (4.1)
VASCULAR DISORDERS	13 (22.8)	2 (15.4)	2 (50.0)	0	17 (23.0)
CEREBROVASCULAR DISORDERS	0	0	0	0	0
INFECTIONS AND INFESTATIONS	25 (43.9)	6 (46.2)	2 (50.0)	0	33 (44.6)
ANTICHOLINERGIC SYNDROME	22 (38.6)	5 (38.5)	2 (50.0)	0	29 (39.2)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	9 (15.8)	3 (23.1)	0	0	12 (16.2)

CTC Version 4.0; MedDRA Version: 19.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program Source: /projects/bms218374/stats/csr/prog/tables/rt-ae-eusumage142.sas 24OCT2016:07:08:01

Safety related to drug-drug interactions and other interactions

No new information.

Discontinuation due to adverse events

AEs leading to discontinuation were reported in 8.1% of nivolumab monotherapy treated subjects (Table 2.4-1).

Drug-related AEs leading to discontinuation were reported in 5.4% of nivolumab monotherapy treated subjects (Table 2.4-2). Grade 3-4 AEs leading to discontinuation, all considered drug-related, were reported in5.4% of subjects.

There were no AEs or drug-related AEs leading to discontinuation of study therapy within the same PT reported in ≥ 2 subjects.

Table 45 Adverse events Leading to Discontinution by worst CTC Grade- All Nivolumab monotherapy treated subjects

System Organ Class (a) Preferred Term (a)	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74 Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	6 (8.1)	4 (5.4)	1 (1.4)
GASTROINTESTINAL DISORDERS	3 (4.1)	2 (2.7)	0
ABDOMINAL PAIN	1 (1.4)	0	0
COLITIS	1 (1.4)	1 (1.4)	0
STOMATITIS	1 (1.4)	1 (1.4)	0
VOMITING	1 (1.4)	0	0
INVESTIGATIONS	1 (1.4)	1 (1.4)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (1.4)	1 (1.4)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (1.4)	0	1 (1.4)
MALIGNANT NEOPLASM PROGRESSION	1 (1.4)	0	1 (1.4)
RENAL AND URINARY DISORDERS	1 (1.4)	1 (1.4)	0
ACUTE KIDNEY INJURY	1 (1.4)	1 (1.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Source: CA209142 Interim CSR[1] Table S.6.23a

Table 46: Drug-related AEs leading to disontinuation by worst CTC grade - All Nivolumab monotherapy treated subjects

System Organ Class (a) Preferred Term (a)	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74 Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	4 (5.4)	4 (5.4)	0
GASTROINTESTINAL DISORDERS	2 (2.7)	2 (2.7)	0
COLITIS	1 (1.4)	1 (1.4)	0
STOMATITIS	1 (1.4)	1 (1.4)	0
INVESTIGATIONS	1 (1.4)	1 (1.4)	0
ALANINE AMINOTRANSFERASE INCREASED	1 (1.4)	1 (1.4)	0
RENAL AND URINARY DISORDERS	1 (1.4)	1 (1.4)	0
ACUTE KIDNEY INJURY	1 (1.4)	1 (1.4)	0

MedDRA Version: 19.0
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: CA209142 Interim CSR[1] Table S.6.24a

Post marketing experience

Nivolumab was first approved on 04-Jul-2014 in Japan for unresectable melanoma and has since been approved in multiple countries, including the US and in the EU, and for other indications (eg, metastatic NSCLC, advanced RCC, and cHL [US and Argentina only; submitted in the EU]). Based on pharmacovigilance activities conducted by BMS Global Pharmacovigilance and Epidemiology, review of postmarketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab. The safety profile of nivolumab in the postmarketing setting remains favorable and similar to the profile established during clinical trials. To date, no new significant safety concerns have been identified based on global postmarketing reports.

Postmarketing data for nivolumab are subject to continued active pharmacovigilance monitoring and are reported as per applicable post-marketing safety reporting requirements, as well as periodically to global health authorities. For the most current company periodic assessment of postmarketing data and risk management actions, Investigator Brochure Version 15 and PBRER #3 (Jan-2016 to Jul-2016; submitted in separate procedure) should be consulted.

2.9.1. Discussion on clinical safety

For the purpose this variation, the safety dataset consist of 74 patients with MSI-H/dMMRmCRC treated in the monotherapy stage (mStage) in study CA209142, who received at least one dose of nivolumab. Of them, 53 patients had received 5FU-Oxa-Iri, most of them with ≥2L of prior therapy. Separate AE and SAEdata should be provided for this subset of patients, in order to better characterise the safety profile in this heavily pre-treated population. Safety data for the subgroup of 53 more heavily pretreated patients is presented and results are line with the expected profile for nivolumab and also consistent with the overall study population, thought this is not unexpected given that this subgroup represents around 72% of the total study population and thus, is the main driver of these results. Nevertheless, no substantial differences are expected in the less represented subset of less heavily pre-treated patients with dMMR-mCRC

At the date of the clinical database lock (19-Sep-2016), the majority of patients (n=40, 54.1%) continued in the treatment period. The Applicant presented an update on relevant safety data (e.g. deaths, SAEs, and selected AEs) from those patients. **:** the overall incidence of AEs (98.6%), drug-related AEs (70.2%), G3/4 AEs (overall 54%, drug-related 20.2%), SAEs (overall 47.3%, drug-related 12.2%) during treatment with nivolumab in this d-MMR-mCRC population is high. The underlying condition is contributing to a high degree to the overall toxicity, which is not unexpected bearing the mind the overall heavily pretreated population with a metastatic disease. However, it is reassuring that only in few cases these led to treatment discontinuation (12.2% overall AEs, 6.8% drug-related AEs) and that no deaths related to the study treatment have been reporting. At the same time, no unexpected findings have been reported for nivolumab.

The main reason for not continuing in the treatment period was disease progression (36.5%), followed by study drug toxicity (5.4%).
The median duration of study therapy was approximately 20 months for all monotherapy subjects, while at the time of the data cut-off this hadn´t been reached for subjects with prior 5FU-Oxa-Iri.
The majority of patients received over 90% of the planned dose intensity and did not require an infusion interruption or infusion rate decreased.
Dose delays were reported by 47.3% of patients. The most common reason for the delay was“AE” (56.7%), followed by “other reasons” (26.9%), and “not reported” (16.4%).
The most common treatment-related AEs for the nivolumab-treated patients were: fatigue (23%), diarrhea (21.6%), pruritus (13.5%), lipase increased (12.2%) and rash (10.8%). Most of them were mild-moderate in severity. In general, the overall safety profile in the mCRC does not differ from that observed in other indications.
Selected AEs
As with other authorized indications, selected AEs were more frequently reported inthe skin and GI SOCs. Most of them were of mild-moderate intensity. In general, the observed profile of selected AEs is largely similar to that observed in other indications.
In the pulmonary selected AEs, 2 patients experienced pneumonitis, a known treatment related AE for nivolumab. However, surprisingly, both AEs were considered as not treatment-related.
Skin selected AEs were reported in 32.4% of patients (n=24). Most of them were mild-moderate in severity and no grade 4-5 events were reported in this category. Regarding toxic epidermal necrolysis (TEN) cases, no cases were reported in this study.

SAEs and deaths
SAEs (all causalities) were reported in approximately 42% of patients, with 29.7% of patients reporting

grade 3-4 SAEs. There were five grade 5 SAEs, 4 of them due to malignant neoplasm progression, 1 of them reported as a sudden death (see below).
Regarding deaths, at the time of the data cut- off, 19 subjects (25.7%) had died, most of them due to disease progression and two patients due to "unknown" causes. Of these two patients, subject CA209142-3-8 was recovering from a Grade 3 diarrhea/colitis attributed as related to study drug.
AEs leading to discontinuation (all causality)were low (n=6, 8.1%), most of them due to ≥ grade 3 AEs (5 out of 6).The most frequent AE leading to discontinuation were GI disorders (3 out of 6, 4.1%).
In terms of drug-related AEs leading to discontinuation, similar trends can be observed.
Special populations
Elderly
Very few elderly and very elderly patients were included in the study. This should be adequately reflected in the SmPC and RMP.
Renal and hepatic impairment
Patients with pre-established renal/hepatic failure were not explicitly excluded from the pivotal study; it is not known whether any patients actually enrolled in the pivotal study. According to the information presented, patients with hepatic impairment were excluded, whilst patients with some degree of renal impairment might have entered into the trial. It is not clarified if this was the case in the end. If so, feedback on the drug tolerability would be appreciated in view of the actual limited experience of use of nivolumab in these patients.

Additional expert consultations

N/A

Assessment of paediatric data on clinical safety

N/A

2.9.2. Conclusions on clinical safety

In conclusion, the safety profile of nivolumab in patients with MSI-H/dMMRmCRC seems to be consistent with the profile known from previous indications. Minor issues remain for clarification.

2.10. Risk management plan

The RMP issue raised in the previous round has been addressed with the submission of an updated RMP version 9.1. The PRAC considered the RMP version 9.1 acceptable.

Please refer to the PRAC RMP assessment report for further details.

2.11. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.11.1. User consultation

We consider that the submitted variation type II submitted to extend the current approved therapeutic indication for OPDIVO to include "treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based therapy" does not involve a relevant impact on the PIL. Therefore, the company´s justification to not undertake further consultation with target patient groups, is considered acceptable.

2.11.2. Quick Response (QR) code

NA

3. Benefit-Risk Balance

The claimed indication is: OPDIVO is indicated for the treatment of adults with dMMR or MSI H mCRC after prior fluoropyrimidine-based therapy. The recommended dose and schedule of nivolumab monotherapy is 3 mg/kg administered as IV infusion over 60 minutes Q2W, which is consistent with existing approved dose and schedule of nivolumab monotherapy in adults.

Worldwide, CRC is the third most common form of cancer in men, with 746,298 cases (10.1% of the total) and second most common in women, with 614,304 cases (9.2% of the total) per year. Each year, there are about 608,000 deaths from colon cancer, which is approximately 8% of all cancer deaths, making colon cancer the fourth most common cause of cancer death. A small proportion of tumours including CRC have mismatch repair deficient (dMMR), which results in microsatellite instability high (MSI-H) (hereafter, MSI H/dMMR). The prevalence of MSI-H/dMMRin the metastatic CRC is 5%.

The dMMR status is emerging as a relevant biomarker in CRC, with a well-established prognostic and predictive role in the early stages though its role in the metastatic setting is not known.

The current application for mCRC is based on interim analysis of Study CA209142. CA209142 was a single arm, open-label, phase 2 study with nivolumab 3mg/kg IV Q2W as monotherapy or in combination with ipilimumab. Only results from the monotherapy were presented in the CSR.

Patients with disease progression during, after, or had been intolerant to therapy with 5FU-based chemotherapy (combined with at least irinotecan or oxaliplatin) with recurrent or metastatic MSI-H/dMMR CRC were included (n=74). MSI status was locally determined for inclusion and centrally confirmed. The primary endpoint was investigator-assessed ORR and secondary endpoint was IRRC-assessed ORR. Exploratory endpoints included PFS, OS, quality of life, tumour PD-L1 expression, and MSI test result concordance between local and central testing.

Benefits

Beneficial effects

Interim results from the CA209142 study in monotherapy treated subjects showed an **ORR per IRRC-assessed RECIST 1.1** in all treated of 27.0%. For the subgroup of patients receiving prior 5FU-oxa-iri, ORR of 22.6% was observed. These ORRs include CRs observed by IRRC in 2 of 74 subjects (2.7%); one of these received prior 5FU-Oxa-Iri. No CRs were determined by investigators.

The RECIST 1.1IRRC- and **investigator-assessed ORR** were highly concordant (> 90%): ORR for overall population was 31% (20.8%, 42.9%) and 26.4% (15.2, 40.2) for the subgroup with prior 5-FU-oxa-iri treatment.

Median DOR by IRRC has not been reached at the time of this interim CSR (min, max: 1.8+, 22.0+ months for the all treated subjects and 1.8+, 16.6+ for subjects with prior5FU-Oxa-Iri), responses were ongoing at the time of clinical cut-off.

The **median PFS by IRRC** was 7.6 months in the all nivolumab monotherapy treated subjects and4.9 months in subjects with prior 5FU-Oxa-Iri. For all nivolumab monotherapy treated subjects, the 6-month and 12-month PFS rates were 51.5% and 45.6%,respectively. Similar rates were observed for subjects with prior 5FU-Oxa-Iri (47.5% and 43.2%, respectively).

Median follow-up for **OS** was 7.41 months (range 0.3-25.3 months) and with 25.7% of deaths the median for OS was not reached (CI95 17.1-N.A.). For the all nivolumab monotherapy treated subjects the6-month and 12-month OS rate were 83.4% and 73.8%, respectively. For the subjects with prior5FU-Oxa-Iri, these OS rates were 80.5% and 69.8%, respectively.

Updated study results (cut-off Jan 2017) with +5 months additional follow up (minimum FU in all patients 11 months) are presented during the procedure, which are consistent to those initially submitted: ORR by IRRC 32.4% (2.7%CR, 29.7% PR, 33.8% SD), mDoR not reached, and DCR 63.5%.
Investigator-assessed median PFS increased from 9.59 to 14.29 months, for IRRC-assessed PFS this was from 7.59 to 8.31 months. Also an analysis of time to treatment failure was presented using the following as events: progression, treatment discontinuation, initiation of subsequent anti-cancer therapy, or death. Using IRRC assessment, 62.2% of patients had treatment failure after a median of 5.21 months. Using investigator assessment, failure percentage was 56.8% with a median of 8.02 months. TTF2 and PFS2 data were not collected and could therefore not be provided. With a total of 39 death events out of 74 patients, according to the IRRC, the median PFS is 8.3 months, 95%CI (3.0, NA). OS data are still immature and median is not yet reached: 23 events out of 74 patients, OS rate at 6 months 83.4%, OS rate at 12 months 73.4%.

PRO using EORTC QLQ-C30 and EQ-5D VAS questionnaires did not show clinically deteriorations and for some aspects improvements

Efficacy was observed regardless of tumour PD-L1 expression at baseline.

Analyses by subgroups are generally consistent to the overall study results.

Uncertainty in the knowledge about the beneficial effects

The main uncertainties in the knowledge about the beneficial effects are due to the following aspects to the important uncertainties on the actual prognostic and/or predictive value of the MMR status in the metastatic CRC setting and the lack of a controlled arm study, which make it impossible to put these results into context. Uncertainties are also related to the limited sample size, the heterogeneity of the studied population, and the immaturity of data for relevant clinical outcomes.

Study design- MSI-H CRC can be considered a distinct biological entity among colorectal cancers. It is unknown whether increased sensitivity to immune modulation could be translated into a better overall prognosis. Therefore, ideally a double-blind, placebo-controlled, randomised control study should have been performed to test the efficacy of nivolumab in this specific subpopulation of mCRC. AsdMMR CRC makes up approximately 225,000 of the total new CRC cases per year worldwide (11) and for pembrolizumab a phase 3 trial is ongoing in the same patient population, a controlled study would have been feasible. The Applicant also does not place the results into context, e.g. with historical control data, making it impossible to interpret the efficacy results at this point.
Besides the lack of control data, the preferred primary endpoint in clinical trials for mCRC is OS. In CA209142 investigator-assessed ORR was chosen as primary endpoint and IRRC-assessed ORR as secondary endpoint, but the relevance of these endpoints are questionable. PFS and ORR show moderate and low correlation with OS in mCRC. Moreover, by choosing ORR as primary endpoint, the sample size is not powered for OS and no type I error was planned. The study will not be able to detect efficacy results of more clinically relevant endpoints and the robustness of OS data is doubtful.

The study was not conducted according to the predefined plan regarding opening and closing of monotherapy cohorts and the sample size was increased. The internal validity of this single pivotal trial is therefore questioned. The Applicant has made an effort to explain the design and conduct in more detail and some of the explanations are acceptable considering the exploratory and descriptive nature of this

clinical study. However, in view of the study design and given the lack of control over the type I error, the internal validity of the results cannot be firmly concluded.

Patient characteristics-

RAS and *BRAF* mutational status was not known for all patients. Similarly, NRAS mutation was not tested in any patient. These are well known negative prognostic and predictive biomarkers and thus, the lack of a proper characterisation of the studied population for the mutational status of these markers is an important limitation of the dossier. Moroever, the study population of seemed to have a more favourable prognosis as around 25% of patients completed their most recent prior therapy >6 months ago and progression after start of first-line therapy is more than 40 months.

Immaturity of PFS and OS data-In the initially submitted dossier, both PFS and OS data were immature with a high number of censoring before the median for PFS and median is not reached for OS. PFS2 and time to next treatment data are lacking, but are relevant to determine if nivolumab has no detrimental effect on next-line treatments. An update of PFS and OS data has been provided, but OS remains immature.

Response evaluation- Not all patients were response evaluable, but the Applicant does not explain for all patientsthe missing data. Furthermore, the reason for discordant results between assessments by investigator or independent review is not clearly presented.

Responses in the CSR are analysed by tumour evaluation, but not with the use of tumour markers. Since immunotherapy is known to possibly induce pseudo-progression, analysing CEA levels and correlating CEA to PD-L1 expression levels is of additional value.

PD-L1 expression- PD-L1 expression was determined by counting positive tumour cells. PFS and OS was lower in PD-L1 positive patients compared to PD-L1 negative patients. This might suggest that PD-L1 expression in tumour cells is not a predictive biomarker. This is supported by the finding that in MSI colorectal cancer, the PD-L1 expression appears not to be on tumour cells, but rather on tumour-infiltrating lymphocytes and/or myeloid cells. This implicates that using PD-L1 expression on the tumour-infiltrating cells would be a more suitable biomarker and results of expression in the tumour environment should be provided. An update of study results based on PD-L1 tumour expression is presented, which show consistent results based either on a 1% or 5% cut-off. The majority of the studied population are <1% (63.5%) or <5% (77%), whilst information is missing for a small number of patients, i.e. 6 patients (8.1%) of the study population, results in this group should be taken with caution.

Post-hoc analysis for PD-L1 expression in tumour-associated immune cells (TAICs) was performed using a non-validated, qualitative assay with one pathologist defining expression as rare, intermediate of numerous without using numerical cut-off points. IRRC-assessed ORR was 21% in patients with rare PD-L1 expression in TAICs, 23.8% in the intermediate group, and higher in the numerous group, namely 43.5%. Results were given for 68 patients and the two patients with CR were not in the analysed group. In the Kaplan-Meier plot for survival, the curve for rare expression is above the one for intermediate and numerous expressions. The lines for intermediate and numerous cross and for the tails of the plot, the curve for numerous expression is below the one with intermediate expression. Although the numbers are low, this might suggest that rare expression is correlated with the best survival, which is contradicting the hypothesis of PD-1 inhibition in MSI-H mCRC. The MAH states that understanding the role for TAICs is an area of active exploratory investigation in ongoing trials, but also for CA209142 more efforts should be taken to investigate PD-L1 expression in both tumour and immune cells with a validated assay, especially because of the rationale of using anti-PD1 therapy in these tumours. The MAH should commit to continue investigating the role of PD-L1 expression in tumour cells and TAICs in their clinical program, including the population of MSI-H mCRC.

MSI discordance- Patients were included based on locally determined MSI status, but concordance between local and central testing was low. The concern is mostly related to the 14 out of 67 samples with central testing for which discordant local vs central results were observed. It is argued that this discordance rate (which is 21%, and not 19% as reported by the MAH) is in line with that reported in the literature (5-10%) if the variability of the limited sample size is accounted for, but this is not fully clarified.

Patient-reported outcomes-The interpretation of PRO data is difficult in an open label setting.
Subgroup analyses-Efficacy results are also reported for a not predefined subpopulation of patients that received prior fluoropyrimidine, oxaliplatin and irinotecan (prior 5FU-Oxa-Iri). This subgroup has a less favourable effect from nivolumab treatment, possibly due to a more developed disease with worse prognostic features. To be able to interpret the results in the prior 5FU-Oxa-Iri subgroup, progression since the start of primary therapy in the metastatic setting is provided.
Lower rates of tumour response are also seen in some relevant subgroups like, for example, elderly patients, patients with KRAS/BRAF mutations and non-Lynch forms, which raises the question on whether response to treatment might differ between sporadic vs germline MSI-H forms. An update of previous results is presented, which show quite consistent response rates across the relevant subgroups identified, i.e. age, Lynch syndrome, BRAF/KRAS mutations, which is reassuring. Nevertheless, the limited number of patients, lack of mature OS/PFS data and the lack of external supportive evidence preclude firm conclusions at this stage. Concerning NRAS status, no information is available as this was not tested in any patients. Since nowadays this is considered a potential marker of prognostic/response to treatment, a proposal to generate further information for all these biomarkers in the post-marketing will need to be discussed.

Risks

Unfavourable effects
The safety profile for the intended indication has been characterised in study CA209142.

Any-grade AEs were reported in 95.9% of all nivolumab monotherapy treated subjects. The most frequently reported AEs were diarrhoea (43.2%), fatigue (41.9%), anaemia (36.5%), and nausea (33.8%).Grade 3-4 AEs (regardless of causality) were reported in 48.6% of all nivolumab monotherapy treated subjects. The most frequently reported Grade 3AEs were lipase increased (9.5%), and anaemia (8.1%).

The most frequently reported drug-related AEs were fatigue (23.0%), diarrhoea (21.6%), pruritus (13.5%), lipase increased(12.2%) and rash (10.8%). Among all nivolumab monotherapy treated subjects, the most frequently reported Grade 3-4 drug-related AEs were lipase increased (8.1%) and amylase increased (2.7%). One subject with grade 2 pancreatitis was reported between first dose and 100 days after last dose of study therapy (extended follow-up) in one nivolumab monotherapy treated subject. The overall frequency of AEs (regardless of causality) leading to a dose delay or reduction was 31.1% among all treated subjects.

SAEs were reported in 41.9% of nivolumab monotherapy treated subjects. Grade 3-4 SAEs were reported in 29.7% of subjects. The most frequently reported SAEs were malignant neoplasm progression (8.1%), abdominal pain, intestinal obstruction, and vomiting (4.1% each), and diarrhoea, small intestinal obstruction, and pyrexia (2.7% each).

Drug-related SAEs were reported in 10.8% of nivolumab monotherapy treated subjects. Grade 3-4 drug-related SAEs were reported in 9.5% nivolumab monotherapy treated subjects. Drug-related SAEs consisted mainly of gastrointestinal events. An SAE of sudden death was reported for 1 subject, which was not considered drug-related by the investigator.

Disease progression was the most common cause of death. No deaths were attributed to study drug toxicity by the investigator. Two patients died due to unknown cause.

The frequencies of all-causality and drug-related AEs among all treated subjects for subgroups of gender, race and age, consistent with the AE frequencies in the overall treated population, although the interpretation of the data is hampered by the low number of patients.

From all the patients with MSI-H mCRC who received nivolumab monotherapy (N=74), 40 patients continued therapy (54.1%) and 34 (45.9%) discontinued treatment. Most patients discontinued treatment due to progressive disease (N=27; 36.5 %). Drug-related AEs leading to discontinuation were reported in 5.4% of nivolumab monotherapy treated subjects.

Abnormalities in haematology tests and electrolytes were primarily Grade 1-2 in nivolumab monotherapy treated subjects. The majority of subjects had normal TSH levels at baseline and throughout the treatment period. While on treatment, twenty (28.6%) patients had TSH values > upper limit of normal and eleven (15.7%) of patients had TSH values < lower limit of normal. The most frequently reported Grade 3-4 drug-related AEs were lipase increased (18.8%) and amylase increased (4.8%), from which half of cases were considered drug-related. The immunogenic potential of nivolumab was found to be low and did not appear to be affect safety profile.

Uncertainty in the knowledge about the unfavourable effects

At the time of the data cut-off (19-Sep-2016), the majority of patients continued in the treatment period. At that time, the minimum follow-up time was 5 months. An update with a minimum 11-month follow up is presented, which show consistent results.

The majority of patients received nivolumab in a 3rd line setting, with 53 patients receiving it in a later setting. The separate safety profile in the more heavily treated population (>4L) has not been provided.

Although no deaths were attributed to drug toxicities, one patient experience a sudden death while recovering from a grade 3 drug-related toxicity. The contribution of this AE to the outcome of the case is not currently known.

Very few elderly patients were included in the study. This hampers reaching a conclusion in this population subset.

The majority of subjects had normal TSH levels at baseline and throughout the treatment period. While on treatment, twenty (28.6%) patients had TSH values > upper limit of normal and eleven (15.7%) of patients had TSH values < lower limit of normal. More than 17 percent of patients had new onset increased TSH levels compared to baseline during the study and in 15.7%, at least one FT3/FT4 test was <LLN, suggesting true hypothyroidism. From a clinical point of view, however, it is important to know how many patients had overt thyroid dysfunction and in how many subjects therapeutic intervention/suppletion was needed. In this small study of only seventy patients, the incidence of either hypothyroidism or hyperthyroidism requiring medication was low and consistent with data from other nivolumab data. In the SmPC, adequate reference has been made towards the occurrence and treatment of endocrinopathies.

Frequencies of all-causality AEs (Grade 3-4)tended to be higher in the MSI-H CRC population compared to the pooled analysis of subjects in nivolumab monotherapy studies, however, this difference may be of limited interpretability due to low sample size. Grade 3-4 drug-related AEs lipase increased (8.1%) and amylase increased (2.7%) were also higher than in the pooled safety database. The Applicant was asked to discuss whether there is a biological rationale to explain the higher percentage of patients experiencing a grade 3-4 lipase increase and what might be the clinical consequence of such findings. There appears to

be no overall increase in the incidence of grade 3-4 lipase in mCRC patients as compared to patients using nivolumab for other indications. Only in one patient the increased lipase translated into a clinical pancreatitis, which is considered to be in the minority of patients. In the PI, increased lipase has been mentioned as a common AE.

Effects Table

Table 47 Effects Table for OPDIVO in the treatment of MSI-H/dMMRmCRC(updated data clinical cut-off: 02-Jan-2017)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR-investigator	Overall response rate assessed by investigator	%	31.3	N.A.	No comparative data	CSR
ORR- IRRC	Overall response rate assessed by IRRC	%	32.4	N.A.	No comparative data	CSR
PFS-investigator	Progression-free survival in months assessed by investigator	Median	14.3	N.A.	No comparative data	CSR
PFS- IRRC	Progression-free survival in months assessed by investigator	Median	8.3	N.A.	No comparative data	CSR
OS	Overall survival	Median	N.A.	N.A.	No comparative data	CSR
Unfavourable Effects						
Diarrhoea		Proportion	AE 43.2% G3/4 2.7% SAE 2.7%			
Fatigue		Proportion	AE 41.9% G3/4 4.1% SAE <1%			
Anaemia		Proportion	AE 36.5% G3/4 8.1% SAE <1%			
Nausea		Proportion	AE 33.8% G3/4 1.4% SAE 1.4%			
Tolerability			AE 95.9% SAE 41.9%			

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			≥ 1 dose delay: 25.7% ≥ 1 infusion interruption: 9.5% ≥ 1 infusion rate reduction 1.4% AE leading to discontinuations 8.1%			

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Investigator-assessed ORR was 31.3% (CI95 20.8-42.9%) in 74 patients with MSI-H mCRC, ORR by IRRC was 32.4%, with median duration of responses not yet reached with a minimum 11month follow up of patients. Updated PFS results show a median of 14.3 months and 8.3 months per investigator and IRRC assessment, respectively. Median OS has not yet been reached. Observed responses rates in patients with metastatic MSI-H CRC treated with nivolumab seem encouraging when compared with those described for cetuximab monotherapy, panitumumab, regorafenib, and trifluridine/tipiracil (TAS102) for the overall mCRC population, with ORRs in metastatic CRC of 10.8% (CI95 4.1-20.2%), 8.23% (CI95 5.02-12.55%), 1% (CI95 not reported), and 1.6% (CI95 0.7-3.1%), respectively (15-18). However, no historical data are available for the subset of patients with dMMR mCRC, which makes it difficult to put these results in context. Furthermore, contrary to the early stage CRC setting where dMMR is a known marker of good prognostic and poor response to 5-FU based adjuvant chemotherapy, the actual prognostic and/or predictive role of this biomarker in the metastatic setting remains to be elucidated, which further complicates interpretation of the benefit with a lack of control data. In addition, although the response rates suggest therapeutic activity, the benefit cannot be determined also due to the immature results for the preferred endpoint of overall survival, even more in view of the modest correlation between ORR and survival in CRC.

The safety profile of nivolumab monotherapy arm of the CA209142 study has been characterised. No new safety concerns were identified in MSI-H CRC setting except for the high rate of patients experiencing anticholinergic syndrome, Frequencies of all-causality AEs (Grade 3-4)tended to be higher in the MSI-H CRC population compared to the pooled analysis of subjects in nivolumab monotherapy studies, however, this difference is difficult to interpret due to low sample size. Overall, the safety profile of nivolumab in this particular setting is favourable and is considered not to impact the B/R assessment in a negative way.

Benefit-risk balance

The benefit risk balance for the claimed indication is considered negative at present. The toxicity of nivolumab seems manageable and no new safety concerns have been identified. However, the benefit of nivolumab in the subgroup of patients with dMMR mCRC cannot be determined given that control data are lacking (neither concurrent nor historical), and ORR is not considered a valid substitute for clinical benefit.

In addition the internal validity of the data is questioned due to possible selection bias of a study population with a more favourable prognosis, proper definition of the study population by MSI status, and uncertainties regarding type I error control on clinical endpoints caused by deviating of the original study

design (over-enrolment in stage 2 and opening up two studies), that render the results more exploratory than confirmative evidence.

Discussion on the Benefit-Risk Balance

The evidence presented is considered insufficient to support the claimed indication for nivolumab in the treatment of patients with MSI-H mCRC after prior fluoropyrimidine-based combination therapy, most importantly due to the non-comparative study design and the immaturity of data in relevant clinical endpoints. To value the efficacy results, a controlled trial should have been performed, which is regarded feasible for the sought indication. The main drawbacks identified are discussed in some detail below:

- The MAH argues that patients with MSI have a worse prognosis and that response to therapy is lower than that in non-MSI (MSS) mCRC patients. However, current knowledge in the field is limited and no sound evidence has been provided to substantiate that this general statement is true across the different lines of treatment. Contrary to the situation in early stages of CRC (II and even III) where the presence of MMRd is regarded as a marker of good prognosis and of poor response to 5-FU based adjuvant chemotherapy regimens, the role of MMR status as a prognostic and predictive marker of response in the metastatic CRC setting is an area not well elucidated at the present time. It is agreed that treatment options available in late lines offer modest benefits for the overall mCRC population, but the actual benefit in patients with dMMR mCRC in 2nd and later lines of treatment is uncertain, and not necessarily worse than that seen in the general mCRC population. In this context and in the absence of comparative data over current SOC for these patients, it is difficult to interpret the study results provided, in particular when treatment options are available with well-established efficacy and safety (particularly in earlier lines of treatment). This fact is precluding a benefit/risk assessment at the present time. Beside this, it is important to note the following consideration:

  The CHMP considers that results in late 3rd/4th lines may be encouraging given the poor prognostic and high toxicity of available treatment options, but even there the immaturity of the data preclude any firm conclusion at present. The main concern stands for the 2nd L mCRC setting, where well established treatment options are available for the general mCRC, including patients with dMMR. In fact, it is unknown if patients with dMMR benefit differently from these treatment options. Furthermore, it is uncertain to what extent treatment with nivolumab may interfere with the response to subsequent treatments, thus, placing nivolumab in second line can hardly be supported in the absence of a truly convincing evidence of benefit over current SOC. So, further justification of the claimed indication in view of the lack of context and difficulties in interpreting the study results is needed for the overall intended target population, which should include a separate discussion for the second vs later lines of mCRC treatment.

- Furthermore, the required primary endpoint in clinical trials for mCRC is OS. The relevance of the chosen primary and secondary endpoints of investigator- and IRRC-assessed ORR are questionable. The provided additional analyses with OS data for the different responses cannot resolve this uncertainty. With these results the MAH concludes that durable response and sustained disease control are predictive of favorable OS outcomes in this population. However, the CHMP disagrees that this can be concluded based a very small sample size, immature OS data, no comparative arm and lack of external validation. Moreover, in a literature-based review based on 20 trials, ORR and OS correlate poorly (Cremolini et al. Cancer Research and Treatment 2016). Updated OS data are still immature and comparisons to other treatments cannot be reliably made.

- In addition, internal validity is questioned due to possible selection bias of a study population with a more favourable prognosis, lack of proper definition of the study population by MSI status, and uncertainties regarding type I error control on clinical endpoints caused by deviating of the original study design (over-enrolment in stage 2 and opening up two studies), rendering the results more exploratory than confirmative evidence.

In conclusion, the single pivotal, non-controlled study of nivolumab monotherapy in MSI-H recurrent and metastatic CRC after fluoropyrimidine based combination therapy does not provide compelling evidence to approve the proposed indication at this time.

The CHMP considers a **SAG-Oncology** should be convened to provide scientific expertise on the uncertainties identified in this application (see section 1).

4. Recommendations

The application for:
Extension of indication to include treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine based therapy for OPDIVO.

As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated in order to add the new indication and update the safety information. The Package Leaflet is updated in accordance.
RMP version 9.0 is submitted with this application,

☒**is not approvable** since major objection and other concernshave been identified, which preclude a recommendation at the present time (See annex 3).

☐could be approvable since other concerns <has><have> been identified, which preclude a recommendation at the present time.

The details of these <major objections>< other concerns> are provided in Annex <> (RSI 1) and should be addressed in writing <and in an oral Explanation>.

☐is approvable <since other concerns <major objections><has><have> all been resolved>.

Annex 1: CHMP proposed Request for Supplementary Information

Clinical pharmacology aspects

Major Objections

None

Other concerns

1. Pharmacokinetics of nivolumab is described by a time-varying clearance. Reasons for this change in clearance over tie are not entirely clear. The inter-subject variability in the change in clearance over time is rather high and the Applicant is requested to discuss if the change in nivolumab clearance over time is related to efficacy e.g. change in tumour burden, ORR/PFS.

Clinical efficacy aspects

Major Objections

2. The evidence presented to support the proposed indication is considered insufficient to determine the benefit/risk at this time due to difficulties in the interpretation of the results due to lack of context, uncertainties regarding MSI test results, and lack of mature data for relevant clinical outcomes like OS. Therefore, the following aspects should be addressed before a final conclusion can be drawn:

    a. Although only 4% of mCRCs are MSI-H, the incidence of mCRC is high and therefore, there is no justification for the lack of a control arm. The Applicant is asked to elaborate on the choice for the single arm design, clarify the unplanned opening and closing of the trial and the consequences for the internal validity of the trial and how the effect of nivolumab should be compared to the results of current available treatments in the dMMR subpopulation, both sporadic and germline forms and across the different lines of treatment.

    b. Central testing showed a substantial number of discordant results between local and central MSI testing. The Applicant is requested to discuss possible explanations, but more importantly the discussion should also cover the general technical challenges with MSI testing and how the indicated population can be clearly defined in clinical practice. Moreover, efficacy results, including PFS and OS, should be provided for centrally confirmed MSI-H tumours and compared with patients for whom there was no central confirmation.

    c. Investigator-assessed ORR was chosen as primary endpoint, which in literature shows poor correlation with gain in survival and is therefore not considered a valid surrogate endpoint. OS is the preferred primary endpoint, but survival data are currently immature. The Applicant should provide updated OS data and discuss them in relation to the answer to part a of this question on the interpretation of the effect of nivolumab compared to the results of current available treatments in the dMMR subpopulation across the broad spectrum of the intended target population.

    d. Considering the exploratory nature of the evidence provided, the Applicant should also discuss on any plans to generate additional confirmatory data within the mCRC setting.

3. The proposed indication for nivolumab is the treatment of dMMR or MSI-H mCRC after prior fluoropyrimidine based therapy. The study population included patients with recurrent or metastatic patients being progressive during, after, or intolerant to ≥1 line treatment for their metastatic disease, which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan. The indication should reflect the studied population and therefore the Applicant is asked:
    a) To clarify the number of patients included with recurrent disease and adjust the proposed indication as needed
    b) Adjust the indication to fluoropyrimidine-based combination therapy.

Other concerns

4. Clarification is requested on the IHC results, i.e. on the number of patients with MMRd and loss of expression of MLH1/PMS2 proteins vs MSH2/MSH6 proteins.

5. There are a high proportion of patients with unknown forms of MMRd, i.e. germlinevs sporadic. Clarification is provided on the reasons why these patients have not been classified and efforts to do so should be made.

6. The study provided consisted of 3 cohorts: non-MSI-H cohort, MSI-H cohort, and cohort C3 (MSI-H subjects who have not had prior therapy for their metastatic disease). Information has only been presented for the MSI-H previously treated cohort. The Applicant is requested to present available information for the two other cohorts, in particular those with non-MSI-H, in order to further support the hypothesis that benefit from nivolumab is restricted to the MSI-H subset of patients.

7. Regardless of the type of therapy received, 75.7% had progressed within 6 months of their most recent regimen, with 64.9% progressing within 3 months. Considering the protocol inclusion criteria, which require mCRC progression during, after, or intolerance to ≥ 1 line treatment(s) for their metastatic disease, one would expect that nearly 100% of patients would have progressed within 6 months (an even within 3 months) of their most recent regimen. This speaks in favour of a rather benign mCRC population. The Applicant is invited to clarify this finding and discuss on the relevance of the high rates of stable diseases considering that a substantial portion of patients did not have a progressive disease.

8. In general, subgroup analysis presented show rather consistent results, with some exceptions noted, i.e. the lower rates of response in the elderly population and in patients with mutatedBRAF. Also, in line with these results, lower rates of response are seen in the subset of patients with non-Lynch Syndrome. The Applicant should clarify to what extent these might be representing sporadic MSI cases and discuss the extent to which lower efficacy can be expected in these sporadic cases.

9. Analyses are presented by PD-L1 expression, which is based on tumour cell expression. Given the immaturity of the results, a new analysis should be provided.

10. Mutational status for *KRAS*, *NRAS* and *BRAF* for all 74 patients should be reported and be related to efficacy results, because the mutational status has prognostic and predictive value and could influence efficacy results.

11. The Applicant should clarify how identified protocol deviations were accounted for in the analysis of results presented

12. The Applicant should clarify the reasons why 37 (14.2%) subjects in the CA209142 study did not enter the treatment period despite being enrolled.

13. Clarification is also requested about the single case where maximum clinical benefit was reported as the reasons for treatment discontinuation, given that this was not a reason established in the protocol.

14. Internal validity is also questioned regarding the conduct of the single pivotal trial.
    a. The Applicant should explain how the number of confirmed responses under

monotherapy could change from 4 confirmed responses and 2 in SD to 7 confirmed responses.

b. Although the number of 7 confirmed responses formally enabled to open the monotherapy arm, actually both monotherapy and combination therapy were open, while type I error for ORR over the whole study was only planned conditional that either the mono- or the combination arm is open. Therefore it is not clear if and how type I error control is protected for ORR (e.g. if the Applicant would in a later time would also apply for combination therapy using this trial's data) and the Applicant should explain this.
c. The second stage of monotherapy arm raises several issues. Firstly, no testing as preplanned in the Simon two-stage design was reported. Secondly, an unplanned sample size increase. To clarify the impact of this, proper inference is requested (e.g. Koyama & Chen, Stat in Med 2007). Thirdly, the analysis population was changed (from those centrally MSI tested to those locally MSI tested) from stage 2 onwards which makes the design so adaptive that the impact on type I error of ORR should be discussed. An analysis using the first 29 centrally MSI confirmed in second stage, i.e. as planned, would at least be expected.
d. Sample size was powered for analysis of ORR, but for more clinically relevant endpoints, such as PFS and OS, no type I error control was planned. The Applicant should discuss the robustness of these results incorporating at least an analysis with confidence levels adjusted (simultaneously) for the two-stage design, increased sample size at stage 2 and for a 2.5% one-sided (instead of 5% one-sided as planned for ORR) perspective.

15. An update for PFS data is requested, as well as analyses for time to next treatment (TTF), TTF2 and PFS2.

16. Effect on PFS and OS was lower in PD-L1 positive patients. This might suggest that PD-L1 expression in tumour cells is not a predictive biomarker. In MSI colorectal cancer, the PD-L1 expression appears not to be on tumour cells, but rather on tumour-infiltrating lymphocytes and/or myeloid cells. To understand the mechanism of action of nivolumab in MSI-H mCRC it is essential to analyse, amongst other biomarkers, PD-L1 expression on the tumour-infiltrating cells and to correlate expression with efficacy.

17. Efficacy results are also reported for a not predefined subpopulation of patients receiving fluoropyrimidine, oxaliplatin and irinotecan (prior 5FU-Oxa-Iri). This subgroup has a less favourable effect from nivolumab treatment, possibly because this subgroup has a more advanced disease with worse prognostic features, which is also suggested by the higher number of prior lines of chemotherapy. In subgroup analyses nivolumab is less effective when time from initial diagnoses is longer and when the number of prior lines of therapy is higher. The lower response rates are therefore not unexpected and the Applicant is requested to analyse progression since the start of first-line therapy in the metastatic setting for patients with prior 5FU-Oxa-Iri and to compare this with the all treated patient group.

18. From the all monotherapy treated group 68 patients were response-evaluable by investigator assessment and 65 by IRRC. For the investigator assessments, responses in 4 patients were 'unable to determine' having no on-study evaluations because of early discontinuation or death. IRRC assessment could not determine responses in 5 patients (3 had no on-study evaluation because of early discontinuation or death; 2 were censored for subsequent radiotherapy) and response was not reported for 1 patient (no scan sent to IRRC). First of all, this decreases the already small sample size and secondly, not all missing evaluations are accounted for. The Applicant is asked to explain the

number of patients not being evaluable for response.

19. The Applicant demonstrated the number of disconcordant results between assessments by investigator or independent review, but case by case discrepancy per outcome of the tumour evaluation (i.e. CR, PR, PD, or SD) should also be shown.

20. Immunotherapy is known to possibly induce pseudo-progression which could be misinterpreted as progression during tumour evaluation scans. Using tumour markers, such as CEA levels, could guide the decision whether a patient is progressive or not. Therefore, the Applicant should provide CEA levels for the studied population at baseline, during treatment and follow-up and in correlation with PD-L1 expression levels.

Clinical safety aspects

Major Objections

None

Other concerns

21. Two pulmonary selected AEs were reported in the study. According to the interim CSR (Table S.6.101), both of them were "pneumonitis" (both <grade 3). Considering that "pneumonitis" is a known ADR for nivolumab, it is unclear how these two events were considered not treatment related by the investigator. The MAH should provide further details on these pneumonitis AEs and discuss their causality assessment.

22. Separate AE and SAE data should be provided for the 53 patients had received 5FU-Oxa-Iri, in order to better characterise the safety profile in this heavily pre-treated population.

23. At the date of the clinical database lock (19-Sep-2016), the majority of patients (n=40, 54.1%) continued in the treatment period. The Applicant should present an update on relevant safety data (e.g. deaths, SAEs, and selected AEs) from those patients.

24. Two patients died due to "unknown" causes. Of these two patients, subject CA209142-3-8 was recovering from a Grade 3 diarrhoea/colitis attributed as related to study drug. The MAH should discuss to what extent the prior ADR could have contribute to the outcome of this case. Since no deaths were attributed to drug toxicity, the MAH should also discuss their causality assessment of this death.

25. Very few elderly and very elderly patients were included in the study. This should be adequately reflected in the SmPC and RMP.

26. Patients with pre-established renal/hepatic failure were not explicitly excluded from the pivotal study; it is not known whether any patients actually enrolled in the pivotal study. If that would be the case, separate safety data should be provided for these patients.

27. According to the data submitted, the safety profile of nivolumab in MSI-H CRC population has a slight higher rate of AEs Grade 3-4 (regardless of causality and drug-related) than previously submitted pooled data of nivolumab monotherapy in melanoma, NSCLC and RCC. Specifically, the Applicant is asked to discuss whether there is a biological rationale to explain the higher percentage of patients experiencing a grade 3-4 lipase increase (8.1%) compared to the pooled analysis (1.3%) and what

might be the clinical consequence of such findings.

28. Higher frequencies of any grade and Grade 3-4 drug-related AEs were reported in US/Canada subjects (87.1% and 29.0%, respectively) versus Europe (59.0% and 15.4%, respectively) or Rest of World (25.0% [any grade]). The Applicant is asked to discuss these discrepancies in incidence of AEs.

29. The Applicant is asked to discuss the high reported rate of anticholinergic syndrome (up to 50%) in all age groups as this is not considered a known AE of nivolumab and also not a common diagnosis in clinical practice.

30. The majority of subjects had normal TSH levels at baseline and throughout the treatment period. While on treatment, twenty (28.6%) patients had TSH values > upper limit of normal and eleven (15.7%) of patients had TSH values < lower limit of normal. More than 17 percent of patients had new onset increased TSH levels compared to baseline during the study and in 15.7%, at least one FT3/FT4 test was <LLN, suggesting true hypothyroidism. From a clinical point of view, however, it is important to know how many patients had overt thyroid dysfunction and in how many subjects therapeutic intervention/suppletion was needed.

RMP

None

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Annex 2: CHMP assessment report of the MAH responses to the Request for Supplementary Information

Non clinical aspects

N/A

Clinical aspects

Clinical pharmacology aspects

Major Objections

None

Other concerns

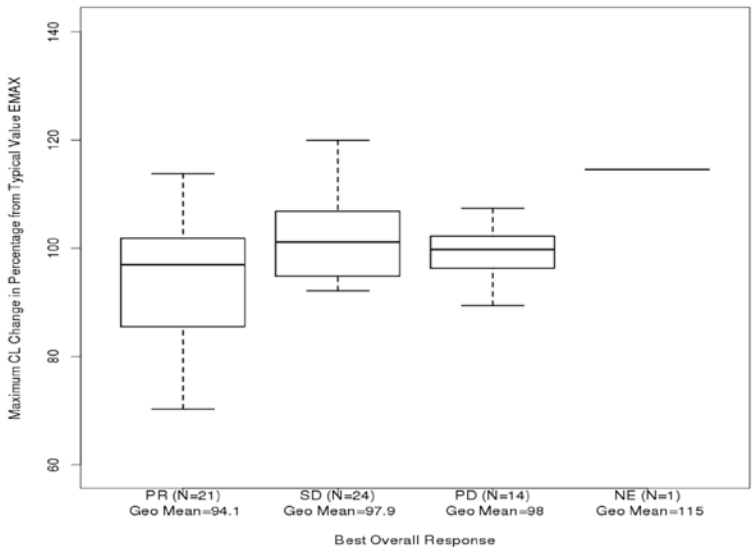
1. Pharmacokinetics of nivolumab is described by a time-varying clearance. Reasons for this change in clearance over tie are not entirely clear. The inter-subject variability in the change in clearance over time is rather high and the Applicant is requested to discuss if the change in nivolumab clearance over time is related to efficacy e.g. change in tumour burden, ORR/PFS.

Summary of MAH answer

Nivolumab total body clearance (CL) was found to be characterized by a time-varying CL described using a sigmoid-maximum effect (Emax) function, with a maximum decrease of approximately 26% from baseline values. Liu et al. described changes in nivolumab CL linked to response to treatment.3 The authors demonstrated that the CL decreases over time as the subjects' condition improved; however, tumour dynamics were not fully able to explain these changes in CL. Other factors including delay in reversal of disease symptoms, such as protein metabolism (the primary route of monoclonal antibody CL), may also contribute to the variability in changes in CL.

The effect of response to nivolumab treatment on CL was not investigated for CRC subjects, as previous analyses demonstrated that baseline tumour burden was not likely to be clinically relevant. Below, the maximal change in CL versus response status was evaluated for subjects with CRC, from CA209142 (Figure 1). It should be noted that only 60 subjects from CA209142 had PK estimates available to plot, with 21 having partial response (PR), 24 having stable disease (SD), 14 having progressive disease (PD), and one subject who was not evaluable (NE). The median values for maximal change in CL were similar across those subjects who had PR, SD, and PD. Further, given the variability across these response groups, there are no clear trends in maximal change in nivolumab CL and response status. This would appear to suggest, as Liu et al. had discussed, that response cannot fully explain changes in CL. Therefore, subject response status can help explain, but is not solely responsible for, the variability in change in CL. Other patient factors, such as baseline albumin and baseline disease state, may contribute to this variability.

Figure 1: **Maximal Change in Nivolumab Clearance Versus Best Overall Response in Subjects with MSI-H CRC, Study CA209142**



Source: global\pkms\data\CA\209\C19\prd\eu-regulatory\final\R\plots\Per-CL-change-by-BOR.png
Abbreviations: NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

CHMP assessment

The population PK analysis showed that nivolumab clearance changed over time. Liu et al. (2017) found that the time-varying clearance of nivolumab was associated with disease response and the magnitude of this clearance reduction was greater in the responders (CR+PR) than nonresponders (SD+PD) (Figure 1C below). It was suggested that the CL decreases over time as the subjects' condition improved, though there was a great overlap between change of clearance over time in responders and non-responders. For mCRC, though differently presented (Figure 1 above), there was no correlation between decrease in CL and response. This might be in part by absence of subjects with complete remissions (CR) for which the decrease in clearance was largest in NSCLC, RCC and melanoma. In conclusion, for mCRC data are insufficient to demonstrate a relationship between response and decrease in clearance over time. However, based on data obtained from other tumour types, the decrease in clearance over time appears to be partly associated with response.

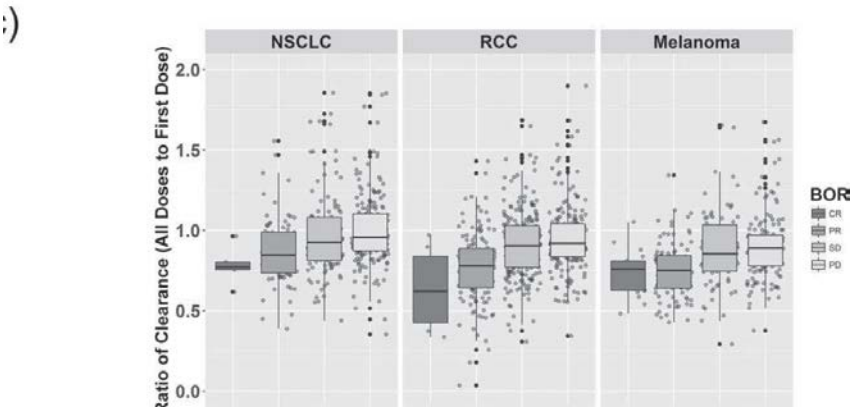


Figure 1C Evaluation of nivolumab time-varying PK based on the popPK modelling (from Liu et al., 2017).The ratio of the TSPK model estimated clearance using data from all doses (CLTSPK) to the clearance estimated based on the first dose (CLTSPK1st-dose).

Issue resolved

Clinical efficacy aspects

Major Objections

2. The evidence presented to support the proposed indication is considered insufficient to determine the benefit/risk at this time due to difficulties in the interpretation of the results due to lack of context, uncertainties regarding MSI test results, and lack of mature data for relevant clinical outcomes like OS. Therefore, the following aspects should be addressed before a final conclusion can be drawn:

    e. Although only 4% of mCRCs are MSI-H, the incidence of mCRC is high and therefore, there is no justification for the lack of a control arm. The Applicant is asked to elaborate on the choice for the single arm design, clarify the unplanned opening and closing of the trial and the consequences for the internal validity of the trial and how the effect of nivolumab should be compared to the results of current available treatments in the dMMR subpopulation, both sporadic and germline forms and across the different lines of treatment.

    f. Central testing showed a substantial number of discordant results between local and central MSI testing. The Applicant is requested to discuss possible explanations, but more importantly the discussion should also cover the general technical challenges with MSI testing and how the indicated population can be clearly defined in clinical practice. Moreover, efficacy results, including PFS and OS, should be provided for centrally confirmed MSI-H tumours and compared with patients for whom there was no central confirmation.

    g. Investigator-assessed ORR was chosen as primary endpoint, which in literature shows poor correlation with gain in survival and is therefore not considered a valid surrogate endpoint. OS is the preferred primary endpoint, but survival data are currently immature. The Applicant should provide updated OS data and discuss them in relation to the answer to part a of this question on the interpretation of the effect of nivolumab compared to the results of current available treatments in the dMMR subpopulation across the broad spectrum of the intended target population.
    h. Considering the exploratory nature of the evidence provided, the Applicant should also discuss on any plans to generate additional confirmatory data within the mCRC setting.

Summary of the MAH´s response

An important difference to note throughout this response: the term IRRC (Independent Radiologic Review Committee) used in the CSR is replaced by BICR (Blinded Independent Central Review) to bring the wording in line with that used across the nivolumab program and current literature across the field. IRRC and BICR may be used interchangeably in tables and figures.
In tables and figures, MSI-H/dMMR CRC and dMMR/MSI-H CRC can be used interchangeably with 'dMMR or MSI-H metastatic CRC'.

Efficacy Update
Responses to questions in this RSI are referencing updated efficacy data with a clinical cut-off of 02-Jan-2017 (database lock [DBL] 06-Feb-2017). In this updated analysis, all 74 patients were analysed for efficacy as well as the 53 patients who received prior 5-FU-Oxa-Iri. This update provides an additional 5 months of follow-up (minimum follow-up of 11 months) since the time of the DBL used to support the filing. Efficacy with nivolumab 3 mg/kg confirms the durability of response and continues to compare favourably to historical control. Since the initial analysis, 4 additional responders were reported.

Responses continue to be observed across all subgroups of patients, including BRAF MT, Lynch, and non-Lynch patients. The added follow-up allows for better characterization of longer term OS, an important clinical manifestation of the durable anti-tumour activity observed with immunotherapy agents. (Table 1)

Table 1: Summary of Efficacy Results (CA209142)

	Nivolumab (n=74) BICR	Nivolumab (n=74) Investigator
Confirmed objective response, n	24 (32.4)	23 (31.1)
(95% CI)	(22.0, 44.3)	(20.8, 42.9)
Complete response (CR), n (%)	2 (2.7)	0
Partial response (PR), n (%)	22 (29.7)	23 (31.1)
Stable disease (SD), n (%)	25 (33.8)	28 (37.8)
Median duration of response		
Months (range)[a, b]	Not reached (1.4+, 26.5+)	Not reached (3.9+, 26.5+)
Median time to response		
Months (range)	2.79 (1.2, 22.6)	2.76 (1.2, 16.1)
Disease control rate[a], n (%)	47 (63.5)	51 (68.9%)
(95% CI)	(51.5, 74.4)	(57.1, 79.2)
Progression-free survival		
Events	39	36
Median (months) (95% CI)	8.3 (3.0, N.A.)	14.3 (4.3, NE)
Overall survival		
Events		23
Median (months) (95% CI)		N.A. (18.0, N.A.)
6-month rate (%) (95% CI)		83.4 (72.6, 90.2)
12-month rate (%) (95% CI)		73.4 (61.5, 82.1)

[a] Symbol + indicates a censored value

[b] Median computed using Kaplan-Meier method.

Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination.

Abbreviation: N.A.= not available

Source: Table S.5.1.1A (BOR per IRRC), Table S.5.1.1B (BOR per inv), Table S.5.1.7A (time to OR and DOR per IRRC), Table S.5.1.7B (time to OR and DOR per inv), Table S.5.2.1A (PFS per IRRC), Table S.5.2.1B (PFS per inv), Table S.5.3.1 (OS) of Appendix 1

a. Although only 4% of mCRCs are MSI-H, the incidence of mCRC is high and therefore, there is no justification for the lack of a control arm. The Applicant is asked to elaborate on the choice for the single arm design, clarify the unplanned opening and closing of the trial and the consequences for the internal validity of the trial and how the effect of nivolumab should be compared to the results of current available treatments in the dMMR subpopulation, both sporadic and germline forms and across the different lines of treatment.

Single-Arm Study Design

The incidence of dMMR/MSI-H in the metastatic colon cancer population is noted to be approximately 4%. The 3-year OS to typical 1L chemotherapy in a trial of bevacizumab +FOLFIRI is only 34.5%, and, specifically for the dMMR population, the mOS is only 15.0 months from first line chemotherapy therefore, it can be expected that only a proportion of this small patient population would be available to receive later line therapies. Furthermore, many experts conclude that in the setting of mCRC, MSI-H tumours do have distinct behaviour and are expected to have lower disease control rates when treated with oxaliplatin-based first line therapy. The available evidence, from a pooled analysis of 4 1L trials, suggests that dMMR or MSI-H metastatic CRC (mCRC) patients have poor prognosis and derive less benefit in trials of chemotherapy. Additionally, compared with proficient MMR pMMR/microsatellite-stable tumours, dMMR or MSI-H CRCs are associated with a higher mutational burden and tumour neoantigen load and dense immune infiltrate. Therefore, inclusion of a control arm in a late line trial focused on a small patient segment with potentially poorer prognosis and higher unmet need was not considered appropriate in the context of the emerging clinical data.

These considerations in this rare biomarker selected population guided the decision to generate preliminary data in a single-arm setting. This was expected to facilitate a more rapid assessment and

confirmation of clinical activity in the dMMR or MSI-H mCRC population. Ultimately, inclusion of a control arm in a late line trial focused on a small patient segment with potentially poorer prognosis and higher unmet need was not considered appropriate in the context of the emerging clinical data.

Recognising the limitations of a single-arm design, but considering observations with nivolumab in other tumours, data from study CA209142 suggests that subjects receiving treatment with nivolumab have the opportunity to derive clinically meaningful benefit, with durable responses. The median DOR has not yet been reached for any of the responders on the study. The Sponsor is continuing to follow up the subjects and characterize long-term benefit in the initial cohort, while planning to enroll a larger cohort to further characterize the benefit/risk in this patient population and increase confidence in the robustness of these results.

Internal Validity
Despite the pause of enrollment between mStage1 and mStage2 and slight over enrolment of the monotherapy cohort, the results of ORR and DOR are robust regardless of the statistical methodologies used (refer to response to Q14a and Q14c for additional details). In addition, ORR and DOR results are consistent between BICR and investigator assessments, across patient population, and regardless of the central confirmation of MSI-H.

The mechanistic rationale and early published data led to many patients from this niche population being referred to enroll into study CA209142. Due to limited knowledge about the time to response from nivolumab (and nivolumab in combination with ipilimumab) as well as operational difficulties in obtaining centrally confirmed MSI-H testing results in real time, the Sponsor enrolled a higher number of patients than initially planned (see also response to Q14a).
The ongoing study CA209142 lead to an increasing body of evidence of the potential long-term benefit from nivolumab for this patient population with limited treatment options. It was considered important to share data publically with the scientific community as follow-up duration increased. Publication of promising early data for nivolumab and other anti PD-1 agents led to changes in treatment-practice guidelines (NCCN, ESMO) including recommendations for immunotherapy in the treatment of mCRC, noting dMMR/MSI-H to be predictive of benefit from checkpoint inhibitors.
The opening and closing of the study enrollment to adapt to the complexity of MSI-testing methodology (refer to response to Q14a), and interim analyses to facilitate publication, are acknowledged as potential limitations to establishing the internal validity. However, given the open label nature of the study, the consistency of the outcomes with what has been reported with a similar mechanism of action in another MSI-H mCRC study as well as across other tumour types for nivolumab, and the BICR review of the primary endpoint of investigator assessed ORR, BMS remains confident in the reliability of the data (See also response to Question 2c below).

Context Relative to Currently Available Treatments

Literature suggests that approximately 3% of all CRC cases (at first diagnosis) are germline (Lynch syndrome). Younger patients are more likely to have Lynch Syndrome; Lynch syndrome patients are unlikely to have BRAF mutation.
Approximately 12% -17% of colorectal tumours, across all stages, are dMMR or MSI-H, depending upon the methods used to detect it, and the majority of MSI-H CRC cases are reported as being sporadic, and more frequently associated with an older patient population that may also frequently (~one-third) present with BRAF mutations. Literature on the prognostic significance of germline versus sporadic CRC is still emerging, however, reflecting on the fact that there is reported to be a higher prevalence of patients with sporadic mutations relative to germline, and that the former tend to be an older population and more likely to be carrying a BRAF mutation, it would not be unexpected that outcomes may be worse in some patients with sporadic mutations.
However, in the context of the small patient population and limited data in the public domain, it is difficult to definitively conclude on the predictive and/or prognostic significance of germline versus sporadic mutations in the metastatic setting.
Historical comparisons in 2L or later mCRC are limited in that neither Lynch Syndrome diagnosis nor MSI status has been published for most mCRC trials. Given that this is an emerging field, treatment recommendations for dMMR/MSI-H mCRC prior to the emergence of data supporting a role for PD-1 inhibitor therapy have fallen under the recommendation for unselected mCRC.
In 2L mCRC, ORR for contemporary combination regimens ranges between 11%-22% and mPFS between 6-7 months. In the 3L/4L, ORR with regorafenib is only 1% with a mPFS of 1.9 months and OS of 6.4

months. Similar results were demonstrated for Trifluridine/tipiracil HCl. See Table 2 for available therapies for this population compared to the data for nivolumab in the dMMR/MSI-H population by local testing.

Table 2: Commonly Used Agents for Standard of Care

Line of Therapy	mCRC subpopulation	Agent	Response Rate	PFS (months)	OS (months)
2L	KRAS mut	FOLFOX or FOLFIRI + bevacizumab[12, 13] or aflibercept[16] or ramucirumab[14]	11% - 22%	6 - 7	12.9 - 13.5
2L	KRAS WT	FOLFOX or FOLFIRI + bev[12,13] or ramucirumab[14] or panitumumab[15]	11% - 22%	6 - 7	12.9 - 14.5
3/4L	KRASmut/WT	Regorafenib[18]	1.0%	1.9	6.4
3/4L	KRASmut/WT	Trifluridine/tipiracil HCl[17]	1.6%	2.0	7.1
All Nivolumab Monotherapya N = 74[a]	dMMR/MSI-H (local testing)	Nivolumab	32.4% 95% CI (22.0, 44.3)	Median 8.3 95% CI (3.0, N.A.)	Median N.A. 95% CI (18.0, N.A.)
Prior 5FU-Oxa-Iri N = 53[a]	dMMR/MSI-H (local testing)	Nivolumab	28.3% 95% CI (16.8, 42.3).	Median N.A, 95% CI (4.17, N.A.)	Median N.A., 95% CI (16.33, N.A.)

[a] BICRdata From 06-Feb-2017 DBL

Abbreviations: 2L = second line, 3/4L = third/fourth line, mut = mutant, N.A. = not available, PFS = progression-free survival, OS = overall survival, WT = wild type

Source: Table S.5.1.1A (BOR per IRRC), Table S.5.2.1A (PFS per IRRC) Table S.5.3.1 (OS) of Appendix 1

The efficacy results of the CA209142 study from an updated 06-Feb-2017 DBL (minimum follow-up 11 months) demonstrate improved ORR and durable responses per BICR to nivolumab monotherapy from those previously reported. Updated efficacy results indicate an ORR per BICR of 32.4% with the majority (83.3%) of the responders in ongoing response, DCR of 63.5%, mPFS of 8.3 months, and mOS not reached for all treated subjects. Please see the response to Q2c for additional OS data. The durability of response and durable DCR are considered clinically relevant in this population with advanced metastatic disease typically associated with poor OS outcomes.

Additionally, OS could be accompanied by an improvement over time in symptoms and functioning and non-disease specific quality of life (QoL) as assessed using valid and reliable scales from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EuroQoL 3-level EQ-5D. When changes in mean scores over time were analyzed adjusting for baseline response (Sep-2016 DBL), significant ($P<0.05$) improvements in least squares mean scores for the EORTC QLQ-C30 were reported in scales measuring pain, insomnia, and social functioning as early as week 13 and were observed at ≥ 1 time points in scales measuring emotional functioning, fatigue, and global health status. Significant improvements in EQ-5D-3L visual analogue scale (VAS) and utility index scores were observed as early as week 7 and at all on-treatment time points through week 79 and week 61, respectively. These observations are considered clinically meaningful, particularly in consideration of the toxicities associated with alternative treatment options such as regorafenib and trifluridine/tipiracil.

Patient subgroups carrying RAS and BRAF mutations are further limited in treatment options as they are not eligible for treatment with EGFR inhibitors. The median OS for subjects with KRAS and BRAF mutations has not yet been met, 9/26 events (95% CI: 10.35, N.A) and 3/12 events (95% CI: 4.27, N.A.), respectively, and also compare favourably to those observed with commonly used agents in this setting.

These results provide evidence that nivolumab is a meaningful therapeutic alternative for patients with dMMR or MSI-H metastatic CRC across both germline and sporadic MSI-H cases as well as lines of therapy and mutational subgroups such as KRAS and BRAF; the Sponsor iscommitted to generate further data for patients in this setting (see response to Q2d).

CHMP assessment of the response

Single arm trial design- According to the MAH the inclusion of a control arm in a late line trial focused on a small patient segment with potentially poorer prognosis and higher unmet medical need, was not considered appropriate in the context of the emerging clinical data. Also, studying anti-PD(L)1 therapies has a biological rationale in dMMR tumours showing high Th1/cytotoxic T lymphocyte infiltrates and upregulation of immune checkpoint proteins (Dudley et al. *Clinical Cancer Research* 2016).
However, this argumentation is not considered sufficient for several reasons.
1) Although only 4-5% of mCRC is dMMR, the high incidence of mCRC would have made a randomised controlled trial achievable with standard of care as a control treatment. While certain subtypes of cancers may be too rare to obtain reasonable sample sizes, dMMR CRC makes up approximately 225,000 of the total new CRC cases per year worldwide (Quiroga et al. *Current Treatment Options in Oncology* 2016). Feasibility of a phase 3 trial is supported by the currently ongoing study comparing pembrolizumab with chemotherapy in MSI-H or dMMR stage IV CRC (NCT02563002).
2) Though the unmet need of the target population is acknowledged, the MAH refers to a poorer prognosis in dMMR mCRC patients as another reason for not using a controlled treatment arm. Median OS for patients with mCRC in general is ~30 months with a 5-year survival rate of 60% (van Cutsem et al. *Annals of Oncology* 2016; van Cutsem et al. *Annals of Oncology* 2014). Compared to MSS tumours, MSI colorectal cancer is associated with a diagnosis at lower stages and has a better prognosis, although conflicting results are observed in stage IV disease. The better prognosis is probably caused by significant immunologic responses provoked by neoepitopes. Therapeutic implications of these observations are at this point controversial. There are reports that MSI colorectal patients do not benefit from 5-FU therapy, hypothetically due to the binding of MMR machinery members to 5-FU incorporated DNA and mediation of the cytotoxic reaction (Dudley et al. *Clinical Cancer Research* 2016). In the MAH's response the study of Venderbosch et al. is referred to as support for the poorer prognosis of dMMR mCRC patients. This study uses the data from patients with mCRC included in four large phase III studies in first-line treatment (n=3,063) and investigates the role of tumour MMR status and *BRAF* mutation status in prognosis. The median PFS and OS were significantly worse for patients with dMMR compared with pMMR tumours (PFS: 6.2 vs 7.6 months, respectively; HR 1.33; CI95% 1.12–1.57; p=0.001; OS: 13.6 vs 16.8 months, respectively; HR 1.35; CI95% 1.13–1.61; p=0.001). Median PFS and OS were also significantly worse for patients with *BRAF* mutated tumours compared with *BRAF* wild type tumours (PFS: 6.2 vs 7.7 months, respectively; HR 1.34; CI95% 1.17–1.54; p<0.001; OS: 11.4 vs 17.2 months, respectively; HR 1.91; CI95% 1.66–2.19; p<0.001). Given the absence of a statistically significant interaction between *BRAF* mutation and dMMR, the authors suggest that the poor prognostic value of dMMR is driven by the *BRAF* mutation status (Venderbosch et al. *Clinical Cancer Research* 2014). This study can therefore not be used to support that the included population in CA209142 has a worse prognosis compared to all mCRC patients, since the poor prognosis seems to be driven by mutational status of the *BRAF* gene. Mutation status was however not known for all included patients in CA209142.

Internal validity- The MAH responded that the opening and closing of the study enrolment was caused by the limited knowledge about time to response to nivolumab and operational difficulties obtaining centrally confirmed MSI-testing results. The MAH acknowledges the possible limitations to establish internal validity, but considers the results robust given the open label nature of the study, consistency between outcomes with pembrolizumab in MSI-H mCRC and other tumour types for nivolumab, and the BICR review of the investigator-assessed responses. The suboptimal conduct of the study however adds to the difficulties in interpreting the results of the trial. Robustness cannot be provided by the comparison of a phase 1 proof-of concept study with pembrolizumab and also not by referring to the effect of nivolumab in other tumours, since the efficacy of immunotherapies is tumour type-dependent.

Comparator- Historical data that can be used to place the efficacy results of nivolumab in dMMR CRC in perspective are not presented. According to the MAH, historical comparisons in 2L or later mCRC are limited in that neither Lynch syndrome diagnosis nor MSI status has been published for most mCRC

trials. Indeed the used historical controls are not representative for the target population with MSI-H status. Since the natural course of MSI-H mCRC is not known in literature, the benefit of nivolumab cannot be determined at this point without the use of comparative controls.

b. Central testing showed a substantial number of discordant results between local and central MSI testing. The Applicant is requested to discuss possible explanations, but more importantly the discussion should also cover the general technical challenges with MSI testing and how the indicated population can be clearly defined in clinical practice. Moreover, efficacy results, including PFS and OS, should be provided for centrally confirmed MSI-H tumours and compared with patients for whom there was no central confirmation.

MSI TEST METHODOLOGIES

Local Testing Procedure:

In study CA209142 local MSI testing could have been done by immunohistochemistry (IHC) and/or polymerase chain reaction (PCR). The IHC MMR testing consists of staining of tumour tissue for loss of expression in any of the 4 mismatch repair proteins known to be mutated in Lynch syndrome, MLH1, MSH2, MSH6, and PMS2. If at least one of these is not normally expressed (i.e., referred to as "absent" upon tissue staining), then the testing indicates the dMMR (MSI) phenotype. PCR amplification of a set of mono- and/or dinucleotide repeats on tumour and normal DNA, followed by comparison of the peak patterns by capillary electrophoresis, can also assess for MSI. In study CA209142, if PCR was the method used for local testing, then an extensive panel of markers, including those associated with the Bethesda panel (central test procedure), could have been utilized, depending on local standards.

Central Test Procedure:

MSI was subsequently evaluated on tumour tissue per central laboratory using PCR (Bethesda panel: BAT25; BAT26; D5S346; D17S250; D2S123); tumour samples with instability in 0, 1, or ≥ 2 markers were identified as microsatellite instability-stable (MSS), MSI-low, and MSI-H, respectively.

The colon was the primary source of tissue for testing for most subjects ("other" was reported as the source for 5 subjects). A by-subject listing with tumour source and test results for all 74 monotherapy treated subjects is provided. Of note, the protocol did not require that the tumour sample submitted for central testing be from the same specimen as that used for local testing.

SUMMARY OF EFFICACY BY CENTRAL AND LOCAL TEST RESULTS

Study CA209142 achieved an ORR per BICR of 32.4% (24/74) with local MSI testing, regardless of the central MSI test outcome. Furthermore, subjects enrolled into CA209142, based on characterization of MSI-H by local testing, still achieved responses to nivolumab monotherapy even though their MSI-H status was not confirmed by a central MSI test. This finding supports that local MSI testing, which is already widely implemented in clinical practice is appropriate for identifying the small subset of dMMR or MSI-H mCRC patients as these patients have the potential to derive meaningful benefit from nivolumab monotherapy.

All 74 nivolumab monotherapy treated subjects had a local laboratory result confirming that a tumour sample was MSI-H or dMMR. Best overall response (per BICR) data below are reported using the 06-Feb-2017 DBL. ORR per BICR (RECIST 1.1) in the 74-subject group was 32.4% (24/74), with 33.8% classified as BOR of SD.

Out of the 74 subjects, 53 had confirmed MSI-H by a central test. Within this 53-subject group, ORR per BICR was 35.8% (19/53), with an additional 35.8% classified as having a BOR of SD (19/53) (Table 3). 7 subjects had missing central testing data due to inadequate amount of tumour tissue and/or no viable tumour in the sample to be centrally tested. Within this 7-subject group, the ORR was 28.6% (2/7) with an additional 42.9% classified as BOR of SD (3/7). The remaining 14 subjects had central test results that did not match the local testing. The ORR per BICR within this 14-subject group was 21.4% (3/14), with an additional 21.4% classified as BOR of SD (3/14).

Figure 1 and Figure 2 summarize the probability of OS for all 74 subjects with local MSI-H or dMMR results and 53 subjects with centrally confirmed MSI-H or dMMR results, respectively. The median OS was N.A. for both subject groups.

Figure 3 and Figure 4 summarize the probability for PFS for all 74 subjects with local MSI-H or dMMR results and 53 subjects with centrally confirmed MSI-H results, respectively. The median PFS for all 74 subjects was 8.31 months (95% CI:2.96, N.A.) and N.A. (95% CI:4.17, N.A.) for the 53 centrally confirmed subjects.

Figure 5 and Figure 6 summarize the best reduction from baseline for all 74 subjects with local or central MSI-H or dMMR, respectively.

Table 3: Best Overall Response per IRRC (MSI Status Defined Using Central Evaluation) - All Central Confirmed Nivolumab Monontherapy Treated Subjects

	Number of Subjects (%)		
	MSI-H/dMMR CRC per Central Lab N = 53	Non MSI-H/pMMR CRC per Central Lab N = 14	No Result Reported per Central Lab N = 7
BEST OVERALL RESPONSE (A):			
COMPLETE RESPONSE (CR)	1 (1.9)	0	1 (14.3)
(95% CI)	(0.0, 10.1)	(0.0, 23.2)	(0.4, 57.9)
PARTIAL RESPONSE (PR)	18 (34.0)	3 (21.4)	1 (14.3)
(95% CI)	(21.5, 48.3)	(4.7, 50.8)	(0.4, 57.9)
STABLE DISEASE (SD)	19 (35.8)	3 (21.4)	3 (42.9)
PROGRESSIVE DISEASE (PD)	12 (22.6)	7 (50.0)	2 (28.6)
UNABLE TO DETERMINE (UTD)	3 (5.7)	1 (7.1)	0
OBJECTIVE RESPONSE RATE (B)	19/53 (35.8%)	3/14 (21.4%)	2/7 (28.6%)
(95% CI)	(23.1, 50.2)	(4.7, 50.8)	(3.7, 71.0)
DISEASE CONTROL RATE (C)	37/53 (69.8%)	5/14 (35.7%)	5/7 (71.4%)
(95% CI)	(55.7, 81.7)	(12.8, 64.9)	(29.0, 96.3)

(A) Per RECIST 1.1 criteria, confirmation of response required
(B) CR+PR
(C) CR+PR+SD (for at least 12 weeks)
Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination
Program Source: /projects/bms218374/stats/upd_feb17/prog/tables/rt-ef-bor-eu.sas 15MAR2017:11:00:18

Figure 1: **Kaplan-Meier Plot of Overall Survival - All Nivolumab Monotherapy Treated Subjects - MSI-H/dMMR CRC per Local Lab - All Subjects**

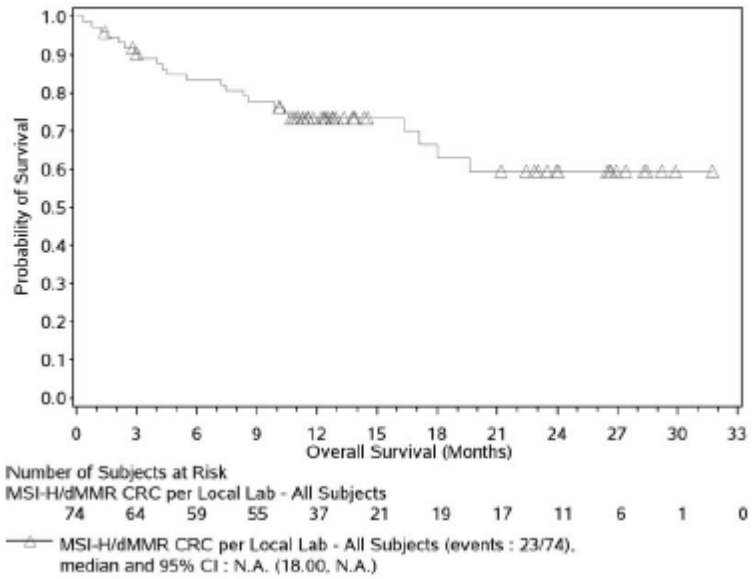


Figure 2: **Kaplan-Meier Plot of Overall Survival - All Nivolumab Monotherapy Treated Subjects with MSI-H per Central Evaluation - All Subjects**

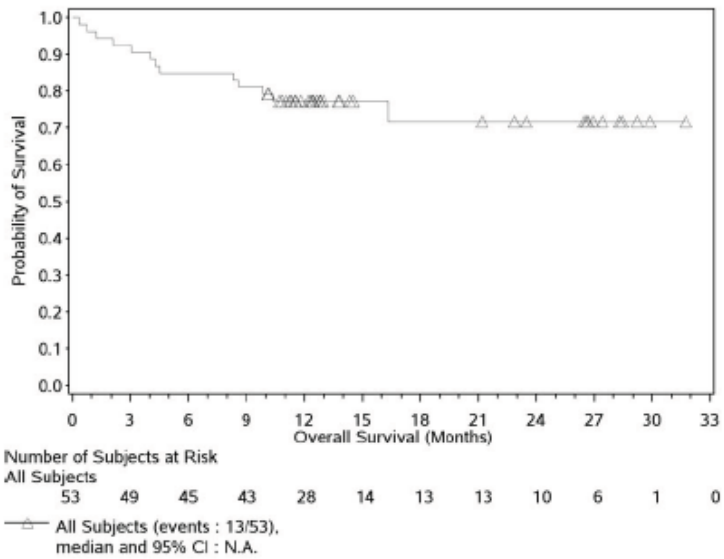


Figure 3: **Kaplan-Meier Plot of Progression-free Survival per IRRC - All Nivolumab Monotherapy Treated Subjects MSI-H/dMMR CRC per Local Lab - All Subjects**

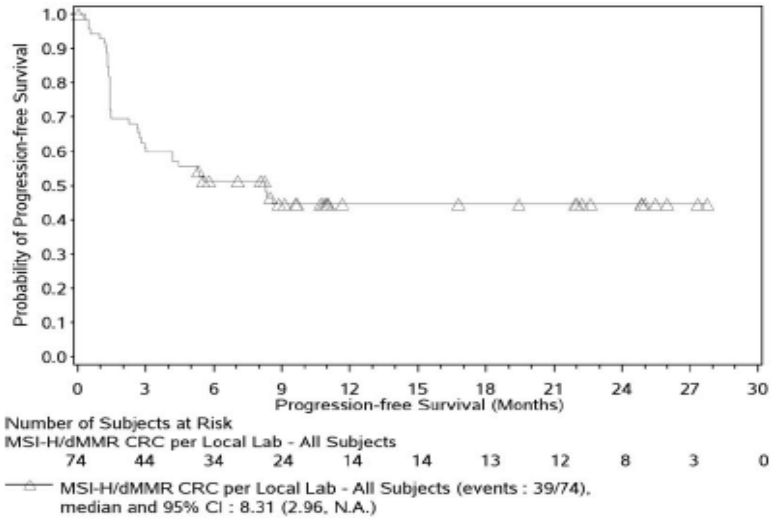


Figure 4: **Kaplan-Meier Plot of Progression-free Survival per IRRC - All Nivolumab Monotherapy Treated Subjects with MSI-H per Central Evaluation - All Subjects**

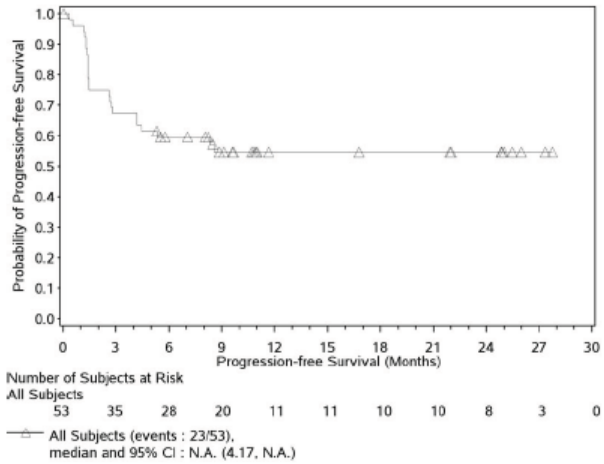
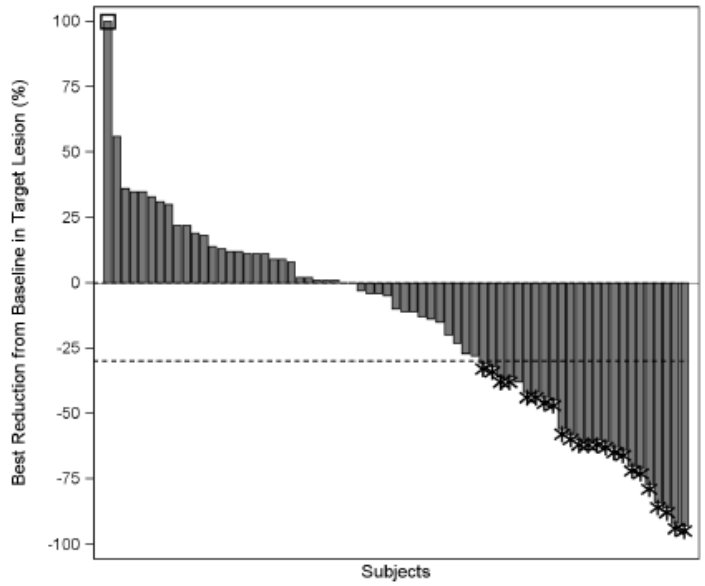
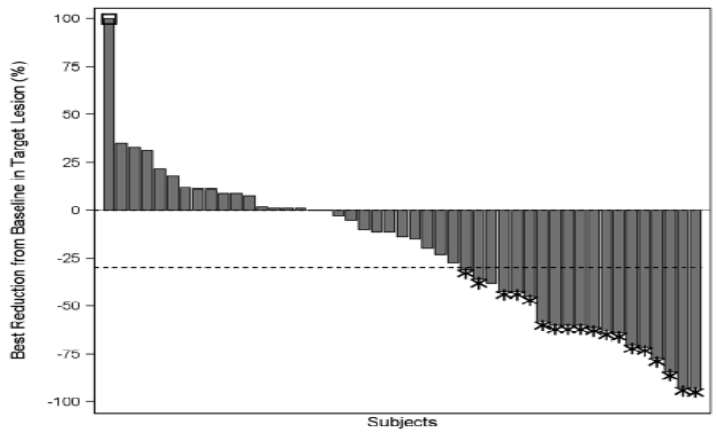


Figure 5: **Waterfall Plot of Best Reduction from Baseline in Sum of Diameters of Target Lesions per IRRC - All Nivolumab Monotherapy Treated Subjects MSI-H/dMMR CRC per Local Lab - All Subjects**



Subjects with target lesion at Baseline and at Least One On-Treatment Tumor Assessment
Negative/positive value means maximum tumor reduction /minimum tumor increase
Best reduction is based on evaluable target lesion measurements up to progression or start of subsequent therapy
Horizontal reference line indicates the 30% reduction consistent with a response per RECIST 1.1 criteria
Asterisk symbol represents responders; Square symbol represents % change truncated to 100%"
Program Source: /projects/bms218374/stats/upd_feb17/prog/figures
Program Name: rg-ef-waterfall.sas 15MAR2017:11:03:06

Figure 6: **Waterfall Plot of Best Reduction from Baseline in Sum of Diameters of Target Lesions per IRRC - All Nivolumab Monotherapy Treated Subjects with MSI-H per Central Evaluation All Subjects**



Subjects with target lesion at Baseline and at Least One On-Treatment Tumor Assessment
Negative/positive value means maximum tumor reduction /minimum tumor increase
Best reduction is based on evaluable target lesion measurements up to progression or start of subsequent therapy
Horizontal reference line indicates the 30% reduction consistent with a response per RECIST 1.1 criteria
Asterisk symbol represents responders; Square symbol represents % change truncated to 100%
Program Source: /projects/bms218374/stats/upd_feb17/prog/figures
Program Name: rg-ef-waterfallch.sas 31MAR2017:08:07:09

LOCAL AND CENTRAL MSI TEST DISCREPANCY

There have been several studies carried out to assess the correlation between IHC and PCR-based testing, and the overall results suggest that firstly neither test is 100% accurate in the detection of MSI-H tumours and secondly, there is actually a high level of concordance between both technologies. The largest study to date was performed by Cicek et al in 2011, when almost 6,000 tumours from patients in the Colorectal Cancer Family Registry were analyzed. The group showed a 90% to 95% concordance between those cases identified as dMMR by PCR-based MSI and those detected by IHC.

The discordance between local and central MSI testing observed in study CA209142 in 14 subjects out of 74 (discounting the 7 subjects with missing central tests) was approximately 19%. Given the higher level of variability associated with this smaller sample size, this discordance rate is considered similar to the 5% to 10% discordance identified by Cicek et al.
The discordant cases were not limited to subjects whose tumours were tested by IHC locally, and were also observed in tumours that were evaluated by PCR locally (Table 5) and 4 Lynch syndrome subjects were tested to be MSI-H by local testing, but MSS by central testing.

Table 5: Summary of Subjects in CA209142 with Discrepancies between Local and Central MSI Testing (Feb 2017 DB)

Subject	Local Test Conducted	Local Test Results[a]	Central Test Result (PCR-based MSI screen)	Lynch Syndrome History[a]	BOR per BICR
CA209142-2-51	IHC	MSI-H	MSI-L[b]	Unknown	PD
CA209142-3-54[c]	IHC	MSI-H	MSS	Not Lynch	PR
CA209142-4-58	IHC	MSI-H	MSS	Lynch	PR
CA209142-6-139	IHC	MSI-H	MSS	Lynch	PD
CA209142-25-55[d]	IHC	pMMR (MSS)	MSS	Not Lynch	SD
CA209142-25-114	IHC	MSI-H	MSS	Lynch	PD
CA209142-25-122	IHC	MSI-H	MSS	Not Lynch	PR
CA209142-25-151	PCR	MSI-H	MSS	Lynch	PD
CA209142-25-153	PCR	IHC/MSI-H	MSS	Lynch	SD
CA209142-29-134	IHC	MSI-H	MSS	Not Lynch	SD
CA209142-30-53	IHC	MSI-H	MSS	Unknown	PD
CA209142-30-103	PCR	MSI-H	MSS	Unknown	NE
CA209142-40-110	IHC	MSI-H	MSI-L	Unknown	PD
CA209142-40-117	IHC	MSI-H	MSS	Unknown	PD

Abbreviations: BICR = blinded independent central review; CRF = case report form; IHC = immunohistochemistry; MSI-H = microsatellite instability-high; MSI-L = microsatellite instability-low; MSS = microsatellite instability-stable; NE = not evaluable; NR = not reported; PCR = polymerase chain reaction; PD = progressive disease; pMMR = proficient mismatch repair (of DNA); PR = partial response; SD = stable disease.

[a] Per CRF. History of Lynch syndrome testing and results obtained from Medical History, excluding Italy.

[b] MSI-L, categorized as MSS.

[c] Subject CA209142-3-54 had 2 primary tumors, one was MSI-H by local testing; the sample sent to the lab for central testing was from a lymph node metastatic tumor. The central lab test result is MSS.

[d] Subject CA209142-25-55 had 2 results from local testing: MSS by IHC and MSI-H by PCR; central test result is MSS, discordant from the local PCR test result.

CONCLUSIONS REGARDING LOCAL AND CENTRAL MSI TESTING

The targeted patient population of study CA209142 includes patients with dMMR or MSI-H, mCRC with disease progression during or after ≥ 1 line of treatment. The U.S. National Comprehensive Cancer Network Guidelines advise MSI testing for all CRC patients and the ESMO consensus guidelines for the management of patients with mCRC advise that MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC. Practitioners are currently using well-established local MSI/MMR test methods as standard of care for patient management. These tests are provided as laboratory developed tests under Clinical Laboratory Improvement Amendments regulations, and are based on Class I cleared reagents in the case of MMR testing. Characterization of MSI by local testing, in practice, allows for rapid and accessible readout of test results. The CA209142 study protocol specified a subsequent confirmation of MSI. In the process, logistical challenges were identified with regard to obtaining adequate tissue. This was evidenced by the fact that the central test could not be

conducted on 9.5% (7/74) of subjects due to the inadequacy of tumour tissue. Despite these limitations, an ORR of 28.6% was observed (2/7) in these subjects for whom there was inadequate tumour material for central testing, demonstrating that subjects identified on the basis of local testing did receive a positive and clinically meaningful outcome from nivolumab therapy. An absolute requirement for central testing would therefore have denied some dMMR/MSI-H patients the opportunity to derive benefit from nivolumab due to lack of available tissue for re-testing.

Overall, study CA209142 achieved an ORR per BICR of 32.4% (24/74) with local MSI testing, regardless of the central MSI test outcome. Furthermore, subjects enrolled into CA209142, based on characterization of MSI-H by local testing, still achieved responses to nivolumab monotherapy even though their MSI-H status was not confirmed by a central MSI test (ORR per BICR at 28.6% for the subjects with no central result, and 21.4% for those with discordant central results). This finding supports that local MSI testing, by IHC or PCR which are already widely implemented in clinical practice, is appropriate for identifying the small subset of dMMR or MSI-H mCRC patients as these patients have the potential to derive meaningful benefit from nivolumab monotherapy. This is of particular importance in patients who may not be eligible for alternate therapies (e.g. EGFR inhibitors) and in later lines of therapy where historical controls offer limited clinical benefit.

CHMP assessment

Different explanations have been provided for the divergent results seen in local vs central MSI testing. The logistic difficulties associated to the repeated central testing of samples are acknowledged, and this accounts for a total of 7 missing central data due to insufficient samples. The concern is mostly related to the 14 out of 67 samples with central testing for which discordant local vs central results were observed. It is argued that this discordance rate (which is 21%, and not 19% as reported by the MAH) is in line with that reported in the literature (5-10%) if the variability of the limited sample size is accounted for. Formally, in this trial the discordance rate is double than that expected, but the potential contribution of the low sample size cannot be omitted. In addition, discrepant results were observed in both cases although most commonly seen in patients using different methods locally and centrally also due to the fact that IHC was the preferred method used locally (40/74 only ICH vs 24/74 only PCR).

Higher response rates are seen in the subset of patients with central PCR confirmation (ORR by BICR: 35.8% in 53/74 with central confirmation, 21.4% in 14/74 with discordant results, and 28.6% in 7/74 with missing central testing), but given the low number of patients in the different subsets these results should be taken with caution; moreover bearing in mind that both methods are extensively used in clinical practice, with no particular preference for one or the other but the choice depending on local preferences/experience. Since according to the study protocol the decision to treat was made based on local testing results, which in fact mimics current clinical practice use, it appears reasonable to accept the MAH´s arguments and rely on the study results in the main studied population, i.e. 74 patients diagnosed based on local testing.
The different rates of response will be borne in mind in the discussion on the internal validity and the relevance of the study results.

c. Investigator-assessed ORR was chosen as primary endpoint, which in literature shows poor correlation with gain in survival and is therefore not considered a valid surrogate endpoint. OS is the preferred primary endpoint, but survival data are currently immature. The Applicant should provide updated OS data and discuss them in relation to the answer to part a of this question on the interpretation of the effect of nivolumab compared to the results of current available treatments in the dMMR subpopulation across the broad spectrum of the intended target population.

<u>Update of ORR per BICR and Investigator using DBL at 06-Feb-2017</u>
Both investigator and BICR-assesed responses demonstrated durability of responses. All subjects now have a range of follow-up between 11 to 32 months (06-Feb-2017 DBL).

The updated efficacy summary is presented in Table 1 above. ORR, DOR, and PFS were consistent between BICR assessment and investigator assessment. These updated results continue to support clinical benefit in patients with MSI-H or dMMR mCRC. No new progressions among original responders in the Sep-2016 database were reported. Median DOR was not reached either in all nivolumab monotherapy treated subjects or centrally confirmed MSI-H or dMMR mCRC subjects. The majority of responders (84.2%, 16/19) had ongoing response at the clinical cut-off date (02-Jan-2017). Median TTR per BICR was 2.73 for all nivolumab monotherapy treated subjects.
When the current (Feb-2017) database is compared with the Sep-2016 database, ORR has improved to 32.4% (24/74) in all nivolumab monotherapy treated subjects; 2 responders have achieved CR and 22 have achieved PR. Median TTR per BICR is similar to results observed for the original responders (2.79 months for all nivolumab monotherapy treated subjects). Of note, 1 subject changed from PR to SD based on the Feb-2017 DBL and 5 new responders were observed with BOR of PR among the all nivolumab monotherapy treated subjects, 3 of whom were central lab confirmed subjects.
In summary, ORR and DOR are consistent between BICR and investigator assessment, across subject groups of all treated subjects and subjects with 5FU-Oxi-Iri, and regardless of central confirmation of MSI-H.

Direct link of durable response and sustained disease control with OS for subjects treated with Nivolumab
While the primary goal of CA209142 was to estimate ORR and durability of response, the other key objectives were to estimate median PFS, median OS, PFS rates, and OS rates at time points in order to make indirect reference to historical data in this patient population. To ensure stable estimates, appropriate sample size with reasonable amount of follow-up was critical. Several exploratory/descriptive analyses were conducted based on the 06-Feb-2017 DBL to explore the correlation of OS and BOR.

Analysis of OS by mStage 1 and mStage 2
As indicated in the response to Q14 (a), the enrolment of the monotherapy arm included 2 parts: mStage1 with an actual treated subject number of 32 and mStage2 with an actual treated subject number of 42 per local MSI-H testing. There was a 7-month enrolment pause to nivolumab monotherapy between the 2 stages. Therefore, the mStage1 had a minimum follow-up of 21 months and the mStage2 had a minimum follow-up of 11 months as of the 06-Feb-2017 DBL. Figure 7 and Figure 8 show the KM curves for OS by subjects enrolled and treated in mStage1 and mStage2 for all treated subjects (N = 74) and for subjects with 5FU-Oxi-Iri (N = 53), respectively. Median OS was not reached in both subgroups for all treated subjects. Median OS was 19.6 (95% CI 4.27, NA) for mStage1 and not reached for mStage2 in subjects with 5FU-Oxi-Iri. In addition, the observation of the flattened tail of the OS curves in mStage1 is consistent with OS curves observed in other tumour types treated with nivolumab representing the potential for long-term benefit.

While historical data in the 3L/4L setting where OS rates at 12 months were less than 30%, OS rates at 12 months were 63.9% (95% CI 40.6, 80.1) for mStage1 and 75.2% (95% CI 54.8, 87.4) for mStage2 for the refractory subset of subjects with 5Fu-Oxi-Iri, demonstrated favourably survival outcome. Of note, among the subjects with 5FU-Oxi-Iri, 11 (47.8%) subjects in mStage1 had OS greater than 21 months and include all the responders per BICR assessment. In addition, 23 (76.7%) subjects in mStage2 had OS greater than 9 months and includes all the responders per BICR

Figure 7: **Kaplan-Meier Plot of Overall Survival by Subjects Enrolled and Treated in Stage 1 or in Stage 2 - All Nivolumab Monotherapy Treated Subjects**

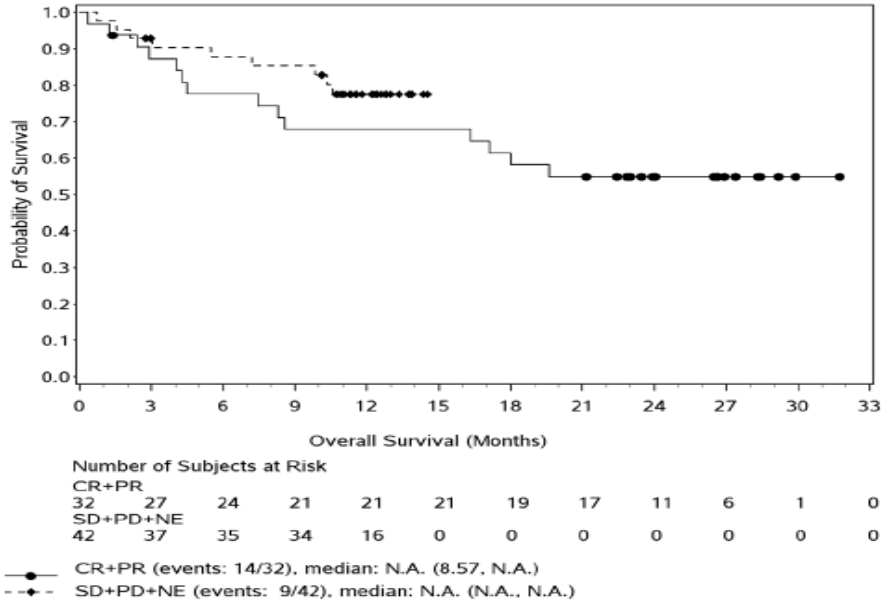
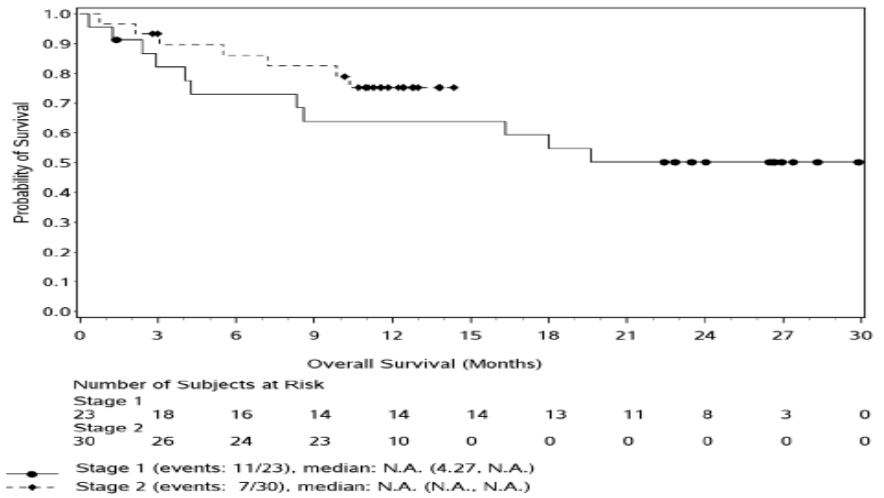


Figure 8: **Kaplan-Meier Plot of Overall Survival by Subjects Enrolled and Treated in Stage 1 or in Stage 2 -All nivolumab Monotherapy Treated Subjects**

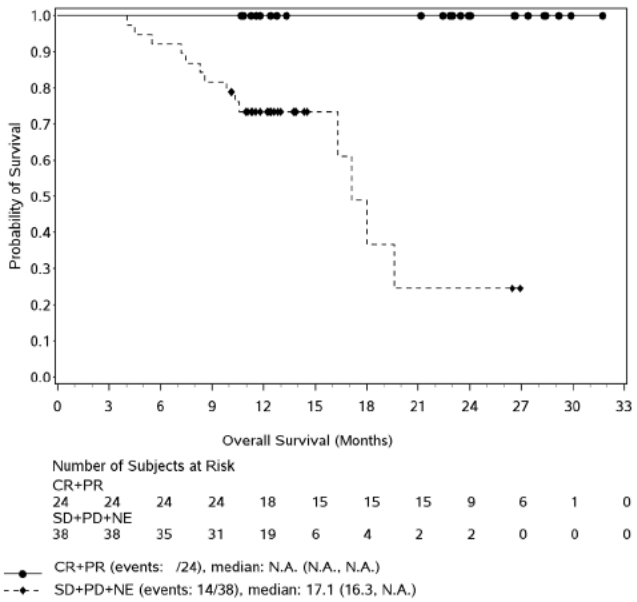


Landmark analysis of OS based on BOR by month 4

In a landmark analysis of OS based on BOR by month 4 in response to Question 8 during procedure EMEA/H/C/003985/II/0008 (RCC indication), responders to nivolumab had improved OS compared to non-responders. A similar analysis was also undertaken for all treated subjects from CA209142 based on the 06-Feb-2017 DBL where OS at month 4 based on BORs of CR/PR versus SD/PD were analyzed. In this analysis, subjects with OS <4 months were excluded as early death may have prevented evaluation of BOR. One subject with BOR of not evaluable (NE) was not included in the plot. As shown in Figure 9 there are no deaths for the 24 responders per BICR assessment after a minimum of 11 months follow-up (including 11 subjects with a minimum of 21 months follow-up) among the all treated subjects (N=74). Additionally, for the 38 subjects with month 4 BOR of SD/PD, the median OS is 17.1 months which compares favourably with the historical data shown in Table 2.

In summary, these results support the correlation of response to survival in MSI-H mCRC and replicate the similar treatment effect previously observed with nivolumab in RCC.

Figure 9: **Kaplan-Meier Plot of Overall Survival by Best Overall Response per IRRC by Month 4 - All Monotherapy Treated Subjects**



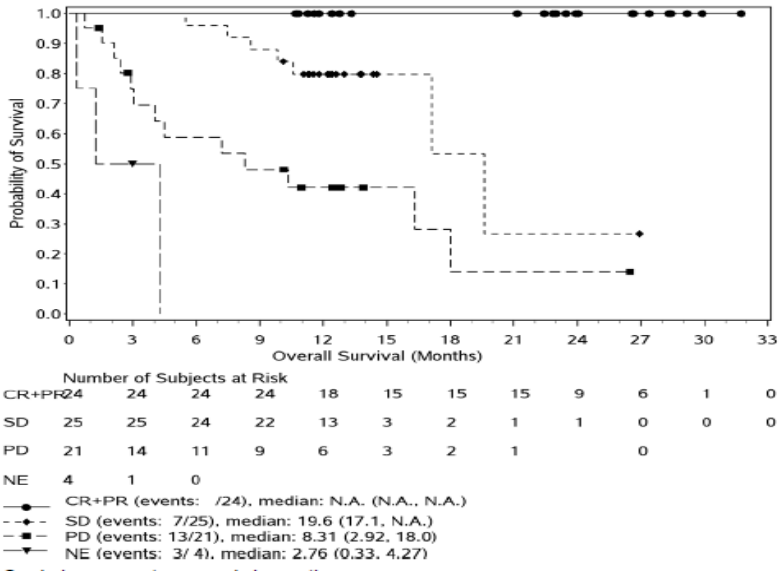
Symbols represent censored observations.
Program Source: /gbs/prod/clin/programs/ca/209/142/csria04/rpt/ebr-eu-req/20170308
Program Name: rg-ef-osbyborirrcland4-v01.sas 07APR2017:11:07:39

OS Kaplan-Meier curves by BOR category

To further understand the correlation of OS by subject BOR, a Kaplan-Meier plot was generated (Figure 10 below). Recognizing the limitation of no control arm in this anlaysis, the prolonged OS observed among responders (per BICR) is noticeable, namely, there was no disease progression or death among the 24 responders per BICR after a minimum of 11 months follow up, including 11 responders with a minimum of 21 months follow-up. In addition, for the 25 subjects with BOR of SD, the median OS was 19.6 months (95% CI 17.1, 19.6).

Collectively, these results demonstrate that durable response and sustained disease control are predictive of favourable OS outcomes in this population.

Figure 10: **Kaplan-Meier Plot of Overall Survival by Best Overall Response per IRRC - All Nivolumab Monotherapy Treated Subjects**



CHMP assessment

Updated data with additional 5-month follow up and a minimum 11-month follow up show consistent results to those initially presented, with some improvements noted in the ORR by BIRC (from 27% to 32.4%), and PFS both by investigator (from 9.6months to 14.3 months) and by IRRC (from 7.6 months to 8.3 months). Median duration of responses has not been reached by any investigator and independent assessment and the same holds true for survival results (23 events/74 patients), which show rather promising results based on survival rates at 6 months (83.4%) and at 12 months (73.4%).

Results are also consistent regardless of whether patients were included in the first enrolment stage (N=32 treated patients, with a minimum FU of 21 months, median OS not reached for the overall population, 19.6 months for the subset of patients in 3/4L) or in the second enrolment stage (N=42 treated patients, minimum FU 11 months, median OS not reached for the overall nor the 3/4L subset population).

Study results have been put in the context of available treatment options for the general mCRC population. Although still immature in terms of duration of responses and OS for the overall population and in some relevant subsets, treatment with nivolumab shows substantially higher rates of tumour responses than those previously seen with available treatment options in the overall mCRC in second and later lines of treatment. In addition, in an attempt to further justify the relevance of the observed effect, the MAH has presented some analyses which give support to the notion that durable response and sustained disease control, as observed in a relevant subset of the treated population, are predictive of favourable survival outcomes in this mCRC population; i.e. there was no disease progression or death among the 24 responders per BICR after a minimum of 11 months follow up, including 11 responders with a minimum of 21 months follow-up. In addition, for the 25 subjects with BOR of SD, the median OS was 19.6 months (95% CI 17.1, 19.6). These results are encouraging, but cannot be considered confirmatory of a clinically relevant benefit. As previously stated, tumour responses are not indicative of any relevant benefit for patients given that is most cases these are asymptomatic and little is known on the actual co-relation between ORR and OS in MCRC. Therefore, considering that we are running late stages of a poor prognostic disease, mature OS data to substantiate the clinical relevance of the results should be provided.

Table 2: Commonly Used Agents for Standard of Care

Line of Therapy	mCRC subpopulation	Agent	Response Rate	PFS (months)	OS (months)
2L	KRAS mut	FOLFOX or FOLFIRI + bevacizumab[12, 13] or aflibercept[16] or ramucirumab[14]	11% - 22%	6 - 7	12.9 - 13.5
2L	KRAS WT	FOLFOX or FOLFIRI + bev[12,13] or ramucirumab[14] or panitumumab[15]	11% - 22%	6 - 7	12.9 - 14.5
3/4L	KRASmut/WT	Regorafenib[18]	1.0%	1.9	6.4
3/4L	KRASmut/WT	Trifluridine/tipiracil HCl[17]	1.6%	2.0	7.1
All Nivolumab Monotherapya N = 74[a]	dMMR/MSI-H (local testing)	Nivolumab	32.4% 95% CI (22.0, 44.3)	Median 8.3 95% CI (3.0, N.A.)	Median N.A. 95% CI (18.0, N.A.)
Prior 5FU-Oxa-Iri N = 53[a]	dMMR/MSI-H (local testing)	Nivolumab	28.3% 95% CI (16.8, 42.3).	Median N.A, 95% CI (4.17, N.A.)	Median N.A., 95% CI (16.33, N.A.)

[a] BICRdata From 06-Feb-2017 DBL

Abbreviations: 2L = second line, 3/4L = third/fourth line, mut = mutant, N.A. = not available, PFS = progression-free survival, OS = overall survival, WT = wild type

Source: Table S.5.1.1A (BOR per IRRC), Table S.5.2.1A (PFS per IRRC) Table S.5.3.1 (OS) of Appendix 1

It is argued that the presence of MSI-H/dMMR in patients with mCRC confer a worse prognostic and a lower response to treatment. However, very limited evidence is provided to substantiate this claim, which is critical to make a benefit/risk assessment in the absence of a control arm. As already discussed under bullet point a, the role of MMR status as a prognostic and predictive marker of response in CRC is an area not well elucidated at present. It is agreed that treatment options available in late lines offer modest benefits for the overall mCRC population, but the actual benefit in patients with dMMR mCRC in 2nd and later lines of treatment is uncertain, and not necessarily worse than that seen in the general mCRC population. This makes challenging putting these results into context. One might agree that in 3rd/4th lines results are very encouraging given the poor prognostic and high toxicity of available treatment options. However, the main concern is for the 2nd L mCRC setting, where well established treatment options are available for the general mCRC, including patients with dMMR. In fact, it is unknown if patients with dMMR benefit differently from these treatment options. Furthermore, it is uncertain to what extent treatment with nivolumab may interfere with the response to subsequent treatments, thus, placing nivolumab in second line can hardly be supported in the absence of a truly convincing evidence of benefit over current SOC.

Therefore, the MO is not considered solved. Mature results in clinically relevant outcomes should be presented. Further, the benefit/risk of nivolumab for the intended target population, particularly for patients in 2nd line deserves further justification.

d. Considering the exploratory nature of the evidence provided, the Applicant should also discuss on any plans to generate additional confirmatory data within the mCRC setting.

Given the potential availability of approved PD-1 agents for the treatment of MSI-H tumours in the short term, in addition to the current inclusion of PD-1 agents in the US National Comprehensive Cancer Network (NCCN) guidelines for MSI-H CRC (and the predictive value of MSI-H with respect to treatment with immunotherapy referenced in the ESMO guideline) in the 2L+ metastatic setting, conducting a global randomized Phase 3 trial in the same patient population, although informative, would no longer be ethical. Of note, the ongoing 1L trial of pembrolizumab versus chemotherapy allows cross-over to PD-1 inhibitor, further illustrating that PD-1 inhibitors are already considered to be an acceptable treatment option in the later line population and highlighting the difficulties that would be encountered if attempting to randomize advanced dMMR or MSI-H mCRC patients to a standard of care comparator arm in the 2L or later.

To generate additional confirmatory data within the MSI-H mCRC setting, BMS is planning the following:

1. Collect long-term follow-up data from all 74 subjects treated with nivolumab monotherapy in study CA209142. ORR will be determined with a minimum of 2 years follow-up from the last patient's first dose to database lock date. Key secondary endpoints will include OS and PFS. ORR and PFS are to be determined by BICR.

2. Evaluation of nivolumab in an additional cohort of MSI-H or dMMR CRC patients (~100 patients) using the same eligibility criteria as the initial cohort to confirm the findings in the initial dataset The primary endpoint would be ORR with a minimum of 2 years followup determined from the last patient's first dose to database lock date. Key secondary endpoints will include OS and PFS. ORR and PFS will be determined by BICR.

The Sponsor remains committed to further investigating the potential for nivolumab to provide clinical benefit in mCRC. Study CA209142 includes an ongoing cohort of nivolumab + ipilimumab in 1L in dMMR or MSI-H metastatic CRC, as well as a recently initiated exploratory cohort examining nivolumab + ipilimumab + cobimetinib in MSS patients which may inform future development across the wider mCRC population.

CHMP assessment

There are no plans for conduct a RCT to provide confirmatory evidence supporting the claimed indication. The difficulties are acknowledged in the late lines of treatment, but not in $1^{st}/2^{nd}$ lines.
Instead, the MAHs is committed to generate additional confirmatory data within the MSI-H mCRC setting:

1. Collect long-term follow-up data from all 74 subjects treated with nivolumab monotherapy in study CA209142. ORR will be determined with a minimum of 2 years follow-up from the last patient's first dose to database lock date. Key secondary endpoints will include OS and PFS. ORR and PFS are to be determined by BICR.

2. Evaluation of nivolumab in an additional cohort of MSI-H or dMMR CRC patients (~100 patients) using the same eligibility criteria as the initial cohort to confirm the findings in the initial dataset The primary endpoint would be ORR with a minimum of 2 years follow-up determined from the last patient's first dose to database lock date. Key secondary endpoints will include OS and PFS. ORR and PFS will be determined by BICR.

In principle, presentation of mature data of the study supporting the claimed indication is expected during current procedure. In addition, concerning the proposal to replicate the study results in a second trial with the same characteristics; this is welcome as a way to add robustness to the actual study results. However, this would not solve our main concern which is related to the lack of controlled data and the little external support on the actual prognostic and/or predictive value of dMMR in mCRC.(see discussion in the overarching MO). Therefore, the current proposal is at present insufficient. Further discussion will be needed in the following round of the procedure.

It is also mentioned that additional research is planned with nivolumab in mCRC in different settings from the one under evaluation. Clarification is requested on the plans to conduct RCT in 1^{st} /2^{nd} line mCRC setting.

Overall conclusion of the assessment of the MAH response to MO

Efficacy Update (clinical cut-off of 02-Jan-2017), which provides an additional 5 months of follow-up (minimum FU of 11 months) since the initial submission. Results are quite consistent to those initially submitted, which is reassuring. Nevertheless, still data are immature in terms of DoR and OS.

Table 1: Summary of Efficacy Results (CA209142)

	Nivolumab (n=74) BICR	Nivolumab (n=74) Investigator
Confirmed objective response, n	24 (32.4)	23 (31.1)
(95% CI)	(22.0, 44.3)	(20.8, 42.9)
Complete response (CR), n (%)	2 (2.7)	0
Partial response (PR), n (%)	22 (29.7)	23 (31.1)
Stable disease (SD), n (%)	25 (33.8)	28 (37.8)
Median duration of response		
Months (range)[a, b]	Not reached (1.4+, 26.5+)	Not reached (3.9+, 26.5+)
Median time to response		
Months (range)	2.79 (1.2, 22.6)	2.76 (1.2, 16.1)
Disease control rate[a] n (%)	47 (63.5)	51 (68.9%)
(95% CI)	(51.5, 74.4)	(57.1, 79.2)
Progression-free survival		
Events	39	36
Median (months) (95% CI)	8.3 (3.0, N.A.)	14.3 (4.3, NE)
Overall survival		
Events		23
Median (months) (95% CI)		N.A. (18.0, N.A.)
6-month rate (%) (95% CI)		83.4 (72.6, 90.2)
12-month rate (%) (95% CI)		73.4 (61.5, 82.1)

CHMP overall conclusion

MSI-H CRC is considered a distinct biological entity among colorectal cancers. It is argued that the presence of MSI-H/dMMR in patients with mCRC confer a worse prognostic and a lower response to treatment. In non-metastatic CRC setting, dMMR represents 12% of all tumours and is associated with good prognosis but also with resistance to adjuvant 5-FU chemotherapy. In metastatic CRC setting, dMMR is found in less than 5% and its influence on prognosis and treatment response is little known. Some evidence indicate that dMMR mCRC are associated with neutral or even poor prognosis and chemoresistance, especially to 5-FU based chemotherapy. However, the actual role of dMMR status as a predictive of response and prognostic marker in the mCRC setting remains to be conclusively determined.

Ideally a double-blind, randomised controlled (e.g. with physician's best choice) study should have been performed to test the efficacy of nivolumab in this specific subpopulation of mCRC. Given the high incidence of dMMR CRC, a controlled study would have been feasible. The lack of historical controls in the specific subpopulation of dMMR colorectal metastatic disease, makes it impossible to determine efficacy at this point.

Moreover, the internal validity is questioned. First of all, e included patients had a more favourable prognosis than mCRC in the general population (see also assessment of Question 7 and 17). Secondly, the MAH cannot guarantee that the study population of MSI-H patients is well defined and characterised. Lastly, with the used design, the study will not be able to detect efficacy in terms of the more clinical relevant endpoint OS and the robustness of current OS data is doubtful (see also assessment of Question 14).

It is agreed that treatment options available in late lines offer modest benefits for the overall mCRC population, but the actual benefit in patients with dMMR mCRC in 2nd and later lines of treatment is uncertain, and not necessarily worse than that seen in the general mCRC population. This makes challenging putting these results into context. One might agree that in 3rd/4th lines results are particularly encouraging given the poor prognostic and high toxicity of available treatment options. However, the

main concern is for the 2nd L mCRC setting, where well established treatment options are available for the general mCRC, including patients with dMMR. In fact, it is unknown if patients with dMMR benefit differently from these treatment options. Furthermore, it is uncertain to what extent treatment with nivolumab may interfere with the response to subsequent treatments, thus, placing nivolumab in second line can hardly be supported in the absence of a truly convincing evidence of benefit over current SOC.

In addition, results initially presented and the new update with + 5-month follow up are very encouraging, but cannot be considered confirmatory of a clinically relevant benefit for these patients. As previously stated, tumour responses are not in itself indicative of a relevant benefit for patients given that mCRC is usually asymptomatic. Long lasting responses might be relevant as long as they correlate with an improvement in survival, but these remains to be determined due to the immaturity of the data presented. Therefore, considering that we are running late stages of a poor prognostic disease, mature OS data to substantiate the clinical relevance of the results should be provided.

Concerning the proposal to replicate the study results in a second trial with the same characteristics; this is welcome as a way to add robustness to the actual study results. However, this would not solve our main concern which is how to interpret the study results in this subset of patients with dMMR in the absence of a controlled arm and in view of the little knowledge on the actual prognostic and/or predictive value of dMMR in mCRC. Therefore, the current proposal is at present insufficient. Further discussion will be needed in the following round of the procedure.

Therefore, **the MO is not considered solved**. Mature results in clinically relevant outcomes should be presented. In addition, the benefit/risk of nivolumab for the intended target population deserves further discussion in view of the uncertainties on the actual role of dMMR status in mCRC as a prognostic and predictive marker. A separate discussion is expected for the 2nd vs later lines of treatment. In view of this response, further discussion may be needed on the possible ways to generate additional evidence.

3. The proposed indication for nivolumab is the treatment of dMMR or MSI-H mCRC after prior fluoropyrimidine based therapy. The study population included patients with recurrent or metastatic patients being progressive during, after, or intolerant to ≥1 line treatment for their metastatic disease, which must include at least a fluoropyrimidine, and oxaliplatin or irinotecan. The indication should reflect the studied population and therefore the Applicant is asked:
    c) To clarify the number of patients included with recurrent disease and adjust the proposed indication as needed
    d) Adjust the indication to fluoropyrimidine-based combination therapy.

Summary of the MAH response

a. To clarify the number of patients included with recurrent disease and adjust the proposed indication as needed: 33/74 subjects (44.6% of all subjects) including 22/53 subjects (41.5% of subjects with prior 5FU-Oxa-Iri) presented with metastatic disease. The remainder presented with earlier stage disease at initial diagnosis, i.e, 41 of the all treated subjects and 31 subjects with prior 5FU-Oxa-Iri; these patients (defined as “recurrent disease”) all had metastatic disease at the time of study entry, as all subjects had at least one site of metastatic disease at study entry. Note that the standard of care for patients with recurrent or metastatic CRC is identical, and there is no expected difference in outcome for patients whose CRC is recurrent versus newly diagnosed as metastatic. Therefore, adjustment of indication is not

needed as there is no expected difference in outcome for patients whose CRC recurred versus those who presented with metastatic disease. The proposed indication reflects the patient population studied.

b. Adjust the indication to fluoropyrimidine-based combination therapy. The Sponsor agrees to adjust the indication as follows: OPDIVO is indicated for the treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based combination therapy.

CHMP assessment

The requested clarification has been provided. As all patient had metastatic disease at study entry, it is agreed that that the indication referring to metastatic patients does not need to be changed.
The Sponsor agrees to adjust the indication as follows: OPDIVO is indicated for the treatment of adults with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer after prior fluoropyrimidine-based combination therapy.

Issue resolved.

Other concerns

4. Clarification is requested on the IHC results, i.e. on the number of patients with MMRd and loss of expression of MLH1/PMS2 proteins vs MSH2/MSH6 proteins.

Summary of the MAH response

The Sponsor conducted new analyses tabulating the loss of expression in protein markers used for MSI evaluation per the local laboratory using the 06-Feb-2017 database lock (DBL). Out of 74 subjects, 52 (70.27%) had used IHC-based MMR testing for local assessment. Of these,

- 71.15% (37/52) of subjects had loss of expression of either MLH1 or PMS2; 50.00% (26/52) of subjects had loss of expression of both MLH1 and PMS2 (Table 1).
- 38.46% (20/52) of subjects had loss of expression of either MSH2 or MSH6; and 23.08% (12/52) of subjects had loss of expression of both MSH2 and MSH6 (Table 1).

Table 1: **Loss of Expression in Protein Markers used for MSI Evaluation per Local Laboratory Summary - All Nivolumab Monotherapy Treated Subjects**

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74
SUBJECTS WITH IHC METHODOLOGY PERFORMED	52 (70.27)
TYPE OF MARKER(S) WITH LOSS IN EXPRESSION BY SUBJECT (A)	
MLH1	3 (5.77)
MLH1 MSH2 *	3 (5.77)
MLH1 MSH2 MSH6 PMS2	1 (1.92)
MLH1 PMS2	25 (48.08)
MSH2	2 (3.85)
MSH2 MSH6	10 (19.23)
MSH2 MSH6 PMS2	1 (1.92)
MSH6	2 (3.85)
MSH6 PMS2	1 (1.92)
PMS2	3 (5.77)
NONE IDENTIFIED	1 (1.92)
LOSS IN EXPRESSION BY SPECIFIC MARKER (A) (B) *	
MLH1	32 (61.54)
PMS2	31 (59.62)
MLH1 OR PMS2	37 (71.15)
MLH1 AND PMS2	26 (50.00)
MSH2	17 (32.69)
MSH6	15 (28.85)
MSH2 OR MSH6	20 (38.46)
MSH2 AND MSH6	12 (23.08)

(A) Percentages are based on subjects with IHC methodology performed
(B) Some Subjects may have loss expression in more than 1 marker
* Subject 3-5, 30-53 and 30-138 are in category of "MLH1 PMS2" in raw data, but incorrectly mapped to "MLH1 MSH2" in SDTM data.
Program Source: /gbs/dev/clin/programs/ca/209/142/csria04/rpt/ebr-eu-req/20170308/rt-dbr-mslosser-v01.sas 17-MAR-2017 09:02
Note: In tables and figures, MSI-H/dMMR CRC and dMMR/MSI-H CRC can be used interchangeably with 'dMMR or MSI-H metastatic CRC'.

CHMP assessment

The requested information has been presented and in line with current clinical practice, 70.27% of patients were tested by IHC at local sites.

Conclusion

Point clarified

5. There are a high proportion of patients with unknown forms of MMRd, i.e. germline vs sporadic. Clarification is provided on the reasons why these patients have not been classified and efforts to do so should be made.

Summary of the MAH response

Per the literature, the vast majority of sporadic CRCs are caused by suppression of MLH1 expression due to hypermethylation of the MLH1 promoter known as CIMP. However, there are also rare cases of sporadic CRC associated with MSH2 and MSH6 inactivation. These sporadic dMMR/MSI-H CRC tumours are also associated with a risk of carrying a BRAF mutation (which may also help distinguish these patients from Lynch syndrome patients carrying germline mutations). The Sponsor considers that the IHC markers alone would be insufficient in determining the germline or sporadic etiology of dMMR.
In general, it is difficult to require genetic testing as part of the inclusion criteria in clinical trials.
For CA209142, the consent form did not explicitly include germline genetic testing as undergoing germline genetic testing has important ethical and sometimes emotional implications for both the patient and potentially their family members. Clinical guidelines are quite clear on the role of genetic counselling for patients with dMMR/MSI-H CRCs. In clinical practice, the treating physician should use his or her best clinical judgement to determine the appropriateness of such testing on an individual patient basis. Lynch Syndrome testing results were collected from the clinical record as follows: was the test done, and if so, was the result positive or negative for Lynch Syndrome. This data collection was conducted only at sites where such abstraction from the clinical record was congruent with local ethics standards (excluded Italy). Specific germline mutation data on individual subjects was not collected. For the proposed

expansion cohort, a revised ICF will be implemented to potentially facilitate identification of germline and sporadic dMMR-MSI-H and corresponding analysis undertaken to characterize any differences in outcomes. Literature does suggest however no conclusive evidence that this is the case. Please see response to Q4

CHMP assessment

The MAH has clarified that this testing was not requested as part of the protocol selection criteria, thus availability depends on local practices and this explains why this information is not available for all patients. Available information (2/3 of patients) shows no differences in the rates of response between inherited and sporadic cases. Although limited to draw any conclusions, this is deemed reassuring.

We see no need to further pursue on this aspect. The MAH´s proposal to include this as an exploratory research in new studies in this setting is welcome.

Conclusion

Issue solved

6. The study provided consisted of 3 cohorts: non-MSI-H cohort, MSI-H cohort, and cohort C3 (MSI-H subjects who have not had prior therapy for their metastatic disease). Information has only been presented for the MSI-H previously treated cohort. The Applicant is requested to present available information for the two other cohorts, in particular those with non-MSI-H, in order to further support the hypothesis that benefit from nivolumab is restricted to the MSI-H subset of patients.

Summary of the MAH response

Study CA209142 consists of several cohorts including a monotherapy cohort, combination therapy cohorts of nivolumab and ipilimumab in non-MSI-H subjects as an independent safety arm (non-MSI-H cohort) and in MSI-H subjects including a combination arm of subjects with ≥ 1 prior treatment, and a cohort of treatment-naive patients (cohort C3).

- The data from the monotherapy cohort forms the basis of the current application.
- Preliminary results of the independent safety arm in non-MSI-H subjects treated with combination treatment (N=20, in 2 different doses of the combination of nivolumab and ipilimumab) were initially presented at the ASCO 2016 Annual Meeting, demonstrating a single PR and no new safety signals.
- The MSI-H nivolumab and ipilimumab combination arm of subjects with ≥ 1 prior treatment is ongoing and data from that cohort are planned to be reported in 2018.
- Cohort C3, nivolumab 240 mg q2 weeks + ipilimumab 1 mg q6 weeks, for MSI-H subjects who have not had prior therapy for their metastatic disease started enrolment in Dec-2016 and data will not be available before 2019-2020.

Other available information to support that the benefit of nivolumab is restricted to the dMMR/MSI-H phenotype and comes from the Phase 1 study that triggered the implementation of study CA209142: Study CA209001. In this Phase 1 study of nivolumab conducted in 39 subjects with refractory solid tumours, 14 subjects with metastatic CRC were included, of which 1 subject was identified as having dMMR or MSI-H metastatic CRC. This subject received 5 doses of 3 mg/kg nivolumab and achieved a durable complete response (CR) persisting for greater than 21 months. There were no responses among other subjects with CRC. Long-term follow-up demonstrated clinical and radiological CR more than 3 years after the initial CR, at which time the subject had not received any antineoplastic therapy for 3 years. In another Phase 1 study of nivolumab (CA209003), 19 patients with metastatic CRC were enrolled, but there were no objective responses in this group.

CHMP assessment

Limited information is available in other mCRC settings or subpopulations at this stage. Concerning patients with non-MSI-H mCRC, there is some preliminary safety and some efficacy data from a 20 patient's cohort treated with the combination of ipi + nivo within ***Study CA209142*** *which show one single PD and no new safety findings in this group of patients. Further support to the hypothesis that the benefit of nivolumab is restricted to the dMMR/MSI-H phenotype comes from a Phase 1 pilot study (****Study CA209001****) conducted in 39 subjects with refractory solid tumours, 14 subjects with metastatic CRC were included, of which 1 subject was identified as having d-MMR or MSI-H metastatic CRC. This subject received 5 doses of 3 mg/kg nivolumab and achieved a durable complete response (CR) persisting for greater than 21 months. There were no responses among other subjects with CRC. Long-term follow-up demonstrated clinical and radiological CR more than 3 years after the initial CR, at which time the subject had not received any antineoplastic therapy for 3 years. In another Phase 1 study of nivolumab (****CA209003****), 19 patients with metastatic CRC were enrolled, but there were no objective responses in this group.*

Based on this limited evidence for nivolumab but also considering some external data from other anti-PD-L1 therapies (1), the MAH´s approach to focus nivolumab monotherapy development in MSI-H mCRC patients is considered well justified.
(1) N Engl J Med 2015;372:2509-20. DOI: 10.1056/NEJMoa1500596

Conclusion

Clarification is provided. Although limited, available information gives support to the hypothesis that benefit from nivolumab therapy is unlikely in patients with non-MSI-H mCRC. ***Point solved***

7. Regardless of the type of therapy received, 75.7% had progressed within 6 months of their most recent regimen, with 64.9% progressing within 3 months. Considering the protocol inclusion criteria, which require mCRC progression during, after, or intolerance to ≥ 1 line treatment(s) for their metastatic disease, one would expect that nearly 100% of patients would have progressed within 6 months (an even within 3 months) of their most recent regimen. This speaks in favour of a rather benign mCRC population. The Applicant is invited to clarify this finding and discuss on the relevance of the high rates of stable diseases considering that a substantial portion of patients did not have a progressive disease.

Summary of the MAH response

To clarify, the reported time from completion of most recent prior therapy regimen to treatment is independent of progression date on most recent prior therapy. 75.7% of subjects had completion of most recent prior therapy regimen within 6 months of starting study therapy, and 64.9% had completion of most recent prior therapy regimen within 3 months of starting study therapy.

The CA209142 protocol required progression during, after, or intolerance to ≥1 line treatment(s) for their metastatic disease for nivolumab monotherapy; documented refusal of standard of care chemotherapy was permitted.

Using the 06-Feb-2017 database lock (DBL), analysis of all subjects with a best overall response (BOR) of stable disease (SD) on nivolumab demonstrates no relationship between BOR of SD and time from completion of most recent therapy. Among the 25 subjects with stable disease per the BICR, 19 subjects had a time from prior therapy of < 3 months, 1 subject had a time of 3 - 6 months, and 5 subjects had a time > 6 months.

Similarly, there is no evident relationship between BOR and time from date of progression on most recent prior therapy to start of treatment.

CHMP assessment

Clarification is presented and the actual data provided correspond to the time from completion of most recent prior therapy regimen to treatment that according to the MAH is independent of progression date on most recent prior therapy. However, no information has been presented on the actual time from progression on most recent prior therapy to treatment. This should be provided.

Conclusion

Issue not solved. *Information on the actual time from progression on most recent prior therapy to treatment should be provided. Additional analysis like relationship between BOR and time from date of progression on most recent prior therapy to start of treatment should be presented.*

8. In general, subgroup analysis presented show rather consistent results, with some exceptions noted, i.e. the lower rates of response in the elderly population and in patients with mutated BRAF. Also, in line with these results, lower rates of response are seen in the subset of patients with non-Lynch Syndrome. The Applicant should clarify to what extent these might be representing sporadic MSI cases and discuss the extent to which lower efficacy can be expected in these sporadic cases.

Summary of the MAH response

The Sponsor conducted additional new Kaplan-Meier (KM) analyses of PFS (per investigator and BICR and overall survival (OS) by clinical history of Lynch Syndrome and by KRAS/BRAF mutation status using the 06-Feb-2017 database lock (DBL) and repeated the CSR analyses of objective response rate (ORR; per investigator and BICR) by subset using that new DBL.

Table 1 (using the 06-Feb-2016 DBL) summarises the ORR outcome in subgroups, based on age, Lynch Syndrome, and KRAS/BRAF status.

The ORRs, per BICR, for the different subgroups are comparable:

- The ORR, per BICR, for subjects < and ≥ 65 years of age are 33.3% (19/57) and 29.4% (5/17), respectively.
- The ORRs, per BICR, for subjects with and without Lynch Syndrome are 29.6% (8/27) and 35.7% (10/28), respectively.
- The ORRs, per BICR, for subjects with wild type KRAS and BRAF, mutant KRAS, and mutant BRAF are 31.0% (9/29), 30.8% (8/26), and 33.3 (4/12) respectively. Note the limited number of subjects with BRAF mutation at baseline (12) that limit the interpretation of these results.

KM plots of OS and progression-free survival (PFS) per BICR are presented in Figure 1 and Figure 2, respectively for subjects with and without Lynch Syndrome and in Figure 3 and Figure 4, respectively for subjects with wild type KRAS and BRAF, mutant KRAS, and mutant BRAF. In summary, comparable PFS (per BICR) and OS are achieved amongst these subgroups. The mutant BRAF subgroup reported somewhat better PFS per BICR but this is based on 12 subjects only.

Literature on the prognostic significance of germline versus sporadic CRC is still emerging, however, reflecting on the fact that there is reported to be a higher prevalence of patients with sporadic mutations relative to germline, and that the former tend to be an older population and more likely to be carrying a BRAF mutation, it would not be unexpected that outcomes may be worse in some patients with sporadic mutations. However, in the context of the small patient population and limited data in the public domain, it is difficult to definitively conclude on the predictive and/or prognostic significance of germline versus sporadic mutations in the metastatic setting.

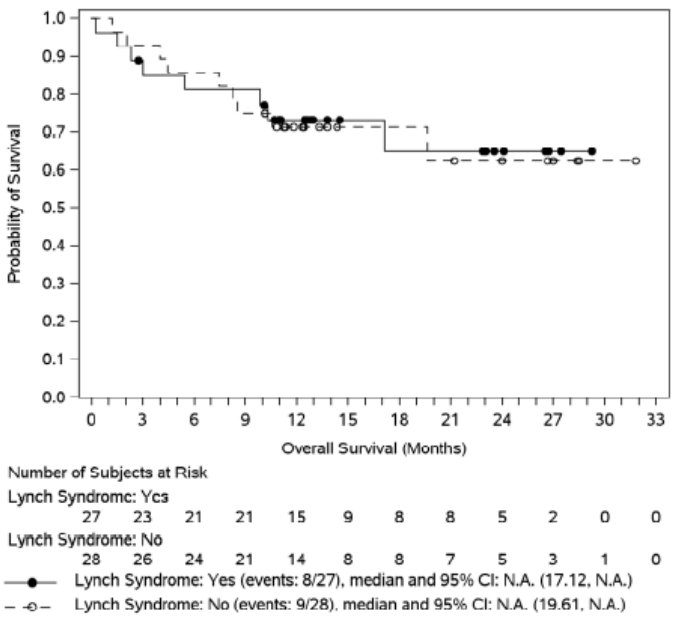
It is challenging to put into historical context the outcome in the sporadic versus germline Lynch syndrome subjects treated on CA209142 as there is little data in the literature regarding differential outcome in the metastatic setting for sporadic dMMR or MSI-H patients, data for the response to anti-PD-1 therapy is limited to a small series from a single institution in which all 6 patients (100%) with mismatch repair–deficient tumours that were not associated with the Lynch syndrome had an objective response, whereas only 3 of 11 patients (27%) with tumours associated with the Lynch syndrome had a response. However, the results in the BRAF subgroup of CA209142 are of particular interest as BRAF mutations are a significant negative prognostic marker for patients with mCRC.

Table 1: Objective Response Rate (per BICR) by Subsets - All Nivolumab Monotherapy Treated Subjects

		OBJECTIVE RESPONSE RATE (%) (A) 95% CI	
		MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53
AGE CATEGORIZATION			
	< 65 YEARS	19/57 (33.3%) (21.4, 47.1)	13/42 (31.0%) (17.6, 47.1)
	>= 65 YEARS	5/17 (29.4%) (10.3, 56.0)	2/11 (18.2%) (2.3, 51.8)
	>= 65 AND < 75 YEARS	2/13 (15.4%) (1.9, 45.4)	0/8 (0.0, 36.9)
LYNCH SYNDROME			
	YES	8/27 (29.6%) (13.8, 50.2)	6/20 (30.0%) (11.9, 54.3)
	NO	10/28 (35.7%) (18.6, 55.9)	3/15 (20.0%) (4.3, 48.1)
	UNKNOWN	6/19 (31.6%) (12.6, 56.6)	6/18 (33.3%) (13.3, 59.0)
KRAS/BRAF MUTATION STATUS			
	KRAS/BRAF WILD-TYPE	9/29 (31.0%) (15.3, 50.8)	6/20 (30.0%) (11.9, 54.3)
	BRAF MUTATION	4/12 (33.3%) (9.9, 65.1)	1/6 (16.7%) (0.4, 64.1)
	KRAS MUTATION	8/26 (30.8%) (14.3, 51.8)	7/22 (31.8%) (13.9, 54.9)
	UNKNOWN	3/7 (42.9%) (9.9, 81.6)	1/5 (20.0%) (0.5, 71.6)

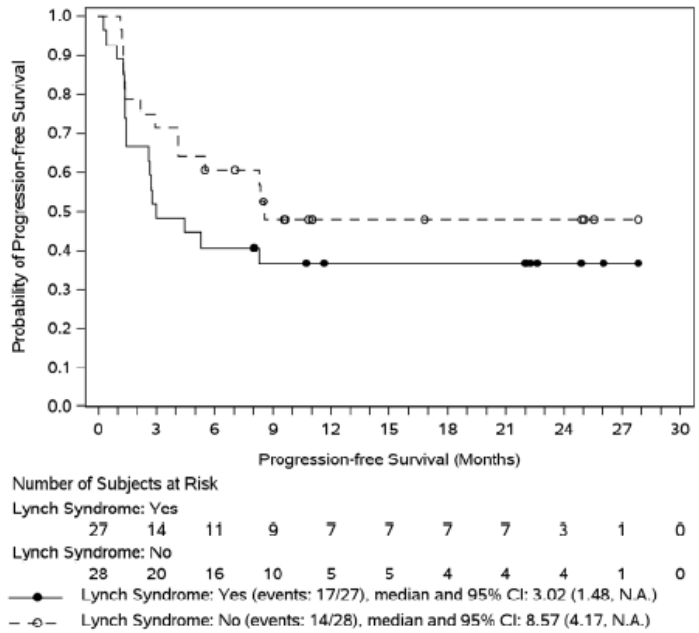
(A) Confidence interval based on the Clopper and Pearson method
Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination
Source: Table 8.5.1.5a of Appendix 3

Figure 1: Kaplan-Meier Plot of Overall Survival by Clinical History of Lynch Syndrome - All Nivolumab Monotherapy Treated Subjects - Subjects with Clinical History of Lynch Syndrome as Yes or No



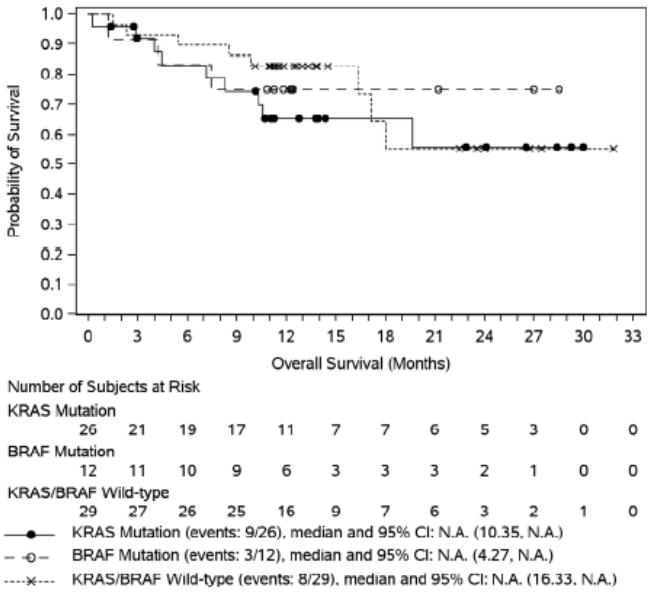
Symbols represent censored observations
Program Source: /projects/bms218374/stats/upd_feb17/prog/figures
Program Name: rg-ef-km-lykr.sas 17MAR2017:08:42:12

Figure 2: **Kaplan-Meier Plot of Progression-free Survival per IRRC by Clinical History of Lynch Syndrome - All Nivolumab Monotherapy Treated Subjects - Subjects with Clinical History of Lynch Syndrome as Yes or No**



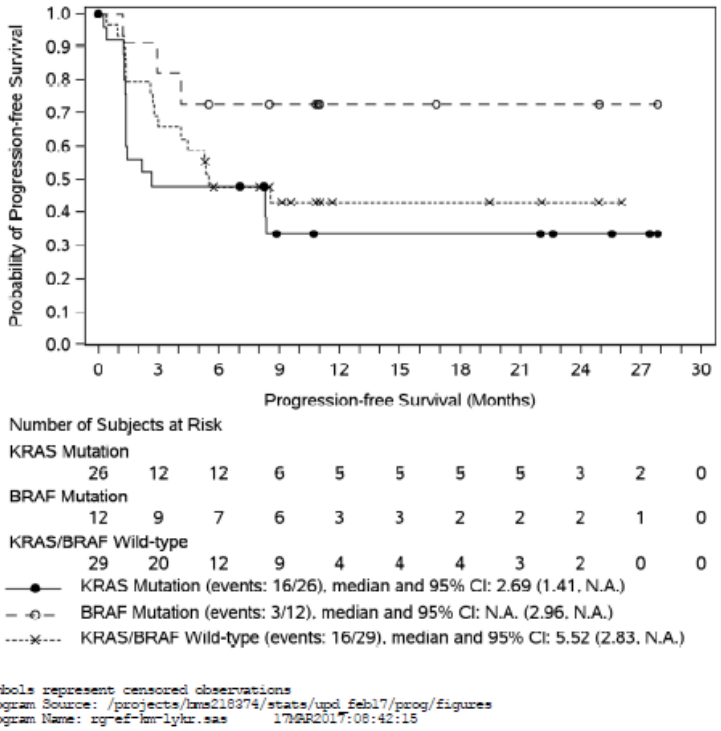
Symbols represent censored observations
Program Source: /projects/bms218374/stats/upd_feb17/prog/figures
Program Name: rg-ef-bm-lykr.sas 17MAR2017:08:42:19

Figure 3: **Kaplan-Meier Plot of Overall Survival by KRAS/BRAF Mutation Status - All Nivolumab Monotherapy Treated Subjects - Subjects with KRAS/BRAF Mutation Status as KRAS Mutation, BRAF Mutation, KRAS/BRAF Wild-type**



Symbols represent censored observations
Program Source: /projects/bms218374/stats/upd_feb17/prog/figures
Program Name: rg-ef-bm-lykr.sas 17MAR2017:08:42:03

Figure 4: **Kaplan-Meier Plot of Progression-free Survival per IRRC by KRAS/BRAF Mutation Status - All Nivolumab Monotherapy Treated Subjects - Subjects with KRAS/BRAF Mutation Status as KRAS Mutation, BRAF Mutation, KRAS/BRAF Wild-type**



Symbols represent censored observations
Program Source: /projects/bms218374/stats/upd_feb17/prog/figures
Program Name: rg-ef-bm-lykr.sas 17MAR2017:08:42:15

CHMP assessment

An update of previous results is presented, which show quite consistent response rates across the relevant subgroups identified, i.e. age, Lynch syndrome, BRAF/KRAS mutations, which is reassuring. Nevertheless, the limited number of patients, lack of mature OS/PFS data and the lack of external supportive evidence preclude firm conclusions at this stage. Further confirmatory data in these relevant subgroups of patients will need to be provided at post-marketing.

Conclusion

Issue solved, provided that the MAH commits to generate additional evidence to confirm these preliminary results in the mentioned relevant subgroups.

9. Analyses are presented by PD-L1 expression, which is based on tumour cell expression. Given the immaturity of the results, a new analysis should be provided.

Summary of the MAH response

The CSR analyses of ORR and PFS (per investigator and BICR) and OS by tumour PD-L1 expression considering the 1% and the 5% threshold were repeated using the 06-Feb-2017 database lock. Subjects with tumour expression of PD-L1 ≥ 1% achieved ORR of 33.3% (7/21) anddisease control rate of 52.4% (11/21), per BICR. Those with tumour expression of PD-L1 < 1% achieved ORR of 27.7%, and disease control rate of 66.0% (31/47), per BICR.

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Best Overall Response and Objective Response (per IRRC) for each PD-L1 Expression Status Group
All Nivolumab Monotherapy Treated Subjects

PD-L1 Expression Result Group	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74
SUBJECTS WITH PD-L1 EXPRESSION >= 1%	21 (28.4)
BEST OVERALL RESPONSE:	
COMPLETE REMISSION (CR)	0
PARTIAL REMISSION (PR)	7 (33.3)
STABLE DISEASE (SD)	5 (23.8)
RELAPSED/PROGRESSIVE DISEASE (PD)	8 (38.1)
UNABLE TO DETERMINE (UTD)	1 (4.8)
OBJECTIVE RESPONSE RATE	7/21 (33.3%)
(95% CI)	(14.6, 57.0)
DISEASE CONTROL RATE	11/21 (52.4%)
(95% CI)	(29.8, 74.3)
SUBJECTS WITH PD-L1 EXPRESSION < 1%	47 (63.5)
BEST OVERALL RESPONSE:	
COMPLETE REMISSION (CR)	0
PARTIAL REMISSION (PR)	13 (27.7)
STABLE DISEASE (SD)	19 (40.4)
RELAPSED/PROGRESSIVE DISEASE (PD)	12 (25.5)
UNABLE TO DETERMINE (UTD)	3 (6.4)
OBJECTIVE RESPONSE RATE	13/47 (27.7%)
(95% CI)	(15.6, 42.6)
DISEASE CONTROL RATE	31/47 (66.0%)
(95% CI)	(50.7, 79.1)

95% CI based on Clopper Pearson method
Program Source: /projects/bms218374/stats/upd_feb17/prog/tables/rt-bm-orrpdl1.sas 15MAR2017:11:00:07

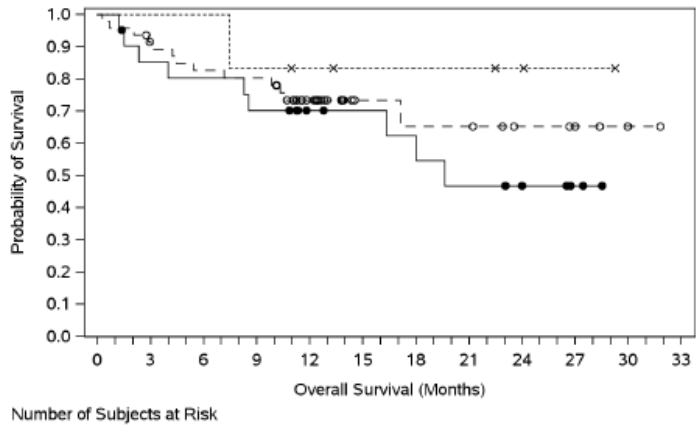
Figure 1 and Figure 2 capture the probability of OS and PFS (per BICR), respectively, for subjects based on tumour PD-L1 expression at the 1% expression level. Similar plots are presented at the 5% expression level in Figure 3 and Figure 4.

In conclusion clinical benefit with nivolumab was observed in both subgroups with tumour expression of PD-L1 ≥ 1% and < 1%. There are 6 subjects with “indeterminate”, “not evaluable” or “missing” tumour PD-L1 result. They achieved 66.7% (4/6) clinical response rate and 83.3% (5/6) disease control rate, per BICR.

Subjects with ≥ 5% tumour PD-L1 expression achieved ORR (per BICR) and disease control rate of 36.4% (4/11) and 54.5% (6/11), respectively. Subjects with < 5% tumour PD-L1 expression had clinical response rate (per BICR) and disease control rate of 28.1% (16/57) and 63.2% (36/57), respectively.

Results suggest that comparable clinical benefit is achieved in subjects regardless of the levels of tumour PD-L1 expression.

Figure 1: **Kaplan-Meier Plot of Overall Survival for each PD-L1 Expression Status Subgroup - All Nivolumab Monotherapy Treated Subjects - Subjects with (≥1 or < 1 % PD-L1 Expression or with Indeterminate, Not Evaluable or Missing PD-L1 Result**

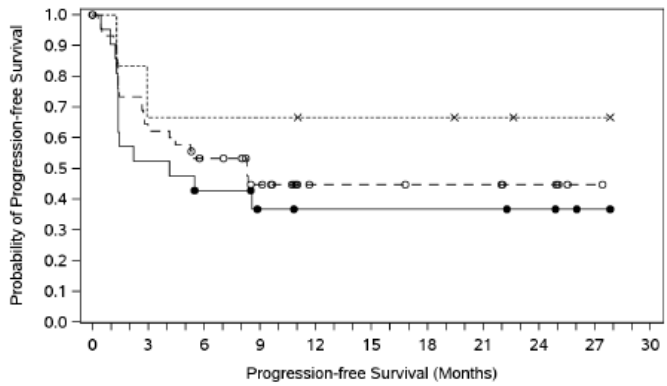


Number of Subjects at Risk

>=1 % PD-L1	21	17	16	14	10	9	8	6	4	2	0	0
<1 % PD-L1	47	41	37	36	23	9	8	8	5	3	1	0
No Result	6	6	6	5	4	3	3	3	2	1	0	0

>=1 % PD-L1 (events: 9/21), median and 95% CI: 19.61 (8.57, N.A.)
<1 % PD-L1 (events: 13/47), median and 95% CI: N.A. (17.12, N.A.)
No Result (events: 1/6), median and 95% CI: N.A. (7.46, N.A.)

Figure 2: **Kaplan-Meier Plot of Progression-free Survival (per IRRC) for each PD-L1 Expression Status Subgroup- All Nivolumab Monotherapy Treated Subjects - Subjects with ≥ 1 or < 1 % PD-L1 Expression or with Indeterminate, Not Evaluable or Missing PD-L1 Result**

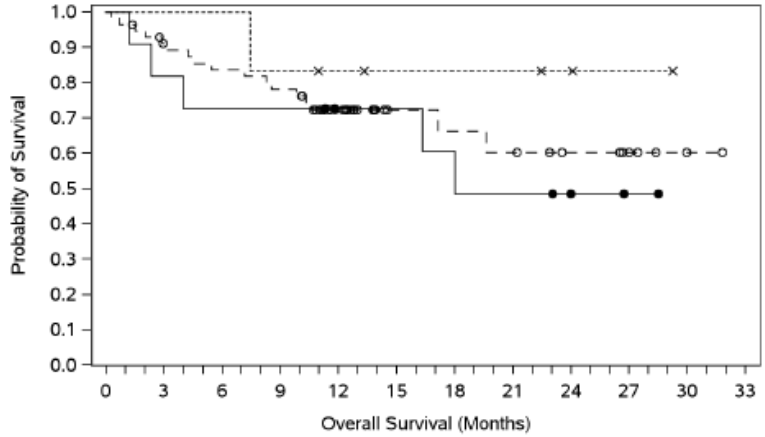


Number of Subjects at Risk

>=1 % PD-L1	21	11	8	5	4	4	4	4	3	1	0
<1 % PD-L1	47	29	22	15	7	7	6	6	4	1	0
No Result	6	4	4	4	3	3	3	2	1	1	0

>=1 % PD-L1 (events: 13/21), median and 95% CI: 4.17 (1.41, N.A.)
<1 % PD-L1 (events: 24/47), median and 95% CI: 8.31 (2.83, N.A.)
No Result (events: 2/6), median and 95% CI: N.A. (1.31, N.A.)

Figure 3: **Kaplan-Meier Plot of Overall Survival for each PD-L1 Expression Status Subgroup - All Nivolumab Monotherapy Treated Subjects Subjects with ≥ 5 or < 5 % PD-L1 Expression or with Indeterminate, Not Evaluable or Missing PD-L1 Result**

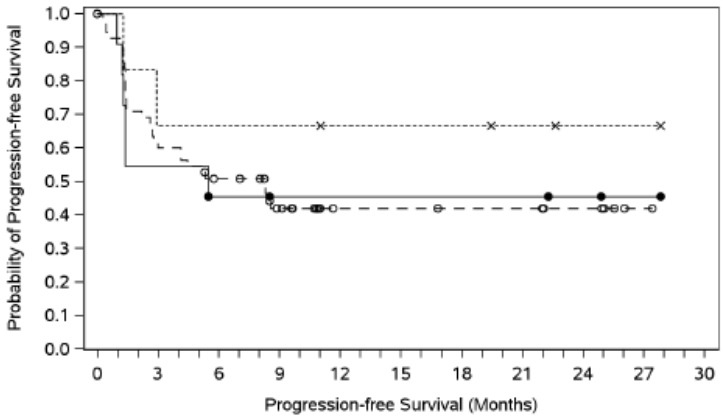


Number of Subjects at Risk

>=5 % PD-L1	11	9	8	8	6	6	5	4	2	1	0	0
<5 % PD-L1	57	49	45	42	27	12	11	10	7	4	1	0
No Result	6	6	6	5	4	3	3	3	2	1	0	0

—●— >=5 % PD-L1 (events: 5/11), median and 95% CI: 18.00 (2.40, N.A.)
– -o– <5 % PD-L1 (events: 17/57), median and 95% CI: N.A. (17.12, N.A.)
----×---- No Result (events: 1/6), median and 95% CI: N.A. (7.46, N.A.)

Figure 4: **Kaplan-Meier Plot of Progression-free Survival (per IRRC) for each PD-L1 Expression Status Subgroup All Nivolumab Monotherapy Treated Subjects Subjects with ≥ 5 or < 5 % PD-L1 Expression or with Indeterminate, Not Evaluable or Missing PD-L1 Result**



Number of Subjects at Risk

>=5 % PD-L1	11	6	4	3	3	3	3	3	2	1	0
<5 % PD-L1	57	34	26	17	8	8	7	7	5	1	0
No Result	6	4	4	4	3	3	3	2	1	1	0

—●— >=5 % PD-L1 (events: 6/11), median and 95% CI: 5.52 (1.25, N.A.)
– -o– <5 % PD-L1 (events: 31/57), median and 95% CI: 8.31 (2.76, N.A.)
----×---- No Result (events: 2/6), median and 95% CI: N.A. (1.31, N.A.)

CHMP assessment

An update of study results based on PD-L1 tumour expression is presented, which show consistent results based either on a 1% or 5% cut-off. The majority of the studied population are <1% (63.5%) or <5% (77%), whilst information is missing for a small number of patients, i.e. 6 patients (8.1%) of the study

population, results in this group should be taken with caution.

Conclusion

Issue solved

10. Mutational status for *KRAS*, *NRAS* and *BRAF* for all 74 patients should be reported and be related to efficacy results, because the mutational status has prognostic and predictive value and could influence efficacy results.

Summary of the MAH response

The KRAS and BRAF information is obtained by local sites and captured in the CRF, per protocol. The NRAS information was not required by the protocol because it was not part of standard of care when the protocol was initiated although it is acknowledged that the recent ESMO consensus guidelines do recommend this testing.

A by-subject listing including BRAF mutation status is presented in Appendix 3.3 of Appendix 5. Please refer to Q8 for new KM analyses of PFS (per investigator and BICR) and OS by KRAS/BRAF mutation status using the 06-Feb-2017 database lock (DBL) and repeated CSR analyses of ORR (per investigator and BICR by subset using that new DBL.

The NRAS genetic lesion is a rare event in MSI-H CRC. According to data reported by The Cancer Genome Atlas, there are only 3 cases of genetic lesions of NRAS in 36 MSI-H CRC (8.3%) tumours.2 Applying that low prevalence to the current study (with 74 subjects), there would potentially be 6 or 7 NRAS subjects; a very low number of subjects that would make It difficult to draw any meaningful information on any correlation with NRAS lesions. While KRAS and NRAS status is mechanistically linked to clinical outcome with EGFR inhibitors, so far there is no clear evidence linking PD-1 antibody response to tumour KRAS or NRAS status.
The Sponsor is planning exploratory next-generation sequencing (NGS) analysis on available tumour samples from Study CA209142. For future subjects, as part of the planned expansion cohort in study CA209142 (see response to Q2d), the sponsor proposes to prospectively capture RAS mutational status (where feasible) and establish any potential correlation with efficacy.

CHMP assessment

Updated results based on the presence of KRAS and BRAF mutations have been provided and discussed in the answer to Question 8.

Concerning NRAS status, no information is available. Since nowadays this is considered a potential marker of prognostic/response to treatment, a proposal to generate this information in the post-marketing as for the other relevant markers, i.e. KRAS and BRAF status should be presented.

Conclusion

Issue solved provided that a proposal to generate additional evidence for these three markers should be presented.

11. The Applicant should clarify how identified protocol deviations were accounted for in the analysis of results presented

Summary of the MAH response

Relevant protocol deviations (significant protocol deviations that were programmable and could potentially affect the interpretability of study results) were reported in 3 subjects (4.1%).Relevant protocol deviation at study entry included no measureable disease at baseline (1 subject), and baseline ECOG > 1 (1 subject). The only relevant protocol deviation during the treatment period was prohibited anti-cancer therapy (1 subject). The Statistical Analysis Plan was not foreseen to exclude any subject from the primary analyses so all these subjects were included in primary analyses. However a sensitivity analysis on "evaluable subjects" was planned for the primary and secondary endpoints of best overall response.

Details of how these deviations were accounted for in the analysis of results are provided below:

- NO MEASURABLE DISEASE AT BASELINE (Subject CA209142-19-52): This subject was included in the primary analyses but was among the subjects excluded in the ORR sensitivity analysis on "evaluable subjects".

- BASELINE ECOG > 1 (Subject CA209142-13-36): This subject was included in the primary analyses. This subject had an ECOG status of 3 on the day of the first dose of study drug (24-Aug-2014). ECOG status at screening was 1. This subject reported a disease progression on 24-Sep-2014 and discontinued for that reason. The date of last dose was on 16-Oct-2014, study day 52. The subject died on 06-Nov-2014.

- PROHIBITED ANTI-CANCER THERAPY (Subject CA209142-22-46): This subject, who began nivolumab on 07-Nov-2014, was included in the primary analyses and no censoring was applied as this treatment was not for a cancer indication. The subject received intraocular bevacizumab on 2 occasions (20-Jan-2015 and 03-Mar-2015) to treat an eye condition (non-cancer indication). The subject was reported as PR (date of first response: 21-Jul-2015) per BICR, this subject is still on-study.

CHMP assessment

Clarification is provided on the relevant protocol deviations and how these were considered in the analyses presented. These 3 cases are not expected to compromise current study results.

Conclusion

Issue clarified. Point solved

12. The Applicant should clarify the reasons why 37 (14.2%) subjects in the CA209142 study did not enter the treatment period despite being enrolled.

Summary of the MAH response

Note that the total of 37 subjects (14.2%) includes all the subjects that did not enter the treatment period for either the monotherapy or combination therapy arms. The IVRS system setting does not detail for which cohort the subject was screened. As the subjects may have been screened for another cohort, this number overestimates the percentage of subjects who no longer met study criteria and did not enter the treatment period for the monotherapy cohort. A total of 119 subjects were treated on the combination arm, and therefore, the overall rate of subjects not entering the treatment period is (37/[74+1190 or 37/193) is low.

Interim CSR and a summary of reasons for not entering treatment period is provided in Table 1. Among these 37 subjects who were enrolled but not treated due to not meeting study criteria, the most common reasons include the following: issues with pathology eligibility criteria (insufficient tissue or subject found not to be MSI-H), chronic hepatitis infections, decline in clinical condition or ECOG performance status, and laboratory values that did not meet eligibility criteria.

Table 1: All Enrolled Subjects - Initial Evaluation Did Not Entered the study - Excluding re-enrolled subjects- Subject no Longer Meets Study Criteria

Subject ID	Specification for Subject no Longer Meets Study Criteria (sorted alphabetically
CA209142-22-207	2E
CA209142-24-97	2G
CA209142-19-63	ALL ASSESSMENT HAVE BEEN DELETED BY THE PATIENT
CA209142-25-118	ASAT, ALAT > 3 ULN
CA209142-11-99	BIOPSY SAMPLE IS NOT AVAILABLE
CA209142-8-4	DECLINED BIOPSY
CA209142-36-147	DID NOT HAVE MEASURABLE DISEASE
CA209142-4-42	DOES NOT MEET INCLUSION CRITERIA 2E
CA209142-25-137	ECOG 2 ,
CA209142-27-145	ECOG AND LABS
CA209142-8-2	ELEVATED BILLIRUBIN LEVELS, DO NOT MEET ELIGIBILITY CRITERIA
CA209142-22-115	EXCLUSION 2A
CA209142-4-65	EXCLUSION 3A --PAST MEDICAL HISTORY OF HEPATITIS C
CA209142-34-47	EXCLUSION CRITERIA 2C. PATIENT RECENTLY DIAGNOSED WITH A SMALL PROSTATE ADENOCARCINOMA, GLEASON GRADE 6 ON 8/20/201
CA209142-39-158	FAILED INCLUSION CRITERIA 1B
CA209142-36-144	FOUND TO BE NOT MSI HIGH
CA209142-32-209	HBV CHRONIC INFECTION
CA209142-24-48	HEPATITIUS C VIRUS ANTIBODY
CA209142-22-61	INCLUSION 2C
CA209142-32-88	INCLUSION CRITERIA 1B
CA209142-11-24	LABORATORY GOT/GPT > 3 X UNL
CA209142-35-132	LOW HEMOGLOBIN
CA209142-28-120	LOW PLATELETS
CA209142-25-244	NO MEASURABLE DISEASE PER RECIST 1.1 AND NEGATIVE BIOPSY
CA209142-10-14	NO TUMOR CELLS EXCEPSY OBTAINED.
CA209142-10-17	NO TUMOR CELLS EXCEPSY OBTAINED.
CA209142-27-249	PATIENT CONDITION DECLINE
CA209142-39-265	PATIENT DID NOT MEET EXCLUSION CRITERIA 3A
CA209142-2-252	PATIENT FOUND TO NOT BE MSI-HIGH
CA209142-2-259	PATIENT WAS FOUND TO NOT BE MSI-H
CA209142-4-254	PLATELETS LESS THAN 100K/CUMM.
CA209142-8-133	SUBJECT DOES NOT MEET ELIGIBILITY CRITERIA DUE TO RECENT HOSPITALIZATION FOR SMALL BOWEL OBSTRUCTION
CA209142-8-66	THE INVESTIGATOR DIDN'T BELIEVE THE SUBJECT WOULD BE COMPLIANT WITH ALL STUDY REQUIREMENTS.
CA209142-10-108	THE PATIENT NOT HAS HIGTH STABILITY OF MSI-H
CA209142-8-67	THE SUBJECT DIDN'T MEET THE PROTOCOL DEFINITION FOR MSI-H EXPRESSION
CA209142-19-140	TRANSAMINASES LEVEL UP TO ALLOWED INCLUSION CRITERIA VALUES-
CA209142-32-236	WORSENING IN GENERAL CONDITIONS (ECOG 3)
	N = 37

Source: Appendix 2.3 of the CA209142 Interim CSR

CHMP assessment

Adequate clarification is presented to the point raised.

Conclusion

Issue solved

13. Clarification is also requested about the single case where maximum clinical benefit was reported as the reasons for treatment discontinuation, given that this was not a reason established in the protocol.

Summary of the MAH response

Note that, per protocol, a subject may discontinue treatment upon request. The subject who discontinued because of the investigator's clinical impression of 'maximum clinical benefit' is Subject CA209142-3-9. This subject had stage IV rectal cancer with multiple metastasis to the liver and began nivolumab therapy on 12-Jun-2014. In Apr-2015, this subject progressed clinically, presenting with worsening rectal pain. The subject was treated with re-irradiation (30 Gy) to the rectal primary. Nivolumab therapy was held during radiation therapy. Repeat imaging on 03-Jun-2015 showed continued response in his liver metastases. The subject then underwent a low anterior resection on 08-Jun-2015 with pathology showing 1% viable tumour.

The subject was consented for treatment beyond progression on 03-Aug-2015, at which time the liver lesions demonstrated continued response (per protocol: treatment beyond investigator assessed RECIST 1.1-defined progression will be permitted if the subject experiences investigator-assessed clinical benefit and the subject is tolerating the study treatment). On 06- Jan-2016 the subject underwent an exploratory laparatomy for an anastamotic leak at his rectal stump. Two liver metastases were resected during that procedure, both demonstrating pCR.

Neither was the measurable lesion that the investigator was following for RECIST 1.1 measurements. The last dose of nivolumab was on 28-Mar-2016. On 21-Apr-2016, the subject was admitted to the hospital with increasing perianal pain and infectious drainage from the surgical site. The subject had a prolonged course of treatment for the post-operative complications. A scan done on 17-Jul-2016 demonstrated continued response in the measurable lesions, although the subject had previously had a per time point response of progressive disease due to the clinical progression in the primary rectal tumour. Nivolumab treatment was discontinued on 18-Jul-2016.

CHMP assessment

The requested clarification has been presented.

Conclusion

Issue solved

14. Internal validity is also questioned regarding the conduct of the single pivotal trial.
    a. The Applicant should explain how the number of confirmed responses under monotherapy could change from 4 confirmed responses and 2 in SD to 7 confirmed responses.
    b. Although the number of 7 confirmed responses formally enabled to open the monotherapy arm, actually both monotherapy and combination therapy were open, while type I error for ORR over the whole study was only planned conditional that either the mono- or the combination arm is open. Therefore it is not clear if and how type I error control is protected for ORR (e.g. if the Applicant would in a later time would also apply for combination therapy using this trial's data) and the Applicant should explain this.
    c. The second stage of monotherapy arm raises several issues. Firstly, no testing as preplanned in the Simon two-stage design was reported. Secondly, an unplanned sample size increase. To clarify the impact of this, proper inference is requested (e.g. Koyama & Chen, Stat in Med 2007). Thirdly, the analysis population was changed (from those centrally MSI tested to those locally MSI tested) from stage 2 onwards which makes the design so adaptive that the impact on type I error of ORR should be discussed. An analysis using the first 29 centrally MSI confirmed in second stage, i.e. as planned, would at least be expected.
    d. Sample size was powered for analysis of ORR, but for more clinically relevant endpoints, such as PFS and OS, no type I error control was planned. The Applicant should discuss the robustness of these results incorporating at least an analysis with confidence levels adjusted (simultaneously) for the two-stage design, increased sample size at stage 2 and for a 2.5% one-sided (instead of 5% one-sided as planned for ORR) perspective.

Summary of MAH answer part A

When the protocol was designed, the assumption was that 24 weeks of follow-up would be sufficient to observe a response and obtaining central MSI status results were not expected to be challenging.

However, in practice the transition from mStage1 to mStage 2 was confounded by both the observation of later responses and delays in obtaining MSI status by central laboratory (usually due to insufficient tissue or necrotic tissue in samples received).

- The monotherapy arm (mStage1) had the first patient first treatment (FPFT) on 01-May-2014.
- The number of confirmed responses per investigator assessment in the first 19 subjects with centrally-confirmed MSI-H was evaluated in May-2015.
- At that point, among these 19 centrally-confirmed MSI-H subjects, the number of confirmed responders was 4 (PIDs: CA209142-3-9, CA209142-3-38, CA209142-22-37, CA209142-24-44); and 2 additional subjects (PIDs: CA209142-25-59, CA209142-28-60) who had not yet reached the week 24 time point had a best response of SD. Therefore, the maximum number of subjects who would demonstrate a BOR of a partial response or better was estimated to be 6 subjects. This did not account for the remainder of the subjects who had sustained SD at that time and might have had the potential to become responders. Per the protocol, if the ORR was 3-6 out of the first 19 central MSI-H confirmed mStage1 subjects, combination stage 1 (cStage1) would open.
- Later evaluation of mStage1 revealed 7 confirmed responders in the monotherapy arm, including 4 prior confirmed responders and 2 potential responders plus 1 late responder (at week 60 tumour assessment, PID CA209142-16-32); therefore the original criteria for progressing to mStage2 were considered reached.
- As a result, the monotherapy arm was initiated for accrual to mStage2 on 30-Oct-2015 after the enrolment to cStage1 was completed (ie, to add 29 subjects with centrally confirmed MSI-H in monotherapy arm).
- During the mStage1 review, approximately 32% (9/28) of subjects who enrolled to monotherapy with MSI-H per local testing did not have confirmed central MSI-H (for a variety of reasons including processing delays at sites and no viable tissue available). Therefore, mStage2 enrolled additional subjects to ensure at least 48 centrally-confirmed MSI-H subjects.
- The mStage1 eventually treated with a total of 32 subjects per local testing MSI-H, of whom 21 later were confirmed with central testing. After mStage2 initiated, an additional 42 subjects with locally tested MSI-H were treated and 32 of them were later centrally confirmed MSI-H. In total, the monotherapy cohort treated a total of 74 subjects per locally tested MSI-H and 53 of them later confirmed with central testing.

CHMP assessment - part A

CA2091425 studies both nivolumab monotherapy as combination therapy of nivolumab and ipilimumab and both arms followed a two-stage design. In the monotherapy arm at first 19 patients would be treated. In case of confirmed response (PR or CR) in 7 or more patients, additional patients would be enrolled in the monotherapy arm. Responses in 2 or less patients would lead to closure of the study and responses in 3-6 patients to closing of the monotherapy arm and opening of the combination arm. The MAH explained that during evaluation of the first stage part in May 2015 4 patient responded and 2 patients had best response of SD (follow-up <24 weeks). The MAH expected the number of responses not to exceed 6 and therefore decided to close the monotherapy arm and start the combination therapy. During later evaluation (date of this evaluation is not reported) 7 patients had confirmed response, including the original confirmed responders, the two patients with SD, and one additional late responder. Now, the threshold of 7 confirmed responders was reached, and at 30-Oct-2015 the second phase was initiated for additional inclusion in the monotherapy arm. With this response the MAH explains the increase in number of responders, and, although the predefined design was not followed, in particular the time to response was allowed beyond 24 weeks, and both mono- and combination therapy

arms were open (see later), this explanation is accepted.

Summary of MAH answer part B

When designing the MSI-H cohort, there was limited historical data regarding response rate in the MSI-H population. It was also uncertain if nivolumab + ipilimumab combination therapy would provide additional benefit over nivolumab monotherapy (refer to response to Q2a). Therefore, both the monotherapy arm and the combination therapy arm in the MSI-H cohort were designed as separate single arm cohorts with very high target ORR. The sample size in each arm was determined independently using Simon's 2-stage design with the same underlying assumptions in order to evaluate the efficacy for each regimen independently (see Section 3.6 of the CA209142 Interim CSR). The only difference was that the start of the combination arm would depend on the acceptable safety profile from the non-MSI-H cohort as well as on the number of responders observed during the stage 1 review in the monotherapy arm. Since the stage 1 review of the monotherapy arm occurred in May-2015 revealed only 4 confirmed responders and 2 potential responders (see response to Q14a), the stage 1 of the combination arm (cStage1) started enrolment per protocol. However, 7 confirmed responses in the monotherapy cohort emerged after longer follow-up and clinical meaningful evidence of efficacy were observed. Of note:

1) the time to response could take longer than the protocol specified window of mStage1 evaluation;
2) the early 4 confirmed responders demonstrated durable responses (1 with DOR of 6.8 months and 3 with ongoing responses with DOR > 5 months);
3) one additional responder (PID CA209142-35-69, with central confirmed MSI-H) was observed among the mStage1 treated subjects beyond the 7 confirmed responders among the first 19 central confirmed MSI-H subjects.

To confirm these preliminary efficacy findings, the Sponsor decided to initiate mStage2 enrolment after the closure of cStage1 enrolment and while waiting for cStage1 review per Simon's design (of note, cStage2 enrolment opened after mStage2 enrolment was completed). Due to this change, the MSI-H cohort of this study actually fully enrolled in both monotherapy and combination therapy arms. Because of the different experimental regimens of the 2 arms and non-overlapping subjects in the 2 arms, the statistical analyses of efficacy and safety will be conducted independently for each arm and the type I error is only controlled at the experimental arm level.

CHMP assessment - part B

According to the MAH the monotherapy and combination therapy arm were designed as separate single arm cohorts with very high target ORR. In that case type I error could be considered controlled.
However, the Applicant's viewpoint is considered questionable, as the original planning was that if mStage1 was successful then it would be followed by mStage 2 (and cStage 1 or 2 would not open); if mStage 1 would be unsuccessful (as it was according to the original design), cStage 1 would open and if successful cStage 2 would open. Therefore, in the original design was more like an adaptive trial that had possibility to change the treatment and pursue success of the combination only after failing of the monotherapy arm. On top of that, actually both the mono- and the combination treatment arms started in Stage 1 and 2, which means that the protection of type I error by preplanning was lost, since the planned design was abandoned. While this is understandable for phase 2 trial, the trial results can be considered retrospective results at best when used for confirmatory testing.

Summary of MAH answer part C

The original statistical analysis plan (SAP) planned to utilize the Atkinson and Brown method for calculating the 95% CI of ORR accommodating the Simon's 2-stage design and that the analysis population would be based on subjects with central confirmed MSI-H. However, due to the real-world impracticality of obtaining central confirmation on all subjects, necessitating a higher actual enrolment of 74 subjects with MSI-H per local testing, the Sponsor revised the SAP to utilize the Clopper and Pearson method for calculating the 95% CI (refer to Section 7.5.1 in Appendix 11.1A of the CA209142 Interim CSR). Due to the lag time of the central testing of MSI-H, the monotherapy arm actually treated a total of 53 subjects with central confirmed MSI-H (refer to Appendix 3.3B of the CA209142 Ad hoc Efficacy Report based on subjects with central confirmed MSI-H using the 19-Sep-2016 DBL).To confirm robustness of the Clopper and Pearson estimate, the Sponsor conducted the following analyses of ORR per IRRC and per investigator assessment based on the 19-Sep-2016 DBL used in the submission package:

- an analysis assuming the study was conducted with a mStage1 of 19 subjects and a mStage2 of 29 subjects per central confirmed MSI-H (ie, using the first 48 subjects with central confirmed MSI-H). Clopper and Pearson method and Atkinson and Brown method were used for the analyses.
- an analysis based on all the 53 central confirmed MSI-H subjects. Clopper and Pearson method and Koyama and Chen method were used for the analyses.

A summary of the results is described in Table 49. ORR and 95% CI per IRRC and investigator were consistent across the 4 analyses. These ORRs also demonstrated consistency with the ORR observed in the all treated subjects per local testing MSI-H (N=74, 27% [Table S.5.1.1A of the CA209142 interim CSR] and 31% [Table S.5.1.1B of the CA209142 interim CSR]) for IRRC and investigator, respectively).1 In addition, the Clopper and Pearson method provides a conservative estimate of the lower bound of 95% CI.

Table 48. ORR per investigator and IRRC in patients with central confirmed MSI-H

Method	Responder/sample size in Stage 1	Responder/sample size in Stage 2	Total responders/sample size	ORR 95% CI
Per Investigator				
Clopper and Pearson	7/19	9/29	16/48	33.3% (20.4, 48.4)
Atkin and Brown	7/19	9/29	16/48	33.3% (22.0, 56.6)
Clopper and Pearson	7/19	12/34	19/53	35.8% (23.1, 50.2)
Koyama and Chen	7/19	12/34	19/53	37.7%, (24.2, 56.7)
Per IRRC				
Clopper and Pearson	8/19	7/29	15/48	31.3% (20.7, 56.6)
Atkin and Brown	8/19	7/29	15/48	31.3% (20.7, 56.6)
Clopper and Pearson	8/19	9/34	17/53	32.1% (19.9, 46.3)
Koyama and Chen	8/19	9/34	17/53	35.9% (21.7, 56.7)

Source: Table S.CH.5A and Figure EU.COQ4C of Appendix 6, Table S.CH.5 of the CA209142 Ad hoc efficacy report [2]

CHMP assessment - part C

Actually the MAH does not discuss possible loss of type I error control due to the possible change in populations (due to testing locally instead of centrally). Given that this is a difficult issue, this issue is not further pursued.

As regards type of confidence intervals, the MAH did originally plan Atkinson & Brown confidence intervals. Those do account for the two stages, but not for the over-enrolment in stage 2. The Clopper-Pearson confidences that were chosen instead are in general more conservative (i.e. a 95% Clopper Pearson interval often turn out to be 96 or higher % CI), but this does not mean per se that they account for two stages, while the method by Koyama and Chen does. From the analyses with the originally planned and the over-enrolled sample size in stage 2, the (lower bound of the) 95%-CI is rather stable and larger than 19.9%. Therefore, the over-enrolment has not substantial impact on the ORR conclusion of the trial.

Summary of MAH answer part D

The Sponsor acknowledges that the type I error control was not planned for PFS and OS. This was due to the nature of the single-arm design where indirect comparison to historical data for time to event

analysis is a challenge. As a single-arm design, while the primary goal was to estimate ORR and durability of response, the other key objectives were to estimate median PFS, median OS, PFS rates, and OS rates at time points in order to enable indirect reference to historical data in this patient population. To ensure stable estimates, appropriate sample size with good amount of follow-up is critical. The sample size of 74 all treated subjects in this study provided reasonable estimate of the precision of the ORR (see Section 2 of the CA209142 Ad hoc Efficacy Report).In addition, as of the 06-Feb-2017 DBL, a minimum follow-up of 11 months has been reached, including a minimum follow-up of 22 months for subjects enrolled to mStage1. This amount of follow-up enabled stable estimate of the duration of response as well as OS rates at 12 months. In summary, as discussed in the response to Q2c, observed durable response and sustained disease control directly linked to prolonged OS which was consistent with other tumours treated with nivolumab monotherapy and compared favourable to treatments in 3L/4L from historical data in metastatic CRC.

The analysis with confidence levels adjusted (simultaneously) for the 2-stage design, increased sample size at stage 2 and for a 2.5% one-sided (instead of 5% one-sided as planned for ORR) was calculated using Atkinson & Brown method and Koyama & Chen method (see response to Question 14c).

CHMP assessment - part D

The MAH states that indeed no type I error control was planned for PFS and OS analysis, but that the sample size of 74 patients would ensure stable estimates. Furthermore, observed durable response and sustained disease control were directly linked to prolonged OS, which is not agreed. The argument that OS in study CA209142 compared favourable to other 3/4L treatments in mCRC is regarded invalid. The request for providing 95%-(two sided) confidence intervals for PFS and OS accounting for the two-stage design seems to be ignored by the MAH. The MAH only refers to the fact that OS should be stable with current follow-up. The latter is not agreed due to censoring present, which if they turn out to be events, would substantially lower OS

CHMP conclusion

The CHMP recognizes the inherent limitations of a single arm exploratory trial, particularly, the potential overestimation of the study results. The uncertainties regarding type I error control on ORR and more importantly PFS and OS due to deviation from original plan (over-enrolment in stage 2 and opening up two studies) remain, and render the results more exploratory than confirmative evidence. **Issue not resolved.**

15. An update for PFS data is requested, as well as analyses for time to next treatment (TTF), TTF2 and PFS2.

Summary of MAH answer

As requested, the Sponsor conducted new progression-free survival (PFS) analyses (per investigator and BICR). Here, updated efficacy are provided using the more mature 06-Feb-2017 data base lock (DBL), which includes approximately 5 months additional follow-up versus the 19-Sep-2017 DBL with a total follow-up of a minimum of 11 months (defined as difference between the 06-Feb-2017 DBL and the first date of treatment for the last treated subject [16-Mar-2016]) (Table 50). A summary of the updated dataset is presented in Q2.

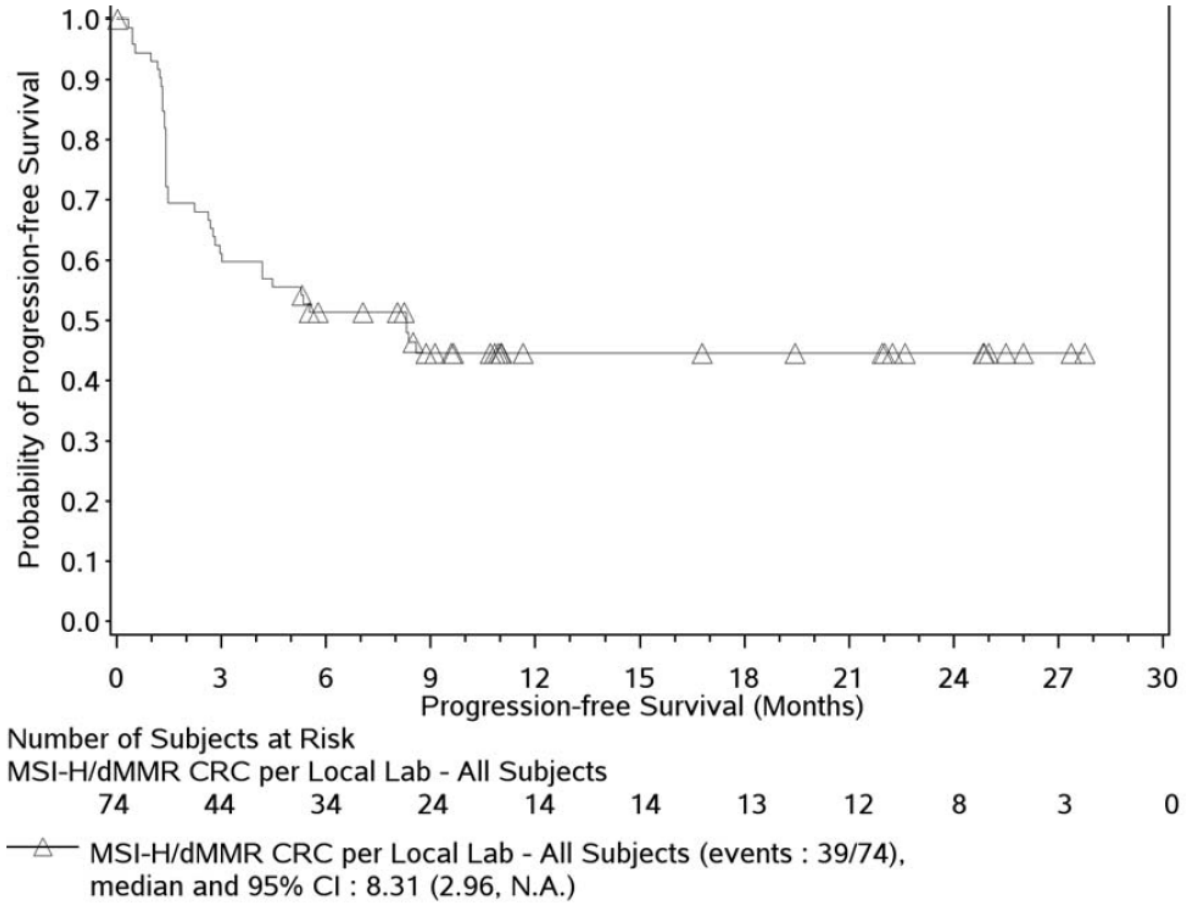
Table 49. PFS per IRRC for all treated patients (DBL 06-Feb-2017)

	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74
# EVENTS / # SUBJECTS (%)	39/74 (52.7)
MEDIAN PFS (MONTHS) (95% CI)	8.3 (3.0, N.A.)
3 MONTHS	
N AT RISK	44
PFS RATE (95% CI)	61.1 (48.9, 71.3)
6 MONTHS	
N AT RISK	34
PFS RATE (95% CI)	51.3 (39.3, 62.1)
9 MONTHS	
N AT RISK	24
PFS RATE (95% CI)	44.6 (32.6, 55.8)
12 MONTHS	
N AT RISK	14
PFS RATE (95% CI)	44.6 (32.6, 55.8)
18 MONTHS	
N AT RISK	13
PFS RATE (95% CI)	44.6 (32.6, 55.8)
24 MONTHS	
N AT RISK	8
PFS RATE (95% CI)	44.6 (32.6, 55.8)

Median computed using Kaplan-Meier method
N.A.: Not Available
Source: Table S.5.2.1A of Appendix 7

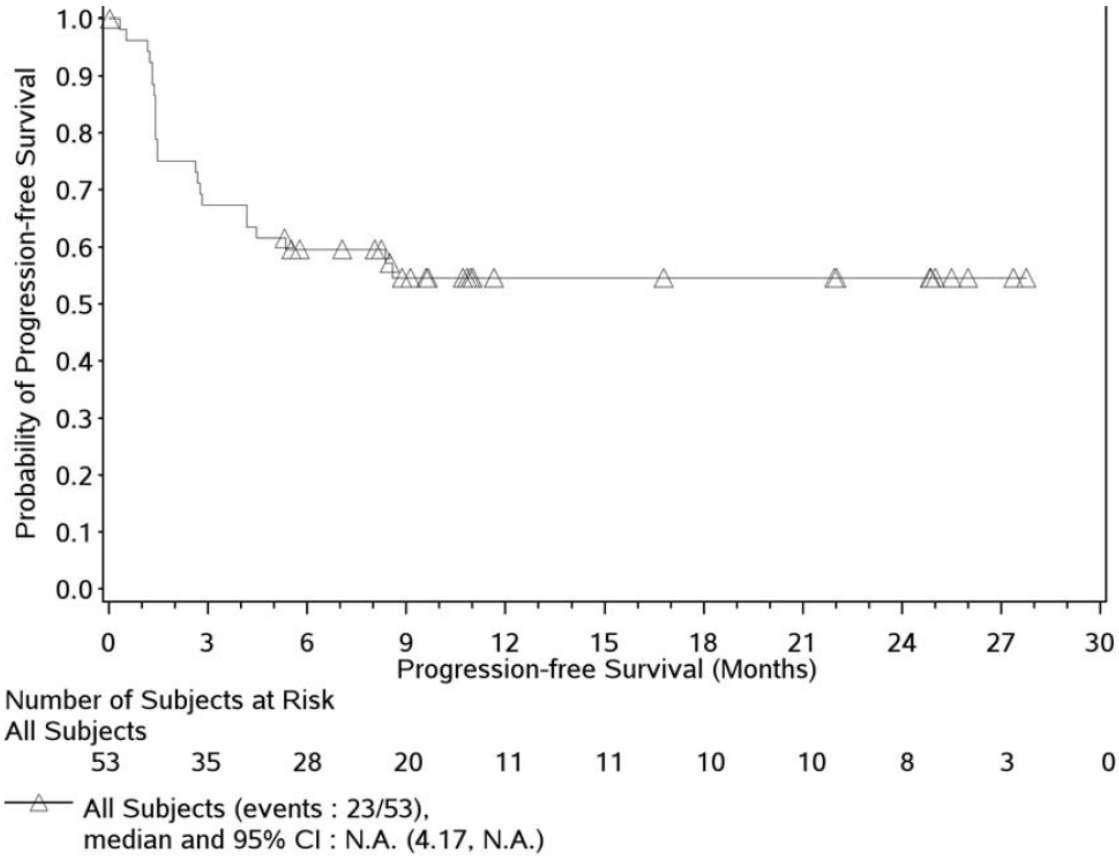
Figure 23 present the PFS Kaplan-Meier (KM) curves using BICR data. As compared with the 19-Sep-2017 DBL, 4 more subjects progressed (for a total of 39/74, 52.7% of subjects), the median PFS increased from 7.59 months (95% CI: 3.02, NA) to 8.31 months (95% CI: 2.96, NA) with a similar 12-month PFS rate (45.6% [95% CI: 32.2, 58.1]). Analysis of PFS per investigator (Figure S.5.2.1B of Appendix 7) showed a similar behaviour with an increase in median PFS from 9.59 months (95% CI: 4.30, NA) to 14.29 months (95% CI: 4.30, NA) and similar 12-month PFS rate (50.4% [95% CI: 38.1, 61.4]).

Figure 17. Kaplan-Meier plot PFS per IRRC for MSI-H patients per local lab



In addition, Figure 24 presents the PFS KM curve per BICR using the centrally confirmed subjects (N = 53). Please see response to Q9 for the other analyses using the centrally confirmed subjects.

Figure 18. Kaplan-Meier plot PFS per IRRC patients with MSI-H per central evaluation



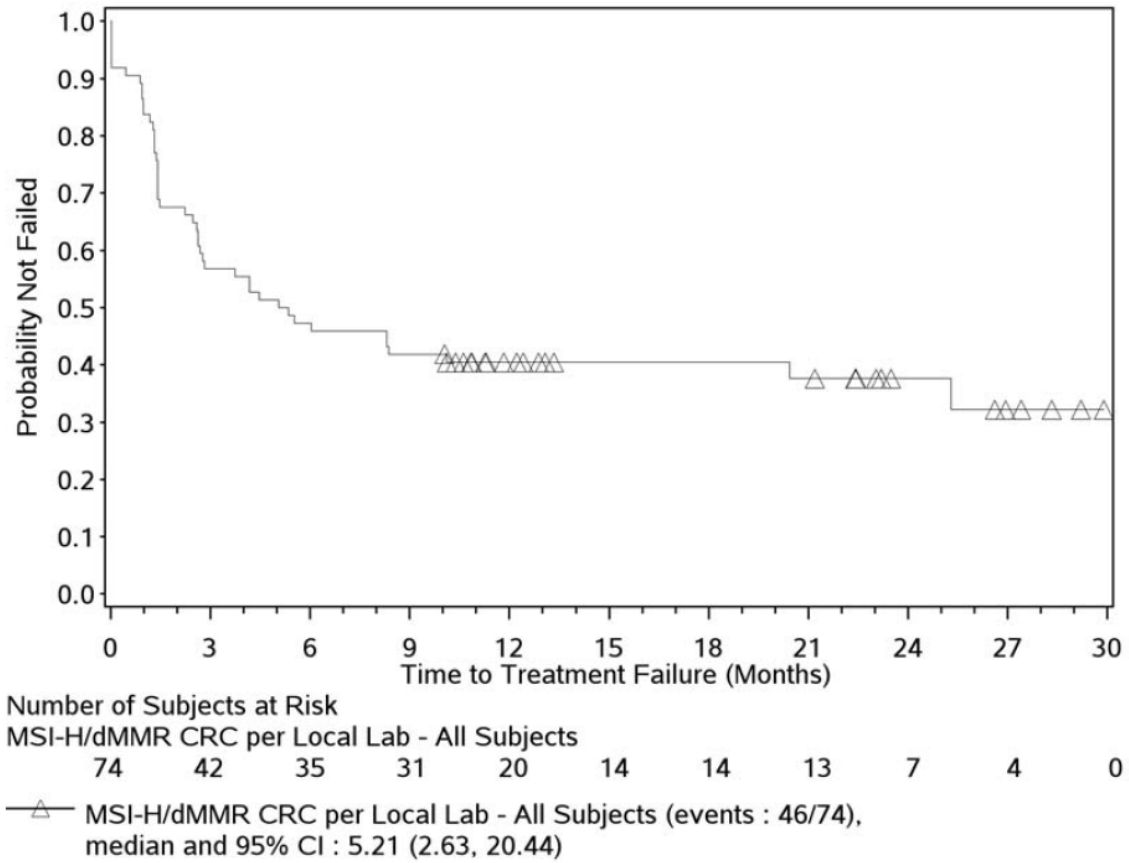
Most of the subjects who were censored did not receive any subsequent therapy. Of the 30 subjects who were censored, 29 were censored on date of last tumour assessment on study. Of these, only 1 received subsequent therapy and 4 were progression-free in follow-up (Table S.5.2.2A and Table S.5.2.2B of Appendix 7).

As requested, the Sponsor conducted an analysis of Time to Treatment Failure, (usually abbreviated as "TTF") on the 06-Feb-2016 DBL. For this analysis, treatment failure (per investigator and BICR, respectively) has been defined for treated subjects as the time from date of first dose to the earliest date of the following events: investigator (or BICR, respectively) progression date, treatment discontinuation for any reason, initiation of subsequent anti-cancer therapy, or death. If the subject did not experience any of these events, TTF was censored at the last dosing date.

Of note, CA209142, the primary reasons for study treatment discontinuation were (in decreasing order and in more than one subject) disease progression and study drug toxicity (Table S.2.5 of Appendix 7).

Figure 25 presents the KM plot of TTF per BICR. 46/74 subjects (62.2%) reported a treatment failure. The median TTF is 5.21 months (95% CI: 2.63, 20.44). TTF per investigator, presented in Figure EU.COQ5B of Appendix 7, reported similar results.

Figure 19. Kaplan-Meier plot TTF per IRRC MSI-H patients per local lab



As per the Sponsor's standards, in which studies do not collect further details of disease progression when on subsequent therapies except continue tumour assessment until first disease progression on study regardless of initiation of subsequent therapy the Case Report Form (CRF) did not include gathering of data that would be needed to conduct an analysis of Time to Treatment Failure on subsequent therapy (usually abbreviated "TTF2") or PFS on subsequent therapy (usually abbreviated "PFS2") and the Sponsor is unfortunately unable to provide these requested analyses.

CHMP assessment

Updated PFS results with the new DBL of 06-Feb-2017 are reported and resulting in an additional follow-up of 5 months. Investigator-assessed median PFS increased from 9.59 to 14.29 months, for IRRC-assessed PFS this was from 7.59 to 8.31 months. Also an analysis of time to treatment failure was presented using the following as events: progression, treatment discontinuation, initiation of subsequent anti-cancer therapy, or death. Using IRRC assessment, 62.2% of patients had treatment failure after a median of 5.21 months. Using investigator assessment, failure percentage was 56.8% with a median of 8.02 months. TTF2 and PFS2 data were not collected and could therefore not be provided.

Issue resolved.

16. Effect on PFS and OS was lower in PD-L1 positive patients. This might suggest that PD-L1

expression in tumour cells is not a predictive biomarker. In MSI colorectal cancer, the PD-L1 expression appears not to be on tumour cells, but rather on tumour-infiltrating lymphocytes and/or myeloid cells. To understand the mechanism of action of nivolumab in MSI-H mCRC it is essential to analyse, amongst other biomarkers, PD-L1 expression on the tumour-infiltrating cells and to correlate expression with efficacy.

Summary of MAH answer

In an exploratory, post-hoc analysis using a non-validated assay, tumour-associated immune cell (TAIC) PD-L1 expression was qualitatively analysed in relation to the magnitude of treatment effect of nivolumab. The Sponsor conducted new efficacy analyses (ORR, PFS [both per investigator and per BICR], and OS) by PD-L1 expression on the tumour-infiltrating cells using the 06-Feb-2017 database lock (DBL). The level of PD-L1 expression was determined by pathologist's qualitative analysis and categorized into "abundance of PD-L1 Expressing Immune Cells" as "rare", "intermediate" or "numerous". The pathologist subjectively assessed the relative presence of mononuclear immune cells in the tumour microenvironment, with "numerous" characterized as the presence of easily detected mononuclear cells in the field, compared to "rare" where few cells could be identified. "Intermediate" was subjectively defined as anything in between "numerous" and "rare" by the pathologist. These categories were used here.

Table 51 tabulates BOR, ORR, and DCR for these categories:

- Subjects with "Rare" expression of PD-L1 by TAICs achieved ORR and DCR of 20.8% (5/24) and 54.2% (13/24), respectively, per BICR.
- Subjects with "Intermediate" expression of PD-L1 by TAICs achieved ORR and DCR of 23.8% (5/21) and 66.7% (14/21), respectively, per BICR.
- Subjects with "Numerous" expression of PD-L1 by TAICs achieved ORR and DCR of 43.5% (10/23) and 65.2% (15/23), respectively, per BICR.

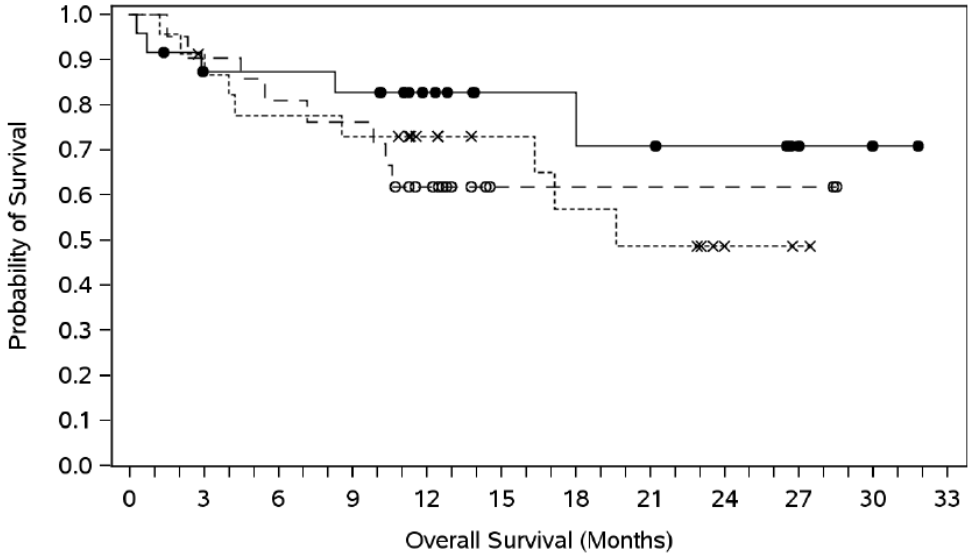
Table 50. BOR and OR per IRRC by abundance of PD-L1 expressing immune cells

Abundance of PD-L1 Expressing Immune Cells	MSI-H/dMMR CRC per Local Lab All Subjects N = 74
SUBJECTS WITH PD-L1 EXPRESSING IMMUNE CELLS: RARE	24 (32.4)
BEST OVERALL RESPONSE:	
COMPLETE REMISSION (CR)	0
PARTIAL REMISSION (PR)	5 (20.8)
STABLE DISEASE (SD)	8 (33.3)
RELAPSED/PROGRESSIVE DISEASE (PD)	9 (37.5)
UNABLE TO DETERMINE (UTD)	2 (8.3)
OBJECTIVE RESPONSE RATE	5/24 (20.8%)
(95% CI)	(7.1, 42.2)
DISEASE CONTROL RATE	13/24 (54.2%)
(95% CI)	(32.8, 74.4)
SUBJECTS WITH PD-L1 EXPRESSING IMMUNE CELLS: INTERMEDIATE	21 (28.4)
BEST OVERALL RESPONSE:	
COMPLETE REMISSION (CR)	0
PARTIAL REMISSION (PR)	5 (23.8)
STABLE DISEASE (SD)	10 (47.6)
RELAPSED/PROGRESSIVE DISEASE (PD)	6 (28.6)
UNABLE TO DETERMINE (UTD)	0
OBJECTIVE RESPONSE RATE	5/21 (23.8%)
(95% CI)	(8.2, 47.2)
DISEASE CONTROL RATE	14/21 (66.7%)
(95% CI)	(43.0, 85.4)
SUBJECTS WITH PD-L1 EXPRESSING IMMUNE CELLS: NUMEROUS	23 (31.1)
BEST OVERALL RESPONSE:	
COMPLETE REMISSION (CR)	0
PARTIAL REMISSION (PR)	10 (43.5)
STABLE DISEASE (SD)	6 (26.1)
RELAPSED/PROGRESSIVE DISEASE (PD)	5 (21.7)
UNABLE TO DETERMINE (UTD)	2 (8.7)
OBJECTIVE RESPONSE RATE	10/23 (43.5%)
(95% CI)	(23.2, 65.5)
DISEASE CONTROL RATE	15/23 (65.2%)
(95% CI)	(42.7, 83.6)

95% CI based on Clopper Pearson method
Program Source: /projects/bms218374/stats/upd_feb17/prog/tables/rt-bm-orrpdl1imm.sas
16MAR2017:13:18:24

Figure 26 and Figure 27capture the probability of OS and PFS (per BICR), respectively, for subgroups based on TAIC PD-L1 expression. PFS and OS curves by category of abundance of PD-L1 expressing TAICs have areas of overlap, suggesting that this parameter is not a clear predictive biomarker of PFS and OS in this population.

Figure 20. Kaplan-Meier plot OS by abundance of PD-L1 expressing immune cells



Number of Subjects at Risk

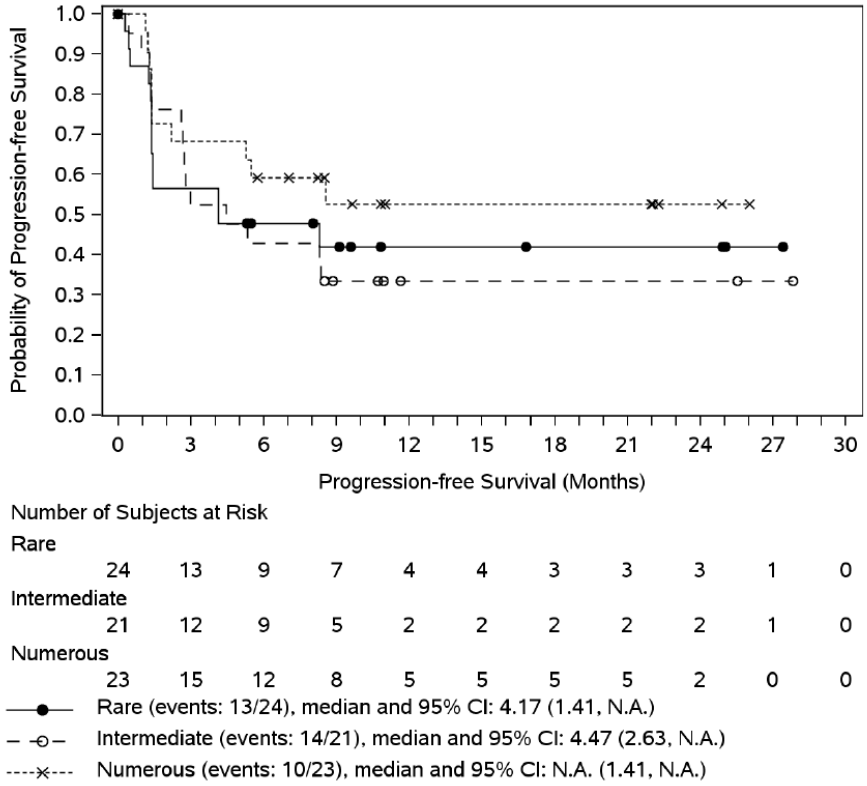
Rare	24	19	19	18	11	7	7	6	5	2	1	0
Intermediate	21	19	17	16	10	2	2	2	2	2	0	0
Numerous	23	20	17	16	12	9	7	6	2	1	0	0

Rare (events: 5/24), median and 95% CI: N.A. (18.00, N.A.)

Intermediate (events: 8/21), median and 95% CI: N.A. (9.86, N.A.)

Numerous (events: 9/23), median and 95% CI: 19.61 (8.57, N.A.)

Figure 21. Kaplan-Meier plot PFS per IRRC by abundance of PD-L1 expressing immune cells



Understanding of the role for tumour-associated immune cells is an area of active exploratory investigation in ongoing trials.

CHMP assessment

Post-hoc analysis for PD-L1 expression in tumour-associated immune cells (TAICs) was performed using a non-validated, qualitative assay with one pathologist defining expression as *rare*, *intermediate* of *numerous* without using numerical cut-off points. IRRC-assessed ORR was 21% in patients with *rare* PD-L1 expression in TAICs, 23.8% in the *intermediate* group, and higher in the *numerous* group, namely 43.5%. Results were given for 68 patients and the two patients with CR were not in the analysed group. In the Kaplan-Meier plot for survival, the curve for *rare* expression is above the one for *intermediate* and *numerous* expression. The lines for *intermediate* and *numerous* cross and for the tails of the plot, the curve for *numerous* expression is below the one with *intermediate* expression. Although the numbers are low, this might suggest that *rare* expression is correlated with the best survival, which is contradicting the hypothesis of PD-1 inhibition in MSI-H mCRC. The MAH states that understanding the role for TAICs is an area of active exploratory investigation in ongoing trials, but also for CA209142 more efforts should be taken to investigate PD-L1 expression in both tumour and immune cells with a validated assay, especially because of the rationale of using anti-PD1 therapy in these tumours.

Issue resolved provided that the MAH will continue to investigate the role of PD-L1 expression in tumour cells and TAICs in their clinical program, including the population of MSI-H mCRC.

17. Efficacy results are also reported for a not predefined subpopulation of patients receiving fluoropyrimidine, oxaliplatin and irinotecan (prior 5FU-Oxa-Iri). This subgroup has a less

favourable effect from nivolumab treatment, possibly because this subgroup has a more advanced disease with worse prognostic features, which is also suggested by the higher number of prior lines of chemotherapy. In subgroup analyses nivolumab is less effective when time from initial diagnoses is longer and when the number of prior lines of therapy is higher. The lower response rates are therefore not unexpected and the Applicant is requested to analyse progression since the start of first-line therapy in the metastatic setting for patients with prior 5FU-Oxa-Iri and to compare this with the all treated patient group.

Summary of MAH answer

As requested, the Sponsor conducted the suggested new analysis. The 06-Feb-2016 database lock (DBL) has been used for the analysis so that more mature data could be considered. This analysis of "progression since the start of first-line therapy in the metastatic setting" uses the same definition as PFS (so events of progression are the ones under the nivolumab monotherapy) but it considers the start of first-line therapy in the metastatic setting as starting date rather than the first dose of study therapy.

Figure 28 and Figure 29present the KM plots of progression since the start of first-line therapy for all subjects and for subjects with prior 5FU-Oxa-Iri. These curves are very similar to each other over their entirety, although with numerically different median progression since start of first line therapy (40.15 months for all subjects [95% CI: 21.26, 57.59] and 49.51 months for subjects with prior 5FU-Oxa-Iri [95% CI: 21.26, 73.63]). The 95% CI of the medians are largely overlapping.

Figure 22. Kaplan-Meier plot progression since start of first line therapy

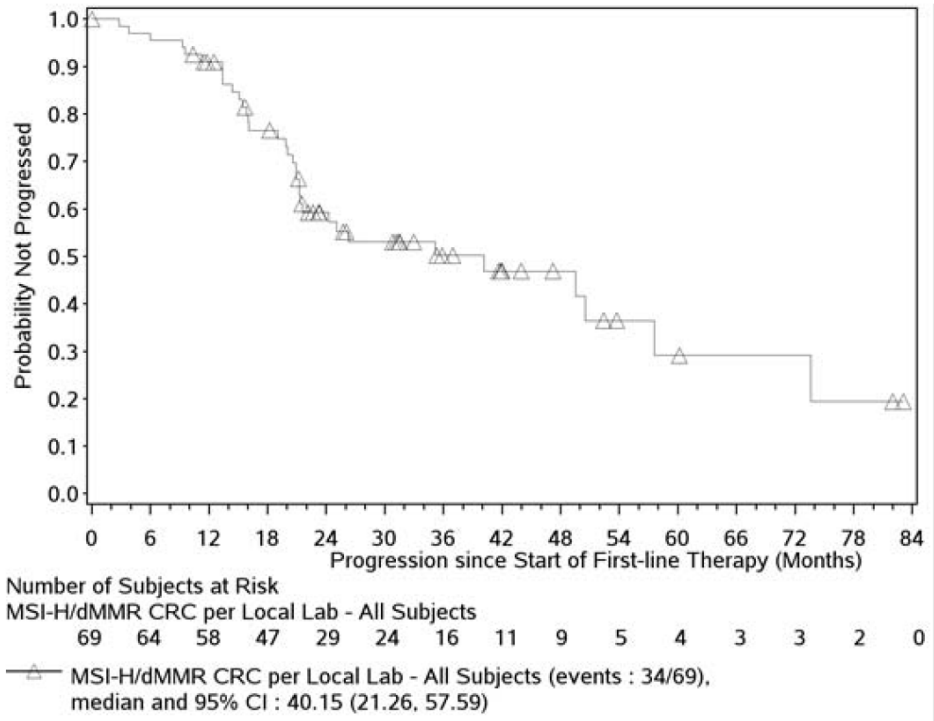
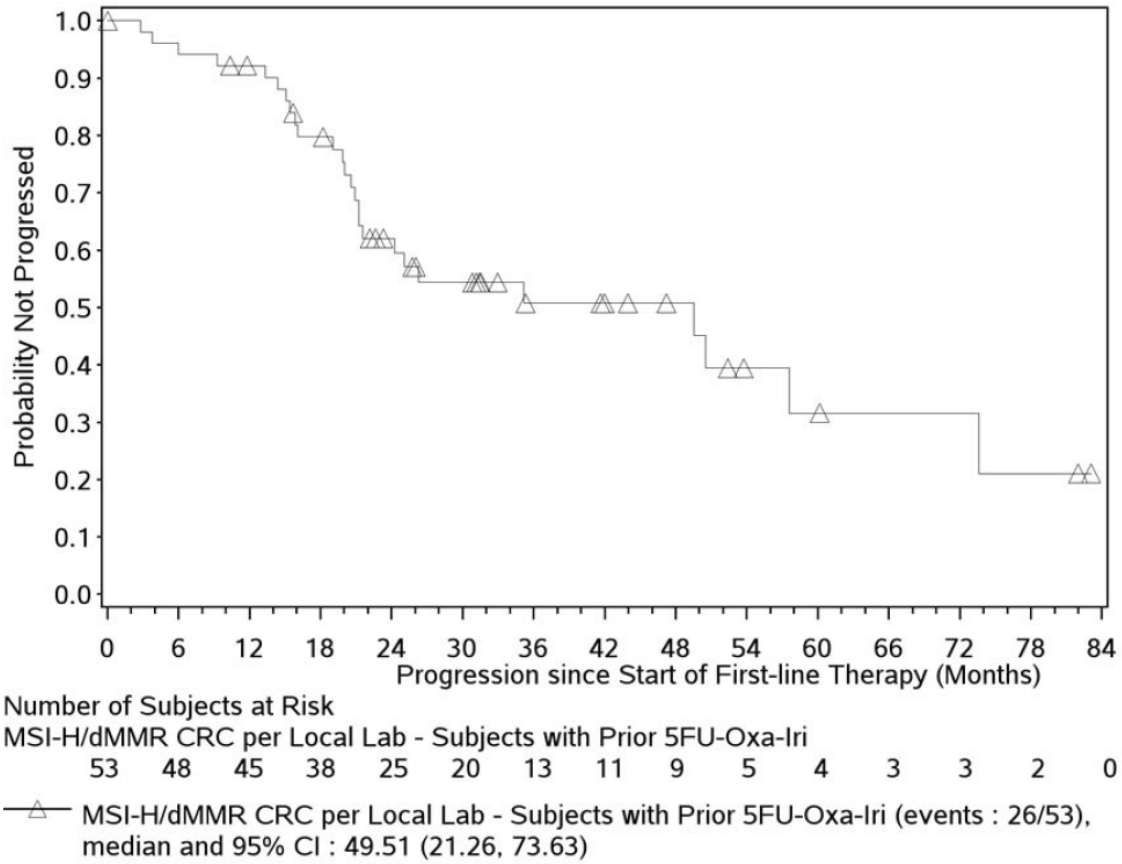


Figure 23. Kaplan-Meier plot progression since start of first line therapy patients with prior 5FU-Oxa-Iri



CHMP assessment

The MAH analysed progression since the start of first-line therapy in the metastatic setting. When analysing all patients, progression was at a median of 40.2 months (CI95% 21.26-57.59). For the subgroup with prior 5FU-Oxa-Iri this was 49.5 months (CI95% 21.23-73.63). Although confidence intervals are overlapping, this indeed suggests that the worse prognosis in the 5FU-Oxa-Iri subgroup might be explained by the more progressed disease.

It is noticed that progression after start of first-line therapy is both groups is more than 40 months, suggesting that the study population has a more favourable prognosis than the general mCRC population. This is an extra argument that a randomised controlled trial is needed to determine the benefit of nivolumab in the subpopulation of dMMR mCRC.

It is not reported if progression was analysed with the IRRC or investigator assessments, so it is unknown with which numbers the results should be compared. For IRRC-assessed PFS the difference in the medians between all patients and the ones with prior 5FU-Oxa-Iri is -3.8 months, for investigator assessment there is no difference.

Issue resolved.

18. From the all monotherapy treated group 68 patients were response-evaluable by investigator assessment and 65 by IRRC. For the investigator assessments, responses in 4 patients were 'unable to determine' having no on-study evaluations because of early discontinuation or death. IRRC assessment could not determine responses in 5 patients (3 had no on-study evaluation because of early discontinuation or death; 2 were censored for subsequent radiotherapy) and response was not reported for 1 patient (no scan sent to IRRC). First of all, this decreases the

already small sample size and secondly, not all missing evaluations are accounted for. The Applicant is asked to explain the number of patients not being evaluable for response.

Summary of MAH answer

Per the Statistical Analysis Plan, "Response Evaluable Subjects" are defined as "treated subjects who have baseline and at least 1 on-study evaluable tumour measurement". For the investigator assessment, 6 subjects were not evaluable. These are as follows:

- 1 subject had no baseline assessment for target disease (CA209142-19-52, reported as SD in the primary analysis) due to a baseline evaluation performed on Day 8.
- 4 subjects (reported as unable to determine (UTD) in the primary analysis) had no on study evaluation because of early discontinuation (CA209142-30-103 and CA209142-34-45), death (CA209142-3-8), or censoring for subsequent radiotherapy (CA209142-37-57).
- 1 subject (CA209142-22-31, reported as PD in the primary analysis) had no on-study evaluations because of censoring for subsequent radiotherapy on his first dose date (07-Aug-2014). This was actually as a result of the imputation of an incomplete pre-treatment radiotherapy start date (2014 that was imputed to 07-Aug-2014, per pre-specified imputation rules). This has been corrected in the 06-Feb-2017 database lock (DBL) following the collection of the exact date (10-May-2014) and this subject is no longer "not evaluable".

For the BICR assessment, 9 subjects were not evaluable including the above 6. These are as follow:

- 2 subjects had no baseline assessment for target disease (CA209142-19-52, reported as SD in the primary analysis due to a baseline evaluation performed on Day 8 and CA209142-3-38, reported as complete response [CR] in the primary analysis due to no finding of target lesion at baseline per BICR).
- 5 subjects (reported as UTD in the primary analysis) had no on-study evaluation because of early discontinuation (CA209142-30-103 and CA209142-34-45), death (CA209142- 3-8), or censoring for subsequent radiotherapy (CA209142-37-57 and CA209142-22-31), see above.
- 1 subject (reported as PD in the primary analysis) had no on-study evaluation because of death (CA209142-12-150).
- 1 subject (reported as 'Not Reported' in the primary analysis) had no baseline nor on-study assessment (CA209142-30-53, for whom no scan was sent to the BICR).

Results of BOR per BICR and per investigator analyses for the All Nivolumab Treated Subjects population (primary population) and the Response Evaluable Subjects population (conducted as a sensitivity analysis) are similar indicating the limited impact of these non-evaluable subjects.

CHMP assessment

The MAH explains for all the patients that were not evaluable for response.
Issue resolved.

19. The Applicant demonstrated the number of disconcordant results between assessments by investigator or independent review, but case by case discrepancy per outcome of the tumour evaluation (i.e. CR, PR, PD, or SD) should also be shown.

Summary of MAH answer

As requested, the Sponsor conducted this new analysis using the CSR (19-Sep-2016) database lock (DBL). Table 52presents the contingency table of BOR as determined by investigator and by BICR per outcome of the tumour evaluation (ie, CR, PR, PD, or SD) at the subject level.

Considering the all nivolumab monotherapy treated subjects, among the 23 PRs per investigator, 16 were confirmed as PR by BICR with 2 evaluated as CR, 3 as SD and 2 as PD. Among the 29 SDs per investigator, 23 were confirmed as SD by BICR with 2 evaluated as PR and 4 as PD. Among the 17 PDs per investigator, 14 were confirmed as PD by BICR with 2 evaluated as SD and 1 as unable to determine (UTD).

Although there were few discrepancies in individual results described above, the concordance rate (defined as the frequency with which Investigator and BICR agreed on classification of a subject as responder (CR/PR) vs. non-responder/UTD (SD/PD/UTD)) as a proportion of the total number of subjects assessed by both the investigator and BICR) is 90.4 %, for the all nivolumab monotherapy treated subjects.

Table 51. Concordance of BOR between investigator and BICR assessments

Number of Subjects (%)

CONFIRMED BOR

MSI-H/dMMR CRC per Local Lab - All Subjects
N = 74

	CR	PR	SD	PD	UTD	TOTAL
BOR PER INVESTIGATOR						
CR	0	0	0	0	0	0
PR	2 (2.7)	16 (21.9)	3 (4.1)	2 (2.7)	0	23 (31.5)
SD	0	2 (2.7)	23 (31.5)	4 (5.5)	0	29 (39.7)
PD	0	0	2 (2.7)	14 (19.2)	1 (1.4)	17 (23.3)
UTD	0	0	0	0	4 (5.5)	4 (5.5)
TOTAL	2 (2.7)	18 (24.7)	28 (38.4)	20 (27.4)	5 (6.8)	73 (100.0)
CONCORDANCE RATE (1):		90.4 %				

Number of Subjects (%)

CONFIRMED BOR

MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri
N = 53

	CR	PR	SD	PD	UTD	TOTAL
BOR PER INVESTIGATOR						
CR	0	0	0	0	0	0
PR	1 (1.9)	10 (19.2)	1 (1.9)	2 (3.8)	0	14 (26.9)
SD	0	1 (1.9)	16 (30.8)	3 (5.8)	0	20 (38.5)
PD	0	0	2 (3.8)	12 (23.1)	0	14 (26.9)
UTD	0	0	0	0	4 (7.7)	4 (7.7)
TOTAL	1 (1.9)	11 (21.2)	19 (36.5)	17 (32.7)	4 (7.7)	52 (100.0)
CONCORDANCE RATE (1):		92.3 %				

CR: Confirmed complete response PR: Confirmed partial response SD: Stable disease PD: Progressive disease UTD: Unable to determine
(1) Quantifies the frequency with which Investigator and IRRC agreed on classification of a subject as responder (CR/PR) vs. non-responder/UTD (SD/PD/UTD) as a proportion of the total number of subjects assessed by both the investigator and IRRC
Program Source: /projects/bms218374/stats/upd_feb17/prog/tables/rt-ef-borconc-eu.sas
22MAR2017:09:53:32.

CHMP assessment

The MAH provided the case by case discrepancy numbers as requested.

Issue resolved.

20. Immunotherapy is known to possibly induce pseudo-progression which could be misinterpreted as progression during tumour evaluation scans. Using tumour markers, such as CEA levels, could guide the decision whether a patient is progressive or not. Therefore, the Applicant should provide CEA levels for the studied population at baseline, during treatment and follow-up and in correlation with PD-L1 expression levels.

Summary of MAH answer

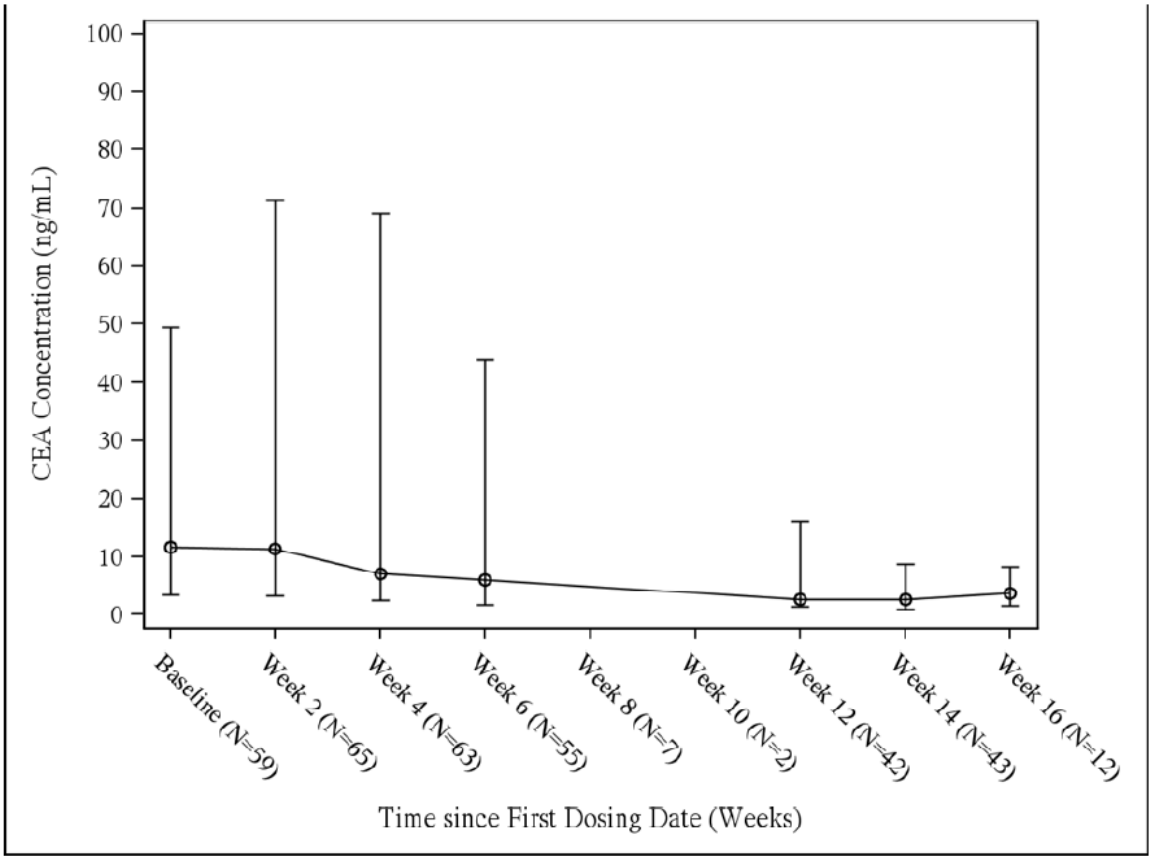
Carcinoembryonic antigen (CEA) levels were measured in Study CA209142. The Sponsor conducted new analyses using the 06-Feb-2017 database lock (DBL) to address this request (Table 53). Figure 30, Figure 31, and Figure 32 present the median CEA levels over time for all subjects and by subgroup of PD-L1 expression level (note that only two data points were reported during a follow-up visit, these are included in the data used to generate these figures).

Table 52. Baseline and Week 6 CEA levels

	MSI-H/dMMR CRC per Local Lab – All Subjects N = 74				
Nominal Timepoint	N	Mean	STD	Median	Q25-Q75
ALL SUBJECTS					
BASELINE	59	143.26	595.060	11.70	3.40 - 49.40
ON-TREATMENT WEEK 6	55	52.65	139.655	6.00	1.70 - 43.90
WEEK 6 % CHANGE FROM BASELINE	44	-15.82	69.376	-36.89	-68.22 - 6.25
SUBJECTS WITH TUMOR PD-L1 >= 1%					
BASELINE	16	30.67	68.671	5.15	1.85 - 26.75
ON-TREATMENT WEEK 6	14	68.26	183.742	2.75	1.00 - 24.80
WEEK 6 % CHANGE FROM BASELINE	10	-13.26	71.850	-44.35	-53.33 - 40.00
SUBJECTS WITH TUMOR PD-L1 < 1%					
BASELINE	38	207.18	735.731	18.90	4.70 - 77.20
ON-TREATMENT WEEK 6	36	48.81	130.434	7.05	2.40 - 45.40
WEEK 6 % CHANGE FROM BASELINE	30	-23.72	64.157	-37.99	-70.69 - -0.23
SUBJECTS WITH PD-L1 EXPRESSING IMMUNE CELLS: RARE					
BASELINE	18	315.95	1054.193	13.80	3.70 - 39.10
ON-TREATMENT WEEK 6	18	78.75	182.526	6.75	2.30 - 38.10
WEEK 6 % CHANGE FROM BASELINE	14	-6.13	68.553	-23.57	-50.59 - 0.00
SUBJECTS WITH PD-L1 EXPRESSING IMMUNE CELLS: INTERMEDIATE					
BASELINE	18	35.57	54.204	13.35	5.80 - 42.10
ON-TREATMENT WEEK 6	14	20.79	25.404	5.55	2.50 - 43.90
WEEK 6 % CHANGE FROM BASELINE	13	-15.20	79.440	-57.72	-70.69 - 15.68
SUBJECTS WITH PD-L1 EXPRESSING IMMUNE CELLS: NUMEROUS					
BASELINE	18	113.13	210.406	20.00	2.30 - 78.50
ON-TREATMENT WEEK 6	18	55.80	160.309	6.70	1.50 - 46.90
WEEK 6 % CHANGE FROM BASELINE	13	-43.15	40.738	-50.00	-80.30 - -11.80
WEEK 6 CHANGE FROM BASELINE FOR ALL SUBJECTS BY BEST OVERAL RESPONSE PER IRRC CATEGORY					
WEEK 6 % CHANGE FROM BASELINE	44	-15.82	69.376	-36.89	-68.22 - 6.25
CR+PR	19	-44.29	42.388	-56.41	-83.63 - -16.22
SD (>=12 Weeks)	17	-11.46	68.804	-45.06	-57.72 - 15.68
CR+PR+SD (>=12 Weeks)	36	-28.79	58.004	-47.92	-69.55 - -1.28
PD+SD (<12 Weeks)	8	42.53	89.373	-4.66	-21.12 - 143.86

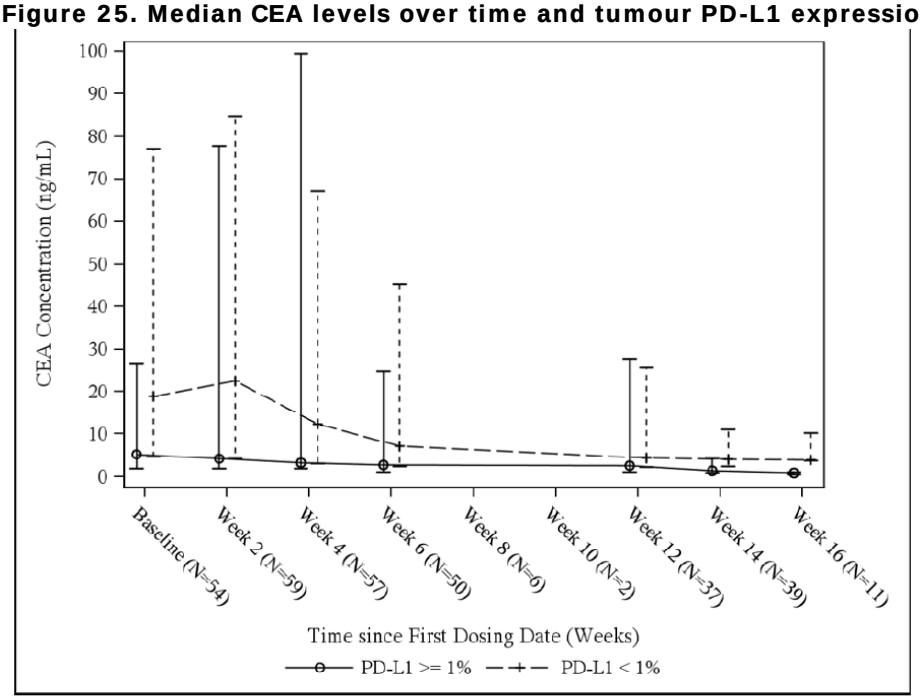
Note: For subsets involving PD-L1, the population is "All PD-L1 Evaluable Nivolumab Monotherapy Treated Subjects" Week 6 is defined by selecting the closest value to study day 42 using the window >=35 and <49 "Week 6 change from baseline" is only defined for subject with baseline and Week 6 data. CR: Confirmed complete response PR: Confirmed partial response SD: Stable disease PD: Progressive disease Program Source: /gbs/prod/clin/programs/ca/209/142/csria04/rpt/ebr-eu-req/20170308/rt-km-ceasum-v01.sas 24-MAR-2017 09:54

Figure 24. Median CEA levels over time



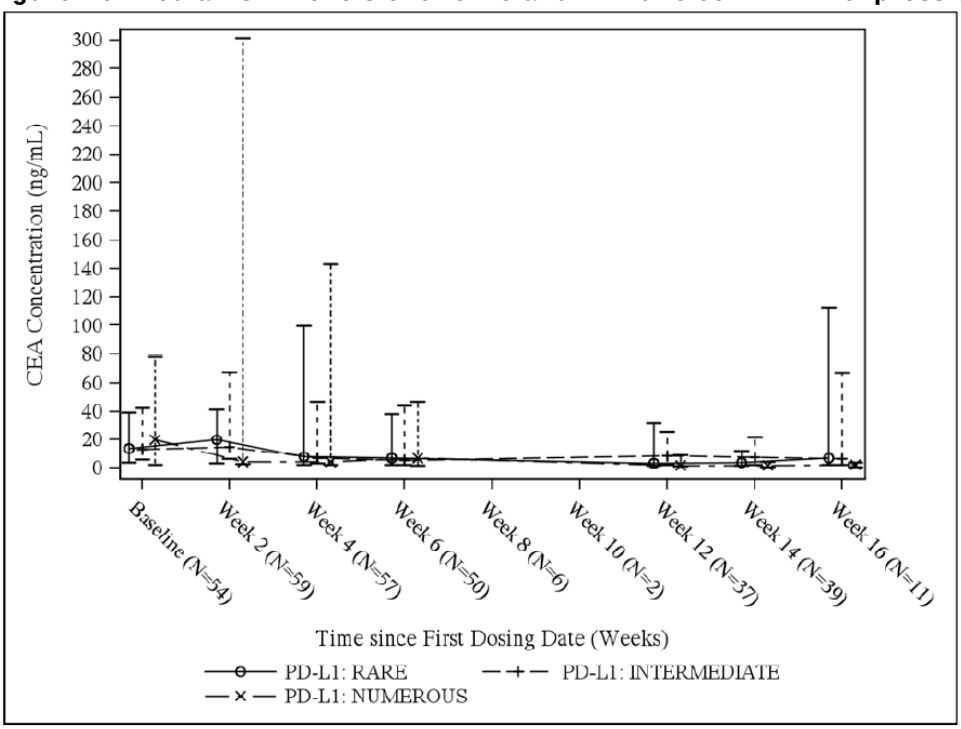
Note 1: only the timepoints where at least 10 subjects among the All Nivolumab Monotherapy Treated Subjects have data are reported.
Note 2: Bars around each median represent Q1 and Q3.
Program Source: /gbs/prod/clin/programs/ca/209/142/csria04/rpt/ebr-eu-req/20170308
Program Name: rg-bm-ceaall-v01.sas 22MAR2017:10:12:51

Figure 25. Median CEA levels over time and tumour PD-L1 expression



Note 1: only the timepoints where at least 10 subjects among the All Nivolumab Monotherapy Treated Subjects have data are reported.
Note 2: Bars around each median represent Q1 and Q3.
Program Source: /gbs/prod/clin/programs/ca/209/142/csria0

Figure 26. Median CEA levels over time and immune cell PD-L1 expression



Note 1: only the timepoints where at least 10 subjects among the All Nivolumab Monotherapy Treated Subjects have data are reported.
Note 2: Bars around each median represent Q1 and Q3.
Program Source: /gbs/prod/clin/programs/ca/209/142/csria04/rpt/ebr-eu-req/20170308
Program Name: rg-bm-ceaimm-v01.sas 22MAR2017:10:13:00

The CEA results by tumour PD-L1 (using a cut-off of 1%, Figure 31) and by tumour-associated immune cell (Figure 32) did not reveal differences in median CEA level over time. Furthermore, analysis on change from baseline by Week 6, a particular time point of interest which coincides with the first radiographic analysis, showed similar changes from baseline in median value for each of the reported PD-L1 subgroups (-44.35, -37.99, -23.57, -57.72, and -50.00 for tumour cell PD-L1 □1%, <1%, and PD-L1 expressing tumour-associated immune cells "rare", "intermediate" and "numerous", respectively), suggesting absence of association between CEA levels and PD-L1 expression levels. At Week 6, subjects achieving durable disease control (CR+PR+SD□12 week) had median CEA reduction of 28.79%. In contrast, subjects experiencing PD and SD < 12weeks had median CEA increase of 42.53% from baseline (Table 53).

Overall, the changes of CEA levels on treatment (Week 6, relative to baseline) trend with durable disease control with nivolumab. However, given the small sample size and the variability of the CEA levels, further characterization is needed before a conclusion can be drawn.

Treatment beyond progression did require informed consent, however was not captured on the CRF. The Sponsor is committed to future analyses of this population to identify subjects who experienced 'pseudo-progression' to address possible prognostic factors such as CEA level.

CHMP assessment

At week 6, when the first radiographic assessments was scheduled, patients with CR+PR+SD ≥12 weeks had a median reduction in CEA levels of 29%, patients with PD and SD <12 weeks had a median increase in CEA of 43%. CEA levels were variable and the number of treated patients is small prohibiting definitive conclusions. The MAH is committed to collect CEA levels further in patients with possible pseudo-progression, which is encouraged.

Issue resolved.

Clinical safety aspects

Major Objections

None

Other concerns

21. Two pulmonary selected AEs were reported in the study. According to the interim CSR (Table S.6.101), both of them were "pneumonitis" (both <grade 3). Considering that "pneumonitis" is a known ADR for nivolumab, it is unclear how these two events were considered not treatment related by the investigator. The MAH should provide further details on these pneumonitis AEs and discuss their causality assessment.

Summary of the MAH response

Both of these cases of pulmonary select AEs occurred at site #32 in Italy in Apr-2016. The verbatim term for each was "lung inflammation," which mapped to the MedDRA preferred term "pneumonitis." The AE

resolved in both subjects after being treated empirically with levofloxacin and without steroids, suggesting the event was probably due to an infectious etiology rather than an immune-mediated inflammation, even though no causal infectious agent was identified in either case. In neither case did the investigator attribute the AE to nivolumab.
No hypoxia, fever, or lung changes on imaging were reported for these 2 cases. Neither subject has received radiation.

CHMP assessment

Point adequately clarified

Conclusion

Issue resolved

22. Separate AE and SAE data should be provided for the 53 patients had received 5FU-Oxa-Iri, in order to better characterise the safety profile in this heavily pre-treated population.

Summary of the MAH response

In tables and figures, MSI-H/dMMR CRC and dMMR/MSI-H CRC can be used interchangeably with 'dMMR or MSI-H metastatic CRC'. AE and SAE data are presented for the 53 subjects who received 5FU-Oxa-Iri using the 06-Feb-2017 clinical database lock (DBL).The subjects with prior 5FU-Oxa-Iri (N = 53) represent a more heavily pretreated subset of subjects. Among these subjects, AEs were consistent with those reported in the all treated group (see Response to Question 23). 21 subjects (39.6%) experienced any Grade 3 event and 8 subjects (15.1%) experienced a grade 4 event (Table 1).

All 53 (100%) subjects had reported at least 1 AE. Most AEs were Grade 1 - 3. The majority of AEs were reported in the gastrointestinal disorders System Organ Class (SOC) (44 subjects, 83.0%) with diarrhoea, nausea, and vomiting reported with the greatest frequencies (49.1%, 34.0%, 28.3%, respectively) (Table 1).
The rate of SAEs in this group was low, with 14 subjects (26.4%) experiencing any Grade 3 SAE, and 5 subjects (9.4%) experiencing a Grade 4 SAE (Table 3).

Among this group of 53 subjects, the incidence of drug-related AEs by Worst CTC Grade reported in ≥ 10% of subjects were consistent with expected toxicities to nivolumab: Any grade drug-related AEs were reported in 38 (71.7%) subjects with prior 5FU-Oxa-Iri (Table 2). The most commonly reported drug-related AEs were diarrhoea (13, 24.5%) and fatigue (8, 15.1%). 13 patients experienced a Grade 3-4 SAE, of which 3 (5.7%) were gastrointestinal, and 8 (15.1%) were laboratory investigations, of which 5 (9.4%) were lipase increased. Drug-related SAEs were reported for 7 (13.2%) subjects (Table 4).

Table 1: Summary of Any Adverse Events by Worst CTC Grade Reported in ≥ 10% of Subjects- Subjects with Prior 5FU-Oxa-Iri

Cohort: MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown	Total
TOTAL SUBJECTS WITH AN EVENT	6 (11.3)	15 (28.3)	21 (39.6)	8 (15.1)	3 (5.7)	0	53 (100.0)
GASTROINTESTINAL DISORDERS	17 (32.1)	18 (34.0)	9 (17.0)	0	0	0	44 (83.0)
DIARRHOEA	18 (34.0)	6 (11.3)	2 (3.8)	0	0	0	26 (49.1)
NAUSEA	11 (20.8)	7 (13.2)	0	0	0	0	18 (34.0)
VOMITING	8 (15.1)	6 (11.3)	1 (1.9)	0	0	0	15 (28.3)
ABDOMINAL PAIN	5 (9.4)	6 (11.3)	3 (5.7)	0	0	0	14 (26.4)
CONSTIPATION	10 (18.9)	2 (3.8)	0	0	0	0	12 (22.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	25 (47.2)	13 (24.5)	3 (5.7)	0	1 (1.9)	0	42 (79.2)
FATIGUE	12 (22.6)	8 (15.1)	2 (3.8)	0	0	0	22 (41.5)
PYREXIA	13 (24.5)	4 (7.5)	0	0	0	0	17 (32.1)
ASTHENIA	7 (13.2)	2 (3.8)	1 (1.9)	0	0	0	10 (18.9)
OEDEMA PERIPHERAL	5 (9.4)	2 (3.8)	0	0	0	0	7 (13.2)
INFECTIONS AND INFESTATIONS	5 (9.4)	15 (28.3)	6 (11.3)	1 (1.9)	0	0	27 (50.9)
NASOPHARYNGITIS	4 (7.5)	2 (3.8)	0	0	0	0	6 (11.3)
UPPER RESPIRATORY TRACT INFECTION	1 (1.9)	5 (9.4)	0	0	0	0	6 (11.3)
URINARY TRACT INFECTION	2 (3.8)	3 (5.7)	1 (1.9)	0	0	0	6 (11.3)
INVESTIGATIONS	10 (18.9)	4 (7.5)	10 (18.9)	3 (5.7)	0	0	27 (50.9)
ASPARTATE AMINOTRANSFERASE INCREASED	8 (15.1)	1 (1.9)	1 (1.9)	0	0	0	10 (18.9)
LIPASE INCREASED	2 (3.8)	0	4 (7.5)	2 (3.8)	0	0	8 (15.1)
ALANINE AMINOTRANSFERASE INCREASED	6 (11.3)	0	1 (1.9)	0	0	0	7 (13.2)
BLOOD ALKALINE PHOSPHATASE INCREASED	5 (9.4)	1 (1.9)	1 (1.9)	0	0	0	7 (13.2)
AMYLASE INCREASED	2 (3.8)	1 (1.9)	3 (5.7)	0	0	0	6 (11.3)
BLOOD CREATININE INCREASED	3 (5.7)	2 (3.8)	1 (1.9)	0	0	0	6 (11.3)
WEIGHT INCREASED	3 (5.7)	1 (1.9)	2 (3.8)	0	0	0	6 (11.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	18 (34.0)	6 (11.3)	1 (1.9)	0	0	0	25 (47.2)
PRURITUS	11 (20.8)	1 (1.9)	0	0	0	0	12 (22.6)
RASH	7 (13.2)	2 (3.8)	0	0	0	0	9 (17.0)
RASH MACULO-PAPULAR	5 (9.4)	0	1 (1.9)	0	0	0	6 (11.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	11 (20.8)	5 (9.4)	7 (13.2)	1 (1.9)	0	0	24 (45.3)
ANAEMIA	12 (22.6)	5 (9.4)	6 (11.3)	0	0	0	23 (43.4)

Table 1: Summary of Any Adverse Events by Worst CTC Grade Reported in ≥ 10% of Subjects- Subjects with Prior 5FU-Oxa-Iri

Cohort: MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown	Total
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	14 (26.4)	9 (17.0)	1 (1.9)	0	0	0	24 (45.3)
ARTHRALGIA	8 (15.1)	4 (7.5)	0	0	0	0	12 (22.6)
BACK PAIN	4 (7.5)	4 (7.5)	0	0	0	0	8 (15.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	16 (30.2)	5 (9.4)	2 (3.8)	0	0	0	23 (43.4)
COUGH	14 (26.4)	1 (1.9)	0	0	0	0	15 (28.3)
METABOLISM AND NUTRITION DISORDERS	10 (18.9)	8 (15.1)	2 (3.8)	0	0	0	20 (37.7)
HYPERGLYCAEMIA	4 (7.5)	5 (9.4)	0	0	0	0	9 (17.0)
DECREASED APPETITE	5 (9.4)	2 (3.8)	0	0	0	0	7 (13.2)
DEHYDRATION	2 (3.8)	3 (5.7)	1 (1.9)	0	0	0	6 (11.3)
NERVOUS SYSTEM DISORDERS	9 (17.0)	7 (13.2)	1 (1.9)	0	0	0	17 (32.1)
HEADACHE	5 (9.4)	3 (5.7)	0	0	0	0	8 (15.1)
DIZZINESS	6 (11.3)	0	0	0	0	0	6 (11.3)
VASCULAR DISORDERS	1 (1.9)	9 (17.0)	2 (3.8)	0	0	0	12 (22.6)
HYPERTENSION	0	6 (11.3)	1 (1.9)	0	0	0	7 (13.2)
RENAL AND URINARY DISORDERS	7 (13.2)	1 (1.9)	2 (3.8)	0	0	0	10 (18.9)

MedDRA Version: 19.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.1a.501 of Appendix 1

Table 2: **Summary of Drug-Related Adverse Events by Worst CTC Grade Reported in ≥ 10% of Subjects- Subjects with Prior 5FU-Oxa-Iri**

System Organ Class (a) Preferred Term (a)	MSI-H/dMMR CRC per Local Lab - All Subjects N = 53 Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	38 (71.7)	13 (24.5)	1 (1.9)
GASTROINTESTINAL DISORDERS	21 (39.6)	3 (5.7)	0
DIARRHOEA	13 (24.5)	1 (1.9)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	17 (32.1)	1 (1.9)	1 (1.9)
FATIGUE	8 (15.1)	1 (1.9)	0
INVESTIGATIONS	14 (26.4)	8 (15.1)	0
LIPASE INCREASED	6 (11.3)	5 (9.4)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	12 (22.6)	1 (1.9)	0
PRURITUS	6 (11.3)	0	0
ENDOCRINE DISORDERS	7 (13.2)	1 (1.9)	0
HYPOTHYROIDISM	6 (11.3)	0	0

MedDRA Version: 19.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program Source: /projects/bms218374/stats/upd_feb17/pirog/tables/rt-ae-aecat-eu.sas 15MAR2017:11:00:59
Source: Table 8.6.3a.50I of Appendix 1

Table 3: **Summary of Serious Adverse Events by Worst CTC Grade Reported in ≥ 10% of Subjects - Subjects with Prior 5FU-Oxa-Iri**

Cohort: MSI-H/dMMR CRC per Local Lab - Subjects with Prior 5FU-Oxa-Iri N = 53

System Organ Class (a) Preferred Term (a)	I	II	III	IV	V	Unknown	Total
TOTAL SUBJECTS WITH AN EVENT	1 (1.9)	1 (1.9)	14 (26.4)	5 (9.4)	3 (5.7)	0	24 (45.3)
GASTROINTESTINAL DISORDERS	0	2 (3.8)	8 (15.1)	0	0	0	10 (18.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (1.9)	1 (1.9)	4 (7.5)	2 (3.8)	0	8 (15.1)
MALIGNANT NEOPLASM PROGRESSION	0	0	1 (1.9)	4 (7.5)	2 (3.8)	0	7 (13.2)
INFECTIONS AND INFESTATIONS	0	0	5 (9.4)	1 (1.9)	0	0	6 (11.3)

MedDRA Version: 19.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Table 8.6.17a.50I of Appendix 1

Table 4: **Summary of Drug-Related Serious Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) - All Nivolumab Monotherapy Treated Subjects - Subjects with Prior 5FU-Oxa-Iri**

System Organ Class (a) Preferred Term (a)	MSI-H/dMMR CRC per Local Lab - All Subjects N = 53 Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	7 (13.2)	6 (11.3)	1 (1.9)
GASTROINTESTINAL DISORDERS	3 (5.7)	3 (5.7)	0
COLITIS	1 (1.9)	1 (1.9)	0
DIARRHOEA	1 (1.9)	1 (1.9)	0
STOMATITIS	1 (1.9)	1 (1.9)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (3.8)	1 (1.9)	1 (1.9)
PAIN	1 (1.9)	1 (1.9)	0
SUDDEN DEATH	1 (1.9)	0	1 (1.9)
ENDOCRINE DISORDERS	1 (1.9)	1 (1.9)	0
ADRENAL INSUFFICIENCY	1 (1.9)	1 (1.9)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.9)	1 (1.9)	0
ARTHRITIS	1 (1.9)	1 (1.9)	0
RENAL AND URINARY DISORDERS	1 (1.9)	1 (1.9)	0
ACUTE KIDNEY INJURY	1 (1.9)	1 (1.9)	0

MedDRA Version: 19.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Program Source: /projects/bms218374/stats/upd_feb17/pirog/tables/rt-ae-aecat-eu.sas 15MAR2017:11:01

CHMP assessment

Safety data for the subgroup of 53 more heavily pretreated patients is presented and results are line with the expected profile for nivolumab and also consistent with the overall study population, thought this is not unexpected given that this subgroup represents around 72% of the total study population and thus, is the main driver of these results. Nevertheless, no substantial differences are expected in the less represented subset of less heavily pre-treated patients with dMMR-mCRC.

Conclusion

Point solved.

23. At the date of the clinical database lock (19-Sep-2016), the majority of patients (n=40, 54.1%) continued in the treatment period. The Applicant should present an update on relevant safety data (e.g. deaths, SAEs, and selected AEs) from those patients.

Summary of the MAH response

In tables and figures, MSI-H/dMMR CRC and dMMR/MSI-H CRC can be used interchangeably with 'dMMR or MSI-H metastatic CRC'. Updated safety data is presented for the 06-Feb-2017 clinical database lock (DBL; Table 1).
Based on these updated analyses, no new safety signals were identified. Frequencies of Grade 3- 4 all causality AEs and SAEs, as well as any-grade and Grade 3-4 drug-related AEs, SAEs, and AEs leading to discontinuation, were mostly consistent with other nivolumab monotherapy studies across tumour types in the metastatic setting. The majority of SAEs were not considered related to study drug.

Deaths
As of the 06-Feb-2017 DBL, a total of 23 subjects died (4 additional deaths since the 19-Sep-2016 DBL). Disease progression was the most common cause of death, including deaths occurring within 30 days of last dose and deaths occurring within 100 days of last dose. No deaths were attributed to study drug toxicity.

SAEs
Any grade SAEs were reported in 47.3% of subjects (versus 41.9% for the 19-Sep-2016 DBL) with Grade 3-4 reported in 36.5% of subjects (versus 29.7% for the 19-Sep-2016 DBL), and Grade 5 reported in 5.4% of subjects. The most frequently reported drug-related SAEs were in the gastrointestinal disorders SOC (4 subjects, 5.4%) and were Grade 3-4.
AEs and AEs leading to discontinuation As of the 06-Feb-2017 DBL, all causality AEs were reported in 73 (98.6%) subjects compared to 71 (95.9%) of subjects for the 19-Sep-2016 DBL (Table 8.1-1 of the CA209142 Interim CSR).; with Grade 3-4 AEs reported in 40 (54.0%) subjects. The most commonly reported AEs were diarhhoea (47.3%) and fatigue (47.3%). AEs were considered drug-related in 52 (70.3%) subjects (vs 51, 68.9%). AEs leading to discontinuation were reported in 12.2% of subjects; Grade 3-4 AEs led to discontinuation in 5.4% and Grade 5 in 4.1%.

Select AEs
At the 06-Feb-2017 DBL, the most frequently reported select AEs were diarrhoea (47.3%), pruritus 16 (21.6%), rash 13 (17.6%), and aspartate aminotransferase increased 12 (16.2%). Select AEs were primarily Grade 1-2, there were no Grade 5 select AEs. All hypersensitivity/infusion reaction select AEs, and the majority of endocrine select AEs were considered drug-related by the investigator (Table 1). A lower proportion of select AEs were 26 reported as drug-related in the, GI, hepatic, renal, and skin categories. There were no pulmonary select AEs considered drug-related by the investigator.

Other Events of Special Interest
OESI included the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis, pancreatitis, rhabdomyolysis, and uveitis. As of the 06-Feb-2017 DBL, no additional OESIs were reported beyond the 1 subject with pancreatitis described in the CA209142 Interim CSR.

Table 1: Summary of Safety Results - All Nivolumab Monotherapy Treated Subjects

	MSI-H/dMMR CRC per Local Lab All Subjects N = 74
DEATHS	
NUMBER OF SUBJECTS WHO DIED (%)	23 (31.1)
WITHIN 30 DAYS OF LAST DOSE (%)	5 (6.8)
WITHIN 100 DAYS OF LAST DOSE (%)	12 (16.2)
DUE TO STUDY DRUG TOXICITY	0

	Number (%) Subjects	
	MSI-H/dMMR CRC per Local Lab - All Subjects N = 74	
	Any Grade	Grade 3-4
ALL CAUSALITY SAEs	35 (47.3)	27 (36.5)
DRUG-RELATED SAEs	9 (12.2)	8 (10.8)
ALL CAUSALITY AEs LEADING TO DC	9 (12.2)	4 (5.4)
DRUG-RELATED AEs LEADING TO DC	5 (6.8)	4 (5.4)
ALL CAUSALITY AEs	73 (98.6)	40 (54.0)
DRUG-RELATED AEs	52 (70.3)	15 (20.3)
Most Frequent Drug-related AEs (≥15% of Any Grade)		
DIARRHOEA	16 (21.6)	1 (1.4)
FATIGUE	17 (23.0)	1 (1.4)
ALL CAUSALITY SELECT AES, BY CATEGORY		
ENDOCRINE	11 (14.9)	2 (2.7)
GASTROINTESTINAL	37 (50.0)	3 (4.1)
HEPATIC	18 (24.3)	4 (5.4)
PULMONARY	2 (2.7)	0
RENAL	8 (10.8)	2 (2.7)
SKIN	28 (37.8)	1 (1.4)
HYPERSENSITIVITY/INFUSION REACTIONS	3 (4.1)	0
DRUG-RELATED SELECT AES, BY CATEGORY		
ENDOCRINE	9 (12.2)	1 (1.4)
GASTROINTESTINAL	18 (24.3)	2 (2.7)
HEPATIC	6 (8.1)	2 (2.7)
PULMONARY	0	0
RENAL	3 (4.1)	2 (2.7)
SKIN	17 (23.0)	1 (1.4)
HYPERSENSITIVITY/INFUSION REACTIONS	3 (4.1)	0

MedDRA Version: 19.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Table S.6.1a (AEs); Table S.6.15 (deaths); Table S.6.17a (SAEs) Table S.6.19a (drug-related SAEs), Table S.6.23a (AEs leading to discontinuation); Table S.6.24a (drug-realated AEs leading to discontinuation); Table S.6.101 (select AEs)Table S.6.103 (drug-related select AEs), Table S.6.105 (select endocrine AEs), Table S.6.9a(drug-related AEs)of Appendix 2.

CHMP assessment

The overall incidence of AEs (98.6%), drug-related AEs (70.2%), G3/4 AEs (overall 54%, drug-related 20.2%), SAEs (overall 47.3%, drug-related 12.2%) during treatment with nivolumab in this d-MMR-mCRC population is high. The underlying condition is contributing to a high degree to the overall toxicity, which is not unexpected bearing the mind the overall heavily pretreated population with a metastatic disease. However, it is reassuring that only in few cases these led to treatment discontinuation (12.2% overall AEs, 6.8% drug-related AEs) and that no deaths related to the study treatment have been reporting. At the same time, no unexpected findings have been reported for nivolumab. This safety profile is overall considered acceptable and manageable in the current context, put should be put in the context of the demonstrated benefits for a final conclusion.

Conclusion

The point is considered resolved.

24. Two patients died due to “unknown” causes. Of these two patients, subject CA209142-3-8 was recovering from a Grade 3 diarrhea/colitis attributed as related to study drug. The MAH should discuss to what extent the prior ADR could have contributed to the outcome of this case. Since no deaths were attributed to drug toxicity, the MAH should also discuss their causality assessment of this death.

Summary of the MAH response

CA209142-3-8, was a 36 year-old female subject with advanced colon cancer and colostomy who experienced severe abdominal pain, diarrhoea, fever, hypotension, and hypoxia four days after receiving the first and only dose of nivolumab therapy. Sigmoidoscopy demonstrated mild inflammation. The subject was diagnosed with Grade 3 colitis and was treated with fluid resuscitation, broad-spectrum antibiotics, and corticosteroids. 2 days after presentation to the hospital, IV methylprednisolone was started and diarrhoea normalized to baseline bowel movements within 24 hours. The subject remained hospitalized for management of abdominal pain. 5 days after presentation, on the day of planned hospital discharge, the subject was found unresponsive and pulseless. Sudden death with unknown cause was reported by the investigator.

Autopsy exam revealed bilateral adnexal massive metastases with peritoneal adhesion, no evidence of myocardial infarction, myocardial abnormalities, or pulmonary emboli was identified. No inflammation in the colon was noted on the autopsy. Given the clinical course in this subject with underlying late stage malignancy, with treatment-related diarrhoea resolved, lack of evidence of colitis on autopsy, and the subject being prepared for hospital discharge with bowel movements reported at baseline frequency, the prior colitis was unlikely to have been the proximal cause of this outcome.

CHMP assessment

The MAH explanation is considered adequate

Conclusion

Issue solved

25. Very few elderly and very elderly patients were included in the study. This should be adequately reflected in the SmPC and RMP.

Summary of the MAH response

The Sponsor will add to the revised RMP version 9.1, under Section 2.4.3 (Limitations in respect to populations typically under-represented in clinical trial development programs) a statement to include "very elderly patients (N=4 for ≥ 75 years of age) were included in study CA209142". In line with this, the Sponsor is able to conclude that data from dMMR or MSI-H metastatic CRC patients 75 years of age or older are too limited to draw conclusions on this population and agrees to update the EU RMP version 9.1 to include as missing information 'Elderly patients with dMMR or MSI-H metastatic CRC ≥ 75 years of age' in Section 2.4.4 (Conclusions on the Populations Not Studied). Sections 4.2, 4.8, and 5.1 of the SmPC are revised accordingly. The Sponsor does not propose to include this statement for elderly patients (N = 17 for ≥ 65 years of age), as this subset in the context of the small sample size represents 23% (17/74) of the total number of patients included in the study.

CHMP assessment

The MAH agrees to reflect the limitations in the RMP and SmPC. Therefore, this point is considered solved as no further discussion is needed. Concerning the specific proposal for the SmPC, its acceptability is discussed in the attached SmPC document

Conclusion

Issue solved

26. Patients with pre-established renal/hepatic failure were not explicitly excluded from the pivotal study; it is not known whether any patients actually enrolled in the pivotal study. If that would be the case, separate safety data should be provided for these patients.

Summary of the MAH response

Per protocol, subjects with pre-established renal or hepatic failure were excluded. Specifically, to be eligible for study participation, screening laboratory values for serum creatinine and liver function tests must have met the following criteria:

- Serum creatinine ≤1.5 x ULN or creatinine clearance (CrCl) ≥40 mL/min (using the Cockcroft-Gault formula):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

- AST/ALT ≤ 3 x ULN
- Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL).

CHMP assessment

According to this information, patients with some degree of renal impairment might have entered into the trial. It is not clarified if this was the case in the end. If so, feedback on the drug tolerability would be appreciated in view of the actual limited experience of use of nivolumab in these patients.

Conclusion

Point not solved

27. According to the data submitted, the safety profile of nivolumab in MSI-H CRC population has a slight higher rate of AEs Grade 3-4 (regardless of causality and drug-related) than previously submitted pooled data of nivolumab monotherapy in melanoma, NSCLC and RCC. Specifically, the Applicant is asked to discuss whether there is a biological rationale to explain the higher percentage of patients experiencing a grade 3-4 lipase increase (8.1%) compared to the pooled analysis (1.3%) and what might be the clinical consequence of such findings.

Summary of MAH answer

The rate of elevated lipase in CA209142 (8.1%) is similar to previously submitted safety data from nivolumab 3 mg/kg Q2W monotherapy across tumour types (7.9%) (refer to Appendix M142a-PI of the CA209067 Summary of Clinical Safety).

Per protocol, Grade 3 lipase did not require treatment discontinuation, only discussion with the Medical Monitor. Grade 4 lipase that was not associated with any clinical symptoms and was typically allowed after discussion with the Medical Monitor. This is a departure from early nivolumab studies which required that Grade 3-4 lipase be handled like any other Grade 3-4 laboratory abnormality. This change may have allowed more subjects to stay on study, but also allowed more Grade 4 lipase to develop while on study. There were 6 subjects who experienced an AE of lipase increase that were of Grade 3-4 and drug-related. Of these, only 1 was associated with pancreatitis. None required treatment and all resolved to Grade 2 or less.

Based on these data, there are no clear trends nor is there biological rationale to suggest that there is increased risk of lipase increases with nivolumab treatment in this CRC population. We acknowledge that the rate of Grade 3-4 lipase was reported as only 4.2% in the Grothey trial of regorafenib. Rates of elevated lipase have not been reported for other pivotal trials in this population, so a direct comparison is not possible. It is unclear if the small sample size or the advanced nature of gastrointestinal malignancy in CA209142 study influences this result.

CHMP assessment

There appears to be no overall increase in the incidence of grade 3-4 lipase in mCRC patients as compared to patients using nivolumab for other indications. Only in one patient the increased lipase translated into a clinical pancreatitis, which is considered to be in the minority of patients. In the PI, increased lipase has been mentioned as a common AE.

Issue resolved.

28. Higher frequencies of any grade and Grade 3-4 drug-related AEs were reported in US/Canada subjects (87.1% and 29.0%, respectively) versus Europe (59.0% and 15.4%, respectively) or Rest of World (25.0% [any grade]). The Applicant is asked to discuss these discrepancies in incidence of AEs.

Summary of MAH answer

There were 31 treated subjects in US/Canada, 39 treated subjects in Europe, and 4 treated subjects in Rest of World. 58.1% of subjects in US/Canada received at least 3 prior therapies compared to that of 46.2% in Europe; 41.9% of subjects in US/Canada received prior radiotherapy compared to that of 28.2% in Europe. Baseline demographics and disease characteristics were similar across regions. The higher number of prior regimens and radiotherapy in US/Canada might have contributed to the higher

frequencies of AEs in US/Canada versus Europe. On the other hand, variability in AE rates across the regions is likely expected and of limited interpretability due to low sample sizes, which do not alter the overall safety profile of nivolumab in these subgroups.

CHMP assessment

It is agreed with the Applicant that the apparent discrepancy between the incidence of AEs in the US/Canada and Europe is considered most likely to be attributable to the low number of included patients and is not considered clinically relevant. **Issue resolved.**

29. The Applicant is asked to discuss the high reported rate of anticholinergic syndrome (up to 50%) in all age groups as this is not considered a known AE of nivolumab and also not a common diagnosis in clinical practice.

Summary of MAH answer

The reported data for anticholinergic syndrome come from the Standard MedDRA Query (SMQ) for this term; however, the preferred term "anticholinergic syndrome" was not reported for any subject on CA209142. SMQs are tools developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development. Many of the terms included in an SMQ are non-specific and, therefore, SMQs do not capture rates of actual adverse events, but can help identify a safety signal, especially in the context of randomized data. It is difficult to interpret SMQ data in a single arm setting. On clinical review, it is not clear if either of these 2 AEs represent an acute anticholinergic symptom. For example, in the case of the pyrexia, this AE did not correspond closely to an infusion date, and the subject's comorbidities included essential thrombocythemia, which is associated with vasomotor symptoms. Among all SMQs reported as anticholinergic syndrome, the most commonly reported events were pyrexia and dizziness. These terms are individually reported in 11 and 7 subjects, respectively. All of the events under the anticholinergic SMQ were Grade 1-2. Overall, only 14 of the events were related to therapy, affecting a total of 8 subjects. The overall rate of subjects experiencing a term in the anticholinergic SMQ in CA209142 is 39.2% which is similar to that seen in other studies within the nivolumab program. Using SMQs to analyze other nivolumab trials, similar rates of 34.7% (N = 2578) for anticholinergic syndrome have been found in a pooled analysis of trials. AEs were classified as anticholinergic syndrome by SMQ (refer to Appendix M.418EUSCS of the CA209067 Summary of Clinical Safety). Of note, this event rate is consistent across both arms of nivolumab randomized studies and does not indicate a safety signal.

CHMP assessment

It is acknowledged that symptoms such as dry mouth, pyrexia have been scored as anticholinergic syndrome according to the SMQ. The individual symptoms do not meet the criteria for true "anticholinergic syndrome". As the event rate is consistent with other nivolumab study, it is not considered a new safety signal. **Issue resolved.**

30. The majority of subjects had normal TSH levels at baseline and throughout the treatment period. While on treatment, twenty (28.6%) patients had TSH values > upper limit of normal and eleven (15.7%) of patients had TSH values < lower limit of normal. More than 17 percent of patients had

new onset increased TSH levels compared to baseline during the study and in 15.7%, at least one FT3/FT4 test was <LLN, suggesting true hypothyroidism. From a clinical point of view, however, it is important to know how many patients had overt thyroid dysfunction and in how many subjects therapeutic intervention/suppletion was needed.

Summary of MAH answer

The rate of clinical hypothyroid developing on study CA209142 was low, with only 5 subjects requiring therapeutic intervention. Of the 70 nivolumab monotherapy treated subjects with at least one on-treatment TSH measurement, the following was observed:

1. Among the 12 subjects with TSH > ULN but normal TSH at baseline
2. 5 subjects had at least one FT3/FT4 test value < LLN, suggesting true hypothyroidism,
3. 1 subject had thyroid supplementation at baseline, indicating pre-existing hypothyroidism, and
4. 4 subjects initiated thyroid supplementation while on therapy or within 30 days of follow-up (although for 1 of these subjects, the thyroid supplementation was not prescribed to treat an AE but for "other reason"). Therefore, the rate of overt thyroid dysfunction developing on trial was at most 5/70 (7.1%), and therapeutic intervention in the form of thyroid supplementation was needed for 4 of these subjects.

Regarding Hyperthyroidism: The rate of overt hyperthyroid developing on trial was 3/70 (4.3%), and no therapeutic intervention was prescribed for hyperthyroidism for any subject. No subjects were prescribed any of the following concomitant medications that would be used to treat clinically significant hyperthyroidism: Carbimazole, Methimazole, or Propylthiouracil. Only 7 subjects had a TSH < LLN with TSH ≥ LLN at baseline. Of these, 4 subjects also had TSH > ULN but normal TSH at baseline.

1. 3 of these subjects had at least one FT2/FT4 test value > ULN indicating clinical hyperthyroidism, and subsequently they required thyroid supplementation; 2 required synthroid therapy during trial treatment and 1 at 30 days follow-up. These 3 subjects therefore are clinically consistent with a Hashimoto's type of presentation with immune-mediated hyperthyroidism followed by hypothyroidism. The other 4 subjects did not require synthroid therapy and did not have abnormal FT2/FT4 test values.

Therefore the rate of overt hyperthyroid developing on trial was 3/70 (4.3%), and therapeutic intervention was not prescribed for any of these subjects until they developed clinical hypothyroidism.

CHMP assessment

In this small study of only seventy patients, the incidence of either hypothyroididm or hyperthyroidism requiring medication was low and consistent with data from other nivolumab data. In the SmPC, adequate reference has been made towards the occurrence and treatment of endocrinopathies. **Issue resolved.**

RMP

None

Annex 3: CHMP second Request for Supplementary Information

Efficacy

Major Objection

1. The benefit of nivolumab in the treatment of patients with MMRd mCRC cannot presently be determined, as the lack of control data, clinical context and uncertainties on the predictive/prognostic value of MMRd in this metastatic setting preclude a proper interpretation of the study results. In view of the modest correlation of ORR with survival in the mCRC, the immature results for duration of response and overall survival further complicate interpretation of the results. Finally, the validity of the study results is questioned due to possible selection bias of a study population with a more favourable prognosis, lack of proper definition of the study population by MSI status, and uncertainties regarding type I error control on clinical endpoints due to deviations from the original study design. As a consequence, the benefit/risk balance of nivolumab in adults with recurrent or metastatic MSI-H CRC after prior fluoropyrimidine-based combination therapy remains negative. Further justification for the claimed indication is requested. This should include a separate discussion of the benefit-risk balance for the early vs late (post ≥ 2 lines of chemotherapy) mCRC stages

Other concerns

2. Information on the actual time from progression on most recent prior therapy to treatment with nivolumab should be provided. Additional analysis like relationship between ORR and time from date of progression on most recent prior therapy to start of treatment should be presented.

3. Given the limited evidence presented, no firm conclusions can be drawn for patients with BRAF/KRAS/NRAS mutations. A proposal to generate further data in these relevant subgroups of patients will need to be discussed.

4. The MAH should commit to further investigate the role of PD-L1 expression in tumour cells and TAICs in their clinical program, including the population of MSI-H mCRC.

5. According to the information presented, patients with some degree of renal impairment might have entered into the trial. It is not clarified if this was the case in the end. If so, feedback on the drug tolerability would be appreciated in view of the actual limited experience of use of nivolumab in these patients.

Annex 4: Product Information annotated with (Co)Rapporteur(s) comments

Please see Product Information with tracked changes in a different document.