20 May 2021
EMA/314215/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

OPDIVO	nivolumab
Yervoy	ipilimumab

Procedure No. EMEA/H/C/xxxx/WS/1840

Note

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

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List of abbreviations

1L	first line
2L	second line
3L+	third line or later
5FU-Oxa-Iri	5-fluorouracil, oxaliplatin, irinotecan
ADA	anti-drug antibody
AE	adverse event
AGEO	Association des Gastro-entérologues Oncologues
ALT	alanine transaminase
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
BICR	blinded independent central review
BMS	Bristol-Myers Squibb
BOR	best overall response
BSC	best supportive care
CI	confidence interval
cHL	classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CL	clearance
CLss	clearance at steady state
CMS	consensus molecular subtype
CO	Clinical Overview
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CTLA-4	cytotoxic T-lymphocyte antigen-4
CV	coefficient of variation
DBL	database lock
DC	discontinuation
DCR	disease control rate
dMMR	mismatch repair deficient
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group

ECL	electrochemiluminescence
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EHR	electronic health record
EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
ESMO	European Society for Medical Oncology
EU	European Union
FPFT	first patient first treatment
HCC	hepatocellular carcinoma
HLGT	High-level Group Term
HRQoL	health-related quality of life
IA	interim analysis
IB	Investigator Brochure
IHC	immunohistochemistry
IMM	immune-modulating medication
IO	immuno-oncology
IRRC	independent radiology review committee
IV	intravenous/intravenously
K-M	Kaplan-Meier
LPFT	last patient first treatment
LPLV	last patient last visit
LS	least square
mCRC	metastatic colorectal cancer
MMR	mismatch repair
MMRM	mixed models for repeated measurements
mPFS	median PFS
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSI-L	microsatellite instability-low

MSI-S or MSS	microsatellite-stable
MTD	maximum tolerated dose
N.A.	not applicable, not available
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
ESI	other events of special interest
ORR	objective response rate
OS	overall survival
OSCC	oesophageal squamous cell carcinoma
PAM	post-authorisation measure
PBRER	Periodic Risk-Benefit Evaluation Report
PCR	polymerase chain reaction
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PI	product information
pMMR	mismatch repair-proficient
PPK	population pharmacokinetic
PR	partial response
PSM	Pre-Submission Meeting
PRO	patient-reported outcomes
PS	performance status
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk Management Plans
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SCE	Summary of Clinical Efficacy

SCS	Summary of Clinical Safety
SCP	Summary of Clinical Pharmacology
SD	stable disease
SEER	Surveillance, Epidemiology and End Results program
SmPC	Summary of Product Characteristics
SOC	standard of care
t1/2,ss	half-life at steady state
TAS-102	tipiracil/trifluoridine
TTNT	time to next treatment
TTR	time to response
UC	urothelial carcinoma
US	United States
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady state
WT	wild type

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 28 July 2020 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

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 the combination of nivolumab with ipilimumab in the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (CRC) after prior fluoropyrimidine based combination chemotherapy; as a consequence, sections 4.1, 4.2 ,4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 18.0 for Opdivo and version 29.0 for Yervoy of the RMP have also been submitted.

The worksharing procedure requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0026/2020, P/0027/2020 for Opdivo (Nivolumab) and P/0003/2017, P/0085/2015 for Yervoy (Ipilimumab) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0027/2020 was not yet completed as some measures were deferred.

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 WSA 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.

Scientific advice

The MAH sought CHMP scientific advice in November 2019 (EMEA/H/SA/3330/4/2019/II). At that time the MAH presented their proposed approach to characterise the prognosis of patients with MSI-H/dMMR mCRC. Based on the data submitted it was noted that a negative prognostic influence

appeared reasonable to assume, but data were not considered sufficient to define MSI-H/dMMR status as an independent prognostic factor. Indeed, it was emphasised that it was not possible to neither determine an exact effect size or to isolate the relevance of the negative effects of MSI-H/dMMR and BRAF mutation status from the data/publications submitted. In addition during the procedure, agreement was sought on whether data from study CA209142 that include multiple (single-arm) cohorts (and which is the subject of this application) would support assessment of the benefit/risk ratio for nivolumab in combination with ipilimumab in 2L+ MSI-H/dMMR mCRC. The design of the phase 3b randomized study CA2098HW, which is intended to support the extension of the indication of the combination of nivolumab and ipilimumab for the treatment of patients in 1L/across lines of therapy, was also outlined. Lastly, a proposal to use RWE sourced for the Flatiron database as supportive for benefit-risk assessment of nivolumab plus ipilimumab in the intended treatment setting was also discussed.

1.2. Steps taken for the assessment of the product

Appointed Rapporteur for the WS procedure: Blanca Garcia-Ochoa

Timetable	Actual dates
Submission date	28 July 2020
Start of procedure:	15 August 2020
CHMP Rapporteur's preliminary assessment report circulated on:	29 October 2020
PRAC Rapporteur's preliminary assessment report circulated on:	30 October 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	29 October 2020
CHMP Rapporteur's updated Assessment Report circulated on:	8 November 2020
Request for supplementary information and extension of timetable adopted by the CHMP on:	12 November 2020
WSA's responses submitted to the CHMP on:	21 January 2021
CHMP Rapporteur's preliminary assessment report on the WSA's responses circulated on:	14 March 2021
CHMP Rapporteur's updated assessment report on the WSA's responses circulated on:	21 March 2021
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 March 2021
WSA's responses submitted to the CHMP on:	19 April 2021
CHMP Rapporteur's preliminary Assessment Report circulated on:	6 May 2021
CHMP Opinion adopted on:	20 May 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The clinical data submitted for this application are in support of the use of nivolumab in combination with ipilimumab for treatment of patients with mismatch repair deficient (dMMR) or MSIH (hereafter, dMMR or MSI-H) metastatic colorectal cancer (mCRC) after prior fluoropyrimidine-based combination chemotherapy.

Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide with a 5-year survival rate of approximately 14% in patients with metastatic disease (National Cancer Institute: surveillance, epidemiology and end results program – accessed 16 July 2020). Worldwide, CRC is the third most common form of cancer, with 1.8 million new cases diagnosed worldwide in 2018, constituting 10.2% of all new cancers. Among all new CRC cases, 27% were diagnosed in Europe (Globocan 2018). Each year, there are about 880,792 deaths from CRC worldwide, which is 9.2% of all cancer deaths, making CRC the second most common cause of cancer death (Globocan 2018). The risk of developing CRC is influenced by both environmental and genetic factors (Chan and Giovannucci, 2010).

Among metastatic CRC (mCRC) patients, mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) tumor only accounts for approximately 5%. Patients with Lynch-like mCRC are associated with younger age, higher frequency of liver metastasis, more frequent resection of metastatic disease, thus more favourable prognosis compared to those with sporadic dMMR or MSI H mCRC. In both patient groups, alterations in the DNA MMR genes lead to accumulation of errors during DNA replication, especially in repetitive sequences known as microsatellites, causing high level of MSI. Thus, MSI is the molecular fingerprint of a deficient DNA mismatch repair.

State the claimed therapeutic indication

New proposed indication:

- OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.
- YERVOY in combination with nivolumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

Epidemiology and risk factors

Colorectal cancer is one of the leading causes of cancer-related death worldwide with a 5-year survival rate of approximately 14% in patients with metastatic disease (*national cancer institute, surveillance, epidemiology and End Result Program: Cancer Stat Facts: Colon and Rectum Cancer*). Worldwide, CRC is the third most common form of cancer, with 1.8 million new cases diagnosed worldwide in 2018,

constituting 10.2% of all new cancers. Among all new CRC cases, 27% were diagnosed in Europe (*Globocan 2018*). This disease predominately occurs in developed regions with the highest rates being found in Australia/New Zealand and Western Europe and to a lower extent in Africa and South-Central Asia. There is a higher incidence in men vs. women with a ratio of 1.4:1.

Each year, there are about 880,792 deaths from CRC worldwide, which is 9.2% of all cancer deaths, making CRC the second most common cause of cancer death (Globocan 2018). The risk of developing CRC is influenced by both environmental and genetic factors (Chan and Giovannucci, 2010).

Clinical presentation, diagnosis and stage/prognosis

Colorectal cancer is a heterogeneous disease, including different mutation status (e.g., RAS, BRAF), consensus molecular subtype (CMS) categorization (CMS1, 2, 3 and 4), and MS/MMR status (dMMR or MSI-H vs. microsatellite stable [MSS]/proficient MMR [pMMR]). The complex molecular heterogeneity of this disease is not completely understood. Emerging evidence points to microsatellite instability high/mismatch repair deficient (MSI-H/dMMR) as a biomarker-defined distinct population, with an unmet need for effective therapy as compared to the MMR proficient mCRC population.

A pooled analysis of 4 Phase 3 studies in the first-line treatment of mCRC (CAIRO, CAIRO2, COIN, and FOCUS) has shown PFS and OS to be significantly worse for patients with MSI-H/dMMR versus patients with microsatellite stable (MSS) (hazard ratio [HR], 1.33; 95% CI: 1.12, 1.57 and HR 1.35; 95% CI:1.13, 1.61, respectively, p= 0.001 for both). The poor prognosis may be in part 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.

Approximately 15% of all CRC patients (including local and metastic disease) display high level MSI-H due to either a germline mutation in one of the genes responsible for DNA mismatch repair (Lynch syndrome, 3%) or somatic inactivation of the same pathway, most commonly through hypermethylation of the MLH1 gene (sporadic MSI-H, 12 %). Among mCRC patients, dMMR or MSI-H tumor only accounts for approximately 5%. Patients with Lynch-like mCRC are associated with younger age, higher frequency of liver metastasis, more frequent resection of metastatic disease, thus more favorable prognosis compared to those with sporadic dMMR or MSI H mCRC. In both patient groups, alterations in the DNA MMR genes lead to accumulation of errors during DNA replication, especially in repetitive sequences known as microsatellites, causing high level of MSI. Thus, MSI is the molecular fingerprint of a deficient DNA mismatch repair (dMMR).

Patients with early stage MSI-H CRC seem to have better prognosis than non-MSI-H/proficient MMR CRC, however, patients with metastatic MSI-H CRC have been reported to have a worse OS, and seemingly less benefit from conventional chemotherapy. A pooled analysis of four Phase 3 studies (CAIRO, CAIRO2, COIN, and FOCUS) in first-line mCRC participants treated with chemotherapy demonstrated that median PFS (6.2 months vs 7.6 months respectively; hazard ratio [HR], 1.33; 95% confidence interval [CI]: 1.12, 1.57) and OS (13.6 months vs 16.8 months, respectively; HR, 1.35; 95% CI: 1.13, 1.61, respectively; p = 0.001 for both) were significantly worse for patients with dMMR compared with pMMR tumors, respectively. European Society of Medical Oncology (ESMO) Consensus Guidelines for management of mCRC recommend testing for dMMR or MSI-H and indicate that "tumour MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC (II, B)".

Immunohistochemistry (IHC) for MMR and DNA analysis for MSI are different assays measuring the same biologic effect. There are well established methods to detect dMMR or MSI-H that are in use in many countries as standard of care. In addition to its utility in early stage II/III CRC (ie, better overall

prognosis; potential lack of benefit from adjuvant fluoropyrimidines), the predictive value of dMMR or MSI-H status for anti-cancer treatment is becoming increasingly recognised in the metastatic setting.

Despite the numerous treatment options for metastatic colorectal cancer (mCRC), the benefits of these therapies after first line therapy are modest and not durable, thus highlighting the need for more effective therapies. Although the addition of targeted therapy to conventional chemotherapy, including anti-EGFR and anti-VEGFR antibodies, has markedly improved the OS of patients with mCRC (22 to 29 months), these patients experience disease progression due to intrinsic and acquired resistance to such therapies. In addition, limited predictive biomarkers can be used to select subsets of patients who may respond to targeted therapy, except RAS-mutation status, and more recently, BRAF mutation status.

Patients with mCRC that progress post cytotoxic chemotherapy have a high unmet need. The initial control of the MSI-H tumour by immune surveillance gives strong rationale that nivolumab, with its mechanism of action that abrogates immune tolerance, will have significant clinical activity in MSI-H/dMMR mCRC.

Management

Metastatic CRC

Metastatic CRC is a complex and heterogeneous disease, with outcomes ranging from potential cure (ie, upfront resectable mCRC) to dismal (refractory wide-spread disease). Multi-modality treatment including surgery, radiation, and chemotherapy, especially in medically fit patients with borderline or potentially resectable disease, is the preferred approach in earlier lines of treatment in centres capable of providing multidisciplinary approach and adequate supportive care. The active agents in first- and second-line treatment of mCRC consist of fluoropyrimidines (5-FU, capecitabine), oxaliplatin, and irinotecan. Doublet or triplet chemotherapy is often combined with a monoclonal antibody inhibiting VEGF (bevacizumab or ziv-aflibercept); or EGFR (cetuximab or panitumumab; only indicated in RAS wild-type tumors), depending on biomarker status and primary tumour location.

Despite the variation in practice, the most common management in earlier lines of therapy is intensive treatment consisting of combination chemotherapy and targeted agents. Combination chemotherapy leads to adverse events (any grade) or intolerance in approximately 95% of patients, with more than half the patients experiencing grade 3-5 AEs. Some patients are left with life-altering consequences, such as persistent sensory neuropathy. Biologics, such as anti-VEGF or anti-EGFR, bring additional class-specific toxicities. Finally, triplet chemotherapy (ie, FOLFOXIRI) with bevacizumab may be used in first-line setting when a regimen with a chance of higher response is needed (ie, for R0 resection, or symptomatic bulky disease) or in subjects with BRAF mutation. This treatment approach is associated with higher rate of Grade 3-4 events, SAEs, and rarely with AE-related deaths.

Second-line treatment is typically a doublet chemotherapy, depending on the regimen used in first line setting. The multi-targeted tyrosine kinase inhibitor, regorafenib, and the oral nucleoside analogue trifluridine/tipiracil are available options beyond second-line, but efficacy was modest in the pivotal trials, CORRECT and RECOURSE. Another third line option, anti-EGFR antibody with or without irinotecan, is also used in patients with RAS wildtype status who have not received anti-EGFR therapy in prior lines of therapy.

More recently, additional targeted treatments have become available for a small subset of biomarker-defined patients. Patients carrying tumors with BRAF V600E mutation are eligible for doublet targeted therapy against BRAF and EGFR in second line and beyond (combination of an anti-EGFR mAb with

encorafenib). Additionally, larotrectinib is a new treatment option for patients whose tumours are positive for NTRK gene fusion, a rare alteration.

Despite newer treatment options for mCRC, the benefit of systemic therapy beyond second-line treatment remains modest, and responses are rare.

MSI-H mCRC

Patients with dMMR or MSI-H mCRC experience relatively short PFS with first-line chemotherapy with or without targeted therapy (median PFS and OS on first-line chemotherapy were 6.0 and 26.3 months, respectively) based on a recently published retrospective Association des Gastro-entérologues Oncologues (AGEO) study that included consecutive patients with dMMR or MSI-H mCRC from 2007 to 2017 (Tougeron et al., 2020). Longer PFS (8.1 vs. 5.4 months, p = 0.0405) and OS (35.1 vs. 24.4 months, p = 0.0747) were observed for irinotecan-based chemotherapy compared to oxaliplatin-based chemotherapy. Retrospective analyses on several CRC studies also suggest poor outcomes on patients with dMMR or MSI-H mCRC when treated with chemotherapy.

For second-line chemotherapy, median PFS and OS were 4.4 and 21.6 months in MSI-H patients in this AGEO study. Efficacy further diminished as patients progressed to 3L conventional therapy. Median PFS and OS were 3.6 months and 13.7 months, respectively. ORR results were not available in patients beyond 1L in this study.

Despite the lack of consensus on benefit of non-immunotherapy treatment in dMMR or MSI-H mCRC, checkpoint inhibitors were shown to provide substantial and durable benefit in these patients relative to conventional chemotherapies. Breakthrough was made in dMMR or MSI-H mCRC population with immune checkpoint inhibitors in 2015, demonstrating substantial clinical efficacy with programmed cell death 1 (PD-1) inhibitor. ESMO guidelines recommend that MSI testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC. The National Comprehensive Cancer Network (NCCN) colon and rectal cancer clinical practice guidelines list checkpoint inhibition (anti-PD1 monotherapy or combination of nivolumab and ipilimumab) as a treatment option for all patients with dMMR or MSI-H mCRC tumors beyond first-line, and in first-line and beyond for those who are not appropriate for intensive therapy (category 2B). More recently, KEYNOTE-177 study with PD-1 inhibitor monotherapy (pembrolizumab) showed statistically significant improvement in PFS vs chemotherapy in patients with dMMR or MSI-H mCRC in the first line setting.

In summary, there are a number of conventional chemotherapy and targeted therapy options in EU for medically fit patients with 1L dMMR or MSI-H mCRC but these are also associated with a high frequency and severity of adverse events. In dMMR or MSI-H mCRC patients previously treated with fluoropyrimidine-based combination chemotherapy, therapeutic options are less effective and may be limited by prior therapy and/or mutational status.

ESMO guidelines support MSI status testing as this is a predictive marker for immune checkpoint inhibitors, and NCCN guidelines support the use of immune checkpoint inhibitors in this patient population. There remains a high unmet medical need in EU for well tolerated therapeutic options offering meaningful clinical benefit across lines of therapy, and particularly in 2L and later.

The benefit of current treatment with conventional chemotherapy with or without biologics for dMMR or MSI-H mCRC is not fully elucidated due to limited data available for this small subset of patients, but recent evidence suggests both poorer prognosis and abrogated response to cytotoxic chemotherapy in this group (Tougeron et al., 2020). 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.

Within the EU, the existence of investigator-sponsored research studies (e.g. Netherlands – Drug Rediscovery Protocol [DRUP]) as well as requests for compassionate use/named patient use programs (Austria, Czech Republic, France) further emphasizes the need for new efficacious therapies.

2.1.2. About the product

Nivolumab and ipilimumab each have distinct, but complementary, mechanisms of action, which may enhance responsiveness to the combination regardless of baseline tumour PD-L1 expression (Hamanishi et al, 2007; Brahmer et al 2010; Pardoll, 2012; Wang et al, 2014; Das et al, 2015; Wei et al, 2018 and 2019;).

Nivolumab is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2.

Ipilimumab is a human monoclonal antibody that targets CTLA-4. CTLA-4 inhibition can induce *de novo* T-cell responses and recruit novel/additional T cells to the tumour.

Adding limited doses of chemotherapy (2 cycles) to the nivo+ipi regimen could further enhance the immunogenic effect of nivo+ipi by releasing neoantigens from apoptosing tumour cells, increasing antigen presentation to dendritic cells, decreasing the myeloid-derived suppressive cells and increasing the ratio of cytotoxic lymphocytes to regulatory T-cells.

The recommended dose of nivolumab in combination with ipilimumab for the sought indication in this extension of indication variation procedure is 3 mg/kg OPDIVO IV infusion over 30-min followed by 1 mg/kg ipilimumab IV infusion over 30-min Q3W for 4 dosing cycles, then OPDIVO 240 mg IV infusion over 30-min Q2W

2.1.3. General comments on compliance with GCP

Study CA204192 was performed in accordance with GCP as claimed by the MAH.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH did not perform specific studies on the ERA but provided a justification for not providing an ERA according to Guideline CHMP/SWP/4447/00 corr 2, which states that, among others, medicinal products containing proteins due to their nature they are unlikely to result in a significant risk to the environment**.**

2.2.2. Discussion on non-clinical aspects

Not applicable.

2.2.3. Conclusion on the non-clinical aspects

Considering the nature of the products (proteins) the justification providde by the WSA to not submit

data on the environmental risk assessment, which is in line with the Guideline CHMP/SWP/4447/00 corr 2, is acceptable and nivolumab and ipilimumab are not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The foundational trial for the nivolumab + ipilimumab clinical development program in dMMR or MSI-H mCRC is the Phase 2 study, CA209142. The current application for mCRC is based primarily on data of subjects who received nivolumab + ipilimumab therapy in study CA209142 (Cohort 2) , with a 19-Feb-2019 DBL.

Table 1. Tabular listing of nivolumab/ipilimumab clinical studies in subjects with dMMR or MSI-H Metastatic Colorectal Cancer

Study Type	Study Identifier; Report Location in CTD	Primary Study Objective	Study Design	Test Product(s); Dosage Regimen; Route of Administration	No. Subjects Treated	Study Population	Study Status; Type of Report
Efficacy/ Safety	CA209142 Cohort 2 (Interim Combination Study Report) Report location: Module 5.3.5.1	To evaluate the investigator-assessed objective response rate (ORR) of nivolumab in combination with ipilimumab in subjects with metastatic dMMR or MSI-H CRC	A Phase 2 multi-cohort, open-label study including 3 phases: screening, treatment and follow-up. Tumor 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.	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV infusion Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W	Cohort 2: N = 119 treated	Subjects with dMMR or MSI-H mCRC, previously treated. A subset of subjects (n = 82) represent a heavily-pretreated population mainly in the 3L+ setting (subjects with prior 5FU-Oxa-Iri). A subset of subjects (n = 37) represent a less heavily-pretreated population mainly in the 2L setting (subjects without prior 5FU-Oxa-Iri)	Ongoing, interim study report with 18-Aug-2017 DBL
Efficacy/ Safety	CA209142 Cohort 2 (Ad Hoc Combination Efficacy Report) Report location: Module 5.3.5.1	To evaluate the investigator-assessed ORR of nivolumab in combination with ipilimumab in subjects with metastatic dMMR or MSI-H CRC	Same as above	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV infusion Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W	Cohort 2: N = 119 treated	Same as above	Ongoing, ad hoc efficacy report with 19-Feb-2019 DBL
Efficacy/ Safety	CA209142 Cohort 2 (Ad Hoc Combination Safety Report) Report location: Module 5.3.5.1	To evaluate the investigator-assessed ORR of nivolumab in combination with ipilimumab in subjects with metastatic dMMR or MSI-H CRC	Same as above	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg IV infusion Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W	Cohort 2: N = 119 treated	Same as above	Ongoing, ad hoc safety report with 19-Feb-2019 DBL
Efficacy/ Safety	CA209142 Cohort 1 (Interim Monotherapy Study Report) Report location: Module 5.3.5.1	To evaluate the investigator-assessed ORR of nivolumab monotherapy in subjects with metastatic dMMR or MSI-H CRC	Same as above	Nivolumab 3 mg/kg IV Q2W	Cohort 1: N = 74 treated	Subjects with dMMR or MSI-H mCRC, previously treated	Ongoing, interim study report with 19-Sep-2016 DBL
Efficacy/ Safety	CA209142 Cohort 1 (Ad Hoc Monotherapy Efficacy Report) Report location: Module 5.3.5.1	To evaluate the investigator-assessed ORR of nivolumab monotherapy in subjects with metastatic dMMR or MSI-H CRC	Same as above	Nivolumab 3 mg/kg IV Q2W	Cohort 1: N = 74 treated	Subjects with dMMR or MSI-H mCRC, previously treated	Ongoing, ad hoc efficacy report with 19-Feb-2019 DBL
Efficacy/ Safety	CA209142 Cohort 1 (Ad Hoc Monotherapy Safety Report) Report location: Module 5.3.5.1	To evaluate the investigator-assessed ORR of nivolumab monotherapy in subjects with metastatic dMMR or MSI-H CRC	Same as above	Nivolumab 3 mg/kg IV Q2W	Cohort 1: N = 74 treated	Subjects with dMMR or MSI-H mCRC, previously treated	Ongoing, ad hoc efficacy report with 19-Feb-2019 DBL

Abbreviations: 1L: first line; 2L: second line; 3L+: third line and beyond; 5FU: 5-fluorouracil; ASCO: American Society of Clinical Oncology; CRC: colorectal cancer; DBL: database lock; dMMR: mismatch repair-deficient; Iri: irinotecan; IV: intravenous; mCRC: metastatic colorectal cancer; MSI-H: microsatellite instability-high; No.: number; ORR: objective response rate; Oxa: oxaliplatin; QxW: every x weeks; RECIST = Response Evaluation Criteria in Solid Tumors.

2.3.2. Pharmacokinetics and PK/PD modelling

Pharmacokinetics in the target population

The nivolumab clinical pharmacology profile, including single- and multiple-dose pharmacokinetics (PK) described by non-compartmental analysis, QT prolongation potential, and dose selection for Phase 2/3 studies has been previously described. Additionally, the clinical pharmacology profile of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg was characterized previously in subjects with advanced melanoma. In an earlier population PK (PPK) analysis, both nivolumab and ipilimumab PK was described by a time-invariant model. However, a recent comprehensive analysis of nivolumab PPK found that nivolumab clearance (CL) decreased with time over the course of treatment.

For this submission, nivolumab and ipilimumab PK in mCRC patients was characterized by PPK analyses. A pre-planned interim database lock (DBL) of the CA209142 combination cohort occurred on 18-Aug-2017. Nivolumab and ipilimumab PK data from mCRC patients from this lock were pooled together with PK data from 24 and 15 studies for PPK analyses of nivolumab and ipilimumab, respectively. Another DBL of the CA209142 combination arm was performed on 19-Feb-2019 to provide more mature data. At this later DBL, 280 (~ 35% increase) and 56 (~ 12%) new nivolumab and ipilimumab concentration records were provided in CRC patients, respectively. The increase in nivolumab PK data or ipilimumab PK data from Study CA209142 based on the later DBL, represent a < 1% data increase for the PPK datasets. PK parameters were re-estimated using the previously developed PPK model, and included the previous PPK dataset and additional PK data obtained from Study CA209142 (DBL on 19 Feb-2019).

Nivolumab PK

Sparse nivolumab PK data from CA209142 were pooled together with nivolumab PK data from 24 other studies (Table 2) for a PPK analysis.

Nivolumab PK was well described by a linear 2-compartment model with time-varying total body clearance (CL). Nivolumab PK in dMMR or MSI-H mCRC patients is consistent with the known nivolumab PK characteristics.(reference is made to the approved PI) The geometric mean (coefficient of variation [CV]%) values of nivolumab clearance at steady state (CLss), volume of distribution at steady state (Vss), terminal half-life at steady state (t1/2,ss) following IV administration of nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) Q3W in dMMR or MSI-H mCRC patients were 7.23 mL/h (42.4%), 6.19 L (18.2%), and 25.7 days (54.8%), respectively . No covariates were found to have a clinically meaningful effect on nivolumab PK.

Nivolumab PPK analysis was conducted to characterize the PK of nivolumab in 6468 subjects with non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), melanoma, RCC, hepatocellular carcinoma (HCC), or CRC who received nivolumab alone or in combination with ipilimumab from 25 studies (Table 3.3.1.1-1 in the PPK report). The analysis dataset included data for nivolumab doses ranging from 0.1 to 10 mg/kg, 240 mg, or 360 mg, and dosing frequencies of once every 2 or 3 weeks (Q2W or Q3W).

Table 2. samples included in the Updated Nivolumab Population Pharmacokinetic Analysis Dataset

Study	PK DB[a]	Missing dose or sample information	Duplicate samples at same time (set up for NCA)	Day 1 Pre-Dose	LLOQ[b]	Other	Other Tumor Type	Samples included in analysis (%)
Others[f]	39849	400	206	5704	812	26[c,d]	0	32273 (80.99)
CA209142	1085	4	0	205	9	70[e]	0	797 (73.46)
Total	40934	404	206	5909	821	96	428	33070 (80.79)

Abbreviations: DB = database; LLOQ = lower limit of quantification; NCA = non-compartmental analysis; PK = pharmacokinetic.

[a] Samples in eToolbox or Pharmacokinetic/Pharmacodynamic Analysis and Modeling System (PAMS). All which are included in the analysis dataset with flag as noted

[b] LLOQ: Post-dose nivolumab serum concentration values below the lower limited of quantification.

[c] Includes samples with concentration > 2000 µg/mL.

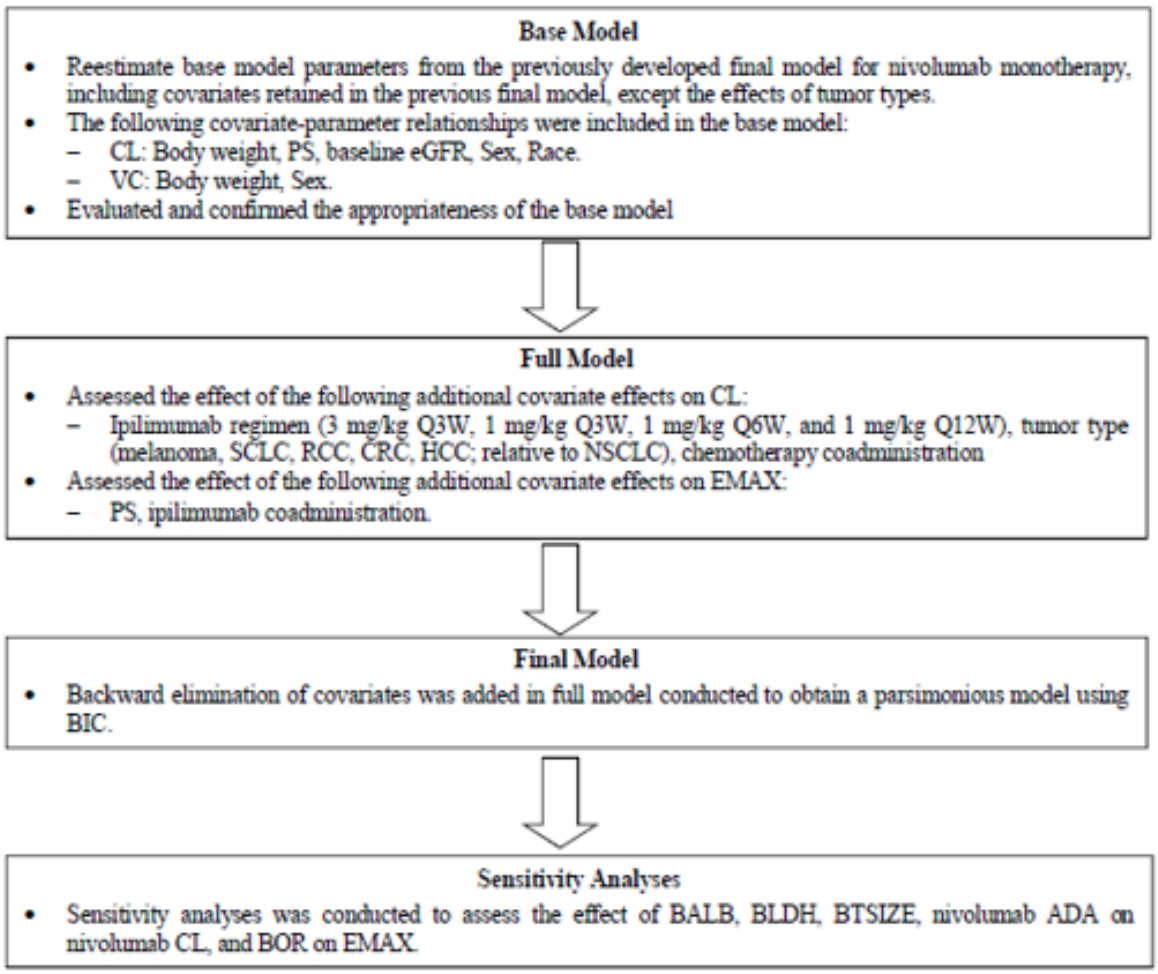
[d] There are samples from subjects in study CA209032 who were crossed-over to nivolumab + ipilimumab combination therapy

[e] Includes samples with concentration > 2000 µg/mL and PK samples used incorrect kit in CA209142.

[f] Includes 24 studies presented in Appendix 3.3.3.1, Table 1.

The nivolumab PPK model was developed in three steps: base, full, and final models (figure 1).

Figure 1. schematic Overview of Nivolumab Population Pharmacokinetic Model Development



The final nivolumab model was a two-compartment, zero-order IV infusion and time-varying CL model (sigmoidal Emax function) with a proportional residual error model, with random effects on CL, VC, VP, and EMAX; and correlation of random effect between CL and VC. The final nivolumab PPK model contained ipilimumab regimen, chemotherapy coadministration, BBWT, eGFR, PS, sex, and race on CL, ipilimumab coadministration and PS on change of CL over time, and BBWT and sex on VC. Table 3.1.1-

1 presents the parameter estimates from the final model, and the expressions describing the functional form of the time-varying CL and covariate effects are given below:

$$CL0_i = CL0_{REF} \cdot \left(\frac{BW_i}{BW_{REF}}\right)^{CL_{BW}} \cdot \left(\frac{eGFR_i}{eGFR_{REF}}\right)^{CL_{eGFR}} \cdot e^{CL_{Ipi3}} \cdot e^{CL_{Ipi1Q6W}} \cdot e^{Chemo} \cdot \cdot e^{CL_{SEX}} \cdot e^{CL_{PS}} \cdot e^{CL_{RAAA}} \cdot e^{CL_{RAAS}} \cdot e^{\eta CLi}$$

$$EMAX_i = EMAX_{REF\,i} + EMAX_{PS1} + EMAX_{Ipico} + \eta EMAXi$$

$$CL_{t,i} = CL0_i \cdot \exp\left(\frac{(EMAXi) * t^{HILL}}{T50_i^{HILL} + t^{HILL}}\right),$$

$$CL_{SS,i} = CL0_i \cdot \exp(EMAX_i)$$

$$VC_i = VC_{REF} * \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}} * e^{VC_{SEX}} * e^{\eta VCi}$$

$$Q_i = Q_{REF} * \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} * e^{\eta CLi}$$

$$VP_i = VP_{REF} * \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{VC_{BBWT}} * e^{\eta VCi}$$

where CL0REF is the typical value of CL at time 0 (CL0) at the reference values of BW, PS, and eGFR, SEX is referenced to male, and race is referenced to white/other. VCREF, QREF, and VPREF are typical values of VC, Q, and VP at the reference values of BBWT, respectively. CLBW, CLeGFR, CLSEX, CLPS, CLRAAA, CLRAAS, CLIpi3, CLIpi1Q6W, CLChemo, EMAXPS1, EMAXIpico, VCBW, and VCSEX are model parameters. Ipi3 indicates nivolumab combined with ipilimumab 3 mg/kg Q3W, Ipi1Q6W indicates nivolumab combined with ipilimumab 1 mg/kg Q6W, Chemo indicates nivolumab combined with chemotherapy, RAAA indicates race (African American), and RAAS indicates race (Asian). EMAXREF represents the reference value of the maximal change in CL. The T50 parameter represent the time at which the change in CLt,i is 50% of EMAX and HILL represents the sigmoidicity of the relationship with time. CL0i represents baseline CL of subject i; CLss,i represents the steady-state CL of subject i. CLt,i is the individual CL at each timepoint, VCi, Qi, VPi, and EMAXi are the individual values of VC, Q, VP, and EMAX, respectively, and ηCLi, ηVCi, and ηEMAXi are normally distributed random variables.

Table 3. Parameter Estimates for the Final Nivolumab Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	10.8	0.162 (1.50)	10.5 - 11.2
VC_{REF} [L]	θ_2	4.27	0.0311 (0.728)	4.21 - 4.34
Q_{REF} [mL/h]	θ_3	34.9	2.41 (6.91)	30.4 - 40.7
VP_{REF} [L]	θ_4	2.70	0.0668 (2.47)	2.58 - 2.83
CL_{BBWT}	θ_7	0.530	0.0286 (5.40)	0.470 - 0.589

Table 3. Parameter Estimates for the Final Nivolumab Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
CL_{GFR}	θ_9	0.202	0.0199 (9.85)	0.162 - 0.243
CL_{FEMALE}	θ_{12}	-0.181	0.0133 (7.35)	-0.206 - -0.155
CL_PS_1	θ_{13}	0.181	0.0130 (7.18)	0.156 - 0.208
CL_{RAAA}	θ_{14}	0.0374	0.0322 (86.1)	-0.0308 - 0.111
CL_{RAAS}	θ_{15}	-0.0354	0.0169 (47.7)	-0.0670 - -0.00215
VC_{BBWT}	θ_{16}	0.534	0.0240 (4.49)	0.489 - 0.579
VC_{FEMALE}	θ_{17}	-0.161	0.0141 (8.76)	-0.189 - -0.132
$EMAX_{REF}$	θ_{18}	-0.240	0.0210 (8.75)	-0.283 - -0.199
T50 [h]	θ_{19}	2200	131 (5.95)	1970 - 2500
HILL	θ_{20}	2.77	0.263 (9.49)	2.30 - 3.34
CL_IPI1_{6W}	θ_{28}	0.159	0.0179 (11.3)	0.124 - 0.191
CL_IPI3_{3W}	θ_{30}	0.227	0.0213 (9.38)	0.185 - 0.269
CL_{CHEMO}	θ_{32}	-0.104	0.0255 (24.5)	-0.155 - -0.0525
$EMAX_{IPICO}$	θ_{33}	-0.0668	0.0234 (35.0)	-0.118 - -0.0249
$EMAX\_PS_1$	θ_{34}	-0.138	0.0200 (14.5)	-0.179 - -0.0987
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.157 (0.396)	0.00856 (5.45)	0.141 - 0.175
ZVC [-]	$\omega_{2,2}$	0.152 (0.390)	0.0149 (9.80)	0.123 - 0.185
ZEMAX	$\omega_{5,5}$	0.0874 (0.296)	0.0113 (12.9)	0.0662 - 0.114
ZCL:*ZVC*	$\omega_{1,2}$	0.0596 (0.386)	0.00894 (15.0)	0.0439 - 0.0792
Residual Error				
PERR [-]	$\omega_{1,2}$	0.245	0.00405 (1.65)	0.237 - 0.253

Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk- nivo/final

Program Source: Analysis Directory/nm/final/final.lst

Source: Analysis Directory/nm/final.rtf

Note: $CL0_{REF}$ is typical values in reference subject with NSCLC, receiving nivolumab monotherapy as a 2nd line therapy, and weighing 80 kg. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject receiving nivolumab monotherapy with a normal PS status. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note: Eta shrinkage (%): ETA_CL: 11.9; ETA_VC: 28.0; ETA_EMAX: 50.3; EPS shrinkage (%):16.4.

[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

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

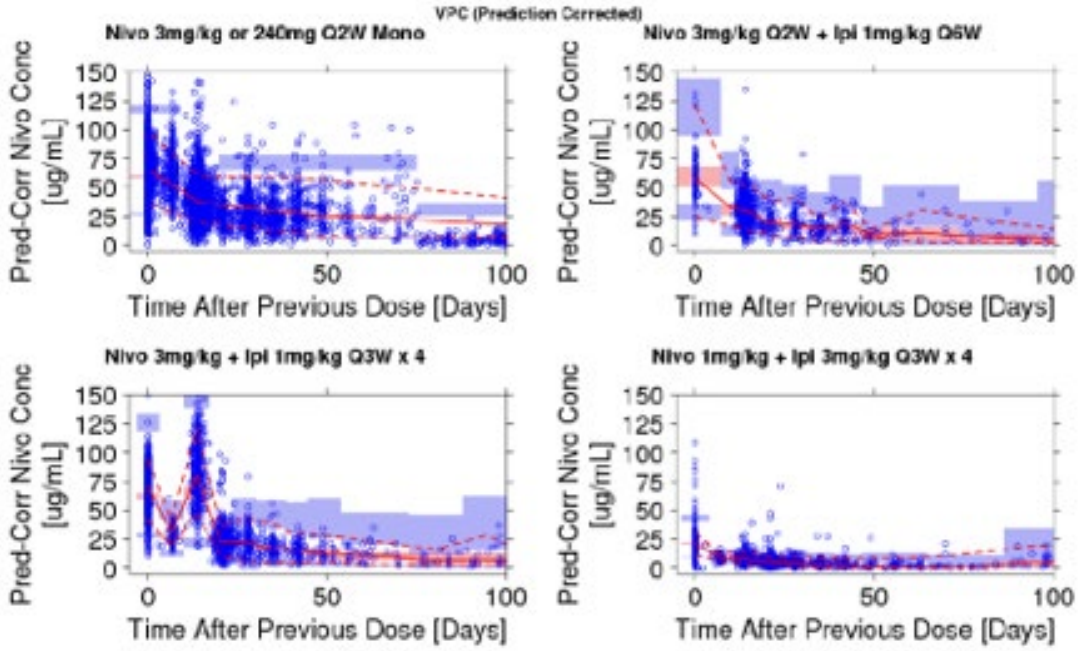
[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

The PPK model parameters were estimated with good precision, and the model evaluation demonstrated that there was good agreement between model predictions and observations (Figure 2, and Figure 3).

Figure 2, Prediction-Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose Stratified by Selected Nivolumab Dosing Regimens (Final Nivolumab Population Pharmacokinetic Model



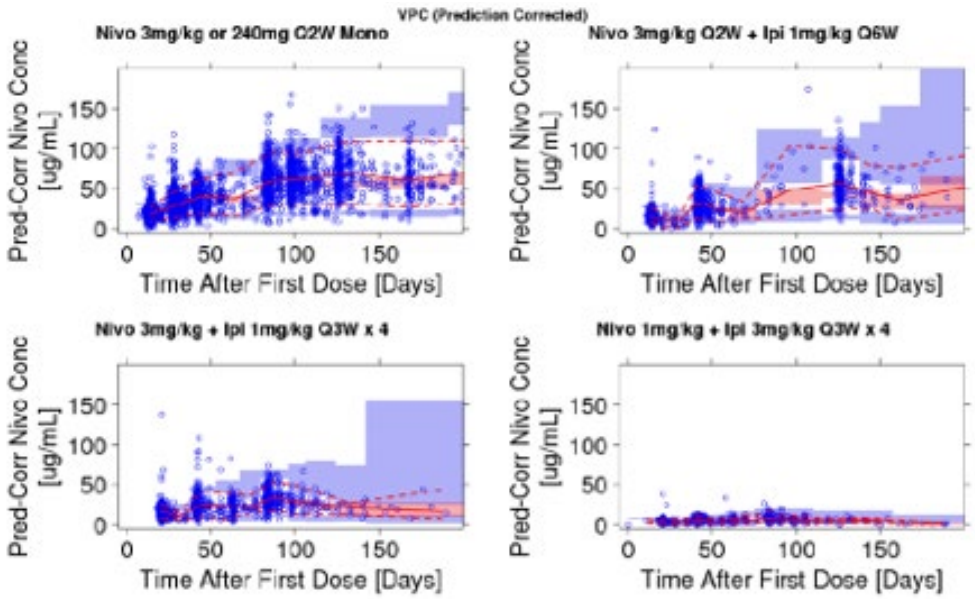
Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/

Program Source: Analysis-Directory/R/scripts/vpc-plots.r

Source: Analysis-Directory/psn/vpc_final_dir5/VPC-plots 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 3. Prediction-Correction Visual Predictive Check of Trough Concentration versus Actual Time after First Dose Stratified by Selected Nivolumab Dosing Regimens (Final Nivolumab Population Pharmacokinetic Model.



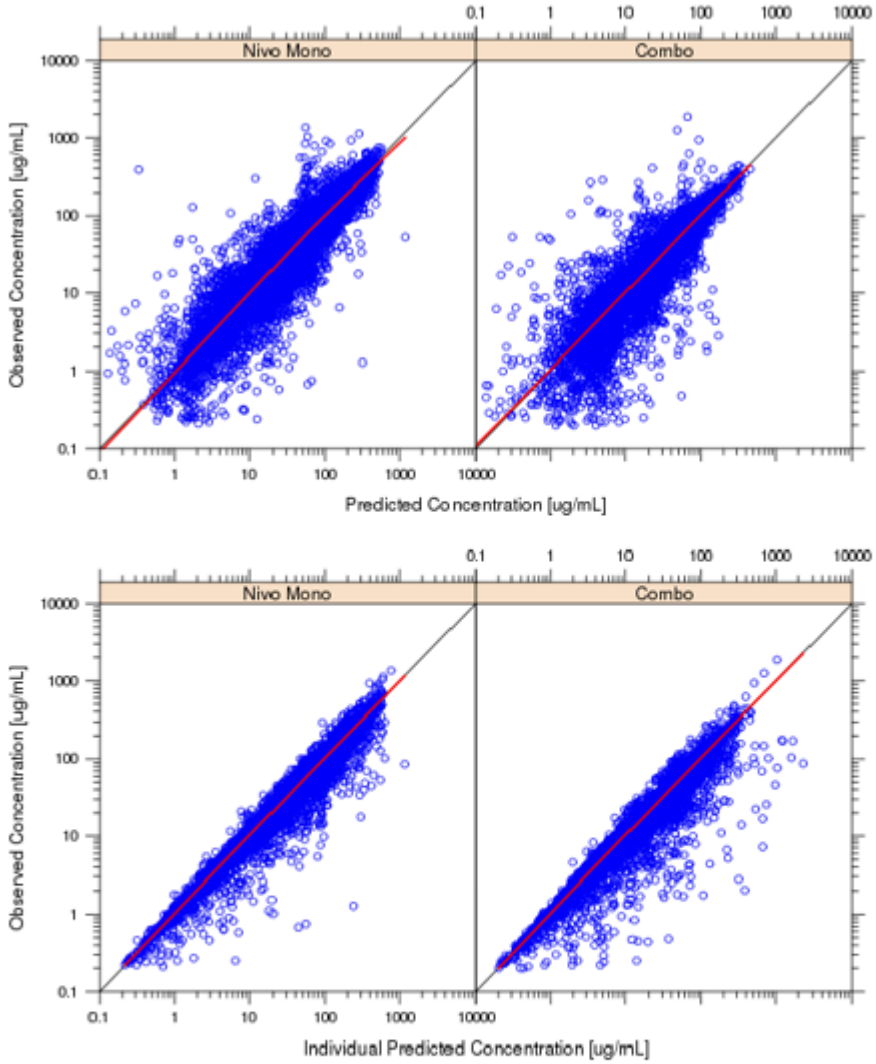
Analysis -Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-nivo/final/

Program Source: Analysis-Directory/R/scripts/vpc-plots.r

Source: Analysis-Directory/psn/vpc_final_dir6/VPC-plots 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 4. Observed versus Predicted Population Average and Individual Concentration in Nivolumab Monotherapy and Combination Therapy (Final Nivolumab Population Pharmacokinetic Model)



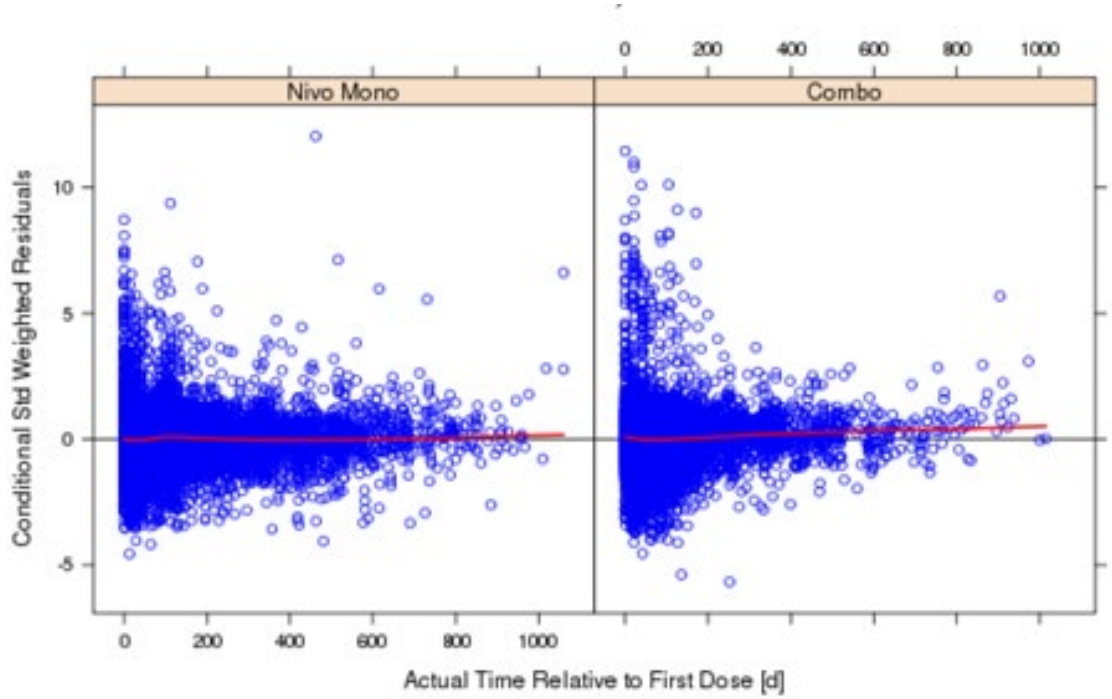
Analysis -Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-nivo/final/

Program Source: Analysis-Directory/R/scripts/main-final-nmplots.r

Source: Analysis-Directory/nm/final/plots/obs-pred/obs-pred-regimen.png
Analysis-Directory/nm/final/plots/obs-pred/obs-pred-regimen.png

Note: Solid red line represents linear regression line; Solid black line represents line of identity.

Figure 5. CWRES versus Time after First Dose in Nivolumab Monotherapy and Combination Therapy (Final Nivolumab Population Model)



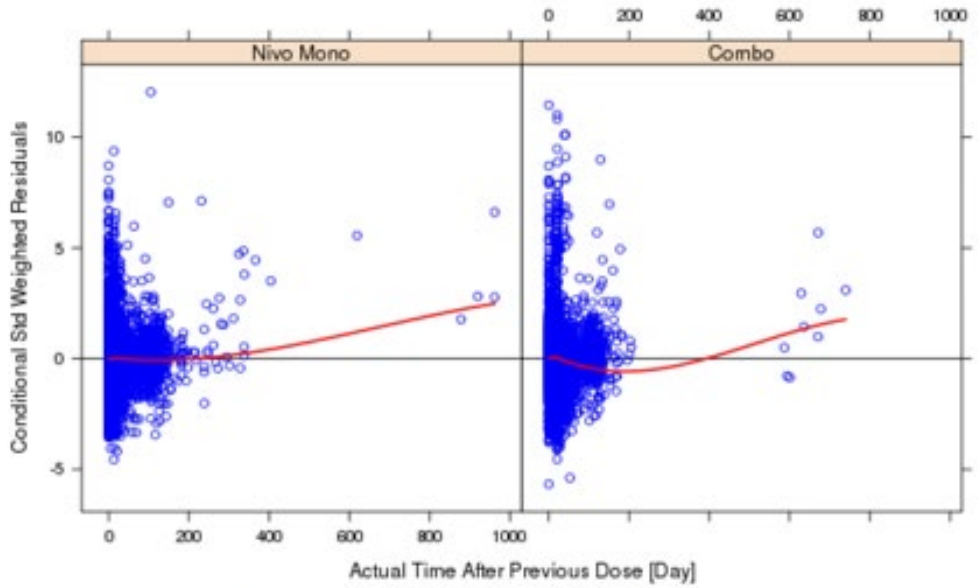
Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/

Program Source: Analysis-Directory/R/scripts/main-final-nmplots.r

Source: Analysis-Directory/nm/final/plots/resid/cwres-time-ipi3.png

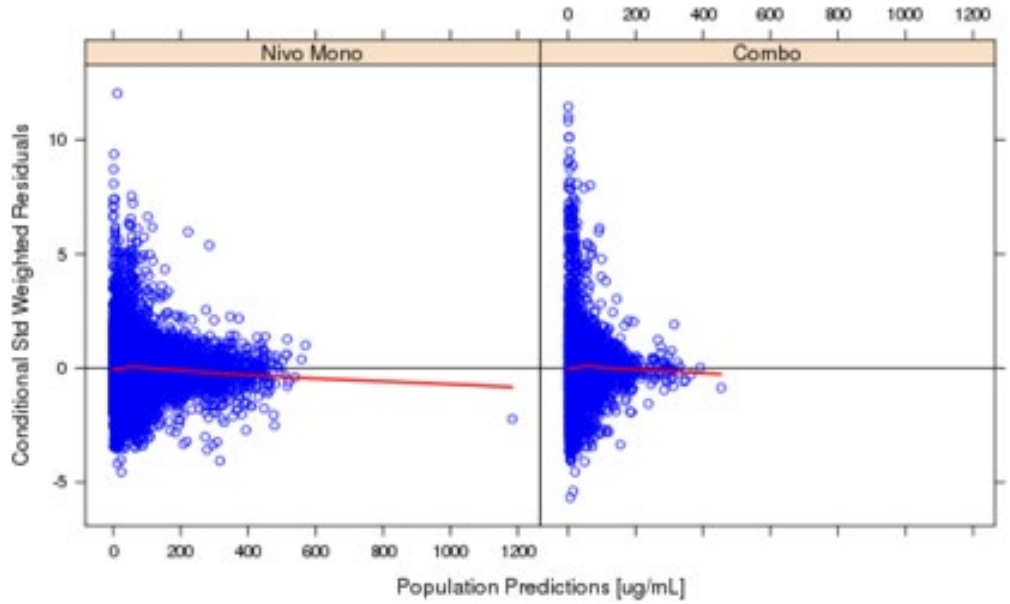
Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

Figure 6. CWRES versus Time after Previous Dose in Nivolumab Monotherapy and Combination Therapy (Final Nivolumab Population Pharmacokinetic Model)



Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/
Program Source: Analysis-Directory/R/scripts/main-final-nmplots.r
Source: Analysis-Directory/nm/final/plots/resid/cwres-time-prev-ipi3mpk.png
Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

Figure 7. CWRES versus Predicted (typical) Serum Concentration in Nivolumab Monotherapy (Final Nivolumab Population Pharmacokinetic Model)



Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/
Program Source: Analysis-Directory/R/scripts/main-final-nmplots.r
Source: Analysis-Directory/nm/final/plots/resid/cwres-pred-Ipi3.png
Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

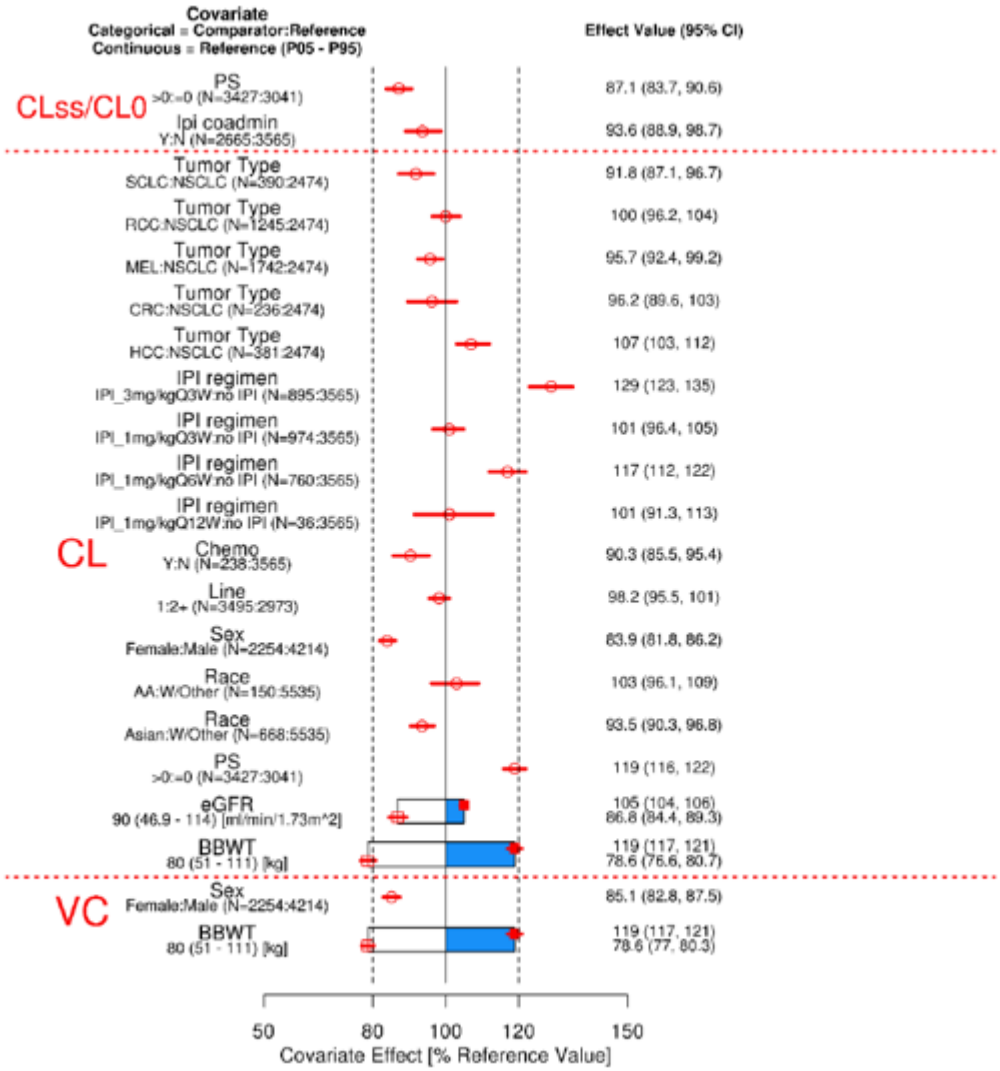
The maximal change in CL (Emax) was similar across dose regimens and tumor types. The maximal model predicted decrease in CL was ~21% in subjects with PS of 0, and ~31% in subjects with PS >

0. The time for half-maximal reduction was ~92 days (2200 hours). Decrease in nivolumab CL appeared to be associated with clinical response. Patients with CR or PR showed the greatest CL reduction.

The effects of tumor type, line of therapy, chemo co-medication, baseline PS, baseline eGFR, BBWT, sex, race on nivolumab PK (CL and/or Vc) were either not statistically significant (the 95% CI includes 0) or not clinically relevant (less than ±20% effect on the typical value of a model parameter relative to the reference value) (Figure 8).

Nivolumab in combination with ipilimumab 1 mg/kg Q3W, Q6W and Q12W regimens did not have a statistically significant or clinically relevant effect on nivolumab CL (Figure 3.1.1-1). The CL of nivolumab when given in combination with ipilimumab 3 mg/kg Q3W was higher (by ~29%) compared to nivolumab monotherapy.

Figure 8. Covariate Effects on Nivolumab Pharmacokinetic Model Parameters (Full Nivolumab Population Pharmacokinetic Model)



Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/

R-Program Source: Analysis-Directory/R/scripts/cov-eff-plot-full.r

Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal 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 lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is male, white/other race, BW = 80 kg, PS = 0, eGFR = 90 mL/min/1.73 m2, and received nivolumab monotherapy, with NSCLC as tumor type. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.
Note 4: The effect of BBWT was also added on Q and VP and their estimates were fixed to be similar to that CL and VC, respectively.
Note 5: Baseline CL of nivolumab in subjects with PS > 0 was higher than subjects with PS = 0 by 19%, whereas the reduction of nivolumab CL over time was greater in subjects with PS > 0 than subjects with PS = 0 by 13%.

The nivolumab PK in dMMR or MSI-H mCRC patients is consistent with the known nivolumab PK characteristics. Nivolumab CL (baseline [CL0] and steady state [CLss]) appeared to be numerically lower following nivolumab monotherapy relative to those following nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W combination therapy. Following the same combination therapy, nivolumab PK parameters are similar between dMMR or MSI-H CRC and mRCC patients (Table 4).

Table 4: Summary Statistics of Nivolumab PK Parameters

Nivolumab PK Parameter	GeoMean (% CV)		
	dMMR or MSI-H mCRC		mRCC
	Nivolumab Monotherapy (n=65)	Nivo 3 mg/kg + Ipi 1 mg/kg Q3W[a] (n=112)	Nivo 3 mg/kg + Ipi 1 mg/kg Q3W[a] (n=496)
CL_0 [mL/h]	9.74 (44.3)	10.7 (39.5)	10.5 (38.0)
CL_{SS} [mL/h]	6.83 (47.1)	7.23 (42.4)	7.41 (38.9)
VSS [L]	6.14 (20.5)	6.19 (18.2)	6.61 (17.8)
$t_{1/2\beta,SS}$[d]	27.0 (37.3)	25.7 (54.8)	26.7 (24.7)

a 2 patients (1 CRC and 1 RCC) were excluded from the summary table due to dosing errors

Consistent with PK parameter results, nivolumab exposure (Cmin/Cmax/Cavg following the first dose and at steady state) appeared to be numerically higher following nivolumab monotherapy relative to those following nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W combination therapy. However the difference is generally less than 20% except for CAVG1 (~ 26%), and thus unlikely to be clinically relevant (Table 3.1.1-3). Following the same combination therapy, nivolumab exposure levels are similar between dMMR or MSI-H CRC and mRCC patients (Table 5).

Table 5: Summary Statistics of Nivolumab Exposure in Combination Therapy (Nivo: 3 mg/kg Q3W, Ipi 1 mg/kg Q3W x 4 Doses)

Nivolumab Exposure Parameters (µg/mL)	**GeoMean (% CV)**		
	dMMR or MSI-H mCRC		**mRCC**
	Nivolumab Monotherapy (n=65)	Nivo 3 mg/kg + Ipi 1 mg/kg Q3W[a] (n=112)	Nivo 3 mg/kg + Ipi 1 mg/kg Q3W[a] (n=496)

CMIN1	20.5 (30.0)	13.1 (35.2)	15.1 (28.2)
CMAX1	66.0 (25.1)	58.2 (20.9)	61.4 (32.8)
CAVG1	31.1 (24.3)	23.1 (24.2)	25.5 (20.5)
CMINSS	82.2 (52.4)	77.1 (87.5)	76.3 (37.1)
CMAXSS	152 (36.7)	144 (57.3)	139 (29.1)
CAVGSS	105 (45.2)	98.8 (73.3)	96.4 (32.6)

a 2 patients (1 CRC and 1 RCC) were excluded from the summary table due to dosing errors

Sensitivity Analyses

Sensitivity analysis have been conducted evaluating the effect of ADA, baseline albumin (BALB), baseline lactose dehydrogenase (BLDH), and baseline tumor burden on nivolumab CL (Table 6 and Table 7).

Table 6: Parameter Estimates for Sensitivity of Baseline Albumin, Lactate Dehydrogenase, and Tumor Size

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	10.9	0.209 (1.92)	10.5 - 11.3
VC_{REF} [L]	θ_2	4.19	0.0379 (0.905)	4.12 - 4.26
Q_{REF} [mL/h]	θ_3	36.4	3.66 (10.1)	29.2 - 43.6
VP_{REF} [L]	θ_4	2.81	0.0862 (3.07)	2.64 - 2.98
CL_{BBWT}	θ_7	0.575	0.0410 (7.13)	0.495 - 0.655
CL_{GFR}	θ_9	0.177	0.0272 (15.4)	0.124 - 0.230
CL_{BLDH}	θ_{10}	0.291	0.0874 (30.0)	0.120 - 0.462
CL_{BALB}	θ_{11}	-0.841	0.0638 (7.59)	(-0.966) - (-0.716)
CL_{FEMALE}	θ_{12}	-0.166	0.0191 (11.5)	(-0.203) - (-0.129)
CL_PS_1	θ_{13}	0.108	0.0178 (16.5)	0.0731 - 0.143
CL_{RAAA}	θ_{14}	0.0107	0.0341 (319)	(-0.0561) - 0.0775
CL_{RAAS}	θ_{15}	0.0244	0.0239 (98.0)	(-0.0224) - 0.0712
VC_{BBWT}	θ_{16}	0.532	0.0328 (6.17)	0.468 - 0.596
VC_{FEMALE}	θ_{17}	-0.156	0.0178 (11.4)	(-0.191) - (-0.121)
$EMAX_{REF}$	θ_{18}	-0.219	0.0287 (13.1)	(-0.275) - (-0.163)
$T50$ [h]	θ_{19}	2.19E+03	134 (6.12)	1.93E+03 - 2.45E+03
$HILL$	θ_{20}	3.26	0.512 (15.7)	2.26 - 4.26

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
CL_IPI1_{6W}	θ_{28}	0.151	0.0229 (15.2)	0.106 - 0.196
CL_IPI3_{3W}	θ_{30}	0.188	0.0300 (16.0)	0.129 - 0.247
CL_{CHEMO}	θ_{32}	-0.200	0.0568 (28.4)	(-0.311) - (-0.0887)
$EMAX_{PVCO}$	θ_{33}	-0.0347	0.0267 (76.9)	(-0.0870)- 0.0176
$EMAX\_PS_1$	θ_{34}	-0.127	0.0283 (22.3)	(-0.182) - (-0.0715)
CL_{BTSIZE}	θ_{35}	0.0845	0.0116 (13.7)	0.0618 - 0.107
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.164 (0.405)	0.0135 (8.23)	0.138 - 0.190
ZVC [-]	$\omega_{2,2}$	0.153 (0.391)	0.0202 (13.2)	0.113 - 0.193
ZEMAX	$\omega_{5,5}$	0.107 (0.327)	0.0158 (14.8)	0.0760 - 0.138
ZCL:ZVC	$\omega_{1,2}$	0.0680 (0.429)	0.0138 (20.3)	0.0410 - 0.0950
Residual Error				
PERR [-]	θ_6	0.260	0.00553 (2.13)	0.249 - 0.271

Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk- nivo/final

Program Source: Analysis Directory/nm/sen-ALB-build-2/sen-ALB-build-2.lst

Source: Analysis Directory/nm/sen-ALB-build-2.rtf

Note: $CL0_{REF}$ is the typical value in a reference subject with NSCLC, receiving nivolumab monotherapy as a 2nd line therapy, and weighing 80 kg. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject receiving nivolumab monotherapy with a normal PS status. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note: Eta shrinkage (%): ETA_CL: 12.2; ETA_VC: 28.0; ETA_EMAX: 49.6; EPS shrinkage (%):16.4.

[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

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

Table 7: Parameter Estimates for Sensitivity of Anti-drug Antibodies

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	10.5	0.152 (1.45)	10.2 - 10.8
VC_{REF} [L]	θ_2	4.27	0.0310 (0.726)	4.21 - 4.33
Q_{REF} [mL/h]	θ_3	35.7	2.64 (7.39)	30.5 - 40.9
VP_{REF} [L]	θ_4	2.68	0.0667 (2.49)	2.55 - 2.81
CL_{BBWT}	θ_7	0.531	0.0282 (5.31)	0.476 - 0.586
CL_{GFR}	θ_9	0.197	0.0196 (9.95)	0.159 - 0.235
CL_{FEMALE}	θ_{12}	-0.178	0.0131 (7.36)	(-0.2040) - (-0.152)
CL_PS_1	θ_{13}	0.181	0.0127 (7.02)	0.156 - 0.206
CL_{RAAA}	θ_{14}	0.0364	0.0322 (88.5)	(-0.0267) - 0.0995
CL_{RAAS}	θ_{15}	-0.0350	0.0163 (46.6)	(-0.0669) - (-0.00305)
VC_{BBWT}	θ_{16}	0.538	0.0240 (4.46)	0.491 - 0.585
VC_{FEMALE}	θ_{17}	-0.160	0.0141 (8.81)	(-0.188) - (-0.132)
$EMAX_{REF}$	θ_{18}	-0.233	0.0204 (8.76)	(-0.273) - (-0.193)
T50 [h]	θ_{19}	2.20E+03	134 (6.09)	1.94E+03 - 2.46E+03
HILL	θ_{20}	2.92	0.292 (10.0)	2.35 - 3.49
CL_IPI1_{6W}	θ_{28}	0.143	0.0173 (12.1)	0.109 - 0.177
CL_IPI3_{3W}	θ_{30}	0.200	0.0208 (10.4)	0.159 - 0.241
CL_{CHEMO}	θ_{32}	-0.103	0.0251 (24.4)	(-0.152) - (-0.0538)
$EMAX_{IPICO}$	θ_{33}	-0.0503	0.0230 (45.7)	(-0.0954) - (-0.00522)
$EMAX\_PS_1$	θ_{34}	-0.131	0.0198 (15.1)	(-0.170) - (-0.0922)
CL_{ADA3}	θ_{36}	1.20	0.0183 (1.52)	1.16 - 1.24
CL_{ADA}-99	θ_{37}	1.03	0.0113 (1.10)	1.01 - 1.05
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.150 (0.387)	0.00861 (5.74)	0.133 - 0.167
ZVC [-]	$\omega_{2,2}$	0.152 (0.390)	0.0150 (9.87)	0.123 - 0.181
ZEMAX	$\omega_{5,5}$	0.0887 (0.298)	0.0113 (12.7)	0.0666 - 0.111

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
ZCL:ZVC	$\omega_{1,2}$	0.0596 (0.395)	0.00886 (14.9)	0.0422 - 0.0770
Residual Error				
PERR [-]	θ_6	0.245	0.00407 (1.66)	0.237 - 0.253

Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk- nivo/final
Program Source: Analysis Directory/nm/sen-ADA-build-2/sen-ADA-build-2.lst
Source: Analysis Directory/nm/sen-ADA-build-2.rtf

Note: *CL0REF* is the typical value in a reference subject with NSCLC, receiving nivolumab monotherapy as a 2nd line therapy, and weighing 80 kg. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject receiving nivolumab monotherapy with a normal PS status. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.
Note: Eta shrinkage (%): ETA_CL: 13.2; ETA_VC: 24.4; ETA_EMAX: 47.7; EPS shrinkage (%):14.8.

[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

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

Baseline Albumine (BALB)

The sensitivity analysis indicated nivolumab CL is higher in subjects with lower BALB.

Baseline lactose dehydrogenase (BLDH)

Nivolumab CL was higher in subjects with higher BLDH, and the 95th percentile can reach 44% relative to a reference subject (200 IU/mL). The sensitivity analysis of BLDH is done together with BTSIZE rather than separately, causing removal of more data due to lack of tumor size, and changed the variability of BLDH values.

BTSIZE

The sensitivity analysis indicated that the effect of BTSIZE on nivolumab CL was statistically significant but was within 20% of the CL of a reference subject. In general, nivolumab CL was higher in subjects with a higher BTSIZE;

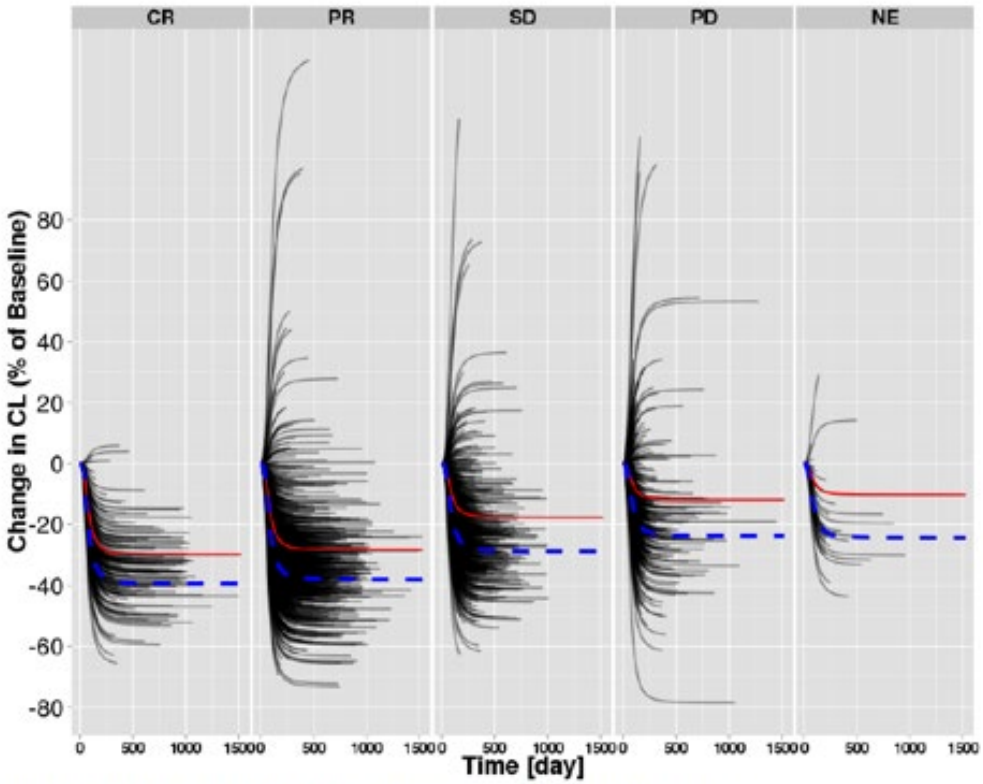
Anti Drug Antibody (ADA)

The effect of ADA (assessed by the 3rd generation assay) on CL was assessed in an ad-hoc sensitivity analysis. When ADA was present, nivolumab CL was estimated to be approximately 20% higher. The effects of positive anti-nivolumab antibody status (using 3rd generations of anti-nivolumab antibody assays) on CL were assessed as time-varying covariate. A positive anti-nivolumab antibody status was estimated to increase nivolumab CL by 20% compared to a negative anti-nivolumab antibody status.

Best Overall response (BOR)

The magnitude of the change in CL was higher in responders than non-responders. In the sensitivity analysis, BOR was a covariate on the change of CL with time. The ratio CLss/CL0 was 65.4%, 65.9%, 75.2%, and 80.4% in CR, PR, SD, and PD subjects, respectively. In general, subjects with CR and PR were observed to have greater decrease in CL compared to non-responders with SD and PD. This observation is consistent with that found for ipilimumab.

Figure 9. Change in Nivolumab Clearance over Time by Best Overall Response, Estimated by the Sensitivity Model.



Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/

R-Program Source: Analysis-Directory/R/scripts/plotcl-time_bor.R

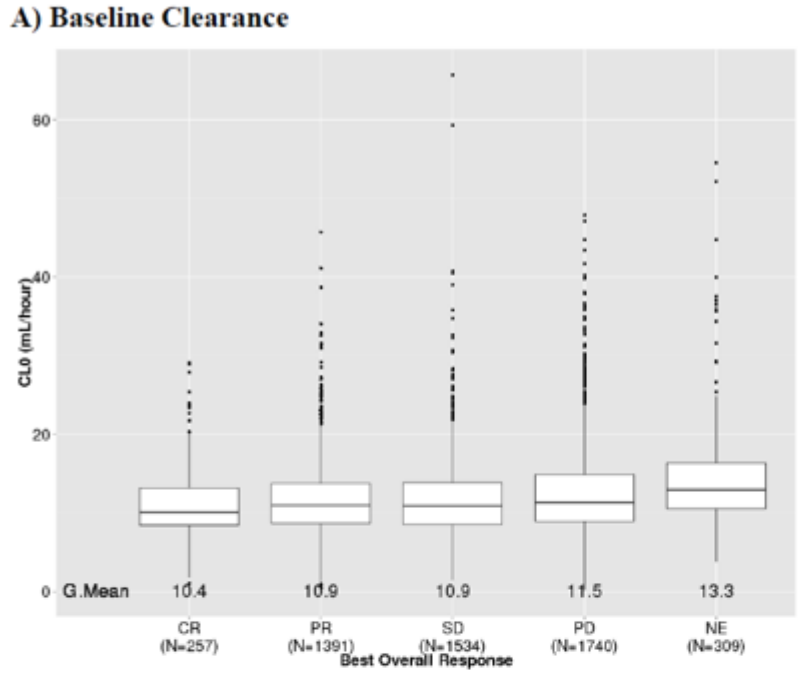
Source: Analysis-Directory/R/plots/changeCL-vs-time-born.png

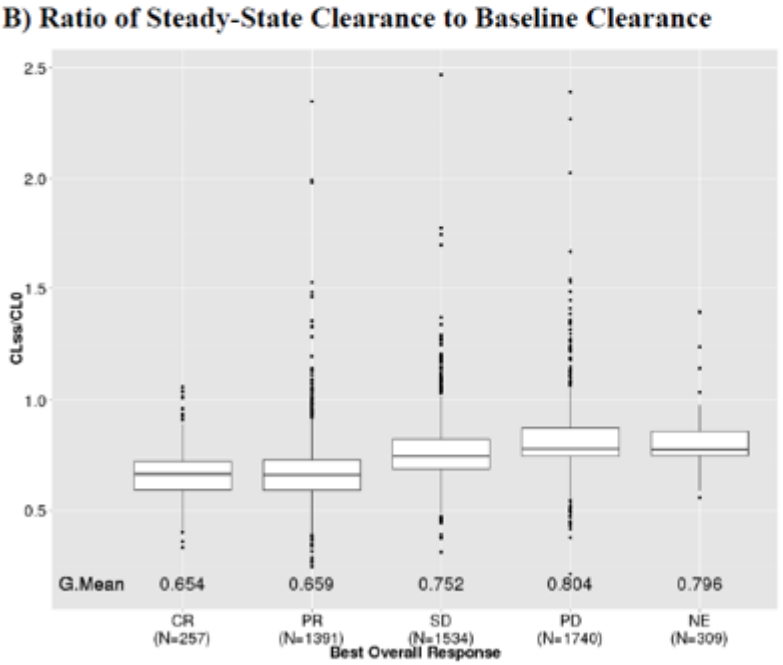
Note: % change in CL was calculated using formula below:

%Difference in CL = 100 * ((CLt-CLt=0)/CLt=0)

Note: The red line represents the CL-Time profile for a typical subject with baseline PS = 0, the blue dashed line represents the CL-Time profile for a typical subject with PS > 0.

Figure 10. Distribution of Nivolumab Baseline Clearance and Ratio of Staedy State Clearance to Baseline Clearance by Best Overall Response



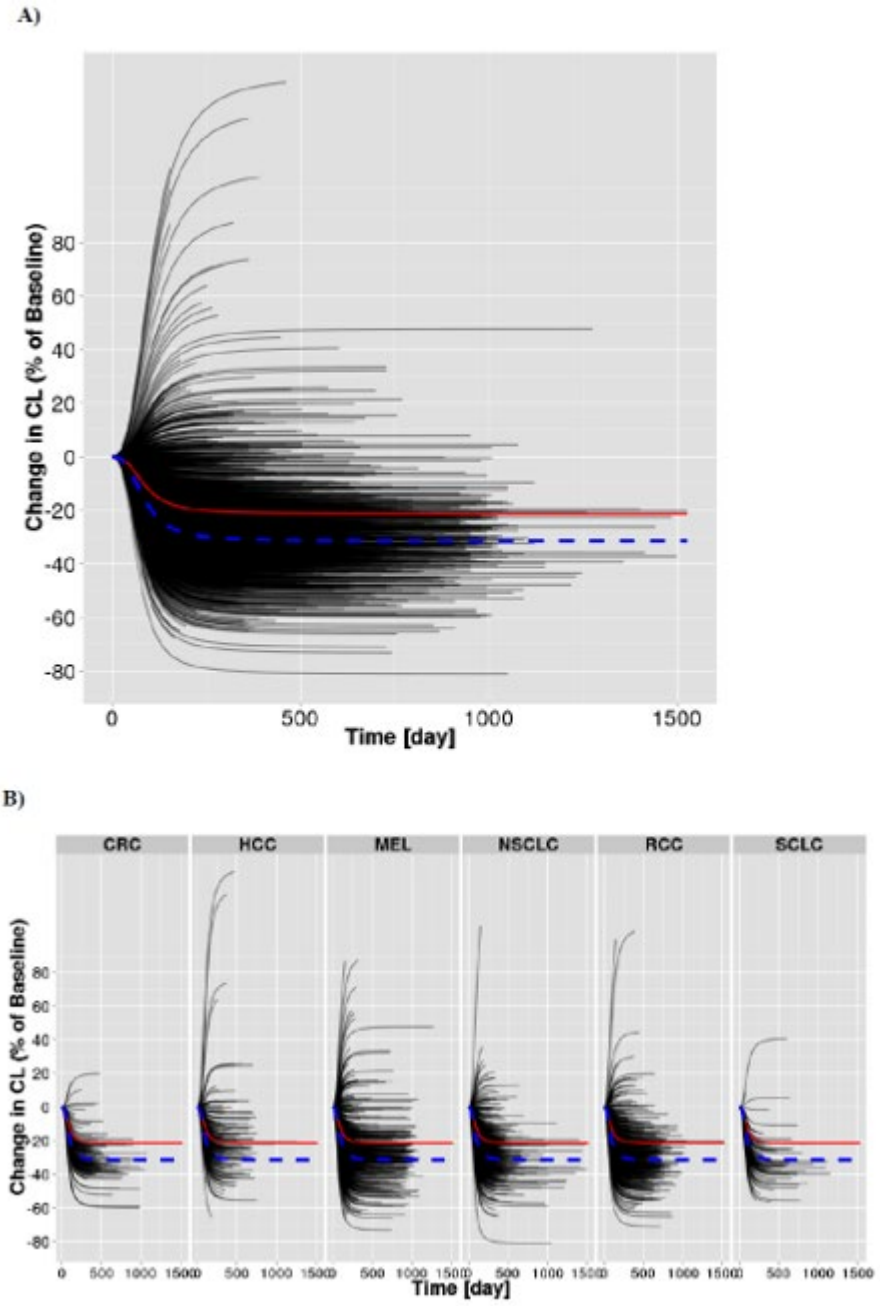


Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/plotcl-time_bor.R
Source: Analysis-Directory/R/plots/CL0-BOR.png
Source: Analysis-Directory/R/plots/CL-ratio-BOR.png

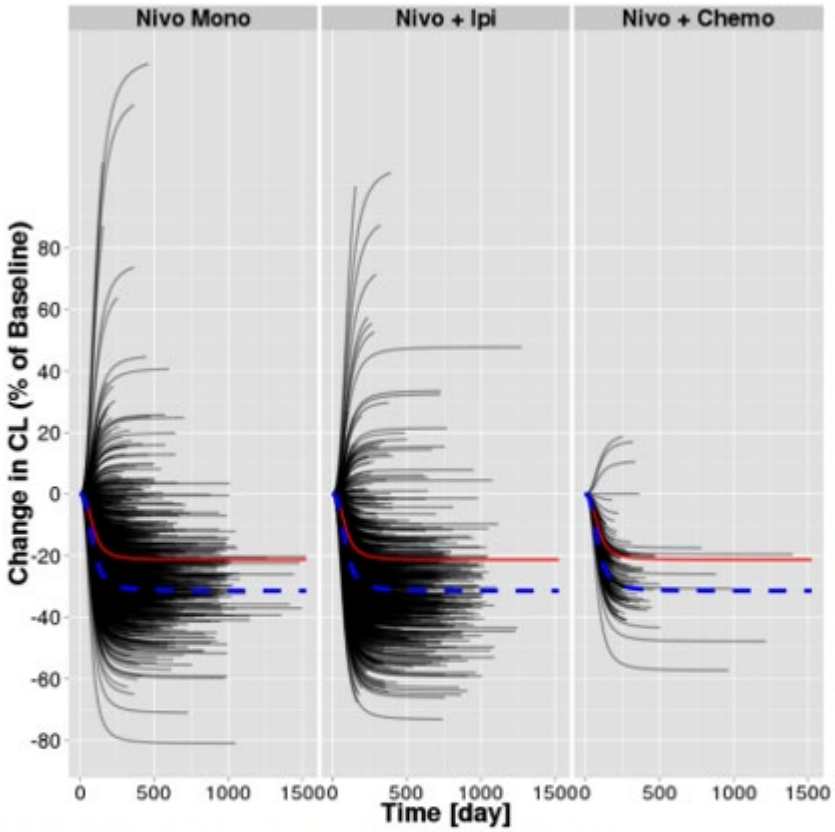
Assessment of Temporal Changes in CL

The maximal model predicted decrease in CL was ~21% in subjects with PS = 0 and ~31% in subjects with PS > 0; the time for half maximal reduction was ~92 days (2200 hours). The EMAX was similar across dose regimens and tumor types.

Figure 11. Model Estimated Change in Nivolumab Clearance versus Time from the Final Model A) Overall, B) by Tumor type and C) by Nivolumab Dosing Regimen



C)



Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/plot-cl-time.r
Source: Analysis-Directory/R/plots/changeCL-vs-time-oppk.png
Source: Analysis-Directory/R/plots/changeCL-vs-time-by_ttypen.png
Source: Analysis-Directory/R/plots/changeCL-vs-time-by_combo.png
Note: % change in CL was calculated using formula below:

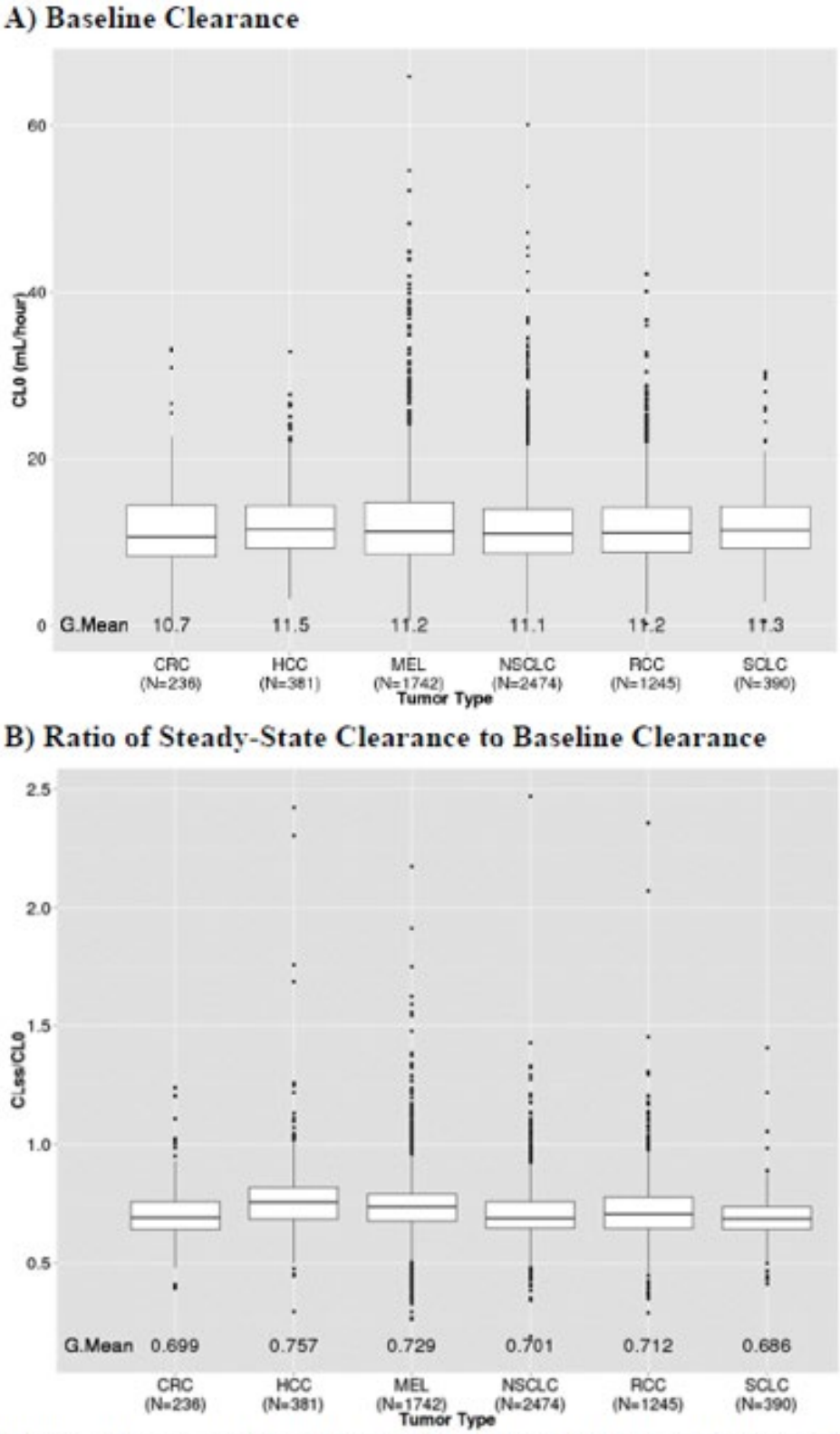
%Difference in CL = 100 * ((CLt-CLt=0)/CLt=0)

Note: The red line represents the CL-Time profile for a typical subject with baseline PS = 0, the blue dashed line represents the CL-Time profile for a typical subject with PS > 0.

Distribution of Nivolumab Clearance per Tumor Type

No clinically relevant difference in CL was found across the tumor types in this analysis.

Figure 12. Distribution of Nivolumab Baseline Clearance and Ratio of Steady-State Clearance to baseline Clearance by Tumor type

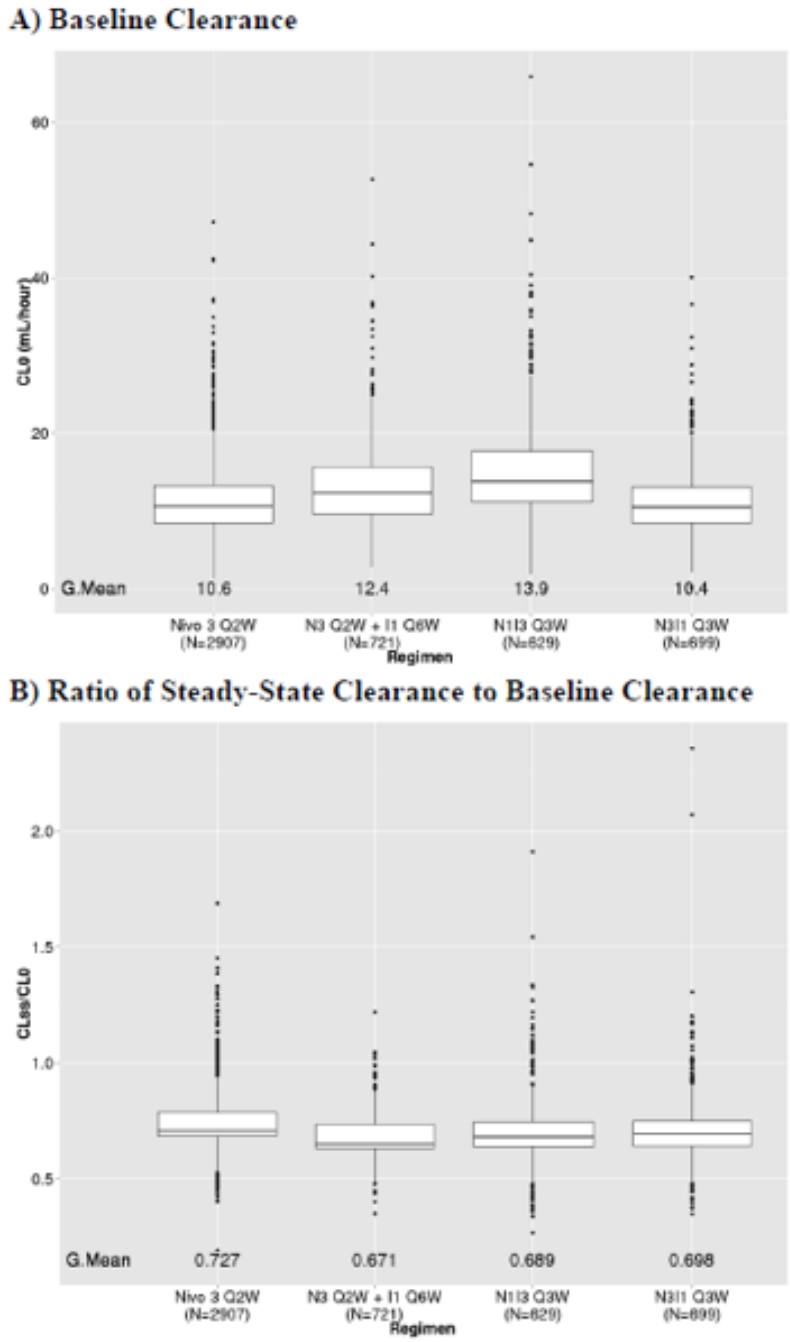


Analysis -Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/plot-cl.R
Source: Analysis-Directory/R/plots/CL_by_TTYPEN.png
Source: Analysis-Directory/R/plots/CL-ratio-TT.png

Distribution of Nivolumab Clearance by Different Combination Dose Regimens

While nivolumab baseline CL was higher in the nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W x 4 dose regimen compared to other dosing regimens, the percentile change of CL during treatment was similar across regimens.#

Figure 13. Distribution of Nivolumab Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance by Select Dosing Regimens of Nivolumab Monotherapy and in Combination with Ipilimumab.

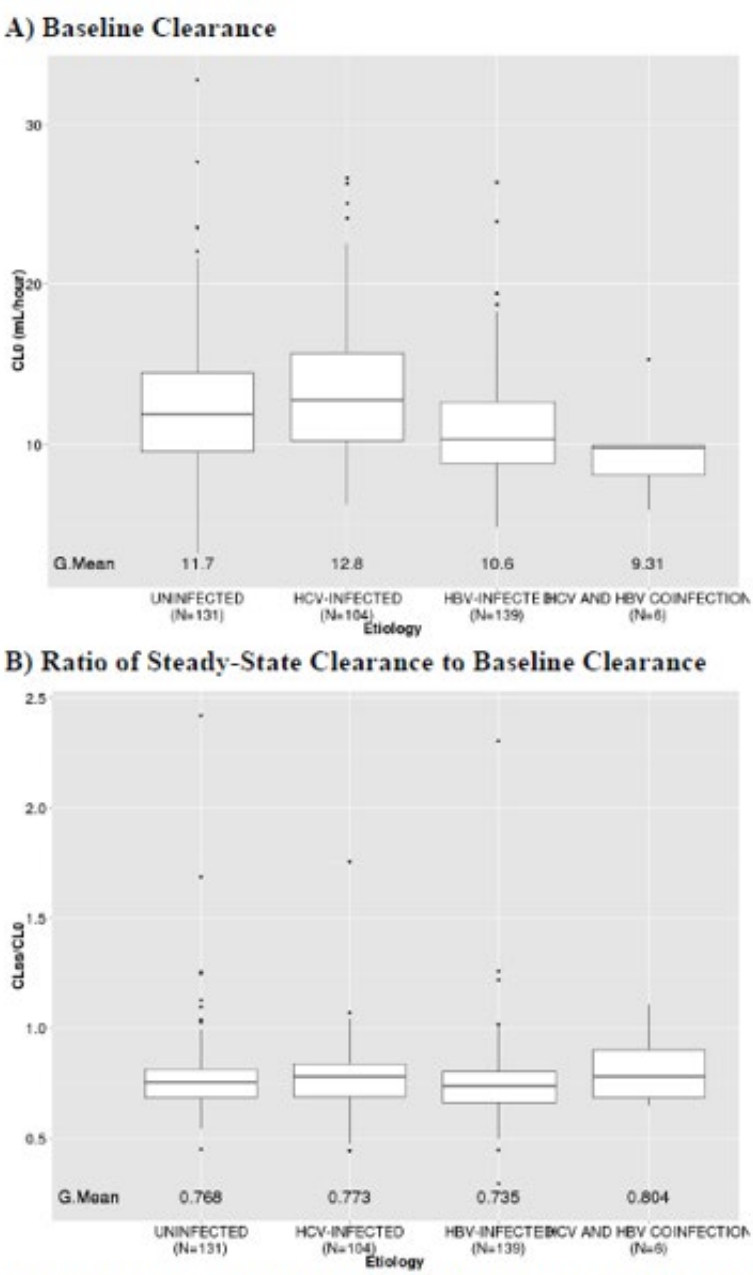


Analysis -Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/plot-cl.R
Source: Analysis-Directory/R/plots/CL0-reg.png
Source: Analysis-Directory/R/plots/CL-ratio-reg.png
Note: Nivo 3 Q2W group includes subjects who received nivolumab 3 mg/kg or 240 mg Q2W as monotherapy.

Distribution of Nivolumab Clearance in Uninfected Subjects and Subjects with HCV or HBV in Study CA204090

Nivolumab CL was similar in HCC subjects with HBV or HCV infection as compared to uninfected subjects (< 20% different). Nivolumab CL was lower (~20%) in HBV and HCV co-infected subjects, but the sample size is small (N = 6).

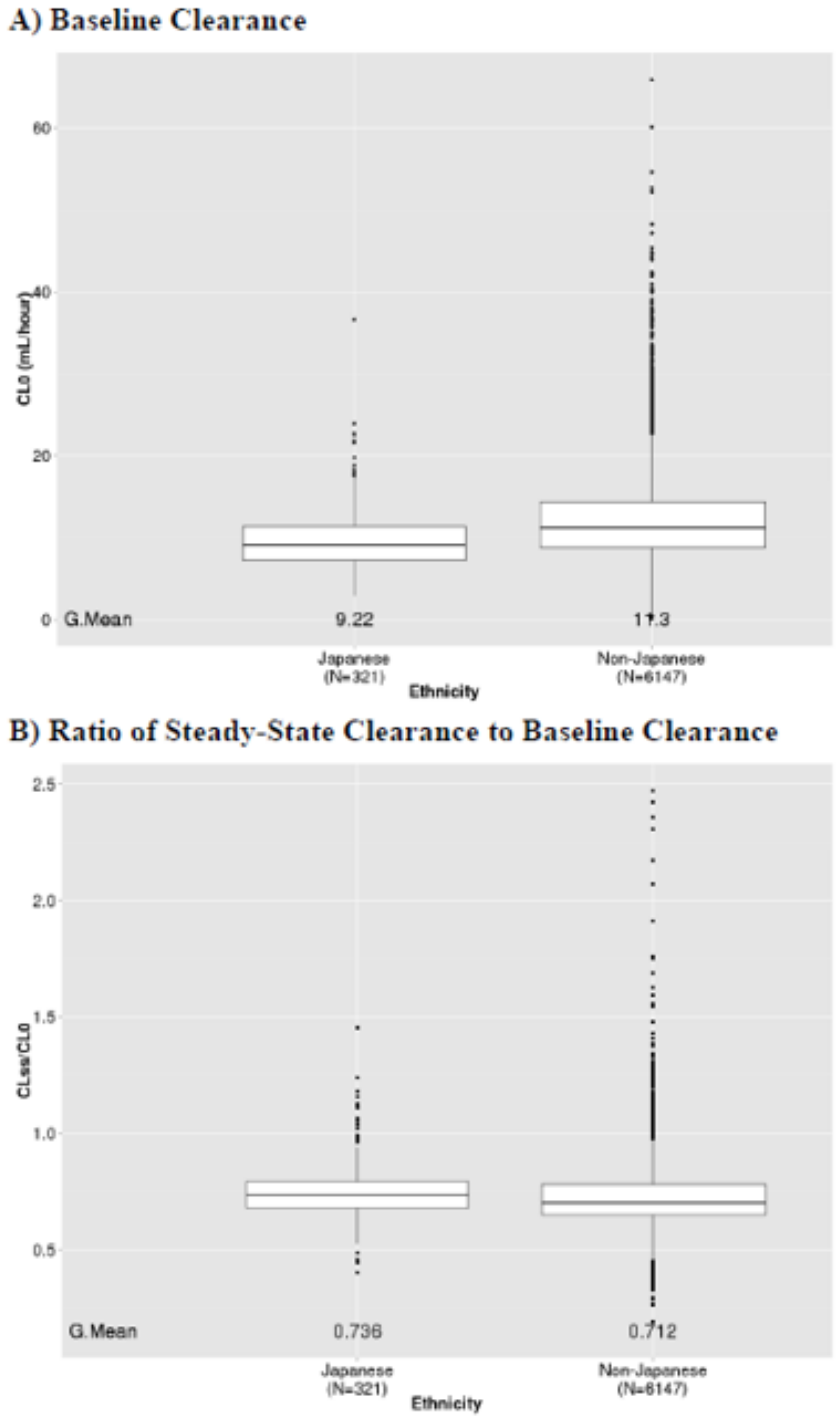
Figure 14. Distribution of nivolumab Baseline Clearance and Ratio of Steady-State Clearance to baseline Clearance by Etiology in HCC Subjects received Nivolumab Monotherapy and in Combination with Ipilimumab (Study CA209040)



Analysis -Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/plot-cl.R
Source: Analysis-Directory/R/plots/CL0-etiology.png
Source: Analysis-Directory/R/plots/CL-ratio-etiology.png

Distribution of Nivolumab Clearance in Japanese and Non-Japanese Subjects

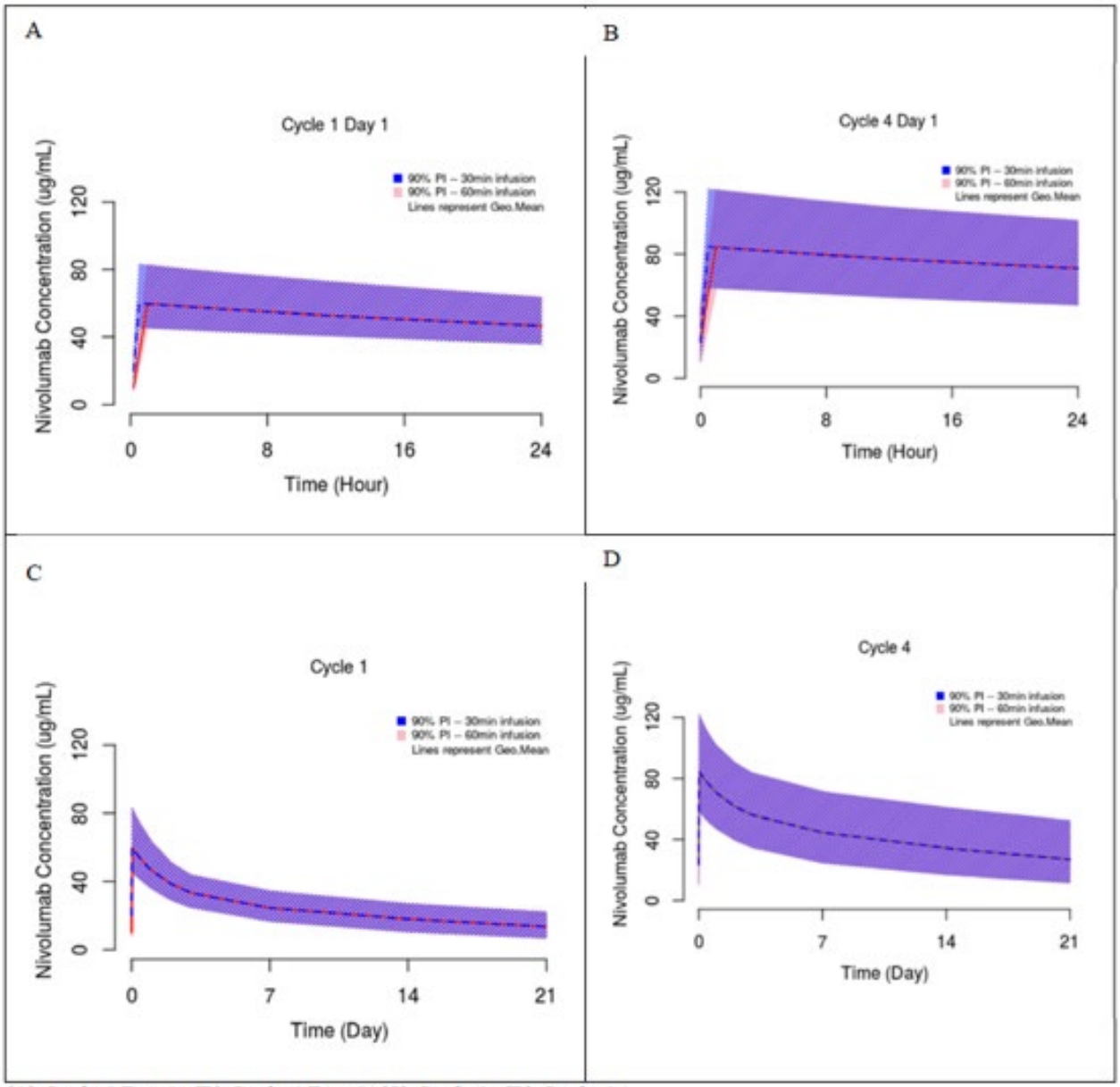
Figure 15. Distribution of Nivolumab Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance in Japanese and Non-Japanese Subjects



Analysis -Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/plot-cl.R
Source: Analysis-Directory/R/plots/CL0-JP.png
Source: Analysis-Directory/R/plots/CL-ratio-JP.png

The nivolumab final PK model was used to simulate nivolumab PK profiles in dMMR or MSI-H CRC patients following nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses) via either a 30 min or 60 min nivolumab infusion duration. Equivalent nivolumab PK profiles were observed between a 30 min and 60 min infusion duration (Figure 16). The only difference is the 30 min infusion achieves Cmax earlier than the 60 min infusion duration as expected.

Figure 16. Nivolumab PK Profile in dMMR or MSI-H CRC following Nivolumab 3 mg/Kg +Ipilimumab 1 mg/Kg Q3W (4 doses) via a 30 min or 60 min Nivolumab Infusion Duration



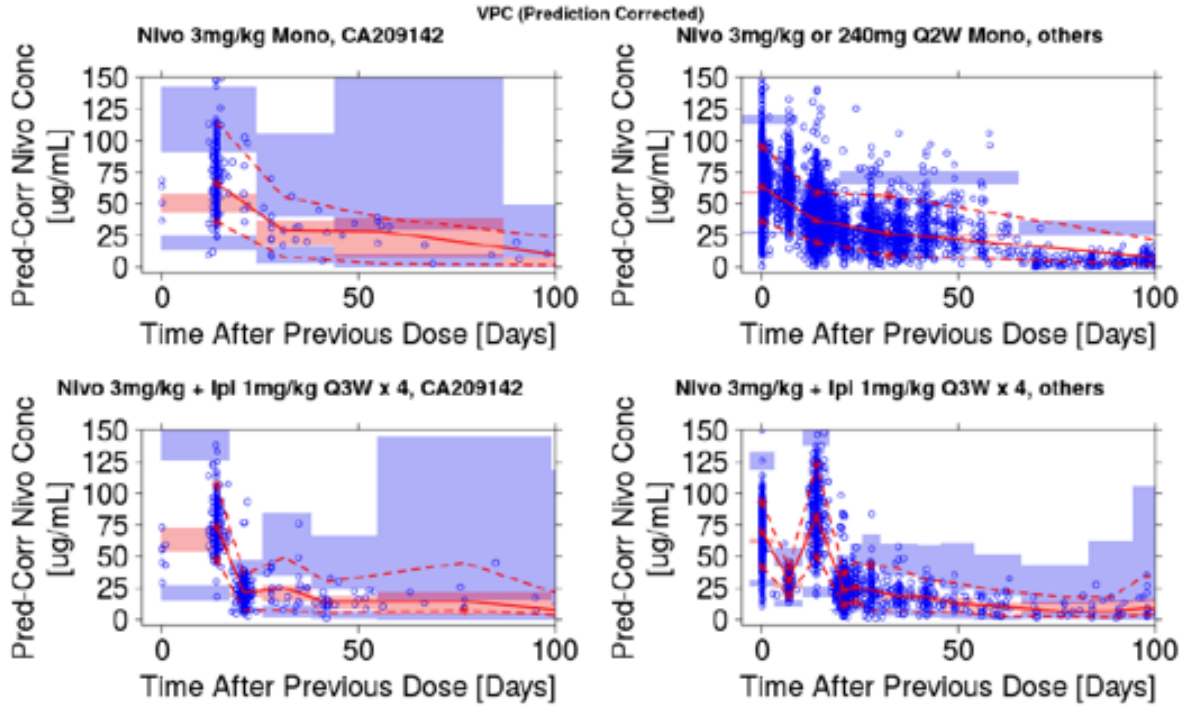
(A) Cycle 1 Day 1; (B) Cycle 4 Day 1; (C) Cycle 1; (D) Cycle 4

The predictive performance of the full nivolumab PPK model was evaluated using pcVPC for the updated dataset. Figure 17 and Figure 18 show the pcVPC plots of all nivolumab concentration versus time after the previous dose and trough concentration versus time after the first dose, respectively.

The pcVPC plots show that the full nivolumab PPK model adequately characterized the data from Study A209142.

The effect of covariates on nivolumab PK was re-estimated using the full model for the updated dataset. Parameter estimates (Table 8) and the covariate effects (Figure 19) obtained from the updated dataset are similar to those obtained from the previous nivolumab PPK analysis dataset (data not shown).

Figure 17. Prediction-Correction Visual Predictive Check of Concentration versus Actual Time after Previous Dose Stratified by Selected Nivolumab Dosing Regimens (Full Nivolumab Population Pharmacokinetic Model) for the Updated Nivolumab PPK Dataset



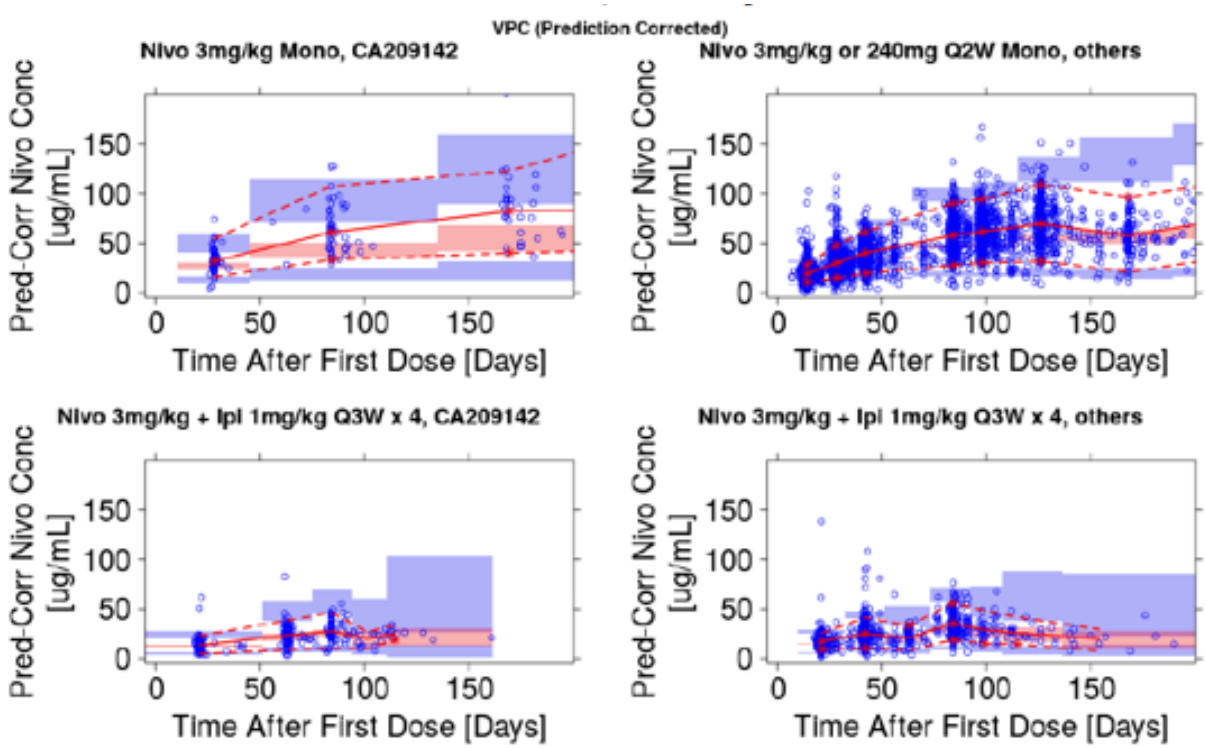
Analysis -Directory: /global/pkms/data/CA/209/crc-2l-combo-EU/prd/ppk-nivo/final/

Program Source: Analysis-Directory/R/scripts/nivoppk.Rmd

Source: Analysis-Directory/psn/vpc_full_dir7/VPC-plots 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 18. Prediction-Corrected Visual Predictive Check of Trough Concentration versus Actual Time after First Dose Stratified by Selected Nivolumab Dosing Regimens (Final Nivolumab Population Pharmacokinetic Model) for the Updated Nivolumab PPK Dataset



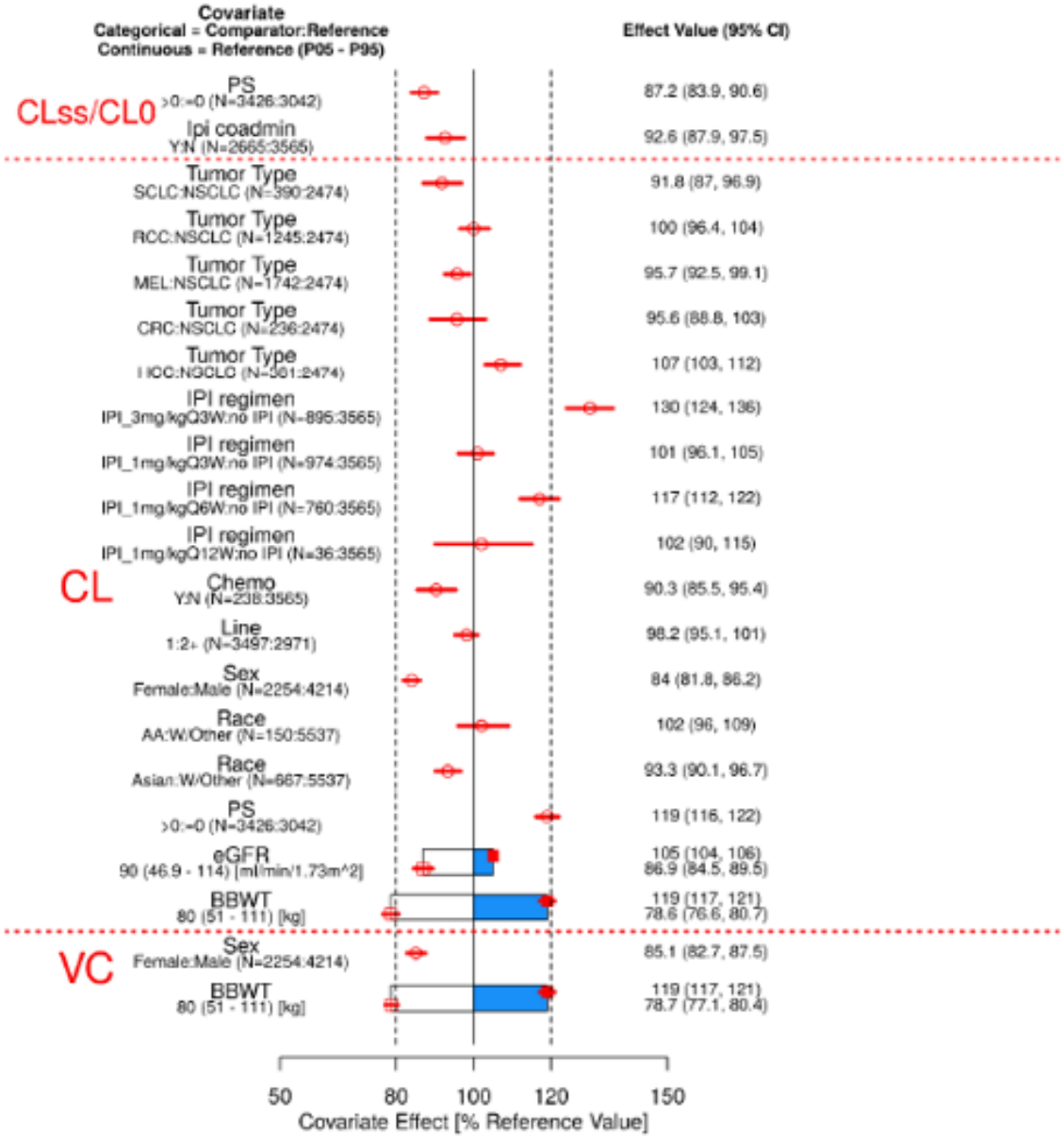
Analysis -Directory: /global/pkms/data/CA/209/ crc-2l-combo-EU /prd/ppk-nivo/final/

Program Source: Analysis-Directory/R/scripts/ nivoppk.Rmd

Source: Analysis-Directory/psn/vpc_full_dir8/VPC-plots 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data

Figure 19. Covariate Effects on Nivolumab Pharmacokinetic Model Parameters (Full Nivolumab Population Pharmacokinetic Model) using the Updated Nivolumab PPK Dataset



Analysis -Directory: /global/pkms/data/CA/209/ crc-21-combo-eu/prd/ppk- nivo/final/nm/full/
R-Program Source: Analysis-Directory/R/scripts/nivoppk.Rmd

Source: Analysis-Directory/R/plots/full-ppk-cov-eff-plot.png
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal 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 lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is male, white/other race, BW = 80 kg, PS = 0, eGFR = 90 mL/min/1.73 m^2, and received nivolumab monotherapy, with NSCLC as tumor type. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.
Note 4: The effect of BBWT was also added on Q and VP and their estimates were fixed to be similar to that CL and VC, respectively.

Source: Analysis-Directory/R/plots/full-ppk-cov-eff-plot.png
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal 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 lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.

Note 3: Reference subject is male, white/other race, BW = 80 kg, PS = 0, eGFR = 90 mL/min/1.73 m^2, and received nivolumab monotherapy, with NSCLC as tumor type. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.
Note 4: The effect of BBWT was also added on Q and VP and their estimates were fixed to be similar to that CL and VC, respectively.

Table 8. Parameter Estimates of the Full Nivolumab Population Pharmacokinetic Model using the Updated Nivolumab PPK Dataset

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	11.0	0.253 (2.29)	10.5 - 11.5
VC_{REF} [L]	θ_2	4.28	0.0311 (0.727)	4.21 - 4.34
Q_{REF}[mL/h]	θ_3	34.9	2.77 (7.93)	29.5 - 40.4
VP_{REF} [L]	θ_4	2.72	0.0703 (2.59)	2.58 - 2.86
CL_{BBWT}	θ_7	0.535	0.0294 (5.50)	0.477 - 0.593
CL_{GFR}	θ_9	0.215	0.0226 (10.5)	0.171 - 0.259
CL_{FEMALE}	θ_{12}	-0.175	0.0135 (7.71)	(-0.201) - (-0.148)
CL_PS_1	θ_{13}	0.175	0.0135 (7.69)	0.149 - 0.202
CL_{RAA}	θ_{14}	0.0232	0.0325 (140)	(-0.0404) - 0.0869
CL_{RAS}	θ_{15}	-0.0690	0.0179 (25.9)	(-0.104) - (-0.0340)
$V1_{BBWT}$	θ_{16}	0.531	0.0239 (4.51)	0.484 - 0.578
$V1_{FEMALE}$	θ_{17}	-0.162	0.0142 (8.80)	(-0.190) - (-0.134)
CL_{EMAX}	θ_{18}	-0.235	0.0230 (9.79)	(-0.280) -(-0.190)
CL_{T50}	θ_{19}	2.24E+03	132 (5.89)	1.99E+03 - 2.50E+03
CL_{HILL}	θ_{20}	2.82	0.245 (8.69)	2.34 - 3.30
CL_{ABL}	θ_{21}	-0.0439	0.0176 (40.0)	(-0.0783) - (-0.00948)
CL_{RCC}	θ_{23}	8.41E-04	0.0192 (2.29E+03)	(-0.0369) - 0.0385
CL_{SCLC}	θ_{24}	-0.0858	0.0275 (32.0)	(-0.140) - (-0.0319)
CL_{CRC}	θ_{25}	-0.0450	0.0377 (83.9)	(-0.119) - 0.0289
CL_{HCC}	θ_{26}	0.0714	0.0236 (33.0)	0.0252 - 0.118
CL_IPI1_{3W}	θ_{27}	0.00588	0.0232 (394)	(-0.0395) - 0.0513
CL_IPI1_{6W}	θ_{28}	0.159	0.0214 (13.5)	0.117 - 0.201
CL_IPI1_{12W}	θ_{29}	0.0172	0.0624 (364)	(-0.105) - 0.140
CL_IPI3_{3W}	θ_{30}	0.260	0.0238 (9.18)	0.213 - 0.306
CL_{LINE}	θ_{31}	-0.0177	0.0166 (93.8)	(-0.0503) - 0.0149
CL_{CHEMO}	θ_{32}	-0.102	0.0280 (27.4)	(-0.157) - (-0.0473)
$EMAX_{IPICO}$	θ_{33}	-0.0770	0.0265 (34.4)	(-0.129) - (-0.0251)
$EMAX\_PS_1$	θ_{34}	-0.137	0.0196 (14.3)	(-0.176) - (-0.0989)
Random Effects				
ZCL [-]	$\omega_{1,1}$	0.156 (0.395)	0.00851 (5.46)	0.139 - 0.172
ZVC [-]	$\omega_{2,2}$	0.152 (0.390)	0.0149 (9.80)	0.123 - 0.181

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
ZEMAX [h]	$\omega_{4,4}$	0.0866 (0.294)	0.0109 (12.6)	0.0652 - 0.108
ZCL:ZVC	$\omega_{1,2}$	0.0592 (0.385)	0.00891 (15.0)	0.0418 - 0.0767
Residual Error				
PERR [-]	θ_6	0.245	0.00406 (1.66)	0.237 - 0.253

Analysis Directory: /global/pkms/data/CA/209/crc-2l-combo-eu/prd/ppk- nivo/final/nm/full

Program Source: Analysis Directory/nm/full/full.lst

Source: Analysis Directory/nm/full.rtf

Note: $CL0_{REF}$ is the typical value in a reference subject with NSCLC, receiving nivolumab monotherapy as a 2nd line therapy, and weighing 80 kg. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject receiving nivolumab monotherapy with a normal PS status. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note: Eta shrinkage (%): ETA_CL: 11.9; ETA_VC: 28.0; ETA_EMAX: 50.2; EPS shrinkage (%): 16.3.

[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

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance*

Ipilimumab PK

Ipilimumab PPK analysis was conducted to characterize the PK of ipilimumab in 3411 subjects with NSCLC, SCLC, melanoma, RCC, HCC, or CRC who received ipilimumab alone or in combination with nivolumab from 15 studies (Table 9 . The analysis dataset included data for ipilimumab doses ranging from 0.1 to 10 mg/kg, and dosing frequencies of once every 3, 6, or 12 weeks (Q3W, Q6W, or Q12W).

Table 9. Subjects Included in the Updated Ipilimumab Population Pharmacokinetic Analysis Dataset

Study	No. of Subjects			
	Ipilimumab Treated	PK Database[a]	Flagged[b]	Included (% of subjects in PK Database)
Others[c]	3786	3548	258	3290 (86.90)
CA209142	142	142	11	131 (92.25)
Total	3928	3690	269	3421 (92.71)

[a] eToolbox or Pharmacokinetic/Pharmacodynamic Analysis and Modeling System (PAMS) included subjects with at least 1 PK sample collected, including pre-dose1 samples (before ipilimumab treatment) and samples collected after ipilimumab treatment.

[b] All records were flagged for exclusion for a subject.

[c] Includes 15 studies presented in Appendix 3.3.3.2, Table 1.

Table 10. Samples Included in the Updated Ipilimumab Population Pharmacokinetics Analysis Dataset

Study	PK DB[a]	Missing dose or sample information	Duplicate sample ID	Duplicate samples at same time (set up for NCA)	Duplicate samples with different conc	Suspect conc value	Day 1 Pre-Dose	LLOQ [b]	Mismatch samples	ATAPD > 5 for EOI samples	Sample from cross-over subjects in CA209032	Samples included in analysis (%)
Others[c]	17671	190	6	34	40	5	3327	1305	256	106	11	12391 (70.12)
CA209142	505	2	0	0	0	0	140	68	0	0	0	295 (58.42)
Total	18176	192	6	34	40	5	3467	1373	256	106	11	12686 (69.80)

Abbreviations: ATAPD=actual time after previous dose; conc=concentration; DB=database; EOI=end of infusion; LLOQ=lower limit of quantification; NCA=non-compartmental analysis.

[a] Samples in eToolbox or Pharmacokinetic/Pharmacodynamic Analysis and Modeling System (PAMS). All which are included in the analysis dataset with flag as noted

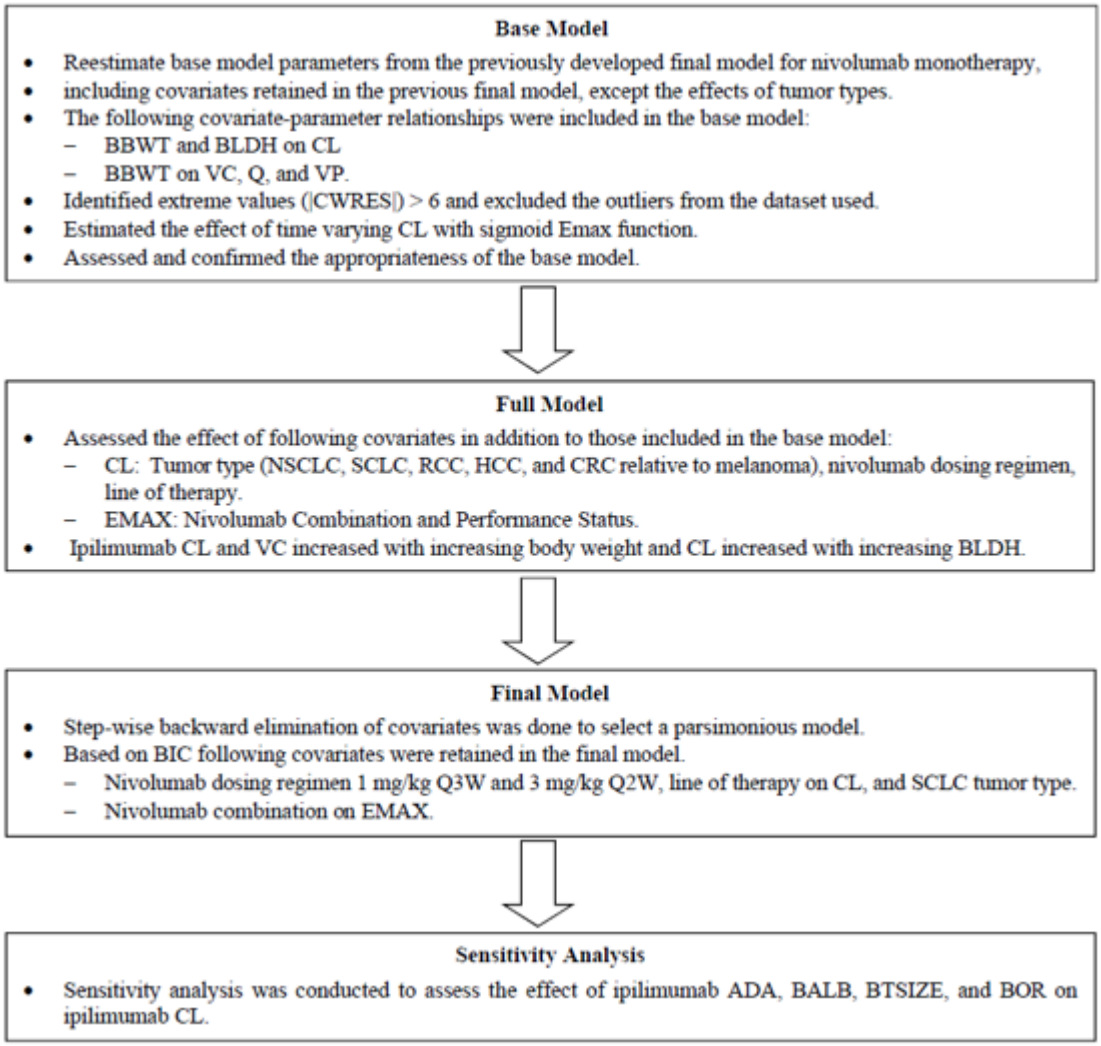
[b] LLOQ: Post-dose ipilimumab serum concentration values below the lower limited of quantification.

[c] Includes 15 studies presented in Appendix 3.3.3.2, Table 2.

Ipilimumab PK was well described by a linear 2-compartment model with time-varying CL. Ipilimumab PK in dMMR or MSI-H mCRC patients is consistent with the known ipilimumab PK characteristics. No covariates were found to have a clinically meaningful effect on ipilimumab PK.

The ipilimumab PPK model was developed in three steps: base, full, and final models.

Figure 20. Schematic Overview of Ipilimumab Population Pharmacokinetic Model Development



The final ipilimumab PPK model was a 2-compartment, zero-order IV infusion model with time-varying CL model (sigmoidal-Emax function). The covariates retained in the final model are SCLC tumor type, line of therapy, nivolumab dose of 1 mg/kg Q3W and 3 mg/kg Q2W on CL and combination therapy on EMAX. Table 11 presents the parameter estimates from the final model and the final model was as follows:

$$CL0_i = CL0_{REF} * \left(\frac{BBWT_i}{BBWT_{REF}}\right)^{CL_{BBWT}} * \left(\frac{\log(BLDH_i)}{\log(BLDH_{REF})}\right)^{CL_{BLDH}} * (e^{CL_{SCLC}}) * (e^{CL_{LINE}})$$

$$* (e^{CL_{NIVO1mg/kgQ3W}}) * (e^{CL_{NIVO3mg/kgQ2W}}) * e^{\eta CLi}$$

$$EMAX_i = EMAX_{REF\,i} + EMAX_{COMBO} + \eta EMAXi$$

$$CL_{t,i} = CL0_i \cdot \exp\left(\frac{(E\max_i) * t^{HILL}}{T50_i^{HILL} + t^{HILL}}\right)$$

$$CL_{SS,i} = CL0_i \cdot \exp(EMAX_i)$$

$$VC_i = VC_{REF} * \left(\frac{BBWT_i}{BBWT_{REF}} \right)^{VC_{BBWT}} * e^{\eta VCi})$$

$$Q_i = Q_{REF} * \left(\frac{BBWT_i}{BBWT_{REF}} \right)^{CL_{BBWT}}$$

$$VP_i = VP_{REF} * \left(\frac{BBWT_i}{BBWT_{REF}} \right)^{VC_{BBWT}}$$

where $CL0_{REF}$ is the typical value of CL at time 0 (CL0) at the reference values of BBWT, BLDH, and 1st line therapy, tumor type referenced to melanoma, and nivolumab combined with ipilimumab is referenced to 0 mg/kg (ie, subject received only ipilimumab monotherapy). VC_{REF}, Q_{REF}, and VP_{REF} are typical values of VC, Q, and VP at the reference values of BBWT, respectively. $EMAX_{REF}$ is the typical value of EMAX at referenced to ipilimumab monotherapy. CL_{BBWT}, CL_{BLDH}, VC_{BBWT}, CL_{SCLC}, $CL_{NIVO1mg/kgQ3W}$, $CL_{NIVO3mg/kgQ2W}$, CL_{LINE}, and $EMAX_{COMBO}$ are model parameters. CLss,i is the individual steady-state CL.

CLt,i is the individual CL at each time, VCi, Qi, VPi and EMAXi are the individual values of VC, Q, VP, and EMAX respectively, and ηCLi, ηVCi and ηEMAXi, are normally distributed random variables with mean of 0 and variance of ω2CL, ω2VC and ω2EMAX, respectively.

Table -11: Parameter Estimates for the Final Ipilimumab Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	14.1	0.231 (1.66)	13.6-14.5
VC_{REF} [L]	θ_2	3.95	0.0255 (0.646)	3.90-4.0
Q_{REF} [mL/h]	θ_3	27.9	2.22 (7.97)	23.9-32.2
VP_{REF} [L]	θ_4	3.18	0.0802 (2.52)	3.04-3.35
CL_{BBWT} [power]	θ_7	0.694	0.0315 (4.55)	0.63-0.75
V_{BBWT} [power]	θ_8	0.600	0.0293 (4.88)	0.54-0.66
CL_{BLDH} [power log]	θ_9	0.703	0.0716 (10.2)	0.57-0.84
$EMAX_{REF}$	θ_{10}	-0.0644	0.0306 (47.4)	-0.12-0.002
T50 [h]	θ_{11}	2540	86.5 (3.41)	2364.0-2727
HILL	θ_{12}	7.43	1.58 (21.3)	4.93-19.3
CL_{SCLC}	θ_{16}	-0.124	0.0317 (25.6)	-0.19--0.06
$CL_{1mg/kg\ Q3W}$	θ_{20}	0.0950	0.0149 (15.6)	0.067-0.12
$CL_{3\ mg/kg\ Q2W}$	θ_{21}	0.191	0.0185 (9.71)	0.15-0.23

Table -11: Parameter Estimates for the Final Ipilimumab Population Pharmacokinetic Model

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
CL_{LINE}	θ_{23}	-0.0949	0.0162 (17.1)	-0.12--0.06
$EMAX_{COMBO}$	θ_{24}	-0.202	0.0305 (15.1)	-0.27--0.14
Random Effects				
ω2*CL*[-]	$\omega_{1,1}$	0.112 (0.334)	0.00514 (4.60)	0.102-0.123
ω2*VC* [-]	$\omega_{2,2}$	0.0884 (0.297)	0.00939 (10.6)	0.070-0.110
ω2*EMAX*	$\omega_{3,3}$	0.0158 (0.126)	0.00797 (50.5)	0.002-0.046
ω2*CL*ω2VC	$\omega_{1,2}$	0.0404 (0.406)	0.00332 (8.22)	0.034-0.123
Residual Error				
Proportional [-]	θ_5	0.223	0.00568 (2.55)	0.21-0.23
Additive [ug/mL]	θ_6	0.607	0.109 (17.9)	0.28-0.77

Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final

Program Source: Analysis Directory/psn/run18_1.dir1NM_run1/psn.lst

Bootstrap Source: Analysis Directory/psn/bootstrap_dir1/bootstrap_results.csv

Note: CL0REF is the typical value in a reference subject with melanoma, NSCLC, RCC, HCC, or CRC tumor type, receiving ipilimumab monotherapy or combination therapy with nivolumab (0.3 mg/kg Q3W, 3 mg/kg Q3W, or 1 mg/kg Q2W) as a 2nd line therapy, weighing 80 kg and BLDH of 217 U/L. EMAXREF is a typical value of change in magnitude of CL in a reference subject receiving ipilimumab monotherapy. VCREF, QREF, and VPREF are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note: Eta shrinkage (%): ETA_CL: 12.9; ETA_VC: 29.1; ETA_EMAX: 78.6; EPS shrinkage (%):17.2.

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

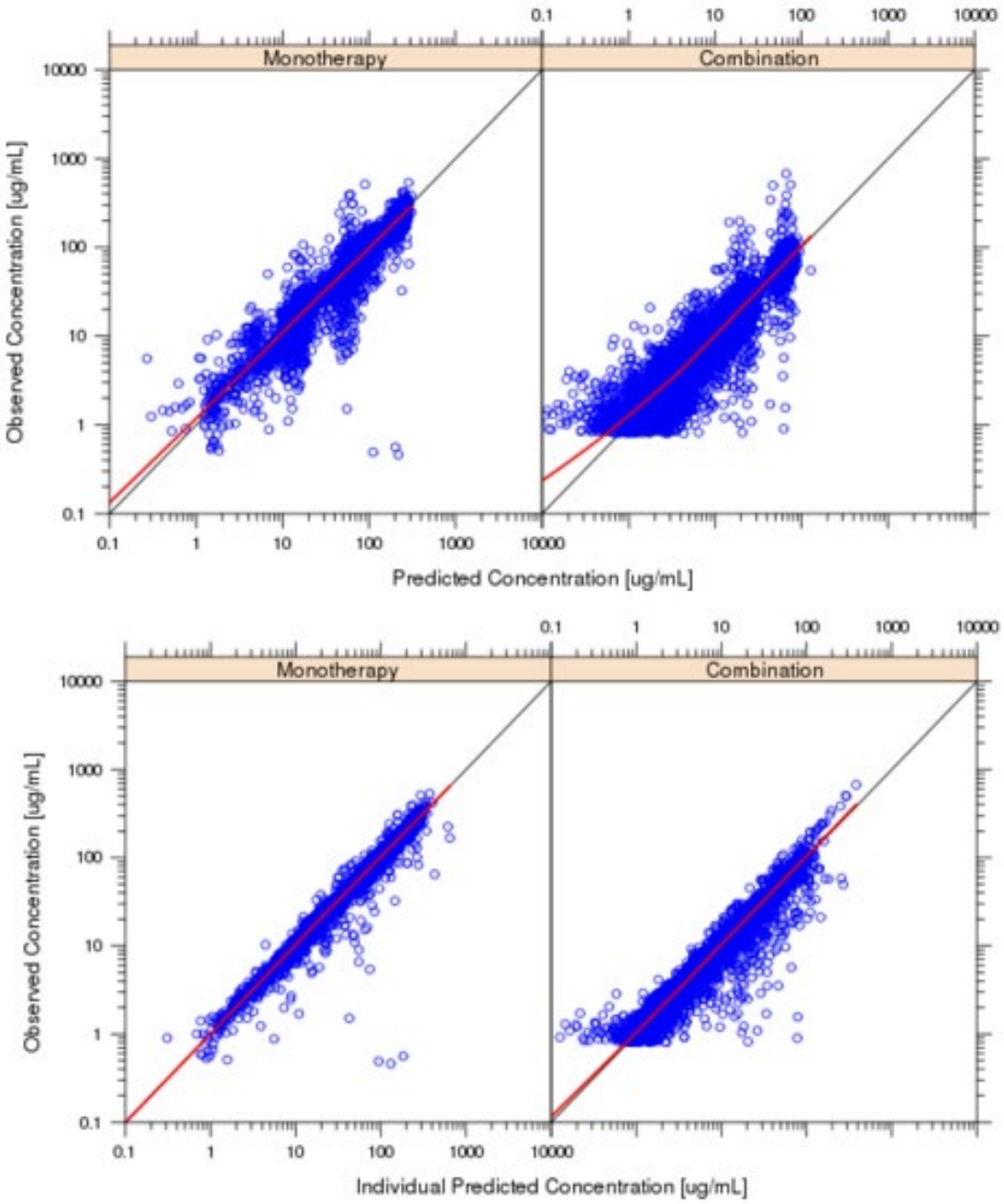
b Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

c Random Effects and Residual Error parameter estimates are shown as Variance (Standard Deviation) for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and Covariance (Correlation) for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

d RSE% is the relative standard error (Standard Error as a percentage of Estimate)

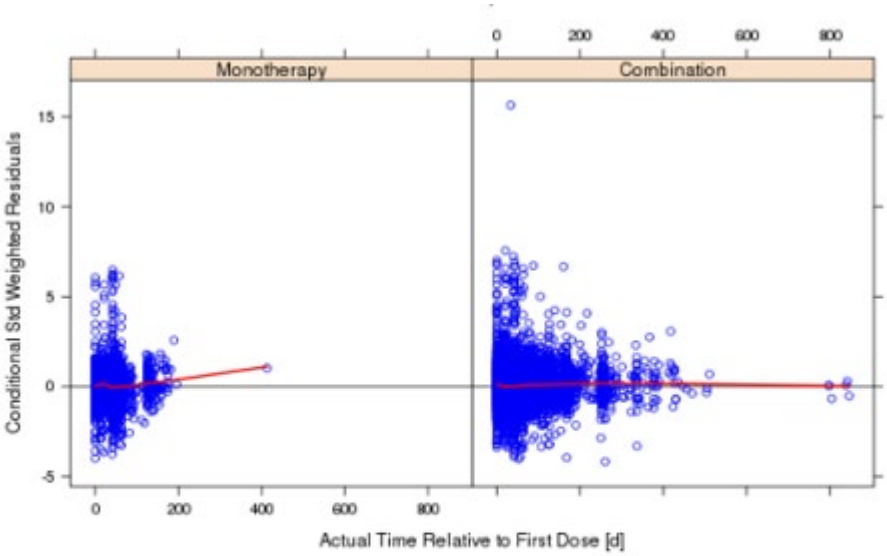
e Confidence interval values are taken from bootstrap calculations (982 out of 1000 successful runs)

Figure 21. Observed versus Predicted Population Average and Individual Concentration in ipilimumab monotherapy and combination Therapy (Final Ipilimumab Population Pharmacokinetic Model)



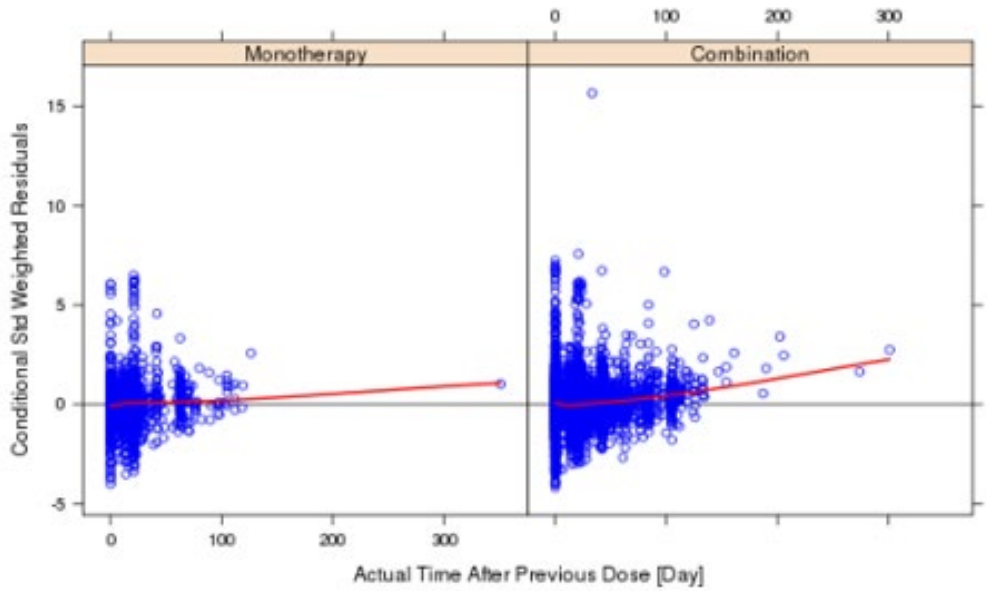
Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final
PsN Program Source: Analysis Directory/psn/run18_1.dir1/NM_run1/sdtab18_1
Program Source: Analysis Directory/R/scripts/main-nmplots-final.r
Figure Source: Analysis Directory/psn/run18_1.dir1/NM_run1/plots/obs-pred/obs-pred-combo.png
Figure Source: Analysis Directory/psn/run18_1.dir1/NM_run1/plots/obs-pred/obs-ipred-combo.png
Note: Solid red line represents linear regression line; Solid black line represents line of identity.

Figure 22. CWRES versus Time After First Dose in Ipilimumab Monotherapy and Combination Therapy (Final Ipilimumab population Pharmacokinetic Model)



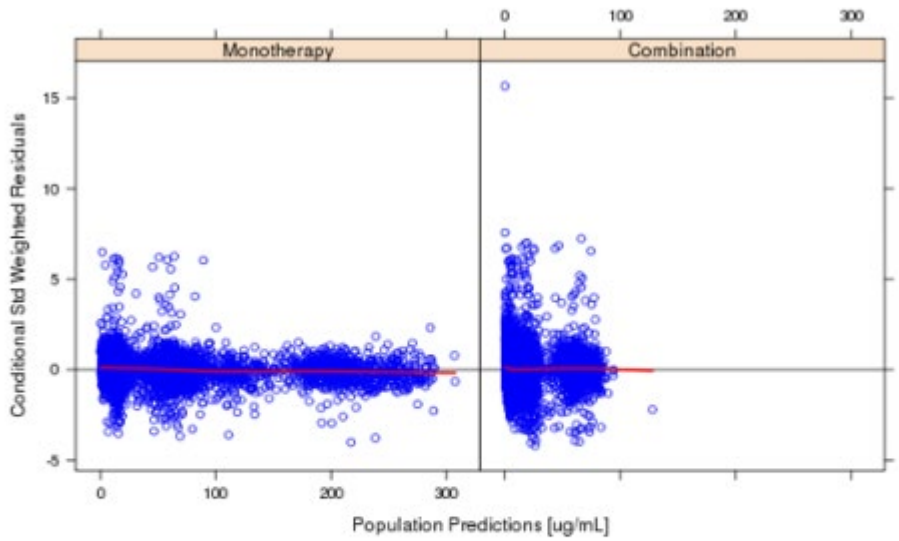
Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final
PsN Program Source: Analysis Directory/psn/run18_1.dir1/NM_run1/sdtab18_1
Program Source: Analysis Directory/R/scripts/main-nmplots-final.r
Figure Source: Analysis Directory/psn/run18_1.dir1/NM_run1/plots/resid/cwres-time-combo.png
Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

Figure 23. CWRES versus Time after Previous Dose in Ipilimumab Monotherapy and combination Therapy (Final Ipilimumab Population Pharmacokinetic Model



Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final
PsN Program Source: Analysis Directory/psn/run18_1.dir1/NM_run1/sdtab18_1
Program Source: Analysis Directory/R/scripts/main-nmplots-final.r
Figure Source: Analysis Directory/psn/run18_1.dir1/NM_run1/plots/resid/cwres-time-prev-combo.png
Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

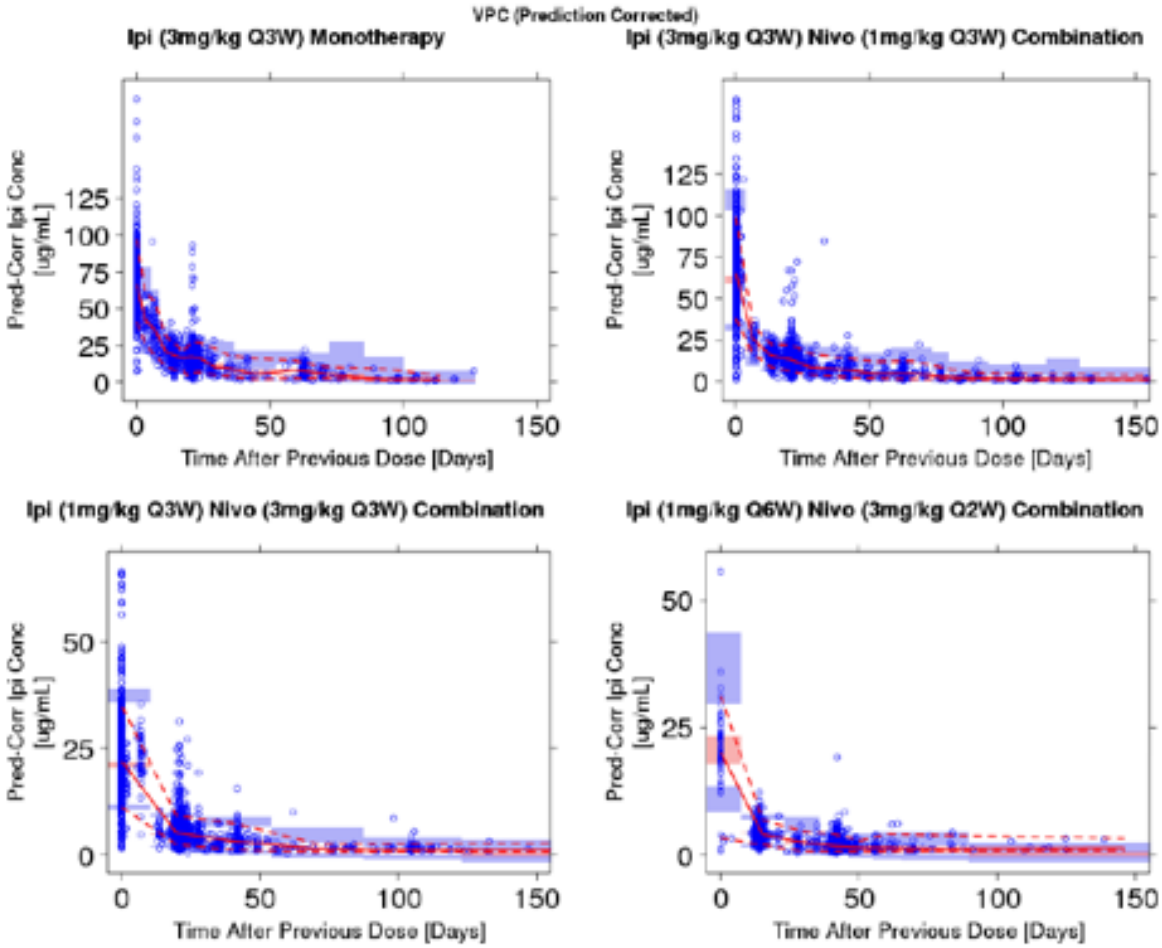
Figure 24. CWRES versus Predicted (typical)Serum Con centration in Ipilimumab Monotherapy and Combination Therapy (Final Ipilimumab Population Pharmacokinetic Model)



Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final
PsN Program Source: Analysis Directory/psn/run18_1.dir1/NM_run1/sdtab18_1
Program Source: Analysis Directory/R/scripts/main-nmplots-final.r
Figure Source: Analysis Directory/psn/run18_1.dir1/NM_run1/plots/resid/cwres-pred-combo.png
Note: Solid red line represents locally weighted smooth line; Solid black line represents line of identity.

The PPK model parameters were estimated with good precision, and the model evaluation demonstrated that there was good agreement between model predictions and observations (Figure 25 and Figure 26.

Figure 25. Prediction -Corrected Visual Predictive Check of Concentrations versus Actual Time after Previous Dose Stratified by Selected Ipilimumab Dosing Regimen (Final Ipilimumab Population Pharmacokinetic Model)



Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final

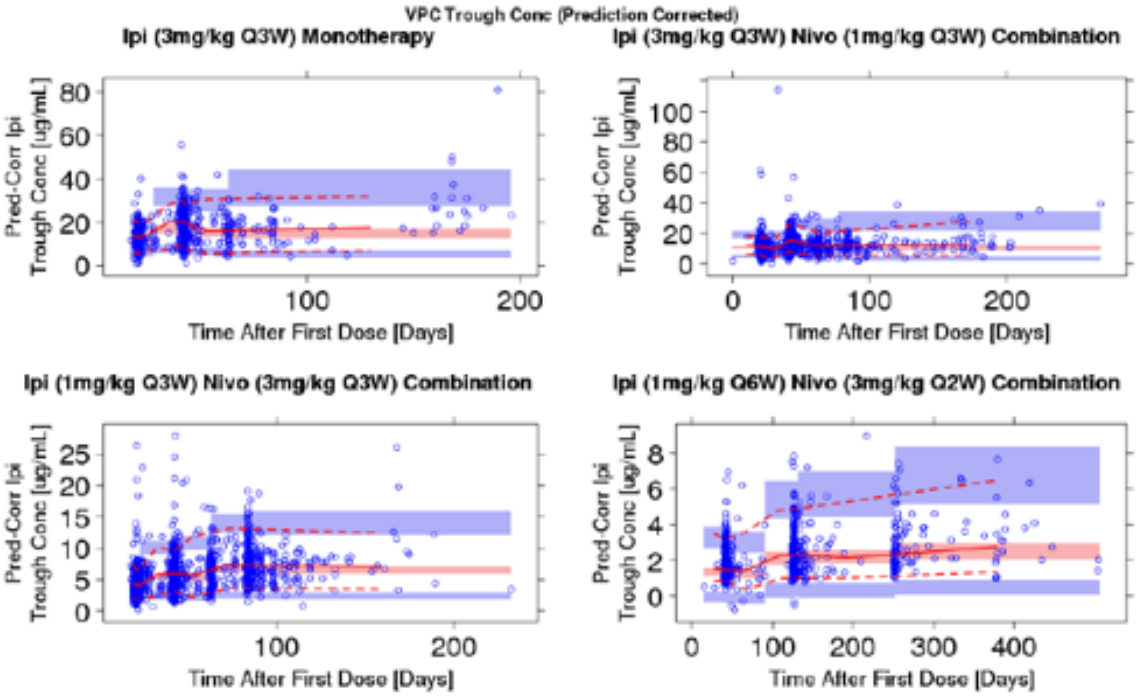
Psn Program Source: Analysis Directory/psn/run19

Program Source: Analysis Directory/R/scripts.vpc-plots.r

Figure Source: Analysis Directory/psn/vpc_full_dir2/VPC-plots1 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 26. Prediction=Corrected Visual Predictive Check of Trough Concentration versus Actual Time after First Dose Stratified by Selected Ipilimumab Dosing Regimens (Final Ipilimumab Population Pharmacokinetic Model)



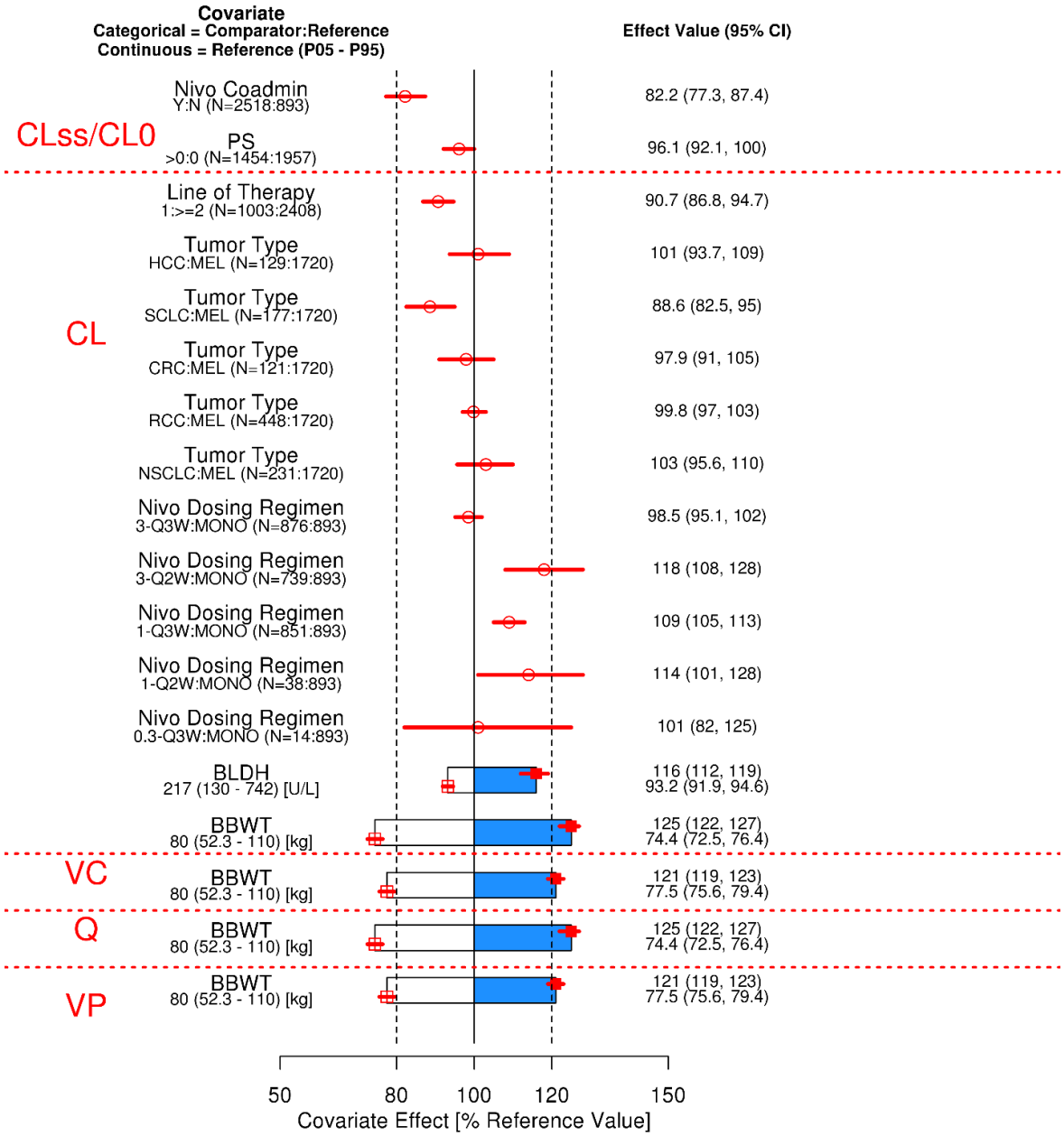
Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final
Psn Program Source: Analysis Directory/psn/run20
Program Source: Analysis Directory/R/scripts.vpc-plots.r
Figure Source: Analysis Directory/psn/vpc_trough_dir2/VPC-plots1 1.png
Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

The maximal change in CL (E_{max}) was similar across tumor types. The maximal model predicted decrease in CL was ~5% and 22% for ipilimumab monotherapy and ipilimumab in combination with nivolumab respectively and the time to half-maximal reduction is ~106 days (2550 hours). In general, responders (CR and PR subjects) showed a greater decrease in CL over time as compared to non-responders (SD and PD subjects).

The effects of tumor type, nivo dosing regimen, line of therapy, BBWT, and BLDH on ipilimumab PK (CL and Vc) were either not statistically significant (the 95% CI includes 0) or not clinically relevant (less than ±20% effect on the typical value of a model parameter relative to the reference value (Figure 27).

In addition, the sensitivity analyses found that the effect of time-varying ADA, BALB, and BTSIZE on ipilimumab CL was either not statistically significant (the 95% CI includes 0) or not clinically relevant (less than ± 20% effect on the typical value of a model parameter relative to the reference value) (data not shown).

Figure 27: Covariate Effects on Ipilimumab Pharmacokinetic Model Parameters (Full Ipilimumab Population Pharmacokinetic Model)



Analysis -Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-nivo/final/
R-Program Source: Analysis-Directory/R/scripts/cov-eff-plot-full.r
Source: Analysis-Directory/R/plots/k-full-3-ppk-cov-eff-plot.png
Note 1: Categorical covariate effects (95% CI) are represented by open symbols (horizontal 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 lines). Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate.
Note 3: Reference subject is male, white/other race, BW = 80 kg, PS = 0, eGFR = 90 mL/min/1.73 m2, and received nivolumab monotherapy, with NSCLC as tumor type. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.
Note 4: The effect of BBWT was also added on Q and VP and their estimates were fixed to be similar to that CL and VC, respectively.
Note 5: Baseline CL of nivolumab in subjects with PS > 0 was higher than subjects with PS = 0 by 19%, whereas the reduction of nivolumab CL over time was greater in subjects with PS > 0 than subjects with PS = 0 by 13%.

The ipilimumab PK in dMMR or MSI-H mCRC patients is consistent with the known ipilimumab PK characteristics. Following the same combination therapy, ipilimumab PK parameters and ipilimumab exposure levels are similar between dMMR or MSI-H CRC and mRCC patients (Table 11 and Table 12).

Table 11: Summary Statistics of Ipilimumab PK Parameters in Combination Therapy (Nivo: 3 mg/kg Q3W, Ipi 1 mg/kg Q3W x 4 Doses)

Ipilimumab PK Parameters	GeoMean (% CV)	
	dMMR or MSI-H mCRC (n=109)	mRCC (n=448)
CL_0 [mL/h]	13.2 (29.8)	12.9 (32.3)
CL_{SS} [mL/h]	10.1 (29.9)	9.90 (32.4)
VSS [L]	6.57 (14.6)	7.35 (18.0)
$t_{1/2\beta,SS}$[d]	20.5 (24.2)	23.1 (27.4)

Source: Table 4 and Table 8 in appendix 5.2.3.2-1 of the PPK report11

Table 12: Summary Statistics of Ipilimumab Exposure in Combination Therapy (Nivo: 3 mg/kg Q3W, Ipi 1 mg/kg Q3W x 4 Doses)

Ipilimumab Exposure Parameters (µg/mL)	dMMR or MSI-H mCRC (n=109)	mRCC (n=448)
	GeoMean (% CV)	GeoMean (% CV)
CMIN1	3.38 (32.5)	3.93 (29.6)
CMAX1	19.7 (16.7)	19.7 (28.2)
CAVG1	6.82 (19.8)	7.35 (20.1)
CMIN4	6.50 (44.9)	7.94 (42.6)
CMAX4	25.7 (22.6)	27.1 (27.1)
CAVG4	11.4 (31.6)	13.0 (30.9)

Sensitivity Analyses

BTSIZE

Ipilimumab CL was significantly [95% CI does not include 0] higher in subjects with higher BTSIZE; however, the magnitude of the difference was within the ± 20% boundary (data not shown) and not likely to be clinically relevant. The resulting parameter estimates obtained from this analysis were in good agreement with those obtained in the final model.

BALB

Ipilimumab CL was significantly [95% CI does not include 0] lower in subjects with higher BALB; however, the magnitude of the difference was within the ± 20% boundary (data not shown) and not likely to be clinically relevant. The resulting parameter estimates obtained from this analysis were in good agreement with those obtained in the final model.

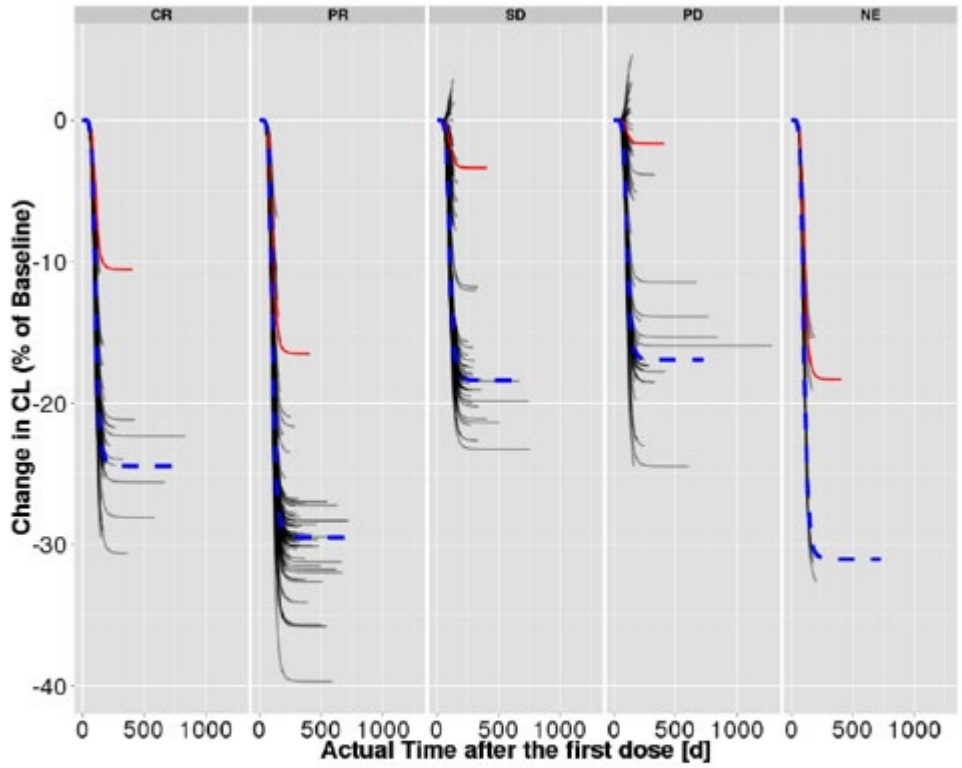
ADA

Ipilimumab ADA measured by the second generation assay with a drug tolerant limit of 75 µg/mL did not have a statistically significant effect on CL (increase by 5.7% [calculated as exp(0.0558)*100-100]) when ipilimumab was administered with nivolumab. The 95% CI (-1.00 to 11.3%) fell within 20% of the reference value. However, anti-ipilimumab antibodies measured by the first generation assay with a drug tolerance limit of 10 µg/mL (), were statistically significant and increased the typical value of CL by 31.5% [calculated as exp (0.274)*100-100] when ipilimumab was administered as monotherapy. Given the complexity associated with incorporation of time-varying CL into the model and the time-varying nature of ADA measurements, graphical assessments of the effect of ADA on nivolumab CL were not made.

BOR

The effect of BOR on change in ipilimumab CL was assessed in an ad-hoc sensitivity analysis This analysis was conducted for studies with available BOR information.

Figure 28. Change in Ipilimumab Clearance over Time by Best Overall response, Estimate by the Sensitivity Model.



Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final

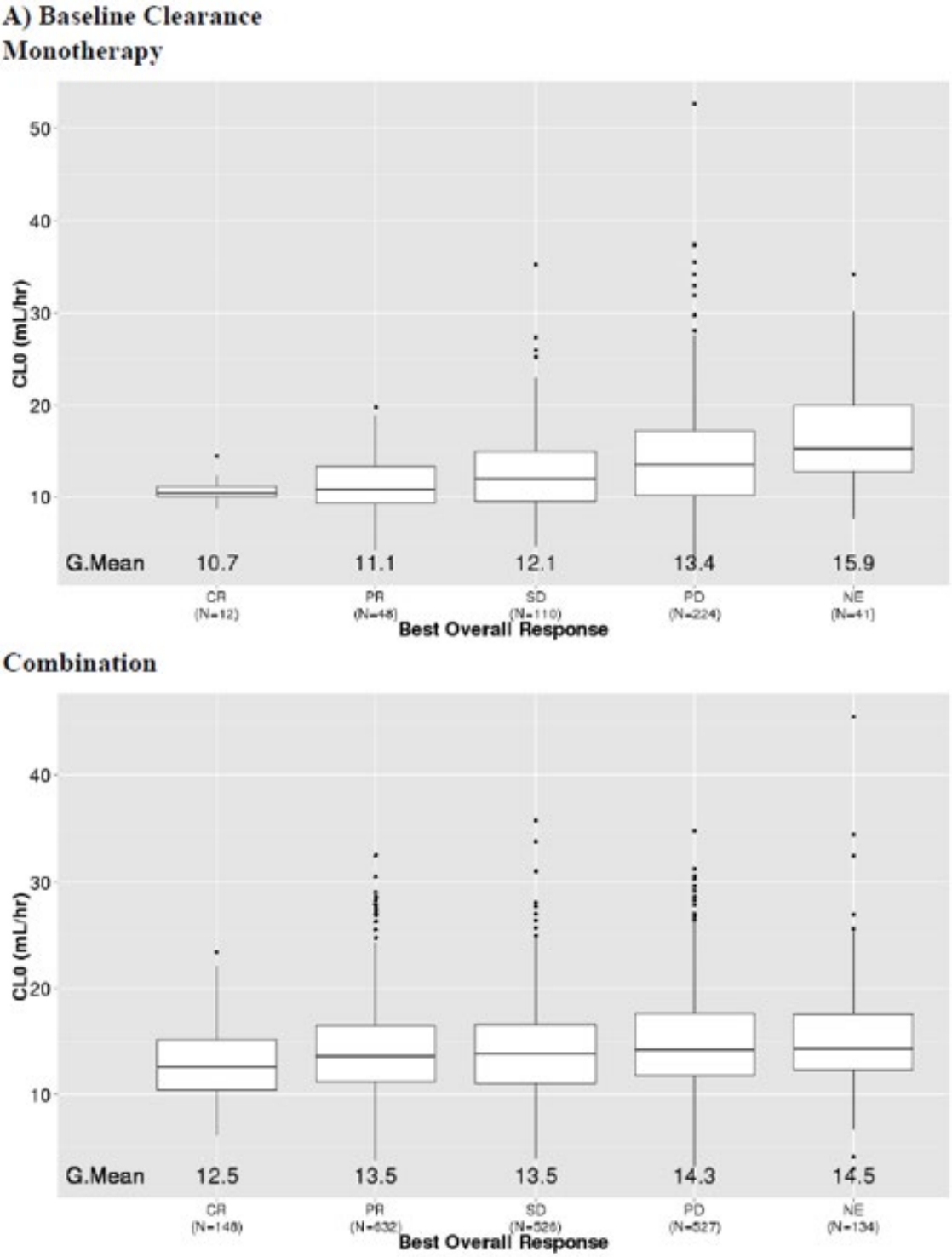
PsN Program Source: Analysis Directory/psn/run27.dir5/NM_run1/sdtab27

Program Source: Analysis Directory/R/scripts/plotcl-time_bor.R

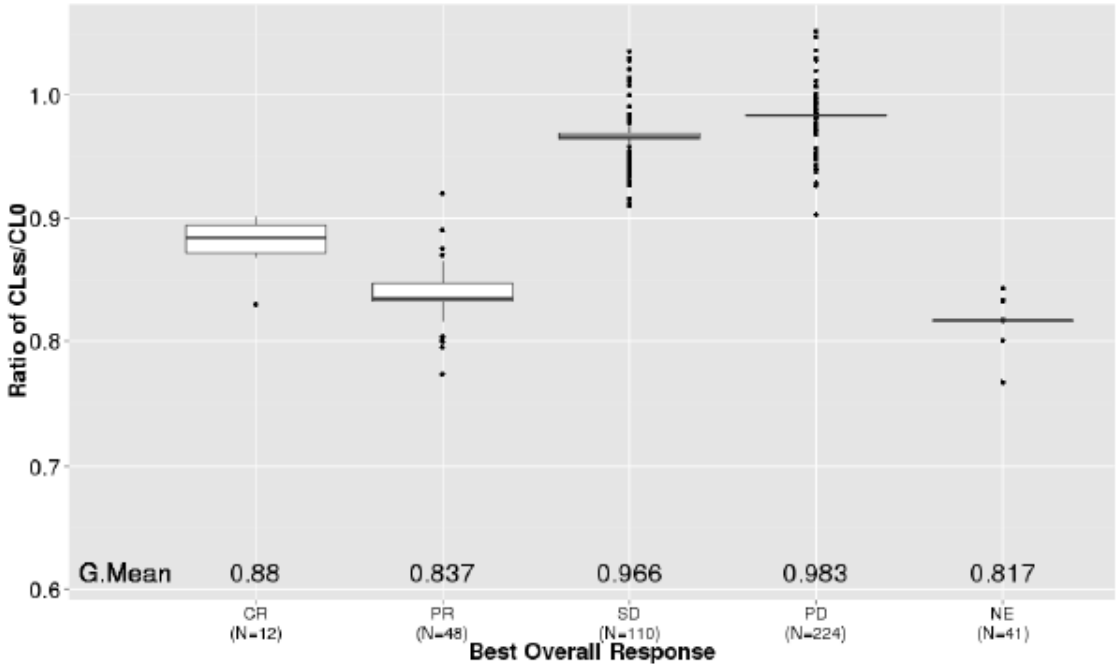
Figure Source: Analysis Directory/R/plots/changeCL-vs-time-born.png

Note: The red line and blue dashed line are typical change in CL over time in ipilimumab monotherapy and in combination with nivolumab respectively.

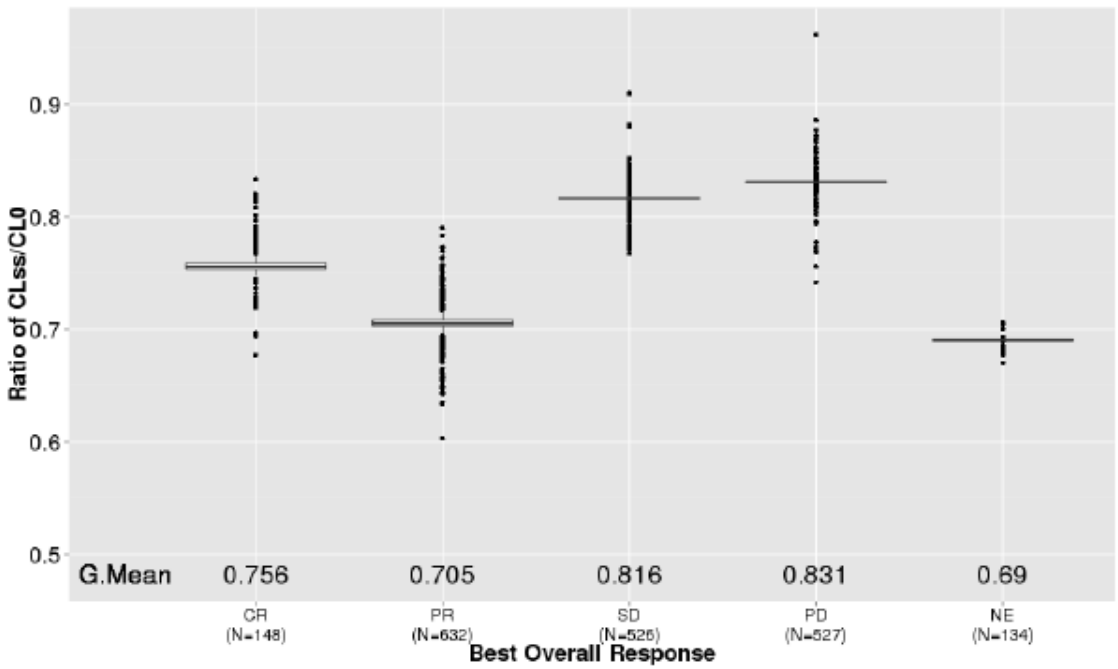
Figure 29. Distribution of Ipilimumab Baseline Clearance and ratio of Steady-State Clearance to baseline Clearance by Best Overall Response



B) Ratio of Steady-State Clearance to Baseline Clearance
Monotherapy



Combination



Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final
PsN Program Source: Analysis Directory/psn/run27.dir5/NM_run1/sdtab27
Program Source: Analysis Directory/R/scripts/plotcl-time_bor.R
Figure Source: Analysis Directory/R/plots/BCL-by-BOR1_mono.png
Figure Source: Analysis Directory/R/plots/BCL-by-BOR1_combo.png
Figure Source: Analysis Directory/R/plots/CLratio-by-BOR1.mono.png
Figure Source: Analysis Directory/R/plots/CLratio-by-BOR1.combo.png

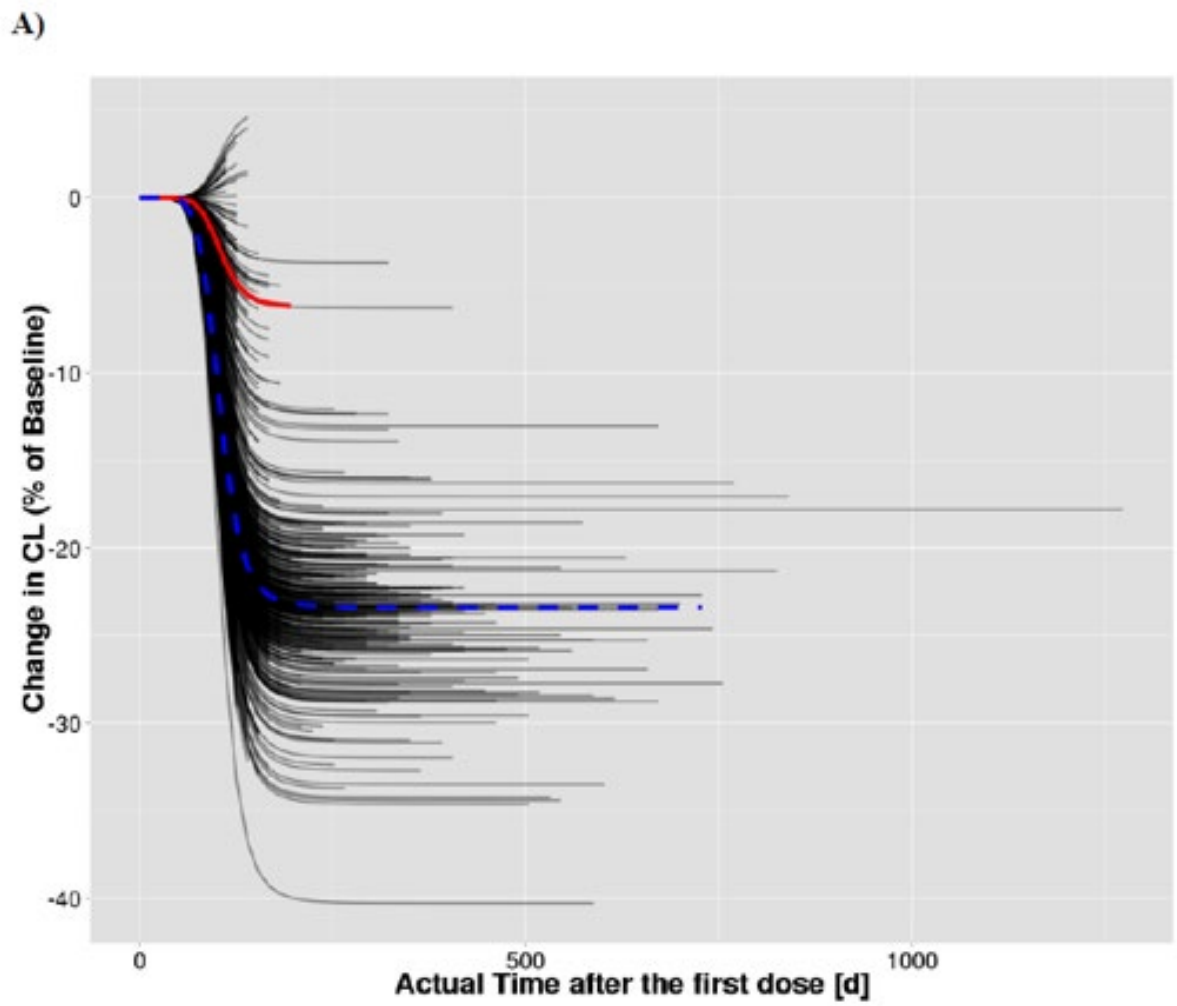
The figures demonstrates that baseline CL in subjects across BOR groups is similar, however the CL at steady-state is significantly lower in responders (CR and PR) as compared to non-responders (SD and

PD). Further CL_{ss} is lower in subjects receiving ipilimumab in combination with nivolumab compared to subjects receiving ipilimumab monotherapy.

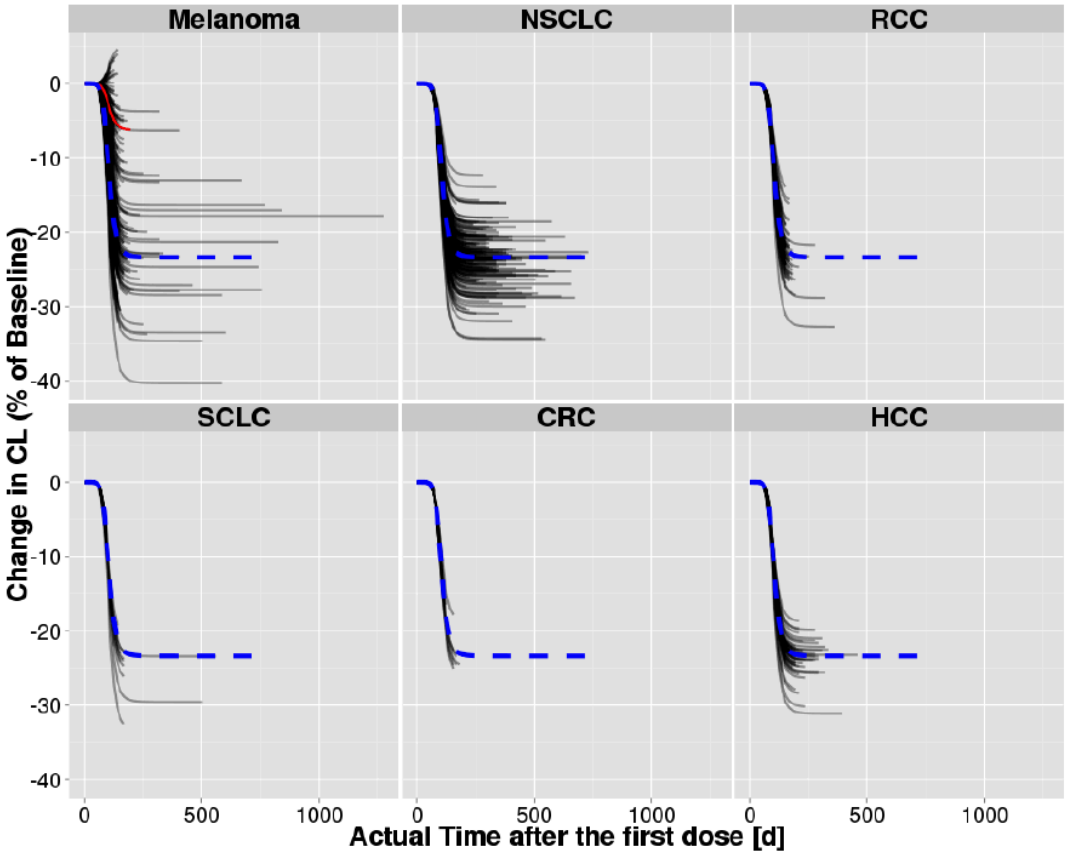
Assessment of Temporal Changes in Clearance

Figure 30 demonstrates the change in ipilimumab CL over time. The maximal model predicted decrease in CL was ~5% and 22% for ipilimumab monotherapy and ipilimumab in combination in nivolumab, respectively; the time for half maximal reduction was ~106 days (2550 hours). The variability around E_{MAX} predicted by the model was ~38.5%. figure 30.

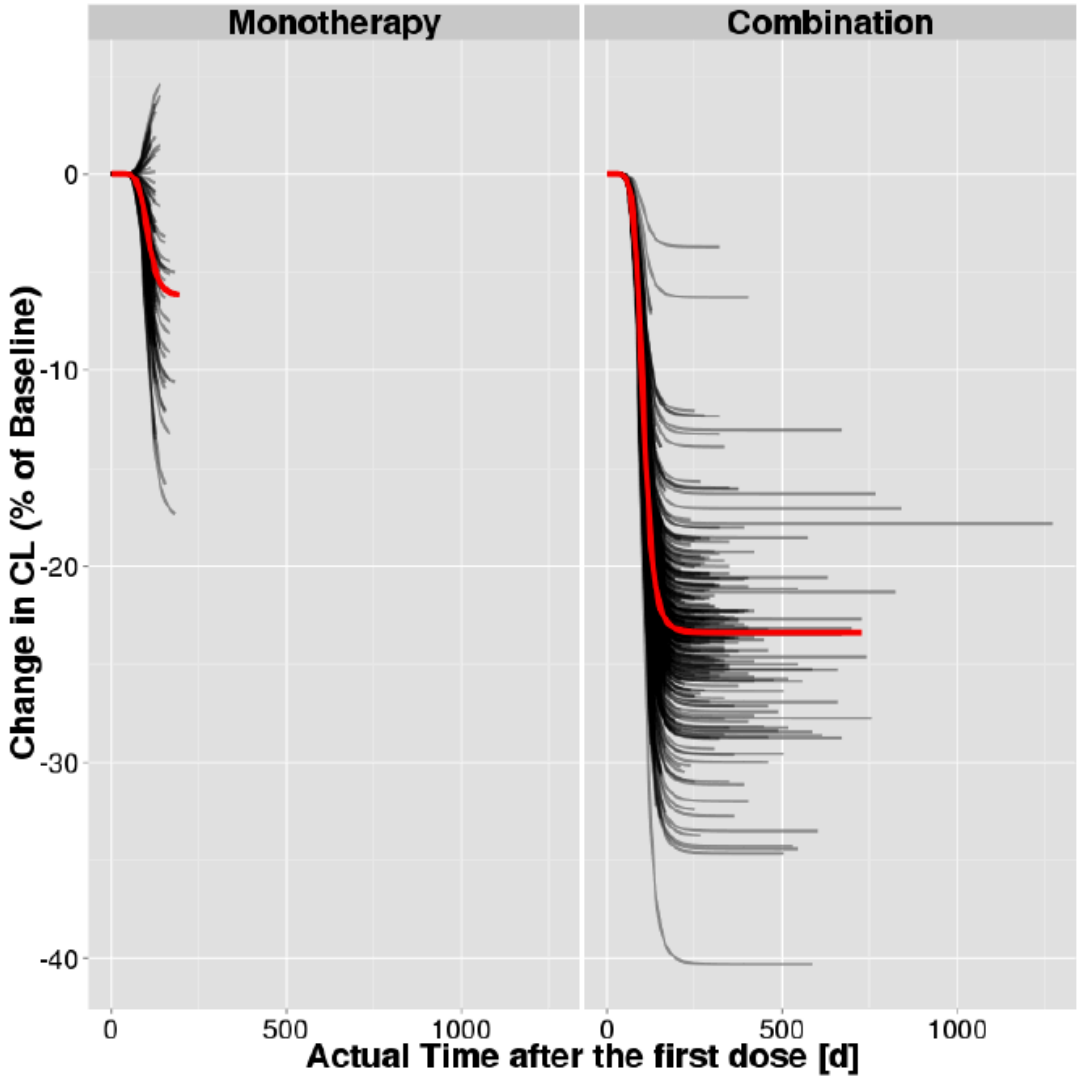
Figure 30. Model estimated Change in Ipilimumab Clearance versus Time from the Final Model A) Overall, B) by Tumor Type, and C)by Ipilimumab Dosing Regimens



B)


Melanoma
NSCLC
RCC
SCLC
CRC
HCC
Change in CL (% of Baseline)
0
-10
-20
-30
-40
0
500
1000
Actual Time after the first dose [d]

C)



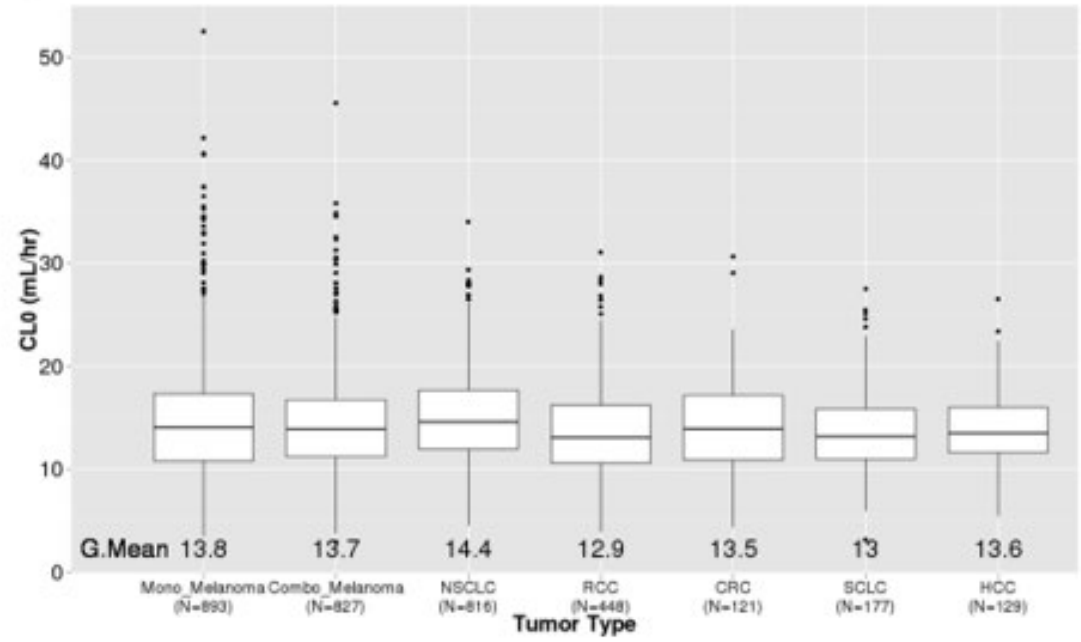
Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final
PsN Program Source: Analysis Directory/psn/run18_1.dir1/NM_run1/sdtab18_1
Program Source: Analysis Directory/R/scripts/plot-cl-time.R
Figure Source: Analysis Directory/R/plots/changeCL-vs-time-by-.png
Figure Source: Analysis Directory/R/plots/changeCL-vs-time-by-ttypen.png
Figure Source: Analysis Directory/R/plots/changeCL-vs-time-by-combo.png
Note: For Figures A and B, the red line and blue dashed line are typical change in CL over time in ipilimumab monotherapy and in combination with nivolumab, respectively. For Figure C, the red line represents is typical change in CL over time.

Distribution of Ipilimumab Clearance by Tumor Type

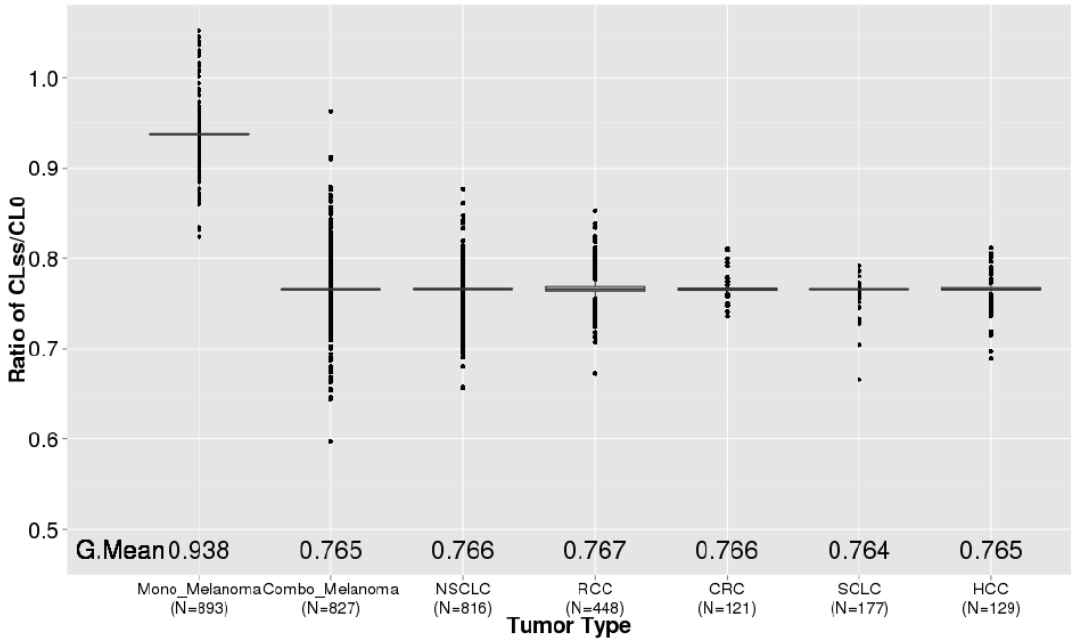
Ipilimumab baseline and steady-state CL was similar across tumor types. Subjects receiving ipilimumab combination therapy with nivolumab had a greater decrease in CL at steady-state as compared to monotherapy.

Figure 31. Distribution of Ipilimumab Baseline Clearance and Ratio of Steady-State Clearance to Baseline Clearance by Tumor type

A) Baseline Clearance



B) Ratio of Steady-State Clearance to Baseline Clearance

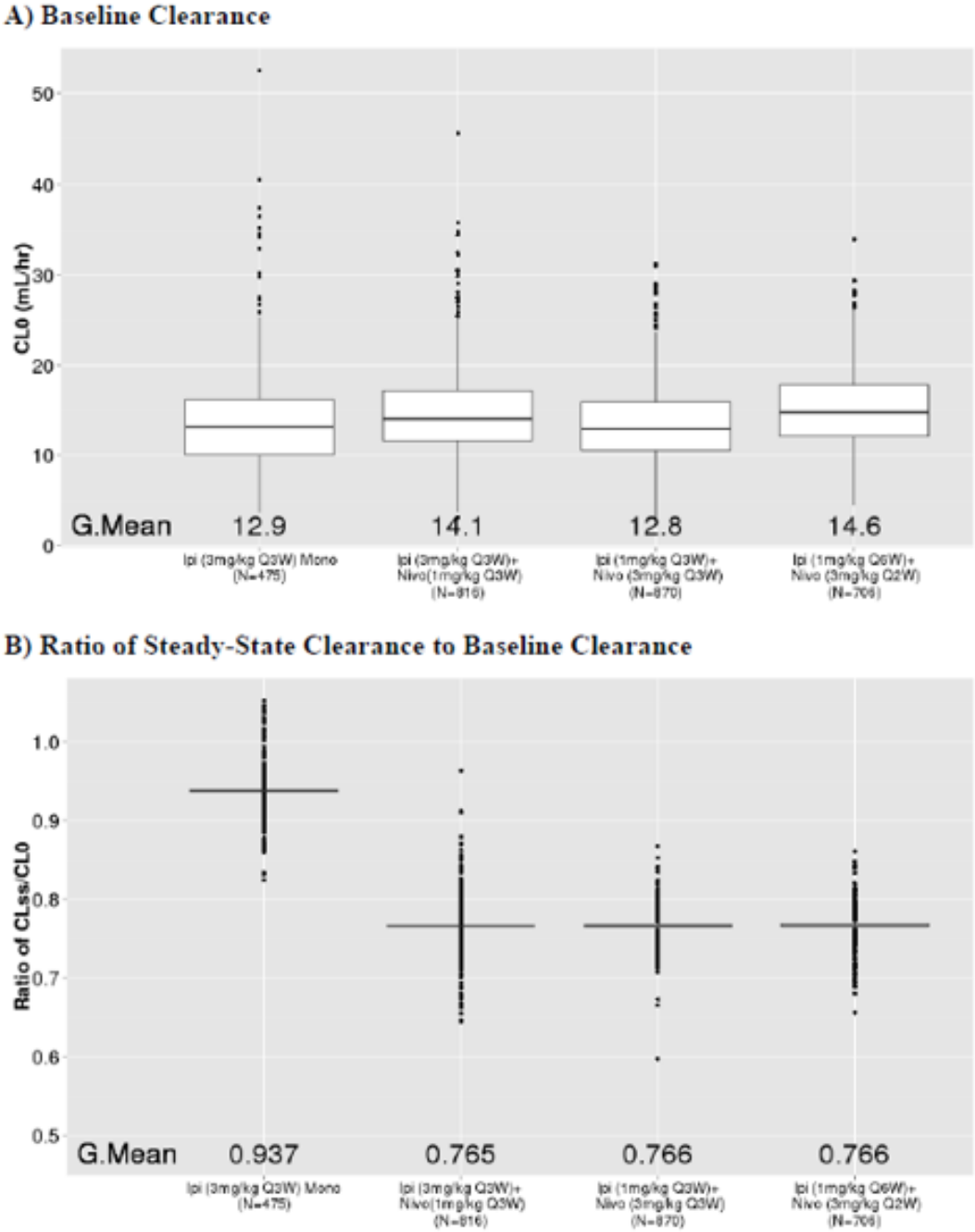


Analysis Directory: /global/pkms/data/CA/209/nsclc-1l-combo/prd/ppk-ipi/final
PsN Program Source: Analysis Directory/psn/run18.dir1/NM_run1/sdtab18_1
Program Source: Analysis Directory/R/scripts/model-application-plot-new.r
Figure Source: Analysis Directory/R/plots/BCL_by_TTYPEN.png
Figure Source: Analysis Directory/R/plots/CLratio_by_TTYPEN1.png

Distribution of Ipilimumab Clearance by Different Combination Dose Regimens

Ipilimumab CL0 was similar in subjects receiving either ipilimumab monotherapy compared to ipilimumab in combination with nivolumab. The magnitude of decrease in CL was greater in subjects receiving combination therapy as compared to ipilimumab monotherapy.

Figure 32. Distribution of Ipilimumab Baseline Clearance and Ratio of Steady-State Clearance to baseline Clearance by Select Dosing Regimen of Ipilimumab Monotherapy and in Combination with Nivolumab

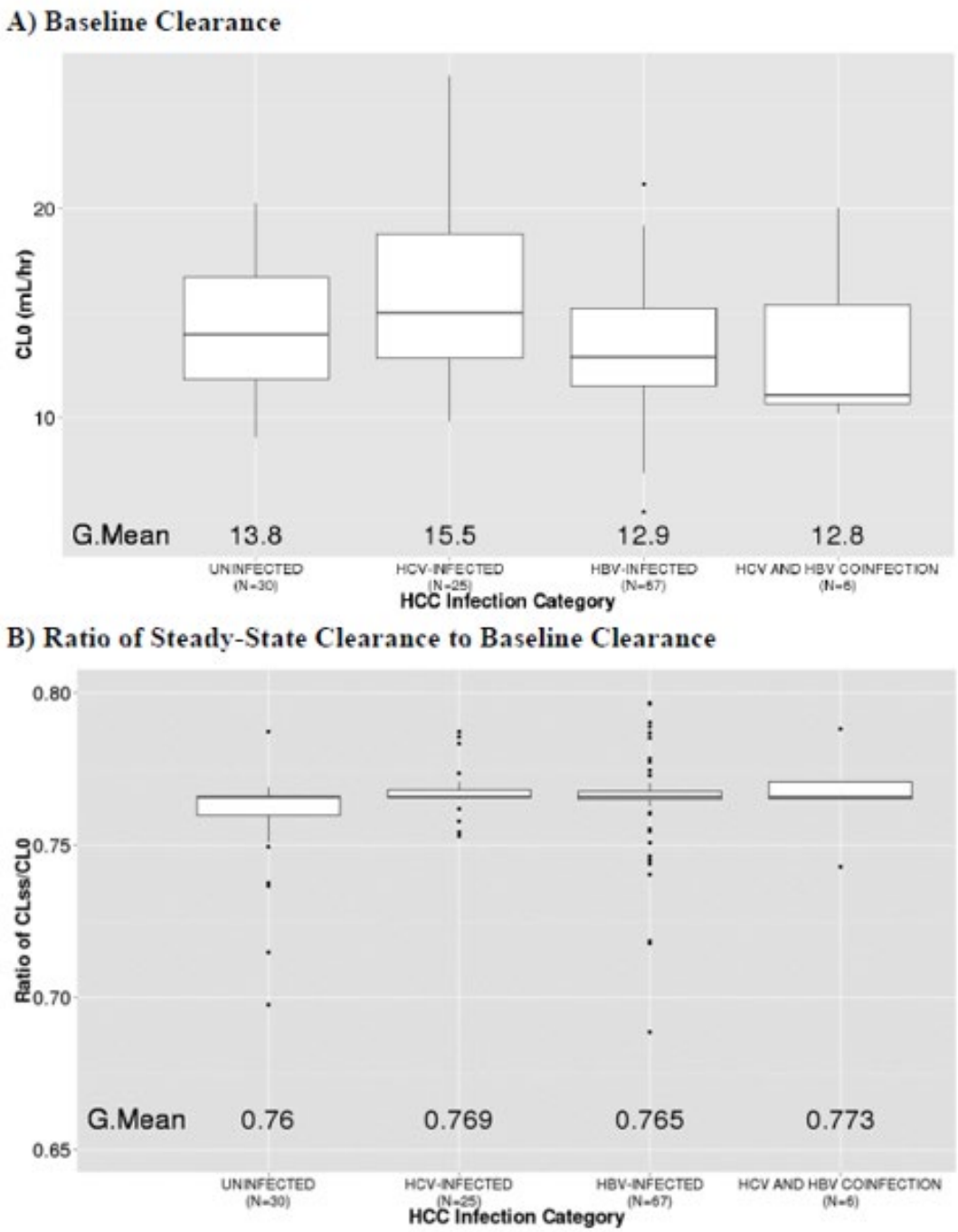


Analysis Directory: /global/pkms/data/CA/209/nsclc-11-combo/prd/ppk-ipi/final
PsN Program Source: Analysis Directory/psn/run18.dir1/NM_run1/sdtab18_1
Program Source: Analysis Directory/R/scripts/model-application-plot-new.r
Figure Source: Analysis Directory/R/plots/BCL_by_Nivo Combo.png
Figure Source: Analysis Directory/R/plots/CLratio_by_Nivo Combo.png

Distribution of Ipilimumab Clearance in Uninfected Subjects and Subjects with HCV or HBV in Study CA204090.

The baseline and steady-state ipilimumab CL were similar in infected versus uninfected subjects with HCC and the magnitude of the changes in ipilimumab CL was also similar across the different etiologies.

Figure 33. Distribution of Ipilimumab Baseline Clearance and Ratio of Steady-State Clearance to baseline Clearance in Etiology in HCC Subjects Received Nivolumab Monotherapy and in Combination with Ipilimumab (Study 209040)

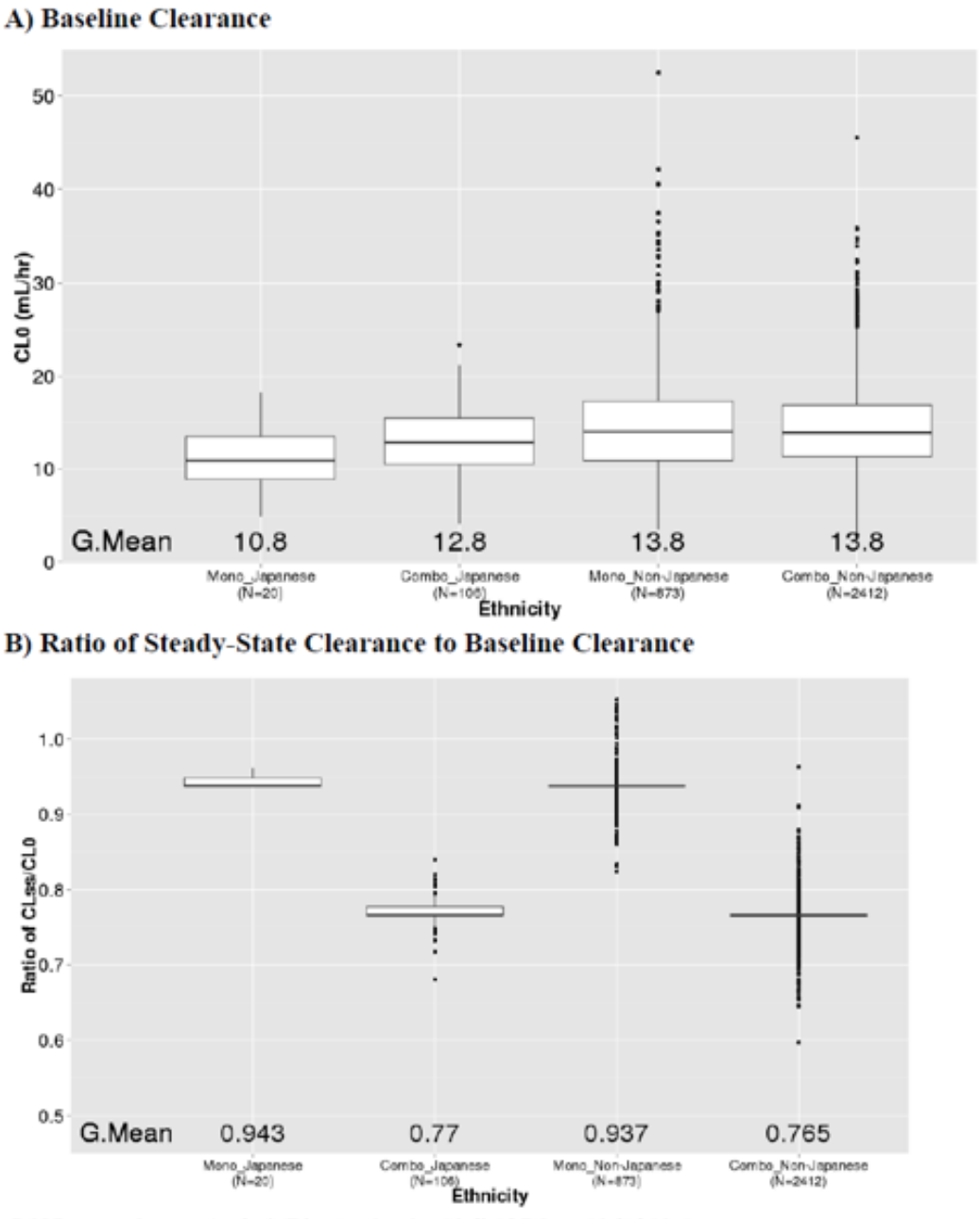


PsN Program Source: Analysis Directory/psn/run18.dir1/NM_run1/sdtab18_1
Program Source: Analysis Directory/R/scripts/model-application-plot-new.r
Figure Source: Analysis Directory/R/plots/BCL_by_HCC.png
Figure Source: Analysis Directory/R/plots/CLratio_by_HCC.png

Distribution of Ipilimumab Clearance in Japanese and Non-Japanese Subjects.

The baseline and steady-state CL for Japanese and non-Japanese subjects were similar. The magnitude of the change in ipilimumab CL was higher in Japanese and non-Japanese subjects receiving ipilimumab in combination with nivolumab as compared to subjects receiving ipilimumab monotherapy.

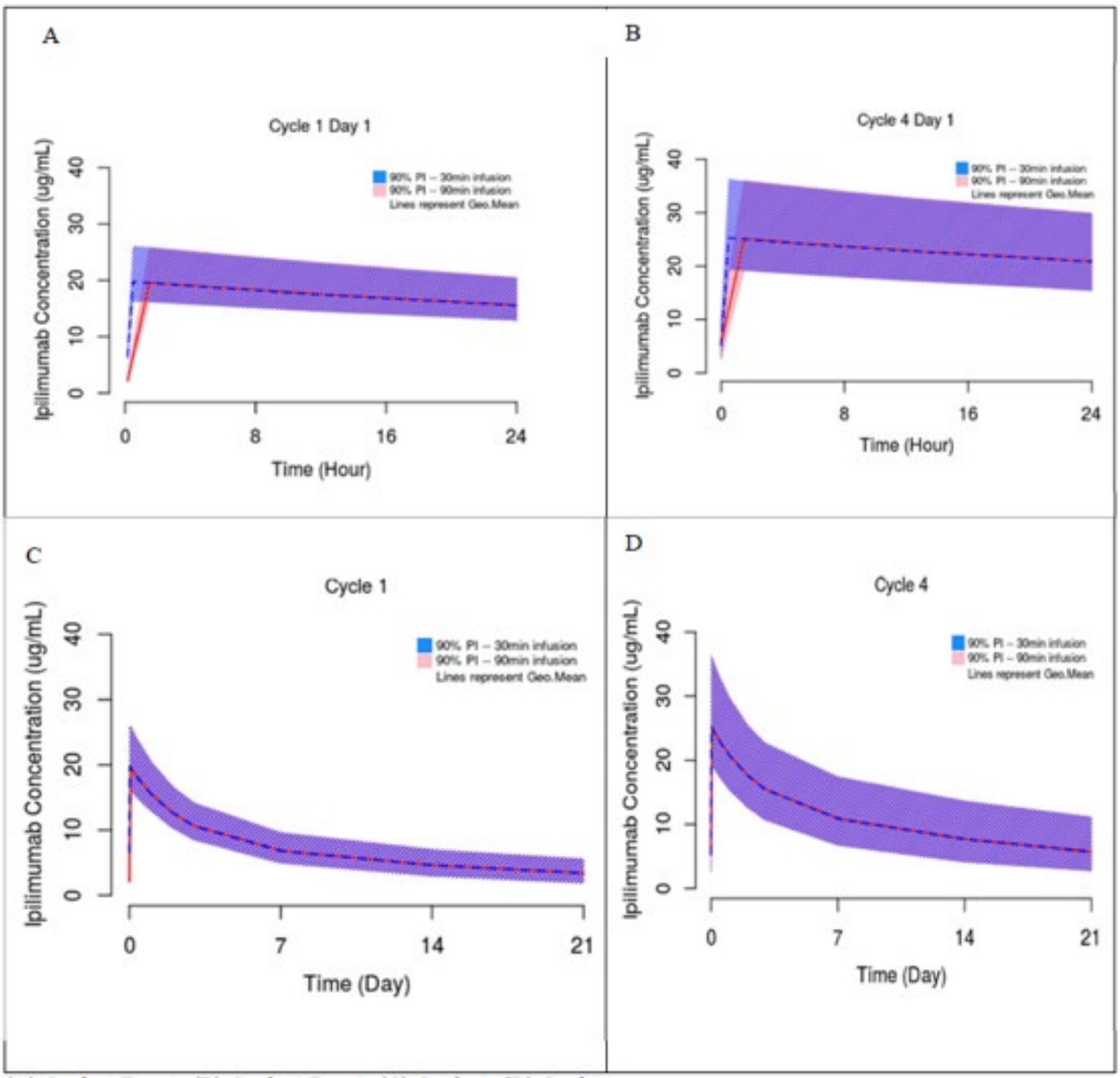
Figure 34. Distribution of Ipilimumab Baseline Clearance and Ratio of Steady-State Clearance to baseline Clearance in Japanese and Non-Japanese Subjects



PsN Program Source: Analysis Directory/psn/run18.dir1/NM_run1/sdtab18_1
Program Source: Analysis Directory/R/scripts/model-application-plot-new.r
Figure Source: Analysis Directory/R/plots/BCL_by_ETH1.png
Figure Source: Analysis Directory/R/plots/CLratio_by_ETH1.png

The ipilimumab final PK model was used to simulate ipilimumab PK profiles in dMMR or MSI-H CRC patients following nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses) via either a 30 min or 90 min ipilimumab infusion duration. Equivalent ipilimumab PK profiles were observed between a 30 min and 90 min infusion duration (Figure 35). The only difference is the 30 min infusion achieves Cmax earlier than the 90 min infusion duration as expected.

Figure 35. Ipilimumab PK Profile in dMMR or MSI-H CRC following Nivolumab 3 mg/Kg + Ipilimumab 1 mg/Kg Q3W (4 doses) via a 30 min or 90 min Ipilimumab Infusion Duration.



(A) Cycle 1 Day 1; (B) Cycle 4 Day 1; (C) Cycle 1; (D) Cycle 4

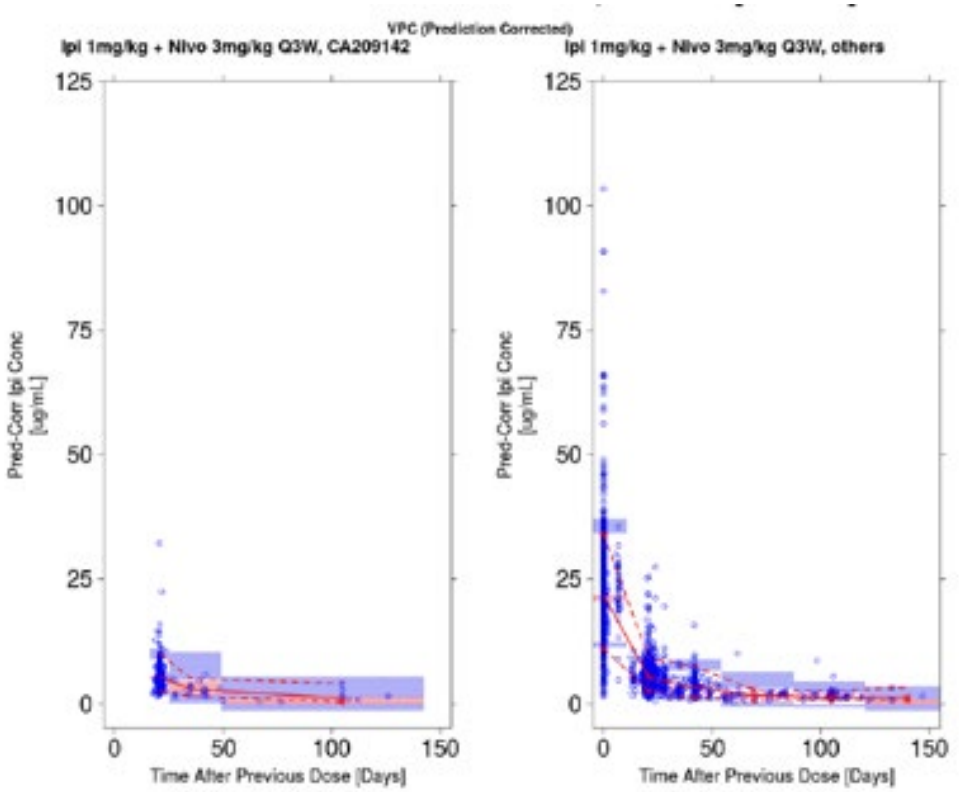
Source: Figure 5.2.3.6-1 in the PPK Report[11]

The predictive performance of the final ipilimumab PPK model was evaluated using pcVPC for the updated ipilimumab dataset.

Figure 36 and Figure 37 show the pcVPC plots of all ipilimumab concentration versus time after the previous dose and trough concentration versus time after the first dose, respectively. The pcVPC plots show that the full ipilimumab PPK model adequately characterized the data from Study CA209142.

The effect of covariates on ipilimumab PK was re-estimated using the full model for the updated ipilimumab dataset. Parameter estimates (Table 13) and the covariate effects (Figure 38) obtained from the validation dataset are similar to those obtained from the previous ipilimumab PPK analysis dataset (data not shown).

Figure 36. Prediction-Corrected Visual Predictive Check of Concentration versus Actual Time after Prevsin Dose Startified by Selected Ipilimumab Dosing Regimens (Full Ipilimumab Population Pharmacokinetic Model) for the Updated Ipilimumab PPK Dataset



Analysis Directory: /global/pkms/data/CA/209/crc-2l-combo-EU/prd/ppk-ipi/final

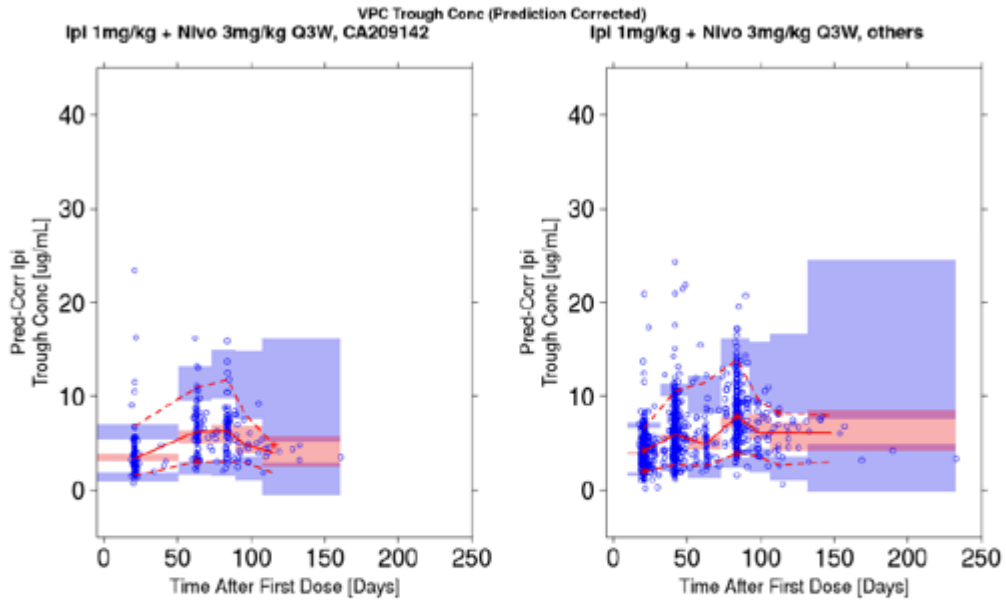
Psn Program Source: Analysis Directory/psn/run4_6

Program Source: Analysis Directory/R/ipippk.Rmd

Figure Source: Analysis Directory/psn/vpc_full_dir2/VPC-plots1 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 37. Prediction=Corrected Visual Predictive Check of Trough Concentration versus Actual Time after First Dose Stratified by Selected Ipilimumab Dosing Regimens (Full Ipilimumab Population Pharmacokinetic Model) for the Updated Ipilimumab PPK Dataset



Analysis Directory: /global/pkms/data/CA/209/crc-2l-combo-EU /prd/ppk-ipi/final

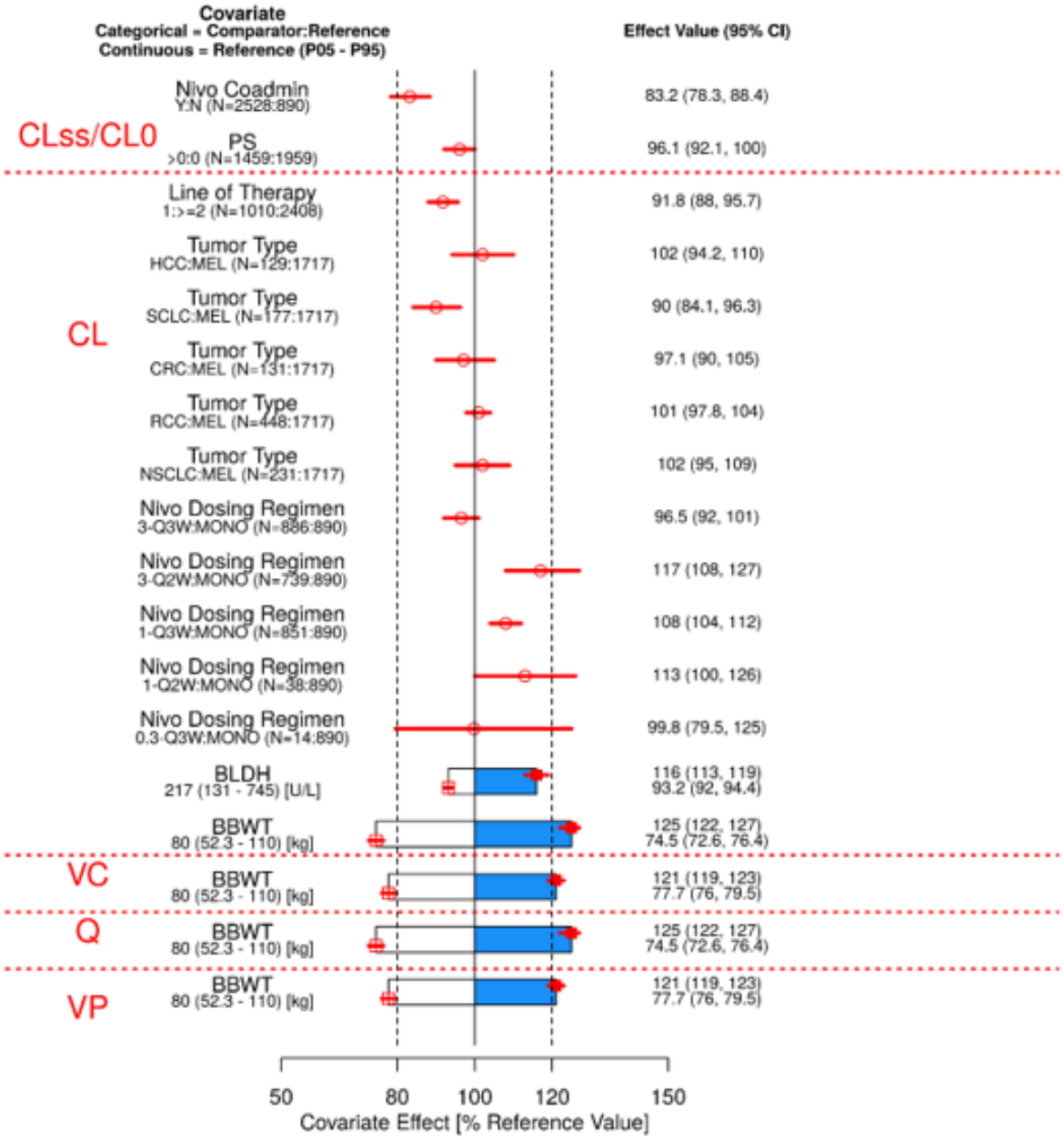
Psn Program Source: Analysis Directory/psn/run4_7

Program Source: Analysis Directory/R/ipippk.Rmd

Figure Source: Analysis Directory/psn/vpc_trough_dir2/VPC-plots1 1.png

Note: Dots are observed data. The lines represent the 5th, 50th, and 95th percentiles of observed data, respectively. The shaded areas represent the simulation-based 90% CIs for the 5th, 50th, and 95th percentiles of the predicted data.

Figure 38. Covariate Effects on Ipilimumab Pharmacokinetics Model Parameters (Full Ipilimumab Population Pharmacokinetic Model) using the Updated Ipilimumab PPK Dataset



Analysis Directory: /global/pkms/data/CA/209/ crc-2l-combo-EU/prd/ppk-ipi/final/psn/full.dir

PsN Program Source: Analysis Directory/psn/full.dir/NM_run1/sdtab4_5

Program Source: Analysis Directory/R/scripts/ipippk.Rmd

Figure Source: Analysis Directory/R/plots/full-ipi-ppk-coefff-plot.png

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

Note 3: Reference subject with melanoma as tumor type, receiving ipilimumab monotherapy as a 2nd line therapy, weighing 80 kg and BLDH of 217 U/L. Parameter estimate in a reference subject is considered as 100% (vertical solid line) and dashed vertical lines are at 80% and 120% of this value.

Note 4: Covariate effects on CL apply to both CL0 and CLss.

Table 13. Parameter Estimates of the Full Ipilimumab Population Pharmacokinetic Model (run4_5) using the Updated Ipilimumab

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
Fixed Effects				
$CL0_{REF}$ [mL/h]	θ_1	14.2	0.266 (1.87)	13.7 - 14.7
VC_{REF} [L]	θ_2	3.96	0.0243 (0.613)	3.91 - 4.01
Q_{REF} [mL/h]	θ_3	27.7	1.98 (7.12)	23.9 - 31.6
VP_{REF} [L]	θ_4	3.17	0.0700 (2.21)	3.03 - 3.31
CL_{BW} [power]	θ_7	0.693	0.0303 (4.38)	0.634 - 0.753
V_{BW} [power]	θ_8	0.594	0.0272 (4.58)	0.540 - 0.647
CL_{LDH} [power log]	θ_9	0.719	0.0679 (9.44)	0.586 - 0.852
$EMAX_{REF}$	θ_{10}	-0.0672	0.0315 (46.9)	(-0.129) - (-0.00540)
$T50$ [h]	θ_{11}	2510	93.9 (3.75)	2320 - 2690
$HILL$	θ_{12}	7.84	1.66 (21.2)	4.59 - 11.1
CL_{NSCLC}	θ_{13}	0.0194	0.0358 (185)	(-0.0508) - 0.0895
CL_{RCC}	θ_{14}	0.00694	0.0146 (211)	(-0.0218) - 0.0357
CL_{CRC}	θ_{15}	-0.0294	0.0388 (132)	(-0.105) - 0.0465
CL_{SCLC}	θ_{16}	-0.106	0.0345 (32.6)	(-0.173)- (-0.0382)
CL_{HCC}	θ_{17}	0.0163	0.0388 (238)	(-0.0598) - 0.0924
$CL_{0.3\ mg/kg\ Q3W}$	θ_{18}	-0.00167	0.116 (6.94E+03)	(-0.229) - 0.226
$CL_{1mg/kg\ Q2W}$	θ_{19}	0.119	0.0589 (49.4)	0.00388 - 0.235
$CL_{1mg/kg\ Q3W}$	θ_{20}	0.0761	0.0206 (27.1)	0.0356 - 0.117
$CL_{3\ mg/kg\ Q2W}$	θ_{21}	0.157	0.0426 (27.2)	0.0731 - 0.240
$CL_{3mg/kg\ Q3W}$	θ_{22}	-0.0352	0.0244 (69.5)	(-0.0830) - 0.0127
CL_{LINE}	θ_{23}	-0.0859	0.0212 (24.7)	(-0.127) - (-0.0443)
$EMAX_{COMBO}$	θ_{24}	-0.184	0.0309 (16.8)	(-0.244) - (-0.123)
$EMAX_{PS}$	θ_{25}	-0.0393	0.0219 (55.7)	(-0.0822) - 0.00360
Random Effects				

Name[a,b] [Units]	Symbol	Estimate[c]	Standard Error (RSE%)[d]	95% Confidence Interval[e]
ω2CL[-]	$\omega_{1,1}$	0.103 (0.320)	0.00465 (4.53)	0.0934 - 0.112
ω2VC [-]	$\omega_{2,2}$	0.0716 (0.268)	0.00717 (10.0)	0.0576 - 0.0857
ω2EMAX	$\omega_{3,3}$	0.0222 (0.149)	0.00840 (37.9)	0.00571 - 0.0386
ω2CL[-]:ω2VC	$\omega_{1,2}$	0.0352 (0.411)	0.00281 (7.97)	0.0297 - 0.0407
Residual Error				
Proportional [-]	θ_5	0.208	0.00521 (2.51)	0.197 - 0.218
Additive [ug/mL]	θ_6	0.618	0.107 (17.4)	0.408 - 0.829

Analysis Directory: /global/pkms/data/CA/209/crc-2l-combo-EU/prd/ppk-ipi/final/psn/full.dir

Program Source: Analysis Directory/psn/full.dir/NM_run1/psn.lst

Source: Analysis Directory/psn/pirana_reports/run4_5_RTF.rtf

Note: $CL0_{REF}$ is the typical value in a reference subject with melanoma tumor type, receiving ipilimumab monotherapy as a 2nd line therapy, weighing 80 kg and BLDH of 217 U/L. $EMAX_{REF}$ is a typical value of change in magnitude of CL in a reference subject receiving ipilimumab monotherapy with a normal PS status. VC_{REF}, Q_{REF}, and VP_{REF} are typical values in a reference subject weighing 80 kg. These reference values represent the approximate median values in the PPK analysis dataset.

Note: Eta shrinkage (%): ETA_CL: 12.5; ETA_VC: 30.2; ETA_EMAX: 97.7; EPS shrinkage (%): 16.3.

[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

[b] Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters

[c] Random Effects and Residual Error parameter estimates are shown as *Variance (Standard Deviation)* for diagonal elements ($\omega_{i,i}$ or $\sigma_{i,i}$) and *Covariance (Correlation)* for off-diagonal elements ($\omega_{i,j}$ or $\sigma_{i,j}$)

[d] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

[e] Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance5.2.4*

Immunogenicity

There were 109 subjects with evaluable ADA for nivolumab, and 107 subjects with evaluable ADA for ipilimumab in nivo with ipi combination treated dMMR or MSI-H mCRC subjects from Study CA209142.

The incidence of nivolumab ADA was 25.7% with 0 persistent-positive subjects and 2 neutralising antibody-positive subjects (Table 14). In all nivolumab ADA positive subjects, the greatest titer value observed was 128, which occurred in 2 subjects. All other ADA positive subjects had titer values of 64 or less.

The incidence of ipilimumab ADA was 4.7% with 0 persistent-positive subjects and 0 neutralizing antibody-positive subjects. In all ipilimumab ADA positive subjects, the greatest titer value observed was 8.

The observed incidences of nivolumab ADA and ipilimumab ADA in dMMR or MSI-H mCRC patients were similar to those observed in mRCC patients in CA209214, for which the same nivolumab plus ipilimumab regimen was applied.

Table 14. Summary of ADA Assessments – All Treated Subjects with Baseline and at Least One Post-Baseline Assessment

Subjects ADA Status	All Subjects [N (%)]	
	Nivolumab ADA N=109	Ipilimumab ADA N=107
Baseline ADA Positive	4 (3.7)	2 (1.9)
ADA Positive	28 (25.7)	5 (4.7)
Persistent Positive (PP)	0	0
Not PP-Last Sample Positive	4 (3.7)	2 (1.9)
Other Positive	24 (22.0)	3 (2.8)
Neutralizing ADA Positive	2 (1.8)	0
ADA Negative	81(74.3)	102 (95.3)

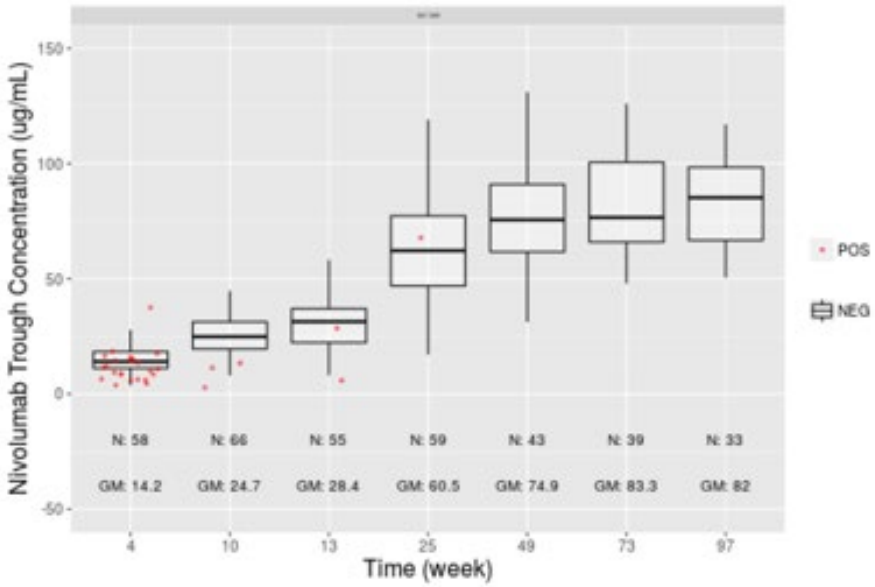
Baseline ADA Positive: A subject with baseline ADA-positive sample; ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment;
Persistent Positive (PP): ADA-positive sample at 2 or more consecutive timepoints, where the first and last ADA-positive samples are at least 24 weeks apart; Not PP-Last Sample Positive: Not PP with ADA-positive sample at the last sampling timepoint; Other Positive: Not PP but some ADA-positive samples with the last sample being negative;
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.
Program Source: /opt/zfs001/prd/bms218374/stats/feb2019/prog/tables/rt-im-c2sum-can.sas

Effect of Immunogenicity on Pharmacokinetics

Nivolumab

Nivolumab trough PK samples were collected on Weeks 4, 10, 13, 25 and every 24 weeks thereafter in dMMR or MSI-H mCRC patients in the CA209142 combination arm. Trough PK samples collected within +/- 3 days collection window were plotted by their ADA status. As shown in Figure 39, distribution of nivolumab trough concentrations in patients with positive nivolumab ADA appeared to be within the trough concentration range observed in patients with negative nivolumab ADA. No positive nivolumab ADA trough samples were observed beyond Week 25.

Figure 39. Time Course of Observed Nivolumab Trough Concentration by Nivolumab ADA Status in dMMR/MSIH mCRC Patients in the CA209142 Combination Arm

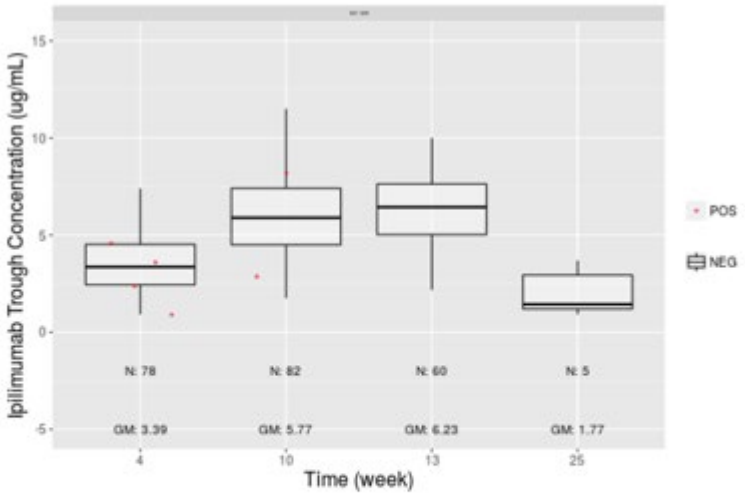


Analysis Directory: /global/pkms/data/CA/209/crc-2l-combo-EU/prd/ppk-nivo/final
Program Source: Analysis Directory/R/scripts/nivoppk.Rmd
Figure Source: Analysis Directory/R/plots/nivo-ada-box-jitter.png
Acronym: POS: with ADA Positive; NEG: without ADA positive; GM: GeoMetric Mean
Note 1: N and GeoMetric mean (GM) are summary of trough concentration for samples without ADA positive
Note 2: The line in the middle of box represents median; the lower and upper lines of the box represent the first and third quartiles (the 25th and 75th percentiles); the lower and upper whiskers represent 1.5 interquartile range (IQR).

Ipilimumab

Ipilimumab trough PK samples were collected on Weeks 4, 10, 13, and 25 in dMMR or MSI-H mCRC patients in the CA209142 combination arm. Trough PK samples collected within +/- 3 days collection window were plotted by their ADA status. As shown in Figure 40, distribution of ipilimumab trough concentrations in patients with positive ipilimumab ADA appeared to be within the trough concentration range observed in patients with negative ipilimumab ADA. However, the sample size for positive trough samples was limited. No positive ipilimumab ADA trough samples were observed beyond week 10.

Figure 40. Time Course of Observed Ipilimumab Trough Concentration by Ipilimumab ADA Status in dMMR or MSI=H mCRC Patients in the CA209142 Combination Arm



Analysis Directory: /global/pkms/data/CA/209/crc-2l-combo-EU/prd/ppk-ipi/final
Program Source: Analysis Directory/R/scripts/ipippk.Rmd
Figure Source: Analysis Directory/R/plots/ipi-ada-box-jitter.png
Acronym: POS: with ADA Positive; NEG: without ADA positive; GM: GeoMetric Mean
Note 1: N and GeoMetric mean (GM) are summary of trough concentration for samples without ADA positive
Note 2: The line in the middle of box represents median; the lower and upper lines of the box represent the first and third quartiles (the 25th and 75th percentiles); the lower and upper whiskers represent 1.5 interquartile range (IQR).

Justification of the Recommended Dose

The recommended dosing regimen for the treatment of adult patients with dMMR or MSI-H mCRC after prior fluoropyrimidine-based combination therapy is 3 mg/kg nivolumab over 30 min plus 1 mg/kg ipilimumab over 30 min every 3 weeks (Q3W) for 4 dosing cycles, then nivolumab 240 mg every 2 weeks over 30 min.

Dose and Schedule

The safety and tolerability results from the dose ranging study in melanoma patients (Study CA209004) and the dose ranging cohort in subjects with non-MSI-H CRC in Study CA209142 informed the selected investigational combination regimen, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W for 4 doses, in dMMR or MSI-H CRC patients.

In Study CA209004, Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W) exceeded the protocol-defined maximum tolerated dose (MTD) and Cohorts 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W) and 2a (3 mg/kg nivolumab+1 mg/kg ipilimumab Q3W) were identified as the MTDs. Therefore, the following 3 combination dose levels were selected for the safety cohort in Study CA209142 in subjects with non-MSI-H mCRC:

- Level 1: 1 mg/kg nivolumab +1 mg/kg ipilimumab Q3W
- Level 2
    - Level 2a: 1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W
    - Level 2a: 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W

While both regimens at Level 2 were deemed tolerable, the combination regimen of 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W was selected for evaluation in MSI-H metastatic CRC subjects in Study CA209142 due to the following considerations:

- Similar clinical activity was observed between the 1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W (n = 17, ORR: 47%) and the 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W (n = 16, ORR: 50%) cohorts in CA209004 (CA209004 CSR, Table 7.2-1)21
- Numerically higher safety events were observed in the 1 mg/kg nivolumab + 3 mg/kg ipilimumab Q3W (drug related Grade 3-4 AEs leading to discontinuation: 4 out of 10 patients) group relative to the 3 mg/kg nivolumab +1 mg/kg ipilimumab Q3W (drug related Grade 3-4 AEs leading to discontinuation: 1 out of 10 patients) group in non-MSI-H mCRC patients in CA209142 (CA209142 CSR, Table S.NH.6.24)12

Additionally, the majority of responses to the combination of nivolumab and ipilimumab occur in the first 12 weeks in CA209004. At the time of initial CA209142 study design, safety data following continuous ipilimumab administration was very limited since the approved ipilimumab monotherapy regimen is every 3 weeks for four doses in the FDA and EMA approved label. Therefore, a total of 4 doses of ipilimumab administration Q3W was chosen for the duration of nivolumab plus ipilimumab combination phase in the first combination cohort of Study CA209142 in dMMR or MSI-H CRC patients after prior fluoropyrimidine-based combination therapy.

Moreover, the maintenance dose of nivolumab 3 mg/kg Q2W was selected for Study CA209142 based upon collective experience of nivolumab monotherapy across multiple tumor types. The analyses of safety, efficacy, and E-R data from the Phase 1 study CA209003 evaluating antitumor activity over a dose range of 0.1 mg/kg to 10 mg/kg Q2W in several tumor types including RCC, NSCLC, and melanoma has shown that nivolumab 3 mg/kg Q2W is active across multiple tumor types. Thus starting at week 12, which is after the completion of the four doses of combined nivolumab and ipilimumab, nivolumab would continue to be administered every two weeks until progression.

The selected dosing regimen, nivolumab 3 mg/kg Q3W + ipilimumab 1 mg/kg Q3W for 4 doses followed by nivolumab 3 mg/kg Q2W maintenance, demonstrated a favourable benefit-risk in Study CA209142 in dMMR or MSI-H mCRC patients after prior fluoropyrimidine-based combination therapy. Compelling efficacy was observed with median PFS of 36.0 months, median OS not reached after a median follow up of 31.5 months (range 27.5 –43.3months), and a BICR-assessed ORR of 59.7%. The safety profile is consistent with safety outcomes observed across other tumour types with the same posology.

Previously, PK modelling and simulations demonstrated that the range of nivolumab systemic exposures resulting from either nivolumab 3 mg/kg Q2W or 240 mg Q2W were similar across a wide range of body weights for nivolumab monotherapy. Based on the current PPK analyses, nivolumab PK following co-administration of ipilimumab 1 mg/kg Q3W was similar to that seen with nivolumab monotherapy. The same conclusions were drawn with the current combination PPK models, similar exposures were predicted for nivolumab 240 mg Q2W and nivolumab 3 mg/kg Q2W monotherapy administered during the maintenance phase following combination nivolumab and ipilimumab therapy, thus supporting the use of nivolumab 240 mg Q2W flat dose maintenance treatment.

Infusion Duration

In Study CA209142, the combination of nivolumab and ipilimumab used a 60 minute infusion duration for nivolumab, and a 90 minute infusion duration for ipilimumab. Reducing the nivolumab infusion time from 60 minutes to 30 minutes, and ipilimumab infusion time from 90 min to 30 min, are supported by the following clinical data.

Nivolumab

The safety of nivolumab 3 mg/kg administered as a 30 min infusion (n=369) or a 60 min infusion (n=368) was assessed in Study CA209153 in patients with previously treated advanced NSCLC. No

clinically meaningful differences were observed in the overall safety profile between the 30 minute and the 60 minute infusion group, including the frequency (2% for both groups) of hypersensitivity/infusion-related reactions (of any cause or treatment-related).

In addition, nivolumab final PK model was used to simulate nivolumab PK profiles in dMMR or MSI-H CRC patients following nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses) via either a 30 min or 60 min nivolumab infusion duration. Equivalent nivolumab PK profiles were observed between a 30 min and 60 min infusion duration (Figure 16).

Ipilimumab

Ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In Study CA184022,25 where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1 - 2) were reported in 1 (1.4%) subject in the 0.3 mg/kg and in 2 (2.8%) subjects in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3 - 4 drug-related hypersensitivity events were reported, and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as a 90 minute infusion in large phase 3 studies, in prostate cancer (Study CA184043) 26 and as adjuvant therapy for stage 3 melanoma (Study CA184029),27 with no infusion reactions occurring in subjects. Administering 1 mg/kg of ipilimumab represents one-tenth of the 10 mg/kg dose.

Additionally, the same combination regimen (3 mg/kg nivolumab over 30 min plus 1 mg/kg ipilimumab over 30 min every 3 weeks (Q3W) for 4 dosing cycles) has been studied in melanoma patients (n=180). The reported hypersensitivity/infusion reactions (all-causality, any grade) was 5.0% (n=9). Grade 3 drug-related hypersensitivity/infusion reactions were reported in 1 subject (0.6%; infusion related reaction) which led to permanent discontinuation of study therapy.

Moreover, ipilimumab final PK model was used to simulate ipilimumab PK profiles in dMMR or MSI-H CRC patients following nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses) via either a 30 min or 90 min ipilimumab infusion duration. Equivalent ipilimumab PK profiles were observed between a 30 min and 90 min infusion duration (Figure 35).

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Exposure-response (E-R) analyses for safety and efficacy in subjects with dMMR or MSI-H metastatic CRC from Study CA209142 were not conducted, as only one dosing regimen was evaluated in dMMR or MSI-H mCRC patients.

2.3.4. Discussion on clinical pharmacology

The Applicant has presented the results from two population PK assessments of nivolumab and ipilimumab with interim and full datasets from its clinical evaluation in patients with mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (CRC). The methodological aspects are adequate to address the objective planned.

A previously developed structural population PK model was implemented to characterize the time-course of nivolumab in dMMR or MSI-H mCRC patients. The Applicant conducted a joint analysis including all available experimental information from clinical trials but showing no differences in terms

of PK parameters between the claimed indications (dMMR or MSI-H mCRC) and previous cancer indications.

Nivolumab

In general, the model (2017) shares the same elements that were identified in previous submissions, showing an adequate description of the data. Then, the MAH conducted a separate analysis (Full Nivolumab popPK model) when data from the CA209142 combination arm was available (2019). A negligible difference could be appreciated between both dataset in the effect of covariates. The discrepancies could be attributed to unprecise parameters (>RSE), but no clinically relevant differences were observed. PPK parameters estimated from the updated PPK analysis are comparable with those from the previous PPK model, indicating that these additional nivolumab concentration data had no impact on PPK model results, and therefore did not change any conclusions from the previous PPK analyses.

No relevant PK differences were observed when the duration of the infusion was evaluated (30 vs 60 min), showing that a shorter infusion times does not anticipate changes in safety or efficacy profile. In addition, the sensitivity analysis revealed the lack of parameter differences by tumor type. Other covariates were evaluated in the forest plot and sensitivity analysis, showing the lack of any clinically relevant effect, except for Best Overall Response: as expected, patients with complete or partial remission (CR or PR) showed a greater decrease in CL compared to non-responders with SD and PD. However, the magnitude of the effect is not considered clinically relevant. The justification might be related to disease progression, where responder patients showed a greater decrease in CL. The hypothetical reason for this observation is that higher CL is associated with greater disease severity. Thus, in subjects when disease condition is improved over time in responders, a decrease in CL was observed. The underlying mechanism is unclear and may be related to decreases in cachexia in subjects who respond to therapy. Nevertheless, no clinical biomarker has been identified to anticipate the classification of individual patients for an optimal dose schedule selection. Differences in exposure across the different exposure endpoints vs the type of patients revealed the lack of any significant/clinical trend or threshold that would help to optimise the efficacy/safety balance. Furthermore, the higher CL of nivolumab when given in combination with ipilimumab 3 mg/kg Q3W was higher (by ~29%) compared to nivolumab monotherapy is not expected to be clinically relevant since the dosing regimen of nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W x 4 doses has demonstrated a significant clinical benefit in melanoma patients. In addition, the sensitivity analyses found that the effects of ADA, baseline albumin (BALB), baseline lactose dehydrogenase (BLDH), and baseline tumor burden on nivolumab CL were either not statistically significant (the 95% CI include 0) or not clinically relevant (≤ 20%). In particular, lower levels of serum ALB are indicative of cancer related cachexia, which causes higher elimination and metabolic turnover of proteins. An association of lower BALB with higher nivolumab CL may therefore be a surrogate for an underlying cachexic condition and a decrease in nivolumab CL may be indicative of decreased cachexia and improvement in disease state. The effect of can reach 24% of subject (ie, 4.0 g/dL) at 5th percentile of BALB value. But the effect is still not clinically relevant (< 20%), because both 5th and 95th percentiles of BALB could fall within 20% of a reference subject if the reference value was chosen as 3.8 g/dL. As well, the sensitivity analysis indicated that the effect of BTSIZE on nivolumab CL was statistically significant but was within 20% of the CL of a reference subject. In general, nivolumab CL was higher in subjects with a higher BTSIZE; however, the magnitude of the effect is not expected to be clinically relevant. Furthermore, the effect of anti-nivolumab antibody positive status on nivolumab CL is not clinically relevant. No clinically relevant difference in nivolumab CL was found in Japanese and non-Japanese subjects.

Ipilimumab

Ipilimumab PK in dMMR or MSI-H mCRC patients is consistent with the known ipilimumab PK characteristics. Based on the results from the forest plot analyses, clinically relevant changes in CL, VC, Q and VP are predicted on patients with extreme BBWT. According to the distribution of ipilimumab exposure in dMMR/MSI-H CRC patients in patients with body weight <50, 50-90, and >90kg demonstrates a roughly clinically relevant increase (>20%) in exposure across the body weight sub-groups compared to patients between 50-90 kg. However, no statistical relationship was established between body weight and clinical responses, indicating that the different exposure in patients with extreme body weights does not explain differences in terms of efficacy.

Sensitivity analyses did not identify any clinically relevant changes in exposure in the evaluated covariates. In the same line as observed for nivolumab, a trend is observed based on the BOR, since CR and PR patients showed a greater decrease in CL compared to SD and PD patients. No clinical biomarker has been identified able to anticipate the classification of individual patients for an optimal dose schedule selection. Differences in exposure across the different exposure endpoints vs the type of patients revealed the lack of any significant/clinical trend or threshold that would help to optimise the efficacy/safety balance. The magnitude of the effect is not considered clinically relevant.
Ipilimumab CL was significantly [95% CI does not include 0] higher in subjects with higher BTSIZE; however, the magnitude of the difference was within the ± 20% boundary and not likely to be clinically relevant. The resulting parameter estimates obtained from this analysis were in good agreement with those obtained in the final model. Ipilimumab CL was significantly [95% CI does not include 0] lower in subjects with higher BALB; however, the magnitude of the difference was within the ± 20% boundary and not likely to be clinically relevant. The resulting parameter estimates obtained from this analysis were in good agreement with those obtained in the final model. Taken together, the data presented on ADA findings suggest that the effect of immunogenicity was not clinically relevant.

Dose selection

For the combination treatment, the clinical data from Study CA209142 and the results of the PPK analysis support the recommended dose of 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W followed by nivolumab 240 mg Q2W in the treatment of subjects with recurrent or metastatic dMMR or MSI-H CRC. As well, for both products, the reduction of the infusion duration from 60 minutes to 30 minutes for Nivolumab and 90 minutes to 30 minutes for Ipilimumab seems adequate based on the simulations and safety data provided and a change in safety or efficacy profile is not anticipated for the proposed combination treatment of patients with mCRC.

Analyses from E-R across multiple monoclonal antibodies including nivolumab have shown that the clearance of these antibodies is associated with the efficacy endpoints investigated. Adequate resolution of the effect of exposure of nivolumab/ipilimumab and their clearance on efficacy would require data from multiple dose levels.

The observed safety profile of nivolumab plus ipilimumab combination is acceptable in subjects with advanced metastatic CRC. The safety profile of nivolumab plus ipilimumab combination in MSI-H metastatic CRC was consistent with safety outcomes for other indications for which the same nivolumab plus ipilimumab combination regimen is approved for use (metastatic RCC).

In summary, while the E-R analyses were not conducted for efficacy or safety endpoints in combination nivolumab + ipilimumab therapy because of lack of dosing range data in the dMMR or MSI-H mCRC patients, the observed data from MSI-H metastatic CRC subjects in Study CA209142 shows a clinically meaningful benefit and acceptable safety profile. These data were supportive of the dosing recommendation for this combination therapy in metastatic CRC patients.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology properties of nivolumab and ipilimumab have been characterised in dMMR or MSI-H mCRC patients using all PK available information from previous clinical trials and the previously developed population PK models for each drug. No clinical concerns remain, and the uncertainties have been properly solved.

2.4. Clinical efficacy

2.4.1. Dose response study

No specific dose response studies were included in this application.

2.4.2. Main study

Title of Study

Study CA209142 - A Phase 2 Clinical Trial of Nivolumab and Nivolumab Plus Ipilimumab in Recurrent and Metastatic Microsatellite High (MSI-H) Colon Cancer (CheckMate 142)

Methods

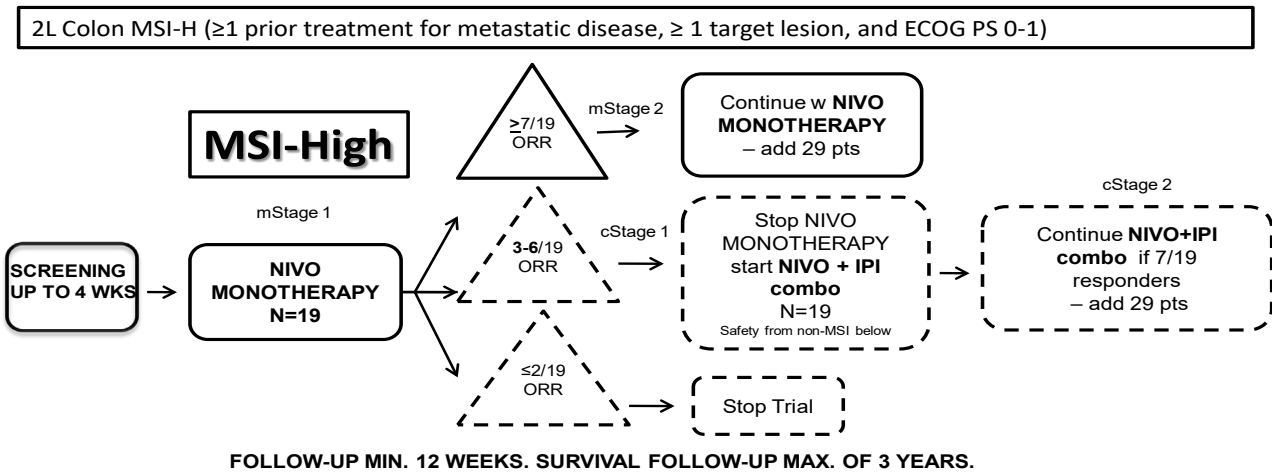
CA209142 (Overman et al. 2018, NCT02060188) is an ongoing Phase 2, open-label, multi-center, multi-cohort study including nivolumab monotherapy or nivolumab combinations in adults with dMMR or MSI-H and pMMR/non-MSI-H unresectable mCRC with an efficacy objective of demonstrating a clinically meaningful ORR > 30% in these distinct subject populations, i.e., dMMR or MSI-H mCRC. The cohorts evaluated in CA209142 were as follows:

- Cohort 1: nivolumab monotherapy in MSI-H mCRC
- Cohort 2: nivolumab + ipilimumab in MSI-H mCRC
- Cohort 3: nivolumab + ipilimumab in first-line MSI-H mCRC
- Cohort 4: nivolumab + ipilimumab + cobimetinib in pMMR/non-MSI-H mCRC
- Cohort 5: nivolumab + BMS-986016 in MSI-H mCRC
- Cohort 6: nivolumab + daratumumab in non-MSI-H mCRC

The interim CSR for CA209142, object of this report, is based on the 18-Aug-2017 clinical database lock (DBL) and presents the results of the subjects with MSI-H/dMMR CRC treated with nivolumab in combination with ipilimumab (cStage1 and cStage2, nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg) cohort (all combination treated, N=119) and the results from a subset of these subjects who had received prior 5-FU, oxaliplatin, and irinotecan (5FU-Oxa-Iri), (N=82).

A later DBL of the combination arm (Cohort 2) was performed on 19-Feb-2019 to provide more mature data and the updated results have been submitted as part of this application.

Figure 41. CA209142 Study Design Schema (MSI-H cohort)



The study consisted of 3 phases: screening, treatment and follow up. Tumor 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 a clinical benefit and was tolerating study drug per investigator assessment.

Study participants

The study population included adults (≥ 18 years) who had disease progression during, after, or had been intolerant to therapy with fluoropyrimidine-based chemotherapy with dMMR or MSI-H mCRC.

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

- Subjects must have signed the approved written informed consent form before the performance of any related procedures and must have been willing to comply with scheduled visits, treatment, tests, tumor biopsies and other requirements
- Histologically confirmed CRC
- **Metastatic or recurrent CRC**
- **Microsatellite instability expression** detected by an accredited laboratory **per local regulations**
- Prior treatment:
    - For subjects with recurrent or metastatic MSI-H CRC:
        - **Progression during, after, or have been intolerant to ≥ 1 line treatment(s) for their metastatic disease**, which must have included, at least,
            - A fluoropyrimidine, and
            - Oxaliplatin or irinotecan,

- 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

- Subject actively refused 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 have been thoroughly documented. The investigator was to discuss each individual subject refusing chemotherapy with the Applicant's medical monitor to confirm eligibility.

- Subjects must have **measurable disease per RECIST 1.1**. Subjects with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enrol provided the lesions had demonstrated clear progression and can be measured accurately
- Subjects willing to comply to provide tumour tissue for PD-L1 expression analysis and other biomarker correlative studies
- **ECOG** performance status of **0-1**
- Prior palliative radiotherapy must have been completed, at least, 2 weeks prior to study drug administration
- Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose:
    - WBC ≥ 2000/µL
    - Neutrophils ≥ 1500/µL
    - Platelets ≥ 100 $x10^3$/µL
    - Haemoglobin > 9.0 g/dL
    - Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (Cockcroft-Gault formula)
    - 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)
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 24h prior to any study drug, they must agree to follow instructions for methods of contraception during the period defined by the protocol and must not be breastfeeding
- Men who are sexually active with WOCBP must agree on methods of contraception during the defined period

Main **exclusion criteria** are defined below:

- **Active brain metastases** or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging evidence of progression for, at least, 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive

doses of systemic corticosteroids (>10 mg/day prednisone or equivalents) for, at least, 2 weeks prior to study drug administration

- Prior malignancy active within the previous 3 years except for locally curable cancers
- Active autoimmune disease
- Any condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration
- **Prior treatment with an anti-PD-1, anti-PD-L1, anti-CTLA-4** antibody or any drug targeting T-cell co-stimulation or immune checkpoints pathways
- Positive for HBV sAg, HCV antibody or VIH
- Allergy to study drugs or history of severe hypersensitivity reaction to any monoclonal antibody

Subject enrolment

CA209142 was originally designed using a single Simon optimal two-stage design including both monotherapy and combination therapy cohorts which meant a sequential enrolment of C1 and C2. Per the protocol, if the ORR was 3-6 out of the first 19 centrally-confirmed MSI-H subjects in C1 mStage 1, C2 cStage 1 would open. Following this, enrolment in C2 cStage 1 was initiated and first patient first treatment (FPFT) took place on 29 May 2015. Enrolment in C2 cStage 1 took place, then, from May to October 2015, and a total of 27 subjects received the investigational product. Of these, 20 were assessed as being MSI-H by the central laboratory. On 18-Feb-2016, confirmation of response in at least 7 of the first 19 subjects who had been assessed as MSI-H by the central laboratory in C2 cStage1 was reached and therefore, C2 cStage 2 was opened for enrolment on 19-Feb-2016 after closure of enrolment of C1 mStage 2.

The original version of the study protocol and SAP specified that the analysis set would be those subjects who had been assessed as being MSI-H by the central laboratory and the target sample size would be 48 subjects, although enrolment was based on local lab determination of dMMR or MSI-H. As the trial was in progress, some challenges and delays in obtaining the MSI status results from the central laboratory were observed, which led to a need for over-enrolment to ensure sufficient number of centrally-confirmed MSI-H subjects were treated. Based on experience form Cohort 1 and the observed rate of unconfirmed dMMR or MSI-H subjects in C2 cStage 1 (approximately 30%), it was estimated that, at least, 70 subjects would need to be enrolled to ensure the planned 48 centrally confirmed subjects. After the criteria for initiating C2 cStage 2 had been met on 18-Feb-2016, enrolment in C2 cStage 2 was initiated. In September of 2016, enrolment in C2 cStage 2 was closed with a total of 119 MSI-H subjects based on the local testing. Among them, 70 subjects were confirmed as MSI-H by the central laboratory.

Treatments

Subjects with DMMR/MSI-H CRC treated with nivolumab in combination with ipilimumab (cStage1 and cStage2) cohort were treated with **nivolumab** administered IV over 60 minutes at **3 mg/kg** combined with **ipilimumab** administered IV over 90 minutes at **1 mg/kg every 3 weeks for 4 doses** followed by **nivolumab** administered IV over 60 minutes at **3 mg/kg every 2 weeks until progression**. By changes included in Revised Protocol version 08 (8 Jun 2020), nivolumab infusion duration was reduced to 30 minutes for all cohorts.

Dose reductions were not permitted. Criteria for dose delays, resumption and treatment discontinuation were included in the protocol.

Treatment would continue until disease progression or unacceptable toxicity.

Based on preliminary data from this study, in subjects with MSI-H mCRC tumours suggest that some subjects achieve response and deepening of response with longer treatment duration. Therefore, a strict stopping rule at 2-years was not considered ideal for CA209-142. Instead, **Revised Protocol 07** (05-Feb-2019), incorporated the option to discontinue treatment after minimum of 24 months of treatment in subjects who had achieved maximum clinical benefit as assessed by the Investigator and described below.

Subjects who attain **all** the following **criteria** would have the option to discontinue treatment due to **maximum clinical benefit**:

- Maximum clinical benefit per Investigator
- Minimum 12 months of treatment after date of first response (PR or CR) if the patient achieved response
- Minimum 24 months between first dose of study treatment and discontinuation for maximum clinical benefit
- No progression since week 12 of study treatment

Re-initiation was an option for subjects who progressed within 1 year (≤ 52 weeks) of discontinuation for maximum clinical benefit, as long as the eligibility **criteria for re-initiation** were met:

- Investigator assessed clinical benefit and no rapid disease progression
- Tolerance of study drug
- Stable performance status
- Adequate blood, liver, kidney and cardiac function per Inclusion criteria 2i (Section 3.3.1)
- Adequate re-initiation screening requirements per Table 5.1-8
- Treatment Re-initiation will not delay an imminent intervention to prevent serious complications of disease progression (eg. CNS metastases)
- Subjects have signed and dated an IRB/IEC approved written informed consent form for re-initiation in accordance with regulatory and institutional guidelines.

Clinical activity of reinitiating study treatment with nivolumab or nivolumab combinations will be evaluated in CA209142.

Objectives

The objectives of the nivolumab in combination with ipilimumab cohort (C2) were as follows:

Primary objective:

- To evaluate the investigator-assessed ORR of nivolumab in combination with ipilimumab in subjects with metastatic dMMR or MSI-H CRC.

Secondary objectives:

- To evaluate the independent radiology review committee (BICR)-assessed ORR of nivolumab in combination with ipilimumab in subjects with metastatic dMMR or MSI-H CRC.
- To evaluate the disease control rate (DCR)

Key exploratory objectives: assessments of safety, PFS and OS, immunogenicity, association between PD-L1 and efficacy, discordance between repeat MSI testing by a central lab and prior MSI testing pep local labs, and evaluation of patient-reported outcomes, including health related quality of life and general health status.

Outcomes/endpoints

- Primary endpoint:
    - **ORR assessed by the investigator**: number of MSI-H subjects with a best overall response (BOR) of confirmed CR or PR, according to RECIST 1.1 criteria, divided by the number of treated MSI-H subjects. The investigator-assessed ORR was further characterized by the **duration of response (DOR)**: time from first confirmed response (CR or PR) to the date of the first documented tumour progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurred first. DOR was computed for subjects with a BOR of confirmed PR or CR.

To assess consistency of ORR, **investigator-assessed ORR** (primary analysis) will be summarized for the following **subgroups** with at least 5 subjects:

- Age (< 65, ≥ 65, ≥ 65 and < 75, ≥ 75)
- Region (US/Canada, Europe, Rest of World).
- Gender (Male, Female)
- Race (white, black, Asian, and other)
- Lynch syndrome (yes/no)
- K-RAS and B-RAF wild-type, K-RAS mutation, B-RAF mutation
- ECOG (0, ≥ 1)
- Time from the initial diagnosis to first dose of nivolumab (0 - < 1, 1 - < 2, 2 - < 3, ≥ 3 years)
- Number of prior therapies (0, 1, 2, 3, ≥ 4)
- Time from most recent prior regimen to first dose of nivolumab (< 3 months, 3 - 6 months, > 6 months)
- Time from date of progression on most recent prior regimen to first dose of nivolumab (< 3 months, 3 - 6 months, > 6 months)

- Secondary endpoints:
    - **ORR assessed by the BICR**: similar analyses as the primary endpoint were performed for the BICR-assessed ORR.
    - **DCR** assessed by the investigator and the BICR will also be reported, defined as the number of subjects with a BOR of confirmed CR or PR or SD lasting, at least, 12 weeks divided by the number of treated subjects.

- Exploratory endpoints:
    - **Safety**: frequency of AEs, SAEs, AEs leading to discontinuation and specific lab abnormalities, graded using the NCI CTCAE version 4.0.
    - **PFS** based on investigator and BICR assessments: time from first dosing date to the date of the first documented progression, as determined per RECIST 1.1, or death due to any cause, whichever occurred first.
    - **OS**: time from first dosing date to the date of death.
    - Serum **ADA** and neutralizing ADA response to nivolumab.
    - Association between baseline PD-L1 expression and safety (AEs) and efficacy (OS, PFS, ORR) for the subgroups:
        - Each PD-L1 status subgroup by 1 and 5% cut off
        - PD-L1 indeterminate, not evaluable or missing subgroup
    - MSI discordance: the discordance rate between repeat MSI testing and prior MSI testing was summarized.
    - PRO: **QLQ-C30** and **EQ-5D.**

PD-L1 expression was defined as the percent of tumor cells with membrane staining in a minimum of 100 evaluable tumour cells per Dako PD-L1 IHC assay (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 values below the cut off were referred to as PD-L1 as negative, respectively.

Sample size

This study consists of 5 cohorts. For the MSI-H cohort (C1 and C2), 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 (C1) or the combination of nivolumab/ipilimumab (C2). 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.

The null hypothesis will be rejected if 20 or more responses are observed in 48 treated subjects in the open arm (nivolumab monotherapy and/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

For nivolumab monotherapy (C1) and nivolumab in combination with ipilimumab (C2) cohorts, the subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered.

Blinding (masking)

This was an open-label study. However, as secondary objectives, the assessment of response and disease progression, for the primary analysis, was determined by an independent radiology review committee (BICR).

Statistical methods

For each treatment arm in the MSI-H cohort (mStage 1 monotherapy and combination therapy, if applicable), one interim analysis of investigator-assessed ORR will be performed on the first 19 treated subjects with confirmed MSI-H CRC. If there are 6 or fewer responses in these first 19 treated subjects, accrual to the corresponding treatment arm will be stopped. Otherwise, approximately 29 additional confirmed MSI-H subjects will be accrued into the corresponding treatment arm to target a total of 48 treated subjects in that arm.

The interim analysis will be performed when all the subjects in nivolumab monotherapy stage 1 (mStage 1) or in combination with ipilimumab stage 1 (cStage 1) complete 24-week follow-up for an assessment of ORR.

The timing of final analysis of either monotherapy or combination therapy will be after a minimum 6 months of follow-up after the last enrolled subject's first dose of study therapy.

In addition, other interim analyses may be conducted to seek initial efficacy signal or for external data disclosure for these cohorts.

C1 mStage 1 had the first patient first treatment (FPFT) on 01 May 2014. Following the initial 2 stage design of the protocol, the number of confirmed responses per investigator assessment in the first 19 subjects of the monotherapy cohort with centrally-confirmed MSI-H was evaluated. At that time (in May-2015), among these 19 centrally-confirmed MSI-H subjects, the number of confirmed responders was 4 and 2 additional subjects 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 best overall response 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 as was later observed. Per the protocol, if the ORR was 3-6 out of the first 19 centrally-confirmed MSI-H subjects in C1 mStage 1, then this cohort would close, and C2 cStage 1 would open. Following this, enrolment in C2 cStage 1 was initiated and FPFT took place on 29-May-2015.

Later evaluation of C1 mStage 1 revealed 7 confirmed responders in the monotherapy cohort, including 4 prior confirmed responders and 2 potential responders later became confirmed responders, plus 1 late responder (at week 60 tumour assessment); therefore, the original protocol criteria for progressing to C1 mStage 2 was reached. As a result, the monotherapy cohort was opened for accrual in C1 mStage 2 (on 30 Oct 2015) after enrolment of C2 cStage 1 was completed.

Enrolment in C2 cStage 1 took place from May to Oct-2015, and a total of 27 subjects received the investigational product. Of these, 20 were assessed as being MSI-H by the central laboratory. On 18-Feb-2016, confirmation of response in ≥ 7 of the first 19 subjects who had been assessed as MSI-H by

the central laboratory in C2 cStage1 was reached and therefore, C2 cStage 2 was opened for enrolment on 19-Feb-2016 after closure of enrolment of C1 mStage 2. The enrolment in C1 and C2 opened sequentially as described above and the two cohorts were in fact conducted independently, each following the protocol-described Simon optimal 2-stage design.

Primary endpoint (investigator-assessed)

The investigator-assessed ORR will be summarized for each cohort by treatment (monotherapy and combination therapy, if applicable). A response rate estimate and corresponding two-sided 95% exact CI will be provided using the method of Clopper-Pearson. For the reporting following a 2-stage design, the method proposed by Atkinson and Brown will be used to estimate a 90% CI. This confidence interval takes into account the group sequential nature of the two-stage Simon design. ORR will be further characterized by the duration of response (DOR) and rate of complete response (CR). DOR will be summarized for subjects who achieve 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), will also be calculated. Investigator-assessed CR will be summarized for each cohort by treatment (monotherapy and combination therapy, if applicable). An estimate of complete response rate (CRR) and corresponding two-sided 95% exact CI will be provided using Clopper-Pearson method.

Sensitivity analyses

As sensitivity analysis, a summary of investigator-assessed ORR based on response evaluable subjects instead of all treated subjects will also be presented.

Another sensitivity analysis will consider a summary of ORR using a classification according to the repeated evaluation performed by a central laboratory.

The following subject-level graphics will also be provided:

For All Treated Subjects, time courses of the following events of interest will be graphically displayed (investigator assessed): first tumour response, tumour progression, last dose received, and death.

For response evaluable subjects, a waterfall plot showing the best reduction from baseline in target lesion based on Investigator assessment will be produced (excluding assessments after PD and assessments after start of subsequent anti-cancer therapy).

Results

Participant flow

Figure 42. CA209142 Study Design Schema and patient disposition

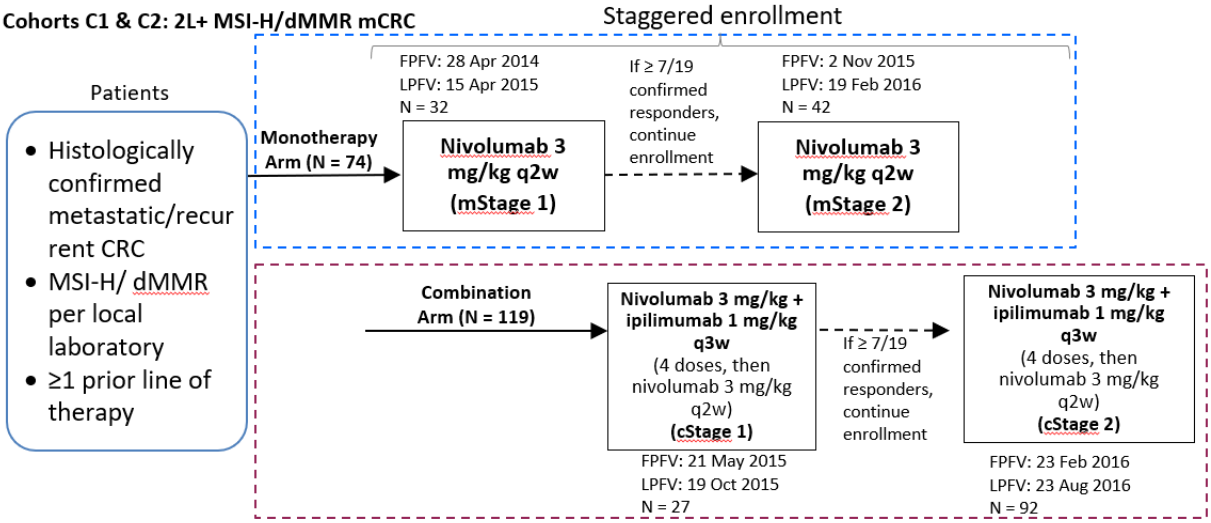


Table 152. Subjects status summary – All enrolled and treated subjects (cut off date 18-Aug-2017)

	Total
SUBJECTS ENROLLED	167
SUBJECTS ENTERING NON-MSI-H COHORT TREATMENT PERIOD (%)	23 (13.8)
SUBJECTS ENTERING MSI-H COHORT TREATMENT PERIOD (%)	119 (71.3)
MSI-H SUBJECTS NOT ENTERING THE TREATMENT PERIOD (%)	25 (15.0)
REASON FOR NOT ENTERING TREATMENT PERIOD (%)	
ADVERSE EVENT	1 (0.6)
SUBJECT WITHDREW CONSENT	1 (0.6)
SUBJECT NO LONGER MEETS STUDY CRITERIA	21 (12.6)
OTHER	2 (1.2)

	All MSI-H Subjects	MSI-H Subjects with Prior 5FU-Oxa-Iri
SUBJECTS	119	82
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	75 (63.0)	53 (64.6)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	44 (37.0)	29 (35.4)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)		
DISEASE PROGRESSION	23 (19.3)	16 (19.5)
STUDY DRUG TOXICITY	16 (13.4)	10 (12.2)
DEATH	1 (0.8)	1 (1.2)
ADVERSE EVENT UNRELATED TO STUDY DRUG	2 (1.7)	2 (2.4)
LOST TO FOLLOW-UP	1 (0.8)	0
OTHER (A)	1 (0.8)	0
SUBJECTS CONTINUING IN THE STUDY (%) (B)	114 (95.8)	78 (95.1)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	5 (4.2)	4 (4.9)

[A] Subject unable to return to site for restaging.
[B] Includes subjects still on treatment and subjects off treatment continuing in the Follow-up period
Percentages based on subjects enrolled

Source: Table S.2.4 and Table S.2.5

A total of 119 subjects were treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg, 82 of whom had received prior treatment with 5FU-Oxa-Iri. At the cut-off date (18-Aug-2017), 75 (63%) subjects were still on treatment of which 53 (64.6%) subjects treated with prior 5FU-Oxa-Iri; at the time of the Feb-2019 DBL, there were 51 (42.9%) of all treated subjects of which 36 (43.9%) subjects treated with prior 5FU-Oxa-Iri that were still receiving treatment.

At the time of the initial interim analysis, 44 (37%) subjects had discontinued treatment and 29 (35.4%) subjects treated with prior 5FU-Oxa-Iri. The most common reason for discontinuing treatment in both groups was disease progression (23 [19.3%] of all treated subjects and 16 [19.5%] of the 5FU-Oxa-Iri group). In the later Feb 2019 DBL, there were 24 additional subjects (17 with prior 5FU Oxa Iri treatment) that discontinued compared with the Aug 2017 DBL. Of these 24 additional subjects that discontinued treatment between the Feb 2019 and Aug 2017 DBLs, the reasons were: disease progression (10 subjects), maximum clinical benefit (7 subjects), subject request to discontinue study treatment (5 subjects), study drug toxicity (1 subject), and "other" (1 subject).

Updated efficacy analyses based on a later DBL (Oct-2020) were provided, with a minimum follow up of 46.9 months. At that time, 14 subjects were still on treatment.

Table 16. End of Treatment Period Subject Status Summary All dMMR/MSI-Combination Therapy Treated Subjects (Nivolumab 3 mg/kg with Ipilimumab 1 mg/kg) (cut off date 19 Feb 2019)

	All Subjects	Subjects with Prior 5FU-Oxa-Iri
SUBJECTS	119	82
SUBJECTS CONTINUING IN THE TREATMENT PERIOD (%)	51 (42.9)	36 (43.9)
SUBJECTS NOT CONTINUING IN THE TREATMENT PERIOD (%)	68 (57.1)	46 (56.1)
REASON FOR NOT CONTINUING IN THE TREATMENT PERIOD (%)		
DISEASE PROGRESSION	33 (27.7)	24 (29.3)
STUDY DRUG TOXICITY	17 (14.3)	11 (13.4)
DEATH	1 (0.8)	1 (1.2)
ADVERSE EVENT UNRELATED TO STUDY DRUG	2 (1.7)	2 (2.4)
SUBJECT REQUEST TO DISCONTINUE STUDY TREATMENT	5 (4.2)	4 (4.9)
LOST TO FOLLOW-UP	1 (0.8)	0
MAXIMUM CLINICAL BENEFIT	7 (5.9)	3 (3.7)
OTHER	2 (1.7)	1 (1.2)
SUBJECTS CONTINUING IN THE STUDY (%) (A)	112 (94.1)	76 (92.7)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	7 (5.9)	6 (7.3)

Percentages based on subjects entering period
(A) Includes subjects still on treatment and subjects off treatment continuing in the Follow-up period
Program Source: /projects/bms218374/stats/feb2019/prog/tables/rt-ds-offtrt.sas 21MAR2019:08:52:01

Recruitment

The enrolment period into the combination cohort (for MSI-H subjects who have been previously treated) lasted approximately 15 months (May-2015 to Oct-2015 for C2 cStage 1 and Feb-2016 to Aug-2016 for C2 cStage 2). The study was conducted at 31 sites in 8 countries (Australia, Belgium, Canada, France, Ireland, Italy, Spain, and the United States of America).

The primary DBL for the combination cohort occurred on 18-Aug-2017 and an updated DBL occurred on 19-Feb-2019. The Feb-2019 DBL, provides an overall minimum follow-up of 27.5 months for subjects enrolled and treated in Cohort 2 of CA209142.

Conduct of the study

The original protocol for this study was dated 18-Nov-2013. Six global amendments and 3 country-specific amendments were issued for this study. More cohorts were added to CA209142 study over time by these amendments to evaluate treatment options that were not related to the current submission.

Table 17. Summary of changes to Protocol CA209142 relevant for Cohort 2

Document (Sites)/Date	**Summary of Change**	**Subjects enrolled at time of protocol amendment in C2**
Original Protocol / 18-Nov-2013		
Revised Protocol 01 (Amendment 01) / 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.	0
Revised Protocol 01a (Amendment 02) / 01-Apr-2014	Based on a request from the French health authority, a urinalysis per local standard of care (including testing for proteinuria 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.	0
Revised Protocol 02 (Amendment 03) / 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.	35
Revised Protocol 01b / 23-Apr-2014	French specific Amendment to incorporate Amendment 03	39
Revised Protocol 03 (Amendment 4) / 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	95

Document (Sites)/Date	Summary of Change	Subjects enrolled at time of protocol amendment in C2
	added. Other minor details were modified to increase comprehensibility.	
Revised Protocol 01c / 08-Jun-2015	French specific amendment to incorporate Amendment 4	119
Revised Protocol 04 (Amendment 05)/ 10-Aug-2016	The main purpose of this amendment is to add a cohort of subjects who have had no prior treatment of their metastatic CRC. Subjects in this cohort, C3 Cohort, are to be treated with nivolumab + ipilimumab. MSI Status determination was further defined. Other minor details were modified to increase comprehensibility.	Completed
Revised Protocol 04a (Amendment 06) / 11-Aug-2016	The purpose of this site-specific amendment is to add cohort C4 to the study. The C4 Cohort consists of subjects with non-MSI-H mCRC who are to be treated with nivolumab + ipilimumab + cobimetinib.	Completed
Revised Protocol 04b (Amendment 07) / 18-Nov-2016	This site-specific amendment was primarily written to ensure safety monitoring for subjects receiving cobimetinib (COTELLIC) as outlined in the prescribing information. Entry criteria and safety assessments were added to rule-out subjects with, and to monitor for, serous retinopathy, retinal vein occlusion, and rhabdomyolysis.	Completed
Revised Protocol 05 (Amendment 08) / 28-Nov-2016	The main purpose of this amendment is to add two treatment arms, consisting of nivolumab combined with an anti-LAG3 agent (BMS-986016) and nivolumab combined with daratumumab.	Completed
Revised Protocol 06 and Revised Protocol 04c (Amendment 09) / 19-Apr-2017	This purpose of this amendment is to add information to change the dose of BMS-986016 in Cohort C5, to align with the daratumumab program standards, and to add clarity to various sections of the protocol.	Completed

Protocol deviations

After review of the reported protocol deviations, it was determined that there was no impact on the interpretability of study results.

Relevant protocol deviations (significant protocol deviations that were programmable and could potentially affect the interpretability of study results) were reported in 1 (0.8%) of all combination treated subjects. Relevant protocol deviations were predefined in the SAP. There were **no relevant**

protocol deviations at study entry. The only relevant protocol deviation during the treatment period was prohibited anti-cancer therapy: **one** subject with prior 5FU-Oxa-Iri treatment received bicalutamide for the treatment of prostate cancer.

Baseline data

Table 18. Baseline demographic characteristics – All combination treated subjects

	All Subjects	Subjects with Prior 5FU-Oxa-Iri
	N = 119	N = 82
AGE		
N	119	82
MEAN	56.6	56.2
MEDIAN	58.0	57.5
MIN, MAX	21, 88	26, 88
Q1, Q3	45.0, 67.0	45.0, 66.0
STANDARD DEVIATION	13.79	12.77
AGE CATEGORIZATION (%)		
< 65	81 (68.1)	57 (69.5)
>= 65 AND < 75	27 (22.7)	20 (24.4)
>= 75	11 (9.2)	5 (6.1)
>= 65	38 (31.9)	25 (30.5)
GENDER (%)		
MALE	70 (58.8)	51 (62.2)
FEMALE	49 (41.2)	31 (37.8)
RACE (%)		
WHITE	109 (91.6)	78 (95.1)
BLACK OR AFRICAN AMERICAN	2 (1.7)	0
ASIAN	3 (2.5)	1 (1.2)
AMERICAN INDIAN OR ALASKA NATIVE	1 (0.8)	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0
OTHER	4 (3.4)	3 (3.7)
ETHNICITY (%)		
HISPANIC OR LATINO	2 (1.7)	2 (2.4)
NOT HISPANIC OR LATINO	40 (33.6)	24 (29.3)
NOT REPORTED	77 (64.7)	56 (68.3)

Source: Table S.3.1

Table 19. Baseline disease characteristics – All combination treated subjects

	All Subjects	Subjects with Prior 5FU-Oxa-Iri
	N = 119	N = 82
WEIGHT (KG)		
N	119	82
MEAN	73.69	73.82
MEDIAN	72.40	72.50
MIN, MAX	41.0 , 136.9	42.0 , 124.2
Q1, Q3	60.40 , 83.00	62.50 , 83.00
STANDARD DEVIATION	18.046	17.329
PERFORMANCE STATUS (ECOG) [%]		
0	54 (45.4)	39 (47.6)
1	65 (54.6)	43 (52.4)
SMOKING STATUS		
CURRENT/FORMER	63 (52.9)	44 (53.7)
NEVER SMOKER	55 (46.2)	37 (45.1)
UNKNOWN	1 (0.8)	1 (1.2)
REGION		
US/CANADA	34 (28.6)	21 (25.6)

EUROPE	76 (63.9)	56 (68.3)
REST OF THE WORLD	9 (7.6)	5 (6.1)
DISEASE STAGE AT INITIAL DIAGNOSIS		
STAGE I	0	0
STAGE II	14 (11.8)	9 (11.0)
STAGE III	52 (43.7)	36 (43.9)
STAGE IV	53 (44.5)	37 (45.1)
DISEASE STAGE AT STUDY ENTRY		
STAGE I	0	0
STAGE II	0	0
STAGE III	0	0
STAGE IV	119 (100.0)	82 (100.0)
PRIMARY TUMOR LOCATION		
RECTUM	6 (5.0)	5 (6.1)
LEFT COLON	21 (17.6)	15 (18.3)
RIGHT COLON	65 (54.6)	43 (52.4)
TRANSVERSE COLON	15 (12.6)	11 (13.4)
COLON NOS	3 (2.5)	1 (1.2)
SIGMOID	9 (7.6)	7 (8.5)

Iri	All Subjects N = 119	Subjects with Prior 5FU-Oxa- N = 82
BRAF/KRAS MUTATION STATUS		
KRAS/BRAF WILD-TYPE	31 (26.1)	21 (25.6)
BRAF MUTATION	29 (24.4)	16 (19.5)
KRAS MUTATION	44 (37.0)	38 (46.3)
UNKNOWN	15 (12.6)	7 (8.5)
LYNCH SYNDROME		
YES	35 (29.4)	26 (31.7)
NO	31 (26.1)	22 (26.8)
UNKNOWN	53 (44.5)	34 (41.5)
LOCAL MICROSATELLITE INSTABILITY METHOD		
PCR	43 (36.1)	30 (36.6)
IHC	53 (44.5)	34 (41.5)
PCR/IHC	23 (19.3)	18 (22.0)
UNKNOWN	0	0
LOCAL MICROSATELLITE INSTABILITY RESULT		
MSI-H	118 (99.2)	81 (98.8)
MSI-H/MSI-S (1)	1 (0.8)	1 (1.2)
MSI-L	0	0
MSI-S	0	0
CENTRAL MICROSATELLITE INSTABILITY RESULT		
MSI-H	62 (52.1)	39 (47.6)
MSI-L	4 (3.4)	3 (3.7)
MSI-S	22 (18.5)	17 (20.7)
MSI-L/MSI-S	1 (0.8)	1 (1.2)
NOT REPORTED	30 (25.2)	22 (26.8)
TIME FROM INITIAL DIAGNOSIS TO FIRST DOSE		
N	119	82
MEDIAN (MIN - MAX)	1.62 (0.1 - 19.6)	2.15 (0.4 - 19.6)
< 1 YEAR	34 (28.6)	10 (12.2)
1- < 2 YEARS	34 (28.6)	27 (32.9)
2- < 3 YEARS	21 (17.6)	18 (22.0)
3- < 4 YEARS	13 (10.9)	12 (14.6)
4- < 5 YEARS	5 (4.2)	5 (6.1)
>= 5 YEARS	12 (10.1)	10 (12.2)

(1) 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 20. Pre-Treatment Tumour Assessments- All Combination Treated Subjects

	All Subjects	Subjects with Prior 5FU-Oxa-Iri
	N = 119	N = 82
PER INVESTIGATOR		
SUBJECTS WITH AT LEAST ONE LESION (%)	119 (100.0)	82 (100.0)
SITE OF LESION (A) (B) (%)		
BONE WITH SOFT TISSUE COMPONENT	1 (0.8)	0
BONE, NO SOFT TISSUE COMPONENT	5 (4.2)	5 (6.1)
CHEST WALL	2 (1.7)	1 (1.2)
GASTRIC	3 (2.5)	2 (2.4)
INTESTINE	5 (4.2)	3 (3.7)
LIVER	51 (42.9)	36 (43.9)
LUNG	31 (26.1)	22 (26.8)
LYMPH NODE	74 (62.2)	54 (65.9)
MEDIASTINUM	3 (2.5)	1 (1.2)
OTHER	27 (22.7)	21 (25.6)
PANCREAS	2 (1.7)	1 (1.2)
PELVIS	8 (6.7)	6 (7.3)
PERITONEUM	40 (33.6)	30 (36.6)
PLEURA	6 (5.0)	4 (4.9)
SKIN/SOFT TISSUE	9 (7.6)	8 (9.8)
SPLEEN	4 (3.4)	4 (4.9)
VISCERAL, ADRENAL	6 (5.0)	2 (2.4)
VISCERAL, OTHER	8 (6.7)	5 (6.1)
NUMBER OF SITES WITH AT LEAST ONE LESION (B) (%)		
1	30 (25.2)	19 (23.2)
2	36 (30.3)	22 (26.8)
3	35 (29.4)	27 (32.9)
4	13 (10.9)	10 (12.2)
>=5	5 (4.2)	4 (4.9)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)		
N	119	82
MEDIAN (MIN - MAX)	86.0 (11 - 295)	98.0 (11 - 295)

	All Subjects	Subjects with Prior 5FU-Oxa-Iri
	N = 119	N = 82
PER BICR		
SUBJECTS WITH AT LEAST ONE LESION (%)	117 (98.3)	80 (97.6)
SITE OF LESION (A) (B) (%)		
ABDOMINAL LYMPH NODE	42 (35.3)	28 (34.1)
ABDOMINAL WALL	10 (8.4)	9 (11.0)
ADRENAL GLAND	8 (6.7)	4 (4.9)
AXILLARY LYMPH NODE	2 (1.7)	2 (2.4)
BONE	1 (0.8)	1 (1.2)
CHEST WALL	1 (0.8)	1 (1.2)
COLON	5 (4.2)	4 (4.9)
COMMON ILIAC LYMPH NODE	6 (5.0)	4 (4.9)
EXTERNAL ILIAC LYMPH NODE	4 (3.4)	4 (4.9)
HILAR LYMPH NODE	5 (4.2)	4 (4.9)
LIVER	48 (40.3)	34 (41.5)
LUMBAR VERTEBRA	2 (1.7)	2 (2.4)
LUNG	32 (26.9)	23 (28.0)
LYMPH NODE	8 (6.7)	4 (4.9)
MEDIASTINAL LYMPH NODE	16 (13.4)	11 (13.4)
MEDIASTINUM	2 (1.7)	2 (2.4)
MESENTERIC LYMPH NODE	9 (7.6)	4 (4.9)
MESENTERY	12 (10.1)	8 (9.8)
MUSCLE	3 (2.5)	3 (3.7)
OTHER	1 (0.8)	1 (1.2)
PANCREAS	1 (0.8)	0
PARA-AORTIC LYMPH NODE	13 (10.9)	11 (13.4)
PELVIC LYMPH NODE	3 (2.5)	3 (3.7)
PELVIS	3 (2.5)	1 (1.2)
PERITONEUM	33 (27.7)	25 (30.5)
PLEURA	1 (0.8)	1 (1.2)
RECTUM	2 (1.7)	2 (2.4)
RETROCRURAL LYMPH NODE	1 (0.8)	1 (1.2)
RETROPERITONEAL LYMPH NODE	27 (22.7)	20 (24.4)
RETROPERITONEUM	6 (5.0)	4 (4.9)
SKIN	1 (0.8)	1 (1.2)
SOFT TISSUE	3 (2.5)	2 (2.4)
SPLEEN	7 (5.9)	6 (7.3)
STOMACH	2 (1.7)	2 (2.4)
SUPRACLAVICULAR LYMPH NODE	2 (1.7)	1 (1.2)
THORACIC LYMPH NODE	7 (5.9)	5 (6.1)

	A	
All Subjects	Subjects with Prior 5FU-Oxa-Iri	
	N = 119	N = 82
NUMBER OF SITES WITH AT LEAST ONE LESION (B) (%)		
1	30 (25.2)	17 (20.7)
2	31 (26.1)	23 (28.0)

3	21 (17.6)	12 (14.6)
4	16 (13.4)	13 (15.9)
>=5	19 (16.0)	15 (18.3)
SUM OF REFERENCE DIAMETERS OF TARGET LESIONS (MM)		
N	111	75
MEDIAN (MIN - MAX)	73.0 (16 - 302)	88.0 (16 - 302)

(A) Subjects may have lesions at more than one site
(B) Includes both target and non-target lesions

Medical history

Among all combination treated subjects, abnormal physical examination findings were reported at baseline for 37.8% of subjects. The most frequent body systems with abnormal physical exam findings at baseline were abdomen (15.1%), and skin and musculoskeletal (both at 8.4%).

Among those subjects previously treated with 5FU-Oxa-Iri, abnormal physical examination findings were reported at baseline for 35.4% of subjects. The most frequent body systems with abnormal physical exam findings at baseline were abdomen (18.3%), extremities (8.5%) and skin and musculoskeletal (both at 7.3%).

In all combination treated subjects, the most frequent (> 10%) pre-treatment events were abdominal pain (18.5%), back pain (14.3%), diarrhea (11.8%), constipation (10.9%) and anaemia (10.9%).

Previous treatments

The majority of all combination treated subjects (76.5%) and as well as those subjects receiving prior 5FU-Oxa-Iri (98.8%), received 2 or more prior lines or regimens of systemic cancer therapy.

Table 21. Prior Cancer Therapy Summary - All Combination Treated Subjects

	Number of Subjects (%)	
	All Subjects	Subjects with Prior 5FU-Oxa-Iri
	N = 119	N = 82
REGIMEN SETTING (A)		
ADJUVANT THERAPY	61 (51.3)	47 (57.3)
METASTATIC DISEASE	107 (89.9)	82 (100.0)
NEO-ADJUVANT THERAPY	8 (6.7)	6 (7.3)
NUMBER OF PRIOR REGIMEN RECEIVED		
0	1 (0.8)	0
1	27 (22.7)	1 (1.2)
2	43 (36.1)	35 (42.7)
3	29 (24.4)	27 (32.9)
>=4	19 (16.0)	19 (23.2)
TYPE OF PRIOR THERAPY RECEIVED (A)		
OXALIPLATIN	111 (93.3)	82 (100.0)
IRINOTECAN	87 (73.1)	82 (100.0)
5FU (FLUOROURACIL, CAPECITABINE)	118 (99.2)	82 (100.0)
VEGF-INHIBITORS (BEVACIZUMAB, AFLIBERCEPT, RAMUCIRUMAB)	68 (57.1)	58 (70.7)
EGFR INHIBITORS (CETUXIMAB, PANITUMUMAB)	35 (29.4)	29 (35.4)
REGORAFENIB	11 (9.2)	11 (13.4)
TAS-102	2 (1.7)	2 (2.4)
IMMUNOTHERAPY	0	0
OTHER -EXPERIMENTAL DRUGS	3 (2.5)	2 (2.4)
OTHER -CHEMOTHERAPY	8 (6.7)	6 (7.3)
SUBJECT WITH PRIOR 5FU + OXALIPLATIN + IRINOTECAN	82 (68.9)	82 (100.0)
TIME FROM COMPLETION OF MOST RECENT PRIOR THERAPY REGIMEN TO START OF TREATMENT		
< 3 MONTHS	84 (70.6)	63 (76.8)
3-6 MONTHS	17 (14.3)	8 (9.8)
> 6 MONTHS	17 (14.3)	11 (13.4)
NOT REPORTED	1 (0.8)	0

TIME FROM DATE OF PROGRESSION ON MOST RECENT PRIOR THERAPY TO START OF TREATMENT		
< 3 MONTHS	84 (70.6)	60 (73.2)
3-6 MONTHS	11 (9.2)	9 (11.0)
> 6 MONTHS	8 (6.7)	6 (7.3)
NOT REPORTED	16 (13.4)	7 (8.5)
PRIOR SURGERY RELATED TO CANCER		
YES	113 (95.0)	77 (93.9)
NO	6 (5.0)	5 (6.1)
PRIOR RADIOTHERAPY		
YES	20 (16.8)	17 (20.7)
NO	99 (83.2)	65 (79.3)

(A) Some Subjects may have been treated with more than 1 type of therapy
Source: Table S.3.6

At **19 Feb2019 DBL**, key baseline demographics and disease characteristics remained the same.

Updates to baseline disease characteristics for combination treated subjects included the following:

•There were 2 subjects who were reported as "colon not otherwise specified (NOS)" as primary tumor location in the CA209142 CSR that were reported as "left colon" (1 subject) and as "sigmoid" (1 subject) in the Feb-2019 DBL.

•There was 1 subject who was reported as unknown BRAF/KRAS mutation status in the CA209142 CSR that was reported as having BRAF mutation in the Feb-2019 DBL.

•There were 4 subjects who were reported as unknown status for Lynch syndrome in the CA209142 CSR that were reported as not having Lynch Syndrome in the Feb-2019 DBL.

Table 22. Baseline Disease Characteristics - All dMMR/MSI-H Combination Therapy Treated Subjects (Nivolumab 3 mg/kg with Ipilimumab 1 mg/kg)

	Number of Subjects (%)	
	All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82
SMOKING STATUS		
CURRENT/FORMER	63 (52.9)	44 (53.7)
NEVER SMOKER	55 (46.2)	37 (45.1)
UNKNOWN	1 (0.8)	1 (1.2)
REGION		
US/CANADA	34 (28.6)	21 (25.6)
EUROPE	76 (63.9)	56 (68.3)
REST OF THE WORLD	9 (7.6)	5 (6.1)
DISEASE STAGE AT INITIAL DIAGNOSIS		
STAGE I	0	0
STAGE II	14 (11.8)	9 (11.0)
STAGE III	52 (43.7)	36 (43.9)
STAGE IV	53 (44.5)	37 (45.1)
DISEASE STAGE AT STUDY ENTRY		
STAGE I	0	0
STAGE II	0	0
STAGE III	0	0
STAGE IV	119 (100.0)	82 (100.0)
PRIMARY TUMOR LOCATION		
RECTUM	6 (5.0)	5 (6.1)
LEFT COLON	22 (18.5)	16 (19.5)
RIGHT COLON	65 (54.6)	43 (52.4)
TRANSVERSE COLON	15 (12.6)	11 (13.4)
COLON NOS	1 (0.8)	0
SIGMOID	10 (8.4)	7 (8.5)
BRAF/KRAS MUTATION STATUS		
KRAS/BRAF WILD-TYPE	31 (26.1)	21 (25.6)
BRAF MUTATION	30 (25.2)	16 (19.5)
KRAS MUTATION	44 (37.0)	38 (46.3)
UNKNOWN	14 (11.8)	7 (8.5)

LYNCH SYNDROME		
YES	35 (29.4)	26 (31.7)
NO	35 (29.4)	25 (30.5)
UNKNOWN	49 (41.2)	31 (37.8)
LOCAL MICROSATELLITE INSTABILITY METHOD		
PCR	43 (36.1)	30 (36.6)
IHC	53 (44.5)	34 (41.5)
PCR/IHC	23 (19.3)	18 (22.0)
UNKNOWN	0	0
LOCAL MICROSATELLITE INSTABILITY RESULT		
MSI-H	118 (99.2)	81 (98.8)
MSI-H/MSI-S (1)	1 (0.8)	1 (1.2)
MSI-L	0	0
MSI-S	0	0
CENTRAL MICROSATELLITE INSTABILITY RESULT		
MSI-H	69 (58.0)	45 (54.9)
MSI-H/MSI-S	1 (0.8)	0
MSI-L	4 (3.4)	3 (3.7)
MSI-S	23 (19.3)	18 (22.0)
MSI-L/MSI-S	1 (0.8)	1 (1.2)
NOT REPORTED	21 (17.6)	15 (18.3)
TIME FROM INITIAL DIAGNOSIS TO FIRST DOSE		
N	119	82
MEDIAN (MIN - MAX)	1.62 (0.1 - 19.6)	2.15 (0.4 - 19.6)
< 1 YEAR	34 (28.6)	10 (12.2)
1- < 2 YEARS	34 (28.6)	27 (32.9)
2- < 3 YEARS	21 (17.6)	18 (22.0)
3- < 4 YEARS	13 (10.9)	12 (14.6)
4- < 5 YEARS	5 (4.2)	5 (6.1)
>= 5 YEARS	12 (10.1)	10 (12.2)

Prior cancer therapies for the current Feb-2019 DBL were similar to the results from the previous DBL (Aug-2017). There were 82 subjects that were still reported as having received prior 5-fluorouracil-irinotecan-oxaliplatin (5FU-Oxa-Iri).

Numbers analysed

The all combination treated population, which includes a subpopulation of subjects who had received prior 5FU-Oxa-Iri, was the primary population used for efficacy and safety analyses.

Table 23. Analysis Populations in CA209142 Cohort 2

Population	Total N
All Combination Treated Subjects: All MSI-H subjects by local testing who received at least one dose of study medication.	119
All Combination Treated Subjects with Prior 5FU-Oxaliplatin-Irinotecan: A subset population of all combination treated subjects who have received prior 5FU-Oxa-Iri	82
All Combination Treated Subjects without Prior 5FU-Oxaliplatin-Irinotecan: A subset population of all combination treated subjects who have not received prior 5FU-Oxa-Iri	37
All BICR Response Evaluable Subjects: All Combination Treated Subjects who have baseline and at least one on-study evaluable tumour measurement per BICR.	111
All Investigator Response Evaluable Subjects: All Combination Treated Subjects who have baseline and at least one on-study evaluable tumour measurement per investigator.	115
All Immunogenicity Subjects: All nivolumab + ipilimumab-treated subjects with baseline and at least 1 post-baseline assessment for ADA.	109 ADA evaluable for nivolumab; 107 ADA evaluable for ipilimumab
All PD-L1 Evaluable Subjects: All Combination Treated Subjects with quantifiable baseline PD-L1 expression.	102
Modified population: all combination treated subjects excluding those who had not received previous treatment in the metastatic setting	109

Outcomes and estimation

Nivolumab in combination with ipilimumab demonstrated improved ORRs per investigator and per BICR in subjects with recurrent or metastatic dMMR/MSI-H CRC who had progression during or after, or have been intolerant to ≥ 1 line of treatment(s) for their metastatic disease. Efficacy endpoints related to tumour response were assessed by the investigator and the BICR based on RECIST 1.1 criteria.

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.

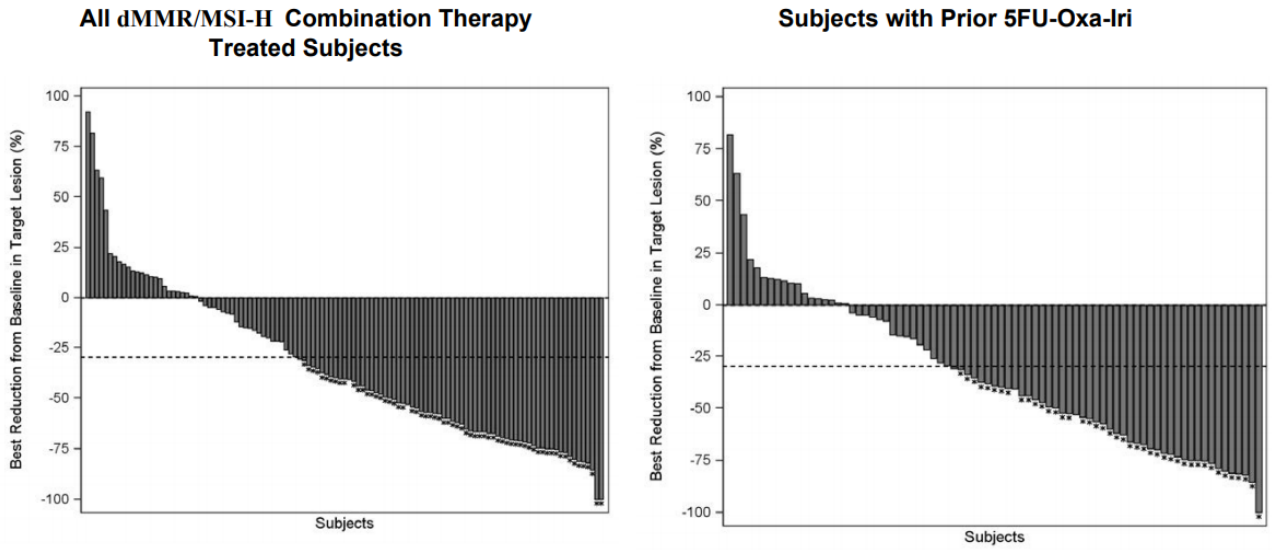
The investigator-assessed **ORR** using RECIST 1.1 are reported in table 24.

Table 24. Best Overall Response per Investigator Assessment - All Combination Treated Subjects

	Number of Subjects (%)	
	All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82
BEST OVERALL RESPONSE (A):		
COMPLETE RESPONSE (CR)	4 (3.4)	2 (2.4)
(95% CI)	(0.9, 8.4)	(0.3, 8.5)
PARTIAL RESPONSE (PR)	61 (51.3)	41 (50.0)
(95% CI)	(41.9, 60.5)	(38.7, 61.3)
STABLE DISEASE (SD)	37 (31.1)	28 (34.1)
PROGRESSIVE DISEASE (PD)	14 (11.8)	8 (9.8)
UNABLE TO DETERMINE (UTD)	3 (2.5)	3 (3.7)
OBJECTIVE RESPONSE RATE (B)	65/119 (54.6%)	43/82 (52.4%)
(95% CI)	(45.2, 63.8)	(41.1, 63.6)
DISEASE CONTROL RATE (C)	95/119 (79.8%)	67/82 (81.7%)
(95% CI)	(71.5, 86.6)	(71.6, 89.4)

(A) Per RECIST 1.1 criteria
(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

Figure 43. Waterfall Plot of Best Reduction from Baseline in Sum of Diameters of Target Lesions per Investigator - All Combination Treated 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%.

Table 25. Objective Response Rate (per BICR) by Subsets

		OBJECTIVE RESPONSE RATE (%) (A) 95% CI	
		All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82
AGE CATEGORIZATION			
	< 65 YEARS	48/81 (59.3%) (47.8, 70.1)	34/57 (59.6%) (45.8, 72.4)
	>= 65 YEARS	17/38 (44.7%) (28.6, 61.7)	9/25 (36.0%) (18.0, 57.5)
	>= 65 AND < 75 YEARS	14/27 (51.9%) (31.9, 71.3)	8/20 (40.0%) (19.1, 63.9)
	>= 75 YEARS	3/11 (27.3%) (6.0, 61.0)	1/5 (20.0%) (0.5, 71.6)
REGION			
	US/CANADA	16/34 (47.1%) (29.8, 64.9)	8/21 (38.1%) (18.1, 61.6)
	EUROPE	43/76 (56.6%) (44.7, 67.9)	31/56 (55.4%) (41.5, 68.7)
	REST OF WORLD	6/9 (66.7%) (29.9, 92.5)	4/5 (80.0%) (28.4, 99.5)
GENDER			
	MALE	40/70 (57.1%) (44.7, 68.9)	29/51 (56.9%) (42.2, 70.7)
	FEMALE	25/49 (51.0%) (36.3, 65.6)	14/31 (45.2%) (27.3, 64.0)
RACE			
	WHITE	61/109 (56.0%) (46.1, 65.5)	42/78 (53.8%) (42.2, 65.2)
	OTHER	1/5 (20.0%) (0.5, 71.6)	1/3 (33.3%) (0.8, 90.6)
LYNCH SYNDROME			
	YES	25/35 (71.4%) (53.7, 85.4)	19/26 (73.1%) (52.2, 88.4)
	NO	15/31 (48.4%) (30.2, 66.9)	9/22 (40.9%) (20.7, 63.6)
	UNKNOWN	25/53 (47.2%) (33.3, 61.4)	15/34 (44.1%) (27.2, 62.1)
KRAS/BRAF MUTATION STATUS			
	KRAS/BRAF WILD-TYPE	17/31 (54.8%) (36.0, 72.7)	9/21 (42.9%) (21.8, 66.0)
	BRAF MUTATION	16/29 (55.2%) (35.7, 73.6)	9/16 (56.3%) (29.9, 80.2)
	KRAS MUTATION	25/44 (56.8%) (41.0, 71.7)	22/38 (57.9%) (40.8, 73.7)
	UNKNOWN	7/15 (46.7%) (21.3, 73.4)	3/7 (42.9%) (9.9, 81.6)
BASELINE ECOG PERFORMANCE STATUS			
	0	30/54 (55.6%) (41.4, 69.1)	20/39 (51.3%) (34.8, 67.6)
	>= 1	35/65 (53.8%) (41.0, 66.3)	23/43 (53.5%) (37.7, 68.8)
TIME FROM INITIAL DIAGNOSIS TO FIRST DOSE			
	< 1 YEAR	22/34 (64.7%) (46.5, 80.3)	8/10 (80.0%) (44.4, 97.5)
	1 - < 2 YEARS	21/34 (61.8%) (43.6, 77.8)	17/27 (63.0%) (42.4, 80.6)
	2 - < 3 YEARS	9/21 (42.9%) (21.8, 66.0)	7/18 (38.9%) (17.3, 64.3)
	>= 3 YEARS	13/30 (43.3%) (25.5, 62.6)	11/27 (40.7%) (22.4, 61.2)

		All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82
NUMBER OF PRIOR SYSTEMIC REGIMEN RECEIVED			
	1	17/27 (63.0%) (42.4, 80.6)	0/1 (0.0, 97.5)
	2	25/43 (58.1%) (42.1, 73.0)	21/35 (60.0%) (42.1, 76.1)
	3	15/29 (51.7%) (32.5, 70.6)	15/27 (55.6%) (35.3, 74.5)
	>= 4	7/19 (36.8%) (16.3, 61.6)	7/19 (36.8%) (16.3, 61.6)
TIME FROM COMPLETION OF MOST RECENT PRIOR THERAPY REGIMEN TO TREATMENT			
	< 3 MONTHS	39/84 (46.4%) (35.5, 57.6)	31/63 (49.2%) (36.4, 62.1)
	3 - 6 MONTHS	14/17 (82.4%) (56.6, 96.2)	6/8 (75.0%) (34.9, 96.8)
	> 6 MONTHS	11/17 (64.7%) (38.3, 85.8)	6/11 (54.5%) (23.4, 83.3)
TIME FROM PROGRESSION ON MOST RECENT PRIOR THERAPY TO TREATMENT			
	< 3 MONTHS	42/84 (50.0%) (38.9, 61.1)	30/60 (50.0%) (36.8, 63.2)
	3 - 6 MONTHS	8/11 (72.7%) (39.0, 94.0)	6/9 (66.7%) (29.9, 92.5)
	> 6 MONTHS	4/8 (50.0%) (15.7, 84.3)	3/6 (50.0%) (11.8, 88.2)
	NOT REPORTED	11/16 (68.8%) (41.3, 89.0)	4/7 (57.1%) (18.4, 90.1)

(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

Secondary Endpoints

BICR -assessed ORR

The secondary endpoint of BICR-assessed ORR required confirmation of response at least 4 weeks after the first scan showing response in accordance with RECIST 1.1.

The BICR-assessed **ORR** using RECIST 1.1 is shown in table 26.

The BICR-assessed **DCR** is shown in table 26.

Table 3. Best Overall Response per BICR Assessment - All Combination Treated Subjects

	Number of Subjects (%)	
	All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82
BEST OVERALL RESPONSE (A):		
COMPLETE RESPONSE (CR)	5 (4.2)	3 (3.7)
(95% CI)	(1.4, 9.5)	(0.8, 10.3)
PARTIAL RESPONSE (PR)	53 (44.5)	35 (42.7)
(95% CI)	(35.4, 53.9)	(31.8, 54.1)
STABLE DISEASE (SD)	39 (32.8)	31 (7.8)
PROGRESSIVE DISEASE (PD)	17 (14.3)	8 (9.8)
UNABLE TO DETERMINE (UTD)	4 (3.4)	4 (4.9)
NOT REPORTED	1 (0.8)	1 (1.2)
OBJECTIVE RESPONSE RATE (B)	58/119 (48.7%)	38/82 (46.3%)
(95% CI)	(39.5, 58.1)	(35.3, 57.7)
DISEASE CONTROL RATE (C)	94/119 (79.0%)	66/82 (80.5%)
(95% CI)	(70.6, 85.9)	(70.3, 88.4)

(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

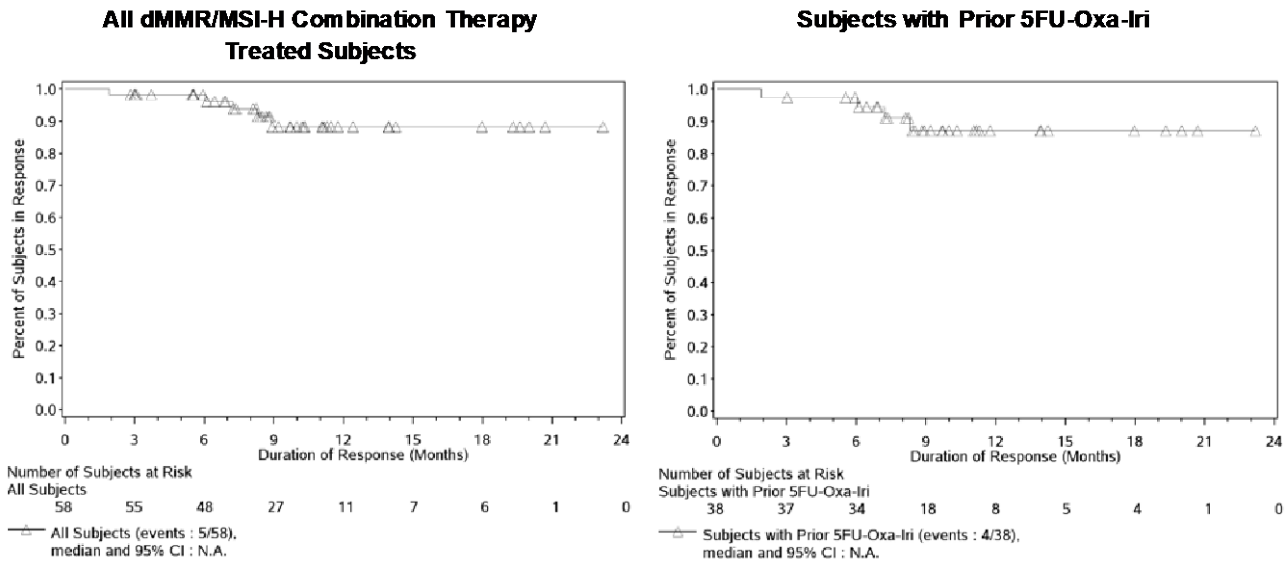
Investigator-assessed TTR and DOR

Table 27. Time to Objective Response and Duration of Response per Investigator - All Combination Treated Subjects

	All Subjects N = 65	Subjects with Prior 5FU-Oxa-Iri N = 43
TIME TO RESPONSE (MONTHS)		
NUMBER OF RESPONDERS	65	43
MEAN	3.48	3.65
MEDIAN	2.76	2.76
MIN, MAX	1.1, 14.0	1.3, 14.0
Q1, Q3	1.41, 4.07	1.54, 4.50
STANDARD DEVIATION	2.754	2.651
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.0+, 21.8+	1.0+, 21.8+
MEDIAN (95% CI) (B)	N.A.	N.A.
N EVENT/N RESP (%)	3/65 (4.6)	2/43 (4.7)
SUBJECTS WITH ONGOING RESPONSE (C)	61 (93.8)	40 (93.0)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)		
3 MONTHS	58 (89.2)	39 (90.7)
6 MONTHS	54 (83.1)	37 (86.0)
12 MONTHS	12 (18.5)	9 (20.9)

(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

Figure 44. Kaplan-Meier Plot of duration of response per BICR – All combination treated subjects, dMMR/MSI-H CRC per local lab



BICR -assessed TTR and DOR

Table 28. Time to Objective Response and Duration of Response per BICR, All Combination Treated Subjects – All BICR-assessed Responders

	All Subjects	Subjects with Prior 5FU-Oxa-Iri
	N = 58	N = 38
TIME TO RESPONSE (MONTHS)		
NUMBER OF RESPONDERS	58	38
MEAN	3.59	3.96
MEDIAN	2.76	3.33
MIN, MAX	1.1, 11.1	1.3, 11.1
Q1, Q3	2.33, 4.14	2.56, 4.24
STANDARD DEVIATION	2.287	2.410
DURATION OF RESPONSE (MONTHS)		
MIN, MAX (A)	1.9, 23.2+	1.9, 23.2+
MEDIAN (95% CI) (B)	N.A.	N.A.
N EVENT/N RESP (%)	5/58 (8.6)	4/38 (10.5)
SUBJECTS WITH ONGOING RESPONSE (C)	51 (87.9)	34 (89.5)
NUMBER OF SUBJECTS WITH DURATION OF RESPONSE OF AT LEAST (%)		
3 MONTHS	55 (94.8)	37 (97.4)
6 MONTHS	48 (82.8)	34 (89.5)
12 MONTHS	11 (19.0)	8 (21.1)

(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

In order to compare BICR and investigator-assessed endpoints, a summary of efficacy results is included in the following table.

Table 29. Summary of Efficacy Results - All Combination Treated Subjects

	Number of Subjects (%)			
	BICR Assessment		Investigator Assessment	
	All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82	All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82
OBJECTIVE RESPONSE RATE (A)	58/119 (48.7%)	38/82 (46.3%)	65/119 (54.6%)	43/82 (52.4%)
(95% CI)	(39.5, 58.1)	(35.3, 57.7)	(45.2, 63.8)	(41.1, 63.6)
DISEASE CONTROL RATE (B)	94/119 (79.0%)	66/82 (80.5%)	95/119 (79.8%)	67/82 (81.7%)
(95% CI)	(70.6, 85.9)	(70.3, 88.4)	(71.5, 86.6)	(71.6, 89.4)
BEST OVERALL RESPONSE (C):				
COMPLETE RESPONSE (CR)	5 (4.2)	3 (3.7)	4 (3.4)	2 (2.4)
(95% CI)	(1.4, 9.5)	(0.8, 10.3)	(0.9, 8.4)	(0.3, 8.5)
PARTIAL RESPONSE (PR)	53 (44.5)	35 (42.7)	61 (51.3)	41 (50.0)
(95% CI)	(35.4, 53.9)	(31.8, 54.1)	(41.9, 60.5)	(38.7, 61.3)
STABLE DISEASE (SD)	39 (32.8)	31 (37.8)	37 (31.1)	28 (34.1)
PROGRESSIVE DISEASE (PD)	17 (14.3)	8 (9.8)	14 (11.8)	8 (9.8)
UNABLE TO DETERMINE (UID)	4 (3.4)	4 (4.9)	3 (2.5)	3 (3.7)
NOT REPORTED	1 (0.8)	1 (1.2)	0	0
TIME TO RESPONSE (MONTHS)				
NUMBER OF RESPONDERS	58	38	65	43
MEDIAN	2.76	3.33	2.76	2.76
MIN, MAX	1.1, 11.1	1.3, 11.1	1.1, 14.0	1.3, 14.0
DURATION OF RESPONSE (MONTHS)				
MIN, MAX (D)	1.9, 23.2+	1.9, 23.2+	1.0+, 21.8+	1.0+, 21.8+
MEDIAN (95% CI) (E)	N.A.	N.A.	N.A	N.A
SUBJECTS WITH ONGOING RESPONSE (F)	51 (87.9)	34 (89.5)	61 (93.8)	40 (93.0)
PROGRESSION-FREE SURVIVAL				
MEDIAN (MONTHS) (95% CI) (G)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
# EVENTS / # SUBJECTS (%)	38/119 (31.9)	26/82 (31.7)	33/119 (27.7)	22/82 (26.8)

	All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82
--**OVERALL SURVIVAL**		
# EVENTS / # SUBJECTS (%)	23/119 (19.3)	14/82 (17.1)
MEDIAN OS (MONTHS) (95% CI)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
6 MONTHS		
N AT RISK	107	74
OS RATE (95% CI)	89.9 (82.9, 94.1)	90.2 (81.4, 95.0)
12 MONTHS		
N AT RISK	78	59
OS RATE (95% CI)	84.8 (77.0, 90.2)	87.8 (78.4, 93.2)

--Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination. N.A.: Not Available.
(A) CR+PR.
(B) CR+PR+SD (for at least 12 weeks).
(C) Per RECIST 1.1 criteria, confirmation of response required.
(D) Symbol + indicates a censored value.
(E) Median computed using Kaplan-Meier method.
(F) 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.
(G) Median computed using Kaplan-Meier method.
Source: BICR-Assessment - Table S.5.1.1A (BOR), Table S.5.1.7A (time to response, duration of response), Table S.5.2.1A (PFS); Investigator Assessment - Table S.5.1.1B (BOR), Table S.5.1.7B (time to response, duration of response), Table S.5.2.1B (PFS); Table S.5.3.1 (OS)

Exploratory Endpoints

Investigator-assessed PFS

The median PFS per investigator was not reached in all combination treated subjects and subjects with prior 5FU-Oxa-Iri. For all combination treated subjects the 6 month and 12-month PFS rates per

investigator were 76.8% and 71.1%, respectively. Similar rates were observed for subjects with prior 5FU-Oxa-Iri (78.9% and 72.2%, respectively).

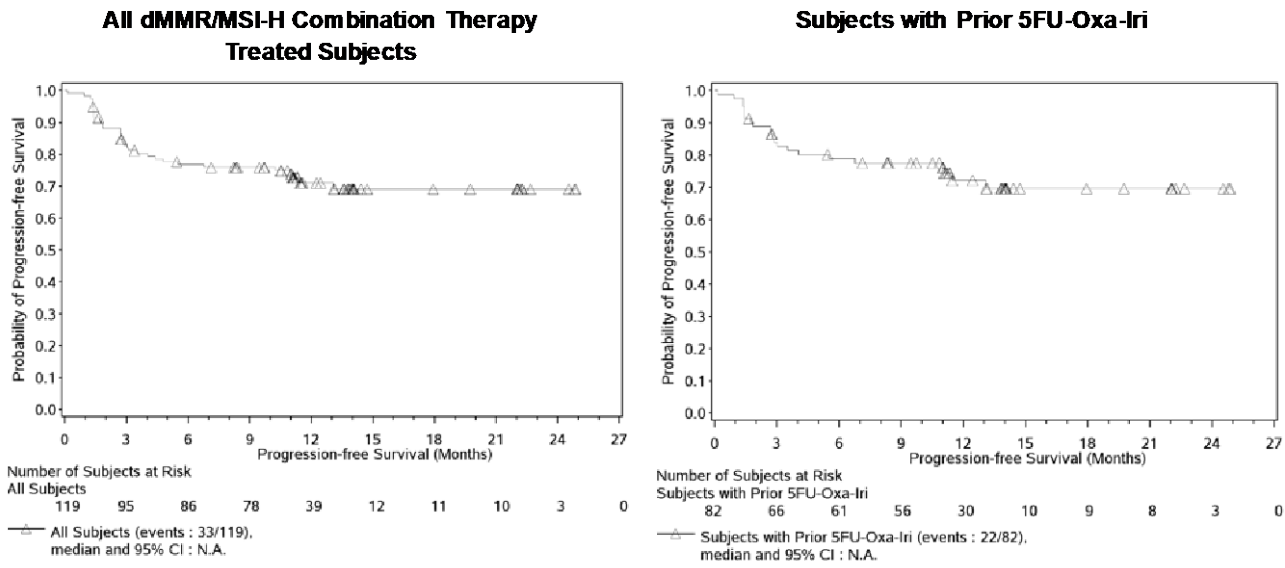
86 (72.3%) all combination treated subjects and 60 (73.2%) subjects with prior 5FU-Oxa-Iri were censored. 86 (72.3%) and 60 (73.2%) subjects had their PFS time censored on the date of last on-study tumour assessment, respectively. The most common reason for censoring among these subjects was 'still on treatment'.

Table 30. Status of Censored Subjects, Progression-free Survival per Investigator, All dMMR/MSI-H Combination Therapy Treated Subjects.

	All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82
NUMBER OF EVENTS (%)	33 (27.7)	22 (26.8)
TYPE OF EVENTS (%)		
PROGRESSION (1)	26 (21.8)	17 (20.7)
DEATH	7 (5.9)	5 (6.1)
NUMBER OF SUBJECTS CENSORED (%)	86 (72.3)	60 (73.2)
CENSORED ON FIRST DOSING DATE	0	0
NO BASELINE TUMOR ASSESSMENT AND NO DEATH (2)	0	0
NO ON-STUDY TUMOR ASSESSMENT AND NO DEATH (2)	0	0
CENSORED ON DATE OF LAST TUMOR ASSESSMENT ON-STUDY	86 (72.3)	60 (73.2)
RECEIVED SUBSEQUENT THERAPY (3)	5 (4.2)	5 (6.1)
SCT	2 (1.7)	2 (2.4)
OTHER	3 (2.5)	3 (3.7)
STILL ON TREATMENT	70 (58.8)	49 (59.8)
PROGRESSION-FREE IN FOLLOW-UP	11 (9.2)	6 (7.3)
OFF STUDY	0	0
LOST TO FOLLOW-UP	0	0
SUBJECT WITHDREW CONSENT	0	0
OTHER	0	0

(1) RECIST 1.1 criteria
(2) Tumor assessments and death if any, occurring after start of subsequent anti-cancer therapy are not considered
(3) Includes subjects, regardless of treatment status, who received subsequent anti-cancer therapy without a prior reported PFS event. Those subjects were censored at the last evaluable tumor assessment prior to/on start date of subsequent anti-cancer therapy
Program Source: /projects/bms218374/stats/upd aug2017/prog/tables/rt-ef-pfsreasocns.sas 20SEP2017:07:45:19

Figure 45. Kaplan-Meier Plot of PFS per Investigator – All combination treated subjects

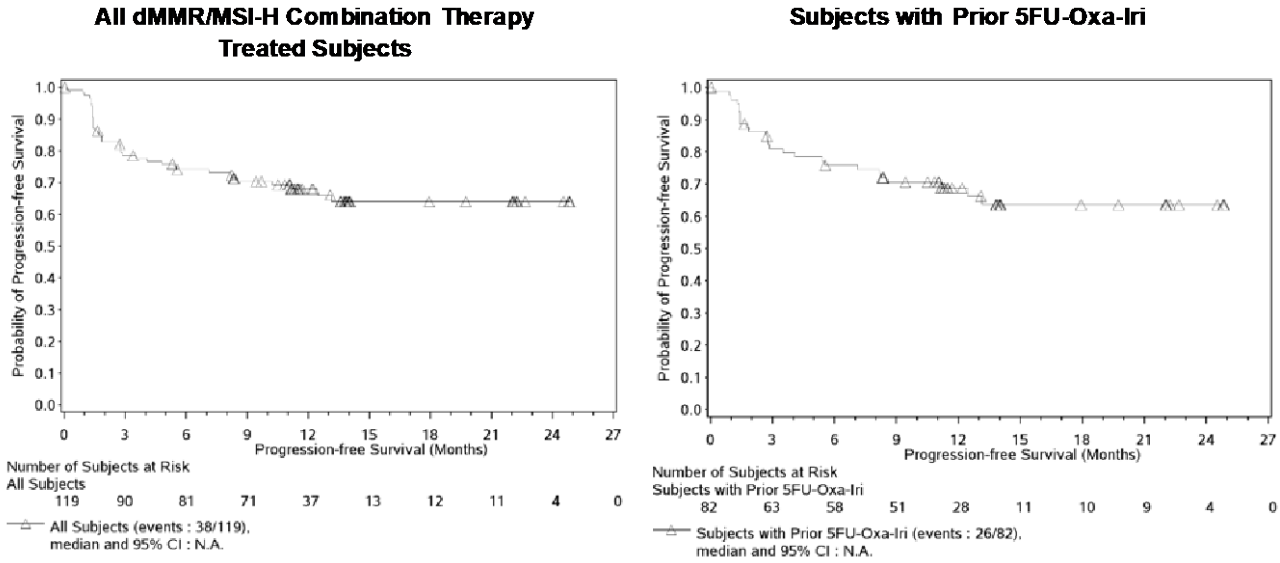


BICR-assessed PFS

The median PFS per BICR was not reached in all combination treated subjects and subjects with prior 5FU-Oxa-Iri. For all combination treated subjects the 6 month and 12-month PFS rates per investigator were 74.1% and 68.0%, respectively. Similar rates were observed for subjects with prior 5FU-Oxa-Iri (75.9% and 68.8%, respectively).

81 (68.1%) all combination treated subjects and 56 (68.3%) subjects with prior 5FU Oxa-Iri were censored. 79 (66.4%) and 54 (65.9%) 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 46. Kaplan-Meier Plot of PFS by BICR – All combination treated subjects



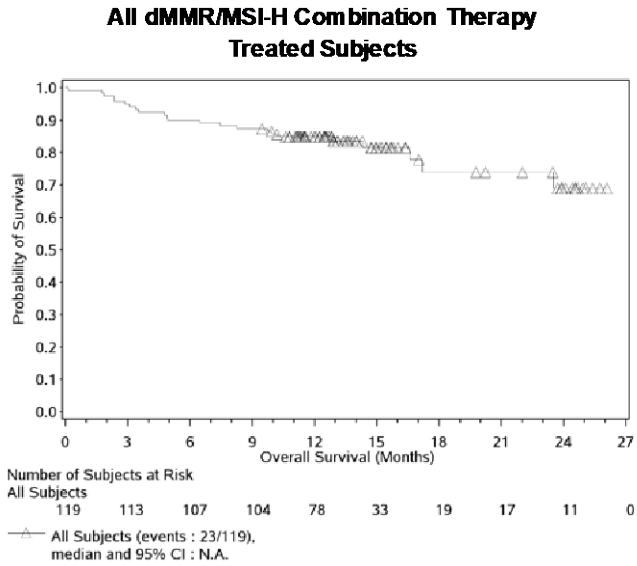
Overall Survival

Median OS for all combination treated subjects or subjects with prior 5FU-Oxa-Iri has not yet been reached (Table 31).

At the time of the DBL, among all combination treated subjects, 96 (80.7%) were censored . Among those censored, 75 (63.0%) subjects were still on treatment (71 [59.7%] subjects had not progressed), and 21 (17.6%) subjects were in follow up.

68 (82.9%) subjects with prior 5FU-Oxa-Iri were censored, of which 53 (64.6%) were still on treatment (50 [61.0%] subjects had not progressed), and 15 (18.3) subjects were in follow-up. No subjects were off-study in either group.

Figure 47. Kaplan-Meier Overall Survival Plot – All combination treated subjects



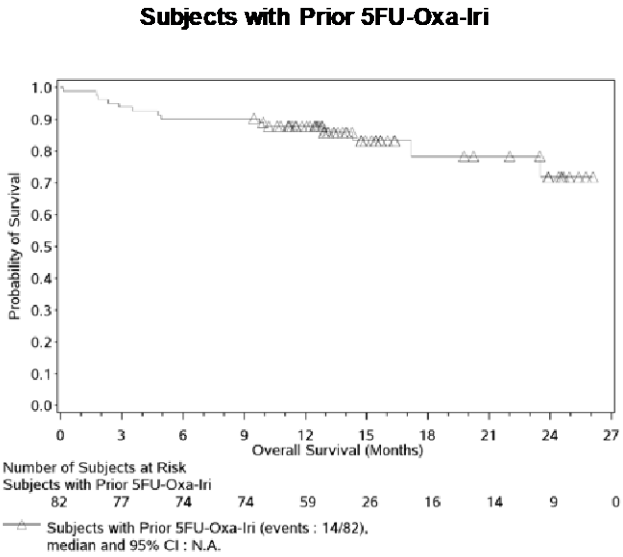


Table 31. Overall Survival Rates – All combination treated subjects

	All Subjects	Subjects with Prior 5FU-Oxa-Iri
	N = 119	N = 82
# EVENTS / # SUBJECTS (%)	23/119 (19.3)	14/82 (17.1)
MEDIAN OS (MONTHS) (95% CI)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
3 MONTHS		
N AT RISK	113	77
OS RATE (95% CI)	95.0 (89.1, 97.7)	93.9 (86.0, 97.4)
6 MONTHS		
N AT RISK	107	74
OS RATE (95% CI)	89.9 (82.9, 94.1)	90.2 (81.4, 95.0)
9 MONTHS		
N AT RISK	104	74
OS RATE (95% CI)	87.4 (80.0, 92.2)	90.2 (81.4, 95.0)
12 MONTHS		
N AT RISK	78	59
OS RATE (95% CI)	84.8 (77.0, 90.2)	87.8 (78.4, 93.2)

Median computed using Kaplan-Meier method
N.A.: Not Available

Follow-up for OS

Median follow-up for OS (time between first dose date and last known date alive or death) was 12.94 months (range: 0.1 to 26.1 months) among all combination treated subjects and 13.11 months (range: 0.1 to 26.1 months) in subjects with prior 5FU-Oxa-Iri.

Follow-up for OS was current for the majority of subjects; 106 (89.1%) all combination treated subjects and 70 (85.4%) subjects with prior 5FU-Oxa-Iri either died or had a last known alive date on or after the last patient last visit date (clinical cut-off date of 06-Jul-2017) for the CSR.

Updated efficacy data (DBL 19 Feb 2019)

CA209142 efficacy data from the Feb-2019 DBL (clinical cutoff 7-Jan-2019) with a minimum follow-up of 27.5 months (median follow up of 31.5 months) supported the clinical benefit of nivolumab + ipilimumab combination therapy in subjects with dMMR or MSI-H mCRC who have been previously treated with fluoropyrimidine-based chemotherapy.

From the original 58 responders in the Aug-2017 DBL, an efficacy summary of 57 subjects is presented below, as one subject was no longer evaluated as a responder. Additionally, 14 subjects achieved response per BICR during this period.

Table 32. Per Investigator summary of efficacy – All combination treated subjects

	Nivolumab + ipilimumab (N = 119)	Subjects with Prior 5FU-Oxa-Iri (N = 82)	Subjects without Prior 5FU-Oxa-Iri (N = 37)
Objective Response Rate[a]	72/119 (60.5)	49/82 (59.8)	23/37 (62.2)
95% CI	(51.1, 69.3)	(48.3, 70.4)	(44.8, 77.5)
Disease Control Rate[b]	96/119 (80.7)	68/82 (82.9)	28/37 (75.7)
95% CI	(72.4, 87.3)	(73.0, 90.3)	(58.8, 88.2)
Best Overall Response[c]			
Complete Response (CR)	9 (7.6)	5 (6.1)	4 (10.8)
95% CI	(3.5, 13.9)	(2.0, 13.7)	(3.0, 25.4)
Partial Response (PR)	63 (52.9)	44 (53.7)	19 (51.4)
95% CI	(43.6, 62.2)	(42.3, 64.7)	(34.4, 68.1)
Stable Disease (SD)	30 (25.2)	22 (26.8)	8 (21.6)
Progressive Disease (PD)	14 (11.8)	8 (9.8)	6 (16.2)
Unable to Determine (UTD)	3 (2.5)	3 (3.7)	0
TTR (months)			
Median (min, max)	2.76 (1.1, 26.0)	2.83 (1.3, 26.0)	2.69 (1.1, 24.4)
DOR (months)			
Min, Max[d]	1.4+, 38.9+	1.4+, 38.6+	8.3+, 38.9+
Median (95% CI)[e]	N.R. (34.60, N.A.)	N.R. (34.60, N.A.)	N.R. (N.A., N.A.)
Subjects with ongoing response[f]	45 (62.5)	30 (61.2)	15 (65.2)
Progression-Free Survival (PFS)			
# Events / # Subjects (%)	48/119 (40.3)	33/82 (40.2)	15/37 (40.5)
Median (months) (95% CI)[e]	41.5 (32.8, 41.6)	41.5 (27.8, 41.6)	N.R. (16.9, N.A.)
PFS Rates (95% CI)			
12 months	71.6 (62.5, 78.9)	72.7 (61.5, 81.1)	69.2 (51.3, 81.7)
24 months	61.3 (51.7, 69.6)	63.0 (51.2, 72.7)	57.7 (39.9, 72.0)
Overall Survival (OS)			
# Events / # Subjects (%)	33/119 (27.7)	22/82 (26.8)	11/37 (29.7)
Median OS (months) (95% CI)	N.R. (N.A., N.A.)	N.R. (N.A., N.A.)	N.R. (N.A., N.A.)
OS Rates (95% CI)			
6 months	89.9 (82.9, 94.1)	90.2 (81.4, 95.0)	89.2 (73.7, 95.8)
12 months	84.9 (77.1, 90.2)	87.8 (78.5, 93.2)	78.4 (61.4, 88.5)
24 months	74.8 (66.0, 81.6)	75.6 (64.8, 83.5)	73.0 (55.6, 84.4)

Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination.
DOR: duration of response
N.A.: Not Available.

N.R.: Not Reached
TTR: time to response
(a) CR+PR.
(b) CR+PR+SD (for at least 12 weeks).
(c) Per RECIST 1.1 criteria, confirmation of response required.
(d) Symbol + indicates a censored value.
(e) Median computed using Kaplan-Meier method.
(f) 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: Table S.5.1.1B.1 (BOR), Table S.5.1.7B.1 (time to response, duration of response), Table S.5.2.1B.1 (PFS), Table S.5.3.1.2 (OS)

The updated BICR-assessed objective response rate (ORR) using RECIST 1.1 was 59.7% (71/119) in MSI-H/dMMR per Local Lab, all combination therapy treated subjects; 17 responders achieved complete response (CR) (vs. 5 in the Aug-2017 DBL; there were 11 subjects with partial response [PR] in the Aug-2017 DBL are CR in the current DBL) and 54 achieved PR. The ORR was 56.1% (46/82) in the prior 5FU-Oxa-Iri combination therapy treated subjects with 11 subjects achieving a CR (vs. 3 in the Aug-2017 DBL).

Table 33. Per BICR Summary of Efficacy - All Combination Treated Subjects

	Nivolumab + ipilimumab (N = 119)	Subjects with Prior 5FU-Oxa-Iri (N = 82)	Subjects without Prior 5FU-Oxa-Iri (N = 37)
Objective Response Rate[a]	71/119 (59.7)	46/82 (56.1)	25/37 (67.6)
95% CI	(50.3, 68.6)	(44.7, 67.0)	(50.2, 82.0)
Disease Control Rate[b]	98/119 (82.4)	68/82 (82.9)	30/37 (81.1)
95% CI	(74.3, 88.7)	(73.0, 90.3)	(64.8, 92.0)
Best Overall Response[c]			
Complete Response (CR)	17 (14.3)	11 (13.4)	6 (16.2)
95% CI	(8.5, 21.9)	(6.9, 22.7)	(6.2, 32.0)
Partial Response (PR)	54 (45.4)	35 (42.7)	19 (51.4)
95% CI	(36.2, 54.8)	(31.8, 54.1)	(34.4, 68.1)
Stable Disease (SD)	29 (24.4)	24 (29.3)	5 (13.5)
Progressive Disease (PD)	14 (11.8)	7 (8.5)	7 (18.9)
Unable to Determine (UTD)	5 (4.2)	5 (6.1)	0
TTR (months)			
Median (min, max)	3.22 (1.1, 34.3)	3.86 (1.3, 34.3)	2.73 (1.1, 24.4)
DOR (months)			
Min, Max[d]	1.9, 36.9+	1.9, 36.9+	5.6+, 36.5+
Median (95% CI)[e]	N.R. (30.03, N.A.)	33.38 (30.03, N.A.)	N.R. (N.A., N.A.)
Subjects with ongoing response[f]	49 (69.0)	30 (65.2)	19 (76.0)
Progression-Free Survival (PFS)			
# Events / # Subjects (%)	48/119 (40.3)	35/82 (42.7)	13/37 (35.1)
Median (months) (95% CI)[e]	36.0 (27.9, N.A.)	36.0 (27.4, N.A.)	N.R. (16.5, N.A.)
PFS Rates (95% CI)			
12 months	69.8 (60.5, 77.3)	69.7 (58.3, 78.6)	70.1 (52.5, 82.2)
24 months	63.5 (53.9, 71.5)	63.0 (51.3, 72.7)	64.5 (46.8, 77.6)

Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination. DOR: duration of response N.A.: Not Available. N.R.: Not Reached TTR: time to response

(a) CR+PR.
(b) CR+PR+SD (for at least 12 weeks).
(c) Per RECIST 1.1 criteria, confirmation of response required.
(d) Symbol + indicates a censored value.
(e) Median computed using Kaplan-Meier method.
(f) 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: Table S.5.1.1A.1 (BOR), Table S.5.1.7A.1 (time to response, duration of response), Table S.5.2.1A.1 (PFS)

In the Feb-2019 DBL, median TTR was 3.22 months for all subjects and was 3.86 months in subjects with prior 5FU-Oxa-Iri. In the Aug-2017 DBL, median TTR was 2.76 months for all subjects and was 3.33 months for subjects with prior 5FU-Oxa-Iri. In the Feb-2019 DBL, median DOR was not reached for the all treated subjects group, and median DOR was 33.38 months (95%CI: 30.03, NA) in the prior 5FU-Oxa-Iri group. The majority of responders (69.0%, 49/71) had ongoing response at the clinical cut-off date (07-Jan-2019).

ORR by Subgroups

Analyses of the primary and secondary endpoints of ORR were repeated in subgroups of interest.

ORR by KRAS/BRAF Mutation Status

• In subjects who had KRAS/BRAF WT the ORR for all combination treated subjects and subjects with prior 5FU-Oxa-Iri was 58.1% (18/31) and 47.6% (10/21), respectively, at the Feb 2019 DBL, similar to 51.6% (16/31) and 42.9% (9/21), respectively, at the Aug-2017 DBL.

• In subjects who had **KRAS** mutation, the ORR for all combination treated subjects and subjects with prior 5FU-Oxa-Iri was 56.8% (25/44) and 55.3% (21/38), respectively, at the Feb 2019 DBL, similar to 45.5% (20/44) and 44.7% (17/38), respectively at the Aug-2017 DBL.

• In subjects who had **BRAF** mutation, the ORR for all combination treated subjects and subjects with prior 5FU-Oxa-Iri was 66.7% (20/30) and 68.8% (11/16), respectively, at the Feb-2019 DBL and was 51.7% (15/29) and 56.3% (9/16), respectively, at the Aug-2017 DBL.

ORR by Lynch Syndrome

- ORR per BICR:
    - In all combination treated subjects with Lynch Syndrome (n = 35), the ORR was 62.9% (95% CI: 44.9, 78.5).
    - In all combination treated subjects without Lynch Syndrome (n = 35), the ORR was 60.0% (95% CI: 42.1, 76.1).
    - In all combination treated subjects with unknown Lynch Syndrome status (n = 49), the ORR was 57.1% (95% CI: 42.2, 71.2).
- ORR per investigator:
    - In all combination treated subjects with Lynch Syndrome (n = 35), the ORR was 77.1% (95% CI: 59.9, 89.6).
    - In all combination treated subjects without Lynch Syndrome (n = 35), the ORR was 57.1% (95% CI: 39.4, 73.7).

In all combination treated subjects with unknown Lynch Syndrome status (n = 49), the ORR was 51.0% (95% CI: 36.3, 65.6).

ORR by Time from Progression on Most Recent Prior Therapy to Treatment

BICR- and investigator-assessed ORR by time from progression on most recent prior therapy to treatment in all combination treated subjects were similar:

- In subjects who started treatment in < 3 months, the ORR was 57.1% (48/84) and 56.0% (47/84), respectively
- In subjects who started treatment in 3-6 months, the ORR was 63.6% (7/11) and 90.9% (10/11), respectively
- In subjects who started treatment in > 6 months, the ORR was 50.0% (4/8) and 50.0% (4/8), respectively

ORR by Subjects Enrolled and Treated in cStage 1 or cStage 2

Considering the subgroups of subjects enrolled and treated in cStage 1 or in cStage 2, ORR per BICR were numerically lower for subjects enrolled and treated in cStage 1 (ORR of 48.1% [13/27], 95% CI [28.7, 68.1]) as compared to subjects enrolled and treated in cStage 2 (63.0% [58/92], 95% CI [52.3, 72.9]). However, the related CIs are overlapping.

PFS

Regarding **PFS**, there were 10 new events of progression in the Feb-2019 DBL compared to the Aug-2017 DBL. The median PFS per BICR was 36.0 months (95% CI: 27.9, NA) in all treated subjects and was 36.0 months (95% CI: 27.4, NA) in prior 5FU-Oxa-Iri combination treated subjects. For all combination treated subjects the 12- and 24-month PFS rates per BICR were 69.8% and 63.5%, respectively. Similar rates were observed for prior 5FU-Oxa-Iri combination treated subjects (69.7% and 63.0%, respectively).

There were 71 (59.7%) of all combination treated subjects and 47 (57.3%) of prior 5FU-Oxa-Iri combination treated subjects that were censored as of the Feb-2019 DBL. There were 69 (58.0%) of all combination treated subjects and 45 (54.9%) of prior 5FU-Oxa-Iri combination treated subjects that had their PFS time censored on the date of last on-study tumour assessment. The most common reason for censoring among these subjects was 'still on treatment'.

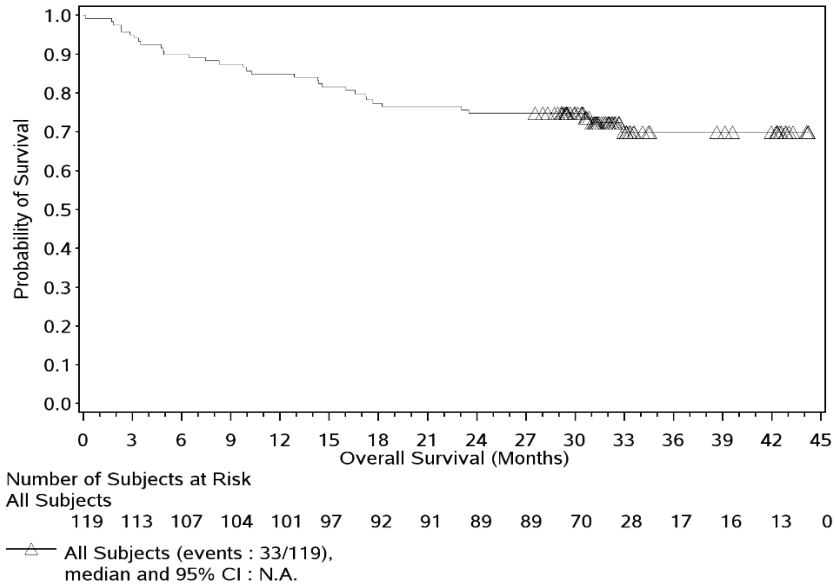
OS

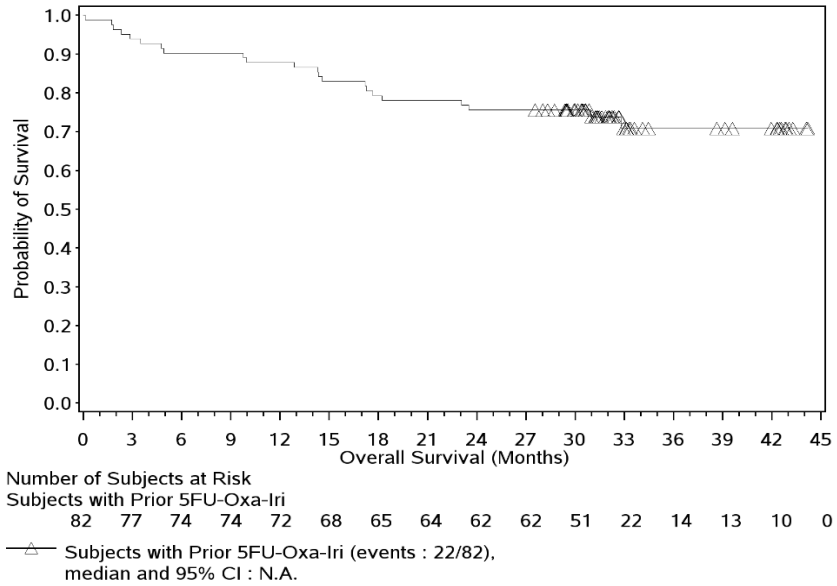
Per the Feb-2019 DBL, median **OS** for all combination treated subjects or prior 5FU-Oxa-Iri combination treated subjects has not yet been reached, with 10 additional events compared with the Aug-2017 DBL; in total 33 events occurred in 119 subjects (27.7%) and 22 events occurred in 82 (26.8%) subjects, respectively. For all combination treated subjects the 12- and 24-month OS rates were 84.9% and 74.8%, respectively. Similar rates were observed for prior 5FU-Oxa-Iri combination treated subjects (the 12- and 24-month OS rates were 87.8% and 75.6%, respectively).

At the time of the Feb-2019 DBL among all combination treated subjects, 86 (72.3%) subjects were censored and 60 (73.2%) of prior 5FU-Oxa-Iri subjects were censored. Among all treated subjects that were censored, 51 (42.9 %) subjects were still on treatment (43 [36.1%] subjects had not progressed), and 34 (28.6%) subjects were in follow-up. Among subjects with prior 5FU-Oxa-Iri treatment that were censored, 36 (43.9%) were still on treatment (30 [36.6%] subjects had not progressed), and 23 (28.0%) were in follow-up.

Median follow-up for OS was 30.65 months (range: 0.1 to 44.2 months) among all combination treated subjects and 30.98 months (range: 0.1 to 44.2 months) in prior 5FU-Oxa-Iri combination treated subjects.

Figure 48. Kaplan-Meier Plot of Overall Survival - All dMMR/MSI-H Therapy Treated Subjects (Nivolumab 3 mg/kg with Ipilimumab 1 mg/kg)





Latest efficacy results *(DBL Oct-2020)*

Updated efficacy analyses were provided based on a later cut-off date (Oct-2020) with a minimum follow up of 46.9 months and a median follow-up of 51.1 months. These analyses were originally performed in the known as "modified population" (n=109) where 10 subjects were excluded due to not having received previous treatment in the metastatic setting, from the not prior 5Fu-Oxa-Iri subjects dataset (N=27). Data in the 'all treated population' (N=119), 3L (N=82) and all 2L subjects (N=37) were also provided.

The investigator assessed-ORR and DOR are summarized in table 9. Regarding secondary endpoint, ORR by BICR, results were similar and are presented in table 34.

Table 34: Side-by-Side Summary of Efficacy per BICR and per Investigator for the All Combination Therapy Treated Population in CA209142 Cohort 2 (Oct-2020 DBL)

	Per BICR			Per Investigator		
	Total (N = 119)	**With 5FU-Oxa-Iri (N = 82)**	**Without 5FU-Oxa-Iri (N = 37)**	**Total (N = 119)**	**With 5FU-Oxa-Iri (N = 82)**	**Without 5FU-Oxa-Iri (N = 37)**
ORR, n/N (%) (A) (95% CI)	73/119 (61.3) (52.0, 70.1)	48/82 (58.5) (47.1, 69.3)	25/37 (67.6) (50.2, 82.0)	77/119 (64.7) (55.4, 73.2)	52/82 (63.4) (52.0, 73.8)	25/37 (67.6) (50.2, 82.0)
DCR, n/N (%) (B) (95% CI)	98/119 (82.4) (74.3, 88.7)	68/82 (82.9) (73.0, 90.3)	30/37 (81.1) (64.8, 92.0)	96/119 (80.7) (72.4, 87.3)	68/82 (82.9) (73.0, 90.3)	28/37 (75.7) (58.8, 88.2)
BOR, n (%) (C)						
CR	24 (20.2)	16 (19.5)	8 (21.6)	15 (12.6)	10 (12.2)	5 (13.5)
(95% CI)	(13.4, 28.5)	(11.6, 29.7)	(9.8, 38.2)	(7.2, 19.9)	(6.0, 21.3)	(4.5, 28.8)
PR	49 (41.2)	32 (39.0)	17 (45.9)	62 (52.1)	42 (51.2)	20 (54.1)
(95% CI)	(32.2, 50.6)	(28.4, 50.4)	(29.5, 63.1)	(42.8, 61.3)	(39.9, 62.4)	(36.9, 70.5)
SD	27 (22.7)	22 (26.8)	5 (13.5)	25 (21.0)	19 (23.2)	6 (16.2)
PD	14 (11.8)	7 (8.5)	7 (18.9)	14 (11.8)	8 (9.8)	6 (16.2)
UTD	5 (4.2)	5 (6.1)	0	3 (2.5)	3 (3.7)	0
DOR (month)						
Min, Max (D)	1.9, 58.0+	1.9, 57.6+	8.9, 58.0+	1.4+, 58.0+	1.4+, 58.0+	8.9, 58.0+
Median (95% CI) (E)	N.R.	N.R.	N.R.	N.R.	N.R.	N.R. (39.36, N.A.)
Subjects with Ongoing Response (F)	31 (42.5)	19 (39.6)	12 (48.0)	37 (48.1)	24 (46.2)	13 (52.0)
PFS						
# Events / # Subjects (%)	51/119 (42.9)	37/82 (45.1)	14/37 (37.8)	51/119 (42.9)	35/82 (42.7)	16/37 (43.2)
Median (month) (95% CI) (E)	56.3 (30.3, N.A.)	56.3 (27.8, N.A.)	N.R. (16.5, N.A.)	N.R. (38.4, N.A.)	N.R. (32.8, N.A.)	N.R. (16.9, N.A.)
12 months PFS rate (95% CI)	70.6 (61.3, 78.0)	70.8 (59.4, 79.6)	70.1 (52.5, 82.2)	72.5 (63.4, 79.7)	73.9 (62.9, 82.2)	69.3 (51.4, 81.7)
24 months PFS rate (95% CI)	63.2 (53.6, 71.3)	63.9 (52.1, 73.5)	61.7 (44.0, 75.2)	63.0 (53.4, 71.2)	65.5 (53.7, 74.9)	57.8 (39.9, 72.0)
36 months PFS rate (95% CI)	56.9 (47.1, 65.6)	54.5 (42.3, 65.1)	61.7 (44.0, 75.2)	60.0 (50.2, 68.4)	60.8 (48.8, 70.9)	57.8 (39.9, 72.0)
48 months PFS rate (95% CI)	54.5 (44.6, 63.5)	50.8 (38.5, 61.9)	61.7 (44.0, 75.2)	52.8 (42.6, 62.0)	51.9 (39.3, 63.0)	54.4 (36.5, 69.2)
OS						
# Events / # Subjects (%) (E)	Refer to Investigator results as OS was assessed by Investigator only			35/119 (29.4)	23/82 (28.0)	12/37 (32.4)
Median OS (month) (95% CI)				N.R. (N.A., N.A.)	N.R. (N.A., N.A.)	N.R. (41.2, N.A.)
12 months OS rate (95% CI)				84.9 (77.1, 90.2)	87.8 (78.5, 93.2)	78.4 (61.4, 88.5)
24 months OS rate (95% CI)				74.8 (66.0, 81.6)	75.6 (64.8, 83.5)	73.0 (55.6, 84.4)
36 months OS rate (95% CI)				71.4 (62.3, 78.6)	71.9 (60.8, 80.3)	70.3 (52.8, 82.3)
48 months OS rate (95% CI)				70.5 (61.4, 77.9)	71.9 (60.8, 80.3)	67.5 (49.9, 80.0)

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

Abbreviations: BICR - blinded independent central review; BOR - best overall response, CI - confidence interval; CR - complete response; DCR - disease control rate; DOR - duration of response; N.A. - not available; N.R. - not reached, ORR - objective response rate; OS - overall survival; PFS - progression-free survival; PR - partial response; SD - stable disease, UTD - unable to determine

(A) CR+PR.

(B) CR+PR+SD (for at least 12 weeks).

(C) Per RECIST 1.1 criteria, confirmation of response required.

(D) Symbol + indicates a censored value.

(E) Median computed using Kaplan-Meier method.

(F) 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.

Ancillary analyses

- **Concordance between Investigator and BICR-assessed**

Investigator and BICR assessments for responders, non-responders, and unable to determine were highly concordant (Table 35)

Table 35. Concordance between Investigator and BICR Assessments - All Combination Treated Subjects

	Number of Subjects (%)							
	All Subjects N = 119				Subjects with Prior 5FU-Oxa-Iri N = 82			
	BICR ASSESSMENT							
	RESPONDER	NON-RESPONDER	UTD	NOT REPORTED	RESPONDER	NON-RESPONDER	UTD	NOT REPORTED
INVESTIGATOR ASSESSMENT								
RESPONDERS	56 (47.1)	8 (6.7)	1 (0.8)	0	36 (43.9)	6 (7.3)	1 (1.2)	0
NON-RESPONDERS	2 (1.7)	48 (40.3)	0	1 (0.8)	2 (2.4)	33 (40.2)	0	1 (1.2)
UTD	0	0	3 (2.5)	0	0	0	3 (3.7)	0
CONCORDANCE RATE OF RESPONDERS (1)		90.7 %				88.9 %		

Responder: Subject with confirmed PR/CR. UTD : Unable to Determine
(1) Quantifies the frequency with which Investigator and BICR agreed on classification of a subject as responder vs. non-responder/UTD as a proportion of the total number of subjects assessed by both the investigator and BICR
Source: Table S.5.1.6

- **Concordance between Local MSI Testing and Central MSI Testing**

By the initial DBL (18 Aug 2017), out of the 119 subjects, 62 had confirmed MSI H by a central test. An additional 30 subjects had missing central testing data due to inadequate amount of tumor tissue and/or no viable tumour in the sample to be centrally tested. The remaining 27 subjects had central test results that did not match the local testing.

Table 36. Concordance between local MSI testing and central MSI testing (DBL 18 Aug 2017)

	Number of Subjects (%)					
	All Subjects N = 119			Subjects with Prior 5FU-Oxa-Iri N = 82		
	CENTRAL MSI ASSESSMENT					
	MSI-H	NON MSI-H	NOT REPORTED	MSI-H	NON MSI-H	NOT REPORTED
LOCAL MSI ASSESSMENT						
MSI-H	62 (52.1)	27 (22.7)	30 (25.2)	39 (47.6)	21 (25.6)	22 (26.8)
NON MSI-H	0	0	0	0	0	0
CONCORDANCE RATE OF RESPONDERS (A):		69.7 %			65.0 %	
REASON FOR MISSING CENTRAL MSI EVALUATION						
H&E PROCESSING						
NO ISOLATABLE NORMAL TISSUE		1 (0.8)			1 (1.2)	
NO SPECIMEN RECEIVED		16 (13.4)			12 (14.6)	
NO TUMOR IDENTIFIED		2 (1.7)			2 (2.4)	
NO VIABLE NORMAL TISSUE IDENTIFIED		1 (0.8)			0	
NO VIABLE TUMOR IDENTIFIED		1 (0.8)			1 (1.2)	
PCR PROCESSING						
NORMAL CONTROL DNA LOW/NO PCR AMPLIFICATION		1 (0.8)			1 (1.2)	
TUMOR & NORMAL CONTROL DNA LOW/NO PCR AMPLIFICATION		1 (0.8)			1 (1.2)	
TUMOR DNA LOW/NO PCR AMPLIFICATION		2 (1.7)			1 (1.2)	
NO REASON PROVIDED		5 (4.2)			3 (3.7)	

(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
Program Source: /projects/bms218374/stats/upd_aug2017/prog/tables/rt-dx-c2msiconc.sas 20SEP2017:07:42:35

Concordance rate of responders was 69.7% in all subjects (n=119) and 65.0% in subjects with prior 5Fu-Oxa-Iri (n=82).

Focusing on updated efficacy data (DBL 19 Feb-2019), out of the 119 subjects, 70 had confirmed MSI-H by a central test, known as centrally confirmed MSI-H population, as defined in the study protocol. An additional 28 subjects had central test results that did not match the local testing. The remaining 21 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.

- ORR and DCR: BICR-assessed ORR was 64.3% (45/70) and investigator-assessed ORR was 65.7% (46/70). The BICR-assessed DCR was 84.3% and investigator-assessed DCR was 80.0%. These results were similar to the overall population evaluated by the local laboratories as dMMR or MSI-H.
- BICR-assessed median PFS was not reached in all central lab confirmed combination therapy treated subjects. The investigator-assessed median PFS was 41.59 months.

Table 37. Best Overall Response per BICR Assessment - All Central Lab Confirmed dMMR/MSI-H Therapy Treated Subjects (Nivolumab 3 mg/kg with Ipilimumab 1 mg/kg) (DBL 19 Feb 2019)

	Number of Subjects (%)	
	All Subjects N = 70	Subjects with Prior 5FU-Oxa-Iri N = 45
BEST OVERALL RESPONSE (A):		
COMPLETE RESPONSE (CR)	11 (15.7)	9 (20.0)
(95% CI)	(8.1, 26.4)	(9.6, 34.6)
PARTIAL RESPONSE (PR)	34 (48.6)	20 (44.4)
(95% CI)	(36.4, 60.8)	(29.6, 60.0)
STABLE DISEASE (SD)	16 (22.9)	12 (26.7)
PROGRESSIVE DISEASE (PD)	6 (8.6)	1 (2.2)
UNABLE TO DETERMINE (UTD)	3 (4.3)	3 (6.7)
OBJECTIVE RESPONSE RATE (B)	45/70 (64.3%)	29/45 (64.4%)
(95% CI)	(51.9, 75.4)	(48.8, 78.1)
DISEASE CONTROL RATE (C)	59/70 (84.3%)	39/45 (86.7%)
(95% CI)	(73.6, 91.9)	(73.2, 94.9)

(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

Similarly to MSI-H subjects evaluated by the local laboratories, median OS for all central lab confirmed MSI-H combination therapy treated subjects had not yet been reached. The 12- and 24-month OS rates were 85.7% and 80.0%, respectively.

- **Sensitivity Analyses of ORR (DBL 19 Feb 2019)**

The following sensitivity analyses were performed in order to assess the robustness of the results of the primary analysis of ORR and the impact of the changes in the sample size and the primary analysis method.

1) The first 19 subjects in C2 cStage 1 and the first 29 subjects in C2 cStage 2 who had been identified as MSI-H by the central laboratory (i.e., the first 48 subjects identified as MSI-H by the central laboratory) were analysed on the assumption that the study had been conducted in accordance with the study protocol. The SAP version 2.0 Clopper and Pearson method and the protocol-specified Atkinson and Brown method were used in these analyses.

2) Analysis were performed based on the total of 70 subjects identified as being MSI-H by the central laboratory. The Clopper and Pearson method and the Koyama and Chen method were used in these analyses. In the Koyama and Chen method, the analysis was adjusted for the actually increased sample size in the Simon 2-stage design.

These results are summarised in the following table.

Table 38. Objective Response Rates per BICR and Investigator - Subjects with Central Confirmed MSI-H

Method	Responder/sample size in cStage 1	Responder/sample size in cStage 2	Total responders/ sample size	ORR 95% CI
Per BICR (1)				
1 - Clopper and Pearson	10/19	21/29	31/48	64.6% (49.5,77.8)
1 - Atkinson and Brown	10/19	21/29	31/48	64.6% (49.5,77.8)
2 - Clopper and Pearson	10/19	30/43	45/70	64.3% (51.9, 75.4)
2 - Koyama and Chen	10/19	30/43	45/70	64.3% (50.1, 73.4)
Per Investigator (2)				
1 - Clopper and Pearson	10/19	23/29	33/48	68.8% (53.7, 81.3)
1 - Atkinson and Brown	10/19	23/29	33/48	68.8% (53.7, 81.3)
2 - Clopper and Pearson	10/19	46/51	56/70	65.7% (53.4, 76.7)
2 - Koyama and Chen	10/19	46/51	56/70	65.7% (51.4, 74.6)

Source: (1) Table S.CH.5.1.8A; (2) Table S.CH.5.1.8B

A sensitivity analysis accounting for the two independent 2-stage designs that were conducted is also provided. This analysis is considering a correction to the overall alpha level according to Bonferroni. In that approach, the original 0.05 alpha level (corresponding to a 95% CI) is divided by two (for the two independent designs), resulting into a 0.025 alpha level (corresponding to a 97.5% CI). That correction was used to rectify the CI for all the key efficacy results (ORR, PFS and OS).

CIs resulting from this correction were all consistent with the ones from the original analyses and specifically from the primary efficacy analysis.

Table 4. Summary of BICR- and Investigator-Assessed Efficacy Results (Considering a 97.5% Confidence Interval) - All Combination Treated Subjects

	Number of Subjects (%)	
	BICR Assessment All Subjects N = 119	**Investigator Assessment** All Subjects N = 119
OBJECTIVE RESPONSE RATE (A) (97.5% CI)	71/119 (59.7) (49.0, 69.7)	72/119 (60.5) (49.8, 70.5)
DISEASE CONTROL RATE (B) (97.5% CI)	98/119 (82.4) (73.1, 89.5)	96/119 (80.7) (71.2, 88.1)
BEST OVERALL RESPONSE (C):		
COMPLETE RESPONSE (CR) (97.5% CI)	17 (14.3) (7.9, 23.0)	9 (7.6) (3.1, 14.8)
PARTIAL RESPONSE (PR) (97.5% CI)	54 (45.4) (35.0, 56.0)	63 (52.9) (42.3, 63.4)
PROGRESSION-FREE SURVIVAL (PFS)		
MEDIAN (MONTHS) (97.5% CI)	36.0 (27.8, N.A)	41.5 (27.8, 41.6)
12 MONTHS PFS RATE	69.8 (59.1, 78.2)	71.6 (61.0, 79.8)
24 MONTHS PFS RATE	63.5 (52.4, 72.6)	61.3 (50.2, 70.7)
30 MONTHS PFS RATE	59.7 (48.3, 69.4)	60.0 (48.7, 69.6)
OVERALL SURVIVAL (OS)		
MEDIAN (MONTHS) (97.5% CI)		N.A. (N.A., N.A.)
12 MONTHS OS RATE		84.9 (75.7, 90.8)
24 MONTHS OS RATE		74.8 (64.5, 82.5)
30 MONTHS OS RATE		74.8 (64.5, 82.5)

(A) CR+PR
(B) CR+PR+SD (for at least 12 weeks)
(C) Per RECIST 1.1 criteria, confirmation of response required
Confirmed best overall response where response designations before start of subsequent therapy contribute to the BOR determination.

- **Baseline PD-L1 Expression and Efficacy - Exploratory Endpoint**

Subjects were enrolled regardless of 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 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 PD-L1 expression using the Dako PD-L1 IHC 28-8 pharmDx test.

As of the 18 Aug 2017 DBL, the majority (85.7%) of subjects had PD-L1 tested at baseline and of these, most (89.2%) had quantifiable PD-L1 expression at baseline. 11 (10.8%) subjects did not have quantifiable PD-L1 expression at baseline (including PD-L1 tumour sample PD L1 not evaluable). No subjects had indeterminate PD-L1 expression at baseline.

As of the 19 Feb 2019 DBL, the majority (95.0%) of subjects had PD-L1 tested at baseline and of these, most (90.3%) had quantifiable PD-L1 expression at baseline. 9.7% of subjects did not have quantifiable PD-L1 expression at baseline (including subjects without baseline tumour sample and PD-L1 not evaluable). No subjects had indeterminate PD-L1 expression at baseline.

PD-L1 Expression and Efficacy

ORR

Objectives responses were observed in all combination treated subjects regardless of 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:
    - DBL Aug-2017
        - In all combination treated subjects with **≥ 1%** baseline tumour PD-L1 expression (n= 26), the ORR was **53.8%** (95% CI: 33.4, 73.4); 1 (3.8%) had a CR and 13 (50.0%) had a PR.
        - In all combination treated subjects with **< 1%** baseline tumour PD-L1 expression (n= 65), the ORR was **52.3%** (95% CI: 39.5, 64.9); 34 (52.3%) had a PR.
    - DBL Feb-2019
        - In all combination treated subjects with **≥ 1%** baseline tumour PD-L1 expression (n= 27), the ORR was **59.3%** (95% CI: 38.8, 77.6); 3 (11.1%) had a CR and 13 (48.1%) had a PR.
        - In all combination treated subjects with **< 1%** baseline tumour PD-L1 expression (n= 75), the ORR was **60.0%** (95% CI: 48.0, 71.1); 5 (6.7%) had a CR and 40 (53.3%) had a PR.
- ORR per BICR:
    - DBL Aug-2017
        - In all combination treated subjects with **≥ 1%** baseline tumour PD-L1 expression (n= 26), the ORR was **46.2%** (95% CI: 26.6, 66.6); 2 (7.7%) had a CR and 10 (38.5%) had a PR.
        - In all combination treated subjects with **< 1%** baseline tumour PD-L1 expression (n= 65), the ORR was **50.8%** (95% CI: 38.1, 63.4); 33 (50.8%) had a PR.
    - DBL Feb-2019
        - In all combination treated subjects with **≥ 1%** baseline tumour PD-L1 expression (n = 27), the ORR was **63.0%** (95% CI: 42.4, 80.6); 7 (25.9%) had a CR and 10 (37%) had a PR.
        - In all combination treated subjects with **< 1%** baseline tumour PD-L1 expression (n = 75), the ORR was **58.7%** (95% CI: 46.7, 69.9); 9 (12%) had a CR and 35 (46.7%) had a PR.

PFS:

- DBL Aug-2017
    - Median PFS per investigator assessment was not reached (95% CI: 11.07, NA months) in all combination treated subjects with ≥ 1% baseline PD-L1 expression (n = 26) and not reached (95% CI: 13.08, NA months) in all combination treated subjects with < 1% baseline PD-L1 expression (n = 65).

- Median PFS per BICR assessment was not reached (95% CI: 4.07, NA) in subjects with ≥ 1% baseline PD-L1 expression (n = 26) and not reached (95% CI: 12.45, NA) in subjects with < 1% baseline PD-L1 expression (n = 65).

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.

- DBL Feb-2019
  - Median PFS per BICR assessment was not reached (95% CI: 8.54, N.A.) in subjects with ≥ 1% baseline PD-L1 expression (n = 27) and was 35.98 (95% CI: 19.12, N.A.) months in subjects with < 1% baseline PD-L1 expression (n = 75).
  - Median PFS per investigator assessment was not reached (95% CI: N.A.) in all combination treated subjects with ≥ 1% baseline PD-L1 expression (n = 27) and was 41.49 (95% CI: 16.89, 41.59) months in all combination treated subjects with < 1% baseline PD-L1 expression (n = 75).

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 not reached in either PD-L1 ≥ 1% or < 1% baseline expression level (PD-L1 ≥ 1% expression level, 95% CI: NA, NA; PD-L1 < 1% expression level, 95% CI: 17.18, NA months).

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.

Efficacy of Combination Therapy Relative to Monotherapy

Table 40. Summary of Efficacy per BICR from Nivolumab + Ipilimumab Cohort and Nivolumab Cohort at Feb-2019 DBL - All Treated Subjects

	Nivolumab + ipilimumab Cohort BICR Assessment All Subjects N = 119	Nivolumab Cohort BICR Assessment All Subjects N = 74
Minimum follow-up (months)	27.5	33.7
Median follow-up (months)	31.5	37.6
Objective Response Rate (A)	71/119 (59.7)	28/74 (37.8)
(95% CI)	(50.3, 68.6)	(26.8, 49.9)
Disease Control Rate (B)	98/119 (82.4)	48/74 (64.9)
(95% CI)	(74.3, 88.7)	(52.9, 75.6)
Best Overall Response (C)		
Complete Response (CR)	17 (14.3)	8 (10.8)
(95% CI)	(8.5, 21.9)	(4.8, 20.2)
Partial Response (PR)	54 (45.4)	20 (27.0)
(95% CI)	(36.2, 54.8)	(17.4, 38.6)
Stable Disease (SD)	29 (24.4)	22 (29.7)
Progressive Disease (PD)	14 (11.8)	21 (28.4)
Unable to Determine (UTD)	5 (4.2)	3 (4.1)
TTR (month)		
Number of Responders	71	28

	Nivolumab + ipilimumab Cohort BICR Assessment All Subjects N = 119	Nivolumab Cohort BICR Assessment All Subjects N = 74
Median	3.22	4.42
Min, Max	1.1, 34.3	1.2, 27.9
DOR (month)		
Min, Max (D)	1.9, 36.9+	1.4+, 48.4+
Median (95% CI) (E)	N.R. (30.03, N.A.)	N.R. (N.A., N.A.)
Subjects with Ongoing Response (F)	49 (69.0)	14 (50.0)
Progression-free Survival		
# Events / # Subjects (%)	48/119 (40.3)	47/74 (63.5)
Median (month) (95% CI) (E)	36.0 (27.9, N.A.)	5.6 (3.0, 30.7)
Overall Survival		
# Events / # Subjects (%)	33/119 (27.7)	34/74 (45.9)
Median OS (month) (95% CI)	N.R. (N.A., N.A.)	52.6 (19.6, N.A.)
6 months OS rate (95% CI)	89.9 (82.9, 94.1)	81.1 (70.2, 88.3)
12 months OS rate (95% CI)	84.9 (77.1, 90.2)	68.9 (57.0, 78.1)
24 months OS rate (95% CI)	74.8 (66.0, 81.6)	57.8 (45.7, 68.1)

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

Abbreviations: DOR: duration of response; N.A.: Not Available; N.R.: Not Reached; TTR: time to response

(A) CR+PR.

(B) CR+PR+SD (for at least 12 weeks).

(C) Per RECIST 1.1 criteria, confirmation of response required.

(D) Symbol + indicates a censored value.

(E) Median computed using Kaplan-Meier method.

(F) 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.

- **Data analysis in subject ≥ 75 years of age**.

Of the 109 subjects in the modified population, 11 (11.2%) were 75 years or older. The ORR per BICR in subjects ≥ 75 years was 27.7% (3/11) at the Aug-2017 DBL and 36.4% (4/11) at the Oct-2020 DBL.

Baseline characteristics for these 109 subjects, including demographics, disease characteristics, and prior therapy, were analyzed by age categories. Selected characteristics related to baseline disease and prior therapy for subjects < 75 years and subjects ≥ 75 years are provided in Table 41. Baseline characteristics were generally consistent between the 2 age categories except for BRAF and KRAS status, and microsatellite instability (MSI) by central testing.

Table.41: Selected Characteristics Related to Baseline Disease and Prior Therapy by Age Category - Modified Population (N = 109) - CA209142 Cohort 2

	Number of Subjects (%)	
	Age: < 75 Years N = 98	Age: >= 75 Years N = 11
SEX		
MALE	60 (61.2)	5 (45.5)
FEMALE	38 (38.8)	6 (54.5)
DISEASE STAGE AT INITIAL DIAGNOSIS		
STAGE I	0	0
STAGE II	13 (13.3)	1 (9.1)
STAGE III	38 (38.8)	5 (45.5)
STAGE IV	47 (48.0)	5 (45.5)
PRIMARY TUMOR LOCATION		
RECTUM	5 (5.1)	0
LEFT COLON	21 (21.4)	0
RIGHT COLON	51 (52.0)	8 (72.7)
TRANSVERSE COLON	12 (12.2)	1 (9.1)
COLON NOS	1 (1.0)	0
SIGMOID	8 (8.2)	2 (18.2)
BRAF/KRAS MUTATION STATUS		
KRAS/BRAF WILD-TYPE	26 (26.5)	2 (18.2)
BRAF MUTATION	20 (20.4)	7 (63.6)
KRAS MUTATION	40 (40.8)	1 (9.1)
UNKNOWN	12 (12.2)	1 (9.1)
LOCAL MICROSATELLITE INSTABILITY RESULT		
MSI-H	97 (99.0)	11 (100.0)
MSI-H/MSI-S (1)	1 (1.0)	0
CENTRAL MICROSATELLITE INSTABILITY RESULT		
MSI-H	58 (59.2)	3 (27.3)
MSI-H/MSI-S	0	1 (9.1)
MSI-L	3 (3.1)	1 (9.1)
MSI-S	18 (18.4)	4 (36.4)
MSI-L/MSI-S	1 (1.0)	0
NOT REPORTED	18 (18.4)	2 (18.2)
TIME FROM INITIAL DIAGNOSIS TO FIRST DOSE		
MEDIAN (MIN -MAX) YEARS	1.73 (0.3 - 19.6)	2.12 (0.5 - 10.7)
< 1 YEAR	24 (24.5)	3 (27.3)
1- < 2 YEARS	30 (30.6)	2 (18.2)
2- < 3 YEARS	17 (17.3)	4 (36.4)
3- < 4 YEARS	12 (12.2)	1 (9.1)
4- < 5 YEARS	5 (5.1)	0
>= 5 YEARS	10 (10.2)	1 (9.1)
NUMBER OF PRIOR REGIMEN RECEIVED		
0	0	0
1	15 (15.3)	4 (36.4)
2	40 (40.8)	2 (18.2)
3	26 (26.5)	3 (27.3)
>=4	17 (17.3)	2 (18.2)

(1) For analysis purpose, Subject in this category will be considered MSI-H per local lab

The 11 subjects who were ≥75 years of age discontinued treatment for the following reasons: disease progression (n=5), maximum clinical benefit (n=3), drug-related AE (n=1), unrelated AE (n=1), and subject request (n=1).

Efficacy analyses by age categories were performed and are summarized in Table 42.

Table.42: Efficacy by Age Categorization - All Combination Therapy Treated Subjects - Modified Population (N = 109) - CA209142 Cohort 2 (BICR) (DBL Oct 2020)

	Age: < 75 Years N = 98	Age: >= 75 Years N = 11
ORR per BICR, %		
RESPONDERS/TOTAL	59/98 (60.2)	4/11 (36.4)
95% CI	(49.8, 70.0)	(10.9, 69.2)
DOR per BICR, MONTHS		
EVENTS/RESPONDERS (%)	11/59 (18.6)	0/4 (0)
MIN, MAX (A)	1.9, 58.0+	12.5+, 47.6+
MEDIAN (95% CI) (B)	N.A.	N.A.
SUBJECTS WITH ONGOING RESPONSE (C)	25 (42.4)	2 (50.0)
PFS per BICR, MONTHS		
EVENTS/TOTAL (%)	42/98 (42.9)	7/11 (63.6)
MEDIAN (95% CI) (B)	56.34 (30.29, N.A.)	16.89 (1.31, N.A.)
OS, MONTHS		
EVENTS/TOTAL (%)	27/98 (27.6)	6/11(54.5)
MEDIAN ((95% CI) (B)	N.A.	23.06 (4.76, N.A.)

(A) Symbol + indicates a censored value

(B) Median computed using KM 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

Abbreviations: BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; KM = Kaplan-Meier; N. A. = not available; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

The investigator assessed ORR in patients ≥ 75 years (overall population) was 45.5% (95% CI: 16.7, 76.6) (DBL Oct 2020).

Table.43: ORR (per Investigator) by subsets – All combination therapy treated subjects (N=119) – CA209142 Cohort 2 (DBL Oct 2020)

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Objective Response Rate (per Investigator) by Subsets (All Subjects and Subjects With or Without Prior 5FU-Oxa-Iri)

All dMMR/MSI-H Combination Therapy Treated Subjects (Nivolumab 3 mg/kg with Ipilimumab 1 mg/kg)

		OBJECTIVE RESPONSE RATE (%) (A) 95% CI		
		All Subjects N = 119	Subjects with Prior 5FU-Oxa-Iri N = 82	Subjects without Prior 5FU-Oxa-Iri N = 37
AGE CATEGORIZATION				
	< 65 YEARS	54/81 (66.7%) (55.3, 76.8)	38/57 (66.7%) (52.9, 78.6)	16/24 (66.7%) (44.7, 84.4)
	>= 65 YEARS	23/38 (60.5%) (43.4, 76.0)	14/25 (56.0%) (34.9, 75.6)	9/13 (69.2%) (38.6, 90.9)
	>= 65 AND < 75 YEARS	18/27 (66.7%) (46.0, 83.5)	12/20 (60.0%) (36.1, 80.9)	6/7 (85.7%) (42.1, 99.6)
	>= 75 YEARS	5/11 (45.5%) (16.7, 76.6)	2/5 (40.0%) (5.3, 85.3)	3/6 (50.0%) (11.8, 88.2)

Summary of main study

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 44. Summary of Main Study

Title: CA209142 Phase II multi-cohort, open-label, multi-centre trial including nivolumab in combination with ipilimumab (cohort 2) in adults who had disease progression during, after, or had been intolerant to therapy with 5FU-based chemotherapy with recurrent or metastatic dMMR or MSI-H CRC.	
Study identifier	CheckMate 142 (CA209142; NCT02060188)
	Phase II, multicentre, multi-cohort, open label, 2-stage design

Design	Duration of enrollment (cStage1): Duration of enrollment (cStage2):		May to Oct-2015 Feb to Sep-2016
Hypothesis			
Treatments groups	**Nivolumab + Ipilimumab** Cohort 2		Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg Q3W, followed by Nivolumab 240 mg Q2W until disease progression per RECIST 1.1, or unacceptable toxicity **N = 119**
Endpoints and definitions	Primary endpoint	Objective Response Rate (**ORR**)	**Investigator-assessed**
	Secondary endpoints	**ORR** **DCR**	**BICR-assessed** Investigator- and BICR-assessed
	Exploratory endpoints	**PFS**, **OS** Safety, ADA, PRO	 QLQ-C30 and EQ-5D
Database lock	**19-Feb-2019**		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	dMMR or MSI-H CRC per local lab, all nivolumab + ipilimumab combination subjects (N=119) Clinical cut-off date: 07-Jan-2019 Minimum follow-up: 33.7 months Median follow-up for OS: 30.65 months (range: 0.1 to 44.2 months)		
Descriptive statistics and estimate variability	Treatment group	All combination subjects	Prior 5FU-Oxa-Iri
	Number of subjects	119	82
	Investigator-assessed **ORR** (%)	60.5	59.8
	95% CI	(51.5, 69.3)	(48.3, 70.4)
	BICR-assessed **ORR** (%)	59.7	56.1
	95% CI	(50.3, 68.6)	(73.0, 90.3)
	Median **DoR** (months) BICR-assessed 95% CI	NR (30.03, NA)	33.38 (30.03, NA)
	Median **DoR** (months) Investigator-assessed 95% CI	NR	NR
		(34.60, NA)	(34.60, NA)
	Median **PFS** BICR-assessed 95% CI	36.0	36.0
		(27.9, NA)	(27.4, NA)
	Median **PFS** Investigator-assessed 95% CI	41.5	41.5
		(32.8, 41.6)	(27.8, 41.6)
Notes	Median **OS** was not reached in any case		
Database lock	**Oct-2020**		
Results and Analysis			

Analysis population and time point description	dMMR or MSI-H CRC per local lab, all nivolumab + ipilimumab combination subjects who had received previous treatment (n=119) Minimum follow-up: 46.9 months			
Descriptive statistics and estimate variability	Treatment group	All combination subjects	Prior 5FU-Oxa-Iri	No prior 5Fu-Oxa-Iri
	Number of subjects	119	82	37
	Investigator-assessed **ORR,** n (%)	77 (64.7)	52 (63.4)	25 (67.6)
	95% CI	(55.4, 73.2)	(52.0, 73.8)	(50.2, 82.0)
	Investigator assessed **BOR**			
	Complete response (CR), n(%)[95% CI]	15 (12.6) [7.2, 19.9]	10 (12.2) [6.0, 21.3]	5 (13.5) [4.5, 28.8]
	Partial response (PR), n(%) [95% CI]	62 (52.1) [42.8, 61.3]	42 (51.2) [39.9, 62.4]	20 (54.1) [36.9, 70.5]
	Stable disease (SD), n (%)	25 (21.0)	19 (23.2)	6 (16.2)
	Median DoR (months) investigator-assessed	N.R.	N.R.	N.R. (39.36, N.A.)
	95% CI	1.4+, 58.0+	1.4+, 58.0+	8.9, 58.0+
	BICR-assessed **ORR** (%)	61.3	58.5	67.6
	95% CI	(52.0, 70.1)	(47.1, 69.3)	(50.2, 82.0))
	BICR assessed **BOR**			
	Complete response (CR), n(%)[95% CI]	24 (20.2) [13.4, 28.5]	16 (19.5) [11.6, 29.7]	8 (21.6) [9.8, 38.2]
	Partial response (PR), n(%) [95% CI]	49 (41.2) [32.2, 50.6]	32 (39.0) [28.4, 50.4]	17 (45.9) [29.5, 63.1]
	Stable disease (SD), n (%)	27 (22.7)	22 (26.8)	5 (13.5)
	Median **DoR** (months) BICR-assessed	NR	NR	NR
	95% CI	(1.9, 58.0+)	(1.9, 57.6+)	(14.1, 58.0+)
	Median **PFS** BICR-assessed	56.3	56.3	NR
	95% CI	(27.8, NA)	(27.8, NA)	(2.8, NA)
	Median time to response - Months (range) per investigator assessment	2.8 (1.1, 37.1)	3.47(1.3, 37.1)	2.73(1.1, 33.2)

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Not applicable.

Supportive study

Study CA2097XM

The MAH conducted a retrospective cohort study (CA2097XM) using the Flatiron electronic health record (EHR) database from Jan-2013 through Apr-2020 to assess OS and time to next treatment (TTNT) among 2L and 3L patients with dMMR or MSI-H mCRC on standard of care treatment, respectively. While OS data (date of death) is very complete in the Flatiron dataset, there are no recordings of PFS available at this time for the mCRC patient population. Thus, TTNT was used as a surrogate for PFS. TTNT is defined as the period of time from the initial line of therapy to a subsequent line of therapy.

A matched cohort of patients with dMMR or MSI-H stage IV or recurrent mCRC treated with systemic therapy were identified in Flatiron using the eligibility criteria from CA209142.

Descriptive statistics were used to describe baseline demographics and clinical characteristics. The Kaplan-Meier estimator was used to estimate median OS, TTNT, and their associated 95% confidence intervals, respectively. For both OS and TTNT, patients were followed from initiation of 2L or 3L systemic treatment until the event of interest, censoring, or death. Censoring events were loss to follow-up, end of study period, and use of immunotherapy in later-line therapy.

Seventy-eight patients met inclusion criteria on 2L and 26 patients met inclusion criteria on 3L and were compared in terms of baseline demographics and clinical characteristics to the 37 and 82 patients from study CA209142 respectively.

Median OS and TTNT for CA2097XM patients on 2L were 15.3 months (95% CI: 11.1, 22.4) and 6.5 months (95% CI: 5.1, 8.1), respectively. Median OS and TTNT for CA2097XM patients on 3L were 14.8 months (95% CI: 5.1, 28.7) and 5.1 months (95% CI: 3.3, 7.0), respectively Median OS and PFS per BICR for CA209142 patients without prior 5FU-Oxa-Iri had not been reached. For CA209142 patients with prior 5FU-Oxa-Iri, median OS had not been reached and median PFS per BICR was 36.0 months (95% CI: 27.4, NA).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The data submitted to support this new indication is based on the results of the cohort 2 (combination therapy) (cStage1 and cStage2) from Study CA209142 (Checkmate 142). This is an open-label, multi-centre, 2-stage Simon design study of nivolumab monotherapy (mStage) or in combination with ipilimumab (cStage) to estimate the response rate in MSI-H/dMMR mCRC.

It is noted that, in the context of this new application data from cohort 1 (nivolumab monotherapy cohort) are submitted mainly to justify the contribution of the mono-components in the proposed combination of nivolumab + ipilimumab. No indication for nivolumab in monotherapy in the intended disease setting is currently sought.

The sample size has been arranged according to the Simon's Two-Stage design (optimal). The assumptions and the number of subjects for each stage are endorsed. A total of 119 subjects were enrolled in cohort 2 treatment period, 82 of whom had received prior treatment with 5FU-Oxa-Iri. There were also 23 non MSI-H subjects that were also treated with nivolumab in combination with ipilimumab (not included in this report). The MAH has provided results based on the 18-Aug-2017

clinical database lock (DBL) as well as updated efficacy data based on a later DBL (19-Feb-2019) and results for the main endpoints based on the latest DBL (Oct-2020).

The main limitation of the pivotal study submitted is the lack of a control arm, which hampers the interpretation of the reported results. In order to address these uncertainties and to further contextualise results from study CA209142, the MAH has provided results from a retrospective study (Study CA2097XM) based on real word data from the Flatiron database in MSI-H mCRC treated with SOC. However, ORR data are not available in this dataset which is a major limitation, i.e. data outputs from the study CA2097XM are mainly TTNT (as proxy for PFS) and OS that renders any comparison with data from study CA209142 of very limited value as for the challenging interpretation of time to event endpoints in the context of uncontrolled trials. Given the absence of an appropriate historical control, the MAH was asked to provide additional within-patient analyses to better understand the clinical relevance of the study results. The MAH was requested to provide results showing PFS on nivolumab/ipilimumab in relation to time to progression on previous therapy(ies) in the metastatic setting for each patient and statistically test this as well as for ORR. Furthermore, within-patient analyses of ORR per line of treatment were submitted. Overall, no correlation was observed between PFS and ORR to previous treatment and to the combination of nivolumab+ipilimumab. In fact, with regards to ORR, a high number of non-responders to most recent prior therapy did respond to nivolumab+ipilimumab treatment. It should be taken into account that for the overall population, there were missing data (i.e. 16 patients had missing TTP prior values and 29 patients had missing value for best response to most recent prior therapy). These patients were excluded from the analyses, i.e. no imputation of missing data was done. These analyses were also performed for 2L and 3L patients, separately and similar results were observed.

By protocol amendment 04 (Revised Protocol 03), the enrolment was chosen to be done by MSI-H/MMR per local lab instead of central lab due to difficulties in getting the results in time, which led to delays in the study. Previously, an over-enrolment of the Stage 2 had been decided in order to compensate for these delays in getting the central lab confirmed status for dMMR/MSI-H. SAP v. 2.0 (dated 30-Aug-2016) included these already mentioned changes on the primary analysis population. Moreover, a change in the methodology to estimate the CI of the primary endpoint was performed (from Atkinsons & Brown method to a Clopper-Pearson method). The latter was incorporated with SAP v.3.0 (dated 20 Jul 2017). Several sensitivity analyses have been provided to further assess the robustness of the results and the impact of these changes. Overall, results were consistent with the primary analysis.

As stated above, the MSI status of the study population was determined by local tests on either MSI or MMR deficiency by an accredited laboratory per local regulations (local lab). 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 were microsatellite stable (MSI-S, or MSS). However, when more than 5 loci are analysed, MSI-H tumours are defined as having instability in ≥ 30-40% markers, while MSI-L tumours are defined as having instability in < 30-40% markers. In both cases, MSI-S is defined as having no instability detected in any of the markers. Of the 119 patients in cohort 2, 118 (99.2%) were MSI-H by local testing and 1 patient was classified as MSI-H/MSI-S. The method used were in most cases IHC (44.5%) and PCR (36.15). MSI-H was centrally confirmed in 62 (52.1%) patients, with a concordance rate of 69.7%. There were 27 (22.7%) patients classified as non-MSI-H and 30 (25.2%) patients for whom central testing was not reported due to inadequate amount of tissue and/or viable tumour. At the Feb 2019 DBL, the number of patients centrally confirmed with MSI-H mCRC was of 70 (confirmed MSI-H population).

The enrolment of cohort 2 lasted approximately 15 months: May-2015 to Oct-2015 for cStage 1 and Feb-2016 to Aug-2016 for cStage 2. As the recruitment took place in two different timeframes (stage 1

and 2), the MAH was required and has provided baseline characteristics separately for subjects included on stage 1 (n=27) and stage 2 (n=92). There were some unbalances in baseline characteristics between the two stages that might explain the apparently lower ORR reported in patients from cStage 1 compared with cStage 2 (48.1% [95%CI: 28.7, 68.1] vs. 63.0% [95%CI: 52.3, 72.9]). The MAH was asked to further discuss these differences and whether unbalances observed in baseline characteristics may have contributed. In relation to this and in order to provide further confirmation that the observed results from study CA209142 are robust, the ORR results for the patients who were overenrolled in cStage1 and cStage2 (for the remaining patients with confirmed central testing as well as all remaining patients regardless of confirmation by central testing) were submitted and compared to the reported results for patients in protocol-defined cStage1 and 2. In addition, the DoR results for each stage (protocol-defined cStage1 [first 19 patients MSI-h CRC confirmed by central testing], protocol-defined cStage2 [first 29 patients with MSI-h CRC confirmed by central testing], and the remaining patients) were included. No clear trend in the mentioned unbalances has been observed in relation to possible worse prognostic factors and the differences observed in ORR may be due to the small size of cStage 1.

The primary DBL for the combination cohort occurred on 18-Aug-2017, with a minimum follow-up of 9 months. A later DBL was performed on 19-Feb-2019, with a minimum follow-up of 27.5 months. An updated efficacy analysis was performed based on the latest DBL (Oct-2020) upon request, with a minimum follow-up of 46.9 months.

Among combination treated subjects, the baselines seems balanced and overall, subjects included seem to be representative of the target population.

The majority of all treated subjects (82/119, 68.9%) were generally heavily pre-treated and received prior systemic cancer therapies that included all 3 components: 5FU, oxaliplatin and irinotecan (5FU-Oxa-Iri) (e.g., FOLFOX and FOLFIRI). These subjects hereafter referred to as "with 5FU-Oxa-Iri", represented a third line and beyond setting (3L+). Moreover, 57.1% and 29.4% of patients had received prior treatment with VEGF- and EGFR-inhibitors, respectively. As per inclusion criteria, patients must have received at least 1 prior therapy for their metastatic disease or patients had actively refused chemotherapy for the treatment of metastatic or locally advanced disease. One patient did not receive any prior line and refused chemotherapy in order to enter the study, per inclusion criteria. Moreover, there were 9 patients that did not receive prior treatment in the metastatic setting. They received oxaliplatin in the (neo)-adjuvant setting and progressed during or within 6 months of completion of the adjuvant therapy. It was questioned that those patients pertained to a different treatment setting and as a consequence the updated efficacy analysis (DBL Oct-2020) excluded all patients who had not received prior fluoropyrimidine based chemotherapy in the metastatic setting in cohort 2, i.e. 10 patients. It is however recognised that in clinical practice patients progressing on or within 6 months of completion of adjuvant chemotherapy in the non-metastatic setting are considered as having been treated with first-line (1L) chemotherapy. In this regard it is noted that in fact these patients are normally excluded from clinical studies that enrol 1L patients. 'All Combination Treated Subjects' population (n=119) have been the one used for efficacy inference and analysis/data corresponding to that population is included in the SmPC. With this in mind the efficacy analysis / summary of efficacy results for the Oct 2020 DBL was updated to include data for all subjects in the 'without 5FU-Oxa-Iri' population recruited according to the protocol, i.e. 37 patients and, in the same way, efficacy results for 'all prior 5Fu-Oxa-Iri subjects' (N=82). Data from the 'all treated' population (n=119) had already been submitted.

In the majority of patients (70.6%), time from progression to most recent prior treatment to start treatment with nivolumab + ipilimumab was < 3 months. Information of the median time to disease progression on most recent therapy was provided.

Efficacy data and additional analyses

With a minimum follow-up of at least 9 months for the **primary database lock** (Aug-2017), the primary endpoint of investigator-assessed ORR by RECIST 1.1 was 54.6% (95% CI: 45.2, 63.8; 65/119) in all combination treated subjects and 52.4% (95%CI: 41.1, 63.6; 43/82) in subjects with prior 5FU-Oxa-Iri. The BICR-assessed ORR using RECIST 1.1 was 48.7% (95%CI: 39.5, 58.1; 58/119) in all combination treated subjects and 46.3% (95%CI: 35.3, 57.7; 38/82) in subjects with prior 5FU-Oxa-Iri. Median DOR per investigator and per BICR was not reached in either subject population.

The ORR as per investigator in MSI-H centrally confirmed patients was 54.8% (95%CI: 41.7, 67.5) in the overall population (n=62) and 56.4% (95%CI: 39.6, 72.2) in subjects with prior 5FU-Oxa-Iri treatment (n=82).

In general, subgroup analysis showed rather consistent results. Investigator-assessed ORR by KRAS/BRAF wild type (WT) status in all combination treated subjects was 54.8% (17/31) and 42.9% (9/21) in subjects with prior 5FU-Oxa-Iri. ORR was similar in subjects with BRAF mutation status (55.2% vs 56.3% in all combination treated and subjects with prior 5FU-Oxa-Iri, respectively) and KRAS mutation status (56.8% vs 57.9%, respectively). However, ORR appears lower in patients ≥75 years (27.3%) and in patients with 4 or more prior therapies (36.8%). The latter is not unexpected; however, sample size for elderly patients is quite limited (n=11) and interpretation of efficacy results is difficult. This information is included in the PI.

Investigator and BICR assessments for responders was highly concordant; 90.7% in all combination treated subjects and 88.9% in subjects with prior 5FU-Oxa-Iri.

The median PFS per investigator was not reached in all combination treated subjects and subjects with prior 5FU-Oxa-Iri. On the date of the last on-study tumour assessment, 86 (72.3%) and 60 (73.2%) subjects had their PFS time censored, respectively. The most common reason for censoring among these subjects was 'still on treatment'. The median PFS per BICR was not reached in all combination treated subjects and subjects with prior 5FU-Oxa-Iri. Seventy nine (66.4%) and 54 (65.9%) 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'.

Investigator and BICR-assessed KM PFS curves were similar for each subgroup of KRAS/BRAF mutation status in all combination treated subjects as well as in subjects with prior 5FU-Oxa-Iri. Investigator and BICR-assessed KM PFS curves were close for each subgroup of Lynch syndrome in all combination treated subjects as well as in subjects with prior 5FU-Oxa-Iri. Median PFS was not reached in any subgroup/population.

With regard to OS, at the time of the DBL, data were still immature. Median OS has not been reached, neither for all combination treated subjects nor for subjects with prior 5FU-Oxa-Iri. Twenty-three events occurred in 119 subjects (19.3%) and 14 events in the 82 (17.1%) subjects with prior 5FU-Oxa-Iri. At the time of the DBL, among all combination treated subjects, 96 (80.7%) were censored. Of those censored, 75 (63.0%) subjects were still on treatment (71 [59.7%] subjects had not progressed), and 21 (17.6%) subjects were in follow up. Among patients with prior 5FU-Oxa-Iri, 68 (82.9%) subjects were censored, of which 53 (64.6%) were still on treatment (50 [61.0%] subjects had not progressed), and 15 (18.3) subjects were in follow-up. No subjects were off-study in either group. Median follow-up for OS (time between first dose date and last known date alive or death) was 12.94 months (range: 0.1 to 26.1 months) among all combination treated subjects and 13.11 months (range: 0.1 to 26.1 months) in subjects with prior 5FU-Oxa-Iri.

Updated efficacy data with a **later DBL** (Feb-2019) were provided, with a minimum follow-up of 27.5 months. At that time, the investigator-assessed ORR using RECIST 1.1 was 60.5% (95% CI: 51.1,

69.3; 72/119) in dMMR or MSI-H per local lab, in all combination therapy treated subjects, with 9 CR (7.6%) and 63 achieved PR (52.9%). The BICR-assessed ORR using RECIST 1.1 was 59.7% (95% CI: 50.3, 68.6; 71/119) in dMMR or MSI-H per local lab, in all combination therapy treated subjects with 17 having achieved CR (14.3%) and 54 having achieved PR (45.4%). In the subgroup of patients previously treated with 5FU-Oxali-Iri the investigator-assessed ORR was 59.8% and the BIC-assessed ORR was 56.1%. Median DOR per BICR and investigator was not reached for the all treated subjects (95%CI: 30.03, NA and 34.6, NA, respectively). Median DOR in the subgroup of patients previously treated with 5FU-Oxali-Iri was not reached as per investigator assessment (95% CI: 34.60, NA) and was of 33.38 months (95%CI: 30.03, NA) according to BIRC. One subject was no longer considered as a responder in this data update due to a change in the assessment by a different adjudicator.

ORR for confirmed Lynch Syndrome patients was higher: 71.4%. No differences were found between KRAS/BRAF WT, KRAS and BRAF mutated subjects.

Regarding prior treatment lines, ORR was lower when advancing in treatment line: ORR of 63% for 2L patients, 58.1% for 3L, 51.7% for 4L and 36.8% for patients who received this combination for later than 4L treatment. It should be highlighted that 51.7% is a very valuable ORR for 4L patients, as treatment options at this point are limited and this could be a subgroup of patients who could considerably benefit from new treatment options.

Comparable ORR was observed between the central lab confirmed subjects (n=70) and local lab confirmed subjects (n=119, shown above). For the central lab confirmed subjects, ORR was 65.7% (95% CI: 53.4, 76.7; 46/70) per Investigator, and 64.3% (95%CI: 51.9, 75.4) per BICR. Overall, the investigator-assessed and BICR-assessed ORR were comparable across baseline subgroups for all combination treated subjects and in line with prior data analysis.

With regard to PFS, at the time of the DBL, the median Investigator-assessed PFS was of 41.5 months (95%CI: 32.8, 41.6), the same as for prior 5-Fu-Oxa-Iri treated patients. The median BICR-assessed PFS was of 36 months (95%CI: 27.9, N.A). However, the number of events accounted for in this analysis are still low (40.3% in the overall population according to BIRC and Investigator).

At the time of the DBL median OS for all combination treated subjects had not been reached (neither for the subgroup of patients with prior treatment with 5FU-Oxa-Iri). A total of 33 events (27.7%) occurred in 119 combination treated subjects (22 [26.8%] among patients with prior treatment with 5FU-Oxa-Iri). OS rates at 12 months, for the overall population and for the subgroup of patients with prior 5FU-Oxa-Iri were around 84.9% and 87.8% and at 24 months 74.8% and 75.6%, respectively.

The reported data are considered encouraging and of particular value in patients having received prior treatment with 5FU-Oxa-Iri (3L+) in whom currently available systemic therapy options provide very limited overall clinical activity and invariably short-lived. The observed magnitude of durable tumour responses could be regarded as clinically relevant as it is reasonable to expect that these will translate into a survival benefit; though its magnitude is yet to be determined.

Updated efficacy data from the **latest DBL** (Oct-2020) after approximately 20 months of additional follow-up was submitted for the overall population (n=119), 2L and 3L patients. The investigator assessed-ORR was 64.7% (95% CI: 55.4, 73.2) for all subjects who received therapy in the metastatic setting, 63.4% (95% CI: 52.0, 73.8) for subjects with prior 5FU-Oxa-Iri therapy (n=82) and 67.6% (95% CI: 50.2, 73.8) for subjects without prior 5FU Oxa-Iri therapy (n=37). These results were consistent with BICR-assessed ORR. Responses are durable with median duration of response not having been reached in either of the two subpopulations. A significant improvement was observed for BICR-assessed PFS (exploratory endpoint) compared to the previously reported. Up to Oct-2020, median PFS was 56.3 (95% CI: 30.3, N.A.) months for the total population, 56.3 (95% CI: 27.8, N.A.) months for the 3L population and N.R. (16.5, N.A.) for the 2L population, while mPFS was around 36

months in the previous cut-off. Regarding OS, 35 (29.4%) events occurred in the total population of 119 patients. This represents 2 additional events with respect to the previous DBL (Feb 2019). The relatively low number of OS events reported after a minimum follow-up of nearly 4 years , i.e. 86 out of the 119 patients (72.3%) are still alive, is considered to support the clinical benefit of the combination in the intended treatment setting albeit the limitations of the uncontrolled nature of the data set.

The benefit in the 2L was initially regarded as slightly less clear, considering that these patients still have some established treatment options among traditional (chemo)therapy. A discussion of the benefit/risk in the claimed broad indication and the 2L and ≥3L separately was requested. Investigator-assessed and BICR-assessed ORR results and median duration of response (not reached) were similar for 2L and 3L subjects based on the latest DBL, see above, and considering its magnitude are considered clinically meaningful also for 2L patients.

As previously observed, an apparently lower efficacy was observed in patients ≥ 75 years and it is to be noted that only 11 from the 109 subjects in the modified population were 75 years or older (the same than in the all treated population). Up to the new DBL (Oct-2020), the BICR assessed ORR for these 11 subjects was 36.4% (4/11) while the ORR was 27.3% (3/11) at the initial cut-off date (Aug-2017), therefore one more subject was considered as a responder for the updated analysis. Some baseline demographic and disease baseline characteristics by age categories (<75 and ≥75) have been analysed by the MAH to try to explain this low response rate in elderly patients. The percentage of subjects with right colon as primary tumour location was higher in elderly (72.7% vs. 52%), BRAF mutation was also more reported for elderly patients (63.6% vs. 2.4%) and more patients from this group were reported as MSI-S by central assessment (36.4% vs. 18.4%). Results for PFS and OS by these age categories have also been reported. Median PFS was 56.34 (95% CI: 30.26, N.A.) months for <75 years and 16.89 (95% CI: 1.31, N.A.) months for ≥75 years subjects. Due to the small sample size for this group (N=11), it is really difficult to reach any conclusion. This information regarding lower ORR for subjects ≥75 years have been included in the PI.

In addition, as discussed above, a lower ORR was observed in patients from cStage 1 compared to cStage 2 (48.1% [95%CI: 28.7, 68.1] vs. 63.0% [95%CI: 52.3, 72.9]). As observed for the previous data cut-off (Feb-2019), in the modified population (N=109) using Oct-2020 DBL, the ORR in cStage 1 (50.0% [95% CI: 29.9, 70.1]) (N=26) was also numerically lower than that in cStage 2 (60.2% [95% CI: 48.9, 70.8]) (N=83). The differences observed in ORR between patients from cStage 1 and cStage 2 may be due to the small sample size of cStage 1. Baseline characteristics by enrollment stages were evaluated to further investigate this difference. Some unbalances were found between both stages: in cStage 1 there were fewer male subjects, more KRAS mutated patients and more 3L subjects (prior 5Fu-Oxa-Iri) but these differences are not considered to explain the lower ORR in the cStage 1 population. However, it is important to note that there were also differences regarding primary tumor location (left colon location was nearly double in cStage 2 than cStage 1 patients). Tumor location has been postulated as a prognostic factor in CRC. In fact, left-sided primary tumor location has been associated with a reduced risk of death (Petrelli F et al. JAMA Oncol; 2016). Nevertheless, since this is a "selected" population (i.e. patient with MSI-H/dMMR CRC) it is not clear whether a similar effect could be expected in this case. Overall, the MAH's justification is acknowledged.

The MAH was also requested to evaluate if over-enrollment and MSI-H status per central lab had any impact on ORR results. Excluding over-enrolled patients, the first 19 subjects enrolled in cStage 1 appeared to have numerically lower ORR than the first 29 subjects enrolled in cStage 2 across both centrally-confirmed (57.9% vs. 69.0%) and locally-determined (47.4% vs. 69.0%). ORR in over-enrolled subjects with centrally-confirmed MSI-H status (N=14) was 57.1% (95% CI: 28.9, 82.3) and ORR in all centrally-confirmed MSI-H subjects (N=62) was 62.9% (95% CI: 49.7, 74.8). In the same

way, ORR in over-enrolled subjects with locally-confirmed MSI-H status (N=61) was consistent with all locally-determined MSI-H subjects (N=109), being 55.7% and 57.8% respectively. Overall, over-enrollment did not seem to have had an impact on ORR results differently from the efficacy results obtained for centrally and locally-confirmed MSI-H status subjects, as reported in the initial assessment.

In addition, as originally planned, an analysis for cohort 2 for the primary endpoint for the first 48 centrally-confirmed MSI-H patients included was provided, while also using a Bonferroni-correction due to the two cohorts, i.e. using a 97.5% confidence interval and results seemed to confirm those observed for the overall population.

An exploratory analysis of efficacy according to PD-L1 expression was performed. PD-L1 expression was not an inclusion criterion. Of the 119 patients included in Cohort 2 of the study, 102 (90.3%) had quantifiable PD-L1 expression (DBL 19 Feb 2019). The majority of patients had a PD-L1 expression <1% (73.5%). Overall, ORR results were consistent regardless of PD-L1 expression (<1% or ≥1%). However, response appears to be higher in patients with PD-L1 ≥5% (n=15), with an ORR of 80% as per investigator and 86.7% according to BIRC compared with the ORR in patients with PD-L1 <5% (n=87) 56.3% and 55.2%, investigator and BIRC, respectively. However, considering the exploratory nature of this analysis and the low number of patients with PD-L1 ≥ 5% no conclusions can be drawn.

In order to justify the contribution of the combination of nivolumab + ipilimumab over nivolumab monotherapy, the MAH has provided comparative efficacy data from Cohort 1 and Cohort 2 of the CA209142 study. Overall, the ORR reached with the combination was higher than with nivolumab monotherapy (59.7% [95%CI: 50.3, 68.6] vs. 37.8% [95%CI: 26.8, 49.9], respectively). Median duration of response was not reached in either cohort. Even if any comparison between non randomised cohorts requires cautious interpretation and no definitive conclusions can therefore be drawn, the reported results appear to strongly suggest that the addition of ipilimumab to nivolumab leads to better efficacy in the targeted patient population.

Even if results reported in cohort 2 of the CA209142 study are considered clinically relevant, data cannot be regarded as comprehensive as a result of the uncontrolled nature of the study that limits interpretation of data. In this respect the MAH has proposed to provide results from a currently ongoing randomized Phase 3b trial (Study CA2098HW) as a post-authorisation measure (PAM). Results from this study are expected to provide replication of ORR and DOR results in the ≥2L population, and also randomised data to compare numerical differences between chemotherapy and nivolumab (in combination with ipilimumab) in the 2L setting of dMMR or MSI-H mCRC. Results from this study should be submitted when available in the context of a recommendation.

The revised protocol version 03 (dated 28-Mar-2019) has been submitted as part of the documentation for this procedure. CA2098HW is a Phase 3, randomized, 3-arm open-label study of nivolumab monotherapy (Arm A), nivolumab plus ipilimumab combination therapy (Arm B) or an investigator's choice chemotherapy (Arm C) for the treatment of participants with recurrent or metastatic dMMR or MSI-H CRC. The trial was expanded (Revised protocol v.04, 09-Jul-2019) to include more participants in the 1L setting, as discussed at the SA meeting in Sep-2019 (EMEA/H/SA/3330/4/2019/II). As a result, the study enrolment consists of 2 sequential parts. Part 1 enrolment is open to participants across all lines of therapy, and Part 2 enrolment is open only to participants who have not received prior therapy for metastatic disease (1L). It is expected that approximately 748 participants with dMMR or MSI-H mCRC determined by local testing will be randomized to the study, including approximately 492 and 256 during Part 1 and Part 2 enrolment, respectively. Participants will be randomized to arms A, B or C in a 2:2:1 ratio. Randomization to Arm C will be restricted to participants who have received no more than 1 prior line of systemic therapy (0 or 1 line). Part 1 enrolment continues to allow randomization of approximately 492 participants across lines of therapy

with locally determined dMMR or MSI-H mCRC as per protocol revision 3. As of 01-Jul-2020, study had randomized 282 participants across lines of therapy during Part 1 enrolment. The study has dual primary endpoints of BICR assessed PFS between Arms B and A across all randomized patients (PFS in all lines B vs A) and BICR assessed PFS between Arms B and C across patients who have not received prior therapy (PFS in 1L B vs C). The study is also powered for comparison of key secondary endpoint of BICR assessed PFS between Arms B and A in patients who have not received prior therapy (PFS in 1L B vs A). Other secondary endpoints include BICR assessed ORR, safety and OS across arms. As of 30-Nov-2020, Part 1 enrollment is complete and a total of 558 subjects with MSI-H/ dMMR mCRC determined by local testing were randomized as of 31-Dec-2020. Part 2 enrollment started on 01 Dec 2020 and, as of 31-Dec-2020, 5 subjects with MSI-H/ dMMR mCRC determined by local testing have been randomized. Enrollment in the study is projected to be completed by 1Q 2022 and the first IA is projected to occur in 4Q 2022.

2.4.4. Conclusions on the clinical efficacy

Data supporting this variation procedure are based on the analysis of Cohort 2 (combination therapy) of the phase 2 uncontrolled study CA209142 in which a total of 119 dMMR/MSI-H mCRC patients previously treated with fluoropyrimidine-based chemotherapy were included. One of the main limitations of this study is its exploratory nature including the lack of a control arm, which hampers the interpretation of the reported results.

Further, currently available data from the literature do not allow to firmly conclude on the relevance, or to define MSI-H/dMMR status as an independent prognostic factor, which is an additional limitation.

Notwithstanding the above limitations, the results reported in the 119 patients from CA209142 can be considered clinically meaningful and are numerically superior to currently available therapies for (MSI-H) mCRC patients. Even if it is acknowledged that historical data indicating sub-optimal outcomes in mCRC patients treated with 2L chemotherapy come from unselected mCRC patients, in view of the reported data, i.e. ORR of 61.3% (95% CI: 52.0, 70.1) with long durations of response it is difficult to foresee that potential differences in prognosis or response to treatment in the targeted MSI-H mCRC population compared to other CRC patients could challenge the relevance of obtained results, which have notably matured after additional 20 months of follow-up (minimum follow-up of nearly 4 years) and remain consistent. The available dataset for the so called 2L or 'without 5FU-Oxa-Iri' patients is certainly limited, i.e. a total of 37 patients, including 9 patients who progressed on or within 6 months of completion of adjuvant chemotherapy in the non-metastatic setting. However, the reported ORR and DOR are in line with those reported in 3L patients and can be expected to translate into a clinically meaningful effect also in this group.

Taking all the above into account it can be concluded that clinically meaningful efficacy has been reported for nivolumab in combination with ipilimumab in the applied indication, i.e. for the treatment of adult patients with dMMR or MSI-H mCRC after prior fluoropyrimidine based combination chemotherapy. Further relevant information is also included in section 5.1.

Results from part 1 of the ongoing CA2098HW phase 3 study, which are expected to provide replication of ORR and DOR results in the ≥2L population as well as randomised data to compare numerical differences between chemotherapy and nivolumab (in combination with ipilimumab) in the 2L setting of dMMR or MSI-H mCRC, will be submitted when available as a post-authorisation measure (PAM) and capture as recommendation.

2.5. Clinical safety

Introduction

The WSA provided safety data, for the nivolumab + ipilimumab combination in subjects with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC), from Study CA209142.

The Summary of Clinical Safety (SCS) provides safety data for one arm of combination treatment (N=119), where dMMR or MSI-H CRC subjects were treated with nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (Q3W), followed by nivolumab 3 mg/kg every 2 weeks (Q2W). The SCS provides an assessment of safety based on the Feb-2019 DBL, with minimum follow-up of approximately 27.5 months, updated from a previous CSR DBL of Aug-2017.

In addition to the safety data from CA209142, pooled safety data of CA209142 and Study CA2092143 (which examined nivolumab 3 mg/kg + ipilimumab 1 mg/kg treatment Q3W followed by nivolumab 3 mg/kg Q2W in subjects with renal cell carcinoma [RCC]) are presented to provide a safety profile of the same combination regimen in a broader population.

Patient exposure

Table 45. Cumulative Dose and Relative Dose Intensity Summary – All Combination Treated Subjects in CA209142 (Feb-2019 DBL)

	All Subjects N = 119	
	Nivolumab	Ipilimumab
NUMBER OF DOSES RECEIVED		
MEAN (SD)	40.3 (28.62)	3.7 (0.81)
MEDIAN (MIN - MAX)	51.0 (1 - 93)	4.0 (1 - 4)
Q1, Q3	6.0, 65.0	4.0, 4.0
CUMULATIVE DOSE (MG/KG)		
MEAN (SD)	119.39 (84.780)	3.70 (0.815)
MEDIAN (MIN - MAX)	147.03 (3.0 - 278.9)	4.00 (1.0 - 4.2)
Q1, Q3	18.00, 189.42	3.97, 4.02
RELATIVE DOSE INTENSITY		
>= 110%	0	0
90% TO < 110%	91 (76.5)	101 (84.9)
70% TO < 90%	26 (21.8)	15 (12.6)
50% TO < 70%	2 (1.7)	3 (2.5)
< 50%	0	0

Source: refer to Table S.4.1 of the CA209142 Ad Hoc Combination Efficacy Report

Note: the number of ipilimumab doses to be administered in combination with nivolumab was 4 per protocol in Cohort 2.

The median duration of therapy in all combination therapy treated subjects based on Kaplan-Meier analysis was 24.90 months. As of the Feb-2019 DBL, the maximum duration of therapy was 44.09 months and 2.10 months for nivolumab and ipilimumab, respectively.

Adverse events

As of the Feb-2019 DBL, the most common AEs, the most common drug-related AEs and deaths (none were ascribed to study drug toxicity) are reported in table 46.

Safety summaries presented in this section are with follow-up of 30 days after last dose, except those with extended follow-up, which was follow-up of 100 days after last dose.

The overall safety profile of nivolumab 3 mg/kg with ipilimumab 1 mg/kg for the treatment of subjects with dMMR or MSI-H CRC after prior fluoropyrimidine-based combination chemotherapy was consistent with the established safety profile of nivolumab in combination with ipilimumab, in other tumour types, and no new safety concerns were identified.

Table 46. Summary of Safety Results - All Combination Therapy Treated Subjects (Feb-2019 DBL vs Aug-2017 DBL)

	Number (%) Subjects			
	All Combination Therapy Treated Subjects (N = 119)			
	19-Feb-2019 DBL		18-Aug-2017 DBL	
DEATHS	33 (27.7)		23 (19.3)	
WITHIN 30 DAYS OF LAST DOSE	3 (2.5)		2 (1.7)	
WITHIN 100 DAYS OF LAST DDOSE	13 (10.9)		11 (9.2)	
DUE TO DISEASE	29 (24.4)		19 (16.0)	
DUE to STUDY DRUG TOXICITY	0		0	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
ALL CAUSALITY SAEs	63 (52.9)	49 (41.2)	57 (47.9)	45 (37.8)
DRUG-RELATED SAEs	27 (22.7)	24 (20.2)	27 (22.7)	24 (20.2)
ALL CAUSALITY AEs LEADING TO DC	19 (16.0)	13 (10.9)	17 (14.3)	12 (10.1)
DRUG-RELATED AEs LEADING TO DC	16 (13.4)	12 (10.1)	15 (12.6)	12 (10.1)
ALL-CAUSALITY AEs	118 (99.2)	71 (59.7)	118 (99.2)	65 (54.6)
Most Frequent AEs (≥ 25% of Any Grade at either of the DBLs)				
DIARRHOEA	64 (53.8)	7 (5.9)	53 (44.5)	4 (3.4)
PYREXIA	50 (42.0)	0	42 (35.3)	0
COUGH	40 (33.6)	1 (0.8)	22 (18.5)	1 (0.8)
FATIGUE	40 (33.6)	4 (3.4)	39 (32.8)	4 (3.4)
PRURITUS	40 (33.6)	2 (1.7)	33 (27.7)	2 (1.7)
ANAEMIA	39 (32.8)	9 (7.6)	28 (23.5)	9 (7.6)
NAUSEA	35 (29.4)	1 (0.8)	31 (26.1)	1 (0.8)
ABDOMINAL PAIN	34 (28.6)	4 (3.4)	26 (21.8)	4 (3.4)
ASTHENIA	33 (27.7)	3 (2.5)	22 (18.5)	3 (2.5)
BACK PAIN	32 (26.9)	3 (2.5)	24 (20.2)	3 (2.5)
DRUG-RELATED AEs	95 (79.8)	38 (31.9)	87 (73.1)	38 (31.9)
Most Frequent Drug-related AEs (≥15% of Any Grade at either of the DBLs)				
DIARRHOEA	30 (25.2)	3 (2.5)	26 (21.8)	2 (1.7)
PRURITUS	24 (20.2)	2 (1.7)	20 (16.8)	2 (1.7)
FATIGUE	22 (18.5)	2 (1.7)	21 (17.6)	2 (1.7)
HYPOTHYROIDISM	21 (17.6)	1 (0.8)	16 (13.4)	1 (0.8)
AST INCREASED	19 (16.0)	9 (7.6)	17 (14.3)	9 (7.6)
PYREXIA	18 (15.1)	0	18 (15.1)	0
RASH	18 (15.1)	2 (1.7)	13 (10.9)	2 (1.7)
ALL CAUSALITY SELECT AES, BY CATEGORY				
ENDOCRINE	41 (34.5)	7 (5.9)	33 (27.7)	6 (5.0)
GASTROINTESTINAL	64 (53.8)	8 (6.7)	53 (44.5)	6 (5.0)
HEPATIC	41 (34.5)	19 (16.0)	33 (27.7)	15 (12.6)
PULMONARY	7 (5.9)	1 (0.8)	6 (5.0)	1 (0.8)
RENAL	24 (20.2)	4 (3.4)	20 (16.8)	4 (3.4)
SKIN	71 (59.7)	7 (5.9)	54 (45.4)	7 (5.9)
HYPERSENSITIVITY/INFUSION REACTIONS	7 (5.9)	0	5 (4.2)	0
DRUG-RELATED SELECT AES, BY CATEGORY				
ENDOCRINE	38 (31.9)	7 (5.9)	30 (25.2)	6 (5.0)
GASTROINTESTINAL	30 (25.2)	4 (3.4)	27 (22.7)	4 (3.4)
HEPATIC	28 (23.5)	14 (11.8)	23 (19.3)	13 (10.9)
PULMONARY	7 (5.9)	1 (0.8)	6 (5.0)	1 (0.8)
RENAL	7 (5.9)	2 (1.7)	6 (5.0)	2 (1.7)
SKIN	42 (35.3)	5 (4.2)	34 (28.6)	5 (4.2)
HYPERSENSITIVITY/INFUSION REACTIONS	4 (3.4)	0	4 (3.4)	0
ALL CAUSALITY IMMUNE-MEDIATED ADVERSE EVENTS WITHIN 100 DAYS OF LAST DOSE				
Treated with Immune-Modulating Medications				
PNEUMONITIS	3 (2.5)	0	2 (1.7)	0
DIARRHEA/COLITIS	8 (6.7)	4 (3.4)	8 (6.7)	4 (3.4)
HEPATITIS	12 (10.1)	10 (8.4)	10 (8.4)	9 (7.6)
NEPHRITIS AND RENAL DYSFUNCTION	2 (1.7)	2 (1.7)	2 (1.7)	2 (1.7)
RASH	20 (16.8)	5 (4.2)	17 (14.3)	5 (4.2)
HYPERSENSITIVITY/INFUSION REACTIONS	3 (2.5)	0	3 (2.5)	0
ALL CAUSALITY ENDOCRINE IMMUNE-MEDIATED ADVERSE EVENTS WITHIN 100 DAYS OF LAST DOSE				
Treated with or without Immune-Modulating Medications				
ADRENAL INSUFFICIENCY	10 (8.4)	3 (2.5)	7 (5.9)	2 (1.7)
HYPOPHYSITIS	5 (4.2)	3 (2.5)	4 (3.4)	3 (2.5)
HYPOTHYROIDISM/THYROIDITIS	23 (19.3)	3 (2.5)	18 (15.1)	3 (2.5)
HYPERTHYROIDISM	18 (15.1)	0	14 (11.8)	0
DIABETES MELLITUS	1 (0.8)	0	0	0

ALL CAUSALITY OTHER EVENTS OF SPECIAL INTEREST WITHIN 100 DAYS OF LAST DOSE
Treated with or without Immune-Modulating Medications

ENCEPHALITIS	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
MYOSITIS	2 (1.7)	1 (0.8)	1 (0.8)	1 (0.8)
PANCREATITIS	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
UVEITIS	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)

MedDRA Version: 20.0 (Aug-2017 DBL) and 21.1 (19-Feb-2019 DBL); CTC Version 4.0
All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Common adverse events

- **All causality**

Any-grade, all-causality AEs were reported in 99.2 % of subjects. The most common AEs were diarrhoea (53.8%), pyrexia (42.0%), and cough, fatigue, and pruritis (each 33.6%). All causality Grade 3-4 AEs occurred in 59.7% of subjects. The most common Grade 3-4 AEs were lipase increased (12.6%), aspartate transferase (AST) increased (10.1%), and anaemia and ALT increased (each 7.6%).

Table 47. Adverse Events by Worst CTC Grade Reported in ⩾ 10% of Treated Subjects in CA209142

System Organ Class (%) Preferred Term (%)	All Subjects N = 119 Any Grade	 Grade 3-4	 Grade 5
TOTAL SUBJECTS WITH AN EVENT	118 (99.2)	71 (59.7)	3 (2.5)
General disorders and administration site conditions	101 (84.9)	8 (6.7)	1 (0.8)
Pyrexia	50 (42.0)	0	0
Fatigue	40 (33.6)	4 (3.4)	0
Asthenia	33 (27.7)	3 (2.5)	0
Influenza like illness	16 (13.4)	1 (0.8)	0
Pain	14 (11.8)	1 (0.8)	0
Gastrointestinal disorders	97 (81.5)	23 (19.3)	0
Diarrhoea	64 (53.8)	7 (5.9)	0
Nausea	35 (29.4)	1 (0.8)	0
Abdominal pain	34 (28.6)	4 (3.4)	0
Vomiting	27 (22.7)	3 (2.5)	0
Constipation	22 (18.5)	0	0
Abdominal pain upper	13 (10.9)	1 (0.8)	0
Skin and subcutaneous tissue disorders	79 (66.4)	7 (5.9)	0
Pruritus	40 (33.6)	2 (1.7)	0
Rash	25 (21.0)	3 (2.5)	0
Dry skin	18 (15.1)	0	0
Investigations	77 (64.7)	34 (28.6)	0
Aspartate aminotransferase increased	27 (22.7)	12 (10.1)	0
Alanine aminotransferase increased	22 (18.5)	9 (7.6)	0
Lipase increased	22 (18.5)	15 (12.6)	0
Blood creatinine increased	19 (16.0)	1 (0.8)	0
Amylase increased	17 (14.3)	3 (2.5)	0
Weight decreased	13 (10.9)	0	0
Infections and infestations	76 (63.9)	12 (10.1)	0
Nasopharyngitis	19 (16.0)	0	0
Upper respiratory tract infection	13 (10.9)	0	0

Respiratory, thoracic and mediastinal disorders	70 (58.8)	6 (5.0)	0
Cough	40 (33.6)	1 (0.8)	0
Dyspnoea	18 (15.1)	3 (2.5)	0
Oropharyngeal pain	15 (12.6)	0	0
Musculoskeletal and connective tissue disorders	68 (57.1)	7 (5.9)	0
Back pain	32 (26.9)	3 (2.5)	0
Arthralgia	25 (21.0)	1 (0.8)	0
Pain in extremity	14 (11.8)	0	0
Metabolism and nutrition disorders	65 (54.6)	12 (10.1)	0
Decreased appetite	29 (24.4)	3 (2.5)	0
Blood and lymphatic system disorders	52 (43.7)	9 (7.6)	0
Anaemia	39 (32.8)	9 (7.6)	0
Thrombocytopenia	14 (11.8)	1 (0.8)	0
Nervous system disorders	49 (41.2)	4 (3.4)	0
Headache	24 (20.2)	2 (1.7)	0
Dizziness	12 (10.1)	0	0

System Organ Class (%) Preferred Term (%)	All Subjects N = 119 Any Grade	Grade 3-4	Grade 5
Endocrine disorders	38 (31.9)	7 (5.9)	0
Hypothyroidism	22 (18.5)	1 (0.8)	0
Hyperthyroidism	18 (15.1)	0	0
Psychiatric disorders	36 (30.3)	2 (1.7)	0
Insomnia	22 (18.5)	1 (0.8)	0
Anxiety	13 (10.9)	0	0
Vascular disorders	30 (25.2)	4 (3.4)	0
Hypertension	12 (10.1)	2 (1.7)	0

MedDRA Version: 21.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.2a of the CA209142 Ad Hoc Safety Report[2]

- **Drug-Related**

Table 48. Drug-Related Adverse Events by Worst CTC Grade Reported in ⩾ 5% Of Treated Subjects in CA209142

System Organ Class (%) Preferred Term (%)	All Subjects N = 119 Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	95 (79.8)	38 (31.9)	0
Skin and subcutaneous tissue disorders	53 (44.5)	5 (4.2)	0
Pruritus	24 (20.2)	2 (1.7)	0
Rash	18 (15.1)	2 (1.7)	0
Dry skin	11 (9.2)	0	0
Rash maculo-papular	6 (5.0)	0	0
General disorders and administration site conditions	47 (39.5)	3 (2.5)	0
Fatigue	22 (18.5)	2 (1.7)	0
Pyrexia	18 (15.1)	0	0
Asthenia	13 (10.9)	1 (0.8)	0
Influenza like illness	6 (5.0)	0	0
Gastrointestinal disorders	39 (32.8)	7 (5.9)	0
Diarrhoea	30 (25.2)	3 (2.5)	0
Nausea	16 (13.4)	1 (0.8)	0
Abdominal pain	8 (6.7)	2 (1.7)	0
Vomiting	8 (6.7)	1 (0.8)	0
Dry mouth	7 (5.9)	0	0
Endocrine disorders	37 (31.1)	7 (5.9)	0
Hypothyroidism	21 (17.6)	1 (0.8)	0
Hyperthyroidism	17 (14.3)	0	0
Adrenal insufficiency	8 (6.7)	1 (0.8)	0
Metabolism and nutrition disorders	21 (17.6)	5 (4.2)	0
Decreased appetite	13 (10.9)	2 (1.7)	0
Musculoskeletal and connective tissue disorders	20 (16.8)	3 (2.5)	0
Arthralgia	10 (8.4)	1 (0.8)	0
Nervous system disorders	17 (14.3)	1 (0.8)	0
Headache	7 (5.9)	0	0
Blood and lymphatic system disorders	16 (13.4)	3 (2.5)	0
Anaemia	11 (9.2)	3 (2.5)	0
Thrombocytopenia	7 (5.9)	1 (0.8)	0
Respiratory, thoracic and mediastinal disorders	13 (10.9)	2 (1.7)	0
Pneumonitis	7 (5.9)	1 (0.8)	0

MedDRA Version: 21.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to table S.6.3a of the CA209142 Ad Hoc Safety Report[2]

Serious adverse event/deaths/other significant events

Serious adverse events

Table 49. SAEs by Worst CTC Grade Reported in ≥2% of Subjects – All Treated Subjects - CA209142

System Organ Class (%) Preferred Term (%)	All Subjects N = 119 Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	63 (52.9)	49 (41.2)	3 (2.5)
Gastrointestinal disorders	21 (17.6)	17 (14.3)	0
Abdominal pain	3 (2.5)	2 (1.7)	0
Colitis	3 (2.5)	3 (2.5)	0
Intestinal obstruction	3 (2.5)	2 (1.7)	0
Large intestinal obstruction	3 (2.5)	3 (2.5)	0
Small intestinal obstruction	3 (2.5)	3 (2.5)	0
Infections and infestations	13 (10.9)	8 (6.7)	0
General disorders and administration site conditions	9 (7.6)	2 (1.7)	1 (0.8)
Pyrexia	5 (4.2)	0	0
Endocrine disorders	7 (5.9)	5 (4.2)	0
Injury, poisoning and procedural complications	7 (5.9)	4 (3.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (5.9)	3 (2.5)	2 (1.7)
Malignant neoplasm progression	4 (3.4)	2 (1.7)	2 (1.7)
Hepatobiliary disorders	6 (5.0)	6 (5.0)	0
Investigations	5 (4.2)	5 (4.2)	0
Respiratory, thoracic and mediastinal disorders	5 (4.2)	4 (3.4)	0
Cardiac disorders	3 (2.5)	3 (2.5)	0
Metabolism and nutrition disorders	3 (2.5)	2 (1.7)	0
Musculoskeletal and connective tissue disorders	3 (2.5)	3 (2.5)	0
Nervous system disorders	3 (2.5)	1 (0.8)	0
Renal and urinary disorders	3 (2.5)	3 (2.5)	0
Acute kidney injury	3 (2.5)	3 (2.5)	0

MedDRA Version: 21.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.18a of the CA209142 Ad Hoc Safety Report[2]

Drug-related SAEs.

Drug-related any-grade SAEs reported in ≥ 1% of subjects were colitis and pyrexia (each 2.5%), and abdominal pain, increased transaminase, acute kidney injury, anaemia, and hypophysitis (each 1.7%).

Table 50. Drug-related SAEs by Worst CTC Grade Reported in at Least 2 Subjects - All Treated Subjects - CA209142

System Organ Class (%) Preferred Term (%)	All Subjects N = 119 Any Grade	 Grade 3-4	 Grade 5
TOTAL SUBJECTS WITH AN EVENT	27 (22.7)	24 (20.2)	0
Endocrine disorders	7 (5.9)	5 (4.2)	0
Hypophysitis	2 (1.7)	1 (0.8)	0
Gastrointestinal disorders	6 (5.0)	6 (5.0)	0
Colitis	3 (2.5)	3 (2.5)	0
Abdominal pain	2 (1.7)	2 (1.7)	0
General disorders and administration site conditions	3 (2.5)	0	0
Pyrexia	3 (2.5)	0	0
Hepatobiliary disorders	3 (2.5)	3 (2.5)	0
Investigations	3 (2.5)	3 (2.5)	0
Transaminases increased	2 (1.7)	2 (1.7)	0
Blood and lymphatic system disorders	2 (1.7)	2 (1.7)	0
Anaemia	2 (1.7)	2 (1.7)	0
Renal and urinary disorders	2 (1.7)	2 (1.7)	0
Acute kidney injury	2 (1.7)	2 (1.7)	0
Respiratory, thoracic and mediastinal disorders	2 (1.7)	2 (1.7)	0

MedDRA Version: 21.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.
Source: Refer to Table S.6.19a of the CA209142 Ad Hoc Safety Report[2]

Deaths

Table 51. Death Summary - All Combination Therapy Treated Subjects in CA209142

	All Subjects N = 119
NUMBER OF SUBJECTS WHO DIED (%)	33 (27.7)
PRIMARY REASON FOR DEATH (%)	
DISEASE	29 (24.4)
STUDY DRUG TOXICITY	0
UNKNOWN	1 (0.8)
OTHER	3 (2.5)
NUMBER OF SUBJECTS WHO DIED WITHIN 30 DAYS OF LAST DOSE (%)	3 (2.5)
PRIMARY REASON FOR DEATH (%)	
DISEASE	2 (1.7)
STUDY DRUG TOXICITY	0
UNKNOWN	0
OTHER	1 (0.8)
NUMBER OF SUBJECTS WHO DIED WITHIN 100 DAYS OF LAST DOSE (%)	13 (10.9)
PRIMARY REASON FOR DEATH (%)	
DISEASE	11 (9.2)
STUDY DRUG TOXICITY	0
UNKNOWN	0
OTHER	2 (1.7)

MedDRA Version 21.1
Source: Refer to Table 3.2-1 of the CA209142 Ad Hoc Safety Report[2]

Deaths attributed to "other" reasons were reported in 3 (2.5%) subjects. The verbatim terms reported for the 'other' reasons for death are as follows:

- patient 1: Sudden death (died 18 days after the last dose). This death occurred between the DBLs. On Day 998 after the first dose, subject's wife reported subject experienced severe pain and "sweating" around 3 AM. However, subject declined to go to the hospital for evaluation. Subject was found dead in bed later that morning. Very limited information is available due to lack of hospital records and autopsy.
- Patient 2: Respiratory failure (died 83 days after the last dose). This death was reported at the Aug-2017 DBL.
- Patient 3: Patient made voluntary decision to discontinue dialysis, subsequently died from renal failure (died 158 days after the last dose). This death was reported at the Aug-2017 DBL.

Select Adverse Events

Select AEs are AEs of special clinical interest that are potentially associated with the use of nivolumab, which the applicant identified 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 (e.g. 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, diarrhoea/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, gastrointestinal (GI), hepatic, pulmonary, renal, and skin select AE categories, respectively. Select AE analyses included events occurring within 30 days of the last dose. Limited analysis of select AEs with 100 days of follow-up (i.e. extended follow-up) was also performed.

The most common **all-causality select AEs** in CA209142, by category, were skin (59.7%), gastrointestinal (53.8%), and hepatic (34.5%). The majority of select AEs were Grade 1-2, and most were considered drug related by the investigator.

The most frequently reported **drug-related any-grade select AE**, by category, at the Feb-2019 DBL were skin (35.3% for any grade, 4.2% for Grade 3-4), endocrine (31.9% for any grade, 5.9% for Grade 3-4), gastrointestinal (25.2% for any grade, 3.4% for Grade 3-4), and hepatic (23.5% for any grade, 11.8% for Grade 3-4). The most frequently reported drug-related any-grade select AE events (≥ 10% of subjects at the Feb-2019 DBL), by preferred term (PT), were: diarrhoea (25.2% for any grade, 2.5% for Grade 3-4), pruritus (20.2% for any grade, 1.7% for Grade 3-4), hypothyroidism (17.6% for any grade, 0.8% for Grade 3-4), AST increased (16.0% for any grade, 7.6% for Grade 3-4), rash (15.1% for any grade, 1.7% for Grade 3-4), hyperthyroidism (14.3% for any grade, and none for Grade 3-4), and ALT increased (12.6% for any grade and 6.7% for Grade 3-4).

Across the select AE categories, the majority of events were manageable using the established algorithms, with resolution occurring when immune-modulating medications (mainly systemic corticosteroids) were administered. Except for endocrine events, most drug-related select AEs had resolved (ranging from 76.2% to 100.0% across categories) at the time of database lock. Some

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

Table 52. Onset, Management, and Resolution of Drug-Related Select AEs - All Combination Therapy Treated Subjects (N=119) - CA209142

Category	% Treated Subj. with Any Grade/ Grade 3-4 Drug-related Select AE	Median Time to Onset of Drug-related Select AE (range), wks	% Treated Subj. with Drug-related Select AE Leading to DC	% Subj. with Drug-Related Select AE Treated with IMM / High-dose Corticosteroids[a]	Median Time[b] to Resolution of Drug-related Select AE (range), wks[c,d,e]	% Subj. with Drug-related Select AE that Resolved [d,e]
Endocrine	31.9 / 5.9	11.50 (3.0 - 118.1)	0	34.2 / 18.4	N.A. (1.1 - 173.7+)	34.2
Gastrointestinal	25.2 / 3.4	9.71 (0.3 - 132.9))	1.7	20.0 / 13.3	1.43 (0.1 - 77.4+)	96.6
Hepatic	23.5 / 11.8	9.71 (1.3 - 66.1)	5.0	42.9 / 42.9	9.43 (0.3 - 130.7+)	78.6
Pulmonary	5.9 / 0.8	11.86 (3.9 - 110.9)	0.8	42.9 / 42.9	5.43 (1.0 - 110.3+)	85.7
Renal	5.9 / 1.7	18.14 (1.3 - 51.4)	1.7	28.6 / 28.6	6.71 (2.7 - 27.3)	85.7
Skin	35.3 / 4.2	5.93 (0.3 - 69.3)	0	47.6 / 9.5	11.50 (0.4 - 187.4+)	76.2
Hypersensitivity/ Infusion Reaction	3.4 / 0	3.21 (0.1 - 9.1)	0	50.0 / 25.0	0.14 (0.1 - 0.1)	100.0

MedDRA Version: 21.1 CTC Version: 4.0

[a] Denominator is based on the number of subjects who experienced the event.
[b] From Kaplan-Meier estimation
[c] Symbol + indicates a censored value
[d] Subjects who experienced select adverse event without worsening from baseline grade were excluded from time to resolution analysis.
[e] Events without a stop date or with a stop date equal to the death as well as grade 5 events are considered unresolved.
Abbreviations: AE - adverse event, DC - discontinuation, IMM - immune-modulating medication, N.A. - not available/not applicable, subj. - subjects, wks - weeks

Source: Refer to the following tables in the CA209142 Ad Hoc Safety Report[2]: Table S.6.103 (select AEs, drug-related), Table S.6.107 (endocrine select AEs, drug-related), Table S.6.117 (time to onset, drug-related), Table S.6.121 (time to resolution, drug-related), Table S.6.129 (duration of immune-modulating medications, drug-related), Table S.6.139 (drug-related select AEs leading to discontinuation), and Table S.6.141 (drug-related select endocrine AEs leading to discontinuation)

Endocrine events

The endocrine select AE category included the following subcategories: adrenal disorders, diabetes, pituitary disorders, and thyroid disorders.

Table 53. Summary of Drug-Related Select Endocrine Adverse Events by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) All dMMR/MSI-H Combination Therapy Treated Subjects

Sub Category (%) Preferred Term (%)	All Subjects N = 119			Subjects with Prior 5FU-Oxa-Iri N = 82		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	38 (31.9)	7 (5.9)	0	20 (24.4)	6 (7.3)	0
THYROID DISORDER	30 (25.2)	4 (3.4)	0	18 (22.0)	4 (4.9)	0
Hypothyroidism	21 (17.6)	1 (0.8)	0	15 (18.3)	1 (1.2)	0
Hyperthyroidism	17 (14.3)	0	0	10 (12.2)	0	0
Blood thyroid stimulating hormone decreased	3 (2.5)	0	0	2 (2.4)	0	0
Thyroiditis	3 (2.5)	1 (0.8)	0	2 (2.4)	1 (1.2)	0
Autoimmune thyroid disorder	2 (1.7)	1 (0.8)	0	1 (1.2)	1 (1.2)	0
Autoimmune thyroiditis	1 (0.8)	1 (0.8)	0	1 (1.2)	1 (1.2)	0
Blood thyroid stimulating hormone increased	1 (0.8)	0	0	1 (1.2)	0	0
Thyroxine free decreased	1 (0.8)	0	0	1 (1.2)	0	0
ADRENAL DISORDER	9 (7.6)	2 (1.7)	0	3 (3.7)	1 (1.2)	0
Adrenal insufficiency	8 (6.7)	1 (0.8)	0	3 (3.7)	1 (1.2)	0
Secondary adrenocortical insufficiency	1 (0.8)	1 (0.8)	0	0	0	0
PITUITARY DISORDER	4 (3.4)	2 (1.7)	0	3 (3.7)	2 (2.4)	0
Hypophysitis	4 (3.4)	2 (1.7)	0	3 (3.7)	2 (2.4)	0
Hypopituitarism	1 (0.8)	0	0	1 (1.2)	0	0

MedDRA Version: 21.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Gastrointestinal events

Table 54. Summary of Any Drug-Related Select Adverse Events by Worst CTC Grade All dMMR/MSI-H Combination Therapy Treated Subjects

Select Adverse Events Category: GASTROINTESTINAL ADVERSE EVENT
Cohort: All Subjects N = 119

Preferred Term (%)	1	2	3	4	5	Not Reported	Total
TOTAL SUBJECTS WITH AN EVENT	20 (16.8)	6 (5.0)	4 (3.4)	0	0	0	30 (25.2)
Diarrhoea	20 (16.8)	7 (5.9)	3 (2.5)	0	0	0	30 (25.2)
Colitis	0	0	3 (2.5)	0	0	0	3 (2.5)

MedDRA Version: 21.1
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.

Hepatic events

Table 55. Summary of Any Drug-Related Select Adverse Events by Worst CTC Grade All dMMR/MSI-H Combination Therapy Treated Subjects

Select Adverse Events Category: HEPATIC ADVERSE EVENT
Cohort: All Subjects N = 119

Preferred Term (%)	1	2	3	4	5	Not Reported	Total
TOTAL SUBJECTS WITH AN EVENT	10 (8.4)	4 (3.4)	14 (11.8)	0	0	0	28 (23.5)
Aspartate aminotransferase increased	9 (7.6)	1 (0.8)	9 (7.6)	0	0	0	19 (16.0)
Alanine aminotransferase increased	4 (3.4)	3 (2.5)	8 (6.7)	0	0	0	15 (12.6)
Transaminases increased	0	2 (1.7)	4 (3.4)	0	0	0	6 (5.0)
Blood bilirubin increased	2 (1.7)	1 (0.8)	1 (0.8)	0	0	0	4 (3.4)
Blood alkaline phosphatase increased	2 (1.7)	1 (0.8)	0	0	0	0	3 (2.5)
Autoimmune hepatitis	0	0	2 (1.7)	0	0	0	2 (1.7)
Hepatitis	0	0	1 (0.8)	0	0	0	1 (0.8)
Immune-mediated hepatitis	0	0	1 (0.8)	0	0	0	1 (0.8)

MedDRA Version: 21.1
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.

Pulmonary events

Table 56. Summary of Any Drug-Related Select Adverse Events by Worst CTC Grade All dMMR/MSI-H Combination Therapy Treated Subjects

Select Adverse Events Category: PULMONARY ADVERSE EVENT
Cohort: All Subjects N = 119

Preferred Term (%)	1	2	3	4	5	Not Reported	Total
TOTAL SUBJECTS WITH AN EVENT	3 (2.5)	3 (2.5)	1 (0.8)	0	0	0	7 (5.9)
Pneumonitis	3 (2.5)	3 (2.5)	1 (0.8)	0	0	0	7 (5.9)

MedDRA Version: 21.1
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.

Renal events

Table 57. Summary of Any Drug-Related Select Adverse Events by Worst CTC Grade All dMMR/MSI-H Combination Therapy Treated Subjects

Select Adverse Events Category: RENAL ADVERSE EVENT
Cohort: All Subjects N = 119

Preferred Term (%)	1	2	3	4	5	Not Reported	Total
TOTAL SUBJECTS WITH AN EVENT	5 (4.2)	0	0	2 (1.7)	0	0	7 (5.9)
Blood creatinine increased	5 (4.2)	1 (0.8)	0	0	0	0	6 (5.0)
Acute kidney injury	0	0	0	2 (1.7)	0	0	2 (1.7)

MedDRA Version: 21.1
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.

Skin events

Table 58. Summary of Any Drug-Related Select Adverse Events by Worst CTC Grade All dMMR/MSI-H Combination Therapy Treated Subjects

Select Adverse Events Category: SKIN ADVERSE EVENT
Cohort: All Subjects N = 119

Preferred Term (%)	1	2	3	4	5	Not Reported	Total
TOTAL SUBJECTS WITH AN EVENT	23 (19.3)	14 (11.8)	5 (4.2)	0	0	0	42 (35.3)
Pruritus	13 (10.9)	9 (7.6)	2 (1.7)	0	0	0	24 (20.2)
Rash	14 (11.8)	2 (1.7)	2 (1.7)	0	0	0	18 (15.1)
Rash maculo-papular	3 (2.5)	3 (2.5)	0	0	0	0	6 (5.0)
Erythema	4 (3.4)	0	0	0	0	0	4 (3.4)
Eczema	3 (2.5)	0	0	0	0	0	3 (2.5)
Photosensitivity reaction	3 (2.5)	0	0	0	0	0	3 (2.5)
Rash erythematous	3 (2.5)	0	0	0	0	0	3 (2.5)
Dermatitis	1 (0.8)	1 (0.8)	0	0	0	0	2 (1.7)
Rash generalised	0	1 (0.8)	1 (0.8)	0	0	0	2 (1.7)
Rash pruritic	2 (1.7)	0	0	0	0	0	2 (1.7)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.8)	0	0	0	0	0	1 (0.8)
Pruritus generalised	1 (0.8)	0	0	0	0	0	1 (0.8)
Psoriasis	0	0	1 (0.8)	0	0	0	1 (0.8)
Rash macular	0	1 (0.8)	0	0	0	0	1 (0.8)
Rash papular	1 (0.8)	0	0	0	0	0	1 (0.8)
Rash vesicular	1 (0.8)	0	0	0	0	0	1 (0.8)
Skin hypopigmentation	0	1 (0.8)	0	0	0	0	1 (0.8)
Skin irritation	0	1 (0.8)	0	0	0	0	1 (0.8)
Toxic skin eruption	1 (0.8)	0	0	0	0	0	1 (0.8)
Urticaria	1 (0.8)	0	0	0	0	0	1 (0.8)

MedDRA Version: 21.1
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.

Hypersensitivity/infusion reactions

Table 59. Summary of Any Drug-Related Select Adverse Events by Worst CTC Grade All dMMR/MSI-H Combination Therapy Treated Subjects

Select Adverse Events Category: HYPERSENSITIVITY/INFUSION REACTION
Cohort: All Subjects N = 119

Preferred Term (%)	1	2	3	4	5	Not Reported	Total
TOTAL SUBJECTS WITH AN EVENT	0	4 (3.4)	0	0	0	0	4 (3.4)
Infusion related reaction	0	4 (3.4)	0	0	0	0	4 (3.4)

MedDRA Version: 21.1
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.

Other Events of Special Interest

Other events of special interest (OESIs) are events that do not fulfill all criteria to qualify as select AEs. These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management. OESI included the following categories: demyelination, encephalitis, Guillain-Barré syndrome, myasthenic syndrome, myocarditis, myositis, pancreatitis, rhabdomyolysis, and uveitis.

In all combination therapy treated subjects, OESIs with extended follow-up, regardless of causality, were reported in 5 (4.2%) subjects. Events were myositis (2 subjects; 1 Grade 3, 1 Grade 2) and 1 each of encephalitis (Grade 3), uveitis (Grade 3), and pancreatitis (Grade 3). One of the 2 myositis events was reported as necrotizing. All events, except uveitis, were considered drug-related by the investigator. All 5 events resolved.

Safety with Extended Follow-Up in CA209142

In CA209142, the incidence rates of AEs leading to discontinuation, drug-related AEs, and drug-related SAEs, reported within 100 days of the last dose were consistent with those reported within 30 days of the last dose. The most common all-causality AEs with extended follow-up were diarrhoea (54.6%), pyrexia (42.0), fatigue, pruritis, cough, and anaemia (each 33.6).

There were 55.5% of subjects who experienced at least 1 SAE, with extended follow-up. The most common SAEs were malignant neoplasm progression (8.4%), pyrexia (4.2%), abdominal pain, colitis, diarrhoea, intestinal obstruction, large intestinal obstruction, small intestinal obstruction, dehydration, and acute kidney injury (each 2.5%). There were 22.7% of subjects, who experienced a drug-related SAE, with extended follow-up. The most common drug-related SAEs with extended follow-up were colitis and pyrexia (each 2.5%), adrenal insufficiency, hypophysitis, abdominal pain, diarrhoea, transaminases increased, anemia, acute kidney injury (each 1.7%). Compared to 30 days of follow-up, this was slightly higher for adrenal insufficiency (0.8%), diarrhoea (0.8%), but the same for colitis, hypophysitis, abdominal pain, transaminases increased, acute kidney injury.

There were 79.8% of subjects who experienced a drug-related AE, with extended follow-up. Of all treated subjects, 44.5% had skin disorders, 33.6% had gastrointestinal disorders, and 31.1% had endocrine disorders. The most common drug-related select AEs with extended follow-up were diarrhoea (26.1%), pruritus (20.2%), fatigue (18.1%), hypothyroidism (17.6%), rash and pyrexia (each 15.1%), nausea and hyperthyroidism (each 14.3%), AST increased (12.6%), lipase increased (11.8%), asthenia and decreased appetite (each 10.9%). Compared to 30 days of follow-up, this was slightly higher for diarrhoea (25.2%) and nausea (13.4%), slightly lower for fatigue (18.5%) and AST increased (16.0%), and the same for pruritus, hypothyroidism, rash, pyrexia, pruritus, hyperthyroidism, lipase increased, asthenia, and decreased appetite.

Laboratory findings

Clinical laboratory evaluations included assessments of haematology, liver, kidney, and thyroid function, and electrolytes.

Haematology

Among all combination treated subjects, abnormalities in haematology tests that occurred during treatment or within 30 days of last dose of study drug were primarily Grade 1-2.

Grade 3-4 hematologic abnormalities reported in ≥ 5% of subjects were anaemia (8.7% Grade 3) and lymphocytopenia (7.1% Grade 3).

Liver function tests

Among all combination 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. Grade 3-4 liver test abnormalities reported in ≥ 5% of subjects were AST (11.4% Grade 3), ALT (10.5% Grade 3), alkaline phosphatase (6.1% Grade 3), and bilirubin (5.3% Grade 3).

Among all combination treated subjects, nearly half of subjects had abnormalities in ALT or AST parameters (all increases) that occurred during treatment or within 30 days of last dose of study drug and most (19.1%) were more than 3x the upper limit of normal.

6 (5.3%) subjects had concurrent ALT or AST elevation > 3 x ULN with total bilirubin > 2 x ULN within both 1 day and 30 days of last dose of study therapy.

Table 60. Summary of On-Treatment Laboratory Abnormalities in Specific Liver Tests - SI Units - All dMMR or MSI-H CRC Combination Therapy Treated Subjects

Abnormality (%)	All Subjects N = 119
	N = 115
ALT OR AST > 3XULN	22 (19.1)
ALT OR AST > 5XULN	18 (15.7)
ALT OR AST > 10XULN	9 (7.8)
ALT OR AST > 20XULN	2 (1.7)
	N = 114
TOTAL BILIRUBIN > 2XULN	7 (6.1)
	N = 114
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN ONE DAY	7 (6.1)
CONCURRENT ALT OR AST ELEVATION > 3XULN WITH TOTAL BILIRUBIN > 2XULN WITHIN 30 DAYS	7 (6.1)

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.

Kidney Function

Among all combination treated subjects, most subjects had normal kidney function; abnormalities in kidney function that occurred during treatment or within 30 days of last dose of study drug were primarily Grade 1.

The only Grade 3-4 kidney function test abnormality reported in ≥ 5% of subjects was total lipase (8.9% Grade 3).

Thyroid Function

Among all combination treated subjects, 37.5% of subjects had thyroid stimulating hormone (TSH) levels greater than the upper limit of normal, and 43.8% of subjects had TSH levels lower than the lower level of normal.

Table 61. Summary of On-Treatment Laboratory Abnormalities in Specific Thyroid Tests - SI Units - Treated Subjects with at Least One On-Treatment TSH Measurement

Abnormality (%)	All Subjects N = 112
TSH > ULN	42 (37.5)
TSH > ULN	
WITH TSH <= ULN AT BASELINE	38 (33.9)
TSH > ULN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE < LLN (A)	23 (20.5)
WITH ALL OTHER FT3/FT4 TEST VALUES >= LLN (A)	14 (12.5)
WITH FT3/FT4 TEST MISSING (A)(B)	5 (4.5)
TSH < LLN	49 (43.8)
TSH < LLN	
WITH TSH >= LLN AT BASELINE	47 (42.0)
TSH < LLN	
WITH AT LEAST ONE FT3/FT4 TEST VALUE > ULN (A)	27 (24.1)
WITH ALL OTHER FT3/FT4 TEST VALUES <= ULN (A)	20 (17.9)
WITH FT3/FT4 TEST MISSING (A)(B)	2 (1.8)

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: Table S.7.8-SI

Safety in special populations

In CA209142, the frequency of total AEs, AEs leading to discontinuation, and AEs by MedDRA High-level Group Term (HLGT)/SMQs/SOC by age group are presented in table 62.

Small numerical differences infrequencies of AEs were observed in the following:

All causality Grade 3-4 AEs were reported at 58.0% for subjects younger than 65 years old and 63.2% for subjects 65 or older. Grade 3-4 drug-related AEs were reported at 32.1% for subjects younger than 65 years old and 31.6% for subjects 65 or older.

Table 62. Summary of Safety Results by Age Group - All Treated Nivolumab + Ipilimumab Subjects in CA209142

MedDRA Terms (%)	Age Group (Years) < 65 N = 81	65-74 N = 27	75-84 N = 10	>=85 N = 1	Total N = 119
TOTAL SUBJECTS WITH AN EVENT	80 (98.8)	27 (100.0)	10 (100.0)	1 (100.0)	118 (99.2)
SERIOUS AE - TOTAL	43 (53.1)	15 (55.6)	4 (40.0)	1 (100.0)	63 (52.9)
FATAL (DEATH)	3 (3.7)	2 (7.4)	0	0	5 (4.2)
HOSPITALIZATION/PROLONGATION	39 (48.1)	14 (51.9)	4 (40.0)	1 (100.0)	58 (48.7)
LIFE THREATENING	0	1 (3.7)	0	0	1 (0.8)
CANCER	4 (4.9)	0	0	0	4 (3.4)
DISABILITY/INCAPACITY	0	0	0	0	0
AE LEADING TO DISCONTINUATION	11 (13.6)	6 (22.2)	2 (20.0)	0	19 (16.0)
PSYCHIATRIC DISORDERS	31 (38.3)	3 (11.1)	2 (20.0)	0	36 (30.3)
NERVOUS SYSTEM DISORDERS	32 (39.5)	14 (51.9)	2 (20.0)	1 (100.0)	49 (41.2)
ACCIDENT AND INJURIES	16 (19.8)	9 (33.3)	1 (10.0)	0	26 (21.8)
CARDIAC DISORDERS	7 (8.6)	2 (7.4)	1 (10.0)	0	10 (8.4)
VASCULAR DISORDERS	19 (23.5)	8 (29.6)	3 (30.0)	0	30 (25.2)
CEREBROVASCULAR DISORDERS	0	2 (7.4)	0	0	2 (1.7)
INFECTIONS AND INFESTATIONS	54 (66.7)	17 (63.0)	5 (50.0)	0	76 (63.9)
ANTICHOLINERGIC SYNDROME	45 (55.6)	14 (51.9)	3 (30.0)	0	62 (52.1)
QUALITY OF LIFE DECREASED	0	0	0	0	0
SUM OF POSTURAL HYPOTENSION, FALLS, BLACKOUTS, SYNCOPE, DIZZINESS, ATAXIA, FRACTURES	17 (21.0)	6 (22.2)	2 (20.0)	0	25 (21.0)

CTC Version 4.0; MedDRA Version: 22.1
Includes events reported between first dose and 30 days after last dose of study therapy.

Immunogenicity

There were 109 subjects that were ADA evaluable for nivolumab, and 107 subjects that were ADA evaluable for ipilimumab in the CA209142 combination arm from the DBL on 19-Feb-2019.

The incidence of nivolumab ADA was 25.7% (n=28), with no persistent-positive subjects. Among the 28 subjects with positive nivolumab ADA, there were no subjects with AEs of hypersensitivity/infusion reaction. The incidence of ipilimumab ADA was 4.7% (n=5), with no persistent-positive subjects. Among the 5 subjects with positive ipilimumab ADA, there were no subjects with AEs of hypersensitivity/infusion reaction

Safety related to drug-drug interactions and other interactions

No new information have been submitted by the MAH.

Discontinuation due to adverse events

All-causality AEs leading to discontinuation are reported in table 63.

Table 63. Summary of Adverse Events Leading to Discontinuation by Worst CTC Grade (Any Grade, Grade 3-4, Grade 5) All dMMR/MSI-H Combination Therapy Treated Subjects

System Organ Class (%) Preferred Term (%)	All Subjects N = 119			Subjects with Prior 5FU-Oxa-Iri N = 82		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	19 (16.0)	13 (10.9)	1 (0.8)	14 (17.1)	9 (11.0)	1 (1.2)
Investigations	6 (5.0)	4 (3.4)	0	4 (4.9)	3 (3.7)	0
Alanine aminotransferase increased	3 (2.5)	2 (1.7)	0	3 (3.7)	2 (2.4)	0
Aspartate aminotransferase increased	3 (2.5)	2 (1.7)	0	3 (3.7)	2 (2.4)	0
Blood creatinine increased	1 (0.8)	0	0	0	0	0
Lipase increased	1 (0.8)	1 (0.8)	0	0	0	0
Transaminases increased	1 (0.8)	1 (0.8)	0	1 (1.2)	1 (1.2)	0
Hepatobiliary disorders	3 (2.5)	2 (1.7)	0	3 (3.7)	2 (2.4)	0
Autoimmune hepatitis	2 (1.7)	2 (1.7)	0	2 (2.4)	2 (2.4)	0
Hepatocellular injury	1 (0.8)	0	0	1 (1.2)	0	0
Gastrointestinal disorders	2 (1.7)	2 (1.7)	0	0	0	0
Colitis	1 (0.8)	1 (0.8)	0	0	0	0
Diarrhoea	1 (0.8)	1 (0.8)	0	0	0	0
Immune system disorders	2 (1.7)	0	0	2 (2.4)	0	0
Drug hypersensitivity	1 (0.8)	0	0	1 (1.2)	0	0
Sarcoidosis	1 (0.8)	0	0	1 (1.2)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.7)	1 (0.8)	1 (0.8)	2 (2.4)	1 (1.2)	1 (1.2)
Breast cancer	1 (0.8)	1 (0.8)	0	1 (1.2)	1 (1.2)	0
Malignant neoplasm progression	1 (0.8)	0	1 (0.8)	1 (1.2)	0	1 (1.2)
Renal and urinary disorders	2 (1.7)	2 (1.7)	0	1 (1.2)	1 (1.2)	0
Acute kidney injury	2 (1.7)	2 (1.7)	0	1 (1.2)	1 (1.2)	0
Blood and lymphatic system disorders	1 (0.8)	1 (0.8)	0	1 (1.2)	1 (1.2)	0
Thrombocytopenia	1 (0.8)	1 (0.8)	0	1 (1.2)	1 (1.2)	0
Infections and infestations	1 (0.8)	1 (0.8)	0	0	0	0
Encephalitis	1 (0.8)	1 (0.8)	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.8)	1 (0.8)	0	1 (1.2)	1 (1.2)	0
Necrotising myositis	1 (0.8)	1 (0.8)	0	1 (1.2)	1 (1.2)	0
Nervous system disorders	1 (0.8)	0	0	1 (1.2)	0	0
Epilepsy	1 (0.8)	0	0	1 (1.2)	0	0
Reproductive system and breast disorders	1 (0.8)	0	0	1 (1.2)	0	0
Breast mass	1 (0.8)	0	0	1 (1.2)	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.8)	0	0	0	0	0
Pneumonitis	1 (0.8)	0	0	0	0	0

MedDRA Version: 21.1
CTC Version 4.0
Includes events reported between first dose and 30 days after last dose of study therapy.

Drug-related any-grade AEs leading to discontinuation were reported at a frequency of 13.4% in all combination therapy treated subjects. Drug-related any-grade AEs leading to discontinuation in ≥ 1% of subjects were ALT increased (2.5%), AST increased (1.7%), autoimmune hepatitis (1.7%), and acute kidney injury (1.7%).

Drug-related Grade 3-4 AEs leading to discontinuation were reported at a frequency of 10.1% in all combination therapy treated subjects. Drug-related Grade 3-4 AEs leading to discontinuation in ≥ 1% of subjects were ALT increased (1.7%, Grade 3), autoimmune hepatitis (1.7%, Grade 3), and acute kidney injury (1.7%, Grade 4).

Updated safety data

At the Oct-2020 DBL, the minimum follow-up was 46.9 months, and the median follow-up was 50.89 months. A side-by-side comparison of key safety data between the Feb-2019 and Oct-2020 DBLs is presented in Table 10. With longer follow up, no substantial differences in the safety profile of nivolumab + ipilimumab were observed and no new safety signals were identified.

Table 64: Summary of Safety for Feb-2019 DBL and Oct-2020 DBL - All Combination Treated Population in CA209142 Cohort 2

Safety Parameters	All Combination Treated Subjects (N=119)			
	Feb-2019 DBL		Oct-2020 DBL	
	N (%)		N (%)	
Deaths (at any time during the study)	33 (27.7)		35 (29.4)	
Primary reason for death				
Disease	29 (24.4)		31 (26.1)	
Study drug toxicity	0		0	
Unknown	1 (0.8)		1 (0.8)	
Other	3 (2.5)		3 (2.5)	
	Adverse Events Grade		**Adverse Events Grade**	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
All-causality SAEs	63 (52.9)	49 (41.2)	66 (55.5)	53 (44.5)
Drug-related SAEs	27 (22.7)	24 (20.2)	27 (22.7)	24 (20.2)
All-causality AEs leading to DC	19 (16.0)	13 (10.9)	22 (18.5)	16 (13.4)
Drug-related AEs leading to DC	16 (13.4)	12 (10.1)	16 (13.4)	12 (10.1)
All-causality AEs (PT) (≥25% of any grade at either of the DBLs)	118 (99.2)	71 (59.7)	118 (99.2)	74 (62.2)
Diarrhea	64 (53.8)	7 (5.9)	69 (58.0)	8 (6.7)
Pyrexia	50 (42.0)	0	53 (44.5)	0
Cough	40 (33.6)	1 (0.8)	42 (35.3)	1 (0.8)
Fatigue	40 (33.6)	4 (3.4)	41 (34.5)	4 (3.4)
Pruritus	40 (33.6)	2 (1.7)	42 (35.3)	2 (1.7)
Anemia	39 (32.8)	9 (7.6)	40 (33.6)	9 (7.6)
Nausea	35 (29.4)	1 (0.8)	36 (30.3)	1 (0.8)
Abdominal pain	34 (28.6)	4 (3.4)	38 (31.9)	4 (3.4)
Asthenia	33 (27.7)	3 (2.5)	34 (28.6)	3 (2.5)
Back pain	32 (26.9)	3 (2.5)	33 (27.7)	3 (2.5)
Decreased appetite	29 (24.4)	3 (2.5)	31 (26.1)	3 (2.5)
Drug-related AEs (PT) (≥15% of any grade at either of the DBLs)	95 (79.8)	38 (31.9)	101 (84.9)	38 (31.9)
Diarrhea	30 (25.2)	3 (2.5)	32 (26.9)	3 (2.5)

Table 64: Summary of Safety for Feb-2019 DBL and Oct-2020 DBL - All Combination Treated Population in CA209142 Cohort 2

Safety Parameters	All Combination Treated Subjects (N=119)			
	Feb-2019 DBL		Oct-2020 DBL	
	N (%)		N (%)	
Pruritus	24 (20.2)	2 (1.7)	25 (21.0)	2 (1.7)
Fatigue	22 (18.5)	2 (1.7)	22 (18.5)	2 (1.7)
Hypothyroidism	21 (17.6)	1 (0.8)	21 (17.6)	1 (0.8)
AST increased	19 (16.0)	9 (7.6)	20 (16.8)	10 (8.4)
Pyrexia	18 (15.1)	0	19 (16.0)	0
Rash	18 (15.1)	2 (1.7)	19 (16.0)	3 (2.5)
All-causality select AEs by category				
Endocrine	41 (34.5)	7 (5.9)	41 (34.5)	7 (5.9)
Gastrointestinal	64 (53.8)	8 (6.7)	69 (58.0)	9 (7.6)
Hepatic	41 (34.5)	19 (16.0)	43 (36.1)	20 (16.8)
Pulmonary	7 (5.9)	1 (0.8)	9 (7.6)	1 (0.8)
Renal	24 (20.2)	4 (3.4)	25 (21.0)	4 (3.4)
Skin	71 (59.7)	7 (5.9)	72 (60.5)	7 (5.9)
Hypersensitivity/infusion reactions	7 (5.9)	0	6 (5.0)	0
Drug-related select AEs by category				
Endocrine	38 (31.9)	7 (5.9)	38 (31.9)	7 (5.9)
Gastrointestinal	30 (25.2)	4 (3.4)	32 (26.9)	4 (3.4)
Hepatic	28 (23.5)	14 (11.8)	31 (26.1)	14 (11.8)
Pulmonary	7 (5.9)	1 (0.8)	8 (6.7)	1 (0.8)
Renal	7 (5.9)	2 (1.7)	9 (7.6)	2 (1.7)
Skin	42 (35.3)	5 (4.2)	46 (38.7)	5 (4.2)
Hypersensitivity/infusion reactions	4 (3.4)	0	3 (2.5)	0
All-causality OESI within 100 days of last dose treated with or without immune-modulating medications				
Encephalitis	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
Myositis/rhabdomyolysis	2 (1.7)	1 (0.8)	2 (1.7)	1 (0.8)

Table 64: Summary of Safety for Feb-2019 DBL and Oct-2020 DBL - All Combination Treated Population in CA209142 Cohort 2

Safety Parameters	All Combination Treated Subjects (N=119)			
	Feb-2019 DBL		Oct-2020 DBL	
	N (%)		N (%)	
Pancreatitis	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
Uveitis	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)

Abbreviations: AEs - adverse events; CTC - Common Toxicity Criteria; DBL - database lock; DC - discontinuation; OESI - other events of special interest; PT - preferred term; SAEs - serious adverse events.

For Feb-2019 DBL: MedDRA Version: 21.1, CTC Version 4.0; For Oct-2020 DBL: MedDRA Version: 23.0, CTC Version4.0

Includes events reported between first dose and 30 days after last dose of study therapy, unless otherwise indicated.

Safety to support the updates of the SmPC

Safety data to support Section 4.8 of the SmPC were integrated across completed studies in multiple indications using the intended dose and regimen for nivolumab in combination with ipilimumab (nivolumab 3 mg/kg IV Q3W plus ipilimumab 1 mg/kg IV for 4 doses then nivolumab 3 mg/kg IV Q2W).

The studies included in the analyses of nivolumab 3 mg/kg IV Q3W plus ipilimumab 1 mg/kg IV for 4 doses then nivolumab 3 mg/kg IV Q2W were as follows:

Renal cell carcinoma: CA209214

Colorectal cancer: CA209142 (Cohort 2)

In the proposed OPDIVO SmPC, in Section 4.8, Tables 7 and 10 have been updated for nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg. In the proposed YERVOY SmPC, in Section 4.8, Tables 5 and 7 have been updated for ipilimumab 1 mg/kg in combination with nivolumab 3 mg/kg.

Some MedDRA PTs were re-mapped or deleted for the purposes of generating summary tables to support Section 4.8 of the nivolumab and ipilimumab SmPCs (nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg). Remapping allowed for pooling of PTs representing the same or similar clinical conditions. Some MedDRA PTs were deleted from the tables generated to support the SmPC because they were overly general/nonspecific.

In general pooled safety data are reflected on the SmPC as follow:

In the pooled dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg across tumour types (n = 666), with a minimum follow-up ranging from 17.5 to 27.6 months, the most frequent adverse reactions (≥ 10%) were fatigue (58%), diarrhoea (41%), musculoskeletal pain (39%), rash (38%), pruritus (35%), nausea (30%), cough (29%), pyrexia (29%), abdominal pain (22%), arthralgia (22%), decreased appetite (22%), upper respiratory tract infection (21%), vomiting (21%), headache (19%), dyspnoea (19%), hypothyroidism (18%), constipation (18%), oedema (including peripheral oedema) (16%), dizziness (14%), hyperthyroidism (12%), dry skin (11%), hypertension (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Among the patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg, 194/666 (29%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase.

Among the 474 patients in this group who continued treatment in the single-agent phase, 68 (35%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

Immune-related pneumonitis

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI-H CRC, the incidence of pneumonitis including interstitial lung disease was 6.5% (43/666). Grade 2 and Grade 3 cases were reported in 3.3% (22/666) and 1.1% (7/666), of patients, respectively. Median time to onset was 2.7 months (range: 0.25-56.8). Resolution occurred in 39 patients (90.7%) with a median time to resolution of 6.1 weeks (range: 0.7-110.3^{+}).

Immune-related colitis

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI-H CRC, the incidence of diarrhoea or colitis was 27.9% (186/666). Grade 2 and Grade 3 cases were reported in 9.6% (64/666) and 4.7% (31/666) of patients, respectively. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 170 patients (92.4%) with a median time to resolution of 2.2 weeks (range: 0.1-117.0^{+}).

Immune-related hepatitis

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI-H CRC, the incidence of liver function test abnormalities was 19.8% (132/666). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (32/666), 7.4% (49/666), and 1.5% (10/666) of patients, respectively. Median time to onset was 2.1 months (range: 0.3-36.6). Resolution occurred in 112 patients (84.8%) with a median time to resolution of 6.3 weeks (range: 0.1^{+}-175.9^{+}).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI-H CRC, the incidence of nephritis or renal dysfunction was 8.6% (57/666). Grade 2, Grade 3, and Grade 4 cases were reported in 3.8% (25/666), 0.6% (4/666), and 0.8% (5/666) of patients, respectively. Median time to onset was 2.1 months (range: 0.0-34.8). Resolution occurred in 45 patients (78.9%) with a median time to resolution of 10.0 weeks (range: 0.1^{+}-106.0^{+}).

Immune-related endocrinopathies

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI-H CRC, the incidence of thyroid disorders was 26.9% (179/666). Grade 2 and Grade 3 thyroid disorders were reported in 15.3% (102/666) and 1.7% (11/666) of patients, respectively. Hypophysitis occurred in 3.9% (26/666) of patients. Grade 2, Grade 3, and Grade 4 cases were reported in 0.8% (5/666), 2.3% (15/666), and 0.3% (2/666) of patients, respectively. Grade 2 hypopituitarism occurred in 0.5% (3/666) of patients. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 3.5% (23/666), 2.0% (13/666) and 0.3% (2/666) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus (2 Grade 2, 1 Grade 3, and 2 Grade 4), and diabetic ketoacidosis (1 Grade 4) were reported. Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-27.2). Resolution occurred in 89 patients (41.4%). Time to resolution ranged from 0.4 to 257.1^{+} weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI-H CRC, the incidence of rash was 47.7% (318/666). Grade 2 and Grade 3 cases were reported in 13.7% (91/666) and 3.9% (26/666) of patients, respectively. Median time to onset was 1.0 months

(range: 0.0-33.8). Resolution occurred in 228 patients (71.9%) with a median time to resolution of 12.1 weeks (range: 0.1-268.7+).

Infusion reactions

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI-H CRC, the incidence of hypersensitivity/infusion reactions was 3.8% (25/666); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.4% (16/666) of patients. Median time to onset was 0.7 months (range: 0.0-22.6). Resolution occurred in 23 patients (92.0%) with a median time to resolution of 0.1 weeks (range: 0.1-79.1+).

Laboratory abnormalities

In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI-H CRC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.3% for anaemia (all Grade 3), 0.8% for thrombocytopaenia, 0.5% for leucopoenia, 5.3% for lymphopaenia, 1.1% for neutropaenia, 2.8% for increased alkaline phosphatase, 6.7% for increased AST, 7.8% for increased ALT, 1.8% for increased total bilirubin, 2.3% for increased creatinine, 7.2% for hyperglycaemia, 2.2% for hypoglycemia, 11.1% for increased amylase, 20.2% for increased lipase, 0.5% for hypocalcaemia, 1.2% for hypercalcaemia, 2.2% for hyperkalemia, 0.9% for hypermagnesaemia, 0.3% for hypomagnesaemia 2.2% for hypokalaemia, and 9.2% for hyponatraemia.

Immunogenicity

Of the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 25.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralising antibodies against nivolumab was 0.8% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 0.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks, and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 13.7% and neutralising antibodies against ipilimumab ranged from 0 to 0.4%.

Elderly

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from SCCHN and adjuvant melanoma patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). Data from dMMR or MSI-H CRC patients 75 years of age or older are limited (see section 5.1). Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population (see section 5.1).

In MPM patients, there was a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received nivolumab in combination with ipilimumab (54% and 28%, respectively).

For patients treated with nivolumab in combination with cabozantinib, data from RCC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1).

Post marketing experience

Based on pharmacovigilance activities conducted by BMS Worldwide Patient Safety, review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for nivolumab. The safety profile of nivolumab in the post-marketing setting remains favourable and similar to the profile established during clinical trials. To date, no new significant safety concerns have been identified based on global post-marketing reports. Post-marketing 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.

Based on pharmacovigilance activities conducted by BMS Worldwide Patient Safety, review of post-marketing safety data is consistent with, and confirms the clinical trial safety data for ipilimumab. The safety profile of ipilimumab in the post-marketing setting remains favourable and similar to the profile established during clinical trials. Qualitative and quantitative safety information received to date does not raise any significant new safety concerns or substantially alter the overall known safety profile of ipilimumab as described in the prescribing information.

2.5.1. Discussion on clinical safety

The main safety dataset of nivolumab in combination with ipilimumab for the treatment of patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC) after prior fluoropyrimidine-based combination chemotherapy is based on 119 patients included in Cohort 2 (cStage 1 and 2) of Study CA209142. The Study CA209142 was a Phase 2, open-label, multi-cohort (six cohorts) study of nivolumab monotherapy or in combination with ipilimumab or other therapies in patients with recurrent or mCRC.

In addition, integrated safety data (n=666) from the study CA209144 and study CA209214 (in patients with renal cell carcinoma treated with the same combination regimen), have been provided.

Cohort 2 was comprised by patients with metastatic MSI-H/dMMM CRC, with a median age of 58.0 years (range: 21, 88), most of them were White (92%), male (59%) with an ECOG performance status of 0 (45%) or 1 (55%). Patients 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 were excluded from the study. The majority of patients had received at least 2 prior regimens (76.5%) and 82 (69%) patients had received prior treatment with 5-FU, oxaliplatin and irinotecan.

Patients in Cohort 2 received nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for four cycles, followed by nivolumab 3 mg/kg Q2W. However, the proposed posology for the applied indication to be included in the SmPC (i.e. nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 cycles and then nivolumab 240 mg Q2W) differ from the one used in the study. Moreover, the duration of the infusion is also proposed to be shortened (i.e. from 60 min to 30 min for nivolumab and from 90 min to 30 min for ipilimumab). See PK/PD section.

At the date of the last database lock (19 Feb 2019), 43% of patients remained on treatment. Among patients who had discontinued treatment, disease progression was the leading cause (28%) followed by study drug toxicity (14%). The median number of doses received was 51.0 (range: 1 -93) for nivolumab and 4.0 (range: 1-4) for ipilimumab and most of patients (76.5%) received at least 90% of the planned dose intensity of nivolumab and ipilimumab.

Almost all patients reported at least one adverse event (99.2%). The most frequently reported (≥25%) adverse events, regardless of causality, were diarrhoea (54%), pyrexia (42%), fatigue,

pruritus, cough (34%, each), anaemia (33%), nausea, abdominal pain (29%, each), asthenia (28%) and back pain (27%). Of these, 59.7% were adverse events (AEs) of Grade 3-4. AEs of Grade 3-4 most common (≥5%) were lipase increased (13%), AST increased (10%), ALT increased (8%) and diarrhoea (6%).

The safety profile of nivolumab + ipilimumab is characterised by immune-related adverse events. Select AEs include endocrine, gastrointestinal, hepatic, pulmonary, renal, skin events and hypersensitivity/infusion reactions. In this regard, the most commonly reported select AEs in patients treated with nivolumab + ipilimumab in study CA209142, regardless of causality, were skin events (60%), gastrointestinal (54%), endocrine and hepatic events (35%, each). Most of these events were considered drug-related (35%, 25%, 32%, 24%, respectively). By preferred term, the most frequent select AEs considered drug-related were diarrhoea (25.2%), pruritus (20.2%), hypothyroidism (17.6%), AST increased (16%), rash (15.1%), hyperthyroidism (14.3%) and ALT increased (12.6%). Most of events were Grade 1 or 2. Among the AEs of Grade 3-4, the most common were hepatic events (11.8%; mainly AST and ALT increased). No AEs of Grade 5 were reported. The majority of events resolved, with immune-modulating medication and/or corticosteroids, except for endocrine events, since only 34% of evens were resolved at the time of the data cut-off.

There were 5 (2.5%) patients that reported other events of special interest (OESI), including myositis (2 patients), encephalitis, uveitis and pancreatitis (1 patient, each).

Up to the data cut-off, 33 (27.7%) patients had died, most of them due to disease progression (29 [24.4%]). None of the deaths was considered related to study drug toxicity. There were also 3 patients who died due to "other" causes. These causes were sudden death (18 days after the last dose), respiratory failure (83 days after the last dose) and renal failure (158 days after the last dose). None of these events appear to be related to study treatment.

Serious adverse events (SAEs) were reported by 52.9% of patients. Of these, 22.7% were considered related to study treatment. Most of SAEs occurred within the SOC of endocrine and gastrointestinal disorders.

There were 19 (16.0%) patients that required treatment discontinuation due to adverse events, most of them (16 [13.4%]) were considered treatment-related. The main AEs that led to treatment discontinuation were AST and ALT increased (2.5%, each), autoimmune hepatitis and acute kidney injury (1.7, each); all of them were considered related to study treatment.

Safety data according to age have been provided. However, data in elderly and very elderly patients are rather limited (there were only 11 patients 75 years or older).

Updated safety data from the latest DBL of Oct 2020 with longer follow-up have been provided to align data for safety and efficacy. Overall, the safety profile remained comparable to what was observed at the Feb-2019 DBL.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of nivolumab + ipilimumab in patients with dMMR or MSI-H mCRC appear consistent with that observed in patients with RCC, and with the already known safety profile of each monocomponent.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set

out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA submitted updated RMP versions with this application.

Opdivo

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 20.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 20.2 with the following content:

Safety concerns

Table 65 : Summary of Safety Concerns

Important identified risks	Immune-related pneumonitis
	Immune-related colitis
	Immune-related hepatitis
	Immune-related nephritis and renal dysfunction
	Immune-related endocrinopathies
	Immune-related skin ARs
	Other immune-related ARs
	Severe infusion reactions
Important potential risks	Embryofetal toxicity
	Immunogenicity
	Complications of allogeneic HSCT following nivolumab therapy in cHL
	Risk of GVHD with Nivolumab after allogeneic HSCT
Missing information	Patients with severe hepatic and/or renal impairment
	Patients with autoimmune disease
	Patients already receiving systemic immunosuppressants before starting nivolumab

Pharmacovigilance plan

Table 66: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				

Table 66: Ongoing and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CA209234: Pattern of use and safety/effectiveness of nivolumab in routine oncology practice Ongoing	To assess use pattern, effectiveness, and safety of nivolumab, and management of important identified risks of nivolumab in patients with lung cancer or melanoma in routine oncology practice	Post marketing use safety profile, management and outcome of immune-related pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, endocrinopathies, rash, other immune-related adverse reactions (uveitis, pancreatitis, demyelination, Guillain-Barre syndrome, myasthenic syndrome, encephalitis, myositis, myocarditis, rhabdomyolysis, solid organ transplant rejection, and VKH), and infusion reactions	1. Interim report 2. Final CSR submission	Interim results provided annually 4Q2024
CA209835: A registry study in patients with Hodgkin lymphoma who underwent post-nivolumab allogeneic HSCT Ongoing	To assess transplant-related complications following prior nivolumab use	Post marketing safety assessment of the outcome of post-nivolumab allogeneic HSCT	1. Annual update 2. Interim CSR submission 3. Final CSR submission	With PSUR starting at DLP 03-Jul-2017 06-2019 4Q2022

Risk minimisation measures

Table 67: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Immune-related pneumonitis Immune-related colitis Immune-related hepatitis Immune-related nephritis and renal dysfunction Immune-related endocrinopathies Immune-related skin ARs Other immune-related ARs	Routine risk minimization measures: SmPC Sections 4.2, 4.4 and 4.8 Additional risk minimization measures: Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Post-marketing pharmacoepidemiology study (CA209234)

Table 67: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Severe Infusion Reactions	Routine risk minimization measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: Post-marketing pharmacoepidemiology study (CA209234)
Embryofetal toxicity	Routine risk minimization measures: SmPC Sections 4.6 and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimization measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Complications of allogeneic HSCT following nivolumab therapy in cHL	Routine risk minimization measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: Registry study (CA209835)
Risk of GVHD with nivolumab after allogeneic HSCT	Routine risk minimization measures: SmPC Section 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with severe hepatic and/or renal impairment	Routine risk minimization measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimization measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None
Patients already receiving systemic immunosuppressants before starting nivolumab	Routine risk minimization measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimization measures: None	Additional pharmacovigilance activities: None

Yervoy

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 30.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 30.2 with the following content:

Safety concerns

Table 68 : Summary of Safety Concerns

Important identified risks	• GI irARs (eg, diarrhoea, colitis, GI perforation) • Hepatic irARs (eg, hepatitis) • Skin irARs (eg, rash, pruritus, TEN, and DRESS) • Neurologic irARs (eg, neuropathy) • Endocrine irARs (eg, hypopituitarism, hypothyroidism, adrenal insufficiency) • Other irARs (eg, pneumonitis, nephritis, non-infective myocarditis, and pancreatitis) • Severe infusion reactions
Important potential risks	• Immunogenicity
Missing information	• Long-term safety in adolescent patients > 12 years of age • Potential PD interaction with systemic immunosuppressants • Patients with severe hepatic impairment • Patients with severe renal impairment • Patients with autoimmune disease

Pharmacovigilance plan

Table 69: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

Table 69: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
MAH to sponsor extension of the Dutch Melanoma Treatment Registry (DMTR) to include paediatric subjects and to collect their safety data (CA184557)	To obtain additional safety information in paediatric patients	Long-term safety in adolescent patients > 12 years of age	1. Synopsis of the DMTR	16-Apr-2018
			2. Submission of protocol	02-Nov-2019
			3. Start of data collection	End of 2Q 2019
			4. Recruitment period[a]	2Q 2019 until 1Q 2029
			5. Progress Report	End of 2Q 2022
			6. Interim Study Report	End of 2Q 2024
			7. End of data collection	End of Q1 2029
			6. Final report of study results	End of 2Q 2029

[a] The recruitment period began in 2Q 2019, when the Princess Maxima Center officially confirmed its collaboration to the paediatric extension of the DMTR, but the data will include all paediatric patients entered in the DMTR who received ipilimumab prior to the start of data collection.

Risk minimisation measures

Table 70: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Identified Risks Immune-related Adverse Reactions (GI irARs, hepatic irARs, skin irARs, neurological irARs, endocrine irARs, and other irARs)	Routine risk minimisation measures: SmPC Section 4.4 specific warning/precautions; Sections 4.2 and 4.4 guidelines on monitoring, diagnosis, dose modification, and corticosteroids intervention; and Section 4.8 ADR list	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures:Patient Information Brochure and Alert Card	Additional pharmacovigilance activities: None
Severe Infusion Reactions	Routine risk minimisation measures: SmPC Section 4.3 Contraindication, Section 4.4 Special warnings, Section 4.8 Undesirable effects	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Table 70: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: • Patient Information Brochure and Alert Card	Additional pharmacovigilance activities: None
Immunogenicity	Routine risk minimisation measures: SmPC Section 5.1 Immunogenicity	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Long-term safety in adolescent patients > 12 years of age	Routine risk minimisation measures: SmPC Section 4.2, 4.4, 4.8, and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A PIP for ipilimumab in malignant neoplasms (except melanoma, nervous system, haematopoietic, and lymphoid tissue) and a second PIP in melanoma have been completed in the EU. • Reporting of long-term safety data in paediatric patients in studies of nivolumab and ipilimumab combination therapy (CA209070 and CA209908). • Monitoring of initial AEs and continued follow-up while on therapy and/or 100 days after the last dose by the treating physician. Follow-up information obtained by BMS using specified procedures (telephone interviews or mailing a questionnaire to the treating physician).
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: MAH to sponsor extension of the DMTR to include paediatric subjects and to collect their safety data (CA184557).
Potential PD interaction with systemic immunosuppressants	Routine risk minimisation measures: SmPC Section 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with severe renal impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

Table 70: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Patients with autoimmune disease	Routine risk minimisation measures: SmPC Section 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

2.7. Update of the Product information

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

For final adopted wording please refer to the appended and agreed Product Information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The proposed indication for the combination of nivolumab + ipilimumab is *for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy*.

The recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously, over 30 min each, every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at 240 mg every 2 weeks, over 30 min.

3.1.1. Disease or condition

Colorectal cancer (CRC) is one of the leading causes of cancer-related death worldwide with a 5-year survival rate of approximately 14% in patients with metastatic disease (National Cancer Institute: surveillance, epidemiology and end results program – accessed 16 July 2020). Worldwide, CRC is the third most common form of cancer, with 1.8 million new cases diagnosed worldwide in 2018, constituting 10.2% of all new cancers. Among all new CRC cases, 27% were diagnosed in Europe

(Globocan 2018). Each year, there are about 880,792 deaths from CRC worldwide, which is 9.2% of all cancer deaths, making CRC the second most common cause of cancer death (Globocan 2018). The risk of developing CRC is influenced by both environmental and genetic factors (Chan and Giovannucci, 2010).

Among metastatic CRC (mCRC) patients, mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) tumor only accounts for approximately 5%. Patients with Lynch-like mCRC are associated with younger age, higher frequency of liver metastasis, more frequent resection of metastatic disease, thus more favourable prognosis compared to those with sporadic dMMR or MSI H mCRC. In both patient groups, alterations in the DNA MMR genes lead to accumulation of errors during DNA replication, especially in repetitive sequences known as microsatellites, causing high level of MSI. Thus, MSI is the molecular fingerprint of a deficient DNA mismatch repair.

3.1.2. Available therapies and unmet medical need

Metastatic CRC is a complex and heterogeneous disease, with outcomes ranging from potential cure (ie, upfront resectable mCRC) to dismal (refractory wide-spread disease). Multi-modality treatment including surgery, radiation, and chemotherapy, especially in medically-fit patients with borderline or potentially resectable disease, is the preferred approach in earlier lines of treatment in centres capable of providing multidisciplinary approach and adequate supportive care. The active agents in first- and second-line treatment of mCRC consist of fluoropyrimidines (5-FU, capecitabine), oxaliplatin, and irinotecan. Doublet or triplet chemotherapy is often combined with a monoclonal antibody inhibiting VEGF (bevacizumab or ziv-aflibercept); or EGFR (cetuximab or panitumumab; only indicated in RAS wild-type tumors), depending on biomarker status and primary tumour location.

Second-line treatment is typically a doublet chemotherapy, depending on the regimen used in first-line setting. The multi-targeted tyrosine kinase inhibitor, regorafenib, and the oral nucleoside analogue trifluridine/tipiracil are available options beyond second-line, but efficacy was modest in the pivotal trials, CORRECT and RECOURSE. Another third line option, anti EGFR antibody with or without irinotecan, is also used in patients with RAS wild-type status who have not received anti-EGFR therapy in prior lines of therapy. Patients carrying tumors with BRAF V600E mutation are eligible for doublet targeted therapy against BRAF and EGFR in second line and beyond (combination of an anti-EGFR mAb with encorafenib). Additionally, larotrectinib is a new treatment option for patients whose tumors are positive for NTRK gene fusion, a rare alteration.

So far, there are no approved treatment options in the EU specifically for patients with dMMR/MSI-H mCRC.

3.1.3. Main clinical studies

CA209142 (Checkmate 142) is a Phase 2 multi-cohort, open-label, multi-centre trial including nivolumab monotherapy (Cohort 1) or nivolumab in combination with ipilimumab (Cohort 2) in adults (≥ 18 years) who had disease progression during, after, or had been intolerant to therapy with 5FU-based chemotherapy with recurrent or metastatic dMMR or MSI-H CRC. The dMMR or MSI-H evaluation was performed by local lab as part of standard diagnostic testing by investigators. MSI status was to be confirmed by a central testing during the study.

For Cohort 2, which is the objective of this assessment report, study treatment scheme was nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W until disease progression, unacceptable toxicity or maximum clinical benefit, per protocol.

Investigator-assessed ORR according to RECIST 1.1 criteria was the primary endpoint. BICR-assessed ORR according to RECIST 1.1 criteria and DCR were evaluated as secondary endpoints. In this study, PFS and OS were exploratory endpoints.

This study followed a 2-stage design, where an ORR threshold was needed to be met to proceed from Stage 1 to Stage 2. A total of **119 patients** were treated with nivolumab in combination with ipilimumab (including a subset of 82 subjects who received prior 5FU-Oxa-Iri) in Cohort 2 of this study.

3.2. Favourable effects

The efficacy results of nivolumab in combination with ipilimumab presented below are based on the latest updated **database lock of Oct-2020**, with a median follow-up of 46.9months. Data in the 'all treated' population are presented (n=119):

- The **Investigator-assessed ORR** was 64.7% (95% CI: 55.4, 73.2) for the all treated population (n=119), 63.4% (95% CI: 52.0, 73.8)) for subjects with prior 5FU-Oxa-Iri therapy (n=82) and 67.6% (95% CI: 50.2, 82.0) for subjects without prior 5Fu-Oxa-Iri therapy (n=37).
- The **BICR-assessed ORR** was **61.3%** (95% CI: 52.0, 70.1) for the all treated population (n=119), 58.5% (95% CI: 47.1, 69.3) for subjects with prior 5FU-Oxa-Iri therapy (n=82) and 67.6% (95% CI: 50.2, 82.0) for subjects without prior 5FU Oxa-Iri therapy (n=37;).
- Median **DOR** was not reached in either case.
- Median **PFS** per **investigator** was N.R. (95% CI: 38.4, N.A.) and median PFS per BICR was 56.3 (30.3, N.A.) months.

Median **OS** as per investigator assessment was not reached. OS rates at **36 and 48 months**, for the all treated patient population were, respectively, **71.4%** and **70.5%**.

3.3. Uncertainties and limitations about favourable effects

In addition to the small sample size, the main limitation of this study is its non-comparative design, which hampers the interpretation of the reported results, particularly of time to event endpoints. This is of particular relevance taking into account the uncertainties on the actual prognostic value of MMR status in the mCRC setting. As for the predictive value of MSI-H status this appears supported for immune check-point inhibitors with international consensus guidelines noting that MSI testing has strong predictive value for its use to treat patients with mCRC. Also external data from studies investigating checkpoint inhibitors in MSI-H mCRC has emerged, which support concept that patients with MSI-H mCRC may benefit from anti-PD-1 therapy, such as data from KEYNOTE-177 (abstract, Thierry et al. *J Clin Oncol,* 2020) and KEYNOTE-164 (Le *J Clin Oncol*, 2019). Even if results reported in cohort 2 of the CA209142 study are considered clinically relevant, data cannot be regarded as comprehensive as a result of the uncontrolled nature of the study that limits interpretation of data. In this respect the MAH has proposed to provide results from a currently ongoing randomized Phase 3b trial (Study CA2098HW) as a post-authorisation measure (PAM). Results from this study are expected to provide replication of ORR and DOR results in the ≥2L population, and also randomised data to compare numerical differences between chemotherapy and nivolumab (in combination with ipilimumab) in the 2L setting of dMMR or MSI-H mCRC. Results from this study should be submitted when available in the context of a recommendation.

The observed magnitude of durable tumour responses could be regarded as clinically relevant as it is reasonable to expect that these will translate into a survival benefit; though its magnitude is yet to be determined. The dataset of 2L patients to support the claimed broad indication is limited (n=37) though results in this subpopulation are also compatible with clinically meaningful efficacy.

The primary analysis cohort includes 119 patients among whom one patient did not receive any prior line of treatment and 9 received prior fluoropyrimidine based chemotherapy in the (neo)-adjuvant setting and progressed during or within 6 months of completion of treatment. It was initially questioned that patients having received fluoropyrimidine based chemotherapy in the (neo)-adjuvant setting and progressed during or within 6 months of completion of the treatment pertained to a different treatment setting and as a consequence the updated efficacy analysis (DBL Oct-2020, with additional follow-up of ~ 20 months) excluded all patients who had not received prior fluoropyrimidine based chemotherapy in the metastatic setting in cohort 2, i.e. 10 patients. It is however recognised that in clinical practice patients progressing on or within 6 months of completion of adjuvant chemotherapy in the non-metastatic setting are considered as having been treated with first-line (1L) chemotherapy and indeed normally excluded from clinical studies that enrol 1L patients. It is therefore considered that the 'All Combination Treated Subjects' population (n=119) is the one used for efficacy inference and the analysis/data to be included in the SmPC.

A lower ORR was observed in patients from cStage 1 compared to cStage 2 (48.1% [95%CI: 28.7, 68.1] vs. 63.0% [95%CI: 52.3, 72.9]) which could be related to the smaller size of the cStage 1 sample. Some unbalances in baseline characteristics may also have contributed to these results.

Lower rates of tumour response were observed in elderly patients and patients heavily pre-treated (more than 4 prior lines) although the number of subjects included in these subgroups is limited.

The justification for the contribution of ipilimumab in the proposed combination is based on comparative efficacy data from Cohort 1 (nivo monotherapy) and Cohort 2 (nivo/ipi combination) of the CA209142 study. The reported superior ORR for the combination vs. the monotherapy (almost 2-fold; 59.7% [95%CI: 50.3, 68.6] vs. 37.8% [95%CI: 26.8, 49.9], respectively) appears sufficient to justify that the addition of ipilimumab to nivolumab leads to better efficacy in the targeted patient population albeit the limitations of a comparison between non randomised cohorts. No indication for nivolumab in monotherapy in the intended disease setting is currently sought.

3.4. Unfavourable effects

The main safety dataset of nivolumab in combination with ipilimumab for the treatment of patients with dMMR or MSI-H mCRC after prior fluoropyrimidine-based combination chemotherapy is based on 119 patients included in Cohort 2 of Study CA209142 at the DBL of Oct-2020.

The median number of doses received was 51.0 (range: 1 -122) for nivolumab and 4.0 (range: 1-4) for ipilimumab and most of patients (75.6 fro nivolumab and 84.9% for ipilimumab%) received at least 90% of the planned dose intensity of nivolumab and ipilimumab respectively.

Almost all patients reported at least one adverse event (99.2%). The most frequently reported (≥25%) adverse events, regardless of causality, were diarrhoea (58%), pyrexia (44.5%), fatigue, pruritus, cough (35.5%, 34.5%, 35.3% respectively), anaemia (33.6%), nausea, abdominal pain (30.3% and 31.9% respectively), asthenia (28.6%) and back pain (27.7%).

Adverse events (AEs) of Grade 3-4 were reported in 62.2% of patients, being the most common (≥5%) lipase increased, AST increased, ALT increased and diarrhoea.

Select AEs in patients treated with nivolumab in combination with ipilimumab include endocrine, gastrointestinal, hepatic, pulmonary, renal, skin events and hypersensitivity/infusion reactions. The most commonly reported select AEs, regardless of causality, were skin events (60%), gastrointestinal (58%), endocrine and hepatic events (34.5% and 36.1% respectively). Most of these events were considered drug-related (38.7%, 26.9%, 31.9%, 26.1%, respectively). By preferred term, the most frequent select AEs considered drug-related were diarrhoea (26.9%), pruritus (21%), hypothyroidism (17.6%), AST increased (16.8%), rash (16%), hyperthyroidism (14.3%) and ALT increased (14.6%). Most of events were Grade 1 or 2. Among the AEs of Grade 3-4, the most common were hepatic events (11.8%; mainly AST and ALT increased). No AEs of Grade 5 were reported.

There were 5 (2.5%) patients that reported other events of special interest (OESI), including myositis (2 patients), encephalitis, uveitis and pancreatitis (1 patient, each).

Up to the latest data cut-off (oct-2020), 35 (29.4%) patients had died, most of them due to disease progression (31 [26.1%]). None of the deaths was considered related to study drug toxicity. There were also 3 patients who died due to "other" causes (sudden death, respiratory failure and renal failure.

Serious adverse events (SAEs) were reported by 55.5% of patients. Of these, 22.7% were considered related to study treatment. Most of SAEs occurred within the SOC of endocrine and gastrointestinal disorders.

There were 19 (16.0%) patients that required treatment discontinuation due to adverse events, most of them (16 [13.4%]) were considered treatment-related. The main AEs that led to treatment discontinuation were AST and ALT increased (2.5%, each), autoimmune hepatitis and acute kidney injury (1.7, each); all of them were considered related to study treatment.

Safety data according to age have been provided. However, data in elderly and very elderly patients are rather limited (there were only 11 patients 75 years or older).

3.5. Uncertainties and limitations about unfavourable effects

Safety data of the combination of nivolumab + ipilimumab in the applied indication is very limited in elderly patients (≥75 years), which hampers a proper characterisation of the safety profile in this patient population.

3.6. Effects Table

Effects table for nivolumab in combination with ipilimumab for the treatment of adult patients with dMMR or MSI-H metastatic colorectal cancer after prior fluoropyrimidine based combination chemotherapy. CA209142 study (database lock: Oct 2020)

Table 71. Effects Table

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR	Overall response rate investigator-assessed	% (95%CI)	64.7 (55.4, 73.2)	N/A	Based on 119 patients included in the uncontrolled open label Cohort 2 of the study	SCE
	Overall response rate BICR-assessed	% (95%CI)	61.3 (52.0, 70.1)	N/A		SCE
DOR	Duration of	Median	Not reached	N/A		SCE

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	response - investigator-assessed	months (95%CI)				
	Duration of response – BIRC assessed	Median months (95%CI)	Not reached	N/A		SCE
Unfavourable Effects						
AEs G3-4	Adverse events of grade 3 or 4	%	62.2	NA		SCS
SAEs	Serious adverse events	%	55.5	NA		SCS
Discontinuations	Discontinuations due to adverse events	%	18.5%	NA		SCS
Diarrhoea	Common adverse event	%	AE: 58 G3/4: 6.7	NA		SCS
Pyrexia	Common adverse event	%	AE: 42 G3/4: 0	NA		SCS
Fatigue	Common adverse event	%	AE:34.5 G3/4: 3.4	NA		SCS
Pruritus	Common adverse event	%	AE: 35.3 G3/4: 1.7%	NA		SCS
Cough	Common adverse event	%	AE:35.3 G3/4: 0.8	NA		SCS

Abbreviations: SCE: summary of clinical efficacy, SCS: summary of clinical safety, OS: overall survival, PFS: progression free survival, ORR: overall response rate, DOR: duration of response, BICR: blinded independent review committee

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, the reported results with the combination of nivolumab + ipilimumab in the 119 patients with dMMR or MSI-H mCRC who had disease progression during, after, or had been intolerant to therapy with 5FU-based chemotherapy included in cohort 2 of study CA209142 are considered of clinical relevance.

The main limitation of the study, in addition to its limited sample size, is its non-comparative design, which hampers the interpretation of the reported results, particularly of time to event endpoints. This is of particular relevance taking into account the uncertainties regarding the actual prognostic value of MMR status in the metastatic CRC setting.

The ORR and duration of response shown in study CA209142, even if in the context of a single arm trial where results might be overestimated, well exceeds the ORR reported in other mCRC trials (although not selected by dMMR/MSI-H status, trials conducted years ago) where response rates in e.g. second line were around 13-32% depending on the administered treatment and KRAS mutation status (Giantonio BJ, et al J Clin Oncol, 2007; Benouna J, et al Lancet Oncol, 2013). In the recent KEYNOTE-177 study, a phase 3 randomised study in patients with dMMR or MSI-H mCRC previously untreated with chemotherapy, an ORR of 33% (95%CI: 2.8, 37.5) and a median DoR of 10.6 months was reported in patients treated with fluoropyrimidine-based chemotherapy (abstract, Thierry et al. *J of Clin Oncol,* 2020). Additional (within-patient) information/analyses to better understand the clinical relevance of the study results and to confirm their robustness have been submitted together with an update of the efficacy analysis at the latest DBL of Oct 2020. BICR-assessed ORR results previously

observed have been confirmed and are of similar magnitude for 2L and 3L subjects. Median duration of response has not been reached. Of note, even if interpretation of time to event related endpoints is jeopardized by the uncontrolled nature of the study, OS rates at 36 and 48 months are of notable relevance (i.e. 71.4% and 70.5%, respectively).

In summary, efficacy results reported in cohort 2 of study CA209142 are considered clinically meaningful and are numerically superior to that obtained with currently available therapies for (MSI-H) mCRC patients. The available data set for 2L patients of 37 patients, including 9 patients who progressed on or within 6 months of completion of adjuvant chemotherapy in the non-metastatic setting, is certainly limited. However, it is difficult to foresee that potential differences in prognosis or response to treatment in the targeted MSI-H mCRC population compared to other CRC patients could challenge the relevance of the reported ORR with long durations of response that have notably matured after additional 20 months of follow-up (minimum follow-up of nearly 4 years) and remain consistent.

The indication wording is supported and efficacy data from the 'all treated population' (n=119) has been included in section 5.1 of the SmPC. In addition, the patient population enrolled in the study has been described in detail, including specific requirements for patients having received treatment in the adjuvant setting.

The justification for the contribution of ipilimumab in the proposed combination, which is based on comparative efficacy data from Cohort 1 (nivo monotherapy) and Cohort 2 (nivo/ipi combination) of study CA209142, appears sufficient to justify that the addition of ipilimumab to nivolumab leads to better efficacy in the targeted patient population albeit the limitations of a comparison between non randomised cohorts.

From a safety point of view, the safety profile of nivolumab in combination with ipilimumab in the intended indication appears consistent with that previously observed in other indications and is in line with the already known safety profile of each component. The combination of nivolumab + ipilimumab is characterised by a high incidence of adverse events, especially those considered immunomediated.

Finally, the MAH plans to provide results of a currently ongoing randomized Phase 3b trial (Study CA2098HW) in the first line setting as a post-authorisation measure (PAM). Results from this study are expected to provide replication of ORR and DoR results in the ≥2L population, and also randomised data to compare numerical differences between chemotherapy and nivolumab (in combination with ipilimumab) in the 2L setting of dMMR or MSI-H mCRC. Results from this study should be submitted when available in the context of a recommendation.

3.7.2. Balance of benefits and risks

Combination treatment with nivolumab and ipilimumab resulted in an ORR benefit in the treatment of adult patients with mismatch repair deficient or microsatellite instability high metastatic colorectal cancer after prior fluoropyrimidine based combination chemotherapy.

The overall safety profile of the combination appears to be similar to that observed with the same combination in other indications and seems in line with the safety profile of both components

The benefit-risk balance is therefore considered positive in the target population as represented by the adopted indication.

The benefit risk balance for the claimed indication is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

The final adopted indication is:

for Opdivo:

OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

for Yervoy:

YERVOY in combination with nivolumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer after prior fluoropyrimidine-based combination chemotherapy.

3.8. Conclusions

The overall B/R of nivolumab + ipilimumab in the claimed indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**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 the combination of nivolumab with ipilimumab in the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability_high (MSI-H) metastatic colorectal cancer (CRC) after prior fluoropyrimidine based combination chemotherapy; as a consequence, sections 4.1, 4.2 ,4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.2 for Opdivo and version 30.2 for Yervoy of the RMP have also been submitted.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'OPDIVO, Yervoy-H-C-3985 & 2213-WS-1840'