22 April 2022
EMA/257879/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Keytruda

International non-proprietary name: pembrolizumab

Procedure No. EMEA/H/C/003820/II/0110

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

Abbreviation	Definition
AE	Adverse event
AEOSI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
APaT	All Participants as Treated
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BRCA1	Breast cancer type 1 susceptibility protein
cHL	Classic Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
CPS	Combined positive score
CRC	Colorectal cancer
cSCC	Cutaneous squamous cell carcinoma
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
DFS	Disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMEA	European Medicines Evaluation Agency
E-R	Exposure-response
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
HCC	Hepatocellular carcinoma
HER2	Human epidermal growth factor receptor-2
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
IA1	Interim analysis 1

IA2 Interim analysis 2

IA3 Interim analysis 3

IA4 Interim analysis 4

IFNγ Interferon gamma

IgG4 Immunoglobulin G4

IL-2 Interleukin-2

iPSP Initial pediatric plan

IRR Immune-related reaction

ITT Intent-to-treat

IV Intravenous(ly)

mAb Monoclonal antibody

MCC Merkel cell carcinoma

mRNA Messenger RNA

MSI-H Microsatellite instability-high

MSI-H CRC Microsatellite instability-high colorectal cancer

NAC Neoadjuvant chemotherapy

NCCN National Comprehensive Cancer Network

NSCLC Nonsmall cell lung cancer

ODAC Oncologic Drug Advisory Committee

OS Overall survival

pCR Pathological complete response

PD-1 Programmed cell death 1

PD-L1 Programmed cell death 1 ligand-1

PD-L2 Programmed cell death 1 ligand-2

PgR Progesterone receptor

PK Pharmacokinetic(s)

PMBCL Primary mediastinal B-cell lymphoma

PS Performance status

PTEN Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase

Q2W Once every 2 weeks

Q3W Once every 3 weeks

Q6W Once every 6 weeks

RCC	Renal cell carcinoma
RSD	Reference safety dataset
SAE	Serious adverse event
sBLA	Supplemental Biologics License Application
sSAP	Supplemental Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	System organ class
TCGA	The Cancer Genome Atlas
TIL	Tumor-infiltrating lymphocyte
TMB-H	Tumor mutational burden-high
TNBC	Triple-negative breast cancer
TNFα	Tumor necrosis factor alpha
US	United States
USPI	United States Prescribing Information
WBC	White blood cell
ypT0 ypN0	No invasive or noninvasive residual in breast or nodes
ypT0/Tis ypN0	No invasive residual in breast or nodes; noninvasive breast residuals allowed

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 27 July 2021 an application for a variation.

The following variation was requested:

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

Extension of indication for Keytruda in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery of adults with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high-risk of recurrence; as a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 37.1 of the RMP has also been submitted.

The variation 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 (an) EMA Decision(s) P/0043/2018 on the agreement of a paediatric investigation plan (PIP).
At the time of submission of the application, the PIP P/0043/2018 was completed.

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 MAH 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 did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Armando Genazzani Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	27 July 2021
Start of procedure:	14 August 2021
CHMP Rapporteur's preliminary assessment report circulated on	25 October 2021
PRAC Rapporteur's preliminary assessment report circulated on	28 October 2021
CHMP Co-Rapporteur Critique circulated on	1 November 2021
PRAC RMP advice and assessment overview adopted by PRAC on	28 October 2021
Updated CHMP Rapporteur's assessment report circulated on	5 November 2021
Request for supplementary information adopted by the CHMP on	11 November 2021
MAH's responses submitted to the CHMP on	21 December 2021
CHMP preliminary assessment report on the MAH's responses circulated on	2 February 2022
2nd Request for supplementary information adopted by the CHMP on	24 February 2022
MAH's responses submitted to the CHMP on	1 March 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	6 April 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	13 April 2022
CHMP Opinion	22 April 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The scope of this variation is to extend the existing therapeutic indications for Keytruda to include an indication in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high-risk of recurrence.

Epidemiology

In 2020, breast cancer was the most commonly diagnosed malignancy (24.5%) and the leading cause of cancer death (15.5%) among women (Sung H, 2021). In Europe (40 countries), the expected numbers of new cases and deaths from breast cancer in 2020 were 531,086 and 141,765, respectively (Globocan Cancer Observatory).

TNBC represents approximately 15-20% of all breast cancers (Howard, 2021).

Biologic features

TNBC is phenotypically defined by a lack of estrogen receptor (ER) and progesterone receptor (PgR) expression and the absence of human epidermal growth factor receptor 2 (HER2) overexpression or amplification.

TNBC is a heterogeneous entity that encompasses six subtypes with distinct molecular characteristics (basal-like 1 and 2, mesenchymal, mesenchymal stem-like, immunomodulatory, luminal androgen receptor) (Lehmann, 2011).

Approximately 15% of subjects with TNBC carry deleterious BRCA mutations (Sharma, 2014).

The role of programmed cell death ligand 1 (PD-L1) as a potential prognostic and/or predictive biomarker has been intensively explored, with controversial results (Miglietta, 2019). The dynamic nature of PD-L1 has been evaluated in the neoadjuvant setting, where modifications of PD-L1 expression from baseline to post-neoadjuvant chemotherapy (NACT) breast cancer samples were reported (Dieci, 2020; Bianchini, 2020). TNBC is the most frequently breast cancer type infiltrated by Tumor-Infiltrating Lymphocytes (TILs) and there is high interest around the potential prognostic and predictive value (Dieci, 2021), although to date TILs are not yet considered a routine pathological marker in early-stage TNBC (Burstein, 2021).

Clinical presentation, diagnosis and stage/prognosis

TNBC is associated with higher tumor grade at diagnosis, a higher risk of distant disease recurrence, particularly to visceral organs and brain, and poor clinical outcomes, with most of the relapse occurring within the first 3 years after surgery (Dent, 2007; Lin, 2012). The 5-year EFS and OS rates are ~71% and ~77%, respectively for patients with clinical stage II-III (Sikov, 2019).

Management

According to ESMO and NCCN guidelines, medical management of early-stage breast cancer has been based on systemic chemotherapy given prior to (neoadjuvant) or after (adjuvant) definitive surgery. For high-risk, early-stage breast cancer, neoadjuvant chemotherapy NACT is believed to be advantageous, as it can increase the ability to resect tumors, increase breast conservation rates, enable the in vivo evaluation of efficacy of systemic therapy, and provide long-term prognostic information (Cardoso, 2019; NCCN 2021). While chemotherapy is typically given as adjuvant in Stage I, NACT is preferred in stage II and III disease (Burstein, 2021). Patients with TNBC should receive chemotherapy (ChT), with the possible exception of low-risk 'special histological subtypes' such as secretory or adenoid cystic carcinomas or very early (T1aN0) tumours, the standard anthracycline-based regimens are anthracycline (AC) or epirubicin plus cyclophosphamide (EC). Sequential use of anthracyclines and taxanes is superior to concomitant use and is also much less toxic. Some data suggest that a taxane/anthracycline sequence may be slightly more effective than the traditionally used anthracycline/taxane order but both are acceptable. Chemotherapy should be administered for 12–24 weeks (4–8 cycles) (Cardoso, 2019).

The use of carboplatin in the neoadjuvant TNBC setting has shown an increased pathological complete response (pCR) rate according to literature, although with no consistent Event Free Survival improvement, and at the expenses of worse haematological toxicity (Loibl S, 2021; Poggio, 2018; Pandy, 2019), so there is no unanimously consensus as yet on the inclusion of carboplatin in neoadjuvant therapy for TNBC (Burstein HJ, 2021).

In general, patients who achieve pCR after neoadjuvant treatment have demonstrated sustained clinical benefit (Cortazar, 2014). There has been no correlation established between the magnitude of difference in pCR between treatment arms and long-term outcomes as assessed by EFS and OS at the study level (Huang, 2020). Further, the relationship between pCR and long-term outcomes for immunotherapy is currently unknown. The risk stratification based on pCR following neoadjuvant therapy is a strategy for optimizing post-neoadjuvant treatment (Burstein HJ, 2021). Adjuvant capecitabine is an option in TNBC for patients with residual disease (Burstein HJ, 2021; Masuda, 2020; Lluch 2020).

2.1.2. About the product

Pembrolizumab is a highly selective humanized monoclonal antibody that binds to human programmed cell death 1 (PD 1) and blocks the interaction between the PD-1 pathway receptor and its ligands, programmed cell death 1 ligand 1 (PD-L1) and 2 (PD-L2) on antigen presenting tumor cells.

In the EU, pembrolizumab is currently approved, as monotherapy and in combination with other agents, for the treatment of melanoma, NSCLC, RCC, HNSCC, MSI-H or dMMR cancer (CRC, endometrial carcinoma, gastric, small intestine, or biliary cancer), urothelial cancer, oesophageal cancer, breast cancer, endometrial carcinoma, cervical cancer and cHL.

With regard to the TNBC indication, pembrolizumab received positive CHMP opinion in September 2021 in combination with chemotherapy for locally recurrent unresectable or metastatic TNBC with PD-L1 expression CPS ≥ 10, based on the results of the phase III study KEYNOTE-355. This is the second extension of indication sought for pembrolizumab in this disease, in the earlier setting neoadjuvant/adjuvant, based on KEYNOTE-522 trial.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

An overview of the clinical trials for pembrolizumab in TNBC is presented below:

Table: Clinical Development Program for Pembrolizumab in TNBC

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Endpoint(s)
KEYNOTE-012 (Cohort A) Completed	Phase 1b, single-group study of pembrolizumab monotherapy	Adult female participants with mTNBC (1L+, Cohort A), N=32	Pembrolizumab 10 mg/kg Q2W	Safety, tolerability, ORR
KEYNOTE-086 Completed	Phase 2, single-group study of pembrolizumab monotherapy	Adult male and female participants with mTNBC: 2L+ (Cohort A) N=170, 1L PD-L1+ (Cohort B) N=84	Pembrolizumab 200 mg Q3W	ORR

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Endpoint(s)
KEYNOTE-173 Completed	Phase 1b, open-label study of pembrolizumab plus chemotherapy as neoadjuvant treatment	Adult female participants with newly diagnosed, locally advanced, non-metastatic TNBC N=60	Single dose pembrolizumab 200 mg Q3W followed by: **Cohort A**: 4 cycles of pembrolizumab 200 mg Q3W + nab-paclitaxel 125 mg/m^2 QW, followed by 4 cycles of (pembrolizumab 200 mg + doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2) Q3W **Cohorts B**: as Cohort A, but with nab-paclitaxel 100 mg/m^2 QW and addition of carboplatin AUC 6 Q3W in the first 4 cycles **Cohorts C**: as Cohort A, but with addition of carboplatin AUC 5 Q3W in the first 4 cycles **Cohort D**: as Cohort A, but with addition of carboplatin AUC 2 QW in the first 4 cycles **Cohort E**: as Cohort A, but with paclitaxel 80 mg/m^2 QW, instead of nab-paclitaxel, and addition of carboplatin AUC 5 Q3W in the first 4 cycles **Cohort F**: as Cohort A, but with paclitaxel 80 mg/m^2 QW, instead of nab-paclitaxel, and addition of carboplatin AUC 2 QW in the first 4 cycles	Safety, tolerability, and establishing the recommended Phase 2 dose
KEYNOTE-119 Completed	Phase 3, randomized, open-label study of pembrolizumab monotherapy vs chemotherapy	Adult male and female participants with mTNBC (2L or 3L) N=622	Pembrolizumab 200 mg Q3W or Capecitabine, eribulin, gemcitabine, or vinorelbine per physician's choice	OS in all participants and participants with PD-L1+ tumors (CPS ≥1, and CPS ≥10)
KEYNOTE-242 SWOG Study S1418/BR006/ Ongoing	Phase 3, randomized, open-label study of pembrolizumab vs observation	Adult male and female participants with residual invasive breast cancer or positive lymph nodes after neoadjuvant chemotherapy	Pembrolizumab 200 mg Q3W for 1 year (~17 administrations) or observation	IDFS in all participants and participants with PD-L1+ tumors (CPS ≥10)
KEYNOTE-355 Ongoing	Phase 3, randomized, double-blind study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy	Adult male and female participants with locally recurrent inoperable or metastatic TNBC, not previously treated with chemotherapy (1L) (Part 1 and Part 2) N=881	Pembrolizumab 200 mg Q3W or placebo plus nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 every 28 days **or** paclitaxel 90 mg/m^2 on Days 1, 8, and 15 of every 28 days **or** gemcitabine 1000 mg/m^2 + carboplatin AUC 2 on Days 1 and 8 every 21 days	Part 1: Safety and tolerability Part 2: PFS and OS in all participants and participants with PD-L1+ tumors (CPS ≥1 and CPS ≥10)
KEYNOTE-522 Ongoing	Phase 3, randomized, double-blind study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant treatment, followed by pembrolizumab vs placebo as adjuvant treatment	Adult male and female participants with newly diagnosed, locally advanced, centrally confirmed nonmetastatic TNBC (early-stage) N=1174	**Neoadjuvant therapy** prior to surgery: 4 cycles of pembrolizumab 200 mg or placebo Q3W + paclitaxel 80 mg/m^2 QW + carboplatin (AUC 5 Q3W or AUC 1.5 QW); Followed by 4 cycles of pembrolizumab 200 mg or placebo Q3W + (doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2) Q3W + cyclophosphamide 600 mg/m^2 Q3W **Adjuvant therapy** postsurgery: 9 cycles of pembrolizumab 200 mg or placebo Q3W	pCR at the time of surgery (ypT0/Tis ypN0 assessed by local pathologist) EFS (assessed by the investigator)
7339-009/ Ongoing	Phase 2/3, randomized, open-label, adaptively designed study of pembrolizumab plus chemotherapy as induction therapy followed by pembrolizumab plus chemotherapy or pembrolizumab plus olaparib as	Adult male and female participants with previously untreated locally recurrent inoperable or metastatic TNBC Phase 2: Induction: ~317 participants Postinduction: ~212 participants	**Induction:** Pembrolizumab 200 mg Q3W + carboplatin AUC 2 + gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for a maximum of up to 6 cycles, but not less than 4 cycles of treatment. **Postinduction:** Participants who achieve CR, PR, or SD during the induction phase will be randomly assigned in the postinduction portion of the	PFS as assessed by BICR and OS

Study Number/ Status	Design	Population	Dosage, Regimen	Primary Endpoint(s)
	postinduction therapy	Phase 3: Induction: ~615 participants Postinduction: ~412 participants	study in a 1:1 ratio to Arm 1 or Arm 2 of treatment: · Participants in Arm 1 will continue to receive pembrolizumab 200 mg Q3W and will begin a concurrent regimen of olaparib 300 mg orally BID. · Participants in Arm 2 will continue to receive carboplatin and/or gemcitabine at the same dose and schedule administered at the last dose of the induction period plus pembrolizumab 200 mg Q3W.	
Abbreviations: 1L = first line; 1L+ = first or later-line; 2L = second line; 2L+ = second or later-line; 3L = third line; AUC = area under the curve; BICR = blinded independent central review; BID = twice daily; CPS = combined positive score; CR = complete response; EFS = event-free survival; IDFS = invasive disease-free survival; mTNBC = metastatic triple-negative breast cancer; ORR = objective response rate; OS = overall survival; pCR = pathological complete response; PD L1 = programmed cell death 1 ligand 1; PD-L1+ = programmed cell death 1 ligand 1 positive; PFS = progression-free survival; PR = partial response; Q2W = every 2 weeks; Q3W = every 3 weeks; QW = weekly; SD = stable disease; TNBC = triple-negative breast cancer				

2.1.4. General comments on compliance with GCP

The MAH claimed that KEYNOTE-522 study was conducted in accordance with local and/or national regulations (including all applicable data protection laws and regulations), ICH-GCP and with the ethical principles that have their origin in the Declaration of Helsinki. Clinical trials carried out outside of the European Union meet the ethical requirements of Directive 2001/20/EC as claimed by the MAH.

The assessment of KEYNOTE-522 data did not raise concern over GCP compliance leading to request for GCP inspection.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) proteins are exempted from the submission of ERA studies because they are unlikely to result in significant risk to the environment. Pembrolizumab is a protein, therefore an ERA has not been submitted by the MAH. This is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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

Study ID	Phase	Country/ Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
[Ref. 5.3.5.1: P522V03 MK3475]	3	USA Canada Brazil Colombia France Germany Italy Spain Sweden UK Ireland Israel Poland Russia Turkey Australia South Korea Taiwan Portugal Japan Singapore	A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (TNBC)	Randomized, double-blind, parallel-group, placebo-controlled	Neoadjuvant therapy prior to surgery: 4 cycles of pembrolizumab 200 mg or placebo Q3W + paclitaxel 80 mg/m² QW + carboplatin (AUC 5 Q3W or AUC 1.5 QW); Followed by 4 cycles of pembrolizumab 200 mg or placebo Q3W + (doxorubicin 60 mg/m² or epirubicin 90 mg/m2) Q3W + cyclophosphamide 600 mg/m² Q3W Adjuvant therapy post-surgery: 9 cycles of pembrolizumab 200 mg or placebo Q3W	Adult male and female participants with newly diagnosed, locally advanced, centrally confirmed nonmetastatic TNBC (early-stage)	Pembrolizumab + NAC / pembrolizumab: 784 Placebo + NAC / placebo: 390

Study ID	Phase	Country / Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
KEYNOTE-173 [Ref. 5.3.5.2: P173V01 MK3475]	1b	Denmark, Finland, Germany, Singapore, South Korea, Spain, Sweden, UK	A Phase 1b study to evaluate safety and clinical activity of pembrolizumab (MK-3475) in combination with chemotherapy as neoadjuvant treatment for Triple Negative Breast Cancer (TNBC) - (KEYNOTE 173)	Open label study of IV pembrolizumab (K) in combination with chemotherapy regimens in 6 cohorts: Cohort A: KNp / KAC Cohorts B, C: KNpCb / KAC Cohort D: KNpCb / KAC Cohort E: KTCb / KAC Cohort F: KTCb / KAC	For all 6 cohorts, the dose and schedule of pembrolizumab (K) was fixed at 200 mg Q3W. Np: 125 or 100 mg/m² IV QW T: 70 or 80 mg/m² IV QW Cb: AUC6 or AUC5 Q3W; AUC2 or AUC1.5 IV QW AC: doxorubicin 60 mg/m² IV Q3W; cyclophosphamide 600 mg/m² IV Q3W	Females Age: ≥18 years with newly diagnosed, previously untreated locally advanced non-metastatic TNBC	10 per cohort (N=60 overall)
AC = doxorubicin + cyclophosphamide; Cb = carboplatin; IV = Intravenous; K = pembrolizumab; Np = nab-paclitaxel; Q3W = Every 3 weeks; QW = every week; T = paclitaxel; TNBC = triple negative breast cancer; UK = United Kingdom							

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
MK-3475-012 [Ref. 5.3.5.2: P012 MK3475]	Ib	Worldwide Belgium, Israel, USA	A Phase Ib Multi-Cohort Study of MK-3475 in Subjects with Advanced Tumors	Multi-center nonrandomized open label 24 months	10 mg/kg of MK-3475 IV every 2 weeks (Cohort A)	Males/females Age: ≥18 Triple negative breast cancer subjects (Cohort A)	10 mg/kg Q2W: 32 subjects (Cohort A)

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	Participant exposure
[Ref. 5.3.5.2: P086V01 MK3475]	2	Cohort A Australia Belgium Canada France, Germany Israel Italy Japan New Zealand South Africa Spain, United Kingdom, United States Cohort B Australia Belgium Canada Germany Israel Italy Japan South Africa Spain United Kingdom United States	A Phase 2 Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy for Metastatic Triple-negative Breast Cancer (mTNBC) – (KEYNOTE-086) A safety and efficacy study of pembrolizumab as second line or above (2L+) monotherapy in tumors with programmed cell death receptor-ligand 1 (PD-L1) positive (+) expression and independent of PD-L1 expression; and as first line (1L) monotherapy in tumors with PD-L1 (+) and PD-L1 strong (+) expression	Open-label, nonrandomized, single-arm, 2-part, multicenter, multicohort Part 1: Cohort A participants with PD-L1 (+) tumors and all comers, and Cohort B participants with PD-L1 (+) tumors; Cohorts A and B enrolled in parallel; 2 interim analyses (IA 1 and IA 2) for Cohort A IA-1: Futility analysis on the PD-L1 negative (-) subpopulation of Cohort A IA-2: Efficacy analysis of responses in at least 10 participants with PD-L1 strong (+) tumors in Cohort A Part 2: Cohort C participants comprising at least 1 responder in 10-15 participants with PD-L1 strong (+) tumors from Cohort A and ~40-45 participants with PD-L1 strong (+) tumors	Pembrolizumab 200 mg IV Q3W for up to 24 weeks from the date of the first dose	Females/males ≥18 years of age mTNBC participants previously treated with at least 1 systemic treatment for metastatic breast cancer and documented progression after the most recent therapy; and previously treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting	~285 participants Cohort A (2L+) ~160 participants Cohort B (1L) ~80 participants Cohort C (2L+) ~45 participants

Trial ID	Phase	Country / Region	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
3475-119 [Ref. 5.3.5.1: P119V01 MK3475]	3	Argentina Australia Belgium Brazil Colombia France Germany Guatemala Hong Kong Ireland Italy Japan Malaysia Mexico Netherlands New Zealand Peru Philippines Poland Russia Singapore South Africa South Korea Spain Sweden Switzerland Taiwan Thailand Turkey United Kingdom USA	A Randomized Open-Label Phase III Study of Single Agent Pembrolizumab versus Single Agent Chemotherapy per Physician's Choice for Metastatic Triple Negative Breast Cancer (mTNBC) – (KEYNOTE-119) Efficacy and safety in participants receiving second line (2L) or third line (3L) intervention for metastatic triple negative breast cancer (mTNBC)	Randomized, unblinded, open-label, active controlled	Arm 1: Pembrolizumab 200 mg IV Q3W, 35 administrations (approximately 2 years) Arm 2: Capecitabine Or Eribulin Or Gemcitabine Or Vinorelbine (local standard of care)	Male and female participants ≥18 years with Stage IV/M1 mTNBC	Arm 1: 309 participants Arm 2: 292 participants

2.3.2. Pharmacokinetics

No new clinical pharmacology analyses beyond those conducted previously have been generated, and no SmPC revisions for the clinical pharmacology are proposed.

2.3.3. Pharmacodynamics

No new data were submitted.

2.3.4. PK/PD modelling

No new data were submitted.

2.3.5. Discussion on clinical pharmacology

The posology proposed is: in the neoadjuvant setting in combination with chemotherapy, Keytruda should be administered for 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity.

The 8 doses in the neoadjuvant setting are driven by the standard neoadjuvant treatment that is typically 4 cycles of taxane (12 x weekly dosing) followed by 4 cycles of anthracycline/cyclophosphamide combination (e.g., doxorubicin 60 mg/m2 or epirubicin 90 mg/m2 Q3W + cyclophosphamide 600 mg/m2 Q3W).

No clinical data are currently available in participants with high-risk, early-stage TNBC at 400 mg Q6W. The 400 mg Q6W regimen is considered a suitable dosing option for pembrolizumab based on the expected similarity of PK exposures, target saturation, efficacy and safety profile with those for the approved dosing regimens of 200 mg Q3W or 2 mg/kg Q3W. The 400 mg Q6W dosing regimen was approved in the EU for all adult monotherapy indications (procedure number EMEA/H/C/003820/II/0062) and for all adult indications in combination with other anticancer agents (procedure number EMEA/H/C/003820/II/0102).

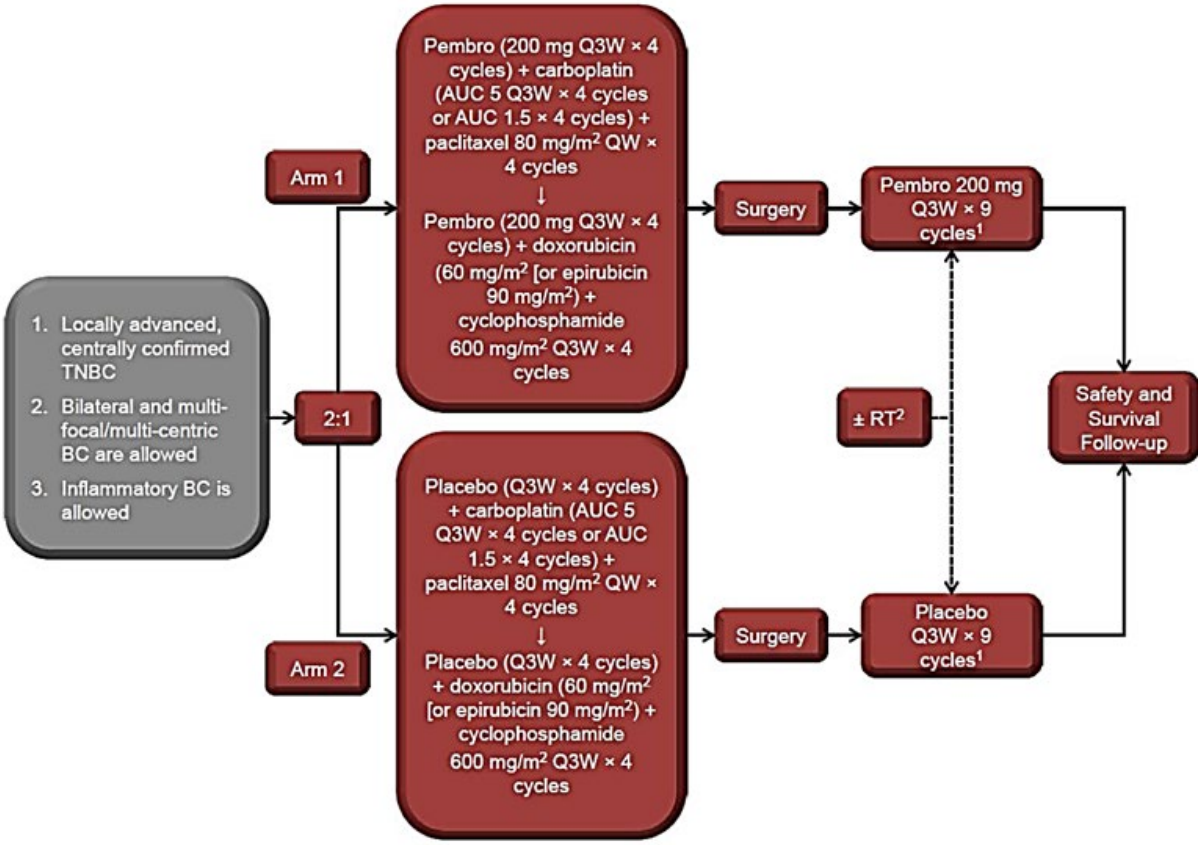
2.4. Clinical efficacy

2.4.1. Main study(ies)

KEYNOTE-522: A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer

Methods

Figure: Study Design Schematic



AUC=area under the curve; BC=breast cancer; TNBC=triple-negative breast cancer; pembro=pembrolizumab; QW=every week; Q3W=every 3 weeks; RT=radiation therapy

1 No crossover from placebo to pembrolizumab was permitted.

2 If postoperative radiation therapy was indicated, adjuvant pembrolizumab or placebo may have been started either concurrently with radiation therapy or 2 weeks post-radiation therapy.

Study participants

Key Inclusion criteria:

- Male or female ≥18 years of age.
- Had centrally confirmed TNBC, as defined by the most recent ASCO / CAP guidelines.
- Had previously untreated locally advanced nonmetastatic (M0) TNBC defined as the following combined primary tumor (T) and regional lymph node (N) staging per current AJCC staging criteria for breast cancer staging criteria as assessed by the investigator based on radiological and/or clinical assessment:
    - T1c, N1-N2
    - T2, N0-N2
    - T3, N0-N2

- T4a-d, N0-N2

Note: bilateral tumors (ie, synchronous cancers in both breasts) and/or multi-focal (ie, 2, separate lesions in the same quadrant)/multi-centric (ie, 2 separate lesions in different quadrants) tumors are allowed, as well as inflammatory breast cancer, and the tumor with the most advanced T stage should be used to assess the eligibility. If the subject has either bilateral or multi-focal/multi-centric disease, TNBC needs to be confirmed for each breast/focus.

- Provided a core needle biopsy consisting of at least 2 separate tumor cores from the primary tumor at screening to the central laboratory.
- Had ECOG performance status of 0 or 1 performed within 10 days of treatment initiation.
- Had adequate organ function as defined in study protocol.
- Had LVEF of ≥50% or ≥ institution LLN as assessed by ECHO or MUGA scan performed at screening.

Key Exclusion Criteria:

- Had received prior chemotherapy, targeted therapy, and radiation therapy within the past 12 months.
- Had a history of (noninfectious) pneumonitis that required steroids or current pneumonitis.
- Had significant cardiovascular disease, such as: History of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months; CHF NYHA Class II-IV or history of CHF NYHA class III or IV
- Has a history of invasive malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
- Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (ie, dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

Treatments

Neoadjuvant phase: patients received carboplatin 3 weekly or weekly + paclitaxel weekly for four cycles (12 weeks), followed by doxorubicin or epirubicin + cyclophosphamide every 3 weeks for 4 cycles (12 weeks), for a total of 24 weeks of neoadjuvant treatment. Along with chemotherapy, pembrolizumab/placebo was administered every 3 weeks for a total of 24 weeks (8 cycles).

Within 3 to 6 weeks of the last cycle of neoadjuvant therapy, definitive breast surgery was performed.

Adjuvant phase: patients received pembrolizumab/placebo every 3 weeks for 9 cycles (27 weeks).

The Adjuvant Treatment Phase was planned to start 30 to 60 days after definitive surgery. Postoperative radiation therapy was administered if indicated, with adjuvant pembrolizumab/ placebo may have been started either concurrently with radiation therapy or 2 weeks post-radiation therapy.

Table: study treatment

Drug	Dose and Frequency	Route of Admin.	Dosing Time of each 3-week Cycle	Use
Pembrolizumab	200 mg Q3W	IV infusion	Day 1 of each cycle in the neoadjuvant and adjuvant phases of the study for a total of 17 cycles	Experimental
Carboplatin	AUC5 Q3W (or AUC1.5 weekly)	IV infusion	Day 1 of Cycles 1-4 (or weekly, on Days 1, 8, 15 of Cycles 1-4) of Treatment 1[a]	Chemotherapy background treatment
Paclitaxel	80 mg/m^2 weekly	IV infusion	Days 1, 8, 15 of Cycles 1-4 of Treatment 1[a]	
Doxorubicin (or Epirubicin)	60 mg/m^2 Q3W (90 mg/m^2 Q3W)	IV injection	Day 1 of Cycles 1-4 of Treatment 2[b]	
Cyclophosphamide	600 mg/m^2 Q3W	IV infusion	Day 1 of Cycles 1-4 of Treatment 2[b]	
Placebo (normal saline or dextrose)	NA Q3W	IV infusion	Day 1 of each cycle in the neoadjuvant and adjuvant phases of the study for a total of 17 cycles	Placebo for pembrolizumab
Filgrastim (G-CSF)	5 µg/kg/day per SOC	SC injection	Administered 24 h after chemotherapy and for at least 72 h after the last dose of chemotherapy	Prophylaxis for neutropenia
Pegfilgrastrim (G-CSF)	100 µg/kg (individualized) or 6 mg (general approach)	SC injection	Administered 24 hours as a single dose after chemotherapy	Prophylaxis for neutropenia
Radiation therapy[c]	Variable	Standard fractionation	Variable	Radiation therapy background treatment

Abbreviations: Admin.=administration AUC=area under the concentration-time curve; G-CSF=granulocyte colony-stimulating factor; IV=intravenous; NA=not applicable; Q3W=every 3 weeks; SC=subcutaneous; SOC=standard of care

Additional details are contained in Section 5.2 of the study protocol [16.1.1].

[a] Paclitaxel/carboplatin regimen

[b] Doxorubicin plus cyclophosphamide or epirubicin plus cyclophosphamide (AC or EC regimen)

[c] Administered per the local standard of care as applicable (eg, in cases of breast conservation surgery [BCS], large primary tumor, subset of participants with positive lymph nodes).

Rationale for treatment selection

Carboplatin in combination with weekly paclitaxel at 80 mg/m2 vs paclitaxel followed by the standard anthracycline/cyclophosphamide combination has shown increased pCR rates as neoadjuvant treatment for TNBC via 2 randomized trials using either weekly carboplatin at AUC 2 (the Phase II GeparSixto trial; Von Minckwitz G, 2014), or carboplatin at AUC 6 Q3W (the Phase III CALGB 40603 trial; Silkov WM, 2015). Due to toxicity, in the GeparSixto trial, the dose of carboplatin was reduced to AUC 1.5. A meta-analysis by Petrelli et al. to compare TNBC patients who received carboplatin vs. those who did not receive carboplatin in the neoadjuvant setting, showed the risk of not having a pCR for those without carboplatin was 1.45 (95% CI, 1.25-1.68, p<0.0001; Petrelli F, 2014) compared to those who have received carboplatin. In the CALGB 40603 study the carboplatin AUC 6 Q3W plus weekly paclitaxel 80 mg/m2 arm showed statistically significant increase in Grade 3/4 neutropenia (56% vs. 22%) and Grade 3/4 thrombocytopenia (20% vs. 4%) compared to paclitaxel alone arm. Therefore, in KEYNOTE-522 study, paclitaxel 80 mg/m2 and carboplatin AUC 5 Q3W or AUC 1.5 QW have been selected as a novel combination regimen to be combined with pembrolizumab.

Objectives

Primary objective/hypothesis
Objective: To evaluate the rate of **pCR** using the definition of ypT0/Tis ypN0 (ie, no invasive residual in breast or nodes; noninvasive breast residuals allowed) as assessed by the **local** pathologist at the time of definitive surgery in participants with locally advanced TNBC. **Hypothesis**: Pembrolizumab is superior to placebo, in combination with chemotherapy, as measured by the rate of pCR using the definition of ypT0/Tis ypN0 as assessed by the local pathologist at the time of definitive surgery in participants with locally advanced TNBC.
Objective: To evaluate the **EFS as assessed by investigator** in participants with locally advanced TNBC. **Hypothesis**: Pembrolizumab is superior to placebo, as measured by EFS as assessed by the investigator, in participants with locally advanced TNBC

The study is considered to have met its primary objective if pembrolizumab is superior to placebo in either pCR or EFS in subjects with locally advanced TNBC at either an interim analysis or the final analysis.

Secondary Objectives
Objective: To evaluate **OS** in participants with locally advanced TNBC. **Hypothesis:** Pembrolizumab is superior to placebo, as measured by OS in participants with locally advanced TNBC.
Objective: To evaluate the rate of **pCR** using an **alternative definition of ypT0 ypN0** (ie, no invasive or noninvasive residual in breast or nodes) as assessed by the local pathologist at the time of definitive surgery in participants with locally advanced TNBC and in individuals with PD-L1 (+) tumors (CPS ≥1).
Objective: To evaluate the rate of **pCR** (ypT0/Tis ypN0) (i.e., no invasive residual in breast or nodes; noninvasive breast residuals allowed) as assessed by the local pathologist at the time of definitive surgery in individuals with PD-L1 (+) tumors (**CPS ≥ 1**).
Objective: To evaluate the **EFS** as assessed by the investigator in individuals with PD-L1 (+) tumors (**CPS ≥ 1**).
Objective: To evaluate the rate of **pCR** using an alternative definition of ypT0/Tis (ie, absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement) as assessed by the local pathologist at the time of definitive surgery in participants with locally advanced TNBC and in individuals with PD-L1 (+) tumors (**CPS ≥1**).
Objective: To evaluate **OS** in in individuals with PD-L1 (+) tumors (**CPS ≥1**).
Objective: To determine the **safety** and **tolerability** of pembrolizumab in combination with neoadjuvant chemotherapy and pembrolizumab as adjuvant therapy in locally advanced TNBC participants, within and across the neoadjuvant and adjuvant phases.

To evaluate **health-related QoL assessments** in TNBC participants and in participants with PD-L1 (+) tumors (CPS ≥1) using the EORTC QLQ-C30 and EORTC QLQ-BR23 within and across the neoadjuvant and adjuvant treatment phases.

Exploratory Objectives
To evaluate the association between pCR and the ORR using RECIST 1.1 as assessed by central radiology review after Treatment 1 (neoadjuvant phase) or at the time of surgery.
To evaluate DRFS post-surgery as assessed by investigator in participants with locally advanced TNBC and in individuals with PD-L1 (+) tumors (CPS ≥1).
To characterize health utilities in participants with locally advanced TNBC and in participants with PD-L1 (+) tumors (CPS ≥1) using the EuroQol-5 EQ-5D- 5LTM.
To evaluate the rate of breast conserving surgery (BCS) at the time of definitive surgery in participants with locally advanced TNBC and in individuals with PD-L1 (+) tumors (CPS ≥1).
To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamics activity, and/or the mechanism of action of pembrolizumab and other treatments.
To evaluate the association between pCR and the ORR using MRI FTV as assessed by central radiology review after Treatment 1 (neoadjuvant phase) and at the time of surgery.
To evaluate Residual Cancer Burden (RCB) as assessed by the local pathologist at the time of definitive surgery in participants with locally advanced TNBC.
To correlate extent of TILs with pCR rate and EFS.

Definition of Pathological Complete Response (pCR) Rate (ypT0/Tis ypN0)

Pathological complete response rate (ypT0/Tis ypN0) is defined as the proportion of subjects without residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy by AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

Subjects who don't receive any study medication and subjects who are discontinued from the study treatment and continue neoadjuvant treatment with drug categories not specified by the study prior to definitive surgery will be classified as not having a pCR (non-responders) in the efficacy analyses, regardless of the results obtained from the surgery. Subjects who are discontinued from study treatment due to the reasons that preclude definitive surgery (including the development of distant metastatic disease) are considered non-responders. Subjects without pCR data due to any reason will be counted as non-responders.

Definition of Event-Free Survival (EFS): EFS is defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy or death due to any cause. Progression of disease, local or distant recurrence, and second primary malignancy are based on investigator determination.

Subjects who had locoregional PD (as assessed radiologically) during the neoadjuvant treatment phase, but went to definitive surgery and had clear margins, will not be classified as having an EFS

event. If the subject had pCR, then the PD will be considered pseudoprogression. Subjects who had locoregional PD (as assessed radiologically) during the neoadjuvant treatment phase, but went to surgery and ended up with positive margins at their last surgery, will be classified as having an EFS event at the time of diagnosis of locoregional PD. Subjects who had distant PD (metastasis, confirmed by biopsy or 2 imaging studies at least 4 weeks apart, if a biopsy is not feasible) during the neoadjuvant treatment phase had an EFS event at the time of diagnosis of distant PD, even if the subjects had palliative breast surgery. Subjects who did not have PD during the neoadjuvant treatment phase, but had positive margins at their last surgery, will be classified as having an EFS event at surgery. Subjects who had cytological, histological, and/or radiological evidence of local or distant recurrence during the adjuvant phase had an EFS event at the time recurrence was diagnosed. In terms of second primary malignancy, any confirmed diagnosis of a second primary cancer other than basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or second primary breast will be considered an event in the analysis of the EFS. Lobular carcinoma in situ of the breast (LCIS), ductal carcinoma in situ of the breast (DCIS) and myelodysplastic syndrome are not considered an event.

Tumor assessment

Assessment of disease progression/recurrence includes (per local or institutional guidelines): disease progression that precludes definitive surgery, local or distant recurrence, development of a second primary malignancy, or death, and it was performed on D1 of each cycle, at surgery, at 30 days FU post-surgery, and on D1 of each adjuvant cycle. Long-term follow-up visits were scheduled at 3-month intervals from the date of randomization for the first 2 years, then at 6-month intervals for Years 3 to 5, and annually thereafter until occurrence of local or/and distant disease progression/ recurrence, death, withdrawal of consent, or the end of the study, whichever occurs first. Imaging (eg, CT, MRI, Bone Scan) were performed at the discretion of the investigator, as per the local institution's standard of care, or at the time of symptoms except for subjects participating in the MRI substudy. Disease assessment was performed per RECIST 1.1, if applicable.

Outcomes/endpoints

Primary Endpoints
pCR rate (ypT0/Tis ypN0): defined as the proportion of participants without residual invasive cancer on H&E evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy by AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.
EFS: defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause.

Secondary Endpoints
OS: defined as the time from randomization to death due to any cause.
pCR rate (ypT0 ypN0): defined as the proportion of participants without residual invasive and in situ cancer on H&E evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy by AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

See definition for pCR rate (ypT0/Tis ypN0) above.
See definition of EFS above.
pCR rate (ypT0/Tis): defined as the proportion of participants without invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement following completion of neoadjuvant systemic therapy by AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.
See definition of OS above.
Safety parameters including incidence of AE/SAEs (including fatal SAEs), irAEs, and laboratory abnormalities, rates of dose interruption and discontinuation due to AEs, and ECI.
Health-related QoL assessments using the EORTC QLQ-C30 and EORTC QLQ-B23.

Exploratory Endpoints
pCR (see definitions above). **ORR based on RECIST 1.1:** defined as the percentage of participants who have achieved CR or PR according to RECIST 1.1 by central radiology review.
DRFS: defined as the time from definitive surgery to distance recurrence event as assessed by investigator.
Assessments using EQ-5D.
The rate of BCS at the time of definitive surgery.
Relationship between molecular (genomic, metabolic and/or proteomic) biomarkers and clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments.
pCR (see definitions above). ORR: defined as the percentage of participants who have achieved CR or PR using MRI FTV as assessed by central radiology review.
RCB: defined as residual disease in either the breast or lymph node at the time of definitive surgery as assessed by the local pathologist.
The rate of pCR and EFS in subjects with different levels of TILs at baseline.

Sample size

The study was planned to randomize approximately 1150 subjects in a 2:1 ratio between the two arms.

Assumptions and methodologies used for sample size calculation are described below.

The study includes multiple hypotheses:

- dual primary hypotheses testing superiority of pembrolizumab compared to placebo in pCR (ypT0/Tis ypN0) or EFS in subjects with locally advanced TNBC;

- secondary hypothesis testing superiority in OS in subjects with locally advanced TNBC.

The overall Type-I error was strongly controlled at 2.5% (one-sided) among the multiple hypotheses, with 0.5% initially allocated to the pCR (ypT0/Tis ypN0) hypothesis and 2.0% initially allocated to the EFS hypothesis. The study uses the graphical method of Maurer and Bretz (Maurer, 2013) to control multiplicity for multiple hypotheses (dual primary hypotheses and the secondary hypothesis).

The following efficacy interim analyses (IAs) were planned:

- two IAs are planned for the rate of pCR (ypT0/Tis ypN0) and should be at least 3 months apart;

- seven efficacy IAs are planned in addition to the FA for EFS. The timing of IAs for EFS is calendar-based and the IAs are planned to be conducted annually after 2 years. In addition, the FA for EFS needs to be at least 1 year apart from the last IA.

The sample size was driven by EFS.

Sample Size and Power Calculations for pCR (ypT0/Tis ypN0) Rate

The first primary endpoint is pCR (ypT0/Tis ypN0) rate. The pCR analysis was to be performed after enrollment is completed, and ~1000 subjects would have completed surgery (if continuing on treatment) after ~6 months neoadjuvant treatment. A sample size of ~1000 gives ~95% power to detect a true pCR rate difference of 15% (pembrolizumab + chemotherapy vs. placebo + chemotherapy) at alpha = 0.5% (one-sided). The sample size calculation is based on the following assumptions: 1) alpha of 0.5% is allocated to the pCR hypothesis; 2) the underlying pCR is 50% in the placebo + chemotherapy arm, and there is 15% increase in pCR in the pembrolizumab + chemotherapy arm (pCR of 65%) in subjects with locally advanced TNBC; and 3) a drop-out rate of ~10%. In addition, a Hwang-Shih-DeCani alpha-spending function with gamma parameter (0) is used to implement group sequential boundaries that control the Type-I error. The power for the pCR endpoint at different true pCRs for subjects with locally advanced TNBC (62%, 65%, 67%) is 77%, 95%, and 99% (summarized in Table below).

Table: Power for pCR

pCR Difference Between the 2 Treatment Arms	Subjects with Locally Advanced TNBC (N = 1000 alpha = 0.005)
12 percentage points	77%
15 percentage points	95%
17 percentage points	99%
All calculations assume pCR is 50% in the placebo + chemotherapy arm.	

The assumptions for a pCR rate of 50% in the placebo + chemotherapy arm were based on the estimates from Sikov et al., 2015, and von Minckwitz et al., 2014.

Sample Size and Power Calculations for EFS

The other dual-primary endpoint is EFS. The final analysis of the study is EFS event-driven and will be conducted after approximately 327 EFS events have been observed, unless the study is terminated early. It may occur at ~102 months after first subject randomized (depending on enrollment rate and event accumulation rate). With the alpha of 2% (one-sided) and sample size of ~1150, the trial has an overall ~80% power for EFS in subjects with locally advanced TNBC, assuming the true HR (pembrolizumab vs. placebo) is 0.71. According to published meta-analysis on this population that suggests a ~50% of subjects may be disease-free in a long-term (Cortazar, 2014), a cure rate model is applied to account

for the failure rates decreasing over time (Hurley, 2013). These calculations are based on the following assumptions: (1) EFS follows a Poisson mixture model (cure rate model with decreasing failure rate) distribution with ~78% EFS rate at 36 months and ~50% cure rate in the placebo arm, (2) an enrollment period of 18 months and at least 84 months follow-up. (3) A yearly drop-out rate of 2% and additional ~3% to ~5% drop-out rate after surgery. The EFS control rate of 78% was estimated from an updated report from CALGB40603, presented at SABCS 2015 (Sikov, 2015-abstract SABC). In addition, a Lan-DeMets O'Brien-Fleming approximation alpha-spending function is constructed to implement group sequential boundaries that control the Type-I error.

OS

The key secondary endpoint is OS. If the null hypothesis for EFS is rejected at an interim analysis, the final OS analysis is event-driven and will be conducted after approximately 297 OS events would have been observed, unless the study is terminated early. It may occur at ~102 months after first subject randomized (depending on enrollment rate and event accumulation rate). If after 102 months after the first subject randomized the estimated number of OS events still haven't been observed, then the final OS analysis may be conducted at that time with the remaining alpha. With the α of 2% (one-sided) and sample size of ~1150, the trial has an overall ~79.7% power for OS in subjects with locally advanced TNBC, assuming the true HR (pembrolizumab vs. placebo) is 0.70. According to published meta-analysis on this population that suggests ~50% of subjects may be disease-free long-term (Cortazar, 2014), a cure rate model is applied to account for the failure rates decreasing over time (Hurley, 2013). These calculations are based on the following assumptions: (1) OS follows a Poisson mixture model (cure rate model with decreasing failure rate) distribution with ~81% OS rate at 36 months (Sikov, 2015-abstract SABC) and ~50% cure rate in the placebo arm, (2) an enrollment period of 18 months and at least 84 months follow-up, and (3) A yearly drop-out rate of 3%. In addition, a Lan-DeMets O'BrienFleming approximation α-spending function is constructed to implement group sequential boundaries that control the Type-I error.

Amendment of the protocol involving sample size calculation

In amendment 02 of the protocol (01-May-2018), the sample size increased from ~ 855 to ~1150. The primary reason of such increase (see table below) occurred because of changes in the analysis plan based on emerging data from the CALGB40603 study: assumption of EFS rate at 36 months in the control arm was changed from 60% to 78% and the dropout rate after surgery has been increased.

Table: primary reasons for Amendment 2

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
8.7.2	Efficacy Interim Analysis	The timing of interim analysis 1 (pCR) was changed to occur after at least 500 subjects have or would have completed surgery. Interim analysis 2 was added, which will occur after approximately 800 subjects have or would have completed surgery.	Two interim analyses are planned for pCR to increase the possibility of success in testing the superiority of pembrolizumab to placebo, in combination with chemotherapy, as measured by the rate of pCR.
8.9	Sample Size and Power Calculations	Assumption of EFS rate at 36 months in the control arm was changed from 60% to 78% and the dropout rate after surgery has been increased, which leads to the increase of sample size from ~855 to ~1150.	These changes were applied to the analysis plan based on emerging data from the CALGB40603 study and updated assumptions.

Data used for the above update were however already available at time of original protocol finalization in 2016 (Sikov, 2015-abstract SABC). The MAH reported the following reason to justify the choice:

- NCCN guidelines were updated to include adjuvant capecitabine as an option for patients with TNBC who do not achieve pCR after neoadjuvant chemotherapy [Masuda, N., et al 2017]

- in 2017, following discussions with the US Food and Drug Administration (FDA), the MAH decided not to allow adjuvant capecitabine in the KEYNOTE-522 so as not to confound the final results;
- an amendment was required to adjust the control EFS rate and drop-out rate after surgery to account for the potential impact of not allowing the use of adjuvant capecitabine;
- based on data from GALGB40603 (N=443), presented at SABCS 2015 (Sikov WM et al, 2015), the 3-year EFS rate for patients with high-risk early-stage TNBC who were treated with platinum-containing neoadjuvant chemotherapy was ~74%.
- by expecting that more participants would not achieve pCR (~40%) and would opt for adjuvant capecitabine, the MAH expected an additional improvement in the 3-year EFS rate in the control arm from 74% to ~78%.

The EFS rate at 36 months obtained in the control arm was 76.8%, a value consistent with value assumed in sample size calculation.

Software used for sample size calculation

The sample size and power calculations were performed in the software R (package "gsDesign").

Number of patients enrolled in the study and in analyses

Based on monitoring of randomization implemented centrally using IVRS, and on screening status of patients at time of approaching the desired enrollment, 1174 have been randomized. First patient was enrolled on 7-mar-2017, last participant was randomized on 24-sep-2018. IA1 was carried out at data cutoff 24-sep-2018, and IA2 at data cutoff 24 apr-2019.

Randomisation

KEYNOTE-522 was a randomized study, with randomization ratio 2:1 between treatment arms.

Stratification factors are as follows:

1. Nodal status (positive vs. negative)

2. Tumor size (T1/T2 vs. T3/T4)

3. Choice of Carboplatin (Cb): Q3W vs. Weekly

Randomization was implemented centrally using IVRS and monitored on a regular basis.

TABLE: Summary of Participants Randomized in Each Stratum - All Participants (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		390		1,174	
Planned Stratum (IVRS)						
Nodal Status Positive, Tumor Size T1/T2, Carboplatin (Cb) Weekly	160	(20.4)	79	(20.3)	239	(20.4)
Nodal Status Positive, Tumor Size T1/T2, Carboplatin (Cb) Q3W	101	(12.9)	50	(12.8)	151	(12.9)
Nodal Status Negative, Tumor Size T1/T2, Carboplatin (Cb) Weekly	178	(22.7)	90	(23.1)	268	(22.8)
Nodal Status Negative, Tumor Size T1/T2, Carboplatin (Cb) Q3W	141	(18.0)	71	(18.2)	212	(18.1)

Nodal Status Positive, Tumor Size T3/T4, Carboplatin (Cb) Weekly	80	(10.2)	39	(10.0)	119	(10.1)
Nodal Status Positive, Tumor Size T3/T4, Carboplatin (Cb) Q3W	64	(8.2)	32	(8.2)	96	(8.2)
Nodal Status Negative, Tumor Size T3/T4, Carboplatin (Cb) Weekly	31	(4.0)	15	(3.8)	46	(3.9)
Nodal Status Negative, Tumor Size T3/T4, Carboplatin (Cb) Q3W	29	(3.7)	14	(3.6)	43	(3.7)
Database Cutoff Date: 23MAR2021						

Blinding (masking)

KEYNOTE-522 is a double-blind study. All pathologists reviewing and interpreting surgical specimens for assessment of pCR were blinded to treatment assignment. Results of the interim analyses were reviewed by an external DMC, which make recommendations for discontinuation of the study or modification to an EOC of the Sponsor, who may be unblinded to study results at the treatment level together with limited additional Sponsor personnel in order to act on these recommendations or facilitate regulatory filing.

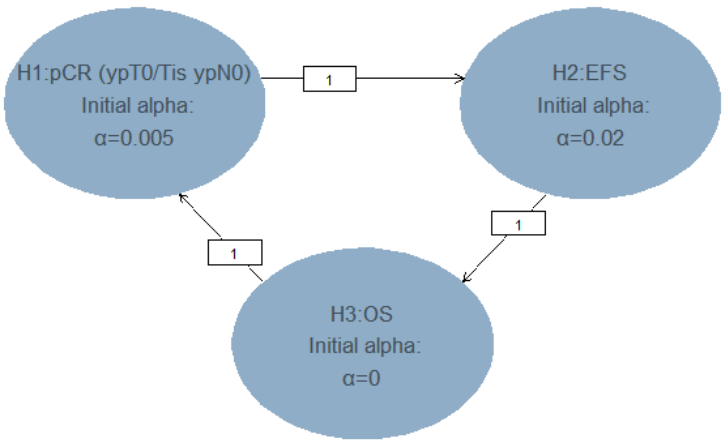
Statistical methods

Efficacy Analysis Populations: the Intention-to-Treat Population (ITT) population will serve as the population for primary efficacy analyses. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized.

PRO Analysis Populations: PRO analyses are based on the PRO Full Analysis Set (FAS) population, defined as randomized subjects who have at least one PRO assessment available and have received at least one study treatment.

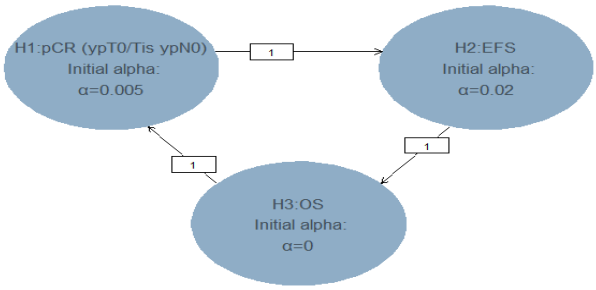
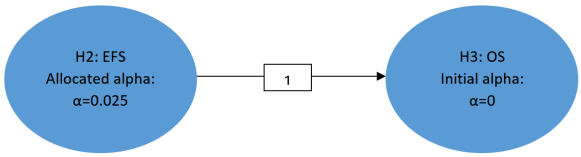
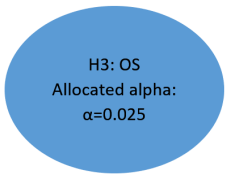
Error probabilities, adjustment for multiplicity

The dual primary hypotheses are testing superiority of pembrolizumab compared to placebo in pCR (ypT0/Tis ypN0) or EFS in subjects with locally advanced TNBC. The secondary hypothesis is testing superiority in OS in subjects with locally advanced TNBC. The overall Type-I error among the multiple hypotheses is strongly controlled at 2.5% (one-sided), with 0.5% initially allocated to the pCR (ypT0/Tis ypN0) hypothesis and 2.0% initially allocated to the EFS hypothesis. The study was considered a success if pCR (ypT0/Tis ypN0) or EFS is demonstrated to be statistically significant at either an IA or the FA under multiplicity control. The study uses the graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses as well as IAs.



Group sequential methods was used to allocate alpha between the interim and final analyses.

Updated graphs according to the methodology of Maurer and Bretz for control of multiplicity for multiple hypotheses have been reported for IA1, IA2, and IA4:

Analysis	Maurer and Bretz Multiplicity Graph for Type-I Error Control of Study Hypotheses
Initial one-sided α allocation for each hypothesis	
Alpha Reallocation for the Study Hypotheses after the Hypothesis of pCR (ypT0/Tis ypN0) (H1) was Rejected at IA1	
Alpha Reallocation for the Study Hypotheses after the Hypothesis of EFS (H2) was Rejected at IA4	

Statistical Methods for Efficacy Analyses

Pathological Complete Response (pCR) Rate

The stratified Miettinen and Nurminen's method was used for the comparison of pCR rates using three definitions between 2 treatment arms (pembrolizumab + chemotherapy vs. placebo + chemotherapy). The difference in pCR rate and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported for subjects with locally advanced TNBC and for individuals with PD-L1 (+) tumors. The stratification factors used for randomization will be applied to the analysis.

Sensitivity analyses will be performed for pCR rates using Cochran-Mantel-Haenszel test. Associated odds ratios and 95% CIs will be calculated. Additional supportive unstratified analyses may also be provided.

For pCR rate calculation (see endpoint definition), the following assumptions were reported: Subjects who don't receive any study medication and subjects who are discontinued from the study treatment and continue neoadjuvant treatment with drug categories not specified by the study prior to definitive surgery will be classified as not having a pCR (non-responders) in the efficacy analyses, regardless of the results obtained from the surgery. Subjects who are discontinued from study treatment due to the reasons that preclude definitive surgery (including the development of distant metastatic disease) are considered non-responders. Subjects without pCR data due to any reason will be counted as non-responders.

In the primary pCR analysis, per clinical judgment subjects who using same neoadjuvant regimens but different doses/schedules from those specified in the study may not be considered as using new anti-cancer therapy in neoadjuvant treatment prior to definitive surgery. Sensitivity analysis may be provided by imputing these subjects as "non-responders" for conservative consideration.

Event-Free Survival (EFS)

The non-parametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. The treatment difference in EFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. Kaplan-Meier estimates and the corresponding 95% CIs at two-year, three-year and five-year will be provided for subjects with locally advanced TNBC and for individuals with PD-L1 (+) tumors. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model. Censoring rules for primary and sensitivity analyses are reported in table below:

Table: Censoring Rules for Primary and Sensitivity Analyses 1 and 2 of EFS

Situation	Primary Analysis	Sensitivity Analysis 1*	Sensitivity Analysis 2§
EFS event documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented EFS event	Progressed at date of documented EFS event	Progressed at date of documented EFS event
EFS event immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Progressed at date of documented EFS event	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented EFS event, if no new anti-cancer therapy; Progressed at the date of new anti-cancer therapy, if there is new anti-cancer therapy
No EFS event; and new anti-cancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No EFS event; new anti cancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anti-cancer treatment	Progressed at the date of new anti-cancer therapy
* The new anti-cancer therapy in the sensitivity analysis 1 is defined as any post surgery new oncology drugs or post surgery radiation to treat metastatic disease. § The new anti-cancer therapy in sensitivity analysis 2 is defined as the radiation and/or oncology drugs to treat metastatic disease.			

Sensitivity analyses with different definitions for EFS may be performed to evaluate the robustness of the EFS analysis.

The proportional hazards assumption on EFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs time for EFS may be plotted for the comparison between pembrolizumab and placebo arms. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies using, for example, Restricted Mean Survival Time (RMST) method or a parametric method.

One assumption for stratified Cox proportional hazard model is that the treatment HR is constant across the strata. If strong departures from this assumption are observed (which can result in a

notably biased and/or less powerful analysis), a sensitivity analysis may be performed based on a two-step weighted Cox model approach by Mehrotra et al., 2012 [6], in which the treatment effect is first estimated for each stratum, and then the stratum specific estimates are combined for overall inference using sample size weights. Additional supportive unstratified analyses may also be provided.

Overall Survival (OS)

Statistical methods used for analysis of EFS will be used also for analysis of OS.

Subjects in the combination of placebo and chemotherapy arm are expected to discontinue treatment earlier compared to subjects in the combination of pembrolizumab and chemotherapy arm and are not allowed to crossover to the combination of pembrolizumab and chemotherapy arm; however, they may be treated with another anti–PD-1 drug. As an exploratory analysis, adjustment for the effect of crossover on OS may be performed using recognized methods (e.g., the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis, two-stage model), based on an examination of the appropriateness of the data to the assumptions required by the methods. Additional supportive unstratified analyses may also be provided.

Table: Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	**Statistical Method†**	**Analysis Population**	**Missing Data Approach**
Primary Hypothesis 1			
pCR(ypT0/Tis ypN0)	Stratified M & N method‡	ITT	Subjects with relevant data missing are considered non-responders
Primary Hypothesis 2			
EFS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive and event free date
Secondary Hypothesis			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
† Statistical models are described in further details in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis. ‡ Miettinen and Nurminen method.			

Interim analyses

Seven efficacy interim analyses (IAs) in addition to the FA are planned.

IAs planned for the rate of pCR (ypT0/Tis ypN0) should be at least 3 months apart. The timing of IAs for EFS is calendar-based and the IAs are planned to be conducted annually after 2 years. In addition, the FA for EFS needs to be at least 1 year apart from the last IA. Expected EFS events will have been observed at IA2, IA3, IA4, IA5, IA6, IA7, and final analyses are 93, 154, 201, 239, 270, 294, and 327, respectively.

Table: Analyses Planned, Endpoints Evaluated, and Drivers of Timing

Analysis	Criteria for Conduct of Analysis	Endpoint	Estimated Time after First Subject andomized	Primary Purpose of Analysis
IA1: Interim pCR Analysis	(1) enrollment is completed, and (2) at least 500 subjects have or would have completedsurgery after ~6 months neoadjuvant treatment	pCR (ypT0/Tis ypN0)	~18 months	pCR IA
IA2: Interim EFS Analysis and Final pCR Analysis	~24 months after first subject randomized.	EFS	~24 months	EFS IA
		pCR (ypT0/Tis ypN0)		pCR FA
IA3: Interim EFS Analysis	~36 months after first subject randomized.	EFS	~36 months	EFS IA
IA4: Interim EFS Analysis	~48 months after the first subject is randomized.	EFS	~48 months	EFS IA
IA5: Interim EFS Analysis	~60 months after the first subject is randomized.	EFS	~60 months	EFS IA
IA6: Interim EFS Analysis	~72 months after the first subject is randomized.	EFS	~72 months	EFS IA
IA7: Interim EFS Analysis	~84 months after the first subject is randomized.	EFS	~84 months	EFS IA
FA: Final EFS Analysis	~327 EFS events have been observed.	EFS	~102 months	EFS FA

OS will be tested only when the null hypothesis for EFS is rejected.

Boundary for superiority hypotheses

Boundary for pCR (ypT0/Tis ypN0)

The trial initially allocates α=0.005, one-sided to test pCR (ypT0/Tis ypN0). Bundary properties for the IAs were derived using a Hwang-Shih-DeCani α- spending function with gamma parameter (0). If the actual number of subjects at the pCR analysis differs from those hypothesized, the bounds will be adjusted using the Hwang-Shih-DeCani α-spending function accordingly.

This study has achieved Last Patient In (LPI) on Sep. 24th, 2018, by then there are total 1174 subjects have been randomized and as pre-specified per protocol the first 602 (> 500) randomized subjects have completed surgery after ~6 months neoadjuvant or would have completed surgery if continuing by LPI. This sample size is defined based on the operational criteria, which includes subjects randomized as late as 9 months prior to LPI. The 9 months (270 days) interval includes 6 months neoadjuvant treatment, 2 months surgery window per protocol, and 1 month from surgery to data available in-house (obtaining the pathology report and site entering data in clinical database). Based on the ITT principle, 602 subjects are the first 602 randomized subjects (chronologically). Therefore, I interim pCR analysis will be conducted in the first 602 randomized subjects (IA1 Population).

A supportive analysis is to summarize the EFS and OS data in IA1 Population and all randomized subjects. This analysis will be performed at IA1 and no hypothesis testing will be performed. A Haybittle-Peto type adjustment with $p<0.0001$ is applied for EFS and OS summary in IA1, respectively. The HR and its 95% CI from the stratified Cox model will be reported, and Kaplan-Meier curve will be provided. No additional sensitivity analyses and/or supportive analyses for EFS and OS will be provided in this IA.

Interim Analysis 2 (Interim EFS Analysis and Final pCR (ypT0/Tis ypN0) Analysis)

It is estimated that approximately 1000 subjects have or would have completed surgery after ~6 months neoadjuvant treatment. If more than 1000 subjects have or would have surgery data in IA2, the pCR results from additional subjects may be included in the analyses.

Since the actual number of subjects in IA1 is 602, the bounds adjusted by using the Hwang-Shih-DeCani α-spending function are shown in Table below.

Table: Boundary Properties for pCR (ypT0/Tis ypN0) with Update Sample Size in IA2 (N=602) Superiority Hypotheses Based on α=0.005

Analysis	Value	α=0.005
IA1: 60%* N: 602	Z p (1-sided) § delta at bound% P(Cross) if delta=0† P(Cross) if delta=0.15#	2.7467 0.003 0.1166 0.003 0.784
IA2 N: 1000	Z p (1-sided) § delta at bound% P(Cross) if delta=0† P(Cross) if delta=0.15#	2.7702 0.0028 0.0913 0.005 0.9661

*Percentage of expected number of subjects at final analysis required at IA
§ p (1-sided) is the nominal α for testing.
% delta at bound is the approximate delta required to reach an efficacy bound.
† P(Cross if delta=0) is the probability of crossing a bound under the null hypothesis, with an underlying pCR rate of 50%.
# P(Cross if delta=0.15) is the probability of crossing a bound under the alternative hypothesis.
Abbreviations: IA = interim analysis; pCR = pathological complete resp

If the test of pCR (ypT0/Tis ypN0) hypothesis does not achieve statistical significance at either IA1 or IA2, the p-value from IA2 (i.e., no new data is added after IA2) can be compared to an updated α-level based on group sequential design with α=0.025 if the null hypotheses for both EFS and OS are rejected at a later time. It gives >99% power to detect a true pCR rate difference of 15 percentage points (pembrolizumab + chemotherapy vs. placebo + chemotherapy) at α=0.025 (one-sided) and the observed difference in pCR between the treatment groups needs to be approximately 6.8 percentage points for the analysis to be considered positive.

Boundary for Event-free Survival (EFS)

The trial initially allocates α=0.02, one-sided to test EFS. If the null hypothesis for pCR (ypT0/Tis ypN0) is rejected, its α=0.005 is fully reallocated to EFS hypothesis testing. Thus, the EFS null hypothesis may be tested at α=0.02, or α=0.025.

Table below shows the boundary properties calculated based on the estimated number of events for each of these α-levels for the IAs and FA, which were derived using a cure rate model and Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for EFS at each α-level. If the actual number of events at the EFS analyses differ from those specified in the table, the bounds will be adjusted using the actual observed numbers of events and the Lan-DeMets O'Brien-Fleming spending function accordingly. At the time of final analysis, the spending time will be 1. Of note, the efficacy interim analysis 2 (IA 2) occurred prior to Amendment 04 and as such the efficacy boundaries for EFS in IA 2 were calculated based on the estimated number of events.

Table: Efficacy Boundaries and Properties for EFS Analyses

Analysis	Value	α=0.02	α=0.025
IA 2: 28%* N: 1149 Events: 93 Month: 24	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.71#	4.225 0.00001 0.3934 <0.0001 0.0039	4.059 0.00002 0.4116 <0.0001 0.0063
IA 3: 47%* N: 1149 Events: 154 Month: 36	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.71#	3.201 0.0007 0.5782 0.0007 0.1191	3.071 0.0011 0.5942 0.0011 0.1470
IA 4: 61%* N: 1149 Events: 201 Month: 48	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.71#	2.773 0.0028 0.6603 0.0030 0.3269	2.660 0.0039 0.6741 0.0042 0.3691
IA 5: 73%* N: 1149 Events: 239 Month: 60	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.71#	2.541 0.0055 0.7054 0.0065 0.5037	2.439 0.0074 0.7177 0.0087 0.5455
IA 6: 82%* N: 1149 Events: 270 Month: 72	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.71#	2.399 0.0082 0.7333 0.0103 0.6277	2.303 0.0106 0.7446 0.0135 0.6646
IA 7: 90%* N: 1149 Events: 294 Month: 84	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.71#	2.304 0.0106 0.7519 0.0141 0.7111	2.213 0.0135 0.7625 0.0181 0.7427
Final N: 1149 Events: 327 Month: 102	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.71#	2.168 0.0151 0.7754 0.0200 0.8005	2.082 0.0187 0.7851 0.0250 0.8248

*Percentage of expected number of events at final analysis required at IA
§ p (1-sided) is the nominal α for testing.
% HR at bound is the approximate HR required to reach an efficacy bound
† P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis
# P(Cross if HR=0.71) is the probability of crossing a bound under the alternative hypothesis
A Haybittle-Peto type adjustment with p<0.0001 may be applied for EFS summary in IA.
Abbreviations: EFS = event-free survival; HR = hazard ratio; IA = interim analysis.

Boundary for Overall Survival

The study initially allocates α=0, one-sided to test OS and OS is tested only when the null hypothesis for EFS is rejected. Thus, the OS null hypothesis may be tested at α=0.02 (if the EFS null hypothesis is rejected but not the pCR [ypT0/Tis ypN0] null hypothesis) or α=0.025 (if both of pCR [ypT0/Tis ypN0] and EFS null hypotheses are rejected). Table below shows the boundary properties calculated based on the estimated number of events for each of these α-levels for the IA and FA, which were derived using a cure model and Lan-DeMets O'BrienFleming spending function. Note that the final row indicates the total power to reject the null hypothesis for OS at each α-level. Similar to EFS, if the actual number of events at the OS analyses differs from those specified in the table, the bounds will be adjusted using the actual observed numbers of events and the Lan-DeMets O'Brien-Fleming spending function accordingly. Of note, at the time of final analysis, the spending time will be 1. If EFS is found to be positive at an interim, but not OS, OS may continue to be followed.

Table: Efficacy Boundaries and Properties for OS Analyses

Analysis	Value	α=0.02	α=0.025
IA 2: 26%* N: 1149 Events: 77 Month: 24	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.70#	4.428 <0.00001 0.3421 <0.0001 0.0017	4.255 0.00001 0.3614 <0.0001 0.0029
IA 3: 44%* N: 1149 Events: 132 Month: 36	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.70#	3.309 0.0005 0.5418 0.0005 0.0872	3.176 0.0007 0.5595 0.0008 0.1104
IA 4: 59%* N: 1149 Events: 176 Month: 48	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.70#	2.827 0.0023 0.6360 0.0025 0.2880	2.712 0.0033 0.6514 0.0036 0.3289
IA 5: 71%* N: 1149 Events: 213 Month: 60	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.70#	2.566 0.0051 0.6881 0.0059 0.4770	2.463 0.0069 0.7017 0.0080 0.5193
IA 6: 82%* N: 1149 Events: 243 Month: 72	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.70#	2.405 0.0081 0.7204 0.0100 0.6144	2.309 0.0105 0.7328 0.0131 0.6519
IA 7: 90%* N: 1149 Events: 267 Month: 84	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.70#	2.297 0.0108 0.7421 0.0142 0.7079	2.206 0.0137 0.7537 0.0181 0.7397
Final N: 1149 Events: 297 Month: 102	Z p (1-sided) § HR at bound% P(Cross) if HR=1† P(Cross) if HR=0.70#	2.168 0.0151 0.7656 0.0200 0.7965	2.082 0.0187 0.7763 0.0250 0.8211

*Percentage of expected number of events at final analysis required at IA
§ p (1-sided) is the nominal α for testing.
% HR at bound is the approximate HR required to reach an efficacy bound
† P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis
# P(Cross if HR=0.70) is the probability of crossing a bound under the alternative hypothesis
A Haybittle-Peto type adjustment with p<0.0001 may be applied for OS summary at IA.
Abbreviations: HR = hazard ratio; IA = interim analysis; OS = overall survival.

Subgroup analyses

Subgroup Analyses and Effect of Baseline Factors are planned.

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables in subjects with locally advanced TNBC and in individuals with PD-L1 (+) tumors (CPS ≥1):

• Nodal status: Positive vs. Negative

• Tumor size: T1/T2 vs. T3/T4

• Choice of Carboplatin (Cb): Q3W vs. Weekly

· Tumor PD-L1 status using different cutoff values for CPS (applies to all subjects with locally advanced TNBC): CPS ≥1 vs. CPS <1; CPS ≥10 vs. CPS <10; CPS ≥20 vs. CPS <20)

• Overall Stage: Stage II vs. Stage III

• Menopausal status (for females only): pre- vs. post-menopausal

· Age: <65 years vs. ≥65 years

• Geographic region: Europe/Israel/North America/Australia vs. Asia vs. Rest of World

• Ethnic origin: Hispanic vs. Non-Hispanic

• ECOG performance status: 0 vs. 1

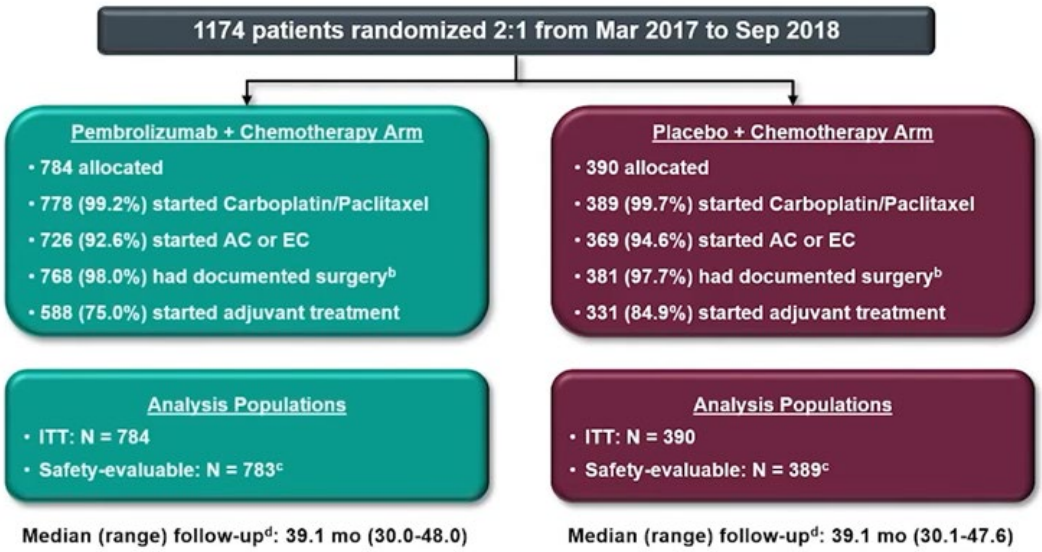
• HER2 status: IHC 2+ (but FISH-) vs. IHC 0-1+

· LDH: >upper limit of normal [ULN] vs. ≤ULN

Similar analysis may be conducted for key secondary endpoint (overall survival), if needed. For tumor PD-L1 status subgroup analyses, stratified model using stratification factors at randomization may be used. For all other subgroup analyses, unstratified model may be used.

Results

Participant flow



[a]Includes radiographic and clinical PD. [b]Patients did not have to complete all neoadjuvant therapy to undergo surgery. [c]Includes all patients who received ≥1 dose of study treatment or underwent surgery.
[d]Defined as the time from randomization to the data cutoff date of March 23, 2021.

Table: Consort Table All Participants (All Enrolled Participants)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants Screened					1608	
Participants Screen Failed					434	(27.0)
Participants Randomized	784		390		1174	
Untreated Participants	1	(0.1)	1	(0.3)	2	(0.2)
Treated Participants	783	(99.9)	389	(99.7)	1172	(99.8)
Participants who had Surgery, but did not Receive Study Medication	5	(0.6)	0	(0.0)	5	(0.4)
Participants who are on Treatments	0	(0.0)	0	(0.0)	0	(0.0)
Participants who Completed All Treatments	487	(62.1)	283	(72.6)	770	(65.6)
Participants who Discontinued from All Treatments	291	(37.1)	106	(27.2)	397	(33.8)
Discontinued in Neoadjuvant Phase	190	(24.2)	58	(14.9)	248	(21.1)

Adverse Event	112	(14.3)	20	(5.1)	132	(11.2)
Clinical Progression	2	(0.3)	3	(0.8)	5	(0.4)
Physician Decision	32	(4.1)	15	(3.8)	47	(4.0)
Progressive Disease	8	(1.0)	7	(1.8)	15	(1.3)
Relapse/Recurrence	7	(0.9)	3	(0.8)	10	(0.9)
Withdrawal By Subject	29	(3.7)	10	(2.6)	39	(3.3)
Discontinued in Adjuvant Phase	101	(12.9)	48	(12.3)	149	(12.7)
Adverse Event	42	(5.4)	10	(2.6)	52	(4.4)
Physician Decision	17	(2.2)	3	(0.8)	20	(1.7)
Relapse/Recurrence	20	(2.6)	18	(4.6)	38	(3.2)
Withdrawal By Subject	22	(2.8)	17	(4.4)	39	(3.3)
Participants with Surgery	768	(98.0)	381	(97.7)	1149	(97.9)
Participants without Surgery	16	(2.0)	9	(2.3)	25	(2.1)

Participants completed all treatments included participants who completed adjuvant treatment.

Participants discontinued in Neoadjuvant Phase included participants who discontinued on/after neoadjuvant treatment 1, on/after neoadjuvant treatment 2 or on/after definitive surgery.

Participants discontinued due to relapse/recurrence in the Neoadjuvant Phase are participants who had surgery but did not receive adjuvant treatment.

Participants discontinued in Adjuvant Phase included participants who discontinued on/after adjuvant radiation only or on adjuvant treatment.

Database Cutoff Date: 23MAR2021

Table: Disposition of Participants Status for Study Medication All Participants (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		390		1174	
Status for Study Medication in Neoadjuvant Treatment 1						
Started	778		389		1167	
Completed	684	(87.9)	356	(91.5)	1040	(89.1)
Discontinued	94	(12.1)	33	(8.5)	127	(10.9)
Adverse Event	73	(9.4)	21	(5.4)	94	(8.1)
Clinical Progression	0	(0.0)	3	(0.8)	3	(0.3)
Physician Decision	11	(1.4)	3	(0.8)	14	(1.2)
Progressive Disease	3	(0.4)	5	(1.3)	8	(0.7)
Withdrawal By Subject	7	(0.9)	1	(0.3)	8	(0.7)
Status for Study Medication in Neoadjuvant Treatment 2						
Started	726		369		1095	
Completed	660	(90.9)	343	(93.0)	1003	(91.6)
Discontinued	66	(9.1)	26	(7.0)	92	(8.4)
Adverse Event	46	(6.3)	14	(3.8)	60	(5.5)
Clinical Progression	2	(0.3)	1	(0.3)	3	(0.3)
Physician Decision	9	(1.2)	5	(1.4)	14	(1.3)
Progressive Disease	5	(0.7)	2	(0.5)	7	(0.6)
Withdrawal By Subject	4	(0.6)	4	(1.1)	8	(0.7)
Status for Study Medication in Adjuvant Treatment						
Started	588		331		919	
Completed	487	(82.8)	283	(85.5)	770	(83.8)
Discontinued	101	(17.2)	48	(14.5)	149	(16.2)
Adverse Event	42	(7.1)	10	(3.0)	52	(5.7)
Physician Decision	17	(2.9)	3	(0.9)	20	(2.2)
Relapse/Recurrence	20	(3.4)	18	(5.4)	38	(4.1)

Withdrawal By Subject	22	(3.7)	17	(5.1)	39	(4.2)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Participants randomized but not treated in neoadjuvant treatment 1 were due to randomization in error, or withdrawal by participant before dosing.
The study allows that participants who either completed or discontinued neoadjuvant treatment 1 can start neoadjuvant treatment 2 or go to surgery, and participants who either completed or discontinued neoadjuvant treatment 2 can go to surgery.
Database Cutoff Date: 23MAR2021

The 7 patients who did not start neoadjuvant treatment did not meet inclusion/exclusion criteria (5 patients, all in the experimental arm) or decided not to proceed with neoadjuvant treatment (1 patient in the experimental and 1 patient in the control arm).

Surgery: A total of 5 patients in the experimental arm (0.6%) vs 0 did receive surgery but did not receive study medication. Overall, participants without surgery were 16 (2%) in the experimental arm and 9 (2.3%) in the control arm.

Screen failure: A total of 1608 participants were screened. Of those, 434 participants failed screening, and 1174 participants were randomized. The main reason for screen failure was not having centrally confirmed TNBC (41.7%), not willing and able to provide written informed consent for the trial (20.6%) and not having previously untreated M0 TNBC with staging as defined by inclusion criteria (20.4%).

Table: Reasons for Discontinuation from All Treatments for Participants Who Did Not Start Adjuvant Phase All Participants (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants Randomized	784		390		1174	
Untreated Participants	1	(0.1)	1	(0.3)	2	(0.2)
Treated Participants	783	(99.9)	389	(99.7)	1172	(99.8)
Participants who Started Adjuvant Phase	588	(75.0)	331	(84.9)	919	(78.3)
Participants who did not Start Adjuvant Phase	195	(24.9)	58	(14.9)	253	(21.6)
Discontinued in Neoadjuvant Phase	190	(24.2)	58	(14.9)	248	(21.1)
Adverse Event	112	(14.3)	20	(5.1)	132	(11.2)
Clinical Progression	2	(0.3)	3	(0.8)	5	(0.4)
Physician Decision	32	(4.1)	15	(3.8)	47	(4.0)
Progressive Disease	8	(1.0)	7	(1.8)	15	(1.3)
Relapse/Recurrence	7	(0.9)	3	(0.8)	10	(0.9)
Withdrawal By Subject	29	(3.7)	10	(2.6)	39	(3.3)
Had Surgery, but did not Receive Study Medication	5	(0.6)	0	(0.0)	5	(0.4)
Still on Treatment in Neoadjuvant Phase	0	(0.0)	0	(0.0)	0	(0.0)

Participants who did not receive study medication but had surgery were included in subjects treated.
Database Cutoff Date: 23MAR2021

Recruitment

The first participant was enrolled (signed informed consent) on 07-MAR-2017, and the last participant was randomized on 24-SEP-2018. This study was conducted at 194 centers; 177 centers in 21 countries randomized at least 1 participant to interventional treatment.

Conduct of the study

Protocol deviation

Important protocol deviations were reported for a total of 83 participants (7.1%) in this study: 8.2% vs 4.9% in the experimental vs the control arm, respectively. Of these, 36 participants (3.1%) had important protocol deviations that were considered clinically important (see table below).

Protocol deviations (important and not important) associated with COVID-19 were reported for 285 participants (24.3%), at similar percentage in both arms. No important deviations associated with COVID-19 were reported.

No patients were excluded from analyses due to protocol deviations.

Summary of Important Protocol Deviations Considered to be Clinically Important
All Participants
(ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		390		1,174	
with one or more clinically important protocol deviations	28	(3.6)	8	(2.1)	36	(3.1)
with no clinically important protocol deviations	756	(96.4)	382	(97.9)	1,138	(96.9)
Discontinuation Criteria	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Participant developed trial specific discontinuation criteria but was not discontinued from the trial.	1	(0.1)	0	(0.0)	1	(0.1)
Inclusion/ Exclusion Criteria	**14**	**(1.8)**	**7**	**(1.8)**	**21**	**(1.8)**
Inclusion 3: Participants who do not have centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines.	1	(0.1)	0	(0.0)	1	(0.1)
Inclusion 4: Participants who do not have previously untreated locally advanced non-metastatic (M0) TNBC defined as the following combined primary tumor (T) and regional lymph node (N) staging per AJCC for breast cancer staging.	12	(1.5)	7	(1.8)	19	(1.6)
Inclusion 8: Participants who do not have left ventricular ejection fraction (LVEF) of >=50% or >= institution lower limit of normal (LLN) as assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan performed at screening.	1	(0.1)	0	(0.0)	1	(0.1)
Safety Reporting	**2**	**(0.3)**	**0**	**(0.0)**	**2**	**(0.2)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	2	(0.3)	0	(0.0)	2	(0.2)
Study Intervention	**11**	**(1.4)**	**1**	**(0.3)**	**12**	**(1.0)**
Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment.	11	(1.4)	1	(0.3)	12	(1.0)
Every participant is counted a single time for each applicable row and column. Database Cutoff Date: 23MAR2021						

Source: [P522V03MK3475: adam-adsl] [P522V03MK3475: sdtm-dv; suppdv]

Protocol amendment

The original protocol was dated 5 Dec 2016. A total of 4 protocol amendment were released up to the data cut-off provided in this submission (23-MAR-2021).

Table: summary of protocol amendment

Amendment	Date of Issue	Overall Rationale
Original	05-DEC-2016	Not applicable.
Amendment 01	16-DEC-2016	The protocol was amended to 1) clarify the dose modification guidelines provided for paclitaxel and carboplatin; and 2) incorporate mandatory overdose language for the pembrolizumab program.
Amendment 02	01-MAY-2018	The protocol was amended to 1) adjust the timing of IA1 to occur after at least 500 subjects have or would have completed surgery; 2) added a second IA (IA2) for pCR; and 3) increase the sample size from ~855 to ~1150 based on a revision to the assumed EFS rate at 36 months in the control arm.
Amendment 03	17-OCT-2018	The protocol was amended to 1) add an analysis of EFS at IA2; and 2) adjust the timing of IA2 accordingly.
Amendment 04	26-FEB-2020	The protocol was amended to clarify an adjustment of efficacy boundaries at interim analyses for EFS based on the actual number of events observed.

There were no changes in the planned conduct of the study implemented by protocol amendment to manage study conduct as result of the COVID-19 pandemic.

Baseline data

Table: Participant Characteristics All Participants (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		390		1,174	
Sex						
Male	1	(0.1)	0	(0.0)	1	(0.1)
Female	783	(99.9)	390	(100.0)	1,173	(99.9)
Age (Years)						
< 65	700	(89.3)	342	(87.7)	1,042	(88.8)
>= 65	84	(10.7)	48	(12.3)	132	(11.2)
Mean	49.2		49.1		49.1	
SD	11.8		11.9		11.8	
Median	49.0		48.0		49.0	
Range	22 to 80		24 to 79		22 to 80	
Race						
American Indian Or Alaska Native	14	(1.8)	7	(1.8)	21	(1.8)
Asian	149	(19.0)	89	(22.8)	238	(20.3)
Black Or African American	38	(4.8)	15	(3.8)	53	(4.5)
Multiple	13	(1.7)	6	(1.5)	19	(1.6)
American Indian Or Alaska Native Black Or African American	0	(0.0)	1	(0.3)	1	(0.1)
American Indian Or Alaska Native Black Or African American White	2	(0.3)	1	(0.3)	3	(0.3)
American Indian Or Alaska Native White	7	(0.9)	2	(0.5)	9	(0.8)
Black Or African American White	3	(0.4)	2	(0.5)	5	(0.4)

White Asian	1	(0.1)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific Islander	1	(0.1)	0	(0.0)	1	(0.1)
White	504	(64.3)	242	(62.1)	746	(63.5)
Missing	65	(8.3)	31	(7.9)	96	(8.2)
Ethnicity						
Hispanic Or Latino	86	(11.0)	39	(10.0)	125	(10.6)
Not Hispanic Or Latino	615	(78.4)	307	(78.7)	922	(78.5)
Not Reported	46	(5.9)	28	(7.2)	74	(6.3)
Unknown	19	(2.4)	11	(2.8)	30	(2.6)
Missing	18	(2.3)	5	(1.3)	23	(2.0)
Geographic Region						
North America	166	(21.2)	78	(20.0)	244	(20.8)
Europe	388	(49.5)	180	(46.2)	568	(48.4)
Australia	23	(2.9)	16	(4.1)	39	(3.3)
Asia	166	(21.2)	91	(23.3)	257	(21.9)
Rest of World	41	(5.2)	25	(6.4)	66	(5.6)
ECOG PS						
0	678	(86.5)	341	(87.4)	1,019	(86.8)
1	106	(13.5)	49	(12.6)	155	(13.2)
Baseline Lactate Dehydrogenase (LDH)						
<=ULN	631	(80.5)	309	(79.2)	940	(80.1)
> ULN	149	(19.0)	80	(20.5)	229	(19.5)
Missing	4	(0.5)	1	(0.3)	5	(0.4)
Menopausal Status						
Pre-menopausal	438	(55.9)	221	(56.7)	659	(56.1)
Post-menopausal	345	(44.0)	169	(43.3)	514	(43.8)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Choice of Carboplatin (Actual)						
Q3W	334	(42.6)	167	(42.8)	501	(42.7)
Weekly	444	(56.6)	220	(56.4)	664	(56.6)
Missing	6	(0.8)	3	(0.8)	9	(0.8)
Choice of Carboplatin (Planned)						
Carboplatin (Cb) Q3W	335	(42.7)	167	(42.8)	502	(42.8)
Carboplatin (Cb) Weekly	449	(57.3)	223	(57.2)	672	(57.2)
Primary Tumor (Actual)						
T1	53	(6.8)	24	(6.2)	77	(6.6)
T2	528	(67.3)	266	(68.2)	794	(67.6)
T3	145	(18.5)	73	(18.7)	218	(18.6)
T4	58	(7.4)	27	(6.9)	85	(7.2)
Primary Tumor (Planned)						
Tumor Size T1/T2	580	(74.0)	290	(74.4)	870	(74.1)
Tumor Size T3/T4	204	(26.0)	100	(25.6)	304	(25.9)
Nodal Involvement (Actual)						
N0	376	(48.0)	194	(49.7)	570	(48.6)
N1	322	(41.1)	153	(39.2)	475	(40.5)
N2	85	(10.8)	42	(10.8)	127	(10.8)
N3	1	(0.1)	1	(0.3)	2	(0.2)
Nodal Involvement (Planned)						
Nodal Status Positive	405	(51.7)	200	(51.3)	605	(51.5)
Nodal Status Negative	379	(48.3)	190	(48.7)	569	(48.5)

Metastases						
M0	784	(100.0)	390	(100.0)	1,174	(100.0)
Overall Stage						
Stage I	0	(0.0)	1	(0.3)	1	(0.1)
Stage II	590	(75.3)	291	(74.6)	881	(75.0)
Stage III	194	(24.7)	98	(25.1)	292	(24.9)
PD-L1 CPS 1 Cutoff						
PD-L1 CPS >= 1	656	(83.7)	317	(81.3)	973	(82.9)
PD-L1 CPS < 1	128	(16.3)	69	(17.7)	197	(16.8)
Unknown	0	(0.0)	4	(1.0)	4	(0.3)
PD-L1 CPS 10 Cutoff						
PD-L1 CPS >= 10	393	(50.1)	177	(45.4)	570	(48.6)
PD-L1 CPS < 10	391	(49.9)	209	(53.6)	600	(51.1)
Unknown	0	(0.0)	4	(1.0)	4	(0.3)
PD-L1 CPS 20 Cutoff						
PD-L1 CPS >= 20	247	(31.5)	121	(31.0)	368	(31.3)
PD-L1 CPS < 20	537	(68.5)	265	(67.9)	802	(68.3)
Unknown	0	(0.0)	4	(1.0)	4	(0.3)
HER2 Status						
0-1+ by IHC	595	(75.9)	286	(73.3)	881	(75.0)
2+ by IHC (but FISH-)	188	(24.0)	104	(26.7)	292	(24.9)
Missing	1	(0.1)	0	(0.0)	1	(0.1)

Missing values in Race and Ethnicity are mainly because France is not permitted to report this information.

The missing value in Menopausal Status is from one male participant.

The missing value in HER2 Status is from the participant with missing IHC, but FISH-.

Database Cutoff Date: 23MAR2021

Table: Summary of BRCA Mutation All Participants (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		390		1,174	
BRCA1/2 Mutation						
BRCA1/2 Mutation Detected	40	(5.1)	14	(3.6)	54	(4.6)
BRCA1/2 Mutation Not Detected	104	(13.3)	52	(13.3)	156	(13.3)
Undetermined	370	(47.2)	194	(49.7)	564	(48.0)
Missing	270	(34.4)	130	(33.3)	400	(34.1)

"BRCA1/2 Mutation Detected" refers to at least one of the BRCA1 and BRCA2 mutation was detected.

"BRCA1/2 Mutation Not Detected" refers to both BRCA1 and BRCA2 mutation were not detected.

"Undetermined" refers to both BRCA1 and BRCA2 mutation were not determined, or one was not determined and the other one was not detected.

"Missing" refers to both BRCA1 and BRCA2 mutation tests were not performed, or one was not performed and the other one was performed with the BRCA mutation not detected or undetermined.

Database Cutoff Date: 23MAR2021

Table: Participants Tumor Characteristics All Participants (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		390		1,174	
Histology Subtype						
Adenoid Cystic	1	(0.1)	1	(0.3)	2	(0.2)
Carcinoma Nos	144	(18.4)	71	(18.2)	215	(18.3)
Carcinoma Of Mixed Type	14	(1.8)	2	(0.5)	16	(1.4)
Carcinoma With Apocrine Differentiation	5	(0.6)	1	(0.3)	6	(0.5)
Carcinoma With Medullary Features	7	(0.9)	0	(0.0)	7	(0.6)
Carcinoma With Neuroendocrine Features	1	(0.1)	2	(0.5)	3	(0.3)
Inflammatory	3	(0.4)	2	(0.5)	5	(0.4)
Invasive Ductal	585	(74.6)	305	(78.2)	890	(75.8)
Invasive Lobular	9	(1.1)	4	(1.0)	13	(1.1)
Invasive Micropapillary	2	(0.3)	0	(0.0)	2	(0.2)
Metaplastic	12	(1.5)	1	(0.3)	13	(1.1)
Papillary	0	(0.0)	1	(0.3)	1	(0.1)
Tubular	1	(0.1)	0	(0.0)	1	(0.1)
Tumor Grade						
Low	55	(7.0)	16	(4.1)	71	(6.0)
Intermediate	151	(19.3)	79	(20.3)	230	(19.6)
High	491	(62.6)	251	(64.4)	742	(63.2)
Not Available	59	(7.5)	22	(5.6)	81	(6.9)
Grade Cannot Be Assessed	27	(3.4)	22	(5.6)	49	(4.2)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Primary Tumor Substage						
IB	0	(0.0)	1	(0.3)	1	(0.1)
IIA	361	(46.0)	178	(45.6)	539	(45.9)
IIB	229	(29.2)	113	(29.0)	342	(29.1)
IIIA	135	(17.2)	70	(17.9)	205	(17.5)
IIIB	58	(7.4)	27	(6.9)	85	(7.2)
IIIC	1	(0.1)	1	(0.3)	2	(0.2)
Inflammatory Breast Cancer						
Yes	10	(1.3)	7	(1.8)	17	(1.4)
No	774	(98.7)	383	(98.2)	1,157	(98.6)
Database Cutoff Date: 23MAR2021						

Chemotherapy treatment:

The use of chemotherapy drugs in the neoadjuvant setting was as follows:

- Neoadjuvant treatment 1 (carboplatin/paclitaxel):
    - patients receiving carboplatin W were 444/778 (57%) and 220/389 (56.5%); carboplatin 3W 334/778 (42.9%) and 167/389 (42.9%) in the experimental and control arm, respectively (all received weekly paclitaxel).
- Neoadjuvant treatment 2 (AC/EC):

- patients receiving doxorubicin 3W were 488/726 (67.2%) and 247/369 (66.9%); epirubicin 3-weekly 238/726 (32.8%) and 122/369 (33%) in the experimental and control arm, respectively (all received Q3W cyclophosphamide).

Radiotherapy treatment:

Postoperative radiation therapy was administered if indicated. Radiotherapy was administered with pembrolizumab/placebo sequentially or concurrently to 674 patients overall (57.4%), in most cases sequentially (see table below). RT was used 10% less frequently in the pembrolizumab arm as compared to the control arm: 54.1% (n=424/784) vs 64.1% (250/390).

Concurrent

MK-3475 + chemotherapy / MK-3475	Placebo + chemotherapy / Placebo	Total
(N=144/784) 18.4%	(N=91/390) 23.3%	(N=235/1174) 20%

Sequential

MK-3475 + chemotherapy / MK-3475	Placebo + chemotherapy / Placebo	Total
(N=280/784) 35.7%	(N=159/390) 40.8%	(N=439/1174) 37.4%

Numbers analysed

Efficacy analyses were based on the **ITT population (N=1174)**, which included all randomized participants (784 in the pembrolizumab arm and 390 in the control arm).

pCR was analysed at IA1 and IA2:

- The **IA1 Population** includes the first **602** participants randomly assigned to study treatment; IA1 was prespecified to occur when ≥500 participants have or would have completed surgery after approximately 6 months neoadjuvant treatment and enrolment was completed (data cut-off 24 SEP 2018)
- The **IA2 Population** includes the first **1002** participants randomly assigned to study treatment. IA2 was prespecified to occur approximately 24 months after the first participant was randomized (calendar driven). Approximately 93 EFS events were estimated at the time of IA2 and approximately 1000 participants have or would have completed surgery after approximately 6 months neoadjuvant treatment (data cut-off 24-APR-2019).

Outcomes and estimation

Results from the Interim Analysis 4 have been submitted, with a data cut-off date of 23 March 2021.

The median follow-up duration was similar between treatment arms (37.8 and 37.6 months in the pembrolizumab and placebo groups, respectively).

Primary Efficacy Endpoints

- **Rate of Pathological Complete Response (ypT0/Tis ypN0)**

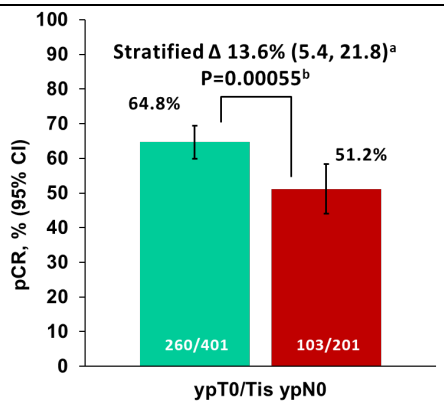
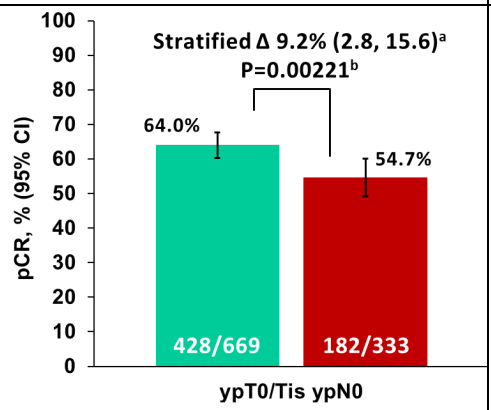
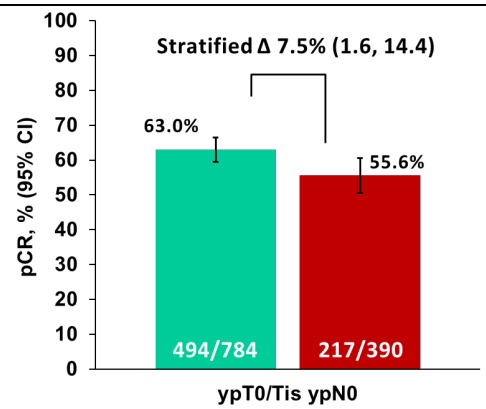
pCR (ypT0/Tis ypN0) was tested twice, at the time of IA1 (interim analysis for pCR, data cut-off 24-SEP-2018) and at IA2 (final analysis for pCR, data cut-off 24-APR-2019). The success criterion for the primary pCR hypothesis was met at IA1 with a p-value that crossed the prespecified boundary for statistical significance of 0.003, and continued to show a statistically significant improvement in the pembrolizumab + NAC group at IA2. pCR was not formally tested at IA4 for the ITT population as pre-specified in the SAP, however a supportive pCR analysis (estimation) was conducted with all randomized participants at IA4 (data cutoff 23-MAR-2021).

Table: Summary of pCR (ypT0/Tis ypN0) Efficacy Results for KEYNOTE-522

Endpoint	Pembrolizumab + NAC	Placebo + NAC
pCR (ypT0/Tis ypN0) at IA1[a]		
All participants	n=401	n=201
Nb of patients with pCR	260	103
pCR rate, % (95% CI)	**64.8 (59.9, 69.5)**	**51.2 (44.1, 58.3)**
Estimated difference, % (95% CI), p-value	**13.6 (5.4, 21.8)[b]**, *p*=0.00055[c]	
pCR (ypT0/Tis ypN0) at IA2[d]		
All participants	n=669	n=333
Nb of patients with pCR	428	182
pCR rate, % (95% CI)	**64.0 (60.2, 67.6)**	**54.7 (49.1, 60.1)**
Estimated difference, % (95% CI), p-value	**9.2 (2.8, 15.6)**[b], *p*=0.00221[e]	
pCR (ypT0/Tis ypN0) at IA4[f]		
All participants	n=784	n=390
Nb patients with pCR	494	217
pCR rate, % (95% CI)	**63.0 (59.5, 66.4)**	**55.6 (50.6, 60.6)**
Estimated difference, % (95% CI)	**7.5 (1.6, 13.4)[b, g]**	

Abbreviations: CI: confidence interval; IA = interim analysis; NAC = neoadjuvant chemotherapy; nb=number; pCR = pathological complete response; ypT0/Tis ypN0 = no invasive residual in breast or nodes; noninvasive breast residuals allowed.

a. First 602 participants randomly assigned to study treatment who were eligible for the analysis of pCR at IA1 (24-SEP-2018 data cutoff).
b. Based on Miettinen & Nurminen method stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4), and choice of carboplatin (Cb) (Q3W vs. Weekly).
c. One-sided p-value for testing H0: difference in % = 0 versus H1: difference in % > 0. The result was statistically significant compared with the prespecified p-value boundary of 0.003.
d. First 1002 participants randomly assigned to study treatment who were eligible for the analysis of pCR at IA2 (24-APR-2019 data cutoff).
e. KEYNOTE-522 met the success criterion for the primary hypothesis of pCR at IA1. At IA2, the updated data continue to be statistically significant (prespecified p-value boundary of 0.0028).
f. All participants in ITT population (N=1174) (23-MAR-2021 data cutoff).
g. Per the Statistical Analysis Plan, pCR was not formally tested at IA4. Updated data are provided for estimation purposes.

IA1 (interim analysis, 24 Sep 2018)	**IA2** (final analysis, 24 Apr 2019)	**IA4** (descriptive analysis, 23 Mar 2021)
		

- **Event-free Survival**

EFS in the pembrolizumab + NAC / pembrolizumab group had an HR of 0.63 (95% CI: 0.48, 0.82), with a one-sided p-value of 0.0003093 that crossed the prespecified boundary for statistical significance (0.00516941) at IA4.

EFS was previously tested at IA2 and IA3, not reaching statistical significance at the previous interim analyses. Across IAs, the EFS HR has remained consistent, being 0.63 (95% CI: 0.43, 0.93) at IA2 and 0.65 (95% CI: 0.48, 0.88) at IA3.

Table: Analysis of Event-Free Survival (EFS) All Participants (ITT Population) (IA4)

	MK-3475 + chemotherapy / MK-3475 (N=784)	Placebo + chemotherapy / Placebo (N=390)	Total (N=1174)
Number of Events (%)	**123 (15.7)**	**93 (23.8)**	216 (18.4)
Number of Censored (%)	661 (84.3)	297 (76.2)	958 (81.6)
Kaplan-Meier Estimates (Months)[a]			
Median (95% CI)	**. (., .)**	**. (., .)**	. (., .)
Q1, Q3	**Not Reached, Not Reached**	**41.9, Not Reached**	Not Reached, Not Reached
Person-Months	26,994.6	12,783.8	39,778.4
Event Rate / 100 Person-Months	0.5	0.7	0.5
EFS Rate at 6 Months (%) (95% CI)	98.3 (97.2, 99.0)	98.5 (96.6, 99.3)	98.4 (97.5, 99.0)
EFS Rate at 12 Months (%) (95% CI)	93.3 (91.4, 94.9)	92.5 (89.4, 94.7)	93.1 (91.5, 94.4)
EFS Rate at 18 Months (%) (95% CI)	90.0 (87.7, 91.9)	85.8 (81.9, 88.9)	88.6 (86.6, 90.3)
EFS Rate at 24 Months (%) (95% CI)	87.8 (85.3, 89.9)	81.0 (76.8, 84.6)	85.6 (83.4, 87.5)
EFS Rate at 30 Months (%) (95% CI)	85.8 (83.1, 88.0)	78.2 (73.7, 82.0)	83.3 (81.0, 85.3)

EFS Rate at 36 Months (%) (95% CI)	84.5 (81.7, 86.9)	76.8 (72.2, 80.7)	81.9 (79.6, 84.0)
EFS Rate at 42 Months (%) (95% CI)	83.5 (80.5, 86.0)	74.9 (69.8, 79.2)	80.6 (78.1, 82.9)
vs Placebo + chemotherapy / Placebo			
Hazard Ratio (95% CI)[b]	**0.63 (0.48, 0.82)**		
p-value[c]	**.0003093**		

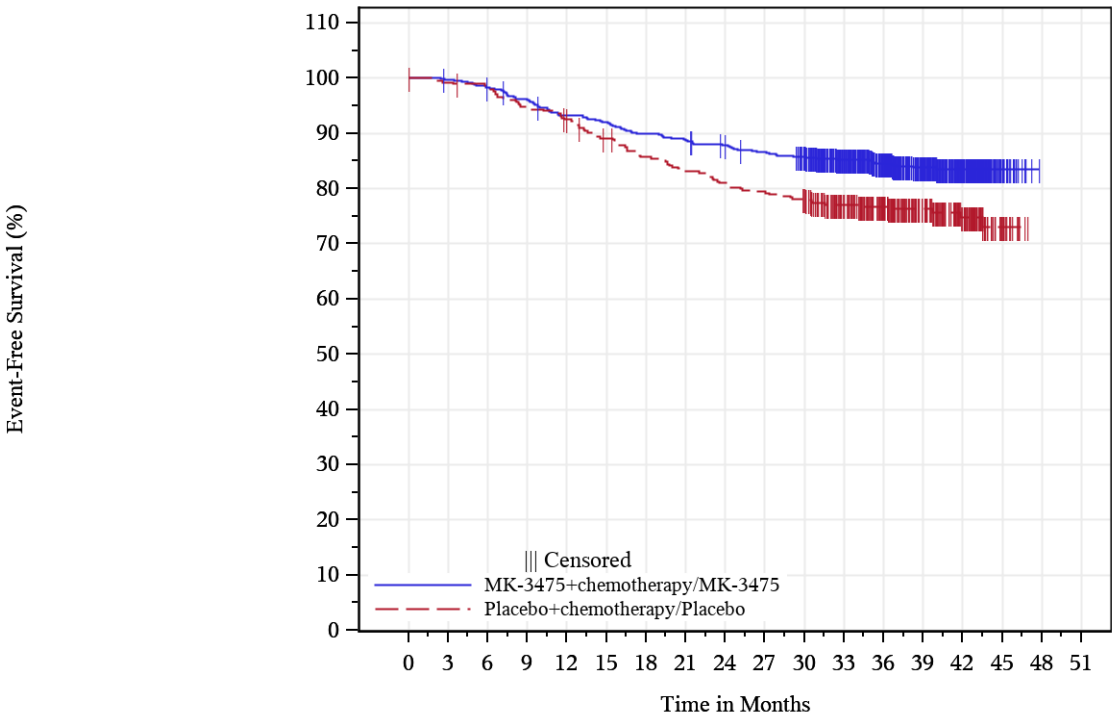
[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).

[c] One-sided p-value based on log-rank test stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).

Database Cutoff Date: 23MAR2021

Figure: Kaplan-Meier Estimates of Event-Free Survival (EFS) All Participants (ITT Population) (IA4)



n at risk

MK-3475+chemotherapy/MK-3475	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo+chemotherapy/Placebo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

Database Cutoff Date: 23MAR2021

Table: summary of first EFS event in EFS analyses All participants (ITT Population) (IA4)*

Event	MK-3475 + chemotherapy / MK-3475 (N=784)		Placebo + chemotherapy / Placebo (N=390)		Total (N=1174)	
	n	(%)	n	(%)	n	(%)
Any EFS Event	123	(15.7)	93	(23.8)	216	(18.4)
Secondary Primary Malignancy	6	(0.8)	4	(1.0)	10	(0.9)
Local PD Precludes Surgery	3	(0.4)	4	(1.0)	7	(0.6)
Local PD Precludes Definitive Surgery	1	(0.1)	0	(0.0)	1	(0.1)
Distant PD	4	(0.5)	1	(0.3)	5	(0.4)
Positive Margin at Last Surgery	6	(0.8)	10	(2.6)	16	(1.4)
Local Recurrence	28	(3.6)	17	(4.4)	45	(3.8)
Distant Recurrence	60	(7.7)	51	(13.1)	111	(9.5)
Death	15	(1.9)	6	(1.5)	21	(1.8)
Database Cutoff Date: 23MAR2021.						

*"PD" (local or distant) is referred to events occurring during the neoadjuvant phase, while "recurrence" (local or distant) is referred to events occurring after surgery.

Out of 45 participants with local recurrence as the first EFS event, 10 participants had subsequent surgery within 3 months after occurrence of local recurrence.

Table 23: Summary of Metastases Sites Participants with Distant PD or Distant Recurrence as the First EFS Event (ITT Population)

Site of Metastases	MK-3475 + chemotherapy / MK-3475 (N = 64)		Placebo + chemotherapy / Placebo (N = 52)		Total (N = 116)	
	n	(%)	n	(%)	n	(%)
Lung	26	(40.6)	20	(38.5)	46	(39.7)
Brain	19	(29.7)	15	(28.8)	34	(29.3)
Bone	11	(17.2)	6	(11.5)	17	(14.7)
Liver	6	(9.4)	8	(15.4)	14	(12.1)
distant lymph node	7	(10.9)	5	(9.6)	12	(10.3)
Breast	2	(3.1)	2	(3.8)	4	(3.4)
chest wall	2	(3.1)	2	(3.8)	4	(3.4)
Abdomen	3	(4.7)	0	(0.0)	3	(2.6)
Pancreas	0	(0.0)	2	(3.8)	2	(1.7)
Skin	1	(1.6)	1	(1.9)	2	(1.7)
supraclavicular lymph node	1	(1.6)	1	(1.9)	2	(1.7)
Axilla	0	(0.0)	1	(1.9)	1	(0.9)
Back	1	(1.6)	0	(0.0)	1	(0.9)
bone marrow	1	(1.6)	0	(0.0)	1	(0.9)
Buttocks	1	(1.6)	0	(0.0)	1	(0.9)
Chest	1	(1.6)	0	(0.0)	1	(0.9)
Pelvis	1	(1.6)	0	(0.0)	1	(0.9)
Each row reflects the number of participants for the corresponding metastases site, a participant may be counted for multiple distant sites. If the location was reported as "other", it is classified for the site of metastases based on the clinical identification. The axilla site of metastases is from a participant who reported lesion site detail of "multiple right axillary, supraclavicular, superior mediastinal, internal mammary chain lymphadenopathies and clustered subcutaneous nodularities in the right chest wall." Database Cutoff Date: 23MAR2021						

Table: Summary of Reasons of Death Participants with Death as the First EFS Event and Did Not Start Adjuvant Treatment

Reasons of Death	MK-3475 + chemotherapy / MK-3475 (N = 11)		Placebo + chemotherapy / Placebo (N = 3)		Total (N = 14)		
	Died up to 90 days of the last treatment	Died after 90 days of the last treatment	Died up to 90 days of the last treatment	Died after 90 days of the last treatment	Died up to 90 days of the last treatment	Died after 90 days of the last treatment	Total
	n	N	n	n	n	n	n
Participants who died	**5**	**6**	**1**	**2**	**6**	**8**	**14**
Death	1	2	0	1	1	3	4
Acute respiratory failure	0	1	0	0	0	1	1
Gastrointestinal haemorrhage	0	0	0	1	0	1	1
Malignant neoplasm progression	0	1	0	0	0	1	1
Myocardial infarction	1	0	0	0	1	0	1
Pneumonia	1	0	0	0	1	0	1
Pneumonia bacterial	0	1	0	0	0	1	1
Pneumonitis	1	0	0	0	1	0	1
Septic shock	0	0	1	0	1	0	1
Shock	1	0	0	0	1	0	1
Sudden death	0	1	0	0	0	1	1

"Death" and "Sudden death" refer to unknown death reason.
The participant who died due to "Malignant neoplasm progression" was not treated with any treatment.
Last treatment includes definitive surgery.
Database Cutoff Date: 23MAR2021

Table: Summary of Reasons of Death Participants with Death as the First EFS Event and Started Adjuvant Treatment

Reasons of Death	MK-3475 + chemotherapy / MK-3475 (N = 4)		Placebo + chemotherapy / Placebo (N = 3)		Total (N = 7)		
	Died up to 90 days of the last treatment	Died after 90 days of the last treatment	Died up to 90 days of the last treatment	Died after 90 days of the last treatment	Died up to 90 days of the last treatment	Died after 90 days of the last treatment	Total
	n	N	n	n	n	n	n
Participants who died	**2**	**2**	**0**	**3**	**2**	**5**	**7**
Cardio-respiratory arrest	0	1	0	0	0	1	1
Completed suicide	0	0	0	1	0	1	1
Encephalitis autoimmune	1	0	0	0	1	0	1
Pneumonia aspiration	0	1	0	0	0	1	1
Pulmonary embolism	1	0	0	0	1	0	1
Sepsis	0	0	0	1	0	1	1
Sudden death	0	0	0	1	0	1	1

"Sudden death" refers to unknown death reason.
Last treatment includes definitive surgery and radiation therapy.
Database Cutoff Date: 23MAR2021

Among patients who died within 90 days from last treatment, in 3 out of 7 in the experimental arm and in 1 out of 1 in the control arm, death was considered treatment-related by investigator

(pneumonitis in 1 participant in the neoadjuvant phase, pulmonary embolism in 1 participant in the adjuvant phase, and autoimmune encephalitis in 1 participant in the adjuvant phase related to pembrolizumab; septic shock in the neoadjuvant phase related to chemotherapy in the control arm). No safety signals were identified upon review of these fatal events.

Secondary Efficacy Endpoints

- **Overall survival**

At IA4, given that the primary hypothesis of EFS was successful, the secondary hypothesis of OS was formally tested at the same alpha level of 2.5% according to the protocol multiplicity strategy.

The success criterion for the secondary OS hypothesis was not met as the observed one-sided p-value did not cross the multiplicity-adjusted one-sided prespecified p-value boundary at IA4 of 0.00085861.

Table: Analysis of Overall Survival (OS) All Participants (ITT Population) (IA4)

	MK-3475 + chemotherapy / MK-3475 (N=784)	Placebo + chemotherapy / Placebo (N=390)	Total (N=1174)
Number of Events (%)	**80 (10.2)**	**55 (14.1)**	135 (11.5)
Number of Censored (%)	704 (89.8)	335 (85.9)	1039 (88.5)
Kaplan-Meier Estimates (Months)[a]			
Median (95% CI)	**. (., .)**	**. (., .)**	. (., .)
Q1, Q3	**Not Reached, Not Reached**	**Not Reached, Not Reached**	Not Reached, Not Reached
Person-Months	28,199.7	13,980.1	42,179.8
Event Rate / 100 Person-Months	0.3	0.4	0.3
OS Rate at 6 Months (%) (95% CI)	99.2 (98.3, 99.7)	99.7 (98.2, 100.0)	99.4 (98.8, 99.7)
OS Rate at 12 Months (%) (95% CI)	97.2 (95.8, 98.1)	98.7 (96.9, 99.5)	97.7 (96.7, 98.4)
OS Rate at 18 Months (%) (95% CI)	95.0 (93.2, 96.3)	93.8 (91.0, 95.8)	94.6 (93.2, 95.8)
OS Rate at 24 Months (%) (95% CI)	92.3 (90.2, 94.0)	91.0 (87.7, 93.5)	91.9 (90.2, 93.3)
OS Rate at 30 Months (%) (95% CI)	91.3 (89.1, 93.1)	88.7 (85.1, 91.5)	90.4 (88.6, 92.0)
OS Rate at 36 Months (%) (95% CI)	89.7 (87.3, 91.7)	86.9 (83.0, 89.9)	88.8 (86.8, 90.5)
OS Rate at 42 Months (%) (95% CI)	89.2 (86.7, 91.3)	84.1 (79.5, 87.7)	87.5 (85.3, 89.4)
vs Placebo + chemotherapy / Placebo			
Hazard Ratio (95% CI)[b]	**0.72 (0.51, 1.02)**		
p-value[c]	**.0321377**		

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).

[c] One-sided p-value based on log-rank test stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).

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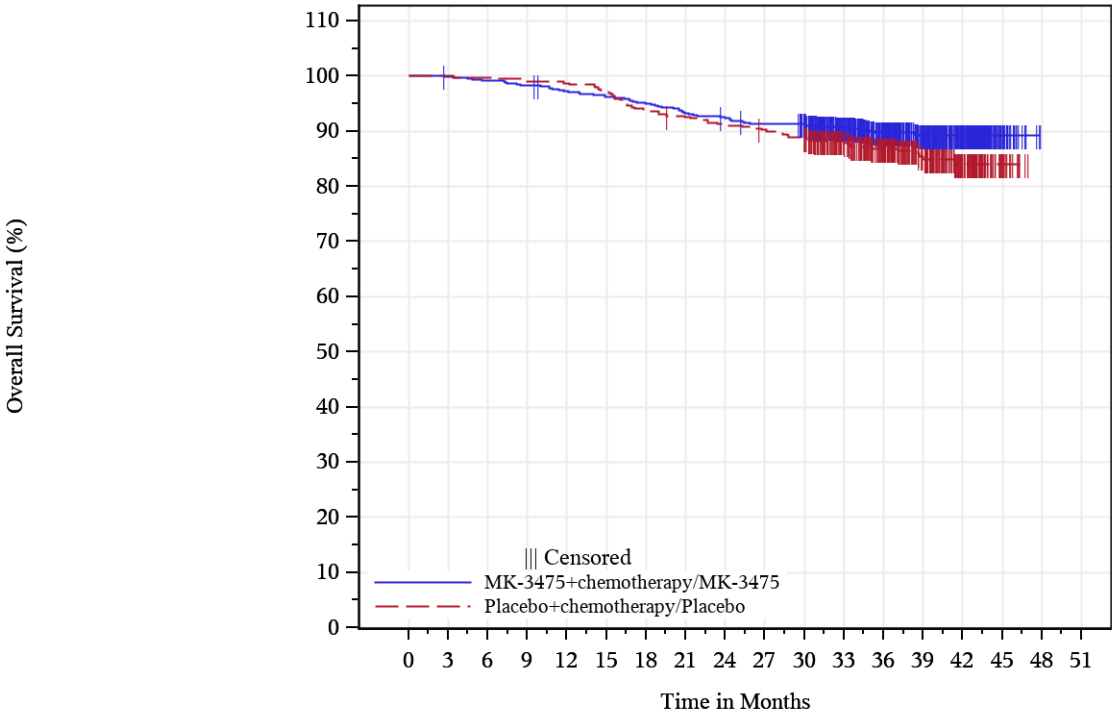
Figure: Kaplan-Meier Estimates of Overall Survival (OS) All Participants (ITT Population) (IA4)



n at risk

MK-3475+chemotherapy/MK-3475	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Placebo+chemotherapy/Placebo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

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Table: Summary of Reasons of Death Participants Who Died <=6 Months from Randomization (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	**784**		**390**		**1,174**	
Participants who died	**6**	**(0.8)**	**1**	**(0.3)**	**7**	**(0.6)**
Malignant neoplasm progression	2	(0.3)	0	(0.0)	2	(0.2)
Death	1	(0.1)	0	(0.0)	1	(0.1)
Myocardial infarction	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonia	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonitis	1	(0.1)	0	(0.0)	1	(0.1)
Septic shock	0	(0.0)	1	(0.3)	1	(0.1)

"Death" refers to unknown death reason.

Database Cutoff Date: 23MAR2021

Table: Summary of Reasons of Death Participants Who Died <=12 Months from Randomization (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	**784**		**390**		**1,174**	
Participants who died	**22**	**(2.8)**	**5**	**(1.3)**	**27**	**(2.3)**
Malignant neoplasm progression	14	(1.8)	4	(1.0)	18	(1.5)
Cardio-respiratory arrest	1	(0.1)	0	(0.0)	1	(0.1)
Death	1	(0.1)	0	(0.0)	1	(0.1)
Myocardial infarction	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonia	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonitis	1	(0.1)	0	(0.0)	1	(0.1)
Pulmonary embolism	1	(0.1)	0	(0.0)	1	(0.1)
Septic shock	0	(0.0)	1	(0.3)	1	(0.1)
Shock	1	(0.1)	0	(0.0)	1	(0.1)
Sudden death	1	(0.1)	0	(0.0)	1	(0.1)
"Death" or "Sudden death" refers to unknown death reason.						
Database Cutoff Date: 23MAR2021						

Table: Summary of Reasons of Death Participants Who Died <=18 Months from Randomization (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	**784**		**390**		**1,174**	
Participants who died	**39**	**(5.0)**	**24**	**(6.2)**	**63**	**(5.4)**
Malignant neoplasm progression	27	(3.4)	18	(4.6)	45	(3.8)
Death	2	(0.3)	2	(0.5)	4	(0.3)
Sepsis	1	(0.1)	1	(0.3)	2	(0.2)
Sudden death	1	(0.1)	1	(0.3)	2	(0.2)
Cardio-respiratory arrest	1	(0.1)	0	(0.0)	1	(0.1)
Encephalitis autoimmune	1	(0.1)	0	(0.0)	1	(0.1)
Gastrointestinal haemorrhage	0	(0.0)	1	(0.3)	1	(0.1)
Myocardial infarction	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonia	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonitis	1	(0.1)	0	(0.0)	1	(0.1)
Postoperative respiratory distress	1	(0.1)	0	(0.0)	1	(0.1)
Pulmonary embolism	1	(0.1)	0	(0.0)	1	(0.1)
Septic shock	0	(0.0)	1	(0.3)	1	(0.1)
Shock	1	(0.1)	0	(0.0)	1	(0.1)
"Death" or "Sudden death" refers to unknown death reason.						
Database Cutoff Date: 23MAR2021						

Table: Summary of Reasons of Death Participants Who Died <=24 Months from Randomization (ITT Population)

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	**784**		**390**		**1,174**	
Participants who died	**60**	**(7.7)**	**35**	**(9.0)**	**95**	**(8.1)**
Malignant neoplasm progression	46	(5.9)	27	(6.9)	73	(6.2)
Death	3	(0.4)	3	(0.8)	6	(0.5)
Sepsis	1	(0.1)	1	(0.3)	2	(0.2)
Sudden death	1	(0.1)	1	(0.3)	2	(0.2)
Cardio-respiratory arrest	1	(0.1)	0	(0.0)	1	(0.1)
Cardiopulmonary failure	1	(0.1)	0	(0.0)	1	(0.1)
Completed suicide	0	(0.0)	1	(0.3)	1	(0.1)
Encephalitis autoimmune	1	(0.1)	0	(0.0)	1	(0.1)
Gastrointestinal haemorrhage	0	(0.0)	1	(0.3)	1	(0.1)
Myocardial infarction	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonia	1	(0.1)	0	(0.0)	1	(0.1)
Pneumonitis	1	(0.1)	0	(0.0)	1	(0.1)
Postoperative respiratory distress	1	(0.1)	0	(0.0)	1	(0.1)
Pulmonary embolism	1	(0.1)	0	(0.0)	1	(0.1)
Septic shock	0	(0.0)	1	(0.3)	1	(0.1)
Shock	1	(0.1)	0	(0.0)	1	(0.1)

"Death" or "Sudden death" refers to unknown death reason.

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There was a total of **7 patients** who died within <=6 months from randomization, mostly the experimental arm (**6 vs 1** in the experimental vs control arm).

- pembrolizumab arm: 2 deaths for PD, 1 death for pneumonitis (related), 1 death for more multiple AEs (MOF and sepsis related, myocardial infarction not related) 1 for death (although considered not related, this subject has an AEOSI of hepatitis before death), 1 death for pneumonia (not related)

- control arm: 1 septic shock (related)

Further, there was a total of **20 patients** who died within 6 -12 months from randomization mostly in the experimental arm (**16 vs 4** in the experimental vs control arm).

- pembro arm: 12 deaths for PD, 1 for pulmonary embolism (related), 1 for sudden death (not related), 1 for shock (not related), 1 for cardiorespiratory arrest

- control arm: 4 deaths for PD

In the time interval 12-18 months from randomization there were 17 vs 19 deaths in the experimental vs control arm, and in the time interval 18-24 months from randomization 21 vs 11 deaths occurred in the experimental vs control arm, respectively.

- **Rate of Pathological Complete Response according to alternative definitions**

pCR results using the alternative definitions of ypT0 ypN0 (i.e., no invasive or noninvasive residual in breast or nodes) and ypT0/Tis (i.e., no invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement) were analyzed as secondary endpoints.

IA1:

- primary definition (ypT0/Tis ypN0):

Events 260/401 vs 103/201, pCR 64.8% (59.9, 69.5) vs 51.2% (44.1, 58.3), delta 13.6% (5.4, 21.8)

- alternative definition (ypT0 ypN0)

Events 240/401 vs 91/201, pCR 59.9% (54.9, 64.7) vs 45.3% (38.3, 52.4), delta 14.5% (6.2, 22.7)

- alternative definition (ypT0/Tis)

Events 275/401 vs 108/201, pCR 68.6% (63.8, 73.1) vs 53.7% (46.6, 60.8), delta 14.8% (6.8, 23.0)

IA2:

- primary definition (ypT0/Tis ypN0)

Events 428/669 vs 182/333, pCR 64.0% (60.2, 67.6) vs 54.7% (49.1, 60.1), delta 9.2% (2.8, 15.6)

- alternative definition (ypT0 ypN0)

Events 393/669 vs 165/333, pCR 58.7% (54.9, 62.5) vs 49.5% (44.1, 55.1), delta 9.1% (2.6, 15.5)

- alternative definition (ypT0/Tis)

Events 447/669 vs 191/333, pCR 66.8% (63.1, 70.4) vs 57.4% (51.8, 62.7), delta 9.3% (3.1, 15.7)

IA4:

- primary definition (ypT0/Tis ypN0)

Events 494/784 vs 217/390, pCR 63.0% (59.5, 66.4) vs 55.6% (50.6, 60.6), delta 7.5% (1.6, 13.4)

- alternative definition (ypT0 ypN0)

Events 453/784 vs 196/390, pCR 57.8% (54.2, 61.3) vs 50.3% (45.2, 55.3), delta 7.6% (1.6, 13.6)

- alternative definition (ypT0/Tis)

Events 516/784 vs 228/390, pCR 65.8% (62.4, 69.1) vs 58.5% (53.4, 63.4), delta 7.4% (1.7, 13.3)

- **Health-related QoL**

Health-related QoL assessments was carried out using the EORTC QLQ-C30 and EORTC QLQ-B23 within and across the neoadjuvant and adjuvant treatment phases, in all participants and in participants with CPS≥1.

Neoadjuvant phase: A timeframe of 21 weeks for analysis of completion rate in the neoadjuvant phase was selected based on a prespecified requirement for a minimum completion rate of 60%. The completion rates of the EORTC QLQ-C30 and of the EORTC QLQ-BR23 were above 90% in both the pembrolizumab + NAC and placebo + NAC groups at baseline and was approximately 80% at Week 21. Compliance rates in the neoadjuvant phase, defined as the percentage of participants completing the measure among those expected to complete the measure (i.e., not missing by design), were similar at

baseline in both the pembrolizumab + NAC and placebo + NAC groups among all participants (over 90%) and remained high (close to 90%) at Week 21.

Over 21 weeks of follow-up in the neoadjuvant phase, all participants in the pembrolizumab + NAC and placebo + NAC groups had similar decreases in the global health status/QoL score of EORTC QLQ-C30. Scores on the physical functioning scale of the EORTC QLQ-C30 were worse for the pembrolizumab + NAC treatment group when compared with the placebo + NAC treatment group, while scores on the emotional functioning scale indicated no differences between the 2 treatment groups.

Participants in both treatment groups had similar decreases (improvement) in the prespecified breast symptoms scale score. The between-group difference in LS mean score changes from baseline at Week 21 were similar for all participants.

Analysis of Change from Neoadjuvant Baseline in EORTC QLQ-C30 Global Health Status/QoL at Neoadjuvant Week 21
All Participants
Neoadjuvant Phase
(FAS Population)

	Baseline		Neoadjuvant Week 21		Change from Neoadjuvant Baseline at Neoadjuvant Week 21	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
MK-3475 + chemotherapy	701	77.08 (18.493)	615	66.79 (19.386)	762	-11.24 (-12.82, -9.66)
Placebo + chemotherapy	366	78.96 (17.124)	309	68.26 (17.816)	383	-10.20 (-12.30, -8.10)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
MK-3475 + chemotherapy vs. Placebo + chemotherapy	-1.04 (-3.46, 1.38)	0.3985

[a] Based on cLDA model with the PRO score as the response variable, and treatment by timepoint interaction, stratification factors (Nodal status (positive vs negative), Tumor size (T1/T2 vs T3/T4), and Choice of Carboplatin (Q3W vs Weekly)) as covariates.

For Neoadjuvant Baseline and Neoadjuvant Week 21, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from Neoadjuvant Baseline, N is the number of participants in the analysis population in each treatment group.

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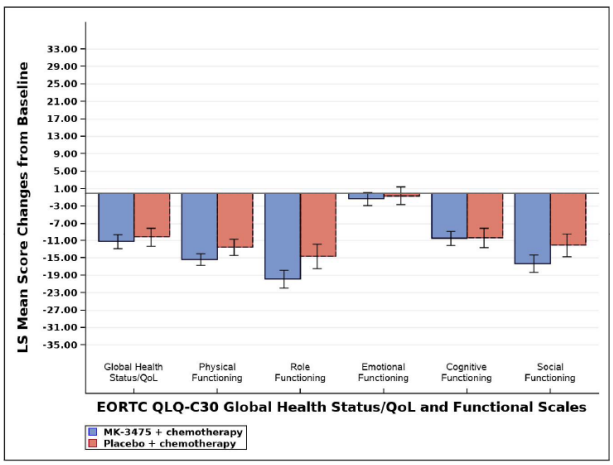
Change from Neoadjuvant Baseline for EORTC QLQ-C30 Global Health Status/QoL and Functional Scales
at Neoadjuvant Week 21*
LS Mean Change and 95% CI
All Participants
Neoadjuvant Phase
(FAS Population)



* For global health status/quality of life score and all functional scales, a higher score denotes better HRQOL or function. For symptoms scales, a higher score denotes worse symptoms.

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Adjuvant phase: A timeframe of 24 weeks for analysis of completion rate in the adjuvant phase was selected based on the prespecified requirement for a minimum completion rate of 60%. The completion rate of the EORTC QLQ-C30 and QLQ-BR23 was above 90% in both the pembrolizumab and

placebo groups at baseline and remained >80% at Week 24. Compliance rates in the adjuvant phase, defined as the percentage of participants completing the measure among those expected to complete the measure (i.e., not missing by design), were similar at baseline in both the pembrolizumab and placebo groups and remained high at Week 24 (approximately 90%).

Over 24 weeks of follow-up in the adjuvant phase, decrease (worsening) in scores on the global health status/QoL, physical functioning, and emotional functioning scales were generally similar between the 2 treatment groups for all participants based on EORTC QLQ-C30.

Participants in both arms had similar decreases (improvement) in the prespecified breast symptoms scale score based on EORTC QLQ-BR23.

Analysis of Change from Adjuvant Baseline in EORTC QLQ-C30 Global Health Status/QoL at Adjuvant Week 24
All Participants
Adjuvant Phase
(FAS Population)

	Baseline		Adjuvant Week 24		Change from Adjuvant Baseline at Adjuvant Week 24	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
MK-3475	489	73.82 (15.678)	444	76.26 (16.671)	539	2.47 (1.05, 3.88)
Placebo	283	73.14 (18.145)	249	76.24 (16.561)	308	2.88 (1.05, 4.71)

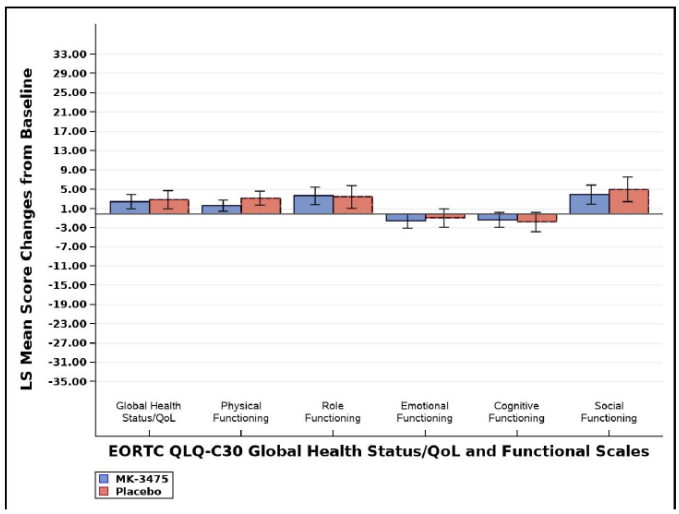
Pairwise Comparison	Difference in LS Means (95% CI)	p-Value
MK-3475 vs. Placebo	-0.41 (-2.60, 1.77)	0.7107

[a] Based on cLDA model with the PRO score as the response variable, and treatment by timepoint interaction, stratification factors (Nodal status (positive vs negative), Tumor size (T1/T2 vs T3/T4), and Choice of Carboplatin (Q3W vs Weekly)) as covariates.

For Adjuvant Baseline and Adjuvant Week 24, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from Adjuvant Baseline, N is the number of participants in the analysis population in each treatment group.

Database Cutoff Date: 23MAR2021

Change from Adjuvant Baseline for EORTC QLQ-C30 Global Health Status/QoL and Functional Scales
at Adjuvant Week 24*
LS Mean Change and 95% CI
All Participants
Adjuvant Phase
(FAS Population)



* For global health status/quality of life score and all functional scales, a higher score denotes better HRQOL or function. For symptoms scales, a higher score denotes worse symptoms.

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Exploratory Efficacy Endpoints

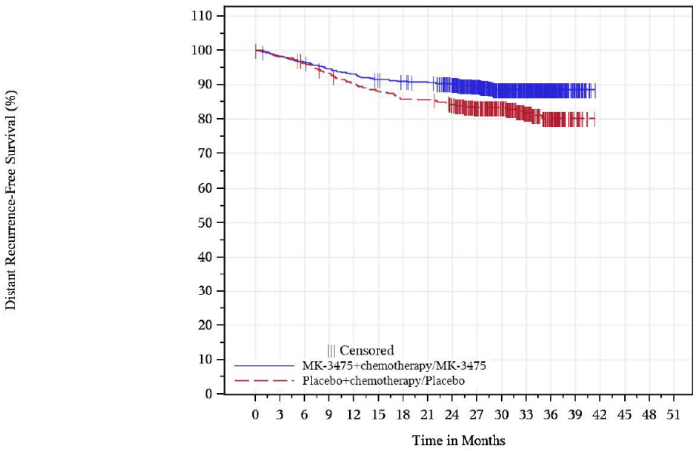
- **Distant Recurrence-free Survival**

Analysis of Distant Recurrence-Free Survival (DRFS)
All Participants
(FAS Population)

	MK-3475 + chemotherapy / MK-3475 (N=761)	Placebo + chemotherapy / Placebo (N=371)	Total (N=1132)
Number of Events (%)	84 (11.0)	66 (17.8)	150 (13.3)
Kaplan-Meier Estimates (months)[a]			
Median (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[,]	[,]	[,]
person-months	22323.1	10451.6	32774.7
Event Rate / 100 person-months	0.4	0.6	0.5
vs Placebo + chemotherapy / Placebo			
Hazard Ratio (95% CI)[b]	0.60 (0.43, 0.82)		
p-value[c]	0.0008		
DRFS Rate at month 6 (%) (95% CI)	96.6 (95.0, 97.7)	96.2 (93.7, 97.7)	96.5 (95.2, 97.4)
DRFS Rate at month 12 (%) (95% CI)	93.2 (91.1, 94.7)	90.2 (86.7, 92.8)	92.2 (90.5, 93.6)
DRFS Rate at month 18 (%) (95% CI)	91.0 (88.8, 92.9)	85.8 (81.8, 89.0)	89.3 (87.4, 91.0)
DRFS Rate at month 24 (%) (95% CI)	90.1 (87.8, 92.0)	84.2 (80.0, 87.5)	88.2 (86.1, 89.9)
DRFS Rate at month 30 (%) (95% CI)	88.6 (86.0, 90.7)	83.3 (79.0, 86.7)	86.8 (84.7, 88.7)
DRFS Rate at month 36 (%) (95% CI)	88.6 (86.0, 90.7)	80.2 (75.2, 84.3)	85.8 (83.5, 87.9)
DRFS Rate at month 42 (%) (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).
[c] One-sided p-value based on log-rank test stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).
NR = Not reached.
FAS population includes all the randomized participants with definitive surgeries, which exclude patients with distant PD in neoadjuvant, without surgery, or with positive margin at the last surgery.
Database Cutoff Date: 23MAR2021

Kaplan-Meier Estimates of Distant Recurrence-Free Survival (DRFS)
All Participants
(FAS Population)



n at risk

MK-3475+chemotherapy/MK-3475	761	747	734	718	707	692	687	681	651	550	426	297	159	30	0	0	0	0
Placebo+chemotherapy/Placebo	371	363	353	341	329	321	313	312	298	252	195	132	83	13	0	0	0	0

Database Cutoff Date: 23MAR2021

- **Distant Progression or Distant Recurrence-free Survival**

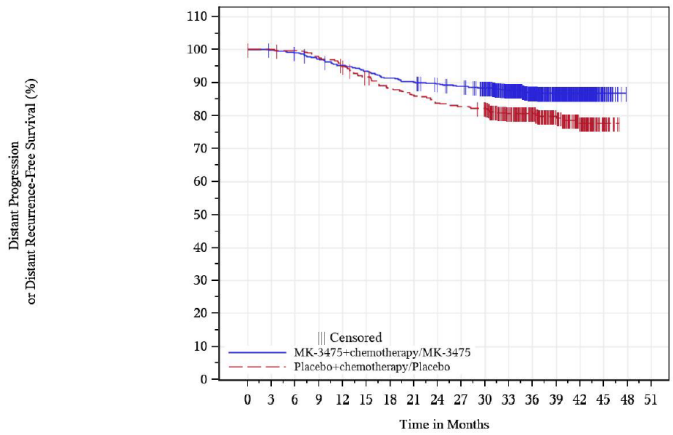
DPDRFS is defined as the time from randomization to first distant progression or distant recurrence event as assessed by investigator, or death due to any cause.

Analysis of Distant Progression or Distant Recurrence-Free Survival (DPDRFS)
All Participants
(ITT Population)

	MK-3475 + chemotherapy / MK-3475 (N=784)	Placebo + chemotherapy / Placebo (N=390)	Total (N=1174)
Number of Events (%)	100 (12.8)	79 (20.3)	179 (15.2)
Kaplan-Meier Estimates (months)[a]			
Median (95% CI)	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
[Q1, Q3]	[,]	[,]	[,]
person-months	27352.2	13145.5	40497.8
Event Rate / 100 person-months	0.4	0.6	0.4
vs Placebo + chemotherapy / Placebo			
Hazard Ratio (95% CI)[b]	0.61 (0.46, 0.82)		
p-value[c]	0.0005		
DPDRFS Rate at month 6 (%) (95% CI)	99.0 (98.0, 99.5)	99.7 (98.2, 100.0)	99.2 (98.5, 99.6)
DPDRFS Rate at month 12 (%) (95% CI)	95.1 (93.4, 96.4)	94.8 (92.1, 96.6)	95.0 (93.6, 96.1)
DPDRFS Rate at month 18 (%) (95% CI)	91.3 (89.1, 93.1)	88.1 (84.4, 90.9)	90.2 (88.4, 91.8)
DPDRFS Rate at month 24 (%) (95% CI)	89.6 (87.2, 91.6)	83.9 (79.8, 87.2)	87.7 (85.7, 89.5)
DPDRFS Rate at month 30 (%) (95% CI)	88.4 (86.0, 90.5)	82.3 (78.1, 85.8)	86.4 (84.3, 88.3)
DPDRFS Rate at month 36 (%) (95% CI)	87.0 (84.4, 89.2)	80.7 (76.3, 84.3)	84.9 (82.7, 86.9)
DPDRFS Rate at month 42 (%) (95% CI)	86.8 (84.1, 89.0)	77.7 (72.7, 82.0)	83.8 (81.4, 85.9)

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).
[c] One-sided p-value based on log-rank test stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).
NR = Not reached.
Database Cutoff Date: 23MAR2021

Kaplan-Meier Estimates of Distant Progression or Distant Recurrence-Free Survival (DPDRFS)
All Participants
(ITT Population)



n at risk

MK-3475+chemotherapy/MK-3475	784	782	773	758	741	728	711	702	692	685	663	561	439	308	167	29	0	0
Placebo+chemotherapy/Placebo	390	389	387	379	367	352	337	330	321	317	312	259	202	143	84	17	0	0

Database Cutoff Date: 23MAR2021

Table: Participants Received Treatment Other Than Study Treatment After An EFS Event (Incidence > 0% in One or More Treatment Groups) All Participants with an EFS Event

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants with An EFS Event	123		93		216	
with one or more treatment other than study treatment	73	(59.3)	65	(69.9)	138	(63.9)
with no treatment other than study treatment	50	(40.7)	28	(30.1)	78	(36.1)
NLRP3 agonist (unspecified)	1	(0.8)	0	(0.0)	1	(0.5)
alpelisib	1	(0.8)	0	(0.0)	1	(0.5)
anetumab ravtansine	1	(0.8)	1	(1.1)	2	(0.9)
anthracyclines (unspecified)	0	(0.0)	1	(1.1)	1	(0.5)
anti-4-1BB/anti-PDL1 bispecific monoclonal antibody	1	(0.8)	0	(0.0)	1	(0.5)
anti-HER2 antibody drug conjugate (DXd conjugate)	0	(0.0)	1	(1.1)	1	(0.5)
antineoplastic (unspecified)	0	(0.0)	1	(1.1)	1	(0.5)
atezolizumab	3	(2.4)	15	(16.1)	18	(8.3)
avelumab	1	(0.8)	0	(0.0)	1	(0.5)
bevacizumab	9	(7.3)	6	(6.5)	15	(6.9)
capecitabine	37	(30.1)	37	(39.8)	74	(34.3)
carboplatin	5	(4.1)	9	(9.7)	14	(6.5)
cisplatin	5	(4.1)	10	(10.8)	15	(6.9)
cyclophosphamide	17	(13.8)	8	(8.6)	25	(11.6)
cytarabine	1	(0.8)	0	(0.0)	1	(0.5)
denosumab	0	(0.0)	2	(2.2)	2	(0.9)
docetaxel	11	(8.9)	8	(8.6)	19	(8.8)
doxorubicin	7	(5.7)	2	(2.2)	9	(4.2)
doxorubicin hydrochloride	2	(1.6)	0	(0.0)	2	(0.9)
durvalumab	0	(0.0)	1	(1.1)	1	(0.5)
epirubicin	6	(4.9)	3	(3.2)	9	(4.2)
eribulin mesylate	19	(15.4)	16	(17.2)	35	(16.2)
etoposide	2	(1.6)	1	(1.1)	3	(1.4)
everolimus	1	(0.8)	0	(0.0)	1	(0.5)
fluorouracil	2	(1.6)	5	(5.4)	7	(3.2)
fulvestrant	1	(0.8)	0	(0.0)	1	(0.5)
gemcitabine	10	(8.1)	14	(15.1)	24	(11.1)
gimeracil (+) oteracil potassium (+) tegafur	1	(0.8)	3	(3.2)	4	(1.9)
idarubicin hydrochloride	1	(0.8)	0	(0.0)	1	(0.5)
investigational drug (unspecified)	1	(0.8)	2	(2.2)	3	(1.4)
ipatasertib	0	(0.0)	3	(3.2)	3	(1.4)
ipilimumab	1	(0.8)	0	(0.0)	1	(0.5)
ixabepilone	1	(0.8)	0	(0.0)	1	(0.5)
ladiratuzumab vedotin	1	(0.8)	0	(0.0)	1	(0.5)
lapatinib	0	(0.0)	1	(1.1)	1	(0.5)
letrozole	1	(0.8)	0	(0.0)	1	(0.5)
methotrexate	3	(2.4)	5	(5.4)	8	(3.7)
nivolumab	1	(0.8)	0	(0.0)	1	(0.5)

olaparib	4	(3.3)	6	(6.5)	10	(4.6)
oxaliplatin	1	(0.8)	0	(0.0)	1	(0.5)
paclitaxel	11	(8.9)	16	(17.2)	27	(12.5)
paclitaxel albumin	3	(2.4)	9	(9.7)	12	(5.6)
palbociclib	1	(0.8)	1	(1.1)	2	(0.9)
pembrolizumab	0	(0.0)	3	(3.2)	3	(1.4)
pertuzumab	0	(0.0)	1	(1.1)	1	(0.5)
picibanil	0	(0.0)	1	(1.1)	1	(0.5)
prexasertib	1	(0.8)	0	(0.0)	1	(0.5)
sacituzumab	0	(0.0)	1	(1.1)	1	(0.5)
sacituzumab govitecan	0	(0.0)	1	(1.1)	1	(0.5)
selicrelumab	0	(0.0)	1	(1.1)	1	(0.5)
trastuzumab	0	(0.0)	1	(1.1)	1	(0.5)
vinorelbine tartrate	9	(7.3)	9	(9.7)	18	(8.3)

In neoadjuvant (reason in the form of Oncology drugs and Biologics - Follow-up (ODBF) is neoadjuvant), for both treatment groups the following are considered study treatments although collected in ODBF: 'carboplatin', 'cyclophosphamide', 'doxorubicin', 'doxorubicin hydrochloride', 'epirubicin' or 'paclitaxel'; so they won't be included in the table(s).

Every participant is counted a single time for each applicable specific treatment.

Database Cutoff Date: 23MAR2021

- **Rate of Breast Conserving Surgery (BCS)**

The rate of BCS at the time of definitive surgery in the overall population receiving pembrolizumab + NAC was similar when compared with placebo + NAC both in the overall ITT population (BCS in 45.2 vs 45.6% of patients in pembrolizumab vs control arm, respectively) and in participants with tumors that express PD-L1 (CPS≥1) (45.6% vs 47.3%).

- **Residual Cancer Burden (RCB)**

RBC, defined as residual disease in either the breast or lymph node was assessed by the local pathologist at the time of definitive surgery. The portion of participants in each RCB category is presented in the table below:

Summary of Residual Cancer Burden (RCB)
All Participants
(ITT Population)

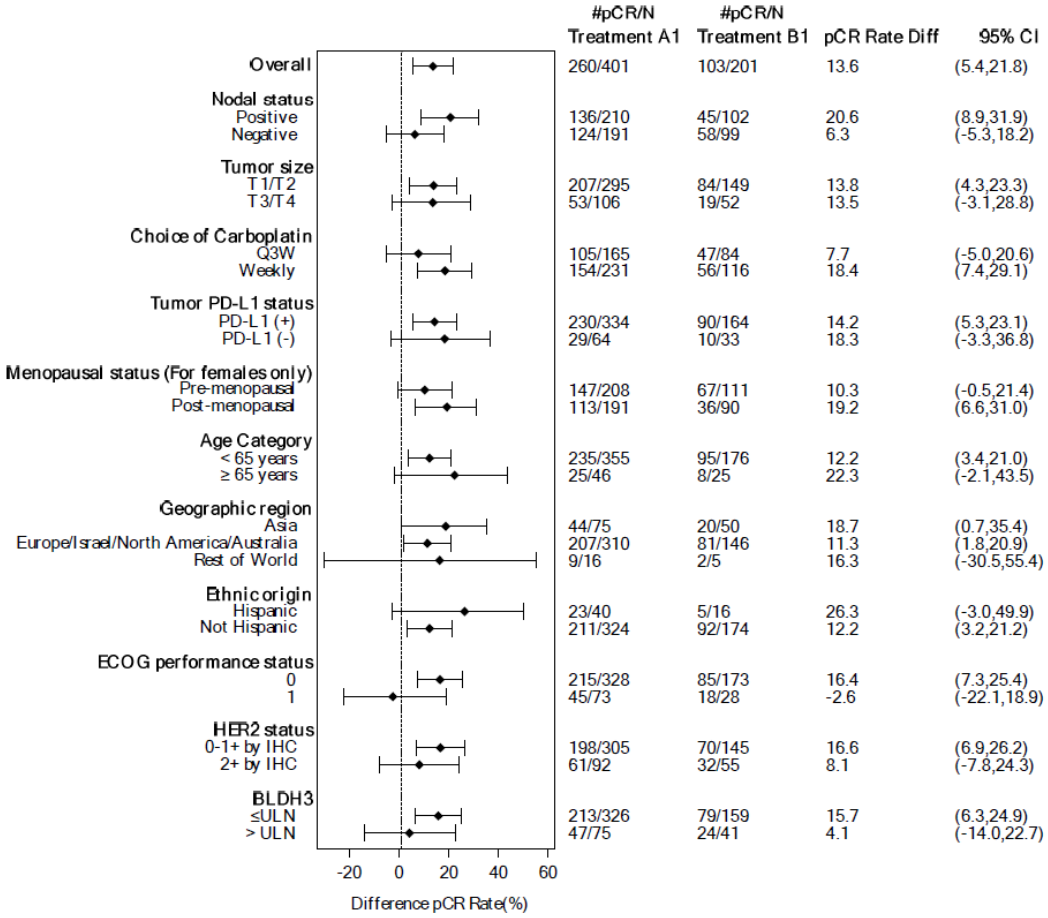
	MK-3475 + chemotherapy		Placebo + chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		390		1,174	
RCB						
RCB-0	497	(63.4)	219	(56.2)	716	(61.0)
RCB-I	69	(8.8)	45	(11.5)	114	(9.7)
RCB-II	145	(18.5)	79	(20.3)	224	(19.1)
RCB-III	40	(5.1)	26	(6.7)	66	(5.6)
Missing	33	(4.2)	21	(5.4)	54	(4.6)
Participants with data	750		368		1118	
Mean	0.7		0.9		0.8	
SD	1.2		1.2		1.2	
Median	0.0		0.0		0.0	
Range	0.0 to 5.2		0.0 to 4.9		0.0 to 5.2	

Database Cutoff Date: 23MAR2021

Ancillary analyses

Subgroup analyses for pCR (IA1)

Forest Plot of pCR by Subgroup Factors (ypT0/Tis ypN0)
IA 1 Population
(ITT Population)



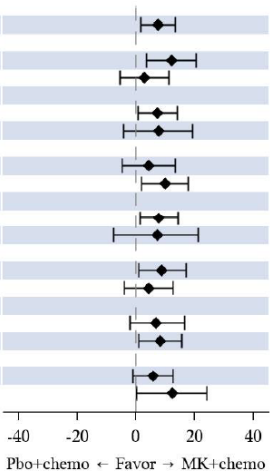
For overall population and the PD-L1 subgroup, analysis is based on Miettinen & Nurminen method stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly). For other subgroups, analysis is based on unstratified Miettinen & Nurminen method.

Database Cutoff Date: 24SEP2018

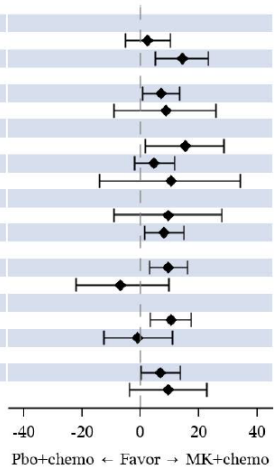
Subgroup analyses for pCR (IA4)

Forest Plot of pCR (ypT0/Tis ypN0) by Subgroup Factors
All Participants
(ITT Population)

	MK+chemo #pCR/N	Pbo+chemo #pCR/N	Total #pCR/N	pCR Rate Diff (%)	95% CI
Overall	494/784	217/390	711/1174	7.5	(1.6,13.4)
Nodal status					
Positive	255/408	99/196	354/604	12.0	(3.6,20.4)
Negative	239/376	118/194	357/570	2.7	(-5.6,11.2)
Tumor size					
T1/T2	393/581	175/290	568/871	7.3	(0.6,14.1)
T3/T4	101/203	42/100	143/303	7.8	(-4.2,19.3)
Choice of Carboplatin					
Q3W	214/334	100/167	314/501	4.2	(-4.7,13.3)
Weekly	280/444	117/220	397/664	9.9	(1.9,17.8)
PD-L1 CPS 1 Cutoff					
PD-L1 CPS >= 1	436/656	187/317	623/973	7.8	(1.4,14.2)
PD-L1 CPS < 1	58/128	27/69	85/197	7.1	(-7.8,21.1)
PD-L1 CPS 10 Cutoff					
PD-L1 CPS >= 10	298/393	119/177	417/570	8.7	(0.8,16.9)
PD-L1 CPS < 10	196/391	95/209	291/600	4.3	(-4.1,12.6)
PD-L1 CPS 20 Cutoff					
PD-L1 CPS >= 20	197/247	89/121	286/368	6.8	(-2.2,16.5)
PD-L1 CPS < 20	297/537	125/265	422/802	8.2	(0.9,15.5)
Overall Stage					
Stage II	385/590	173/291	558/881	5.8	(-1.0,12.7)
Stage III	109/194	43/98	152/292	12.3	(0.2,24.1)



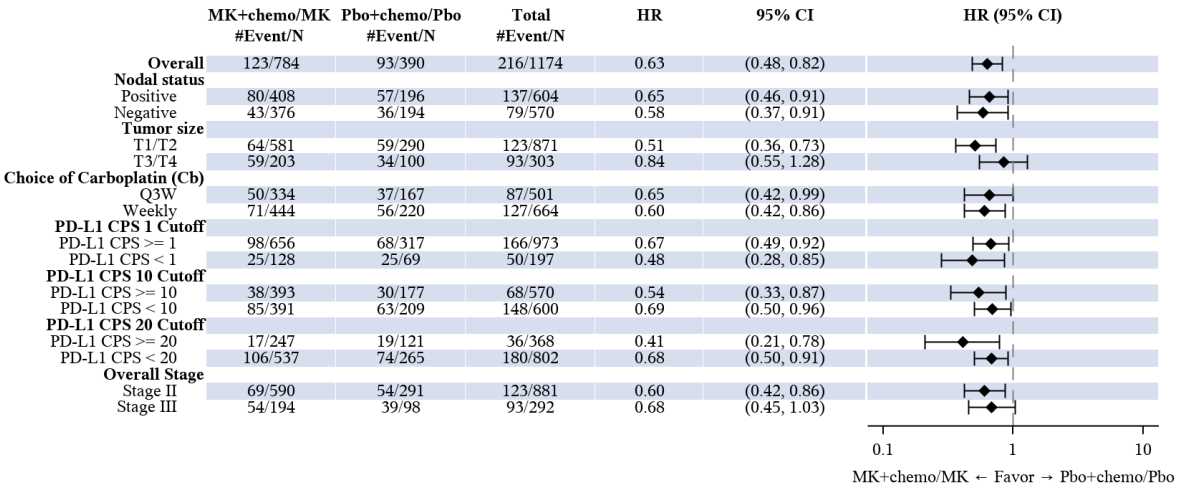
	MK+chemo #pCR/N	Pbo+chemo #pCR/N	Total #pCR/N	pCR Rate Diff (%)	95% CI
Menopausal status (For females only)					
Pre-menopausal	290/438	141/221	431/659	2.4	(-5.2,10.2)
Post-menopausal	204/345	76/169	280/514	14.2	(5.0,23.1)
Age Category					
< 65 years	450/700	196/342	646/1042	7.0	(0.7,13.3)
>= 65 years	44/84	21/48	65/132	8.6	(-9.1,25.7)
Geographic region					
Asia	82/136	36/80	118/216	15.3	(1.5,28.6)
Europe/Israel/North America/Australia	388/607	169/285	557/892	4.6	(-2.2,11.5)
Rest of World	24/41	12/25	36/66	10.5	(-14.0,34.1)
Ethnic origin					
Hispanic	50/86	19/39	69/125	9.4	(-9.2,27.7)
Not Hispanic	390/615	170/307	560/922	8.0	(1.3,14.8)
ECOG performance status					
0	430/678	184/341	614/1019	9.5	(3.1,15.9)
1	64/106	33/49	97/155	-7.0	(-22.2,9.7)
HER2 status					
0-1+ by IHC	384/595	155/286	539/881	10.3	(3.4,17.3)
2+ by IHC (but FISH-)	110/188	62/104	172/292	-1.1	(-12.6,10.8)
LDH					
<=ULN	398/631	174/309	572/940	6.8	(0.1,13.5)
> ULN	94/149	43/80	137/229	9.3	(-3.9,22.6)

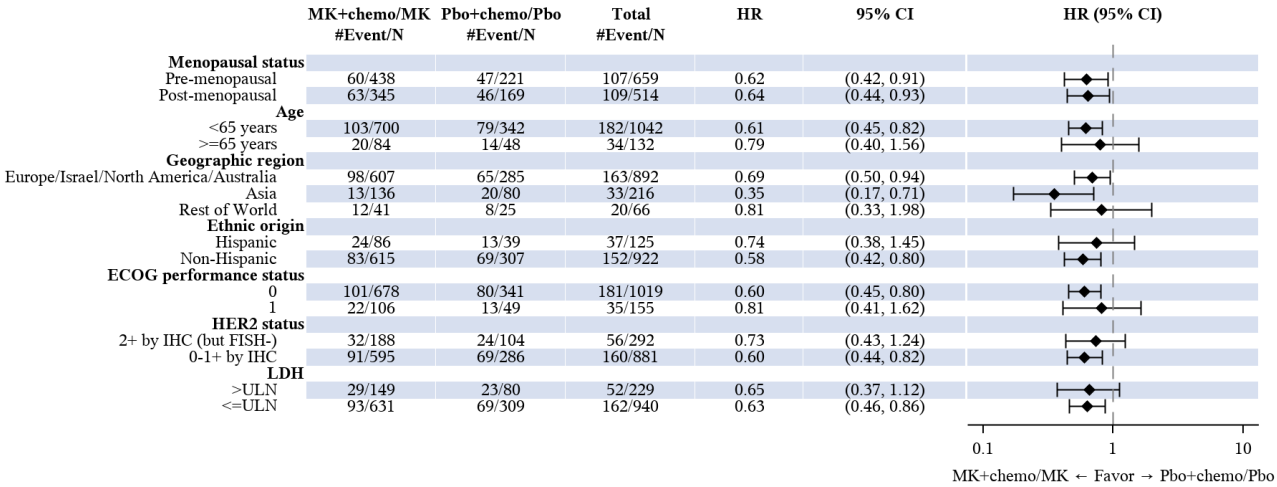


For overall population and the PD-L1 subgroup, analysis is based on Miettinen & Nurminen method stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly). For other subgroups, analysis is based on unstratified Miettinen & Nurminen method.
MK+chemo = MK-3475 + chemotherapy; Pbo+chemo= Placebo + chemotherapy.
Database Cutoff Date: 23MAR2021

Subgroup analysis for EFS (IA4)

Figure: Forest Plot of Event-Free Survival (EFS) by Subgroup Factors All Participants (ITT Population)





Analysis (HR and 95% CI) in the overall population and PD-L1 subgroup is based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly); for other subgroups, analysis is based on the unstratified Cox model.
If patients have missing values in the subgroup category variable, then they are not included in the subgroup analysis.
MK+chemo/MK = MK-3475 + chemotherapy / MK-3475; Pbo+chemo/Pbo = Placebo + chemotherapy / Placebo.
Database Cutoff Date: 23MAR2021

Table: Statistical Test for Interaction between Treatment and Subgroup Variables

INTERACTION	Two-sided P-Value
Treatment*Nodal Status	0.7132
Treatment*Tumor Size	0.0810
Treatment*Choice of Carboplatin (Cb)	0.8041
Treatment*PD-L1 CPS 1 Cutoff	0.2677
Treatment*PD-L1 CPS 10 Cutoff	0.4077
Treatment*PD-L1 CPS 20 Cutoff	0.1667

INTERACTION	Two-sided P-Value
Treatment*Overall Stage	0.6594
Treatment*Menopausal status	0.8879
Treatment*Age	0.5049
Treatment*Geographic region	0.1843
Treatment*Ethnic origin	0.5241
Treatment*ECOG performance status	0.4117
Treatment*HER2 status	0.5367
Treatment*LDH	0.9656
A Cox regression model with covariates of treatment, a subgroup variable, and treatment by subgroup variable interaction was performed for each subgroup variable separately.	

Summary of results according to PD-L1 expression status

In the ITT population, overall 82.9% of patients were PD-L1 CPS≥1, 48.6% were PD-L1 CPS≥10, and 31.3% were PD-L1 CPS≥20. PD-L1 status was not a stratification factor. Assessment of pCR, EFS and OS in PD-L1 positive population (CPS≥1) were among secondary endpoints, but not included in the multiplicity strategy.

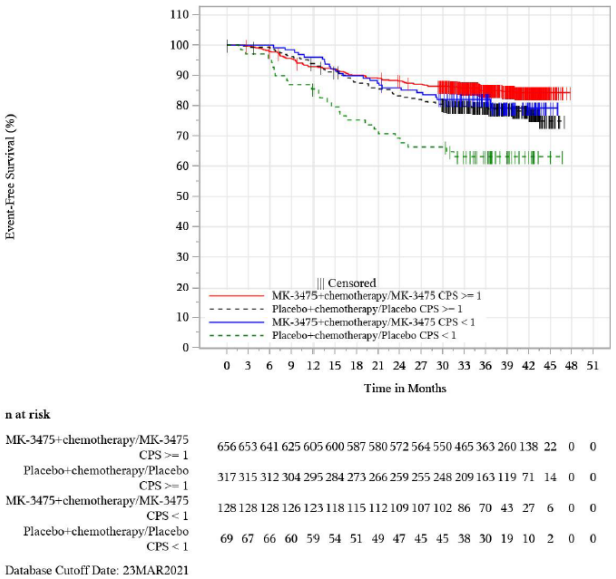
pCR by PD-L1 status (IA2):

	MK-3475 + chemotherapy			Placebo + chemotherapy			MK-3475 + chemotherapy vs Placebo + chemotherapy
	N	Number of pCR	pCR Rate %(95% CI)	N	Number of pCR	pCR Rate %(95% CI)	Difference in % (95% CI)[7]
Overall	669	428	64.0 (60.2, 67.6)	333	182	54.7 (49.1, 60.1)	9.2 (2.8, 15.6)
Tumor PD-L1 status							
PD-L1 (+)	560	376	67.1 (63.1, 71.0)	271	158	58.3 (52.2, 64.2)	9.0 (2.1, 16.0)
PD-L1 (-)	109	52	47.7 (38.1, 57.5)	59	22	37.3 (25.0, 50.9)	10.3 (-5.9, 25.7)

EFS by PD-L1 status (IA4):

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		MK-3475 + chemotherapy / MK-3475 vs. Placebo + chemotherapy / Placebo
	N	Number of Events (%)	N	Number of Events (%)	Hazard Ratio (95% CI)[8]
PD-L1 CPS 1 Cutoff					
PD-L1 CPS >= 1	656	98(14.9%)	317	68(21.5%)	0.67(0.49,0.92)
PD-L1 CPS < 1	128	25(19.5%)	69	25(36.2%)	0.48(0.28,0.85)
PD-L1 CPS 10 Cutoff					
PD-L1 CPS >= 10	393	38(9.7%)	177	30(16.9%)	0.54(0.33,0.87)
PD-L1 CPS < 10	391	85(21.7%)	209	63(30.1%)	0.69(0.50,0.96)
PD-L1 CPS 20 Cutoff					
PD-L1 CPS >= 20	247	17(6.9%)	121	19(15.7%)	0.41(0.21,0.78)
PD-L1 CPS < 20	537	106(19.7%)	265	74(27.9%)	0.68(0.50,0.91)

Kaplan-Meier Estimates of Event-Free Survival (EFS) by Tumor PD-L1 Status (CPS >=1 v CPS <1)
All Participants
(ITT Population)

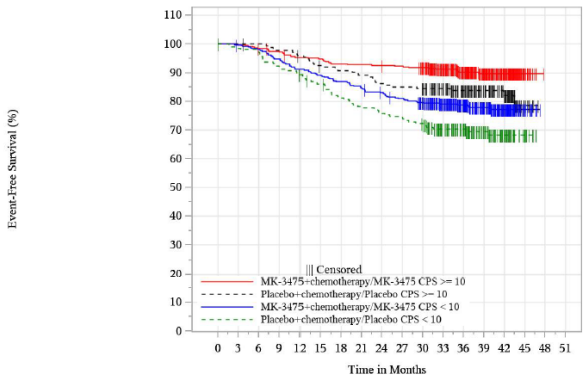


n at risk

MK-3475+chemotherapy/MK-3475 CPS >= 1	656	653	641	625	605	600	587	580	572	564	550	465	363	260	138	22	0	0
Placebo+chemotherapy/Placebo CPS >= 1	317	315	312	304	295	284	273	266	259	255	248	209	163	119	71	14	0	0
MK-3475+chemotherapy/MK-3475 CPS < 1	128	128	128	126	123	118	115	112	109	107	102	86	70	43	27	6	0	0
Placebo+chemotherapy/Placebo CPS < 1	69	67	66	60	59	54	51	49	47	45	45	38	30	19	10	2	0	0

Database Cutoff Date: 23MAR2021

Kaplan-Meier Estimates of Event-Free Survival (EFS) by Tumor PD-L1 Status (CPS >=10 vs. CPS <10)
All Participants
(ITT Population)



n at risk

MK-3475+chemotherapy/MK-3475 CPS >= 10	393	392	386	381	372	370	363	362	360	359	352	300	238	168	94	16	0	0
Placebo+chemotherapy/Placebo CPS >= 10	177	177	176	172	168	161	158	155	150	148	146	127	98	73	48	7	0	0
MK-3475+chemotherapy/MK-3475 CPS < 10	391	389	383	370	356	348	339	330	321	312	300	251	195	135	71	12	0	0
Placebo+chemotherapy/Placebo CPS < 10	209	205	202	192	186	177	166	160	156	152	147	120	95	65	33	9	0	0

Database Cutoff Date: 23MAR2021

Summary of results according to lymph node status (N)

pCR by N status (IA2):

	MK-3475 + chemotherapy			Placebo + chemotherapy			MK-3475 + chemotherapy vs Placebo + chemotherapy
	N	Number of pCR	pCR Rate %(95% CI)	N	Number of pCR	pCR Rate %(95% CI)	Difference in % (95% CI)[†]
Overall	669	428	64.0 (60.2, 67.6)	333	182	54.7 (49.1, 60.1)	9.2 (2.8, 15.6)
Nodal status							
Positive	349	219	62.8 (57.4, 67.8)	167	83	49.7 (41.9, 57.5)	13.1 (3.9, 22.1)
Negative	320	209	65.3 (59.8, 70.5)	166	99	59.6 (51.8, 67.2)	5.7 (-3.3, 14.8)

EFS by N status (IA4):

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		MK-3475 + chemotherapy / MK-3475 vs. Placebo + chemotherapy / Placebo
	N	Number of Events (%)	N	Number of Events (%)	Hazard Ratio (95% CI)[a]
Overall	784	123(15.7%)	390	93(23.8%)	0.63(0.48,0.82)
Nodal status					
Positive	408	80(19.6%)	196	57(29.1%)	0.65(0.46,0.91)
Negative	376	43(11.4%)	194	36(18.6%)	0.58(0.37,0.91)

Summary of results according to tumor size (T stage)

pCR by T stage (IA2):

	MK-3475 + chemotherapy			Placebo + chemotherapy			MK-3475 + chemotherapy vs Placebo + chemotherapy
	N	Number of pCR	pCR Rate %(95% CI)	N	Number of pCR	pCR Rate %(95% CI)	Difference in % (95% CI)[†]
Tumor size							
T1/T2	496	341	68.8 (64.5, 72.8)	246	145	58.9 (52.5, 65.2)	9.8 (2.5, 17.2)
T3/T4	173	87	50.3 (42.6, 58.0)	87	37	42.5 (32.0, 53.6)	7.8 (-5.1, 20.2)

EFS by T stage status (IA4):

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		MK-3475 + chemotherapy / MK-3475 vs. Placebo + chemotherapy / Placebo
	N	Number of Events (%)	N	Number of Events (%)	Hazard Ratio (95% CI)[a]
Tumor size					
T1/T2	581	64(11.0%)	290	59(20.3%)	0.51(0.36,0.73)
T3/T4	203	59(29.1%)	100	34(34.0%)	0.84(0.55,1.28)

Summary of results according to stage

pCR by stage (IA4):

	MK-3475 + chemotherapy			Placebo + chemotherapy			MK-3475 + chemotherapy vs Placebo + chemotherapy
	N	Number of pCR	pCR Rate %(95% CI)	N	Number of pCR	pCR Rate %(95% CI)	Difference in % (95% CI)[a]
Overall Stage							
Stage II	590	385	65.3 (61.3, 69.1)	291	173	59.5 (53.6, 65.1)	5.8 (-1.0, 12.7)
Stage III	194	109	56.2 (48.9, 63.3)	98	43	43.9 (33.9, 54.3)	12.3 (0.2, 24.1)

EFS by stage (IA4):

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		MK-3475 + chemotherapy / MK-3475 vs. Placebo + chemotherapy / Placebo
	N	Number of Events (%)	N	Number of Events (%)	Hazard Ratio (95% CI)[a]
Overall Stage					
Stage II	590	69(11.7%)	291	54(18.6%)	0.60(0.42,0.86)
Stage III	194	54(27.8%)	98	39(39.8%)	0.68(0.45,1.03)

Overall Stage					
Stage II	590	39(6.6%)	291	26(8.9%)	0.73(0.45,1.20)
Stage III	194	41(21.1%)	98	29(29.6%)	0.73(0.45,1.17)

Summary of results according to region

pCR by region (IA2):

	MK-3475 + chemotherapy			Placebo + chemotherapy			MK-3475 + chemotherapy vs Placebo + chemotherapy
	N	Number of pCR	pCR Rate %(95% CI)	N	Number of pCR	pCR Rate %(95% CI)	Difference in % (95% CI)[T]
Geographic region							
Asia	118	69	58.5 (49.0, 67.5)	68	28	41.2 (29.4, 53.8)	17.3 (2.3, 31.4)
Europe/Israel/North America/Australia	514	336	65.4 (61.1, 69.5)	243	144	59.3 (52.8, 65.5)	6.1 (-1.2, 13.6)
Rest of World	37	23	62.2 (44.8, 77.5)	22	10	45.5 (24.4, 67.8)	16.7 (-9.4, 41.0)

EFS by region (IA4):

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		MK-3475 + chemotherapy / MK-3475 vs. Placebo + chemotherapy / Placebo
	N	Number of Events (%)	N	Number of Events (%)	Hazard Ratio (95% CI)[a]
Geographic region					
Europe/Israel/North America/Australia	607	98(16.1%)	285	65(22.8%)	0.69(0.50,0.94)
Asia	136	13(9.6%)	80	20(25.0%)	0.35(0.17,0.71)
Rest of World	41	12(29.3%)	25	8(32.0%)	0.81(0.33,1.98)

Summary of results according to age

pCR by age (IA2):

	MK-3475 + chemotherapy			Placebo + chemotherapy			MK-3475 + chemotherapy vs Placebo + chemotherapy
	N	Number of pCR	pCR Rate %(95% CI)	N	Number of pCR	pCR Rate %(95% CI)	Difference in % (95% CI)[T]
Age Category							
< 65 years	590	387	65.6 (61.6, 69.4)	293	165	56.3 (50.4, 62.1)	9.3 (2.5, 16.1)
≥ 65 years	79	41	51.9 (40.4, 63.3)	40	17	42.5 (27.0, 59.1)	9.4 (-9.6, 27.5)

EFS by age (IA4):

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		MK-3475 + chemotherapy / MK-3475 vs. Placebo + chemotherapy / Placebo
	N	Number of Events (%)	N	Number of Events (%)	Hazard Ratio (95% CI)[a]
Age					
< 65 years	700	103(14.7%)	342	79(23.1%)	0.61(0.45,0.82)
>= 65 years	84	20(23.8%)	48	14(29.2%)	0.79(0.40,1.56)

Age					
< 65 years	700	65(9.3%)	342	45(13.2%)	0.71(0.48,1.03)
>= 65 years	84	15(17.9%)	48	10(20.8%)	0.83(0.37,1.85)

Post-hoc subgroup analysis by **age <40 and ≥40** (n=185 vs 89 patients):

- pCR difference -1.1 (95% CI: -13.5, 12.2)

- EFS HR of 0.74 (95% CI: 0.39, 1.38)

Baseline characteristics in patients < and >=40 years appeared overall well balanced between treatment arms, with the exception of slightly higher number of patients with nodal positive status in the experimental arm (55.1% vs 48.3%), on the contrary slightly more patients with stage II disease in the experimental arm (73.5% vs 68.5%), of unclear impact on results.

Pre-specified sensitivity analyses for Event free survival

- Sensitivity analysis 1: EFS HR 0.64 (95% CI: 0.48, 0.84)

Any events after 2 consecutive missed disease assessments or after initiation of post-surgery new anticancer therapy, were censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and initiation of post-surgery new anticancer therapy, and if no events before new anticancer therapy, participants were censored at last disease assessment before initiation of post-surgery new anticancer treatment.

- Sensitivity analysis 2: EFS HR 0.63 (95% CI: 0.48, 0.82)

New anticancer therapy to treat metastatic disease was also considered for defining an EFS event.

- Sensitivity analysis 3: EFS HR 0.65 (95% CI: 0.50, 0.85)

Positive margins at a participant's last surgery was excluded from the EFS event definition.

- Sensitivity analysis 4: EFS HR 0.63 (95% CI: 0.48, 0.84)

Both positive margins at a participant's last surgery and second primary malignancy were excluded from the EFS event definition.

- Sensitivity analysis 5: EFS HR 0.63 (95% CI: 0.48, 0.82)

Second breast primary malignancy was included in the EFS event definition.

- Additional sensitivity analysis: EFS HR 0.65 (95% CI: 0.50, 0.85)

positive margins at last surgery were excluded from the EFS definition and secondary breast cancer and new anticancer therapy for metastatic disease were included as EFS events.

Prespecified Exploratory Event-free Survival Analyses

A prespecified exploratory analysis of EFS by pCR (ypT0/Tis ypN0) outcome (yes vs no) was performed as an unstratified subgroup analysis. EFS showed improvement that favoured pembrolizumab + NAC / pembrolizumab for participants who achieved pCR and those participants who did not achieve pCR. pCR was highly associated with long-term outcome as measured by EFS, which is consistent with the large meta-analysis performed by Cortazar (Cortazar et al, 2014). As this analysis is a nonrandomized comparison, the results need to be interpreted with caution.

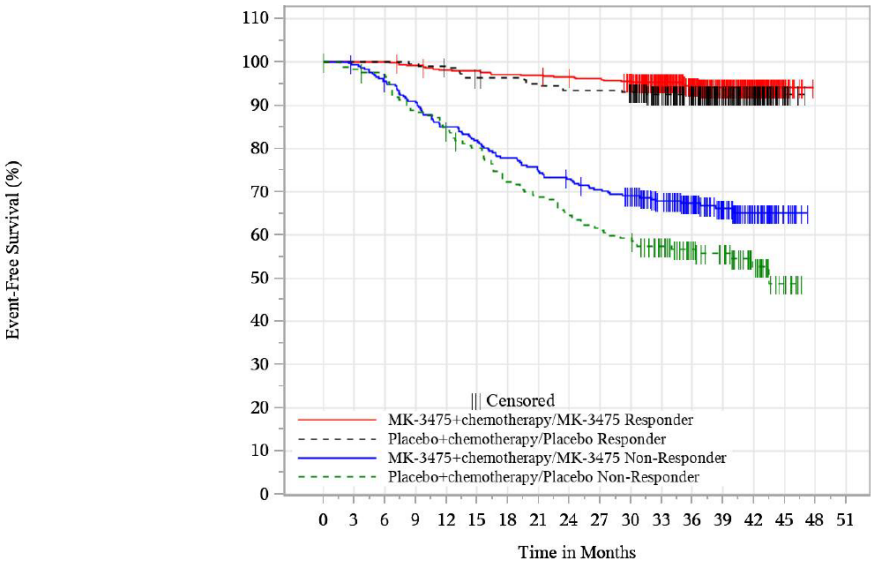
Table: unstratified analysis of EFS by pCR (ypT0/Tis ypN0) All participants (ITT population)

pCR Status		MK-3475 + chemotherapy / MK-3475	Placebo + chemotherapy / Placebo	Total
Responder	N	494	217	711
	Number of Events (%)	27 (5.5)	16 (7.4)	43 (6.0)
	Number of Censored (%)	467 (94.5)	201 (92.6)	668 (94.0)
	Kaplan-Meier Estimates (Months)[a]			
	Median (95% CI)	(,)	(,)	(,)
	Q1, Q3	,	,	,
	Person-Months	18,259.5	7,878.8	26,138.3
	Event Rate / 100 Person-Months	0.1	0.2	0.2
	EFS Rate at 6 Months (%) (95% CI)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
	EFS Rate at 12 Months (%) (95% CI)	98.2 (96.5, 99.0)	99.1 (96.4, 99.8)	98.5 (97.2, 99.1)
	EFS Rate at 18 Months (%) (95% CI)	97.2 (95.2, 98.3)	96.3 (92.7, 98.1)	96.9 (95.3, 97.9)
	EFS Rate at 24 Months (%) (95% CI)	96.5 (94.5, 97.8)	93.5 (89.3, 96.1)	95.6 (93.8, 96.9)
	EFS Rate at 30 Months (%) (95% CI)	95.5 (93.3, 97.0)	93.0 (88.7, 95.7)	94.8 (92.8, 96.2)
	EFS Rate at 36 Months (%) (95% CI)	94.4 (91.9, 96.2)	92.5 (88.1, 95.3)	93.9 (91.8, 95.4)
	EFS Rate at 42 Months (%) (95% CI)	94.1 (91.5, 96.0)	92.5 (88.1, 95.3)	93.6 (91.5, 95.3)
	vs Placebo + chemotherapy / Placebo			
	Hazard Ratio (95% CI)[b]	0.73 (0.39, 1.36)		
	p-value[c]	0.1583		

pCR Status		MK-3475 + chemotherapy / MK-3475	Placebo + chemotherapy / Placebo	Total
Non-Responder	N	290	173	463
	Number of Events (%)	96 (33.1)	77 (44.5)	173 (37.4)
	Number of Censored (%)	194 (66.9)	96 (55.5)	290 (62.6)
	Kaplan-Meier Estimates (Months)[a]			
	Median (95% CI)	(,)	43.5 (30.6,)	(,)
	Q1, Q3	21.0,	16.6,	19.2,
	Person-Months	8,735.1	4,905.0	13,640.1
	Event Rate / 100 Person-Months	1.1	1.6	1.3
	EFS Rate at 6 Months (%) (95% CI)	95.5 (92.4, 97.4)	96.5 (92.4, 98.4)	95.9 (93.6, 97.3)
	EFS Rate at 12 Months (%) (95% CI)	85.1 (80.4, 88.7)	84.2 (77.8, 88.9)	84.8 (81.1, 87.7)
	EFS Rate at 18 Months (%) (95% CI)	77.8 (72.5, 82.2)	72.4 (65.0, 78.5)	75.8 (71.6, 79.4)
	EFS Rate at 24 Months (%) (95% CI)	72.9 (67.4, 77.7)	65.3 (57.6, 71.9)	70.1 (65.7, 74.1)
	EFS Rate at 30 Months (%) (95% CI)	69.1 (63.4, 74.1)	59.3 (51.5, 66.3)	65.5 (60.9, 69.6)
	EFS Rate at 36 Months (%) (95% CI)	67.4 (61.6, 72.5)	56.8 (49.0, 63.9)	63.5 (58.9, 67.7)
	EFS Rate at 42 Months (%) (95% CI)	65.2 (59.0, 70.7)	52.7 (44.0, 60.7)	60.5 (55.4, 65.2)
	vs Placebo + chemotherapy / Placebo			
	Hazard Ratio (95% CI)[b]	0.70 (0.52, 0.95)		
	p-value[c]	0.0104		

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
Database Cutoff Date: 23MAR2021

Kaplan-Meier Estimates of Event-Free Survival (EFS) by pCR (ypT0/Tis ypN0)
All Participants
(ITT Population)



n at risk

MK-3475+chemotherapy/MK-3475 Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Placebo+chemotherapy/Placebo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
MK-3475+chemotherapy/MK-3475 Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Placebo+chemotherapy/Placebo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

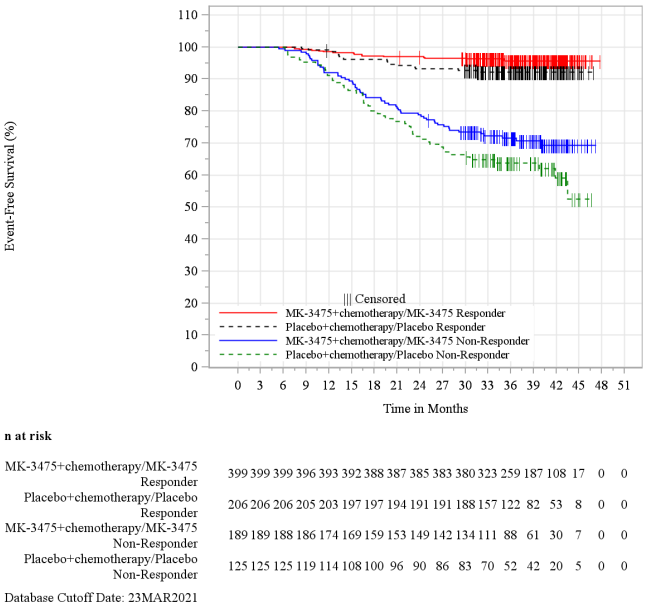
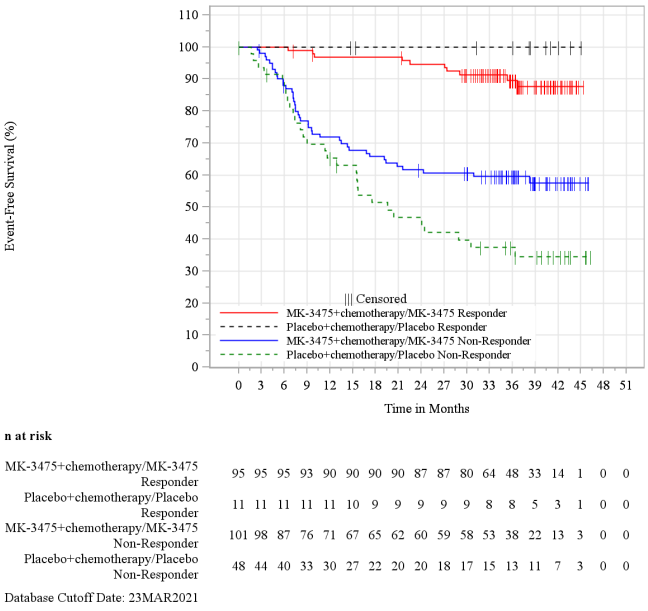
Database Cutoff Date: 23MAR2021

Summary of First Event in EFS Analyses by pCR (ypT0/Tis ypN0)
All Participants
(ITT Population)

pCR Status		MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
Responder	N	494		217		711	
	Any EFS Event	27	(5.5)	16	(7.4)	43	(6.0)
	Secondary Primary Malignancy	1	(0.2)	0	(0.0)	1	(0.1)
	Local Recurrence	3	(0.6)	3	(1.4)	6	(0.8)
	Distant Recurrence	17	(3.4)	12	(5.5)	29	(4.1)
	Death	6	(1.2)	1	(0.5)	7	(1.0)
Non-Responder	N	290		173		463	
	Any EFS Event	96	(33.1)	77	(44.5)	173	(37.4)
	Secondary Primary Malignancy	5	(1.7)	4	(2.3)	9	(1.9)
	Local PD Precludes Surgery	3	(1.0)	4	(2.3)	7	(1.5)
	Local PD Precludes Definitive Surgery	1	(0.3)	0	(0.0)	1	(0.2)
	Distant PD	4	(1.4)	1	(0.6)	5	(1.1)
	Positive Margin at Last Surgery	6	(2.1)	10	(5.8)	16	(3.5)
	Local Recurrence	25	(8.6)	14	(8.1)	39	(8.4)
	Distant Recurrence	43	(14.8)	39	(22.5)	82	(17.7)
	Death	9	(3.1)	5	(2.9)	14	(3.0)
Database Cutoff Date: 23MAR2021							

Post-hoc exploratory analyses for EFS by responders vs non responders for patients who continued with adjuvant treatment compared to patients who did not start adjuvant treatment are presented below:

Figure: Kaplan-Meier Estimates of Event-Free Survival (EFS) by pCR (ypT0/Tis ypN0) and Treatment Participants Who Started or not started Adjuvant Treatment (ITT Population)

Patients who started adjuvant treatment	Patients who did not start adjuvant treatment
	

Summary of main study(ies)

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 1. Summary of Efficacy for KEYNOTE-522

Title: A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (TNBC)		
Study identifier	MK-3475-522 (P522V03MK3475; IND: 124,442; EudraCT: 2016-004740-11; NCT: 03036488)	
Design	Phase 3, randomized, multicenter, double-blind, placebo-controlled study	
	Duration of main phase:	The first patient first visit occurred on 07-MAR-2017; last patient enrolled 28 -SEP-2018. Data cutoff for IA4: 23-MAR-2021; Study is ongoing
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority	
Treatments groups	Pembrolizumab + NAC / pembrolizumab N=784	**Neoadjuvant therapy prior to surgery:** 4 cycles of pembrolizumab 200 mg or placebo Q3W + paclitaxel 80 mg/m^2 QW + carboplatin (AUC 5 Q3W or AUC 1.5 QW); Followed by 4 cycles of pembrolizumab 200 mg or placebo Q3W + (doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2) Q3W +
	Placebo + NAC / placebo N=390	

			cyclophosphamide 600 mg/m^2 Q3W **Adjuvant therapy post-surgery:** 9 cycles of pembrolizumab 200 mg or placebo Q3W
Endpoints and definitions	Dual Primary endpoint	pCR (ypT0/Tis ypN0)	pCR rate (ypT0/Tis ypN0), defined as the proportion of participants without residual invasive cancer on hematoxylin and eosin (H&E) evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy by AJCC staging criteria assessed by the local pathologist at the time of definitive surgery
	Dual Primary endpoint	EFS	EFS, defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause
	Key Secondary endpoint	OS	OS, defined as the time from randomization to death due to any cause
Database lock	24-APR-2019 (IA2; final pCR analysis); 23-MAR-2021 (IA4; all prespecified efficacy analyses)		

Results and Analysis

Analysis description	**Primary Analysis - pCR (ypT0/Tis ypN0) at IA2 (final analysis for pCR)**		
Analysis population and time point description	Intent-to-treat IA2 population (First 1002 participants randomly assigned to study treatment who were eligible for the analysis of pCR at IA2 (24-APR-2019 data cutoff))		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + NAC	Placebo + NAC
	Number of subjects	669	333
	pCR rate (%)	64	54.7
	95% CI	60.2, 67.6	49.1, 60.1
Effect estimate per comparison	pCR (dual primary endpoint)	Comparison groups	Pembrolizumab + NAC Placebo + NAC
		Estimated Treatment Difference (%), IA2	9.2
		95% CI	2.8, 15.6
		P-value	0.00221
Notes	KEYNOTE-522 met the success criterion for the primary hypothesis of pCR at IA1. At IA2, the updated data continue to be statistically significant (prespecified p-value boundary of 0.0028).		

Analysis description	**Primary Analysis - EFS at IA4**		
Analysis population and time point description	Intent-to-treat IA4 (data cutoff 23-MAR-2021)		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + NAC / Pembrolizumab	Placebo + NAC / Placebo
	Number of subjects	784	390
	EFS rate at 24 months (%)	87.8	81.0
	95% CI	85.3, 89.9	76.8, 84.6
	EFS rate at 36 months (%)	84.5	76.8
	95% CI	81.7, 86.9	72.2, 80.7
Effect estimate per comparison	EFS (dual primary endpoint)	Comparison groups	Pembrolizumab + NAC / pembrolizumab Placebo + NAC / placebo

		HR	0.63
		95% CI	0.48, 0.82
		P-value	0.0003093†
Notes	At IA4, KEYNOTE-522 met the success criterion for the primary EFS hypothesis. † The result was statistically significant compared with the prespecified p-value boundary of 0.00516941.		
Analysis description	**Key Secondary analysis – OS at IA4**		
Analysis population and time point description	Intent-to-treat IA4 (data cutoff 23-MAR-2021)		
Descriptive statistics and estimate variability	Treatment group	Pembrolizumab + NAC / Pembrolizumab	Placebo + NAC / Placebo
	Number of subjects	784	390
	OS rate at 24 months (%)	92.3	91.0
	95% CI	90.2, 94.0	87.7, 93.5
Effect estimate per comparison	OS (key secondary endpoint)	Comparison groups	Pembrolizumab + NAC / pembrolizumab Placebo + NAC / placebo
		HR	0.72
		95% CI	0.51, 1.02
		P-value	0.0321377‡
Notes	‡ The result did not reach statistical significance compared with the prespecified p-value boundary of 0.00085861.		

2.4.2. Discussion on clinical efficacy

The applicant is seeking an extension of indication for Keytruda in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adult patients with locally advanced, inflammatory, or early-stage triple-negative breast cancer (TNBC) at high-risk of recurrence. This submission is based on the final analysis of pCR and on an interim analysis of EFS of the pivotal study KEYNOTE-522.

Design and conduct of clinical studies

KEYNOTE-522 is a phase III, randomized (2:1), double-blind study to evaluate pembrolizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs placebo as adjuvant therapy for TNBC.

Adult patient with centrally confirmed non metastatic TNBC were included. According to protocol, subjects must have evidence of M0 disease based on the assessments from their initial diagnosis, and if suspected regional or distant metastasis during screening, subjects should have been thoroughly evaluated as clinically indicated. Inclusion was allowed for tumour size >1 cm but ≤2 cm in diameter (T1c) with nodal involvement (N1-2) or tumour size > 2 cm in diameter (T2-4) regardless of nodal involvement (N0-2), corresponding to stage IIB-IIIA/B. According to guidelines, neoadjuvant chemotherapy is the preferred choice for stage II and III TNBC (Burstein, 2021). The study excluded stage I (and stage IIA); for stage I adjuvant therapy is preferred according to guidelines (Burstein, 2021). The inclusion/exclusion criteria are considered overall acceptable and define a patient population for whom (neo)adjuvant treatment is clearly indicated. However, according to treatment guidelines for subjects with T1C tumors (> 1cm) treatment is also recommended without lymph node involvement (and treatment should be considered for tumor ≥ 0.6 cm). Nonetheless, the exclusion of

these subjects with a lower risk of recurrence in the pivotal study can be considered acceptable. The studied population is reflected in the proposed wording of the indication "locally advanced, or early-stage TNBC at high-risk of recurrence", with details of the tumor size (in cm) and nodal status reported in section 5.1 of the SmPC (a reference to section 5.1 has been included in the indication wording in 4.1 of the SmPC).

Patients were enrolled regardless PD-L1 status, which was centrally assessed in archival or newly obtained formalin-fixed tumor samples collected prior to any treatment by means of the PD-L1 IHC 22C3 pharmDx assay. PD-L1 was not a stratification factor, although assessment of pCR, EFS, OS and QoL data were predefined in individuals with PD-L1 (+) tumors (CPS ≥1) as secondary endpoints. Nonetheless, distribution by PD-L1 status with CPS 1 cutoff appears balanced between treatment arms (83.7% vs 81.3% CPS ≥1 in the pembrolizumab vs the placebo arm). The stratification factors were instead choice of tumor size and lymph node status, which is justified as both factors are prognostic and correlated with outcome, and smaller tumors/N0 disease are more likely to obtain pCR. The stratification factor weekly vs 3-weekly dosing of carboplatin was based on potential difference in tolerability which may affect the ability of patients to complete prescribed regimens and ultimately efficacy outcome. The stratification factors are deemed acceptable.

The backbone chemotherapy used in the neoadjuvant part of the treatment consisted in four cycles (12 weeks) of carboplatin (given weekly or 3 weekly) plus paclitaxel weekly followed by four cycles (12 weeks) of 3 weekly doxorubicin or epirubicin plus cyclophosphamide (not dose dense). Granulocyte-colony stimulating factor (G-CSF) was administered after each cycle of chemotherapy, although its use was recommended but not mandated. Within 3-6 weeks from end of neoadjuvant treatment, breast surgery was performed, after that adjuvant treatment with pembrolizumab/placebo 3 weekly for 9 cycles (27 weeks) was administered, for a total of approximately 1 year of systemic therapy. The trend of 1-year adjuvant immunotherapy has been established by convenience, not necessarily based on precise cancer growth kinetic models.

Postoperative radiation therapy was given in accordance with the standard of care, as applicable, in 54.1% in the pembrolizumab arm vs 64.1% in the control arm, in most cases sequentially.

The justification for the choice of the backbone chemotherapy regimen is acknowledged. The treatment intensification by the addition of carboplatin to paclitaxel in the neoadjuvant TNBC setting has shown an increased pCR rate according to literature, although with no consistent EFS improvement, and at the expenses of worse haematological toxicity (Loibl S, 2021; Poggio, 2018; Pandy, 2019), so the inclusion of platinum agents as neoadjuvant chemotherapy for TNBC remains controversial (Burstein HJ, 2021; NCCN 2021). The inclusion of carboplatin, equally in both treatment arms, is acceptable. AC was administered every 3 weeks, and not as dose-dense regimen every 2 weeks (Burstein HJ, 2021; NCCN 2021). The treatment with dose-dense regimens with primary prophylaxis is overall considered a standard of care for high-risk, early breast cancer. The EBCTCG metanalysis (Gray, 2019) demonstrated an impact of dose-dense regimens on recurrence-free, breast-specific and overall survival. For the type and comorbidity burden of patients enrolled in the clinical trial object of this application, the population is generally deemed eligible to ddAC (Burstein, St Gallen, 2021). Based on the analysis of data on drug, no relevant differences in exposure between arms have been however observed that could affect the ultimate results.

Regarding the adjuvant phase, capecitabine is an option for patients with residual invasive cancer after neoadjuvant therapy in TNBC (Burstein, 2021; NCCN, 2021). Patients without achieving pCR were not offered the option to be treated with capecitabine; however, this was not yet definitely recommended at the start of the trial therefore can be considered acceptable. The decision not to allow adjuvant capecitabine was agreed with FDA in 2017 so as not to confound the final results. Further, recent evidence showed that adjuvant therapy with olaparib for 1 year extended DFS in patients with high-

risk early-stage HER2-negative breast cancer (including TNBC) with BRCA1/2 germline mutations (and no pathological complete response if neoadjuvant therapy was administered), according to the phase III OlympiA trial (Tutt, 2021). However, at the time of study design such options were not included in treatment guidelines (Senkus, 2015), so the comparison vs placebo is accepted.

KEYNOTE-522 study is designed to evaluate whether the addition of pembrolizumab as a neoadjuvant and adjuvant treatment is beneficial compared to standard neoadjuvant chemotherapy. Patients were not re-randomized by pCR status after surgery. By this design, it is not possible to disentangle the contribution of pembrolizumab in the neoadjuvant and adjuvant setting on the EFS and OS outcome, nor to correlate the impact of the observed pCR improvement with the EFS outcome. Regrettably, the MAH did not request CHMP Scientific Advice before designing this study. It is therefore uncertain whether neoadjuvant and/or adjuvant pembrolizumab are both needed, but any conclusion in this regard is impossible based on this pivotal study. No other ongoing pembrolizumab trials in TNBC would be able to clarify this aspect. As a result, it is considered that the data provided may only be discussed for a possible indication for pembrolizumab as neoadjuvant AND adjuvant treatment.

The study had dual primary endpoint of pCR and EFS. OS was a secondary endpoint. The primary definition of pCR (ypT0/Tis ypN0) is in line with current EMA guidelines (EMA/CHMP/703715/2012 Rev. 2) and thus acceptable. pCR according to alternative definitions were analysed, and results were in line with the primary analyses. The definition of EFS (time from randomization to the first occurrence of progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy or death due to any cause) is considered acceptable as well. The definition of EFS was refined with protocol Amendment 2 with the inclusion of positive surgical margins as EFS events. Second breast primary malignancy were instead excluded from the EFS definition. Sensitivity analyses, excluding positive margin as event and including primary breast cancer as event, respectively, were reassuringly consistent with the primary analysis.

Primary endpoints were not verified: pCR was assessed by the local pathologist and EFS was assessed by the investigator; in this context it is of concern that "imaging (eg, CT, MRI, Bone Scan) were performed at the discretion of the investigator", although it is acceptable that the timing of clinical disease assessment was defined at specific timepoints and same in each arm. It is acknowledged that the study has been conducted double-blind for the neoadjuvant and the adjuvant part; nonetheless treatment assignment might be suggested due to differences in toxicities at least in the adjuvant treatment phase. The fact that imaging was performed at investigator's discretion is relevant for EFS analysis, especially with regard to the assessment of distant metastases. However, the double-blind design and additional data provided during the procedure did not raise concern over any relevant impact on results.

Sample size calculation was driven by EFS. For sample size calculation for pCR rate, a sample size of ~1000 gives ~95% power to detect a true pCR rate difference of 15% at alpha = 0.5% (one-sided). For sample size calculation for EFS, with the alpha of 2% (one-sided) and sample size of ~1150, the trial has an overall ~80% power for EFS, assuming the true HR is 0.71. The assumption for EFS was updated with Amendment 2 (occurred before IA1) leading to an increased sample size from 855 to 1150, and the justification provided was deemed acceptable.

Multiplicity strategies were adopted for control type I error. The overall type-I error rate over the dual primary endpoints was 2.5% (one-sided) with 0.5% allocated to pCR (ypT0/Tis ypN0) and 2.0% allocated to EFS hypotheses according to Maurer and Bretz approach.

Statistical methods appear overall appropriate.

Efficacy data and additional analyses

A total of 1174 participants were randomized (784 in the experimental arm and 390 in the control arm). As of data cutoff for Interim analysis 4 (IA4), no participants remained on study intervention. An overall higher proportion of discontinuation from all treatments in the pembrolizumab arm compared to the placebo arm (37.1% vs 27.2%). This difference is driven by discontinuation due to AEs in the neoadjuvant setting (14.3% in the pembrolizumab arm vs. 5.1% in the placebo arm) highlighting an impact of the additional toxicity of pembrolizumab.

The overall number of clinically important protocol deviations appears limited, and no relevant impact on the study results is envisaged.

Overall, the baseline characteristics appear balanced between treatment groups. The majority of randomized participants were female (only 1 male in the experimental arm), with median age of 49 years (<65 years 89%), white (63.5%), premenopausal (56%), and with ECOG PS 0 (87%); about half of the patients were enrolled in Europe. Regarding disease characteristics, the most common tumor size was T2 (68%), approximately half were node negative, with 75% of subjects with overall Stage II disease. With regard to PD-L1 expression, most participants (83%) had a CPS ≥1, treatment arms appear overall balanced for PD-L1 expression at various cut-off analysed (1, 10 and 20). Carboplatin was administered weekly in 57% of the patients; the use of doxorubicin (67%) or epirubicin was balanced.

The MAH has submitted the results of the IA4 (data cut-off date 23 March 2021), with a median follow-up duration of approximately 37 months.

Baseline characteristics of responders (i.e. yes pCR) and non-responders (i.e. no pCR) appear overall similar between treatment arms (data not shown). As compared to responders, non-responders were older, mostly post-menopausal, and more patients had more advanced tumors (stage III and tumor size T3/4). Further, there were more patients with tumor having a PD-L1 expression below a certain cut-off (1, 10, 20) among non-responders than among responders. No relevant differences are noted between IA1, IA2 and IA4.

No relevant unbalances or difference in baseline characteristics of patients enrolled between IA1-IA2 and IA2-IA4 are observed. The pCR difference noted between IA1, IA2 and IA4 seems mostly related to an increase in the pCR rate in the placebo group, while the pCR rate in the pembrolizumab group remained consistent between each IA.

Pathological complete response (pCR)

There were two pre-specified analyses for the primary endpoint pCR (ypT0/Tis ypN0), an interim (at IA1) and a final analysis (at IA2). An updated descriptive analysis was provided at IA4. pCR met the predefined criteria for success at the interim analysis in 602 patients (pCR rate 64.8% vs 51.2%, Δ 13.6% (95%CI 5.4, 21.8), p=0.00055) and at the final analysis in 1002 patients (pCR rate 64% vs 54.7%, Δ 9.2% (95%CI 2.8, 15.6), p=0.00221). The descriptive analysis at IA4 including the entire ITT population (n=1174) showed pCR rate of 63% vs 55.6%, Δ 7.5% (95%CI 1.6, 13.4).

The target Δ pCR between arms at the final analysis was 15%, but the point estimate was 9.2%, with the upper bound of CI minimally above the target (15.6%). The lower bond of CIs are disappointing (improvement in pCR rate of 2.8% at the final analysis, 1.6% at updated analysis). Acknowledging that pCR reached statistical significance, the clinical relevance of this result is questioned. The decreasing pCR difference noted between IA1, IA2 and IA4 seems mostly related to an increase in the pCR rate in the placebo group, while the pCR rate in the pembrolizumab group remained consistent between each IA. No relevant unbalances or difference in baseline characteristics of additional patients included in the subsequent analyses are observed. As compared to responders, non-responders were

older, mostly post-menopausal, and more patients had more advanced tumors (stage III and tumor size T3/4). Further, there were more patients with tumor having a PD-L1 expression below a certain cut-off (1, 10, 20) among non-responders than among responders.

A pCR analyses according to alternative definitions (ypT0 ypN0, and ypT0/Tis) was consistent with the primary pCR analysis.

Event Free Survival (EFS)

At the IA4, EFS in the pembrolizumab + NAC / pembrolizumab group had an HR of 0.63 (95% CI: 0.48, 0.82), with a one-sided p-value of 0.0003093 that crossed the prespecified boundary for statistical significance (0.00516941). Such analysis is based on a not very high number of events (15.7% vs 23.8% in the experimental vs the control arm, respectively), corresponding to approximately 66% of EFS planned events for final analysis. EFS rate at 24 months was 87.8% (85.3, 89.9) vs 81% (76.8, 84.6), and at 30 months 85.8% (83.1, 88) vs 78.2% (73.7, 82). KM curves separate at month 12 and progressively diverge in favour of the pembrolizumab-containing arm, although curves are no more interpretable after month 30 due to censoring.

Most of the EFS events in both arms were distant recurrence (7.7% vs 13.1% in pembrolizumab vs placebo-containing arm, i.e. 49% vs 54.8% of the total EFS event in each respective arm). The most common sites for distant PD or distant recurrence as the first EFS event in both treatment groups were lung, brain, bone, liver and distant lymph node. In the neoadjuvant phase, there were 5 participants in the pembrolizumab + NAC group vs only 1 in the placebo + NACT who had an event of death recorded as the first EFS event within 90 days of the last treatment and in the adjuvant phase 2 vs 0. Death was considered treatment-related by investigator (pneumonitis in 1 participant in the neoadjuvant phase, pulmonary embolism in 1 participant in the adjuvant phase, and autoimmune encephalitis in 1 participant in the adjuvant phase related to pembrolizumab; septic shock in the neoadjuvant phase related to chemotherapy in the control arm). No safety signals were identified upon review of these fatal events.

The provided DFS analysis at IA4 has been performed when all patients have completed/discontinued all treatment. As the last patient was randomized approximately 2.5 years before the analysis, all subjects were observed for at least one year out of treatment, and this is important especially as an active adjuvant therapy was compared to no treatment (last patient randomized on 24-SEP-2018, data cut-off date 23-MAR-2021 for the analysis, for an overall estimated duration of treatment of 1-1.5 years including surgery).

Further, the peak of recurrence in TNBC is within the first 2-3 years after initial diagnosis, decreasing thereafter (Dent, 2007; Lin, 2012). The median follow-up time at IA4 is approximately 37.6 months so most of the highest risk period would have been observed. However, EFS curves are no more interpretable after month 30 and at visual inspection a plateau has not yet been reached, the latter relevant in the context of a curative treatment. It is on the other hand reassuring that the results of prior EFS interim analyses are consistent with the latest one with regard to the direction of the curves.

Taking all aspects above into account, the EFS benefit showed in KEYNOTE-522 is recognized and it has been assessed at a reasonable timepoint; although updated EFS data might provide further reassurance, EFS data appear stable, and it is considered unlikely that subsequent EFS interim analysis (next due in March 2023) will relevantly change the overall result.

Overall survival (OS)

OS was formally tested at IA4 per prespecified multiplicity strategy, but statistical significance was not met. With 10.2% vs 14.1% of OS events in the experimental vs the control arm (45% of the events needed for final analysis), OS HR was 0.72 (95%CI 0.51, 1.02), p=0.0321377. OS rate at 24 months

were 92.3% (95%CI 90.2, 94) vs 91% (95%CI 87.7, 93.5). KM curves are almost superimposed up to month 30, after that, curves are no more interpretable due to censoring. No conclusion can be drawn yet on OS due to the immaturity of the data. An earlier interim OS showed higher initial event/rate in the experimental compared to the control arm. OS KM curves indicated a slightly worse performance compared to the control arm in the first months. This is further corroborated by the result of an immature OS analysis performed at IA2 (data cut-off 24 Apr 2019), showing 31 (4%) v 15 (3.8%) OS events in the experimental vs control arm, respectively, HR of 1.09 (95%CI 0.59, 2.02). Therefore, additional details on deaths were provided and it was further observed that a total of 7 patients died within <=6 months from randomization, mostly in the experimental arm (6 vs 1), and additional 20 patients died within 6 -12 months from randomization, again mostly in the experimental arm (16 vs 4). The number of deaths in the experimental vs control arm, in the first 12 months from randomization (22 vs 5 overall), occurred for progression (14 vs 4) or AEs (7 vs 1) and are not particularly reassuring in the context of a curative setting. Unfortunately, the 2:1 randomization did not help in the safety assessment. As for safety, the worse toxicity of the combination pembrolizumab plus chemotherapy played a role, however no trend for specific AEs driving toxicity in the neoadjuvant setting is observed. The MAH noted that 5 patients who died early in the experimental arm out of 22 were enrolled in Russia (4 from a site which was closed early), and subjects enrolled in Russia had baseline characteristics suggestive of worse prognosis as compared to patients enrolled in non-Russian sites, enrolled more commonly in the experimental arm (study was not stratified by region). Due to the small number of patients, the reason for this difference of deaths between treatment arms might be multifactorial and partly due to chance.

Health-related QoL

Quality of life was affected more in the neoadjuvant part than during the adjuvant phase in both arms, as expected based on the treatment load. Based on the data provided, it is agreed with the MAH that the addition of pembrolizumab to NAC followed by continued treatment with pembrolizumab as adjuvant therapy resulted in an overall similar HRQoL compared with placebo + NAC followed by continued treatment with placebo.

Exploratory Efficacy Endpoints

Distant Recurrence free survival (DRFS) and Distant Progression or Distant Recurrence-free Survival (DPDRFS) were in favour of the pembrolizumab containing arm (HR 0.60 and 0.61, respectively) and supportive of EFS data.

Pembrolizumab + NACT did not improve the rate of breast conserving surgery, and no relevant differences are observed in residual cancer burden I, II and III.

Subgroup analyses

The treatment effect in terms of pCR was generally consistent with the finding in the overall populations. The only subgroup where pCR point estimate is higher in the control arm is ECOG-PS-1, however the limited number of subjects in this subgroup preclude definitive conclusions. Similar trends are seen in OS, but the interpretation is hampered by immaturity of OS data. For EFS, HR estimates were <1 in all subgroups analysed, although in some of the subgroups the 95%CI crossed 1: T3/4, stage III, age >=65 years, region rest of the world, Hispanic ethnicity, ECOG-PS1, LDH> ULN.

PD-L1 status: An improved EFS advantage and a positive OS trend (but OS is immature) is seen in patients with higher PD-L1 expression compared to lower PD-L1 expression (for cut-off 10 and 20), while the trend is almost reversed when considering the CPS cut-off of 1. Differently, pCR improvement is similar regardless PD-L1 expression based on the cut-off of 1. Interestingly, PD-L1 positive tumors appears to have higher pCR rate with chemotherapy and overall longer survivals and

less EFS/PS events in the control arm compared to the low expressors, in line with PD-L1 status as a favourable prognostic marker in this disease according to some literature data.

Overall, a benefit for pembrolizumab based treatment compared to control treatment is seen across PD-L1 subgroups, so such data would not support restricting the indication according to PD-L1 expression. This seems different from the metastatic TNBC setting where the predictive value of PD-L1 status for pembrolizumab-based treatment was shown (KEYNOTE-355 and KEYNOTE-119 studies). However, results according to PD-L1 expression are not clearly interpretable and appear not consistent across strata/endpoints. The MAH provided exploratory results for CPS<1, CPS 1-9, CPS 10-20 and CPS ≥20 as requested. With the exception of OS result in the CPS 1-9 population, pCR EFS and OS data in all subgroups were overall in favour of the pembrolizumab containing arm. Results could be interpreted as a composite impact of prognostic and predictive factors resulting in an absolute benefit independent of PD-L1 status.

Stage, T and N: those are known prognostic factors in early breast cancer. Overall, 75% of subjects had Stage II disease, 75% T1/2 and half were N-. As expected, patients with more advanced tumors at baseline (Stage III, T3/4, N+) had overall lower pCR rates and higher number of EFS and OS events. EFS and OS benefit of the experimental over control was consistent in Stage II and Stage III disease, although pCR delta was higher in Stage III. On the contrary, a higher EFS and OS benefit was seen in smaller tumors T1/2, but this is not evident for pCR, while for N status N+ disease achieved higher benefit from pembrolizumab in terms of pCR and OS but not EFS. No clear consistency across endpoints and subgroups is seen, but at this stage there is no evidence for lack of efficacy in one or more subgroups, justifying restricting the indication based on KEYNOTE-522 data.

Age: In patients ≥65, lower pCR rates are observed compared to <65, although pCR difference between arms remain similar. Higher rates of EFS and OS events are reported in the over 65 population, where no clear advantage is seen with the addition of pembrolizumab. The number of participants over 65 is however limited (11% of the ITT population) and CIs are wide; therefore, it is difficult to draw conclusions about this subgroup. A relevant subgroup to be considered in the treatment of breast cancer is young women population, usually defined as <40 years of age (Paluch-Shimon S, 2019), which showed in this study almost no benefit of pembrolizumab in addition to NACT on improving the pCR. However, an HR point estimate <1 for EFS is observed.

Exploratory EFS analysis by pCR

A prespecified exploratory analysis of EFS by pCR (ypT0/Tis ypN0) outcome (yes vs no) was performed as an unstratified subgroup analysis. According to this analysis, EFS was better in patients achieving pCR compared to patients not achieving pCR. The comparison between patients in the pembrolizumab arm vs the control arm showed a similar HR estimate in the group of subjects who achieved pCR (0.70) and who did not (0.73), although the separation of curves occurred quite late at month 15. However, in absolute terms, the improvement of EFS is minimal in patients with pCR (EFS rate at 24 months 96.5% vs 93.5%) and more marked in patients without pCR (EFS rate at 24 months 72.9% vs 65.3%). The main limit of this analysis is that responders/ not responders is not a baseline characteristic, and the comparison is not randomized, so in the end no conclusions can be made.

2.4.3. Conclusions on the clinical efficacy

KEYNOTE-522 study showed statistically significant improvement of pCR at the final analysis (IA2) and EFS at the interim analysis (IA4). The EFS benefit of the pembrolizumab containing treatment over control arm is recognised; on the contrary, the clinical relevance of the observed pCR difference is questioned, but it is reassuring that both endpoints have the same direction. OS data is still immature, with a positive HR trend although curves are superimposed. Subgroups analyses are not always

coherent across subgroups and endpoints, but at present there is no indication of lack of benefit in some subgroups leading to restricting the indication. A higher rate of treatment discontinuation due to toxicity in the experimental arm was observed, especially when pembrolizumab is associated with neoadjuvant chemotherapy. Given the timing and the results of the EFS analysis provided, an additional interim EFS analysis would unlikely revert the data seen so far. Due to the design of the study, it is not possible to disentangle the benefit of neoadjuvant and adjuvant pembrolizumab, and the treatment has to be considered in its entirety. The final results of KEYNOTE-522 study will be submitted post-approval as a PAM-REC.

2.5. Clinical safety

Introduction

Pembrolizumab is an anti-PD1 monoclonal antibody (mAb) that acts by disrupting the interaction between PD-1 and its ligand (PD-L1) to enhance the efficacy of the endogenous immune response against neoplastic cells. Immune checkpoint molecules are, however, pivotal in assisting self-tolerance and minimizing tissue damage during active immune responses, and the interaction of PD1 and PD-L1 is a key factor that limits T-cell activity in peripheral tissues. The safety profile of pembrolizumab is, therefore, characterised by the onset of autoimmune-like toxicities, defined as immune-related adverse events (IR-AEs), that are recognised as important identified risks in the RMP of pembrolizumab. IR-AEs known to vary according to type of malignancy, patient characteristics and individual susceptibilities; extensive safety data have been produced with pembrolizumab and showed that, although any organ can be affected by IR-AEs, involvement of colon, skin, lungs, endocrine organs and muscle-skeletal tissues is more frequently observed.

Although most IR-AEs are mild and do not require immune-suppressive treatment, moderate and severe toxicity is usually managed with corticosteroids and, in rarer cases, additional immunosuppressive therapy is needed. The occurrence of IR-AEs may require discontinuation of pembrolizumab, depending on the specific AE and its severity.

Patient exposure

Table 5.3.5.3.3-tnbc3: 3
Summary of Drug Exposure
Combined Phases (Neoadjuvant and Adjuvant)
(APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d] (N=783)	KN522 Placebo + Chemotherapy / Placebo[e] (N=389)	TNBC Safety Dataset for Pembrolizumab Monotherapy[f] (N=595)	Pembrolizumab Monotherapy Reference Safety Dataset[g] (N=6185)
Duration of exposure (month)				
Mean	11.2	12.3	4.0	7.5
Median	13.31	13.60	2.10	4.90
SD	4.83	4.19	5.25	7.02
Range	0.03 to 21.91	0.03 to 19.81	0.03 to 25.56	0.03 to 30.62
Number of cycles				
Mean	13.2	14.4	6.7	12.0
Median	17.00	17.00	4.00	8.00
SD	5.26	4.41	7.48	10.40
Range	1.00 to 17.00	1.00 to 17.00	1.00 to 52.00	1.00 to 59.00

Each participant is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.
[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.
[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.
[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.
Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)
Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)
Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)
Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)
Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)
Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)
Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adexsum]

Table 5.3.5.3.3-tnbc3: 1
Drug Exposure by Duration
Combined Phases (Neoadjuvant and Adjuvant)
(APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d] (N=783)			KN522 Placebo + Chemotherapy / Placebo[e] (N=389)			TNBC Safety Dataset for Pembrolizumab Monotherapy[f] (N=595)			Pembrolizumab Monotherapy Reference Safety Dataset[g] (N=6185)		
	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years	n	(%)	Person-years
Duration of Exposure												
>0 m	778	(99.4)	(728.1)	389	(100.0)	(399.1)	595	(100.0)	(198.6)	6,185	(100.0)	(3,873.8)
>=1 m	763	(97.4)	(727.3)	386	(99.2)	(398.9)	459	(77.1)	(193.5)	5,314	(85.9)	(3,845.1)
>=3 m	717	(91.6)	(718.1)	371	(95.4)	(395.9)	222	(37.3)	(156.7)	3,860	(62.4)	(3,602.9)
>=6 m	570	(72.8)	(659.0)	323	(83.0)	(376.9)	105	(17.6)	(116.7)	2,808	(45.4)	(3,220.5)

Demographic and other baseline characteristics of pembrolizumab + NAC / pembrolizumab group were generally well-balanced when compared with the placebo + NAC / placebo group (see the efficacy section above). All enrolled participants had newly diagnosed, locally advanced early-stage TNBC, the majority of participants were female, <65 years of age, premenopausal, and had an ECOG score of 0. Most participants (82.9%) had a tumor tissue PD-L1 expression score of CPS ≥1. More participants in the mTNBC monotherapy group had an ECOG PS status of 1 or missing compared to the pembrolizumab + NAC / pembrolizumab group. Compared with the RSD, a higher percentage of

participants in the pembrolizumab + NAC / pembrolizumab group were female, <65 years of age, Asian, and had an ECOG PS of 0.

Adverse events

Adverse events (AEs) were coded using MedDRA Version 23.1. The incidence of (AEs) in the combined neoadjuvant + adjuvant phases of study KN522 is summarised in Tables below:

Table 2.7.4-tnbc3: 2
Adverse Event Summary
Combined Phases (Neoadjuvant and Adjuvant)
(APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	783		389		595		6,185	
with one or more adverse events	777	(99.2)	389	(100.0)	559	(93.9)	5,984	(96.8)
with no adverse event	6	(0.8)	0	(0.0)	36	(6.1)	201	(3.2)
with drug-related[a] adverse events	774	(98.9)	388	(99.7)	368	(61.8)	4,364	(70.6)
with toxicity grade 3-5 adverse events	645	(82.4)	306	(78.7)	218	(36.6)	2,980	(48.2)
with toxicity grade 3-5 drug-related adverse events	604	(77.1)	285	(73.3)	79	(13.3)	975	(15.8)
with serious adverse events	341	(43.6)	111	(28.5)	140	(23.5)	2,372	(38.4)
with serious drug-related adverse events	267	(34.1)	78	(20.1)	46	(7.7)	705	(11.4)
who died	7	(0.9)	1	(0.3)	11	(1.8)	321	(5.2)
who died due to a drug-related adverse event	4	(0.5)	1	(0.3)	2	(0.3)	40	(0.6)
discontinued any drug due to an adverse event	234	(29.9)	60	(15.4)	30	(5.0)	831	(13.4)
discontinued pembrolizumab or placebo	157	(20.1)	31	(8.0)	30	(5.0)	831	(13.4)
discontinued any chemotherapy	136	(17.4)	42	(10.8)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	217	(27.7)	55	(14.1)	20	(3.4)	444	(7.2)
discontinued pembrolizumab or placebo	140	(17.9)	26	(6.7)	20	(3.4)	444	(7.2)
discontinued any chemotherapy	130	(16.6)	40	(10.3)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	94	(12.0)	15	(3.9)	17	(2.9)	598	(9.7)
discontinued pembrolizumab or placebo	81	(10.3)	14	(3.6)	17	(2.9)	598	(9.7)
discontinued any chemotherapy	48	(6.1)	7	(1.8)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	84	(10.7)	11	(2.8)	10	(1.7)	265	(4.3)
discontinued pembrolizumab or placebo	72	(9.2)	10	(2.6)	10	(1.7)	265	(4.3)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued any chemotherapy	43	(5.5)	6	(1.5)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.0.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-tnbc3: 6
Exposure-Adjusted Adverse Event Summary
(Including Multiple Occurrences of Events)
Combined Phases (Neoadjuvant and Adjuvant)
(APaT Population)

	Event Count and Rate (Events/100 person-years)[a]			
	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]	KN522 Placebo + Chemotherapy / Placebo[e]	TNBC Safety Dataset for Pembrolizumab Monotherapy[f]	Pembrolizumab Monotherapy Reference Safety Dataset[g]
Number of participants exposed	783	389	595	6185
Total exposure[b] in person-years	829.39	444.00	246.83	4333.56
Total events (rate)				
adverse events	20391 (2458.54)	9356 (2107.21)	4210 (1705.61)	65264 (1506.01)
drug-related[c] adverse events	13337 (1608.04)	6000 (1351.36)	1383 (560.30)	20441 (471.69)
toxicity grade 3-5 adverse events	2314 (279.00)	908 (204.51)	424 (171.78)	6506 (150.13)
toxicity grade 3-5 drug-related adverse events	1924 (231.98)	776 (174.78)	106 (42.94)	1470 (33.92)
serious adverse events	624 (75.24)	167 (37.61)	225 (91.16)	4278 (98.72)
serious drug-related adverse events	439 (52.93)	109 (24.55)	56 (22.69)	981 (22.64)
adverse events leading to death	9 (1.09)	1 (0.23)	11 (4.46)	328 (7.57)
drug-related adverse events leading to death	5 (0.60)	1 (0.23)	2 (0.81)	40 (0.92)
adverse events resulting in drug discontinuation	290 (34.97)	68 (15.32)	35 (14.18)	904 (20.86)
drug-related adverse events resulting in drug discontinuation	270 (32.55)	61 (13.74)	24 (9.72)	482 (11.12)
serious adverse events resulting in drug discontinuation	113 (13.62)	16 (3.60)	18 (7.29)	635 (14.65)

	Event Count and Rate (Events/100 person-years)[a]			
	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]	KN522 Placebo + Chemotherapy / Placebo[e]	TNBC Safety Dataset for Pembrolizumab Monotherapy[f]	Pembrolizumab Monotherapy Reference Safety Dataset[g]
serious drug-related adverse events resulting in drug discontinuation	102 (12.30)	11 (2.48)	11 (4.46)	279 (6.44)

[a] Event rate per 100 person-years of exposure=event count *100/person-years of exposure.

[b] Drug exposure is the time from the first dose date to the earlier of the last dose date +30 or the cutoff date.

[c] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE 4.0.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

The incidence of AEs was generally similar between the pembrolizumab + NAC / pembrolizumab and placebo + NAC / placebo group. In the pembrolizumab + NAC / pembrolizumab group, there was a higher incidence (≥5 percentage point difference) of SAEs, serious drug-related AEs, and discontinuations of any drug due to an AE (including due to drug-related AEs, SAEs, or drug-related SAEs).

Except for the overall incidence of AEs, deaths due to AEs, and discontinuations due to SAEs, all other AE parameters had higher incidences (≥5 percentage point difference) in the pembrolizumab + NAC / pembrolizumab group compared with the pembrolizumab monotherapy RSD. This was anticipated, as participants in KEYNOTE-522 received carboplatin- and anthracycline-based NAC in addition to pembrolizumab.

AEs (all and drug-related), Grade 3 to 5 AEs (all and drug-related), serious AEs (SAEs, all and drug-related), AEs leading to treatment discontinuation (all and drug-related), AEs leading to treatment interruption (all and drug-related), and AEOSIs occurred more frequently during the neoadjuvant phase compared with the adjuvant phase, likely due to the concomitant chemotherapy during the neoadjuvant phase (see Tables below).

Table 14.3.1.1-1
Analysis of Adverse Event Summary
Tier-2
All Participants
Neoadjuvant Phase
(ASaT Population)

	MK-3475 + chemotherapy		Placebo + chemotherapy		Difference in % vs Placebo + chemotherapy
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	783		389		
with one or more adverse events	777	(99.2)	389	(100.0)	-0.8 (-1.7, 0.2)
with no adverse event	6	(0.8)	0	(0.0)	0.8 (-0.2, 1.7)
with drug-related[b] adverse events	773	(98.7)	388	(99.7)	-1.0 (-2.1, 0.2)
with toxicity grade 3-5 adverse events	627	(80.1)	295	(75.8)	4.2 (-0.7, 9.5)
with toxicity grade 3-5 drug-related adverse events	593	(75.7)	282	(72.5)	3.2 (-2.0, 8.7)
with serious adverse events	315	(40.2)	101	(26.0)	14.3 (8.6, 19.7)
with serious drug-related adverse events	254	(32.4)	77	(19.8)	12.6 (7.4, 17.7)
with dose modification[c] due to an adverse event	628	(80.2)	296	(76.1)	4.1 (-0.8, 9.3)
who died	5	(0.6)	1	(0.3)	0.4 (-0.8, 1.3)
who died due to a drug-related adverse event	2	(0.3)	1	(0.3)	-0.0 (-1.2, 0.7)
discontinued drug due to an adverse event	205	(26.2)	53	(13.6)	12.6 (7.8, 17.0)
discontinued drug due to a drug-related adverse event	194	(24.8)	49	(12.6)	12.2 (7.5, 16.5)
discontinued drug due to a serious adverse event	82	(10.5)	13	(3.3)	7.1 (4.2, 9.9)
discontinued drug due to a serious drug-related adverse event	75	(9.6)	10	(2.6)	7.0 (4.3, 9.6)

[a] Based on Miettinen & Nurminen method.

[b] Determined by the investigator to be related to the drug.

[c] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Grades are based on NCI CTCAE version 4.0.

Included adverse events started from the first neoadjuvant treatment including definitive surgery and prior to the first adjuvant treatment including radiation therapy or, if no adjuvant treatment, up to 30 days of the definitive surgery for the non-serious adverse events and up to 90 days of the definitive surgery for the serious adverse events or, if no surgery, up to 30 days of last neoadjuvant treatment for the non-serious adverse events and up to 90 days of last neoadjuvant treatment for the serious adverse events.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adsl; adae]

Table 12-2
Adverse Event Summary
All Participants
Adjuvant Phase
(ASaT Population)

	MK-3475		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	588		331		919	
with one or more adverse events	542	(92.2)	294	(88.8)	836	(91.0)
with no adverse event	46	(7.8)	37	(11.2)	83	(9.0)
with drug-related[a] adverse events	316	(53.7)	161	(48.6)	477	(51.9)
with toxicity grade 3-5 adverse events	88	(15.0)	38	(11.5)	126	(13.7)
with toxicity grade 3-5 drug-related adverse events	37	(6.3)	9	(2.7)	46	(5.0)
with serious adverse events	41	(7.0)	14	(4.2)	55	(6.0)
with serious drug-related adverse events	19	(3.2)	2	(0.6)	21	(2.3)
with dose modification[b] due to an adverse event	105	(17.9)	45	(13.6)	150	(16.3)
who died	2	(0.3)	0	(0.0)	2	(0.2)
who died due to a drug-related adverse event	2	(0.3)	0	(0.0)	2	(0.2)
discontinued drug due to an adverse event	32	(5.4)	8	(2.4)	40	(4.4)
discontinued drug due to a drug-related adverse event	25	(4.3)	6	(1.8)	31	(3.4)
discontinued drug due to a serious adverse event	12	(2.0)	2	(0.6)	14	(1.5)
discontinued drug due to a serious drug-related adverse event	9	(1.5)	1	(0.3)	10	(1.1)

[a] Determined by the investigator to be related to the drug.
[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.0.
Included adverse events started from the first adjuvant treatment including radiation therapy and up to 30 days of last adjuvant treatment including radiation therapy for the non-serious adverse events and up to 90 days of last adjuvant treatment for the serious adverse events.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adsl; adae]

Common AEs

The frequency, type, and severity of AEs reported during the study in the pembrolizumab + NAC / pembrolizumab group generally reflected the contributions of the established individual safety profiles of the chemotherapy administered (carboplatin- and anthracycline-based NAC) and pembrolizumab monotherapy. The most frequently reported AEs (incidence ≥30%) in the pembrolizumab + NAC / pembrolizumab group were nausea, alopecia, anaemia, neutropenia, fatigue, constipation, diarrhoea, vomiting, and ALT increased. The most frequently reported AEs (incidence ≥30%) in the placebo + NAC / placebo group were nausea, alopecia, anaemia, neutropenia, fatigue, constipation, diarrhoea, and arthralgia (see Table below).

Table 2.7.4-tnbc3: 3: Participants with AEs by Decreasing Incidence (Incidence ≥ 10% in One or More Treatment Groups) Combined Phases (Neoadjuvant and Adjuvant) (APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	783		389		595		6,185	
with one or more adverse events	777	(99.2)	389	(100.0)	559	(93.9)	5,984	(96.8)

with no adverse events	6	(0.8)	0	(0.0)	36	(6.1)	201	(3.2)
Nausea	522	(66.7)	257	(66.1)	113	(19.0)	1,281	(20.7)
Alopecia	477	(60.9)	226	(58.1)	8	(1.3)	99	(1.6)
Anaemia	463	(59.1)	229	(58.9)	62	(10.4)	872	(14.1)
Neutropenia	376	(48.0)	190	(48.8)	6	(1.0)	62	(1.0)
Fatigue	365	(46.6)	168	(43.2)	152	(25.5)	1,965	(31.8)
Constipation	328	(41.9)	150	(38.6)	98	(16.5)	1,032	(16.7)
Diarrhoea	318	(40.6)	133	(34.2)	75	(12.6)	1,297	(21.0)
Vomiting	244	(31.2)	108	(27.8)	57	(9.6)	785	(12.7)
Alanine aminotransferase increased	238	(30.4)	108	(27.8)	39	(6.6)	428	(6.9)
Headache	234	(29.9)	113	(29.0)	74	(12.4)	747	(12.1)
Rash	234	(29.9)	92	(23.7)	52	(8.7)	937	(15.1)
Arthralgia	225	(28.7)	120	(30.8)	98	(16.5)	1,152	(18.6)
Pyrexia	221	(28.2)	72	(18.5)	70	(11.8)	803	(13.0)
Asthenia	219	(28.0)	111	(28.5)	61	(10.3)	693	(11.2)
Cough	193	(24.6)	86	(22.1)	115	(19.3)	1,199	(19.4)
Neutrophil count decreased	191	(24.4)	113	(29.0)	3	(0.5)	42	(0.7)
Aspartate aminotransferase increased	187	(23.9)	77	(19.8)	60	(10.1)	420	(6.8)
Decreased appetite	178	(22.7)	65	(16.7)	72	(12.1)	1,181	(19.1)
Neuropathy peripheral	163	(20.8)	90	(23.1)	14	(2.4)	123	(2.0)
Insomnia	161	(20.6)	74	(19.0)	22	(3.7)	447	(7.2)
Peripheral sensory neuropathy	156	(19.9)	72	(18.5)	7	(1.2)	71	(1.1)
Myalgia	153	(19.5)	73	(18.8)	42	(7.1)	445	(7.2)
Febrile neutropenia	151	(19.3)	66	(17.0)	2	(0.3)	10	(0.2)
Pruritus	147	(18.8)	56	(14.4)	66	(11.1)	1,111	(18.0)
Stomatitis	141	(18.0)	58	(14.9)	13	(2.2)	158	(2.6)
Dysgeusia	128	(16.3)	49	(12.6)	11	(1.8)	116	(1.9)
Urinary tract infection	123	(15.7)	62	(15.9)	27	(4.5)	414	(6.7)
Dizziness	118	(15.1)	60	(15.4)	36	(6.1)	460	(7.4)
Hypothyroidism	118	(15.1)	22	(5.7)	53	(8.9)	698	(11.3)
Epistaxis	117	(14.9)	63	(16.2)	5	(0.8)	86	(1.4)
Hot flush	117	(14.9)	69	(17.7)	21	(3.5)	88	(1.4)
Radiation skin injury	114	(14.6)	73	(18.8)	3	(0.5)	13	(0.2)
White blood cell count decreased	113	(14.4)	56	(14.4)	6	(1.0)	58	(0.9)
Abdominal pain	112	(14.3)	49	(12.6)	36	(6.1)	527	(8.5)
Mucosal inflammation	112	(14.3)	49	(12.6)	9	(1.5)	100	(1.6)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Dyspepsia	111	(14.2)	56	(14.4)	13	(2.2)	165	(2.7)
Thrombocytopenia	110	(14.0)	68	(17.5)	10	(1.7)	100	(1.6)
Upper respiratory tract infection	106	(13.5)	47	(12.1)	23	(3.9)	431	(7.0)
Dyspnoea	99	(12.6)	50	(12.9)	91	(15.3)	1,021	(16.5)
Leukopenia	98	(12.5)	51	(13.1)	6	(1.0)	46	(0.7)
Back pain	97	(12.4)	63	(16.2)	60	(10.1)	707	(11.4)
Pain in extremity	91	(11.6)	49	(12.6)	42	(7.1)	422	(6.8)
Hypokalaemia	88	(11.2)	24	(6.2)	12	(2.0)	286	(4.6)
Erythema	81	(10.3)	36	(9.3)	16	(2.7)	177	(2.9)
Abdominal pain upper	80	(10.2)	34	(8.7)	22	(3.7)	239	(3.9)
Infusion related reaction	79	(10.1)	27	(6.9)	3	(0.5)	63	(1.0)
Platelet count decreased	78	(10.0)	37	(9.5)	7	(1.2)	76	(1.2)
Bone pain	70	(8.9)	39	(10.0)	13	(2.2)	119	(1.9)
Nasopharyngitis	65	(8.3)	52	(13.4)	28	(4.7)	397	(6.4)
Breast pain	64	(8.2)	43	(11.1)	17	(2.9)	21	(0.3)
Gastrooesophageal reflux disease	57	(7.3)	43	(11.1)	8	(1.3)	125	(2.0)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

AEs (incidence ≥15%) with a greater risk difference for pembrolizumab + NAC / pembrolizumab during the study were pyrexia, hypothyroidism, diarrhea, rash, and decreased appetite. These events were primarily Grade 1 or 2 and mostly occurred during the neoadjuvant phase. In both treatment groups, most AEs occurred in the first 3 months of initiating study intervention: the exposure-adjusted event rate decreased at 3 to 6 months and continued to decrease beyond 12 months.

The overall incidence of AEs observed in the pembrolizumab + NAC / pembrolizumab group was generally consistent with the pembrolizumab monotherapy RSD. There was a higher incidence (≥20 percentage point difference) of the following AEs in the pembrolizumab + NAC / pembrolizumab group compared with the pembrolizumab monotherapy RSD: nausea, alopecia, anaemia, neutropenia,

constipation, ALT increased, and neutrophil count decreased. These differences were consistent with the established safety profiles of the chemotherapies administered during the neoadjuvant phase.

Drug-related AEs

The overall incidences of drug-related AEs during the study, as determined by the Investigator, were similar between the pembrolizumab + NAC / pembrolizumab and placebo + NAC / placebo groups (see Table below).

Table 2.7.4-tnbc3: 4 - Participants With Drug-Related Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) Combined Phases (Neoadjuvant and Adjuvant) (APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	783		389		595		6,185	
with one or more adverse events	774	(98.9)	388	(99.7)	368	(61.8)	4,364	(70.6)
with no adverse events	9	(1.1)	1	(0.3)	227	(38.2)	1,821	(29.4)
Nausea	495	(63.2)	245	(63.0)	67	(11.3)	560	(9.1)
Alopecia	471	(60.2)	220	(56.6)	3	(0.5)	52	(0.8)
Anaemia	429	(54.8)	215	(55.3)	25	(4.2)	212	(3.4)
Neutropenia	367	(46.9)	185	(47.6)	3	(0.5)	35	(0.6)
Fatigue	330	(42.1)	151	(38.8)	100	(16.8)	1,215	(19.6)
Diarrhoea	238	(30.4)	98	(25.2)	43	(7.2)	682	(11.0)
Alanine aminotransferase increased	204	(26.1)	98	(25.2)	25	(4.2)	254	(4.1)
Vomiting	200	(25.5)	86	(22.1)	20	(3.4)	209	(3.4)
Asthenia	198	(25.3)	102	(26.2)	32	(5.4)	377	(6.1)
Rash	196	(25.0)	66	(17.0)	29	(4.9)	701	(11.3)
Constipation	188	(24.0)	85	(21.9)	19	(3.2)	160	(2.6)
Neutrophil count decreased	185	(23.6)	112	(28.8)	2	(0.3)	30	(0.5)
Aspartate aminotransferase increased	157	(20.1)	63	(16.2)	32	(5.4)	243	(3.9)
Neuropathy peripheral	154	(19.7)	84	(21.6)	5	(0.8)	45	(0.7)
Decreased appetite	153	(19.5)	57	(14.7)	33	(5.5)	479	(7.7)
Peripheral sensory neuropathy	148	(18.9)	72	(18.5)	5	(0.8)	32	(0.5)
Febrile neutropenia	144	(18.4)	65	(16.7)	0	(0.0)	0	(0.0)
Pyrexia	138	(17.6)	41	(10.5)	29	(4.9)	288	(4.7)
Stomatitis	132	(16.9)	55	(14.1)	6	(1.0)	80	(1.3)
Dysgeusia	124	(15.8)	49	(12.6)	8	(1.3)	62	(1.0)
Arthralgia	121	(15.5)	59	(15.2)	36	(6.1)	491	(7.9)
Pruritus	116	(14.8)	38	(9.8)	43	(7.2)	873	(14.1)
Myalgia	112	(14.3)	49	(12.6)	22	(3.7)	236	(3.8)
White blood cell count decreased	108	(13.8)	52	(13.4)	3	(0.5)	29	(0.5)
Hypothyroidism	105	(13.4)	19	(4.9)	45	(7.6)	604	(9.8)
Thrombocytopenia	104	(13.3)	65	(16.7)	2	(0.3)	49	(0.8)
Mucosal inflammation	103	(13.2)	45	(11.6)	3	(0.5)	52	(0.8)
Headache	100	(12.8)	42	(10.8)	20	(3.4)	199	(3.2)
Leukopenia	87	(11.1)	49	(12.6)	3	(0.5)	29	(0.5)
Epistaxis	76	(9.7)	41	(10.5)	0	(0.0)	6	(0.1)
Platelet count decreased	74	(9.5)	34	(8.7)	5	(0.8)	35	(0.6)
Infusion related reaction	73	(9.3)	25	(6.4)	3	(0.5)	61	(1.0)
Dyspepsia	71	(9.1)	39	(10.0)	4	(0.7)	37	(0.6)
Abdominal pain	65	(8.3)	22	(5.7)	12	(2.0)	123	(2.0)
Dizziness	61	(7.8)	29	(7.5)	11	(1.8)	87	(1.4)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Hot flush	55	(7.0)	45	(11.6)	7	(1.2)	33	(0.5)
Cough	52	(6.6)	13	(3.3)	20	(3.4)	200	(3.2)
Rash maculo-papular	50	(6.4)	23	(5.9)	12	(2.0)	166	(2.7)
Dry mouth	49	(6.3)	20	(5.1)	11	(1.8)	155	(2.5)
Nail discolouration	48	(6.1)	31	(8.0)	0	(0.0)	2	(0.0)
Dry skin	47	(6.0)	20	(5.1)	7	(1.2)	182	(2.9)
Dyspnoea	46	(5.9)	23	(5.9)	19	(3.2)	204	(3.3)
Dermatitis acneiform	45	(5.7)	10	(2.6)	3	(0.5)	63	(1.0)
Paraesthesia	45	(5.7)	28	(7.2)	6	(1.0)	43	(0.7)
Insomnia	42	(5.4)	13	(3.3)	4	(0.7)	47	(0.8)
Gastrooesophageal reflux disease	41	(5.2)	24	(6.2)	1	(0.2)	14	(0.2)
Abdominal pain upper	39	(5.0)	22	(5.7)	5	(0.8)	56	(0.9)
Oedema peripheral	35	(4.5)	21	(5.4)	9	(1.5)	102	(1.6)
Blood alkaline phosphatase increased	29	(3.7)	20	(5.1)	12	(2.0)	100	(1.6)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

The incidences of the most frequently reported drug-related AEs (incidence ≥30%) during the study were generally similar between the 2 treatment groups and included nausea, alopecia, anaemia, neutropenia, fatigue, and diarrhoea.

The overall incidence of drug-related AEs was higher in the pembrolizumab + NAC / pembrolizumab group compared with the pembrolizumab monotherapy RSD. There was a higher incidence (≥20 percentage point difference) of the following drug-related AEs in the pembrolizumab + NAC / pembrolizumab group compared with the pembrolizumab monotherapy RSD: nausea, alopecia, anaemia, neutropenia, fatigue, ALT increased, vomiting, constipation, and neutrophil count decreased. These differences were consistent with the established safety profiles of the chemotherapies administered during the neoadjuvant phase.

Grade 3 to 5 AEs and drug-related AEs

The overall incidence of Grade 3 to 5 AEs and the types and frequencies of the most common Grade 3 to 5 AEs (incidence ≥5%) during the study were generally similar between the pembrolizumab + NAC / pembrolizumab and placebo + NAC / placebo groups (see Table below).

Participants With Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) Combined Phases (Neoadjuvant and Adjuvant) (APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	783		389		595		6,185	
with one or more adverse events	645	(82.4)	306	(78.7)	218	(36.6)	2,980	(48.2)
with no adverse events	138	(17.6)	83	(21.3)	377	(63.4)	3,205	(51.8)
Neutropenia	276	(35.2)	134	(34.4)	2	(0.3)	19	(0.3)
Anaemia	153	(19.5)	61	(15.7)	18	(3.0)	247	(4.0)
Neutrophil count decreased	149	(19.0)	92	(23.7)	2	(0.3)	9	(0.1)
Febrile neutropenia	144	(18.4)	63	(16.2)	2	(0.3)	10	(0.2)
White blood cell count decreased	61	(7.8)	21	(5.4)	2	(0.3)	4	(0.1)
Alanine aminotransferase increased	50	(6.4)	11	(2.8)	7	(1.2)	67	(1.1)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades are based on NCI CTCAE version 4.0.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Grade 3 to 5 ALT increased was the only AE (incidence ≥5%) with a greater risk difference for pembrolizumab + NAC / pembrolizumab group compared with placebo + NAC / placebo group (ie, the lower bound of the 95% CI for the treatment difference is >0). The overall incidence of the most common (incidence ≥5%) Grade 3 to 5 drug-related AEs were similar between the pembrolizumab + NAC / pembrolizumab and placebo + NAC / placebo groups.

The overall incidence of Grade 3 to 5 AEs and drug-related AEs was higher in the pembrolizumab + NAC / pembrolizumab group compared with the pembrolizumab monotherapy RSD. There was a higher incidence (≥5 percentage point difference) of the following Grade 3 to 5 AEs in the pembrolizumab + NAC / pembrolizumab group compared with the pembrolizumab monotherapy RSD: neutropenia, anemia, neutrophil count decreased, febrile neutropenia, WBC count decreased, and ALT increased. There was a higher incidence (≥5 percentage point difference) of the following Grade 3 to 5 drug-related AEs in the pembrolizumab + NAC group / pembrolizumab compared with the pembrolizumab monotherapy RSD: neutropenia, neutrophil count decreased, anemia, febrile neutropenia, and WBC count decreased.

Serious adverse event/deaths/other significant events

Serious AEs (SAEs)

The overall incidence of SAEs and drug-related SAEs during the study was higher in the pembrolizumab + NAC / pembrolizumab group compared with the placebo + NAC / placebo group (see Table below).

Table 2.7.4-tnbc3: 8 - Participants With Serious Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) Combined Phases (Neoadjuvant and Adjuvant) (APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	783		389		595		6,185	
with one or more adverse events	341	(43.6)	111	(28.5)	140	(23.5)	2,372	(38.4)
with no adverse events	442	(56.4)	278	(71.5)	455	(76.5)	3,813	(61.6)
Febrile neutropenia	118	(15.1)	47	(12.1)	2	(0.3)	7	(0.1)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Febrile neutropenia was the only SAE and drug-related SAE reported with an incidence ≥5% in the pembrolizumab + NAC / pembrolizumab group. Pyrexia was the only event considered higher (ie, the 95% CI for the treatment difference was >0) in the pembrolizumab + NAC / pembrolizumab group compared with the placebo + NAC / placebo group (3.7% vs 0.5%). Except for pyrexia, the frequencies of other most common SAEs (incidence ≥1%) during the study were generally similar between the 2 treatment groups. Over the course of the study, the frequencies of the most common drug-related SAEs (incidence ≥1%) were also generally consistent between the 2 treatment groups. The overall incidence of SAEs and drug-related SAEs observed in the pembrolizumab + NAC / pembrolizumab group was higher (5 percentage point difference) compared with the pembrolizumab monotherapy RSD. Except for blood and lymphatic system disorders SOC (19.7% vs 1.6%), the incidences of SAEs by SOC in the pembrolizumab + NAC / pembrolizumab group were generally consistent with the pembrolizumab RSD.

Deaths

The overall incidence of AEs resulting in death in the pembrolizumab + NAC / pembrolizumab group the and in the placebo + NAC / placebo group was 0.9% and 0.3%, respectively (see Table below).

Table 2.7.4-tnbc3: 7 - Participants With Adverse Events Resulting in Death by Decreasing Incidence (Incidence > 0% in One or More Treatment Groups) Combined Phases (Neoadjuvant and Adjuvant) (APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	783		389		595		6,185	
with one or more adverse events	7	(0.9)	1	(0.3)	11	(1.8)	321	(5.2)
with no adverse events	776	(99.1)	388	(99.7)	584	(98.2)	5,864	(94.8)
Death	1	(0.1)	0	(0.0)	0	(0.0)	44	(0.7)
Encephalitis autoimmune	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	1	(0.1)	0	(0.0)	0	(0.0)	5	(0.1)
Myocardial infarction	1	(0.1)	0	(0.0)	0	(0.0)	6	(0.1)
Pneumonia	1	(0.1)	0	(0.0)	0	(0.0)	37	(0.6)
Pneumonitis	1	(0.1)	0	(0.0)	0	(0.0)	8	(0.1)
Pulmonary embolism	1	(0.1)	0	(0.0)	1	(0.2)	10	(0.2)
Sepsis	1	(0.1)	0	(0.0)	0	(0.0)	9	(0.1)
Shock	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal sepsis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Accidental death	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute coronary syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute graft versus host disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Acute myocardial infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Acute respiratory distress syndrome	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Acute respiratory failure	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Adenocarcinoma gastric	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Alcohol poisoning	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Anaphylactic shock	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Arterial injury	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Aspiration	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Atypical pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Autoinflammatory disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Brain oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cachexia	0	(0.0)	0	(0.0)	1	(0.2)	3	(0.0)
Cardiac arrest	0	(0.0)	0	(0.0)	1	(0.2)	9	(0.1)
Cardiac complication associated with device	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac failure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac failure acute	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac failure congestive	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Cardiac tamponade	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cardio-respiratory arrest	0	(0.0)	0	(0.0)	2	(0.3)	4	(0.1)
Cardiopulmonary failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cellulitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebral haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cerebrovascular accident	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Chronic kidney disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Circulatory collapse	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Clostridium difficile infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Coma	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Completed suicide	0	(0.0)	0	(0.0)	1	(0.2)	3	(0.0)
Diarrhoea	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Diffuse alveolar damage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Disseminated intravascular coagulation	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.0)
Diverticulitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Drug reaction with eosinophilia and systemic symptoms	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Duodenal obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Duodenal perforation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Dyspnoea	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Embolism	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Encephalopathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Failure to thrive	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Fall	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Febrile neutropenia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastric haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Gastric ulcer haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Gastrointestinal perforation	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
General physical health deterioration	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Generalised oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemoptysis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemorrhage intracranial	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemorrhagic infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Haemorrhagic stroke	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Haemothorax	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hepatic failure	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Hyperglycaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hypovolaemic shock	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Hypoxia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Ileus paralytic	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infectious pleural effusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Interstitial lung disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Intestinal ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Intestinal obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Intestinal perforation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Ischaemic cardiomyopathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Ischaemic stroke	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Large intestine perforation	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Lung neoplasm malignant	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Lymphangiosis carcinomatosa	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Malignant neoplasm progression	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Mental status changes	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Metastatic malignant melanoma	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)

Myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Neutropenic sepsis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pelvic neoplasm	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Peripheral artery occlusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumocystis jirovecii pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia aspiration	0	(0.0)	0	(0.0)	0	(0.0)	8	(0.1)
Pneumonia klebsiella	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia staphylococcal	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumonia streptococcal	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pneumothorax	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Post procedural haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Post procedural infection	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pseudobulbar palsy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pseudomonal sepsis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary artery thrombosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Pulmonary oedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pulmonary sepsis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Renal failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Respiratory distress	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Respiratory failure	0	(0.0)	0	(0.0)	1	(0.2)	17	(0.3)
Septic shock	0	(0.0)	1	(0.3)	0	(0.0)	10	(0.2)
Soft tissue infection	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Spinal cord compression	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Stevens-Johnson syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Sudden death	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Superior vena cava syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Traumatic intracranial haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Tumour haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Type 2 diabetes mellitus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Upper gastrointestinal haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Urinary tract obstruction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Urosepsis	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)

Every participant is counted a single time for each applicable row and column.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Of the 7 deaths due to AEs in the pembrolizumab + NAC / pembrolizumab group, 2 deaths occurred in the adjuvant phase (pulmonary embolism and autoimmune encephalitis) while the remaining 5 deaths occurred during the neoadjuvant phase. Four out of 7 deaths due to AEs were considered related to study medication by the investigator: pneumonitis, pulmonary embolism, and autoimmune encephalitis were considered related to pembrolizumab and sepsis/multiple organ dysfunction syndrome were considered related to NAC. No specific AE resulting in death was reported in more than 1 participant.

The overall incidence of AEs resulting in death was 5.2% in pembrolizumab monotherapy RSD. All fatal AEs were reviewed and no new safety concerns for pembrolizumab were identified.

AEs of special interest (AEOSI)

The frequency and maximum severity of AEOSI analyses are based on a predefined list of preferred AE terms deemed clinically consistent with the identified risks of pembrolizumab (AEOSIs) and potentially associated with an immune etiology. This list was developed by the MAH and includes AEOSI terms identified to allow consistent assessment of AEOSIs across pembrolizumab studies. The AEOSIs are presented regardless of investigator-assessed causality and generally include all AE grades (with the exception of severe skin reactions). The list of terms is updated periodically based on emerging pembrolizumab safety data (see Table below).

1.1 MK-3475 AEOSI Preferred Terms

Version 19.0 (05-NOV-2020)
This list is based on MedDRA Version 23.1

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Pneumonitis	Acute interstitial pneumonitis, Autoimmune lung disease, Interstitial lung disease, Pneumonitis, Idiopathic pneumonia syndrome, Organising pneumonia, Immune-mediated pneumonitis	Yes
Colitis	Colitis, Colitis microscopic, Enterocolitis, Enterocolitis haemorrhagic, Necrotising colitis, Colitis erosive, Autoimmune colitis, Immune-mediated enterocolitis	Yes
Hepatitis	Hepatitis, Immune-mediated hepatitis, Autoimmune hepatitis, Hepatitis acute, Hepatitis fulminant, Drug-induced liver injury	Yes
Nephritis	Nephritis, Autoimmune nephritis, Chronic autoimmune glomerulonephritis, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Mesangioproliferative glomerulonephritis, Nephritis haemorrhagic, Tubulointerstitial nephritis, Nephrotic syndrome, Immune-mediated nephritis	Yes
Adrenal Insufficiency	Adrenal insufficiency, Adrenocortical insufficiency acute, Secondary adrenocortical insufficiency, Primary adrenal insufficiency, Addison's disease	Yes
Hypophysitis	Hypophysitis, Hypopituitarism, Lymphocytic hypophysitis	Yes
Hyperthyroidism	Hyperthyroidism, Basedow's disease, Thyrotoxic crisis, Immune-mediated hyperthyroidism	Yes
Hypothyroidism	Hypothyroidism, Hypothyroidic goitre, Myxoedema, Myxoedema coma, Primary hypothyroidism, Autoimmune hypothyroidism, Immune-mediated hypothyroidism	Yes
Thyroiditis	Thyroid disorder, Thyroiditis, Autoimmune thyroiditis, Thyroiditis acute, Silent thyroiditis, Autoimmune thyroid disorder, Immune-mediated thyroiditis	Yes
Type 1 Diabetes Mellitus	Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Fulminant type 1 diabetes mellitus, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Euglycaemic diabetic ketoacidosis, Diabetic ketosis, Ketosis-prone diabetes mellitus	Yes
Severe Skin Reactions Including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): or	Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Pemphigoid, Pemphigus, Skin necrosis, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Toxic skin eruption, SJS-TEN overlap	Yes

AEOSI	Preferred Terms	Immune-mediated (yes/no)
Severe Skin (continued): If Grade 3 or higher:	Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, Pruritus, Pruritus genital, Lichen planus, Oral lichen planus, Cutaneous vasculitis, Vasculitic rash	Yes
Uveitis	Iritis, Uveitis, Cyclitis, Autoimmune uveitis, Iridocyclitis, Vogt-Koyanagi-Harada disease, Chorioretinitis, Choroiditis, Immune-mediated uveitis	Yes
Pancreatitis	Pancreatitis, Autoimmune pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Immune-mediated pancreatitis	Yes
Myositis	Myositis, Necrotising myositis, Polymyositis, Immune-mediated myositis, Rhabdomyolysis, Myopathy, Dermatomyositis, Autoimmune myositis	Yes
Guillain-Barre Syndrome	Demyelinating polyneuropathy, Guillain-Barre syndrome, Axonal neuropathy, Multifocal motor neuropathy, Polyneuropathy idiopathic progressive, Miller Fisher syndrome, Subacute inflammatory demyelinating polyneuropathy	Yes
Myocarditis	Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis	Yes
Encephalitis	Encephalitis, Encephalitis autoimmune, Limbic encephalitis, Noninfective encephalitis, Immune-mediated encephalitis	Yes
Sarcoidosis	Sarcoidosis, Cutaneous sarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis	Yes
Infusion Reactions	Hypersensitivity, Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Cytokine release syndrome, Serum sickness, Serum sickness-like reaction, Infusion related reaction, Infusion related hypersensitivity reaction	No
Myasthenic Syndrome	Myasthenic syndrome, Myasthenia gravis, Myasthenia gravis crisis, Ocular myasthenia	Yes
Myelitis	Myelitis, Myelitis transverse	Yes
Vasculitis	Anti-neutrophil cytoplasmic antibody positive vasculitis, Aortitis, Arteritis, Arteritis coronary, Behcet's syndrome, Central nervous system vasculitis, Cerebral arteritis, Diffuse vasculitis, Eosinophilic granulomatosis with polyangiitis, Granulomatosis with polyangiitis, Haemorrhagic vasculitis, Hypersensitivity vasculitis, Microscopic polyangiitis, Ocular vasculitis, Polyarteritis nodosa, Pulmonary vasculitis, Renal arteritis, Renal vasculitis, Retinal vasculitis, Takayasu's arteritis, Giant cell arteritis, Vasculitis, Vasculitis gastrointestinal, Vasculitis necrotising	Yes
Cholangitis Sclerosing	Cholangitis sclerosing, Autoimmune cholangitis, Immune-mediated cholangitis	Yes

No new indication-specific, immune-related AEs causally associated with pembrolizumab were identified in the pembrolizumab + NAC / pembrolizumab group (see Tables below).

Table 2.7.4-tnbc3: 10 - Adverse Event Summary AEOSI Combined Phases (Neoadjuvant and Adjuvant) (APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	783		389		595		6,185	
with one or more adverse events	341	(43.6)	85	(21.9)	99	(16.6)	1,575	(25.5)
with no adverse event	442	(56.4)	304	(78.1)	496	(83.4)	4,610	(74.5)
with drug-related[a] adverse events	315	(40.2)	74	(19.0)	86	(14.5)	1,367	(22.1)
with toxicity grade 3-5 adverse events	117	(14.9)	8	(2.1)	15	(2.5)	406	(6.6)
with toxicity grade 3-5 drug-related	111	(14.2)	7	(1.8)	12	(2.0)	352	(5.7)

adverse events								
with serious adverse events	83	(10.6)	5	(1.3)	16	(2.7)	410	(6.6)
with serious drug-related adverse events	80	(10.2)	4	(1.0)	16	(2.7)	363	(5.9)
who died	2	(0.3)	0	(0.0)	0	(0.0)	11	(0.2)
who died due to a drug-related adverse event	2	(0.3)	0	(0.0)	0	(0.0)	11	(0.2)
discontinued any drug due to an adverse event	85	(10.9)	10	(2.6)	7	(1.2)	255	(4.1)
discontinued pembrolizumab or placebo	61	(7.8)	4	(1.0)	7	(1.2)	255	(4.1)
discontinued any chemotherapy	45	(5.7)	7	(1.8)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	85	(10.9)	10	(2.6)	7	(1.2)	251	(4.1)
discontinued pembrolizumab or placebo	61	(7.8)	4	(1.0)	7	(1.2)	251	(4.1)
discontinued any chemotherapy	45	(5.7)	7	(1.8)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	48	(6.1)	2	(0.5)	4	(0.7)	172	(2.8)
discontinued pembrolizumab or placebo	43	(5.5)	2	(0.5)	4	(0.7)	172	(2.8)
discontinued any chemotherapy	21	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	48	(6.1)	2	(0.5)	4	(0.7)	170	(2.7)
discontinued pembrolizumab or placebo	43	(5.5)	2	(0.5)	4	(0.7)	170	(2.7)
discontinued any chemotherapy	21	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.0.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Table 5.3.5.3.3-tnbc3: 30
Participants With Adverse Events of Special Interest by AEOSI Category and Preferred Term
(Incidence > 0% in One or More Treatment Groups)
Combined Phases (Neoadjuvant and Adjuvant)
(APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	783		389		595		6,185	
with one or more adverse events	341	(43.6)	85	(21.9)	99	(16.6)	1,575	(25.5)
with no adverse events	442	(56.4)	304	(78.1)	496	(83.4)	4,610	(74.5)
Adrenal Insufficiency	**20**	**(2.6)**	**0**	**(0.0)**	**4**	**(0.7)**	**52**	**(0.8)**
Addison's disease	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Adrenal insufficiency	20	(2.6)	0	(0.0)	2	(0.3)	47	(0.8)
Adrenocortical insufficiency acute	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Secondary adrenocortical insufficiency	0	(0.0)	0	(0.0)	2	(0.3)	1	(0.0)
Colitis	**13**	**(1.7)**	**3**	**(0.8)**	**5**	**(0.8)**	**121**	**(2.0)**
Autoimmune colitis	1	(0.1)	0	(0.0)	0	(0.0)	5	(0.1)
Colitis	8	(1.0)	3	(0.8)	4	(0.7)	104	(1.7)
Colitis microscopic	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.1)
Enterocolitis	4	(0.5)	0	(0.0)	1	(0.2)	8	(0.1)
Immune-mediated enterocolitis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Encephalitis	**2**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**
Encephalitis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Encephalitis autoimmune	2	(0.3)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre Syndrome	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(0.1)**
Axonal neuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Demyelinating polyneuropathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Guillain-Barre syndrome	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Hepatitis	**11**	**(1.4)**	**3**	**(0.8)**	**1**	**(0.2)**	**61**	**(1.0)**
Autoimmune hepatitis	3	(0.4)	1	(0.3)	0	(0.0)	26	(0.4)
Drug-induced liver injury	0	(0.0)	0	(0.0)	0	(0.0)	7	(0.1)
Hepatitis	4	(0.5)	1	(0.3)	1	(0.2)	26	(0.4)
Hepatitis acute	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Immune-mediated hepatitis	5	(0.6)	1	(0.3)	0	(0.0)	2	(0.0)
Hyperthyroidism	**41**	**(5.2)**	**7**	**(1.8)**	**24**	**(4.0)**	**261**	**(4.2)**
Hyperthyroidism	41	(5.2)	7	(1.8)	24	(4.0)	261	(4.2)
Hypophysitis	**15**	**(1.9)**	**1**	**(0.3)**	**0**	**(0.0)**	**38**	**(0.6)**

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Hypophysitis	**15**	**(1.9)**	**1**	**(0.3)**	**0**	**(0.0)**	**38**	**(0.6)**
Hypophysitis	10	(1.3)	0	(0.0)	0	(0.0)	24	(0.4)
Hypopituitarism	5	(0.6)	1	(0.3)	0	(0.0)	14	(0.2)
Hypothyroidism	**118**	**(15.1)**	**22**	**(5.7)**	**53**	**(8.9)**	**699**	**(11.3)**
Hypothyroidism	118	(15.1)	22	(5.7)	53	(8.9)	698	(11.3)
Myxoedema	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Primary hypothyroidism	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Infusion Reactions	**141**	**(18.0)**	**45**	**(11.6)**	**5**	**(0.8)**	**149**	**(2.4)**
Anaphylactic reaction	4	(0.5)	3	(0.8)	0	(0.0)	10	(0.2)
Anaphylactoid reaction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Cytokine release syndrome	3	(0.4)	0	(0.0)	0	(0.0)	8	(0.1)
Drug hypersensitivity	20	(2.6)	8	(2.1)	1	(0.2)	19	(0.3)
Hypersensitivity	40	(5.1)	10	(2.6)	1	(0.2)	50	(0.8)
Infusion related reaction	79	(10.1)	27	(6.9)	3	(0.5)	63	(1.0)
Serum sickness	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Myasthenic Syndrome	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.2)**	**3**	**(0.0)**
Myasthenia gravis	1	(0.1)	0	(0.0)	1	(0.2)	1	(0.0)
Myasthenic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Myelitis	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Myelitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myelitis transverse	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Myocarditis	**5**	**(0.6)**	**0**	**(0.0)**	**1**	**(0.2)**	**7**	**(0.1)**
Myocarditis	5	(0.6)	0	(0.0)	1	(0.2)	7	(0.1)
Myositis	**4**	**(0.5)**	**0**	**(0.0)**	**2**	**(0.3)**	**21**	**(0.3)**
Myopathy	1	(0.1)	0	(0.0)	0	(0.0)	4	(0.1)
Myositis	3	(0.4)	0	(0.0)	2	(0.3)	14	(0.2)
Necrotising myositis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rhabdomyolysis	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.0)
Nephritis	**7**	**(0.9)**	**0**	**(0.0)**	**1**	**(0.2)**	**25**	**(0.4)**
Acute kidney injury	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Nephritis	**7**	**(0.9)**	**0**	**(0.0)**	**1**	**(0.2)**	**25**	**(0.4)**
Autoimmune nephritis	1	(0.1)	0	(0.0)	0	(0.0)	3	(0.0)
Glomerulonephritis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Glomerulonephritis membranous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Nephritis	3	(0.4)	0	(0.0)	0	(0.0)	4	(0.1)
Nephrotic syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Renal failure	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Tubulointerstitial nephritis	4	(0.5)	0	(0.0)	1	(0.2)	11	(0.2)
Pancreatitis	**5**	**(0.6)**	**0**	**(0.0)**	**0**	**(0.0)**	**21**	**(0.3)**
Autoimmune pancreatitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pancreatitis	4	(0.5)	0	(0.0)	0	(0.0)	17	(0.3)
Pancreatitis acute	2	(0.3)	0	(0.0)	0	(0.0)	4	(0.1)
Pneumonitis	**17**	**(2.2)**	**6**	**(1.5)**	**16**	**(2.7)**	**286**	**(4.6)**
Interstitial lung disease	1	(0.1)	0	(0.0)	2	(0.3)	25	(0.4)
Organising pneumonia	0	(0.0)	0	(0.0)	1	(0.2)	3	(0.0)
Pneumonitis	16	(2.0)	6	(1.5)	13	(2.2)	261	(4.2)
Sarcoidosis	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**10**	**(0.2)**
Sarcoidosis	1	(0.1)	0	(0.0)	0	(0.0)	10	(0.2)
Severe Skin Reactions	**45**	**(5.7)**	**4**	**(1.0)**	**6**	**(1.0)**	**102**	**(1.6)**
Dermatitis bullous	5	(0.6)	1	(0.3)	1	(0.2)	8	(0.1)
Dermatitis exfoliative	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Dermatitis exfoliative generalised	3	(0.4)	1	(0.3)	1	(0.2)	2	(0.0)
Erythema multiforme	5	(0.6)	1	(0.3)	1	(0.2)	5	(0.1)
Exfoliative rash	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Oral lichen planus	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Pemphigoid	1	(0.1)	0	(0.0)	0	(0.0)	3	(0.0)
Pemphigus	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Pruritus	2	(0.3)	0	(0.0)	1	(0.2)	12	(0.2)
Pruritus genital	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Rash	14	(1.8)	1	(0.3)	1	(0.2)	31	(0.5)
Rash erythematous	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Rash maculo-papular	15	(1.9)	0	(0.0)	1	(0.2)	17	(0.3)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Severe Skin Reactions	**45**	**(5.7)**	**4**	**(1.0)**	**6**	**(1.0)**	**102**	**(1.6)**
Rash pruritic	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Rash pustular	1	(0.1)	0	(0.0)	0	(0.0)	1	(0.0)
Skin necrosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.0)
Stevens-Johnson syndrome	1	(0.1)	0	(0.0)	0	(0.0)	3	(0.0)
Toxic skin eruption	1	(0.1)	0	(0.0)	0	(0.0)	4	(0.1)
Thyroiditis	**16**	**(2.0)**	**5**	**(1.3)**	**1**	**(0.2)**	**62**	**(1.0)**
Autoimmune thyroiditis	8	(1.0)	2	(0.5)	0	(0.0)	15	(0.2)
Thyroid disorder	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.1)
Thyroiditis	8	(1.0)	3	(0.8)	1	(0.2)	44	(0.7)
Type 1 Diabetes Mellitus	**4**	**(0.5)**	**0**	**(0.0)**	**2**	**(0.3)**	**21**	**(0.3)**
Diabetic ketoacidosis	1	(0.1)	0	(0.0)	1	(0.2)	9	(0.1)
Type 1 diabetes mellitus	4	(0.5)	0	(0.0)	1	(0.2)	17	(0.3)
Uveitis	**2**	**(0.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**23**	**(0.4)**
Chorioretinitis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Iridocyclitis	1	(0.1)	0	(0.0)	0	(0.0)	4	(0.1)
Iritis	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.0)
Uveitis	1	(0.1)	0	(0.0)	0	(0.0)	15	(0.2)
Vasculitis	**4**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		TNBC Safety Dataset for Pembrolizumab Monotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Vasculitis	**4**	**(0.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.0)**
Vasculitis	4	(0.5)	0	(0.0)	0	(0.0)	2	(0.0)

Every participant is counted a single time for each applicable row and column.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

The overall incidence of AEOSIs was higher in the pembrolizumab + NAC group / pembrolizumab compared with the RSD; the longer duration of exposure to study treatment in the pembrolizumab + NAC / pembrolizumab group should be taken into consideration. The types and severity of AEOSIs

observed in the pembrolizumab + NAC / pembrolizumab group were generally consistent with the pembrolizumab monotherapy RSD. Most AEOSIs reported in the pembrolizumab + NAC / pembrolizumab group were mild to moderate in severity (Grade 1 or 2), nonserious, managed with treatment interruption and corticosteroids and/or hormone replacement therapy, and did not result in discontinuation of study intervention. Most Grade 3 to 4 AEOSIs were reported in <5 participants, except for severe skin reactions (n=37 [4.7%]), infusion reactions (n=21 [2.7%]), rash maculopapular (n=15 [1.9%]), rash (n=14 [1.8%]), hypophysitis (n=10 [1.3%]), hepatitis (n=9 [1.1%]), adrenal insufficiency (n=8 [1.0%]), colitis (n=6 [0.8%]), nephritis (n=6 [0.8%], pneumonitis (n=6 [0.8%]), and pancreatitis (n=5 [0.6%]).

Most infusion reactions were Grade 1 or 2 in severity, treated with corticosteroids (60.3%), and considered resolved (57.2%). The median time to onset for infusion reactions was shorter in the pembrolizumab + NAC / pembrolizumab group (16.0 days) compared with pembrolizumab monotherapy RSD (42.0 days); however, the median episode duration was identical to pembrolizumab monotherapy RSD (1.0 day for both). The use of premedication was similar between treatment groups (97.6% and 96.9% in the pembrolizumab + NAC / pembrolizumab group and placebo + NAC / placebo group, respectively). The most commonly used premedications in the ASaT population (incidence ≥ 20%) were dexamethasone (74.6%), acetaminophen (28.8%), and diphenhydramine (22.3%).

Summaries of infusion reaction AEOSIs are provided for participants without premedication and participants with premedication in the tables below.

Table Participants With Selected Adverse Events of Special Interest (AEOSI) by AEOSI Category (Incidence > 0% in One or More Treatment Groups) Participants without Premedication Combined Phases

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	19		12		31	
with one or more adverse events	3	(15.8)	2	(16.7)	5	(16.1)
with no adverse events	16	(84.2)	10	(83.3)	26	(83.9)
Infusion Reactions	**3**	**(15.8)**	**2**	**(16.7)**	**5**	**(16.1)**
Anaphylactic reaction	0	(0.0)	1	(8.3)	1	(3.2)
Hypersensitivity	2	(10.5)	1	(8.3)	3	(9.7)
Infusion related reaction	1	(5.3)	1	(8.3)	2	(6.5)

Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.

"Infusion related reaction" includes infusion related reactions due to pembrolizumab and chemotherapy, for example, Paclitaxel.

Included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events.

The selected AEOSI category is "Infusion Reactions" identified per safety judgement.

Database Cutoff Date: 23MAR2021

Table: Participants With Selected Adverse Events of Special Interest (AEOSI) by AEOSI Category (Incidence > 0% in One or More Treatment Groups) Participants with

Premedication Combined Phases

	MK-3475 + chemotherapy / MK-3475		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	764		377		1,141	
with one or more adverse events	138	(18.1)	43	(11.4)	181	(15.9)
with no adverse events	626	(81.9)	334	(88.6)	960	(84.1)
Infusion Reactions	**138**	**(18.1)**	**43**	**(11.4)**	**181**	**(15.9)**
Anaphylactic reaction	4	(0.5)	2	(0.5)	6	(0.5)
Cytokine release syndrome	3	(0.4)	0	(0.0)	3	(0.3)
Drug hypersensitivity	20	(2.6)	8	(2.1)	28	(2.5)
Hypersensitivity	38	(5.0)	9	(2.4)	47	(4.1)
Infusion related reaction	78	(10.2)	26	(6.9)	104	(9.1)
Serum sickness	1	(0.1)	0	(0.0)	1	(0.1)

Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.

"Infusion related reaction" includes infusion related reactions due to pembrolizumab and chemotherapy, for example, Paclitaxel.

Included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events.

The selected AEOSI category is "Infusion Reactions" identified per safety judgement.

Database Cutoff Date: 23MAR2021

Overall, the incidence of infusion reactions for participants in the pembrolizumab + NAC / pembrolizumab group was generally similar between those who received pre-medication and those who did not (18.1% vs 15.8%).

Most severe skin reactions were Grade 3 in severity, treated with systemic corticosteroids (62.2%), and considered resolved (84.4%). The median time to onset and the median episode duration for severe skin reactions were shorter in the pembrolizumab + NAC / pembrolizumab group (64.0 and 27.0 days, respectively) compared with pembrolizumab monotherapy RSD (106.0 and 58.0 days, respectively).

Most events of hypothyroidism were Grade 1 or 2 in severity. Few events were treated with corticosteroids (3.4%) and most were considered not resolved (54.2%), consistent with an endocrine abnormality and the need for continued hormone replacement therapy. The median time to onset for events of hypothyroidism was 105.0 days in both the pembrolizumab + NAC / pembrolizumab group and pembrolizumab monotherapy RSD.

Events classified as adrenal insufficiency were 2.6% in the pembrolizumab + NAC / pembrolizumab group and 0.8% in the pembrolizumab monotherapy RSD. Most events were Grade 2 or 3 and there were no Grade 5 events. Events of adrenal insufficiency were managed with treatment interruption and corticosteroids. Overall, the severity, outcome, and manageability of adrenal insufficiency events were generally consistent with those previously reported for pembrolizumab monotherapy RSD.

There were 2 deaths due to an AEOSI (pneumonitis [neoadjuvant phase] and autoimmune encephalitis [adjuvant phase]) in the pembrolizumab + NAC / pembrolizumab group, which were considered related to pembrolizumab by the investigator.

The overall incidences of AEOSIs during the neo-adjuvant and adjuvant phases in study KN-522 is summarized in Tables below:

Table 14.3.4.1-1
Adverse Event Summary
Adverse Event of Special Interest (AEOSI)
All Participants
Neoadjuvant Phase
(ASaT Population)

	MK-3475 + chemotherapy		Placebo + chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	783		389		1,172	
with one or more adverse events	308	(39.3)	71	(18.3)	379	(32.3)
with no adverse event	475	(60.7)	318	(81.7)	793	(67.7)
with drug-related[a] adverse events	291	(37.2)	63	(16.2)	354	(30.2)
with toxicity grade 3-5 adverse events	102	(13.0)	7	(1.8)	109	(9.3)
with toxicity grade 3-5 drug-related adverse events	99	(12.6)	6	(1.5)	105	(9.0)
with serious adverse events	71	(9.1)	4	(1.0)	75	(6.4)
with serious drug-related adverse events	69	(8.8)	3	(0.8)	72	(6.1)
with any dose modification[b] due to an adverse event	148	(18.9)	32	(8.2)	180	(15.4)
MK3475/PLACEBO dose modification	83	(10.6)	11	(2.8)	94	(8.0)
PACLITAXEL dose modification	84	(10.7)	22	(5.7)	106	(9.0)
CARBOPLATIN dose modification	64	(8.2)	12	(3.1)	76	(6.5)
DOXORUBICIN dose modification	14	(1.8)	2	(0.5)	16	(1.4)
EPIRUBICIN dose modification	7	(0.9)	1	(0.3)	8	(0.7)
CYCLOPHOSPHAMIDE dose modification	22	(2.8)	3	(0.8)	25	(2.1)
who died	1	(0.1)	0	(0.0)	1	(0.1)
who died due to a drug-related adverse event	1	(0.1)	0	(0.0)	1	(0.1)
discontinued any drug due to an adverse event	77	(9.8)	9	(2.3)	86	(7.3)
discontinued MK3475/PLACEBO	53	(6.8)	3	(0.8)	56	(4.8)
discontinued PACLITAXEL	24	(3.1)	5	(1.3)	29	(2.5)
discontinued CARBOPLATIN	28	(3.6)	2	(0.5)	30	(2.6)
discontinued DOXORUBICIN	7	(0.9)	0	(0.0)	7	(0.6)

	MK-3475 + chemotherapy		Placebo + chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
discontinued EPIRUBICIN	1	(0.1)	0	(0.0)	1	(0.1)
discontinued CYCLOPHOSPHAMIDE	9	(1.1)	0	(0.0)	9	(0.8)
discontinued any drug due to a drug-related adverse event	77	(9.8)	9	(2.3)	86	(7.3)
discontinued MK3475/PLACEBO	53	(6.8)	3	(0.8)	56	(4.8)
discontinued PACLITAXEL	24	(3.1)	5	(1.3)	29	(2.5)
discontinued CARBOPLATIN	28	(3.6)	2	(0.5)	30	(2.6)
discontinued DOXORUBICIN	7	(0.9)	0	(0.0)	7	(0.6)
discontinued EPIRUBICIN	1	(0.1)	0	(0.0)	1	(0.1)
discontinued CYCLOPHOSPHAMIDE	9	(1.1)	0	(0.0)	9	(0.8)
discontinued any drug due to a serious adverse event	43	(5.5)	2	(0.5)	45	(3.8)
discontinued MK3475/PLACEBO	38	(4.9)	2	(0.5)	40	(3.4)
discontinued PACLITAXEL	13	(1.7)	0	(0.0)	13	(1.1)
discontinued CARBOPLATIN	11	(1.4)	0	(0.0)	11	(0.9)
discontinued DOXORUBICIN	7	(0.9)	0	(0.0)	7	(0.6)
discontinued EPIRUBICIN	1	(0.1)	0	(0.0)	1	(0.1)
discontinued CYCLOPHOSPHAMIDE	8	(1.0)	0	(0.0)	8	(0.7)
discontinued any drug due to a serious drug-related adverse event	43	(5.5)	2	(0.5)	45	(3.8)
discontinued MK3475/PLACEBO	38	(4.9)	2	(0.5)	40	(3.4)
discontinued PACLITAXEL	13	(1.7)	0	(0.0)	13	(1.1)
discontinued CARBOPLATIN	11	(1.4)	0	(0.0)	11	(0.9)
discontinued DOXORUBICIN	7	(0.9)	0	(0.0)	7	(0.6)
discontinued EPIRUBICIN	1	(0.1)	0	(0.0)	1	(0.1)

	MK-3475 + chemotherapy		Placebo + chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
discontinued CYCLOPHOSPHAMIDE	8	(1.0)	0	(0.0)	8	(0.7)

[a] Determined by the investigator to be related to the drug.

[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Grades are based on NCI CTCAE version 4.0.

Included adverse events started from the first neoadjuvant treatment including definitive surgery and prior to the first adjuvant treatment including radiation therapy or, if no adjuvant treatment, up to 30 days of the definitive surgery for the non-serious adverse events and up to 90 days of the definitive surgery for the serious adverse events or, if no surgery, up to 30 days of last neoadjuvant treatment for the non-serious adverse events and up to 90 days of last neoadjuvant treatment for the serious adverse events.

Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adsl; adae]

Table 14.3.4.1-2
Exposure-Adjusted Adverse Event Summary
(Including Multiple Occurrences of Events)
Adverse Event of Special Interest (AEOSI)
All Participants
Neoadjuvant Phase
(ASaT Population)

	Event Count and Rate (Events/100 person-years)[a]					
	MK-3475 + chemotherapy		Placebo + chemotherapy		Total	
Number of Participants exposed	783		389		1,172	
Total exposure[b] in person-years	464.24		232.82		697.06	
Total events (rate)						
adverse events	506	(109.00)	105	(45.10)	611	(87.65)
drug-related[c] adverse events	455	(98.01)	94	(40.37)	549	(78.76)
toxicity grade 3-5 adverse events	120	(25.85)	8	(3.44)	128	(18.36)
toxicity grade 3-5 drug-related adverse events	114	(24.56)	6	(2.58)	120	(17.22)
serious adverse events	80	(17.23)	4	(1.72)	84	(12.05)
serious drug-related adverse events	76	(16.37)	3	(1.29)	79	(11.33)
adverse events resulting in dose modification[d]	190	(40.93)	42	(18.04)	232	(33.28)
adverse events leading to death	1	(0.22)	0	(0.00)	1	(0.14)
drug-related adverse events leading to death	1	(0.22)	0	(0.00)	1	(0.14)
adverse events resulting in drug discontinuation	81	(17.45)	9	(3.87)	90	(12.91)
drug-related adverse events resulting in drug discontinuation	81	(17.45)	9	(3.87)	90	(12.91)
serious adverse events resulting in drug discontinuation	44	(9.48)	2	(0.86)	46	(6.60)
serious drug-related adverse events resulting in drug discontinuation	44	(9.48)	2	(0.86)	46	(6.60)

[a] Event rate per 100 person-years of exposure = event count *100/person-years of exposure.
[b] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[c] Determined by the investigator to be related to the drug.
[d] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.0.
Included adverse events started from the first neoadjuvant treatment including definitive surgery and prior to the first adjuvant treatment including radiation therapy or, if no adjuvant treatment, up to 30 days of the definitive surgery for the non-serious adverse events and up to 90 days of the definitive surgery for the serious adverse events or, if no surgery, up to 30 days of last neoadjuvant treatment for the non-serious adverse events and up to 90 days of last neoadjuvant treatment for the serious adverse events.
NOTE: Drug for this table means study treatments.
Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adsl; adae]

Table 14.3.4.1-5
Participants With Adverse Events Special Interest (AEOSI) By Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
All Participants
Neoadjuvant Phase
(ASaT Population)

	MK-3475 + chemotherapy		Placebo + chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	783		389		1,172	
with one or more adverse events	308	(39.3)	71	(18.3)	379	(32.3)
with no adverse events	475	(60.7)	318	(81.7)	793	(67.7)
Hypothyroidism	104	(13.3)	10	(2.6)	114	(9.7)
Infusion related reaction	78	(10.0)	26	(6.7)	104	(8.9)
Hypersensitivity	34	(4.3)	9	(2.3)	43	(3.7)
Hyperthyroidism	36	(4.6)	5	(1.3)	41	(3.5)
Drug hypersensitivity	18	(2.3)	7	(1.8)	25	(2.1)
Adrenal insufficiency	17	(2.2)	0	(0.0)	17	(1.5)
Pneumonitis	10	(1.3)	5	(1.3)	15	(1.3)
Rash maculo-papular	15	(1.9)	0	(0.0)	15	(1.3)
Autoimmune thyroiditis	8	(1.0)	2	(0.5)	10	(0.9)
Colitis	7	(0.9)	3	(0.8)	10	(0.9)
Hypophysitis	10	(1.3)	0	(0.0)	10	(0.9)
Rash	9	(1.1)	1	(0.3)	10	(0.9)
Thyroiditis	8	(1.0)	2	(0.5)	10	(0.9)
Anaphylactic reaction	4	(0.5)	3	(0.8)	7	(0.6)
Hypopituitarism	5	(0.6)	1	(0.3)	6	(0.5)
Immune-mediated hepatitis	5	(0.6)	1	(0.3)	6	(0.5)
Dermatitis bullous	4	(0.5)	1	(0.3)	5	(0.4)
Hepatitis	4	(0.5)	1	(0.3)	5	(0.4)
Autoimmune hepatitis	3	(0.4)	1	(0.3)	4	(0.3)
Enterocolitis	4	(0.5)	0	(0.0)	4	(0.3)
Pancreatitis	4	(0.5)	0	(0.0)	4	(0.3)
Tubulointerstitial nephritis	4	(0.5)	0	(0.0)	4	(0.3)
Vasculitis	4	(0.5)	0	(0.0)	4	(0.3)
Cytokine release syndrome	3	(0.4)	0	(0.0)	3	(0.3)
Dermatitis exfoliative generalised	2	(0.3)	1	(0.3)	3	(0.3)
Erythema multiforme	2	(0.3)	1	(0.3)	3	(0.3)
Myocarditis	3	(0.4)	0	(0.0)	3	(0.3)

	MK-3475 + chemotherapy		Placebo + chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Type 1 diabetes mellitus	3	(0.4)	0	(0.0)	3	(0.3)
Myositis	2	(0.3)	0	(0.0)	2	(0.2)
Nephritis	2	(0.3)	0	(0.0)	2	(0.2)
Pruritus	2	(0.3)	0	(0.0)	2	(0.2)
Autoimmune colitis	1	(0.1)	0	(0.0)	1	(0.1)
Autoimmune nephritis	1	(0.1)	0	(0.0)	1	(0.1)
Diabetic ketoacidosis	1	(0.1)	0	(0.0)	1	(0.1)
Encephalitis autoimmune	1	(0.1)	0	(0.0)	1	(0.1)
Iridocyclitis	1	(0.1)	0	(0.0)	1	(0.1)
Myopathy	1	(0.1)	0	(0.0)	1	(0.1)
Pancreatitis acute	1	(0.1)	0	(0.0)	1	(0.1)
Rash pustular	1	(0.1)	0	(0.0)	1	(0.1)
Sarcoidosis	1	(0.1)	0	(0.0)	1	(0.1)
Serum sickness	1	(0.1)	0	(0.0)	1	(0.1)
Stevens-Johnson syndrome	1	(0.1)	0	(0.0)	1	(0.1)
Toxic skin eruption	1	(0.1)	0	(0.0)	1	(0.1)
Uveitis	1	(0.1)	0	(0.0)	1	(0.1)

Every participant is counted a single time for each applicable specific adverse event.

"Infusion related reaction" includes infusion related reactions due to pembrolizumab and chemotherapy, for example, Paclitaxel.

Included adverse events started from the first neoadjuvant treatment including definitive surgery and prior to the first adjuvant treatment including radiation therapy or, if no adjuvant treatment, up to 30 days of the definitive surgery for the non-serious adverse events and up to 90 days of the definitive surgery for the serious adverse events or, if no surgery, up to 30 days of last neoadjuvant treatment for the non-serious adverse events and up to 90 days of last neoadjuvant treatment for the serious adverse events.

Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adsl; adae]

Table 14.3.4.1-7
Summary of Outcome for Participants With AEOSI
(Incidence > 0%)
All Participants
Neoadjuvant Phase
(ASaT Population)

	Outcome	MK-3475 + chemotherapy		Placebo + chemotherapy		Total	
		n	(%)	n	(%)	n	(%)
Participants in population		783		389		1172	
With one or more AEOSI	**Overall**	**308**	**(39.3)**	**71**	**(18.3)**	**379**	**(32.3)**
	Fatal	2	(0.6)	0	(0.0)	2	(0.5)
	Not Resolved	89	(28.9)	13	(18.3)	102	(26.9)
	Resolving	26	(8.4)	1	(1.4)	27	(7.1)
	Unknown	0	(0.0)	0	(0.0)	0	(0.0)
	Sequelae	15	(4.9)	1	(1.4)	16	(4.2)
	Resolved	176	(57.1)	56	(78.9)	232	(61.2)

Modified from Table 14.3.4.1-7

Table 14.3.4.2-1
Adverse Event Summary
Adverse Event of Special Interest (AEOSI)
All Participants
Adjuvant Phase
(ASaT Population)

	MK-3475		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	588		331		919	
with one or more adverse events	60	(10.2)	20	(6.0)	80	(8.7)
with no adverse event	528	(89.8)	311	(94.0)	839	(91.3)
with drug-related[a] adverse events	45	(7.7)	15	(4.5)	60	(6.5)
with toxicity grade 3-5 adverse events	17	(2.9)	1	(0.3)	18	(2.0)
with toxicity grade 3-5 drug-related adverse events	14	(2.4)	1	(0.3)	15	(1.6)
with serious adverse events	12	(2.0)	1	(0.3)	13	(1.4)
with serious drug-related adverse events	11	(1.9)	1	(0.3)	12	(1.3)
with dose modification[b] due to an adverse event	18	(3.1)	2	(0.6)	20	(2.2)
who died	1	(0.2)	0	(0.0)	1	(0.1)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)	1	(0.1)
discontinued drug due to an adverse event	8	(1.4)	1	(0.3)	9	(1.0)
discontinued drug due to a drug-related adverse event	8	(1.4)	1	(0.3)	9	(1.0)
discontinued drug due to a serious adverse event	5	(0.9)	0	(0.0)	5	(0.5)
discontinued drug due to a serious drug-related adverse event	5	(0.9)	0	(0.0)	5	(0.5)

[a] Determined by the investigator to be related to the drug.

[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Grades are based on NCI CTCAE version 4.0.

Included adverse events started from the first adjuvant treatment including radiation therapy and up to 30 days of last adjuvant treatment including radiation therapy for the non-serious adverse events and up to 90 days of last adjuvant treatment for the serious adverse events.

Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adsl; adae]

Table 14.3.4.2-2
Exposure-Adjusted Adverse Event Summary
(Including Multiple Occurrences of Events)
Adverse Event of Special Interest (AEOSI)
All Participants
Adjuvant Phase
(ASaT Population)

	Event Count and Rate (Events/100 person-years)[a]					
	MK-3475		Placebo		Total	
Number of Participants exposed	588		331		919	
Total exposure[b] in person-years	339.33		195.41		534.74	
Total events (rate)						
adverse events	67	(19.74)	22	(11.26)	89	(16.64)
drug-related[c] adverse events	50	(14.73)	17	(8.70)	67	(12.53)
toxicity grade 3-5 adverse events	17	(5.01)	1	(0.51)	18	(3.37)
toxicity grade 3-5 drug-related adverse events	14	(4.13)	1	(0.51)	15	(2.81)
serious adverse events	12	(3.54)	1	(0.51)	13	(2.43)
serious drug-related adverse events	11	(3.24)	1	(0.51)	12	(2.24)
adverse events resulting in dose modification[d]	18	(5.30)	2	(1.02)	20	(3.74)
adverse events leading to death	1	(0.29)	0	(0.00)	1	(0.19)
drug-related adverse events leading to death	1	(0.29)	0	(0.00)	1	(0.19)
adverse events resulting in drug discontinuation	8	(2.36)	1	(0.51)	9	(1.68)
drug-related adverse events resulting in drug discontinuation	8	(2.36)	1	(0.51)	9	(1.68)
serious adverse events resulting in drug discontinuation	5	(1.47)	0	(0.00)	5	(0.94)
serious drug-related adverse events resulting in drug discontinuation	5	(1.47)	0	(0.00)	5	(0.94)

[a] Event rate per 100 person-years of exposure = event count *100/person-years of exposure.
[b] Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cutoff date.
[c] Determined by the investigator to be related to the drug.
[d] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.0.
Included adverse events started from the first adjuvant treatment including radiation therapy and up to 30 days of last adjuvant treatment including radiation therapy for the non-serious adverse events and up to 90 days of last adjuvant treatment for the serious adverse events.
NOTE: Drug for this table means study treatments.
Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adsl; adae]

Table 14.3.4.2-4
Participants With Adverse Events Special Interest (AEOSI) By Decreasing Incidence
(Incidence > 0% in One or More Treatment Groups)
All Participants
Adjuvant Phase
(ASaT Population)

	MK-3475		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	588		331		919	
with one or more adverse events	60	(10.2)	20	(6.0)	80	(8.7)
with no adverse events	528	(89.8)	311	(94.0)	839	(91.3)
Hypothyroidism	17	(2.9)	12	(3.6)	29	(3.2)
Pneumonitis	6	(1.0)	2	(0.6)	8	(0.9)
Hypersensitivity	6	(1.0)	1	(0.3)	7	(0.8)
Hyperthyroidism	5	(0.9)	2	(0.6)	7	(0.8)
Rash	5	(0.9)	0	(0.0)	5	(0.5)
Drug hypersensitivity	3	(0.5)	1	(0.3)	4	(0.4)
Infusion related reaction	2	(0.3)	2	(0.6)	4	(0.4)
Adrenal insufficiency	3	(0.5)	0	(0.0)	3	(0.3)
Erythema multiforme	3	(0.5)	0	(0.0)	3	(0.3)
Colitis	2	(0.3)	0	(0.0)	2	(0.2)
Myocarditis	2	(0.3)	0	(0.0)	2	(0.2)
Dermatitis bullous	1	(0.2)	0	(0.0)	1	(0.1)
Dermatitis exfoliative generalised	1	(0.2)	0	(0.0)	1	(0.1)
Encephalitis autoimmune	1	(0.2)	0	(0.0)	1	(0.1)
Interstitial lung disease	1	(0.2)	0	(0.0)	1	(0.1)
Myasthenia gravis	1	(0.2)	0	(0.0)	1	(0.1)
Myositis	1	(0.2)	0	(0.0)	1	(0.1)
Nephritis	1	(0.2)	0	(0.0)	1	(0.1)
Pancreatitis acute	1	(0.2)	0	(0.0)	1	(0.1)
Pemphigoid	1	(0.2)	0	(0.0)	1	(0.1)
Thyroiditis	0	(0.0)	1	(0.3)	1	(0.1)
Type 1 diabetes mellitus	1	(0.2)	0	(0.0)	1	(0.1)

Every participant is counted a single time for each applicable specific adverse event.
"Infusion related reaction" includes infusion related reactions due to pembrolizumab and chemotherapy, for example, Paclitaxel.
Included adverse events started from the first adjuvant treatment including radiation therapy and up to 30 days of last adjuvant treatment including radiation therapy for the non-serious adverse events and up to 90 days of last adjuvant treatment for the serious adverse events.
Database Cutoff Date: 23MAR2021

Source: [P522V03MK3475: adam-adsl; adae]

Table 14.3.4.2-6
Summary of Outcome for Participants With AEOSI
(Incidence > 0%)
All Participants
Adjuvant Phase
(ASaT Population)

	Outcome	MK-3475 n	MK-3475 (%)	Placebo n	Placebo (%)	Total n	Total (%)
Participants in population		588		331		919	
With one or more AEOSI	**Overall**	**60**	**(10.2)**	**20**	**(6.0)**	**80**	**(8.7)**
	Fatal	1	(1.7)	0	(0.0)	1	(1.3)
	Not Resolved	19	(31.7)	10	(50.0)	29	(36.3)
	Resolving	10	(16.7)	0	(0.0)	10	(12.5)
	Unknown	1	(1.7)	0	(0.0)	1	(1.3)
	Sequelae	1	(1.7)	0	(0.0)	1	(1.3)
	Resolved	28	(46.7)	10	(50.0)	38	(47.5)

Modified from Table 14.3.4.2-6

Additional tables of AE by category and maximum toxicity grade were provided also including the following preferred terms (PTs):

• The PTs of pericarditis, autoimmune pericarditis, pericardial effusion, cardiac tamponade comprised the category of "Pericarditis"

• The PTs of polyneuropathy, multifocal motor neuropathy, acute polyneuropathy, axonal neuropathy, acute motor-sensory axonal neuropathy, peripheral motor neuropathy; mononeuropathy multiplex and peripheral sensory neuropathy comprised the category of "Polyneuropathies"

• The PTs of autoimmune aplastic anaemia, aplasia pure red cell, and autoimmune haemolytic anaemia comprised the category of "Anaemia"

• The PT haemophagocytic lymphohistiocytosis

• The PT immune thrombocytopenia

There was a higher incidence of polyneuropathies observed in the pembrolizumab + NAC / pembrolizumab group compared with the pembrolizumab monotherapy EU RSD; however, this is consistent with the established safety profile of the chemotherapies administered (see Table below).

Table: Participants With Adverse Events by Category and Preferred Term for Selected Terms (Incidence > 0% in One or More Treatment Groups) Combined Phases (Neoadjuvant and Adjuvant) (APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d] n	(%)	KN522 Placebo + Chemotherapy / Placebo[e] n	(%)	Pembrolizumab Monotherapy Reference Safety Dataset[f] n	(%)
Participants in population	783		389		6,185	
with one or more adverse events	183	(23.4)	93	(23.9)	161	(2.6)
with no adverse events	600	(76.6)	296	(76.1)	6,024	(97.4)
Anemia	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.0)**

Autoimmune haemolytic anaemia	0	(0.0)	0	(0.0)	1	(0.0)
Haemophagocytic lymphohistiocytosis	**0**	**(0.0)**	**1**	**(0.3)**	**0**	**(0.0)**
Haemophagocytic lymphohistiocytosis	0	(0.0)	1	(0.3)	0	(0.0)
Immune thrombocytopenia	**1**	**(0.1)**	**0**	**(0.0)**	**6**	**(0.1)**
Immune thrombocytopenia	1	(0.1)	0	(0.0)	6	(0.1)
Pericarditis	**4**	**(0.5)**	**1**	**(0.3)**	**67**	**(1.1)**
Autoimmune pericarditis	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac tamponade	0	(0.0)	0	(0.0)	10	(0.2)
Pericardial effusion	4	(0.5)	1	(0.3)	52	(0.8)
Pericarditis	0	(0.0)	0	(0.0)	9	(0.1)
Polyneuropathies	**180**	**(23.0)**	**91**	**(23.4)**	**88**	**(1.4)**
Axonal neuropathy	0	(0.0)	0	(0.0)	1	(0.0)
Peripheral motor neuropathy	8	(1.0)	4	(1.0)	9	(0.1)
Peripheral sensory neuropathy	156	(19.9)	72	(18.5)	71	(1.1)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		Pembrolizumab Monotherapy Reference Safety Dataset[f]	
	n	(%)	n	(%)	n	(%)
Polyneuropathies	**180**	**(23.0)**	**91**	**(23.4)**	**88**	**(1.4)**
Polyneuropathy	21	(2.7)	15	(3.9)	8	(0.1)

Every participant is counted a single time for each applicable row and column.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for TNBC (KN522: 23MAR2021)

Laboratory findings

Laboratory abnormalities occurred more frequently during the neoadjuvant phase compared with the adjuvant phase, likely due to the concomitant chemotherapy during the neoadjuvant phase.

Of the protocol-specified laboratory tests, leukocytes decreased (40.8% vs 32.5%) and lymphocytes decreased (27.5% vs 22.2%) were the only CTCAE Grade 3 to 4 events reported at a higher incidence (≥5 percentage point difference) in the pembrolizumab + NAC / pembrolizumab group compared with the placebo + NAC / placebo group.

The incidences of Grade 3 to 4 laboratory abnormalities were generally similar between the pembrolizumab + NAC / pembrolizumab group and the pembrolizumab monotherapy RSD. The following Grade 3 to 4 laboratory abnormalities were reported with an incidence ≥5% and were higher (≥5 percentage point difference) in the pembrolizumab + NAC / pembrolizumab group compared with the pembrolizumab monotherapy RSD: ALT increased (9.4% vs 3.0%), haemoglobin decreased

(21.9% vs 6.4%), leukocytes decreased (40.8% vs 0.8%), lymphocytes decreased (27.5% vs 11.0%), neutrophils decreased (62.2% vs 2.1%), and platelets decreased (10.7% vs 2.0%).

Safety in special populations

AEs were assessed in subgroups of participants stratified by age, ECOG performance status, sex and region.

Age

The observed incidences of Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, SAEs, drug-related SAEs, and discontinuation of study intervention due to an AE (including drug-related AEs, SAEs, serious drug-related AEs) in the pembrolizumab + NAC / pembrolizumab group were higher (≥5 percentage point difference) in the ≥65 years age category (see Table below). Due to the small sample size in the ≥65 years age category/ies, results in the pembrolizumab + NAC / pembrolizumab group should be interpreted with caution.

Table 2.7.4-tnbc3: 12 - Adverse Event Summary by Age Category (<65, >=65 Years) Combined Phases (Neoadjuvant and Adjuvant) (APaT Population)

Table 2.7.4-tnbc3: 12
Adverse Event Summary by Age Category (<65, >=65 Years)
Combined Phases (Neoadjuvant and Adjuvant)
(APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]				KN522 Placebo + Chemotherapy / Placebo[e]				TNBC Safety Dataset for Pembrolizumab Monotherapy[f]				Pembrolizumab Monotherapy Reference Safety Dataset[g]			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	699		84		341		48		474		121		3,587		2,598	
with one or more adverse events	694	(99.3)	83	(98.8)	341	(100.0)	48	(100.0)	441	(93.0)	118	(97.5)	3,466	(96.6)	2,518	(96.9)
with no adverse event	5	(0.7)	1	(1.2)	0	(0.0)	0	(0.0)	33	(7.0)	3	(2.5)	121	(3.4)	80	(3.1)
with drug-related[a] adverse events	692	(99.0)	82	(97.6)	340	(99.7)	48	(100.0)	288	(60.8)	80	(66.1)	2,519	(70.2)	1,845	(71.0)
with toxicity grade 3-5 adverse events	572	(81.8)	73	(86.9)	270	(79.2)	36	(75.0)	171	(36.1)	47	(38.8)	1,594	(44.4)	1,386	(53.3)
with toxicity grade 3-5 drug-related adverse events	535	(76.5)	69	(82.1)	252	(73.9)	33	(68.8)	59	(12.4)	20	(16.5)	495	(13.8)	480	(18.5)
with serious adverse events	296	(42.3)	45	(53.6)	100	(29.3)	11	(22.9)	113	(23.8)	27	(22.3)	1,237	(34.5)	1,135	(43.7)
with serious drug-related adverse events	228	(32.6)	39	(46.4)	72	(21.1)	6	(12.5)	36	(7.6)	10	(8.3)	374	(10.4)	331	(12.7)
who died	5	(0.7)	2	(2.4)	1	(0.3)	0	(0.0)	11	(2.3)	0	(0.0)	148	(4.1)	173	(6.7)
who died due to a drug-related adverse event	2	(0.3)	2	(2.4)	1	(0.3)	0	(0.0)	2	(0.4)	0	(0.0)	22	(0.6)	18	(0.7)
discontinued any drug due to an adverse event	197	(28.2)	37	(44.0)	51	(15.0)	9	(18.8)	21	(4.4)	9	(7.4)	422	(11.8)	409	(15.7)
discontinued pembrolizumab or placebo	132	(18.9)	25	(29.8)	27	(7.9)	4	(8.3)	21	(4.4)	9	(7.4)	422	(11.8)	409	(15.7)
discontinued any chemotherapy	113	(16.2)	23	(27.4)	34	(10.0)	8	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	183	(26.2)	34	(40.5)	46	(13.5)	9	(18.8)	14	(3.0)	6	(5.0)	228	(6.4)	216	(8.3)
discontinued pembrolizumab or placebo	118	(16.9)	22	(26.2)	23	(6.7)	3	(6.3)	14	(3.0)	6	(5.0)	228	(6.4)	216	(8.3)
discontinued any chemotherapy	110	(15.7)	20	(23.8)	32	(9.4)	8	(16.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	73	(10.4)	21	(25.0)	13	(3.8)	2	(4.2)	14	(3.0)	3	(2.5)	301	(8.4)	297	(11.4)
discontinued pembrolizumab or placebo	63	(9.0)	18	(21.4)	12	(3.5)	2	(4.2)	14	(3.0)	3	(2.5)	301	(8.4)	297	(11.4)
discontinued any chemotherapy	36	(5.2)	12	(14.3)	6	(1.8)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	66	(9.4)	18	(21.4)	10	(2.9)	1	(2.1)	8	(1.7)	2	(1.7)	135	(3.8)	130	(5.0)
discontinued pembrolizumab or placebo	57	(8.2)	15	(17.9)	9	(2.6)	1	(2.1)	8	(1.7)	2	(1.7)	135	(3.8)	130	(5.0)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]				KN522 Placebo + Chemotherapy / Placebo[e]				TNBC Safety Dataset for Pembrolizumab Monotherapy[f]				Pembrolizumab Monotherapy Reference Safety Dataset[g]			
	<65		>=65		<65		>=65		<65		>=65		<65		>=65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued any chemotherapy	33	(4.7)	10	(11.9)	5	(1.5)	1	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.0.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

Results were similar for the analysis of age using additional age categories (<65 years old, 65 to 74 years old, and 75 to 84 years old), although sample sizes in the 75 to 84 years old category was small (n=12).

Except for SAEs and Grade 3 to 5 AEs, these differences (≥5 percentage point difference) between the <65 years of age and ≥65 years of age were not noted in the pembrolizumab monotherapy RSD.

Considering the epidemiology of TNBC, additional *post-hoc* analyses stratified by age classes <45 and ≥45-<65 were provided. The safety profile of pembrolizumab + NAC / pembrolizumab was generally similar between the 2 age subgroups (see table below).

Table: Adverse Event Summary by Age (years) All Participants Combined Phases (Neoadjuvant and Adjuvant) (ASaT Population)

	MK-3475 + chemotherapy / MK-3475				Placebo + chemotherapy / Placebo				Total			
	< 45		>= 45 - < 65		< 45		>= 45 - < 65		< 45		>= 45 - < 65	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	279		420		142		199		421		619	
with one or more adverse events	279	(100.0)	415	(98.8)	142	(100.0)	199	(100.0)	421	(100.0)	614	(99.2)
with no adverse event	0	(0.0)	5	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	5	(0.8)
with drug-related[a] adverse events	279	(100.0)	413	(98.3)	141	(99.3)	199	(100.0)	420	(99.8)	612	(98.9)
with toxicity grade 3-5 adverse events	230	(82.4)	342	(81.4)	112	(78.9)	158	(79.4)	342	(81.2)	500	(80.8)
with toxicity grade 3-5 drug-related adverse events	216	(77.4)	319	(76.0)	102	(71.8)	150	(75.4)	318	(75.5)	469	(75.8)
with serious adverse events	111	(39.8)	185	(44.0)	45	(31.7)	55	(27.6)	156	(37.1)	240	(38.8)
with serious drug-related adverse events	87	(31.2)	141	(33.6)	32	(22.5)	40	(20.1)	119	(28.3)	181	(29.2)
with dose modification[b] due to an adverse event	237	(84.9)	334	(79.5)	118	(83.1)	149	(74.9)	355	(84.3)	483	(78.0)
who died	1	(0.4)	4	(1.0)	0	(0.0)	1	(0.5)	1	(0.2)	5	(0.8)
who died due to a drug-related adverse event	1	(0.4)	1	(0.2)	0	(0.0)	1	(0.5)	1	(0.2)	2	(0.3)
discontinued drug due to an adverse event	74	(26.5)	123	(29.3)	20	(14.1)	31	(15.6)	94	(22.3)	154	(24.9)
discontinued drug due to a drug-related adverse event	69	(24.7)	114	(27.1)	20	(14.1)	26	(13.1)	89	(21.1)	140	(22.6)
discontinued drug due to a serious adverse event	29	(10.4)	44	(10.5)	4	(2.8)	9	(4.5)	33	(7.8)	53	(8.6)

discontinued drug due to a serious drug-related adverse event	25	(9.0)	41	(9.8)	4	(2.8)	6	(3.0)	29	(6.9)	47	(7.6)

[a] Determined by the investigator to be related to the drug.

[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Grades are based on NCI CTCAE version 4.0.

Included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 23MAR2021

ECOG

Higher incidences (≥5 percentage point differences) of Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, and SAEs were noted in participants with an ECOG PS of 1. Similar results were generally noted in the placebo + NAC / placebo group and the pembrolizumab monotherapy RSD (see Table below).

Table 2.7.4-tnbc3: 13
Adverse Event Summary by ECOG Status Category (0, 1)
Combined Phases (Neoadjuvant and Adjuvant)
(APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]				KN522 Placebo + Chemotherapy / Placebo[e]				TNBC Safety Dataset for Pembrolizumab Monotherapy[f]				Pembrolizumab Monotherapy Reference Safety Dataset[g]			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	677		106		340		49		160		293		2,920		3,072	
with one or more adverse events	671	(99.1)	106	(100.0)	340	(100.0)	49	(100.0)	156	(97.5)	276	(94.2)	2,826	(96.8)	2,973	(96.8)
with no adverse event	6	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	4	(2.5)	17	(5.8)	94	(3.2)	99	(3.2)
with drug-related[a] adverse events	669	(98.8)	105	(99.1)	339	(99.7)	49	(100.0)	101	(63.1)	186	(63.5)	2,207	(75.6)	2,049	(66.7)
with toxicity grade 3-5 adverse events	549	(81.1)	96	(90.6)	266	(78.2)	40	(81.6)	56	(35.0)	109	(37.2)	1,185	(40.6)	1,682	(54.8)
with toxicity grade 3-5 drug-related adverse events	514	(75.9)	90	(84.9)	248	(72.9)	37	(75.5)	20	(12.5)	36	(12.3)	442	(15.1)	500	(16.3)
with serious adverse events	290	(42.8)	51	(48.1)	94	(27.6)	17	(34.7)	33	(20.6)	77	(26.3)	926	(31.7)	1,346	(43.8)
with serious drug-related adverse events	227	(33.5)	40	(37.7)	66	(19.4)	12	(24.5)	12	(7.5)	23	(7.8)	339	(11.6)	346	(11.3)
who died	4	(0.6)	3	(2.8)	1	(0.3)	0	(0.0)	0	(0.0)	8	(2.7)	83	(2.8)	222	(7.2)
who died due to a drug-related adverse event	3	(0.4)	1	(0.9)	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.3)	14	(0.5)	26	(0.8)
discontinued any drug due to an adverse event	208	(30.7)	26	(24.5)	52	(15.3)	8	(16.3)	7	(4.4)	16	(5.5)	326	(11.2)	471	(15.3)
discontinued pembrolizumab or placebo	135	(19.9)	22	(20.8)	27	(7.9)	4	(8.2)	7	(4.4)	16	(5.5)	326	(11.2)	471	(15.3)
discontinued any chemotherapy	123	(18.2)	13	(12.3)	36	(10.6)	6	(12.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a drug-related adverse event	196	(29.0)	21	(19.8)	49	(14.4)	6	(12.2)	5	(3.1)	10	(3.4)	212	(7.3)	215	(7.0)
discontinued pembrolizumab or placebo	123	(18.2)	17	(16.0)	25	(7.4)	1	(2.0)	5	(3.1)	10	(3.4)	212	(7.3)	215	(7.0)
discontinued any chemotherapy	120	(17.7)	10	(9.4)	34	(10.0)	6	(12.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious adverse event	80	(11.8)	14	(13.2)	12	(3.5)	3	(6.1)	3	(1.9)	8	(2.7)	211	(7.2)	363	(11.8)
discontinued pembrolizumab or placebo	70	(10.3)	11	(10.4)	11	(3.2)	3	(6.1)	3	(1.9)	8	(2.7)	211	(7.2)	363	(11.8)
discontinued any chemotherapy	38	(5.6)	10	(9.4)	7	(2.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	74	(10.9)	10	(9.4)	11	(3.2)	0	(0.0)	2	(1.3)	4	(1.4)	116	(4.0)	140	(4.6)
discontinued pembrolizumab or placebo	65	(9.6)	7	(6.6)	10	(2.9)	0	(0.0)	2	(1.3)	4	(1.4)	116	(4.0)	140	(4.6)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]				KN522 Placebo + Chemotherapy / Placebo[e]				TNBC Safety Dataset for Pembrolizumab Monotherapy[f]				Pembrolizumab Monotherapy Reference Safety Dataset[g]			
	[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory		[0] Normal Activity		[1] Symptoms, but ambulatory	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
discontinued any chemotherapy	36	(5.3)	7	(6.6)	6	(1.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.0.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab in KN012, KN086 and KN119.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018)

Database cutoff date for Head and Neck (KN012-HNSCC: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for Hodgkin Lymphoma (KN013-Cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for TNBC (KN012-TNBC: 26APR2016, KN086: 10NOV2017, KN119: 11APR2019, KN522: 23MAR2021)

Database cutoff date for CRC (KN177: 19FEB2020)

Source: [ISS: adam-adsl; adae]

In the pembrolizumab + NAC / pembrolizumab group, higher incidences (≥5 percentage point differences) of discontinuation of any study intervention due to an AE and due to a drug-related AE were noted in participants with a baseline ECOG PS of 0. This was not noted in the placebo + NAC / placebo group and the pembrolizumab monotherapy RSD.

Sex

One male participant was enrolled in KEYNOTE-522; therefore, a meaningful evaluation of the AE profile of pembrolizumab + NAC by sex could not be performed.

Considering the peculiar epidemiology of TNBC, an additional *post-hoc* subgroup analysis was conducted of females ⩽60 years of age and with an ECOG PS of 0, comparing participants in the combined phases of KEYNOTE-522 (from both treatment groups), matched participants from the Pooled Safety Dataset for pembrolizumab + chemotherapy, and matched participants from the pembrolizumab monotherapy EU Reference Safety Dataset (RSD).

The duration of exposure to study medication in the KEYNOTE-522 pembrolizumab + NAC/ pembrolizumab group was longer than in both the Pooled Safety Dataset for pembrolizumab + chemotherapy and the pembrolizumab monotherapy RSD.

The incidences of AEs, drug-related AEs, deaths (all and drug-related), discontinuations of a drug due to a SAE (all and drug-related) were generally similar between the pembrolizumab + NAC/ pembrolizumab group and the Pooled Safety Dataset for pembrolizumab +chemotherapy. The incidences of Grade 3 to 5 AEs (all and drug-related), SAEs (all and drug-related), discontinuations of a drug due to an AE (all and drug-related) were higher (⩾5 percentage points) in the pembrolizumab + NAC/ pembrolizumab group compared with the Pooled Safety Dataset for pembrolizumab +chemotherapy (see Table below).

Table 1
Adverse Event Summary
(Age ≤ 60 years, Female, ECOG = 0)
Combined Phases (Neoadjuvant and Adjuvant)
(APaT Population)

	KN522 Pembrolizumab +	KN522 Placebo + Chemotherapy /	Pooled Safety Dataset for	Pembrolizumab Monotherapy

	Chemotherapy / Pembrolizumab[d]		Placebo[e]		Pembrolizumab + Chemotherapy[f]		Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	560		277		344		597	
with one or more adverse events	556	(99.3)	277	(100.0)	340	(98.8)	576	(96.5)
with no adverse event	4	(0.7)	0	(0.0)	4	(1.2)	21	(3.5)
with drug-related[a] adverse events	554	(98.9)	276	(99.6)	332	(96.5)	462	(77.4)
with toxicity grade 3-5 adverse events	450	(80.4)	216	(78.0)	251	(73.0)	216	(36.2)
with toxicity grade 3-5 drug-related adverse events	423	(75.5)	202	(72.9)	220	(64.0)	81	(13.6)
with serious adverse events	238	(42.5)	78	(28.2)	99	(28.8)	165	(27.6)
with serious drug-related adverse events	185	(33.0)	56	(20.2)	62	(18.0)	72	(12.1)
who died	3	(0.5)	1	(0.4)	7	(2.0)	14	(2.3)
who died due to a drug-related adverse event	2	(0.4)	1	(0.4)	2	(0.6)	4	(0.7)
discontinued any drug due to an adverse event	159	(28.4)	41	(14.8)	71	(20.6)	78	(13.1)
discontinued pembrolizumab or placebo	105	(18.8)	20	(7.2)	38	(11.0)	78	(13.1)
discontinued any chemotherapy	92	(16.4)	28	(10.1)	49	(14.2)	0	(0.0)
discontinued any drug due to a drug-related adverse event	148	(26.4)	40	(14.4)	63	(18.3)	52	(8.7)
discontinued pembrolizumab or placebo	94	(16.8)	20	(7.2)	32	(9.3)	52	(8.7)
discontinued any chemotherapy	90	(16.1)	27	(9.7)	45	(13.1)	0	(0.0)
discontinued any drug due to a serious adverse event	58	(10.4)	9	(3.2)	34	(9.9)	45	(7.5)
discontinued pembrolizumab or placebo	51	(9.1)	8	(2.9)	27	(7.8)	45	(7.5)
discontinued any chemotherapy	28	(5.0)	5	(1.8)	16	(4.7)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	52	(9.3)	9	(3.2)	29	(8.4)	26	(4.4)
discontinued pembrolizumab or placebo	46	(8.2)	8	(2.9)	23	(6.7)	26	(4.4)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
discontinued any chemotherapy	26	(4.6)	5	(1.8)	14	(4.1)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.0.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for TNBC (KN355: 11DEC2019, KN522: 23MAR2021)

These differences may also reflect the longer median duration of exposure to study medication in KEYNOTE-522 relative to the Pooled Safety Dataset for pembrolizumab + chemotherapy. Additionally, participants in KEYNOTE-522 received a greater number of different chemotherapeutic agents (4 agents) compared with the number administered in the other pooled pembrolizumab + chemotherapy studies (maximum of 2 agents each).

For AEOSI, no new indication-specific, immune-related AEs causally associated with pembrolizumab were identified in KEYNOTE-522. The overall incidence of AEOSIs (including drug-related, Grade 3 to 5 and SAEs) and discontinuation of any drug due to an AEOSI, were higher (≥5 percentage points) in the KEYNOTE-522 pembrolizumab + NAC / pembrolizumab group compared with the Pooled Safety Dataset for pembrolizumab + chemotherapy, and the pembrolizumab monotherapy RSD (see Tables below).

Table 2
Adverse Event Summary
AEOSI
(Age ≤ 60 years, Female, ECOG = 0)
Combined Phases (Neoadjuvant and Adjuvant)
(APaT Population)

	KN522 Pembrolizumab + Chemotherapy / Pembrolizumab[d]		KN522 Placebo + Chemotherapy / Placebo[e]		Pooled Safety Dataset for Pembrolizumab + Chemotherapy[f]		Pembrolizumab Monotherapy Reference Safety Dataset[g]	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	560		277		344		597	
with one or more adverse events	247	(44.1)	66	(23.8)	102	(29.7)	180	(30.2)
with no adverse event	313	(55.9)	211	(76.2)	242	(70.3)	417	(69.8)
with drug-related[a] adverse events	229	(40.9)	58	(20.9)	93	(27.0)	162	(27.1)
with toxicity grade 3-5 adverse events	86	(15.4)	8	(2.9)	24	(7.0)	27	(4.5)
with toxicity grade 3-5 drug-related adverse events	80	(14.3)	7	(2.5)	22	(6.4)	23	(3.9)
with serious adverse events	59	(10.5)	4	(1.4)	20	(5.8)	37	(6.2)
with serious drug-related adverse events	56	(10.0)	3	(1.1)	17	(4.9)	31	(5.2)
who died	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related adverse event	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued any drug due to an adverse event	59	(10.5)	8	(2.9)	20	(5.8)	29	(4.9)
discontinued pembrolizumab or placebo	42	(7.5)	3	(1.1)	14	(4.1)	29	(4.9)
discontinued any chemotherapy	30	(5.4)	6	(2.2)	10	(2.9)	0	(0.0)
discontinued any drug due to a drug-related adverse event	59	(10.5)	8	(2.9)	20	(5.8)	28	(4.7)
discontinued pembrolizumab or placebo	42	(7.5)	3	(1.1)	14	(4.1)	28	(4.7)
discontinued any chemotherapy	30	(5.4)	6	(2.2)	10	(2.9)	0	(0.0)
discontinued any drug due to a serious adverse event	32	(5.7)	1	(0.4)	15	(4.4)	14	(2.3)
discontinued pembrolizumab or placebo	29	(5.2)	1	(0.4)	14	(4.1)	14	(2.3)
discontinued any chemotherapy	13	(2.3)	0	(0.0)	5	(1.5)	0	(0.0)
discontinued any drug due to a serious drug-related adverse event	32	(5.7)	1	(0.4)	15	(4.4)	14	(2.3)
discontinued pembrolizumab or placebo	29	(5.2)	1	(0.4)	14	(4.1)	14	(2.3)
discontinued any chemotherapy	13	(2.3)	0	(0.0)	5	(1.5)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Grades are based on NCI CTCAE version 4.0.

For KN522, included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non-serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events. For the other studies, non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

[d] Includes all participants who received at least one dose of pembrolizumab/chemotherapy or surgery in KN522.

[e] Includes all participants who received at least one dose of placebo/chemotherapy or surgery in KN522.

[f] Includes all participants who received at least one dose of pembrolizumab combo therapy in KN021-A/C/G, KN048, KN189, KN355, KN407 and KN590.

[g] Includes all participants who received at least one dose of pembrolizumab in KN001 Part B1, B2, B3, D, C, F1, F2, F3, KN002 (original phase), KN006, KN010, KN012 cohort B and B2, KN013 cohort 3, KN024, KN040, KN042, KN045, KN048, KN052, KN054, KN055, KN087, KN177, and KN204.

Database cutoff date for Melanoma (KN001-Melanoma: 18APR2014, KN002: 28FEB2015, KN006: 03MAR2015, KN054: 02OCT2017)

Database cutoff date for Lung (KN001-NSCLC: 23JAN2015, KN010: 30SEP2015, KN024: 10JUL2017, KN042: 04SEP2018, KN021: 19AUG2019, KN189: 20MAY2019, KN407: 09MAY2019)

Database cutoff date for HNSCC (KN012 cohort B and B2: 26APR2016, KN040: 15MAY2017, KN048: 25FEB2019, KN055: 22APR2016)

Database cutoff date for cHL (KN013 cohort 3: 28SEP2018, KN087: 21MAR2019, KN204: 16JAN2020)

Database cutoff date for Bladder (KN045: 26OCT2017, KN052: 26SEP2018)

Database cutoff date for CRC (KN177: 19FEB2020)

Database cutoff date for Esophageal (KN590: 02JUL2020)

Database cutoff date for TNBC (KN355: 11DEC2019, KN522: 23MAR2021)

The higher incidence of AEOSIs in the pembrolizumab + NAC / pembrolizumab group was primarily driven by infusion reactions and severe skin reactions.

Region

For participants enrolled in the EU, the incidences of Grade 3 to 5, Grade 3 to 5 drug-related AEs, drug-related SAEs, and discontinuation of any study intervention (including drug-related AEs and SAEs) in the pembrolizumab + NAC / pembrolizumab group were higher (≥5 percentage point difference) compared with participants who were enrolled outside of the EU. There were no other trends identified in the incidence of AEs for each summary category in the pembrolizumab + NAC / pembrolizumab group for participants enrolled in the EU compared with those enrolled outside of the EU. Generally, no trends were identified for differences in the incidence of each AE parameter in the EU versus non-EU in the placebo + NAC / placebo group or the pembrolizumab monotherapy RSD.

Pregnancy and Lactation

Four pregnancy reports occurred in KEYNOTE-522 within the protocol-specified reporting periods relative to last receipt of study medication.

Three pregnancies occurred in the pembrolizumab + NAC / pembrolizumab group: 2 pregnancies resulted in abortion per participant decision and 1 pregnancy resulted in live birth (twins) with no reported complications or congenital abnormalities of the infants. The one pregnancy in the placebo + NAC / placebo group resulted in spontaneous abortion at <20 weeks; this event was reported as a Grade 2 SAE, which resolved and the investigator considered not related to the study intervention.

Overall, no new safety concerns were identified for the participants who became pregnancy during the study. Pembrolizumab should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether pembrolizumab is secreted in human milk. Because

many drugs and IgG antibodies are secreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the importance of the drug to the mother.

Safety related to drug-drug interactions and other interactions

As pembrolizumab is an IgG antibody that is administered parenterally and cleared by catabolism, food and DDI are not anticipated to influence exposure. Drugs that affect the cytochrome P450 enzymes, and other metabolizing enzymes, are not expected to interfere with the metabolism of an IgG antibody. The IgG antibodies, in general, do not directly regulate the expression of cytochrome P450 enzymes, other enzymes, or transporters involved in drug elimination. Therefore, no dedicated DDI studies have been performed.

In vitro experiments and studies conducted in preclinical species have been shown to have limited value in predicting DDI potential in humans. Therefore, no preclinical PK studies were conducted to assess the propensity of pembrolizumab to be a victim or perpetrator of pharmacokinetic DDIs. Similarly, the potential of DDI between pembrolizumab and chemotherapy agents is expected to be low. No impact of co-administered chemotherapy on pembrolizumab PK was observed in KEYNOTE-021 Cohort G.

Studies evaluating pharmacodynamic drug interactions with pembrolizumab have not been conducted. However, as systemic corticosteroids may be used in combination with pembrolizumab to ameliorate potential side effects, the potential for a pharmacokinetic DDI with pembrolizumab as a victim was assessed as part of the population pharmacokinetic analysis. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Systemic corticosteroids, or other immunosuppressants, can be used during pembrolizumab treatment to treat immune-related adverse reactions.

Discontinuation due to adverse events

AEs leading to treatment discontinuation

The overall incidence of AEs resulting in discontinuation of any study intervention during the study was higher (≥10 percentage point difference) in the pembrolizumab + NAC / pembrolizumab group (29.9%; drug-related AEs 27.7%) compared with the placebo + NAC / placebo group (15.4%; drug-related AEs 14.1%). The higher incidence of AEs resulting in discontinuation of study intervention in the pembrolizumab + NAC / pembrolizumab group was primarily driven by events that occurred in <1% of participants. The most frequently reported drug-related AEs resulting in discontinuation of any study intervention (≥1%) in the pembrolizumab + NAC / pembrolizumab group, which were higher (≥1 percentage point difference) compared with the placebo + NAC / placebo group, were ALT increased (2.8% vs 1.3%), AST increased (1.7% vs 0.0%), and febrile neutropenia (1.5% vs 0.5%).

The overall incidence of AEs leading to the discontinuation of any study treatment in the pembrolizumab monotherapy RSD was 13.4% (drug-related AEs 7.2%). The most frequently reported AEs leading to the discontinuation of any study treatment (incidence ≥1%) in the pembrolizumab + NAC / pembrolizumab group (vs RSD) were ALT increased (3.1% vs 0.3%), neutropenia (2.0% vs 0.0%), AST increased (1.8% vs 0.3%), febrile neutropenia (1.5% vs 0.0%), infusion-related reactions (1.3% vs 0.0%), and peripheral neuropathy (1.0% vs 0.0%).

The overall incidence of AEs leading to the discontinuation of pembrolizumab was higher in the pembrolizumab + NAC / pembrolizumab group (20.1%) compared with pembrolizumab monotherapy RSD (13.4%). The most frequently reported AEs leading to the discontinuation of pembrolizumab

(incidence ≥1%) in the pembrolizumab + NAC / pembrolizumab group (vs RSD) were ALT increased (2.7% vs 0.3%) and AST increased (1.5% vs 0.3%).

AEs leading to treatment interruption

The overall incidence of AEs resulting in interruption of any study intervention during the neoadjuvant phase was generally similar in the pembrolizumab + NAC / pembrolizumab group (74.5%, drug-related AEs 67.8%) compared with the placebo + NAC / placebo group (73.0%, drug-related AEs 66.3%).

The overall incidence of AEs leading to the interruption of any study treatment was higher in the pembrolizumab + NAC group / pembrolizumab (74.5%) compared with the pembrolizumab monotherapy RSD (25.8%; drug-related AEs 14.6%). This was primarily driven by neutropenia (26.6% vs 0.1%), neutrophil count decreased (13.7% vs 0.0%), ALT increased (11.2% vs 1.3%), AST increased (5.7% vs 1.2%), and anemia (5.0% vs 0.8%).

The overall incidence of AEs leading to the interruption of pembrolizumab was higher in the pembrolizumab + NAC / pembrolizumab group (57.1%) compared with the pembrolizumab monotherapy RSD (25.8%). The most frequently reported AEs that led to interruption of pembrolizumab (incidence ≥5%) in the pembrolizumab + NAC / pembrolizumab group, which were higher compared with the pembrolizumab monotherapy RSD, were neutropenia (17.5% vs 0.1%), neutrophil count decreased (8.7% vs 0.0%), and ALT increased (6.0% vs 1.3%). The incidences of these AEs leading to interruption of pembrolizumab and placebo were generally similar between the pembrolizumab + NAC / pembrolizumab and placebo + NAC /placebo groups.

Post marketing experience

The safety profile of pembrolizumab was summarized in the Periodic Safety Update Report covering the period 04-SEP-2019 through 03-SEP-2020.

No revocation or withdrawal of pembrolizumab registration has occurred in any country for safety reasons.

2.5.1. Discussion on clinical safety

The safety database supporting the claimed indication is comprised by 783 subjects with newly diagnosed, locally advanced, centrally confirmed TNBC who were randomised in the NAC + pembrolizumab followed by adjuvant pembrolizumab monotherapy arm of Phase III study KN-522. At the data cut-off date (Mar 2021), 778/783 subjects had received at least 1 dose of study medication.

Safety data from the pembrolizumab arm were contextualised by direct comparison in study KN-522 with the "placebo arm" (i.e. NAC + placebo followed by placebo in the adjuvant phase; N=389), and by indirect comparisons to pooled data from pembrolizumab monotherapy studies (RSD, N=6185) and from pembrolizumab monotherapy studies in subjects with TNBC (mTNBC N=595).

Baseline characteristics and exposure

In analysing safety data from study KN-522 it should be considered that, in line with the epidemiology of TNBC, enrolled patients were, for the vast majority, female (99.9%), young (median age 49 years) and in good medical state (ECOG 0 87%).

The median duration of exposure to study drugs was similar for the "active" and "placebo" arm of study KN-522 (13.3 and 13.6 months, respectively), and significantly longer compared to that

observed in the RSD and TNBC datasets (4.9 and 2.1 months, respectively). This is not unexpected considering the more advanced setting of disease in the pooled monotherapy datasets. The majority of patients in study KN-522 received the planned 17 cycles in both treatment arms, as per study protocol.

Adverse events (AEs)

Nearly all (~100%) patients in study KN-522 reported at least one AE during treatment, and most AEs were considered drug-related by the Investigator (98.9% and 99.7% in the "pembrolizumab" and "placebo" arms, respectively). Although most subjects in the monotherapy datasets also experienced at least one AEs (93.9% and 96.8% in the mTNBC and RSD datasets, respectively), the proportion of AEs adjudicated as drug-related was lower with monotherapy (61.8% and 70.6%, respectively), probably reflecting the higher toxicity of the combination therapy and the different setting of disease.

The higher toxicity potential of combination therapy was highlighted by the provided **exposure-adjusted safety analyses**, which showed how AEs and drug-related AEs rates in study KN-522 were higher with combination therapy (2459 and 1608 AEs rate/100 person-year, respectively) compared to both chemotherapy + placebo (2107 and 1351 AE rate/100 person-year, respectively) and pembrolizumab monotherapy (1706 and 560 AE rate/100 person-year, respectively, in the mTNBC dataset and 1506 and 472 AE rate/100 person-year, respectively, in the RSD dataset).

Exposure adjusted AEs and drug-related AEs rates in the pembrolizumab arm of study KN-522 were consistently higher in the **neoadjuvant phase** (3750 and 2687 AEs rate/100 person-year, respectively,) compared to the adjuvant phase (879 and 254.3 AEs rate/100 person-year, respectively). A similar trend could also be observed in the placebo arm, highlighting the impact of chemotherapy on the overall toxicity profile of the combination.

Compared to the neo-adjuvant phase, in the **adjuvant phase** a reduced difference in the exposure adjusted AEs/drug-related AEs rates could be observed across treatment arms, which might be explained by the milder toxicity of pembrolizumab monotherapy. However, in the absence of re-randomisation post-surgery, a possible selection bias cannot be definitely excluded, especially considering that only ~75% (588/783) of all the enrolled patients did proceed to the adjuvant phase in the pembrolizumab arm of study KN-522, compared to ~85% (331/389) in the placebo arm.

The most frequently (incidence ≥20%) reported **treatment-emergent AEs** in the combination therapy arm were nausea (67%), alopecia (61%), anaemia (59%), neutropenia (48%), fatigue (47%), constipation (42%), diarrhoea (41%), vomiting (31%), ALT increase (30%), headache (30%), rash (30%), arthralgia (29%), pyrexia (28%), asthenia (28%), cough (25%), neutrophil count decreased (24%), AST increased (24%), decreased appetite (23%), neuropathy peripheral (21%), insomnia (21%), peripheral sensory neuropathy (20%) and myalgia (20%). Similar type and rates of AEs could be observed with placebo, suggesting that the overall safety profile of the proposed combination is heavily influenced by the common chemotherapy backbone. The AEs that were more frequently (incidence difference across arms ≥5%) reported in the pembrolizumab arm compared to placebo were diarrhoea, rash, pyrexia, decreased appetite, hypothyroidism and hypokalaemia, consistently with the known toxicity profile of pembrolizumab.

The incidence of individual AEs was constantly higher in the combination arm compared to the pembrolizumab monotherapy datasets, further highlighting the higher toxicity of combination therapy.

With respect to **drug-related AEs**, the emerging toxicity profile was consistent with the overall safety analysis: the most commonly reported (incidence ≥20%) drug-related AEs in both treatment arms were nausea, alopecia, anaemia, neutropenia, fatigue, diarrhoea, ALT increased, vomiting, asthenia, rash, constipation, neutrophil count decreased, AST increased neuropathy peripheral and decreased

appetite. Diarrhoea and rash, known ADRs of checkpoint inhibitors, were the only drug-related AEs with a ≥5% incidence difference in the pembrolizumab compared to placebo arm. Diarrhoea and rash are already included in the AEOSI for pembrolizumab.

Grade 3-5 AEs, SAEs and AEs who led to study drug interruption/discontinuation.

Severe (Grade 3 to 5) AEs and **drug-related AEs** were slightly more frequent in the pembrolizumab arm of study KN-522 (82.4% and 77.1%, respectively) compared to placebo (78.7% and 73.3%, respectively), and significantly more common compared to pembrolizumab monotherapy (36.6% and 13.3%, respectively, in the mTNBC dataset and 48.2% and 15.8%, respectively, in the RSD dataset). Consistent results were also shown by the provided **exposure-adjusted analysis**, with the highest incidence rate of severe AEs observed with combination chemotherapy in the neoadjuvant phase (i.e. 470 severe events/100 person-years). It should also be noted, however, that in the adjuvant phase the exposure-adjusted incidence rate of severe AEs in subjects who received pembrolizumab was still approximately 2-fold higher than that observed in subjects who received placebo (i.e. 38 vs. 22 events/100 person-years, respectively).

The pattern of severe AEs was generally similar in both arms of study KN-522, with severe hematologic toxicity (neutropenia, neutrophil count decreased, white blood cell count decreased and anaemia) presenting the highest incidence with both pembrolizumab and placebo: this is in line with the known toxicity profile of the common chemotherapy backbone, as further highlighted by the significantly lower incidence of severe hematologic toxicity in the pembrolizumab monotherapy datasets. ALT increased was the only severe AE whose incidence was significantly higher in the experimental vs. control arm (6.4% and 2.8%, respectively).

The higher rate of severe AEs observed with combination therapy did also result in a consistently higher rate of **SAEs** and **drug-related SAEs** (43.6% and 34.1%, respectively) observed in the pembrolizumab arm of study KN-522 compared to placebo (28.5% and 20.1%, respectively) and to the monotherapy reference datasets (23.5% and 7.7%, respectively, in the mTNBC dataset and 38.4% and 11.4%, respectively, in the RSD dataset). Similar results were observed in the **exposure-adjusted analysis**, with the highest incidence rate of SAEs observed with combination therapy in the neoadjuvant arm (i.e. 121 events/100 person-years). The SAEs rate was approximately two-fold higher with pembrolizumab vs. placebo in both the neoadjuvant and adjuvant phases of study KN-522.

No clear pattern could be identified to explain the increased rate of SAEs observed with pembrolizumab in the combination arm and febrile neutropenia, the only SAE with an incidence ≥5% in both treatment arms (15.1% and 12.1% in the pembrolizumab and placebo arm, respectively), can be mainly attributed to the common chemotherapy backbone. Pyrexia was the only SAE that was significantly more common with pembrolizumab compared to placebo (3.7% vs. 0.5%).

Consistently, the **rate of AEs that resulted in the discontinuation of any study drug intervention** in study KN-522 was highest in the pembrolizumab arm (any drug discontinuation rate 29.9%, pembrolizumab discontinuation rate 20.1%) compared to the placebo arm (any drug discontinuation rate 15.4%, placebo discontinuation rate 8%) and to the RSD dataset (13.4%). Consistently with what observed in terms of SAEs, results from the exposure-adjusted analysis showed that the highest incidence rate of AEs that resulted in study drug discontinuation was observed with combination therapy in the neoadjuvant phase (e.g. 55 events/100 person-years). Of note, the rate of AEs leading to drug discontinuation was constantly at least two-fold higher in the pembrolizumab arm compared to placebo across all treatment phases.

No clear pattern of AEs driving the higher discontinuation rates in patients receiving the combination regimen could be identified, with most AEs occurring in <1% of subjects. Although a trend towards a higher incidence of increased ALT/AST and febrile neutropenia leading to drug discontinuation was

observed in the pembrolizumab arm compared to placebo, limited numbers (frequencies did not exceed 3%) hampered definitive conclusions.

Deaths

Less than 1% of subjects in study KN-522 experienced **AEs resulting in death**, which is significantly lower than the incidence of grade 5 AEs observed in the RSD dataset (i.e. 5.2%), possibly reflecting the younger age, earlier disease setting and better baseline health status of patients in the pivotal study. Seven out of 783 subjects in the experimental arm (0.9%) experienced fatal AEs compared to 1/389 (0.3%) in the control arm. The majority of the fatal AEs (6/8, 5/7 in the pembrolizumab arm and 1/1 in the control arm) were observed in the neoadjuvant phase; only 2 deaths due to AEs were observed with pembrolizumab in the adjuvant phase vs. 0 in the control arm. Even though absolute values were low, the exposure-adjusted incidence rate of AEs leading to death was nearly 5-fold higher compared to that observed in the control arm (1.09 and 0.23 events/100 person-years, respectively), with the highest exposure-adjusted incidence observed in the neoadjuvant phase with combination therapy (1.51 events/100 person-years).

AEs leading to death in the pembrolizumab arm were: death not otherwise specified, autoimmune encephalitis, multi-organ dysfunction syndrome, myocardial infarction, pneumonia, pneumonitis, pulmonary embolism, sepsis and shock not otherwise specified. The only grade 5 AE reported in the control arm was septic shock. The fatal AEs pneumonitis, pulmonary embolism and autoimmune encephalitis were considered related to pembrolizumab by the Investigator, while sepsis/multi organ failure syndrome was attributed to chemotherapy. For 2 of the 3 subjects in the pembrolizumab arm who experienced Grade 5 AEs not considered related to study medications by the Investigator, known anti-PD1 AEOSI (adrenal insufficiency and grade 4 hepatitis with a cholestatic pattern) were ongoing at the time of death. Although it can be recognised that evaluations of causal relationship with pembrolizumab are confounded by concomitant factors, from a conservative perspective it cannot be excluded.

Overall, despite a higher incidence of AEs resulting in death could be observed in the monotherapy RSD dataset (which might be, at least in part, explained by the more advanced setting of disease), the exposure-adjusted incidence of fatal events observed with combination therapy, in particular when compared to chemotherapy alone, is not considered negligible in a potentially curative setting.

AEs of special interests (AEOSI)

The assessment of the **AEOSI** is based on the predefined list of preferred terms (version 19.0) identified by the MAH as potentially associated with an immune aetiology. Although that was agreed to maintain consistency across studies in the pembrolizumab clinical development programme, the knowledge of immune-related AEs with checkpoint inhibitors is continuously evolving (see e.g. Ramon-Casals et al, Nature Reviews 2020). An additional analysis also including pericarditis, aplastic anaemia/pure red cell aplasia, autoimmune haemolytic anaemia, haemophagocytic lymphohistiocytosis, immune thrombocytopenic purpura and polyneuropathies to the predefined list of preferred terms for AEOSI was performed by the MAH. No significant differences in the incidence and severity of these additional "potential" AEOSI were observed across treatment arms. Although the incidence of polyneuropathy AEs was higher in the "pembrolizumab" arm of study KN522 compared to the RSD, a similar rate could be observed in the "placebo" arm of study KN522, suggesting that such toxicity should be mainly ascribed to chemotherapy.

Compared to placebo, an increased incidence of AEOSI (43.6% vs. 21.9%), drug-related AEOSI (40.2% vs. 19%), severe (Grade 3-5) AEOSI (14.9% vs. 2.1%), serious AEOSI (10.6% vs. 1.3%) and AEOSI that resulted in discontinuation of study drug (10.9% vs. 2.6%) could be observed with combination therapy in study KN-522. AEOSI were also more frequent and severe/serious with

combination therapy compared to pembrolizumab monotherapy, as highlighted by the lower rates of AEOSI, drug-related AEOSI, Grade 3-5 AEOSI, serious AEOSI and AEOSI that resulted in discontinuation of pembrolizumab in the mTNBC and RSD datasets.

Only 2 deaths due to AEOSI (0.3%) could be observed with pembrolizumab in study KN-522, compared to none in the control arm and ≤0.2% in the monotherapy datasets. Uncertainties are present, however, on the causality of two additional fatal events (see also the "Deaths" section above).

The exposure-adjusted incidence of all the AEOSI was higher in the NAC + pembrolizumab phase (all AEOSI 109 events/100 person-years) compared to the adjuvant phase (19.7 events/100 person-years). A similar difference could also be observed in terms of severe AEOSI (25.9 vs. 5 events/100 person-years), serious AEOSI (17.2 vs. 3.5 events/100 person-years), and AEOSI leading to drug discontinuation (17.5 vs. 2.4 events/100 person-years), confirming that the greater toxicity of combination therapy did extend to immune-related AEs.

The most common (i.e. incidence ≥5%) AEOSI observed in the pembrolizumab arm of study KN-522 were infusion reactions, hypothyroidism, severe skin reactions and hyperthyroidism, which is in line with the known safety profile of pembrolizumab. In particular, **infusion reactions** were common (18% in the combination arm), mainly occurred in the first month of treatment (median time to onset 16 days) and required systemic corticosteroids in most cases (60%). The vast majority of subjects in study KN522 received premedication before pembrolizumab/placebo was infused. Premedication consisted of dexamethasone (74.6%), acetaminophen (28.8%), and diphenhydramine (22.3%). Such frequent use of corticosteroids can be considered justified in the context of a standard anti-emetic premedication for highly emetogenic regimens, and apparently no detrimental impact on efficacy endpoints could be identified. Reduced numbers in the subgroup of patients who did not receive premedication (N=19) could not allow for reliable evaluations of the effectiveness of premedication in the management of IRs. No firm conclusions could also be drawn on the impact of different premedication regimens on the incidence of IRs.

Skin reactions were also commonly observed in the pembrolizumab arm (~6%), mainly occurred in the initial months of treatment (median time to onset 64 days), were often severe (Grade 3) and required corticosteroids (62%).

Hypothyroidism AEOSI were common (~15% in the combination arm), could occur anytime during treatment (median time to onset 105 days) and were usually mild in severity (grade 1-2). Management of hypothyroidism usually required chronic replacement therapy and only rarely corticosteroids (3.4%) and most events (54%) were not considered resolved at the last data cut-off date.

It is noted that all **myocarditis** (n=5, 0.6%) reported as AEOSI were identified in patients receiving pembrolizumab in study KN-522. Although incidence was low, it was still higher with combination therapy compared to monotherapy (i.e. 0.2% in the mTNBC and 0.1% in the RSD datasets). Considering the potentially fatal nature of cardiac toxicity with immune checkpoint inhibitors and the exposure of patients with locally advanced TNBC to anthracyclines in the neoadjuvant phase, a possible relationship between exposure to anthracyclines and onset of immune-related cardiac toxicity was investigated. The number of subjects who did not receive anthracyclines in study KN522 was, however, too limited (<10%) for meaningful comparisons.

The incidence of AEOSI with combination NAC was also constantly higher compared to monotherapy (RSD), with the notable exceptions of colitis (1.7% vs. 2%), Guillain-Barre Syndrome (0 vs. 0.1%), and pneumonitis (2.2.% vs. 4.6%). Conversely, the incidence of severe skin reactions (5.7% vs. 1.6%), infusion reactions (18% vs. 2.4%) and hypothyroidism (15.1% vs. 11.3%) was increased with combination therapy, which might be at least partially imputed to NAC, the epidemiology of TNBC and

longer exposure in study KN-522. The evaluation of any eventual relationship between possible predisposing conditions, patient characteristics and concomitant medications at baseline and the risk of onset of all and specific AEOSI was, however, hampered by limited numbers in most subgroups.

Laboratory findings

Laboratory abnormalities occurred more frequently during the neoadjuvant phase, due to the known toxicity of the chemotherapy backbone. Leukocytes decreased and lymphocyte decreased were the only findings that occurred with a higher incidence (i.e. difference ≥5%) with pembrolizumab compared to placebo (40.8% vs. 32.5%, respectively, and 27.5% vs. 22.2%, respectively).

A trend towards higher rates of severe **elevated transaminases** could be observed with pembrolizumab vs. placebo in study KN-522 (Grade 3-4 ALT increased 9.4% vs. 4.6% and Grade 3-4 AST increased 6.1% vs. 1.8%, respectively).

Severe laboratory abnormalities that were more common (i.e. difference ≥5%) in the pembrolizumab arm compared to monotherapy (RSD) were, haemoglobin decreased (21.9% vs. 6.4%), leukocytes decreased (40.8% vs. 0.8%), lymphocytes decreased (27.5% vs. 11%), neutrophils decreased (62.2% vs. 2.1%), platelet decreased (10.7% vs. 2%) and ALT increased (9.4% vs. 3%), mainly reflecting the increased haematologic toxicity of chemotherapy.

Safety in special populations

Safety analyses by **age** showed that, compared to younger patients, subjects aged ≥65 years experienced higher rates of severe (Grade 3-5) AEs (81.8% vs. 86.9%, respectively), SAEs (42.3% vs. 53.6%), AEs leading to study drug discontinuation (28.2% vs. 44%) and fatal AEs (0.3% vs. 2.4%). Additional analyses in subjects aged ≥75 years were limited by small numbers (n=12). Considering the peculiar epidemiology of TNBC, additional safety analyses stratified by age classes <45 and ≥45-<65 were provided, and no significant differences in the incidence and severity of AEs could be observed between subjects aged <45 and ≥45 and <65.

Subgroup analyses by **ECOG PS score** (0 vs. 1) showed that frailer subjects who received pembrolizumab were slightly more likely to experience Grade 3-5 AEs (90.6% vs. 81.1%, respectively), SAEs (48.1% vs. 42.8%), and deaths (2.8% vs. 0.6%). Results are, however, difficult to interpret, based on limited numbers in the ECOG 1 subset (N= 106) and inconsistencies (AEs leading to study drug discontinuation were more common in the ECOG 0 subgroup).

Due to the extremely limited number of male subjects in study KN-522 (N=1), no subgroup analysis stratified by **sex** could be provided. The safety profile of pembrolizumab in male subjects with not pre-treated, local-advanced TNBC is not currently assessable. Considering the epidemiology of TNBC, however, to better contextualise the data observed in study KN522 the MAH has provided additional safety analyses in the subgroup defined by female sex, age ≤60 years and baseline ECOG PS score 0, across relevant pembrolizumab datasets (i.e. subjects who received pembrolizumab + NAC / pembrolizumab in study KN522 [n=569], subjects who received placebo + NAC / placebo in study KN522 [n=277], subjects who received pembrolizumab + chemotherapy regimens in the overall clinical development programme [mPCD, n=344]) or in the pembrolizumab monotherapy safety dataset [mRSD n=597]). When compared to "matched" controls, younger and fitter women who received pembrolizumab in study KN522 were still at higher risk of experiencing Grade 3-5 AEs (80.4%, 78%, 73% and 36.2% in the pembrolizumab and placebo arms of study KN522, mPCD and mRSD, respectively), SAEs (42.5%, 28.2%, 28.8% and 27.6%, respectively) and AEs who resulted in any drug discontinuation (28.4%, 14.8%, 20.6%, 13.1%, respectively), confirming the non-negligible toxicity of the proposed combination regimen. No similar trend could be observed for Grade 5 AEs

(0.5%, 0.4%, 2%, 2.3%), yet limited numbers and different disease settings hampered definitive conclusions.

Compared to direct and indirect controls, younger and fitter women who received pembrolizumab in study KN522 were also more likely to experience AEOSI (44.1%, 23.8%, 29.7% and 30.2% in the pembrolizumab and placebo arms of study KN522, mPCD and mRSD, respectively), Grade 3-5 AEOSI (15.4%, 2.9%, 7%, 4.5%, respectively), serious AEOSI (10.5%, 1.4%, 5.8%, 6.2%, respectively) and AEOSI resulting in any study drug discontinuation (10.5%, 2.9%, 5.8%, 4.9%, respectively). Consistently with what observed in the overall population, no clear pattern driving the observed higher rates of AEOSI could be identified also in the "younger and fitter" subset.

Subgroup analyses by **region** showed that EU patients (N=325) were more likely to experience grade 3-5 AES, SAEs, fatal AEs and AEs leading to drug discontinuation. The reasons behind such differences are currently unknown and should be further discussed. The contribution of differences in baseline characteristics to the safety profile observed in the EU and ex-EU subgroups was reduced. However, unique patterns in immune-related AEs have been reported in some studies across ethnicities (Peravali, 2021), and the ethnical composition of the EU and ex-EU subgroups was not homogeneous.

2.5.2. Conclusions on clinical safety

The safety profile of the proposed pembrolizumab + NAC / pembrolizumab regimen for the treatment of adult subjects with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high-risk of recurrence has been characterised based on the results from Phase III study KN-522.

Although, based on the available data, no new safety concern has been identified, subjects receiving pembrolizumab showed higher rates of severe (Grade 3-5) AEs, SAEs, AEs leading to study drug discontinuation and fatal AEs compared to placebo. This was especially evident in the neoadjuvant setting, further highlighting the increased toxicity of the combination therapy. Immune-related AEs (AEOSI) were also consistently higher with pembrolizumab, reaching the highest incident rates in the neoadjuvant phase.

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 MAH submitted an updated RMP version with this application.

The PRAC considered that the risk management plan version 36 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 36 with the following content:

Safety concerns

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Immune-related adverse reactions (including immune related pneumonitis, colitis, hepatitis, nephritis, and endocrinopathies)
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)
Missing information	None

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance studies that are required for pembrolizumab.

Risk minimisation measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: Immune-Related Adverse Reactions		
Immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies)	Routine risk minimisation measures: ▪ The risk of the immune-related adverse reactions (including immune-related pneumonitis colitis, hepatitis, nephritis, and endocrinopathies) associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.	Routine pharmacovigilance activities Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted questionnaire for spontaneous postmarketing reports of all adverse events
	Additional risk minimisation measures: Patient educational materials	Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Potential Risks		
For hematologic malignancies: increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab	Routine risk minimisation measures: ▪ For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: ▪ Safety monitoring in the ongoing HL trial (KN204).
GVHD after pembrolizumab administration in patients with a history of allogeneic SCT	Routine risk minimisation measures: ▪ GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk. No additional risk minimisation measures warranted	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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 MAH and has been found acceptable for the following reasons:

There are only minor changes in the leaflet section 1, currently no changes of the package leaflet are foreseen impacting the safe use of the medicinal product, moreover, no changes are foreseen in the design, layout and format of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early stage triple negative breast cancer at high risk of recurrence.

3.1.2. Available therapies and unmet medical need

Breast cancer is the most commonly diagnosed malignancy and the most common cause of cancer deaths among women (Sung H, 2020). Approximately 15-20% of breast cancer are triple negative (TNBC), an heterogeneous disease characterized by negativity for ER, PgR and HER-2 (Howard, 2021). TNBC is associated with higher tumor grade at diagnosis, a higher risk of distant disease recurrence, with most of the relapse occurring within the first 3 years after surgery (Dent, 2007; Lin, 2012). Neoadjuvant chemotherapy (NACT) is the preferred choice for stage II and III disease. The standard treatments are antracycline-based regimen (adriamicin or epirubicin + cyclophosphamide, AC/EC) with the sequential use of taxane, for 12-24 weeks. The inclusion of carboplatin might be an option in the neoadjuvant therapy for TNBC. Adjuvant capecitabine is an option in TNBC for patients with residual disease after NACT (Cardoso, 2019; Burstein, 2021; NCCN, 2021).

3.1.3. Main clinical studies

The pivotal study for this submission is KEYNOTE-522, a phase 3, randomized, double blind study of pembrolizumab plus chemotherapy (AC or EC followed by carboplatin/paclitaxel) vs placebo plus chemotherapy as neoadjuvant treatment, followed by pembrolizumab vs placebo as adjuvant treatment. The results of the final analysis for pCR (IA2) and an interim analysis for EFS (IA4) have been submitted. Median follow-up at IA4 is approximately 37 months. Last patient was randomized approximately 2.5 years before the data cut-off. All patients have discontinued/terminated treatment.

3.2. Favourable effects

- Statistical significance reached for pCR at the interim analysis (IA1), confirmed at final analysis (pCR rate 64% vs 54.7%, Δ 9.2% (95%CI 2.8, 15.6), p=0.00221). Same direction of benefit of EFS.
- Statistically significant EFS advantage for pembrolizumab at interim analysis (IA4): EFS HR of 0.63 (95% CI: 0.48, 0.82), with a one-sided p-value of 0.0003093, EFS rate at 24 months was 87.8% (85.3, 89.9) vs 81% (76.8, 84.6). The benefit seems relevant. Analysis has been performed when all patients have already completed/discontinued treatment and followed at least one year out of treatment. Median follow-up is 37 months with most of the recurrence occurring within 3 years.
- Positive OS trend at early analysis. OS HR was 0.72 (95%CI 0.51, 1.02), not reaching statistical significance.

3.3. Uncertainties and limitations about favourable effects

- KEYNOTE-522 design does not allow to disentangle the contribution of pembrolizumab to each treatment phase. Whether neoadjuvant and/or adjuvant pembrolizumab are both needed is unknown based on this study. Data may only be discussed in the context of an indication for pembrolizumab as neoadjuvant AND adjuvant treatment.
- The assessment is based on interim analysis. Final results are expected post-approval.

3.4. Unfavourable effects

- Nearly all patients in study KN-522 reported at least one treatment-emergent AE, and most AEs were considered drug-related by the Investigator (98.9% and 99.7% in the "pembrolizumab" and "placebo" arms, respectively). AEs and drug-related AEs rates in the provided exposure-adjusted safety analyses from study KN-522 were higher with combination therapy (2459 and 1608 AEs rate/100 person-year, respectively) compared to both chemotherapy + placebo (2107 and 1351 AE rate/100 person-year, respectively) and pembrolizumab monotherapy (1706 and 560 AE rate/100 person-year, respectively, in the mTNBC dataset and 1506 and 472 AE rate/100 person-year, respectively, in the RSD dataset). Exposure adjusted AEs and drug-related AEs rates in the pembrolizumab arm were consistently higher in the neoadjuvant phase (3750 and 2687 AEs rate/100 person-year, respectively,) compared to the adjuvant phase (879 and 254.3 AEs rate/100 person-year, respectively).

- The most frequently (incidence ≥20%) reported treatment-emergent AEs in the combination therapy arm were nausea (67%), alopecia (61%), anaemia (59%), neutropenia (48%), fatigue (47%), constipation (42%), diarrhoea (41%), vomiting (31%), ALT increase (30%), headache (30%), rash (30%), arthralgia (29%), pyrexia (28%), asthenia (28%), cough (25%), neutrophil count decreased (24%), AST increased (24%), decreased appetite (23%), neuropathy peripheral (21%), insomnia (21%), peripheral sensory neuropathy (20%) and myalgia (20%). Similar type and rates of AEs could be observed with placebo, suggesting that the overall safety profile of the proposed combination is heavily influenced by the common chemotherapy backbone. The overall pattern of drug-related AEs was consistent with the overall safety analysis.

The AEs that were more frequently (incidence difference across arms ≥5%) reported in the pembrolizumab arm compared to placebo were diarrhoea, rash, pyrexia, decreased appetite, hypothyroidism and hypokalaemia, consistently with the known toxicity profile of pembrolizumab.

The incidence of individual AEs was constantly higher in the combination arm compared to the pembrolizumab monotherapy datasets, further highlighting the higher toxicity of combination therapy.

- Severe (Grade 3 to 5) AEs and drug-related AEs were slightly more frequent with the pembrolizumab + NAC /pembrolizumab regimen (82.4% and 77.1%, respectively) compared to placebo (78.7% and 73.3%, respectively), and significantly more common compared to pembrolizumab monotherapy (36.6% and 13.3% in the mTNBC dataset, respectively, and 48.2% and 15.8% in the RSD dataset, respectively). Although the highest exposure-adjusted severe AEs incidence rate was observed with combination chemotherapy in the neoadjuvant phase (i.e. 470 events/100 person-years), even in the adjuvant phase the incidence rate of severe AEs was still approximately 2 fold higher with pembrolizumab compared to placebo (i.e. 38 vs. 22 events/100 person-years, respectively). The pattern of severe AEs was generally similar in both arms of study KN-522, with severe hematologic toxicity presenting the highest incidence with both pembrolizumab and placebo, in line with the known toxicity profile of the common chemotherapy backbone. ALT increased was the

only severe AE whose incidence was significantly higher in the experimental vs. control arm (6.4% and 2.8%, respectively).

- SAEs and drug-related SAEs were more common with the pembrolizumab + NAC / pembrolizumab regimen (43.6% and 34.1%, respectively) compared to placebo (28.5% and 20.1%, respectively) and to the monotherapy reference datasets (23.5% and 7.7%, respectively, in the mTNBC dataset and 38.4% and 11.4%, respectively, in the RSD dataset). In the exposure-adjusted analysis, the highest incidence rate of SAEs was observed with combination therapy in the neoadjuvant phase (e.g. 121 events/100 person-years), and the SAE incidence rate was approximately two-fold higher with pembrolizumab in both the neoadjuvant and adjuvant phases. No clear pattern could be identified to explain the increased rate of SAEs observed with pembrolizumab with combination therapy, pyrexia being the only SAE significantly more common with pembrolizumab compared to placebo (3.7% vs. 0.5%).

- AEs that resulted in the discontinuation of any study drug intervention were also more frequently observed in the pembrolizumab + NAC /pembrolizumab arm (any drug discontinuation rate 29.9%, pembrolizumab discontinuation rate 20.1%) compared to placebo (any drug discontinuation rate 15.4%, placebo discontinuation rate 8%) and to the RSD dataset (pembrolizumab discontinuation rate 13.4%). The exposure-adjusted analysis showed that, although the highest incidence rate of AEs leading to study drug discontinuation was observed with combination therapy in the neoadjuvant phase (e.g. 55 events/100 person-years), it remains at least two-fold higher in the pembrolizumab arm compared to placebo across all treatment phases. No clear pattern of AEs driving the higher discontinuation rates in patients receiving the combination regimen could be identified, with most AEs occurring in <1% of subjects.

- Deaths due to AEs were observed in less than 1% of subjects in study KN-522. Seven out of 783 subjects in the experimental arm (0.9%) experienced fatal AEs compared to 1/389 (0.3%) in the control arm. The majority of the fatal AEs (6/8, 5/7 in the pembrolizumab arm and 1/1 in the control arm) were observed in the neoadjuvant phase. The exposure-adjusted incidence rate of AEs leading to death was nearly 4-fold higher compared to that observed in the control arm (1.09 and 0.23 events/100 person-years, respectively), with the highest exposure-adjusted incidence observed in the neoadjuvant phase with combination therapy (1.51 events/100 person-years).

- An increased incidence of AEOSI (43.6% vs. 21.9%), drug-related AEOSI (40.2% vs. 19%), severe (Grade 3-5) AEOSI (14.9% vs. 2.1%), serious AEOSI (10.6% vs. 1.3%) and AEOSI resulting in study drug discontinuation (10.9% vs. 2.6%) could be observed with combination therapy compared to placebo. AEOSI were also more frequent and severe/serious with combination therapy compared to pembrolizumab monotherapy. The exposure-adjusted incidence of all the AEOSI was higher in the NAC + pembrolizumab phase (all AEOSI 109 events/100 person-years) compared to the adjuvant phase (19.7 events/100 person-years). A similar difference could also be observed in terms of severe AEOSI (25.9 vs. 5 events/100 person-years), serious AEOSI (17.2 vs. 3.5 events/100 person-years), and AEOSI leading to drug discontinuation (17.5 vs. 2.4 events/100 person-years). The most common (i.e. incidence ≥5%) AEOSI in the pembrolizumab arm of study KN-522 were infusion reactions, hypothyroidism, severe skin reactions and hyperthyroidism. Infusion and skin reactions usually requiring corticosteroid therapy.

3.5. Uncertainties and limitations about unfavourable effects

- In line with the epidemiology of TNBC, enrolled patients were, for the vast majority, female (99.9%), young (median age 49 years) and in good medical state (ECOG 0 87%). Potential relationship between predisposing conditions, patient characteristics and concomitant medications at

baseline and the onset of all/specific AEOSI could not be characterized due to limited sample size in subgroups.

- Compared to the neo-adjuvant phase, in the adjuvant phase a reduced difference in the exposure adjusted AEs/drug-related AEs rates could be observed across treatment arms, which might be explained by the milder toxicity of pembrolizumab monotherapy. However, in the absence of re-randomisation post-surgery, the possibility of selection bias cannot be excluded, especially considering that only ~75% (588/783) of all the enrolled patients did proceed to the adjuvant phase in the pembrolizumab arm of study KN-522, compared to ~85% (331/389) in the placebo arm.

- Only Grade 5 pneumonitis, pulmonary embolism and autoimmune encephalitis were considered related to pembrolizumab by the Investigator. Uncertainties remain, however, on the causality of other fatal AEs observed in the pembrolizumab arm of study KN-522, since deaths occurred in the context of toxicities whose immune-related nature could not be excluded based on the currently available data.

- All myocarditis AEs (n=5, 0.6%) were reported as AEOSI in patients receiving pembrolizumab in study KN-522. Although the incidence was low, it was still higher than that observed in the monotherapy datasets (i.e. 0.2% in the mTNBC and 0.1% RSD). Considering the potentially fatal nature of cardiac toxicity with immune checkpoint inhibitors and the exposure of patients with locally advanced TNBC to cardiotoxic anthracyclines in the neoadjuvant phase, a possible relationship between anthracyclines exposure and the onset of immune-related cardiac toxicity was investigated. The number of subjects who did not receive anthracyclines in study KN522 was, however, too limited (<10%) for meaningful comparison.

- Compared to younger patients, subjects aged ≥65 years experienced higher rates of severe (Grade 3-5) AEs (81.8% vs. 86.9%, respectively), SAEs (42.3% vs. 53.6%), AEs leading to study drug discontinuation (28.2% vs. 44%) and fatal AEs (0.3% vs. 2.4%). Safety analyses in subjects aged ≥75 years were, however, limited by small numbers (n=12).

- Frailer subjects who received pembrolizumab were slightly more likely to experience Grade 3-5 AEs (90.6%), SAEs (48.1%) and deaths (2.8%). Results are, however, difficult to interpret, because of the limited numbers in the ECOG 1 subset (N= 106) and inconsistencies across subgroups (AEs leading to study drug discontinuation were more common in the ECOG 0 subgroup). No safety data are available for subjects with baseline ECOG PS ≥2.

- Due to the extremely limited number of male subjects in study KN-522 (N=1), no subgroup analysis stratified by sex could be provided. The safety profile of pembrolizumab in male subjects with locally advanced TNBC is not currently assessable.

- Subgroup analyses by region showed that EU patients (N=325) were more likely to experience grade 3-5 AES, SAEs, fatal AEs and AEs leading to drug discontinuation. The reasons behind such differences are currently unknown, although the impact of ethnical differences could not be excluded.

3.6. Effects Table

Table 2. Effects Table for pembrolizumab + chemotherapy as neoadjuvant treatment followed by pembrolizumab as adjuvant treatment - KEYNOTE-522 study, data cut-off for IA2: 24-APR-2019 (final pCR analysis); data cut-off for IA4: 23-MAR-2021 (interim EFS and OS analyses)

Effect	Short description	Unit	Treatment pembro+ NACT → pembro	Control placebo+ NACT → placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
pCR (ypT0/Tis ypN0)	Pathological complete response rate	% (95%CI)	N= 669 64% (60.2, 67.6)	N=333 54.7% 49.1, 60.1	IA2 (final analysis for pCR): unclear clinical relevance, reduction of pCR advantage with more patients / statistical significance reached	CSR KN-522
			Delta pCR 9.2% (2.8, 15.6), p= 0.00221			
EFS	Event free survival	Median months, HR (95%CI)	N=784 Median NR EFS 24m: 87.8 (85.3, 89.9)	N=390 Median NR EFS 24m: 81 (76.8, 84.6)	IA4 (interim analysis for EFS): Interim analysis /statistical significance reached, all patients observed off treatment, stability with prior interim data, consistency of sensitivity analysis	
			HR 0.63 (0.48, 0.82), p=0.0003093			
OS	Overall survival	Median months, HR (95%CI)	N=784 Median NR OS 24m: 92.3 (90.2, 94)	N=390 Median NR OS 24m: 91 (87.7, 93.5)	IA4 (interim analysis): Interim analysis, immature data / HR<1	
			HR 0.72 (0.51, 1.02) p=0.0321377			
Unfavourable Effects						
AEs Summary	G3-5 AEs	%	82.4	78.7	Increased toxicity with the addition of pembrolizumab to SOC. No new safety signals identified.	CSR KN-522
	G3-5 AEs exp.-adj.	AEs/100 p-y	279.00	204.51		
	Drug-rel. G3-5 AEs	%	77.1	73.3		
	SAEs	%	43.6	28.5		
	SAEs exp-adj.	SAEs/100 p-y	75.24	37.61		
	Drug-related SAEs	%	34.1	20.1		
	AEs leading to death	%	0.9	0.3		
	AEs leading to death exp.-adj.	AEs/100 p-y	1.09	0.23		
	Drug-related AEs leading to death	%	0.5	0.3		
	Drug discontinuation due to AEs	%	29.9	15.4		
	Drug discontinuation due to AEs exp.adj.	AEs/100 p-y	34.97	15.32		
AEOSI	All AEOSI	%	43.6	21.9		
	G. 3-5 AEOSI		14.9	2.1		
	Serious AEOSI		10.6	1.3		
	AEOSI leading to death		0.3	0		
	AEOSI resulting in study drug discontinuation		10.9	2.6		
	Infusion reactions		18	11.6		
	Hypothyroidism		15.1	5.7		
	Severe skin reactions		5.7	1		
	Hyperthyroidism		5.2	1.8		

Abbreviations: AE: adverse event; AEOSI: AE of special interest; exp-adj: exposure-adjusted; p-y: person-years; SAE: serious AE; NR: not reached

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

KEYNOTE-522 study showed statistically significant and relevant advantage in EFS at interim analysis for pembrolizumab+NACT followed by pembrolizumab vs placebo+NACT followed by placebo as neoadjuvant and adjuvant treatment of early stage TNBC. pCR was also statistically significant at final analysis; although the clinical relevance of the delta pCR is questioned, pCR points towards the same direction of the EFS advantage. OS was immature, but with HR point estimate <1. Along with sensitivity analyses, the overall data are considered supportive of the main EFS benefit.

Subjects receiving pembrolizumab showed higher rates of severe (Grade 3-5) AEs, SAEs, AEs leading to study drug discontinuation and fatal AEs compared to placebo, which was especially evident in the neoadjuvant setting, highlighting the increased toxicity of the combination therapy. A higher number of deaths was observed in the experimental vs control arm (6 vs 1 in the first 6 months from randomization, i.e. neoadjuvant treatment period; 16 vs 4 in the time interval 6-12 months from randomization), for progression (14 vs 4) or for AEs (7 vs 1), which is of note in the context of a curative setting, possibly related to a mix of higher toxicity of the combination of pembrolizumab with chemotherapy, worse baseline characteristics in one site and partly due to chance due to small numbers.

Subgroup analysis did not show clear any clear evidence for lack of efficacy in one or more subgroups, that could support any considerations for restricting the indication.

As the study design does not allow to disentangle the benefit of pembrolizumab added in the neoadjuvant or adjuvant setting, so whether both parts are needed, the treatment package should be considered in its entirety.

Acknowledging that the main benefit has been seen in an EFS interim analysis, based on the overall data provided, on the timing of such analysis with all patients off treatment as well as on the natural history of TNBC, it is considered unlikely that an additional EFS interim analysis might change the overall picture. Final results of KEYNOTE-522 are however awaited post-approval.

3.7.2. Balance of benefits and risks

The overall benefits of the proposed treatment shown in KEYNOTE-522 is considered to outweigh its risks.

3.7.3. Additional considerations on the benefit-risk balance

Inclusion in KEYNOTE-522 clinical study was allowed for patients whose TNBC had tumour size >1 cm but ≤2 cm in diameter with nodal involvement or tumour size > 2 cm in diameter regardless of nodal involvement, corresponding to stage IIB-IIIA/B (AJCC 7th ed). According to guidelines, neoadjuvant chemotherapy is the preferred choice for stage II and III TNBC (Burstein, 2021; Cardoso, 2019). The study excluded stage I (and stage IIA); for stage I adjuvant therapy is preferred according to guidelines (Burstein, 2021). The population seems overall reflected in the proposed wording of the indication "locally advanced or early-stage TNBC at high-risk of recurrence", with the exact tumour size

(in cm) and nodal status reported in section 5.1 of the SmPC. Therefore, a reference to section 5.1 has been included in the wording of indication in 4.1 in order to refer to the description of the population at high risk of recurrence.

3.8. Conclusions

The overall B/R of Keytruda is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 for Keytruda in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery of adults with locally advanced, or early-stage triple-negative breast cancer at high-risk of recurrence; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 36.0 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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 ‘Keytruda-H-C-3820-II-0110’

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