Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Nivolumab and ipilimumab

Proprietary Product Name: Opdivo and Yervoy/Winglore

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

April 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ARTG	Australian Register of Therapeutic Goods
BICR	Blinded independent central review
BMS	Bristol Myers Squibb (the sponsor)
BRAF	V-raf murine sarcoma viral oncogene homolog B1
CHEMO	Chemotherapy
cHL	Classical Hodgkin lymphoma
CI	Confidence interval
CSR	Clinical study report
CTLA-4	Cytotoxic T lymphocyte associated antigen-4
EC	Ethics committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Endothelial growth factor receptor
EMA	European Medicines Agency (European Union)
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration (United States of America)
GCP	Good Clinical Practice
HCC	Hepatocellular carcinoma
HR	Hazard ratio
ICH	International Council for Harmonisation
IHC	Immunohistochemistry

Abbreviation	Meaning
IPI	Ipilimumab
IRB	Institutional review board
IRT	Interactive randomisation technology
IV	Intravenous(ly)
mut/Mb	Mutations per megabase
NIVO	Nivolumab
NA	Not applicable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OSCC	Oesophageal squamous cell carcinoma
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression free survival
PT	Preferred Term
RCC	Renal cell carcinoma
ROS	Proto-oncogene tyrosine-protein kinase
SCCHN	Squamous cell carcinoma of the head and neck
TMB	Tumour mutational burden
UAE	United Arab Emirates
UC	Urothelial carcinoma
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	Extension of indication
Product names:	Opdivo and Yervoy/Winglore
Active ingredients:	Nivolumab and ipilimumab
Decision:	Withdrawn
Date of decision:	Not applicable
Date of entry onto ARTG:	Not applicable
ARTG number:	Not applicable
, *Black Triangle Scheme:*[1]	Not applicable
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd Level 2, 4 Nexus Court, Mulgrave VIC 3170
Dose form:	Concentrate solution for infusion
Strengths:	5 mg/mL and 10 mg/mL
Container:	Vial
Pack size:	1
Approved therapeutic use:	Not applicable
Route of administration:	Intravenous (IV) push or bolus injection
Dosage:	**Metastatic non-small cell lung cancer** The recommended dose is 3 mg/kg Opdivo administered as an intravenous infusion over 30 minutes every two weeks in combination with 1 mg/kg Yervoy/Winglore administered intravenously over 30 minutes every six weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	Not applicable

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Product background

This AusPAR describes the application by Bristol-Myers Squibb Australia Pty Ltd (the sponsor) to register Opdivo and Yervoy/Winglore (nivolumab and ipilimumab) 5 mg/mL and 10 mg/mL, concentrate solution for infusion for the following proposed extension of indications:

> *Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have tumour mutational burden ≥ 10 mutations per megabase with no known EGFR or ALK positive tumour mutations.*
>
> *Yervoy, in combination with nivolumab, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have tumour mutational burden ≥ 10 mutations per megabase with no known EGFR or ALK positive tumour mutations.*

Opdivo and Yervoy/Winglore are concurrent applications to extend the indications for two existing registered therapeutic products, for use in a new indication as a non-fixed dose combination.

Lung cancer is the most common cancer worldwide, with 1.8 million new cases diagnosed yearly, and an estimated 1.6 million deaths worldwide. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer (approximately 80% to 85% in Australia;[2]) and incorporates squamous cell carcinoma and non-squamous cell carcinoma. Approximately half of patients will be found to have metastatic disease at diagnosis.[2]

First line treatment of metastatic NSCLC is guided by molecular testing.[3] In the absence of a mutation for which a targeted therapy is available, such as the endothelial growth factor receptor gene (*EGFR*), the anaplastic lymphoma kinase gene (*ALK*), proto-oncogene tyrosine-protein kinase (*ROS1*), or v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), the current standard-of-care first-line therapy is an anti-programmed death ligand 1 (PD-L1)) antibody administered with a platinum-based combination chemotherapy (CHEMO) regimen. This superseded the previous standard-of-care first line treatment (histology-directed platinum doublet chemotherapy) in March 2019, with the TGA approval of pembrolizumab plus chemotherapy based on the KEYNOTE-407 trial.[4] Alternative anti-PD-L1 based regimens within this new standard-of-care include atezolizumab (only for patients with non-squamous histology; in combination with bevacizumab as well as chemotherapy; approved in April 2019) and nivolumab (in combination with ipilimumab as well as chemotherapy; approved in July 2020). Pembrolizumab as monotherapy is also registered in this therapeutic space for patients with a tumour PD-L1 score ≥ 1, and is a treatment option with lower toxicity than chemotherapy. Direct comparisons between pembrolizumab and pembrolizumab plus chemotherapy or between different PD-L1 inhibitors are not available.[3]

Patients with metastatic NSCLC have a poor prognosis, with a five year survival rate of about 10% for Stage IVA and 1% for Stage IVB.[5] First-line platinum-based chemotherapy results in a median progression free survival (PFS) of approximately 5 to 6 months.

[2] Walters, S. et al. Lung Cancer Survival and Stage at Diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a Population-based Study, 2004-2007, *Thorax*, 2013; 68(6): 551-564.
[3] Hellman, M. and West, H.J. Management of Advanced Non-small Cell Lung Cancer Lacking a Driver Mutation: Immunotherapy. In: UpToDate (accessed 7 September 2020).
[4] A randomized, double-blind, Phase III study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic squamous non-small cell lung cancer subjects (KEYNOTE-407).
[5] American Cancer Society. Non-small Cell Lung Cancer Survival Rates, by Stage. Available from American Cancer Society website. (Accessed on 17 July 2018).

Incorporating subsequent therapies in patients with adequate performance status, median overall survival (OS) from diagnosis is between 10 to 14 months.

First-line immunotherapy (pembrolizumab) has shown substantial benefit in patients with NSCLC tumours with high levels (≥ 50%) of PD-L1 expression. Patients receiving first line pembrolizumab achieved a median OS of 30.2 months.[6]

First-line immunotherapy in combination with chemotherapy with or without bevacizumab has also shown some improvement in PFS, although data for OS remain immature.

The sponsor has claimed that the combination of programmed cell death protein 1 (PD-1) inhibitors with cytotoxic T lymphocyte associated antigen-4 (CTLA-4) inhibitors may broaden the population of first-line NSCLC to whom a chemotherapy-free regimen may be offered.

The following studies have been undertaken in first-line NSCLC involving combination nivolumab and ipilimumab (see Table 1).

Table 1: Studies undertaken in first-line metastatic non-small cell lung cancer involving combination nivolumab and ipilimumab

Study ID	Phase, PD-L1 criteria	Presented in the dossier
CA209012	Phase I, PD-L1 unselected	Final clinical study report
CA209568	Phase II, PD-L1 unselected	Interim clinical study report for Part 1
CA209227	Phase III Part 1a, PD-L1 positive Part 1b, PD-L1 negative Part 2, PD-L1 unselected	Pivotal study Interim clinical study report for Part 1
CA2099LA	Phase III, PD-L1 unselected	Not provided Estimated completion date August 2019

Part 2 contained a small number of patients receiving triple therapy with nivolumab, ipilimumab and chemotherapy for which the primary endpoint was dose limiting toxicities.

Combination nivolumab and ipilimumab was chosen as an experimental arm in Study CA209227 (the pivotal study) on the basis of preclinical and preliminary clinical evidence suggesting synergy between the two classes of drug. Evidence suggests that PD-1 and CTLA-4 use distinct mechanisms for limiting T-cell activation.

Peripheral T-cell assessments suggest that a given T-cell checkpoint inhibitor may modulate immune cell phenotypes rendering them more susceptible to alternative checkpoint inhibitors. In patients who did not respond to nivolumab in CA209006, CTLA-4 positive and regulatory T-cells were increased. In preclinical models, CTLA-4 inhibition increased the number of tumour infiltrating T-cells expressing PD-1, PD-L1 and CTLA-4.

Clinical evidence from Study CA209012 (a Phase I study) demonstrated higher investigator assessed objective response rate (ORR) in treatment naive NSCLC patients

[6] Brahmer, J. et al. OA 17.06 Updated Analysis of KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy for Advanced NSCLC with PD-L1 TPS ≥50%, J Clin Oncol, 2017; 12(11): S1793-S4.

receiving combination nivolumab and ipilimumab than with nivolumab monotherapy (42.9% versus 23.1%) regardless of PD-L1 expression.

In patients with metastatic melanoma (Study CA209067, a Phase III study), the combination of nivolumab and ipilimumab resulted in longer PFS compared with either agent used as monotherapy.

Tumour PD-L1 is a predictive biomarker for PD-L1 inhibitors, although patients with low PD-L1 expression may still benefit. It is suggested that additional biomarkers are required to better identify patients for treatment with immunotherapies.

During the conduct of Study CA209227, emerging clinical data suggested that tumour mutational burden (TMB) may be an important predictive biomarker of response to checkpoint inhibition, independent of PD-L1 expression, in first-line NSCLC. The sponsor has stated that this evidence came from:

- Study CA209026, conducted in first-line NSCLC comparing nivolumab monotherapy with investigator's choice of platinum based chemotherapy; and
- Study CA209568, conducted in first-line NSCLC (non-comparative) which treated patients with combination nivolumab and ipilimumab.

The protocol for Study CA209227 was subsequently amended to include a comparison of PFS for nivolumab + ipilimumab versus chemotherapy in subjects with TMB ≥ 10 mutations per megabase (mu/Mb) as a co-primary endpoint.

Regulatory status

Opdivo (nivolumab) received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 11 January 2016 as monotherapy for the treatment of unresectable (Stage III) or metastatic (Stage IV) melanoma; in combination with Yervoy (ipilimumab) for the treatment of metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase; and, as monotherapy for the treatment of locally advanced or metastatic squamous NSCLC with progression on or after prior chemotherapy.

Since the initial registration, multiple submissions for the extension of indications have been approved. The current approved indications for Opdivo (nivolumab) in Australia are as follows:

> ***Melanoma***
>
> *Opdivo, as monotherapy, is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.*
>
> *Opdivo, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma.*
>
> *Opdivo, in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma. The approval of this indication is based on a pre-specified comparison to ipilimumab monotherapy. All analyses comparing nivolumab monotherapy with the nivolumab/ipilimumab combination are descriptive.*
>
> ***Non-Small Cell Lung Cancer (NSCLC)***
>
> *Opdivo, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumour aberrations.*

Opdivo, as monotherapy, is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy.

Opdivo, as monotherapy, is indicated for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Opdivo should be used after progression on or after targeted therapy.

Renal cell carcinoma (RCC)

Opdivo, in combination with ipilimumab, is indicated for the treatment of patients with intermediate/poor-risk, previously untreated advanced renal cell carcinoma.

Opdivo, as monotherapy, is indicated for the treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy.

Classical Hodgkin lymphoma (cHL)

Opdivo, as monotherapy, is indicated for the treatment of patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant and treatment with brentuximab vedotin. The approval of this indication is based on objective response rate in a single arm study.

Squamous cell carcinoma of the head and neck (SCCHN)

Opdivo, as monotherapy, is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in patients progressing on or after platinum based therapy. urothelial carcinoma (UC).

Opdivo, as monotherapy, is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response in a single arm study.

Hepatocellular carcinoma (HCC)

Opdivo, as monotherapy, is indicated for the treatment of patients with hepatocellular carcinoma after prior sorafenib therapy. This indication is approved based on objective response rate and duration of response in a single arm study. An improvement in survival or disease-related symptoms has not been established.

Oesophageal squamous cell carcinoma (OSCC)

Opdivo, as monotherapy, is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine and platinum based chemotherapy.

Ipilimumab, with the dual product names of Yervoy and Winglore, received initial registration on the ARTG on 4 July 2011 for us as monotherapy in the treatment of unresectable or metastatic melanoma who have failed or are intolerant to prior therapy.

Since the initial registration, multiple submissions for the extension of indications have been approved. The current approved indications for Yervoy/Winglore (ipilimumab) in Australia are as follows:[7]

Melanoma

Yervoy, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma. Yervoy, in combination with nivolumab, is indicated for the treatment of patients with unresectable or metastatic melanoma. The approval of

[7] The approved indications for Winglore are the same as for Yervoy.

this indication is based on a pre-specified comparison to ipilimumab monotherapy. All analyses comparing nivolumab monotherapy with the nivolumab/ipilimumab combination are descriptive.

Renal cell carcinoma (RCC)

Yervoy, in combination with nivolumab, is indicated for the treatment of patients with intermediate/poor-risk, previously untreated advanced renal cell carcinoma.

Non-small cell lung cancer (NSCLC)

Yervoy, in combination with nivolumab and 2 cycles of platinum-based chemotherapy, is indicated for the first-line treatment of patients with metastatic or recurrent non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumour aberrations.

At the time the TGA considered this application, similar applications had been approved in the United States of America (USA) (approved on 15 May 2020), Canada (approved on 18 November 2020), Japan (approved on 27 November 2020), Lebanon (approved on 16 June 2020), Peru (approved on 23 July 2020), the United Arab Emirates (UAE) (approved on 9 September 2020), Qatar (approved on 22 September 2020), South Korea (approved on 16 December 2020), Argentina (approved on 27 November 2020), Jordan (approved on 17 November 2020) and Kuwait (approved on 3 December 2020).

Similar applications were withdrawn in the European Union (EU) (withdrawn on 30 January 2020), Singapore (withdrawn on 1 December 2020) and Switzerland (withdrawn on 31 August 2020).

Similar applications were under consideration in Taiwan (submitted on 26 May 2020), Israel (submitted on 1 June 2020), Brazil (submitted on 1-2 June 2020), Chile (submitted on 12 June 2020), Thailand (submitted on 31 July 2020), Mexico (submitted on 22 September 2020), India (submitted on 29 September 2020), Oman (submitted on 28 October 2020) and Hong Kong (submitted on 23 December 2020).

Table 2, shown below, summarises these applications and provides the indications where approved.

Table 2: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	15 November 2019	Approved on 15 May 2020	*Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.*
European Union	11 April 2018	Withdrawn on 30 January 2020	Not applicable

Region	Submission date	Status	Approved indications
Canada	6 December 2019	Approved on 18 November 2020	*Opdivo, in combination with ipilimumab, is indicated for the treatment of adult patients with metastatic NSCLC, expressing PD-L1 ≥ 1% as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic therapy for metastatic NSCLC.*
Singapore[8]	29 September 2020	Withdrawn on 1 December 2020	Not applicable
Switzerland	22 November 2019	Withdrawn on 31 August 2020	Not applicable
Japan	25 December 2019	Approved on 27 November 2020	*Unresectable advanced or recurrent non-small cell lung cancer.*
Lebanon	16 June 2020	Approved on 16 June 2020	*Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.*
Peru	17 June 2020	Approved on 23 July 2020	*Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.*

[8] Only addition of text to clinical trials section is proposed.

Region	Submission date	Status	Approved indications
United Arab Emirates	7 September 2020	Approved on 9 September 2020	*Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.*
Qatar	7 September 2020	Approved on 22 September 2020	*Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.*
Taiwan	26 May 2020	Under consideration	Under consideration
South Korea	29 May 2020	Approved on 16 December 2020	*First-line treatment of patients with metastatic or recurrent non-small cell lung cancer whose tumors express PD-L1 (≥1%) with no EGFR or ALK genomic tumor aberrations, in combination with ipilimumab.*
Israel	1 June 2020	Under consideration	Under consideration
Brazil	1-2 June 2020[9]	Under consideration	Under consideration
Chile	12 June 2020	Under consideration	Under consideration

[9] Nivolumab was submitted in Brazil on 1 June 2020 and ipilimumab was submitted in Brazil on 2 June 2020.

Region	Submission date	Status	Approved indications
Argentina	19 June 2020	Approved on 27 November 2020	*Opdivo in combination with ipilimumab or in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic or recurrent NSCLC in patients with no EGFR or ALK genomic tumor mutations.*
Thailand	31 July 2020	Under consideration	Under consideration
Jordan	10 September 2020	Approved on 17 November 2020	*Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.*
Kuwait	14 September 2020	Approved on 3 December 2020	*Opdivo, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.*
Mexico	22 September 2020	Under consideration	Under consideration
India	29 September 2020	Under consideration	Under consideration
Oman	28 October 2020	Under consideration	Under consideration
Hong Kong	23 December 2020	Under consideration	Under consideration

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 3: Timeline for Submission PM-2018-02005-1-4 and PM-2018-02012-1-4

Description	Date
Submission dossier accepted and first round evaluation commenced	29 June 2018
First round evaluation completed	29 November 2018
Sponsor provides responses on questions raised in first round evaluation	2 January 2020
Second round evaluation completed	11 August 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 October 2020
Sponsor's pre-Advisory Committee response	17 November 2020
Advisory Committee meeting	3 and 4 December 2020
Registration decision (Outcome)	Not applicable; withdrawn by sponsor on 24 December 2020
Completion of administrative activities and registration on the ARTG	Not applicable
Number of working days from submission dossier acceptance to registration decision*	Not applicable

*Statutory timeframe for standard applications is 255 working days.

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Relevant guideline or guidance document referred to by the Delegate is listed below:

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Harmonised Guideline, Integrated Addendum to ICH E6(R2): Guideline For Good Clinical Practice; current Step 4 version, dated 9 November 2016.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Study CA209227 was considered as being pivotal to the claimed indication.

Study CA209227 (CheckMate-227 trial)

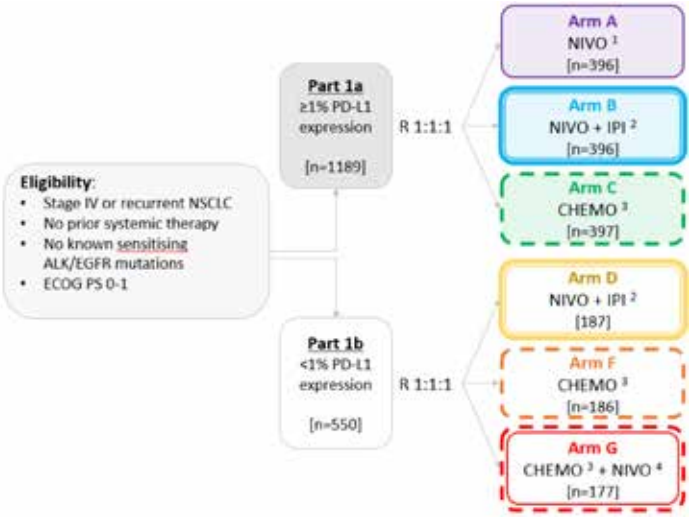
Study design

Study CA209227 (the CheckMate-227 trial) was an open-label, randomised, Phase III study of nivolumab monotherapy, nivolumab plus ipilimumab, nivolumab plus platinum doublet chemotherapy, or platinum doublet chemotherapy alone in subjects with previously untreated recurrent or metastatic NSCLC. The study design is summarised in Figure 1, shown below.

The first patient first visit date was 5 August 2015. The main comparator in the study was histology selected platinum doublet chemotherapy, which was an appropriate first line standard-of-care option at the time of study design.

This study was organised into two parts: Part 1 (further separated into two sub-studies, Part 1a and Part 1b) and Part 2. Part 1a and Part 1b enrolled patients with tumour PD-L1 expression ≥ 1% or < 1%, respectively, by Dako 28-8 immunohistochemistry (IHC) assay. Patients with undetectable tumour PD-L1 expression were not eligible for enrolment. In Part 2, subjects regardless of PD-L1 expression status were randomised to either nivolumab + chemotherapy (Arm H) or chemotherapy (Arm I). Results for Part 2 were reported separately, and are not relevant to this submission.[10]

Figure 1: Study CA209227 (CheckMate-227 trial) Part 1, study design



NSCLC = non-small cell lung cancer; R = randomisation, stratified by histology; NIVO = nivolumab; IPI = ipilimumab; ECOG PS = Eastern Cooperative Oncology Group Performance status; ALK = anaplastic lymphoma kinase gene; EGFR = epidermal growth factor receptor gene; PD-L1 = programmed death ligand 1.
Dose regimens:
1: Nivolumab 240 mg once every two weeks
2: Dose regimen for Arms B and D was identical: nivolumab 3 mg/kg every two weeks + ipilimumab 1 mg/kg every six weeks
3: Platinum doublet chemotherapy was histology specific: investigator's choice of cisplatin or carboplatin, plus pemetrexed (non-squamous) or gemcitabine (squamous)
4: Nivolumab 360 mg every three weeks

[10] European Medical Society for Oncology (ESMO) First-line nivolumab plus chemotherapy did not meet the primary endpoint of overall survival in non-squamous NSCLC, 12 December 2019. Available from the ESMO website.

The final CheckMate-227 trial clinical study report (CSR) states that in the initial protocol, Arm E was included to study an alternative dose regimen of nivolumab + ipilimumab. Early phase data suggested the Arm E regimen had less efficacy than the regimen being studied in Arms B and D. Therefore, as part of Amendment 9, Arm E (alternative dose nivolumab + ipilimumab) was replaced with Arm G (nivolumab + chemotherapy). The CSR states that no patients had been randomised to Arm E, but that ten patients had been randomised to each of Arms D and F, prior to this change.

Protocol amendments

The original CheckMate-227 trial study protocol, dated 29 May 2015, contained two sub-studies, one in subjects with PD-L1 expressing tumours (≥ 1%) and one in subjects with PD-L1 non-expressing tumours (< 1%), each randomising three arms (including one control arm), with an OS/PFS co-primary endpoint for each experimental arm versus the respective control.

The CheckMate-227 trial featured a number of substantial major protocol changes including multiple changes to the primary efficacy endpoints. The effects of major protocol changes on primary efficacy outcomes in the two sub-studies of Part 1 of the CheckMate-227 trial (Part 1a and Part 1b) are summarised in Table 4. The sponsor's description of how external data drove their protocol changes is presented in a timeline in Figure 2.

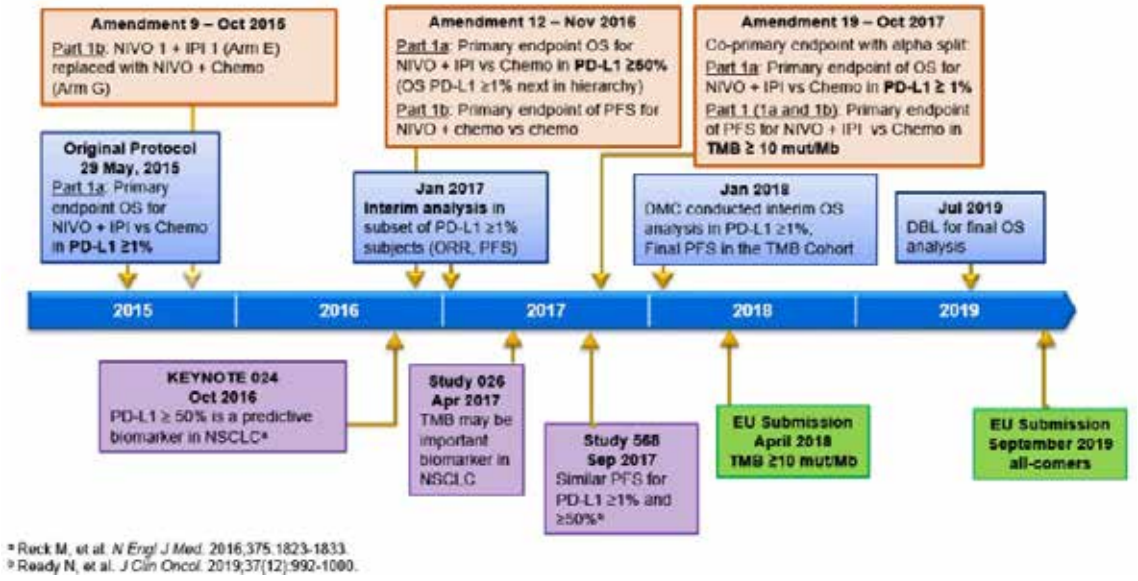
Table 4: Study CA209227 (CheckMate-227 trial) Summary of changes to primary efficacy outcomes in each of the sub-studies (Part 1a and Part 1b) through three major protocol amendments

Date (amendments)	Primary endpoints for Part 1A (PD-L1 ≥ 1%)	Primary endpoints for Part 1B (PD-L1 < 1%)
29 May 2015	Co-primary: OS + PFS	Co-primary: OS + PS
	Nivolumab versus chemotherapy Arm A versus Arm C	Nivolumab + ipilimumab versus chemotherapy Arm D versus Arm F
	Nivolumab + ipilimumab versus chemotherapy Arm B versus Arm C	Alternative dose nivolumab + ipilimumab versus chemotherapy Arm E versus Arm F
21 October 2015 (incorporating up to Amendment 9)	No change	Co-primary: OS + PFS
		Nivolumab + ipilimumab versus chemotherapy Arm D versus Arm F
		Nivolumab + chemotherapy versus chemotherapy Arm G versus Arm F
17 November 2016	Primary: OS	Primary: PFS

Date (amendments)	Primary endpoints for Part 1A (PD-L1 ≥ 1%)	Primary endpoints for Part 1B (PD-L1 < 1%)
(incorporating up to Amendment 12)	Nivolumab + ipilimumab versus chemotherapy (sub-group PD-L1 > 50%) Arm B versus Arm C	Nivolumab + chemotherapy versus chemotherapy Arm G versus Arm F
January 2017	Interim efficacy analysis conducted; ORR in PD-L1 > 1% (n = 484)	
5 October 2017 (incorporating up to Amendment 19)	Co-primary: – OS: § Nivolumab + ipilimumab versus chemotherapy § Arm B versus Arm C – PFS: § Nivolumab + ipilimumab versus chemotherapy PD-L1 agnostic, pooled across Part 1a + Part 1b Subgroup TMB ≥ 10 Mut/Mb § Arms (B + D) versus Arms (C + F)	

PD-L1: programmed death ligand 1; OS = overall survival; PFS = progression free survival; ORR = objective response rate; TMB = tumour mutational burden; Mut/Mb = mutations per megabase.

Figure 2: Study CA209227 (CheckMate-227 trial) Part 1, global amendments driven by emerging science and data independent of the trial



blue = key events and analyses; orange = all global amendments for Part 1; purple = key external data informing amendments; green = EU submissions.

PD-L1 = programmed death ligand 1; NIVO = nivolumab; IPI = ipilimumab; chemo = chemotherapy; NSCLC = non-small cell lung cancer; PFS = progression free survival; OS = overall survival; ORR = objective response rate; TMB = tumour mutational burden; mut/Mb = mutations per megabase; DBL = database lock; EU = European Union.

The extent and nature of protocol amendments were commented on by the clinical evaluators, and contributed to the European Medicines Agency (EMA)'s decision to undertake clinical trial site inspections for Good Clinical Practice (GCP).[11,12]

Population demographics and baseline disease characteristics

In Part 1a, 1189 patients were randomised 1:1:1 between the three arms.

The median age was 64 years (range: 26 to 87) with 48% of patients > 65 years and around 10% of patients > 75 years. The majority of patients were white (77%) and male (66%). Baseline Eastern Cooperative Oncology Group (ECOG) performance status;[13] was 0 (35%) or 1 (65%), 29% had squamous and 68% had non-squamous histology, 10% had brain metastases, and 85% were former or current smokers.

Part 1a only enrolled patients whose tumours had PD-L1 expression ≥ 1%, so the population had a higher prevalence of PD-L1 expression compared to the general population with metastatic NSCLC. Around half the subjects (51% of patients) had a tumour PD-L1 score > 50%.

Efficacy

Efficacy in Part 1a of the CheckMate-227 trial is summarised in Table 5 and Figure 3.

The co-primary efficacy outcome was OS in Part 1a. Progression-free survival and ORR were also measured but were nominal based on the statistical testing hierarchy (summarised with outcomes in Table 6). The other co-primary efficacy endpoint is not relevant to the proposed indication but was also significant.

A statistically significant increase in OS was seen with nivolumab + ipilimumab compared to chemotherapy, with a difference of 2.2 months between the Kaplan-Meier estimated medians, and a hazard ratio (HR) of 0.79 (see Table 5, below).

The Kaplan-Meier curve shows crossing of the survival curves for Arm B and Arm C at around seven months, indicating a higher rate of early mortality with nivolumab + ipilimumab than chemotherapy.

[11] EMA, Withdrawal Assessment Report for Opdivo and Yervoy, EMA/CHMP/193977/2020, 23 April 2020, Available from the EMA website.

[12] **Good Clinical Practice** (GCP) is a code of international standards and guidance following the International Council on Harmonisation (ICH) concerning the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials. Good Clinical Practice provides assurance that a study's results are credible and accurate and that the rights and confidentiality of the study subjects are protected.

[13] **ECOG Performance Status**: The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work

2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 – Dead

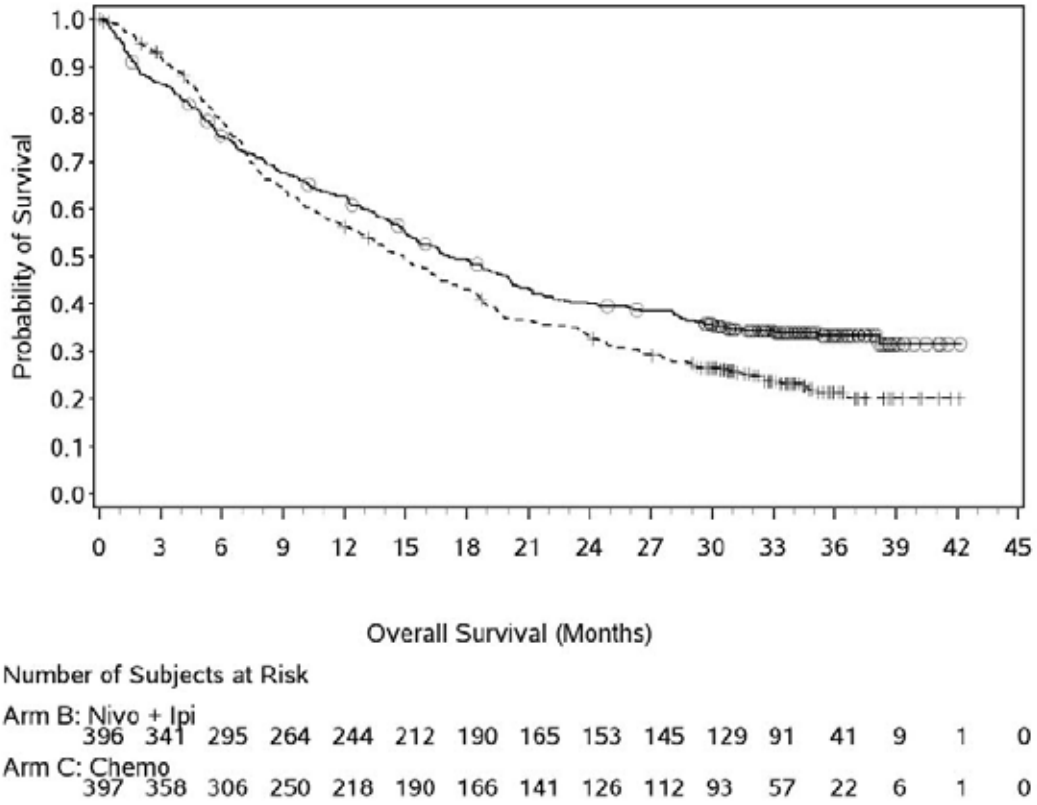
Table 5: Study CA209227 (CheckMate-227 trial) Part 1a, summary of overall survival (programmed death ligand 1 ≥ 1%) (database lock 2 July 2019)

	Arm A Nivolumab (n = 396)	Arm B Nivolumab + ipilimumab (n = 396)	Arm C Chemotherapy (n = 397)
Deaths, n (%)	274 (69.2%)	258 (65.2%)	298 (75.1%)
Hazard ratio (95% CI)[a]		Co-primary: Nivolumab + ipilimumab versus chemotherapy: 0.79 (0.67, 0.94); p = 0.0066[b]	
	Nivolumab versus nivolumab + ipilimumab: 0.90 (0.76, 1.07)		Nivolumab versus chemotherapy: 0.88 (0.75, 1.04)
Median, months (95% CI)[c]	15.70 (13.27, 18.14)	17.08 (14.95, 20.07)	14.88 (12.71, 16.72)
Overall survival rates, % (95% CI)[c]			
At 12 months:	57.0% (51.9, 61.7)	62.6% (57.7, 67.2)	56.2% (51.1, 61.0)
At 18 months:	45.6% (40.6, 50.4)	49.4% (44.4, 54.3)	43.0% (38.0, 47.9)
At 24 months:	36.2% (31.5, 41.0)	40.0% (35.1, 44.9)	32.8% (28.2, 37.5)

CI = confidence interval.

a) hazard ratio (stratified Cox proportional hazards model; b) stratified log-rank, threshold for two-sided Type 1 error rate = 0.0228; c) Kaplan-Meier estimate.

Figure 3: Study CA209272 (CheckMate-227 trial) Part 1a, Kaplan-Meier plot of overall survival for Arm B (nivolumab + ipilimumab) versus Arm C (chemotherapy) (programmed death ligand 1 ≥ 1% population)



Nivo = nivolumab; Ipi = ipilimumab; Chemo = chemotherapy.

Table 6: Study CA209227 (CheckMate-227 trial) Part 1, results of the statistical testing hierarchy

	p-Value Threshold	Actual p-Value	Met the Threshold
PD-L1 Hierarchy (2-sided type I error rate = 0.0228 for the final analysis)			
Co-primary objective: In subjects with PD-L1 ≥ 1% tumors, compare OS of nivo + ipi (Arm B) to chemo (Arm C)	< 0.0228	0.0066	Yes
Secondary Objectives (2-sided type I error rate = 0.0228)			
1. Compare PFS of nivo + chemo (Arm G) to chemo (Arm F) in subjects with PD-L1 < 1%	< 0.0228	0.0070	Yes
2. Compare OS of nivo + chemo (Arm G) to chemo (Arm F) in subjects with PD L1 < 1%	< 0.0228	0.0352	No (Statistical testing was stopped)
3. Compare OS of nivo (Arm A) to chemo (Arm C) in subjects with PD L1 ≥ 50%	< 0.0228	NA	NA
TMB Hierarchy (2-sided type I error rate = 0.025 for the interim analysis)			
Co-primary objective: In subjects with TMB ≥ 10 mut/Mb, compare PFS (per BICR) of nivo + ipi (Arms B + D) to chemo (Arms C + F) regardless of PD-L1 expression	< 0.025	0.0002[a]	Yes
Secondary Objectives (2-sided type I error rate = 0.025)			
1. Compare PFS between nivo (Arm A) and chemo (Arm C) among subjects with TMB ≥ 13 mut/Mb	< 0.025	0.7776[a]	No (statistical testing was stopped)
2. Compare OS of nivo + ipi (Arms B and D) and chemo (Arms C and F) in subjects with TMB ≥ 10 mut/Mb regardless of PD L1 expression	< 0.025	NA	NA
3. Compare OS of nivo (Arm A) and chemo (Arm C) in subjects with TMB ≥ 13 mut/Mb	< 0.025	NA	NA

a) Data from the 24 January 2018 database lock, reported in the Study CA209227 interim Part 1 CSR.

PD-L1 = programmed death ligand 1; OS = overall survival; nivo = nivolumab; ipi = ipilimumab; chemo = chemotherapy; PFS = progression free survival; TMB = tumour mutational burden; mut/Mb = mutations per megabase; BICR = blinded independent central review; NA = not applicable.

Safety

Safety populations

Part 1 of the CheckMate-227 trial was divided into two sub-studies: Part 1a (tumours with PD-L1 ≥ 1%) and Part 1b (tumours with measurable PD-L1 < 1%).

In the final Part 1 CSR for the CheckMate-227 trial, safety data were pooled across these two sub-studies for patients that received identical treatment regimens (Arms B + D and Arms C + F). Based on experience with the nivolumab + ipilimumab combination in other tumour settings and with checkpoint inhibitor drugs more broadly, safety is not expected to differ based on PD-L1 expression. The presentation of data in this pooled PD-L1-detectable population is therefore acceptable.

Adverse events

An overview of adverse events (AE) is provided in Table 7. Toxicity was higher in the nivolumab + ipilimumab arm than chemotherapy or nivolumab arms, with higher rates of AEs that were serious, higher grade, late onset (up to 100 days after treatment cessation) or led to treatment modification or discontinuation.

Table 7: Study CA209227 (CheckMate-227 trial) Part 1, overview of adverse events in patients treated with nivolumab + ipilimumab, nivolumab or chemotherapy

	Nivolumab + ipilimumab (Arm B + D; N = 576) %		Nivolumab (Arm A; N = 391) %		Chemotherapy (Arm C + F; N = 570) %	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
All adverse events (AE)	98.6	68.8	98.5	61.4	97.2	57.2
Drug-related AEs	76.7	33.0	65.5	19.7	81.9	36.0
Serious AEs (SAE)	61.6	51.3	52.9	44.5	40.0	31.4
SAEs with extended follow-up[a]	70.0	61.0	61.4	54.4	52.8	45.1
Drug-related SAEs	24.5	18.6	11.3	8.5	13.9	10.7
Drug-related SAEs with extended follow-up[a]	27.3	20.7	12.8	9.8	13.9	10.9
AEs leading to discontinuation	33.0	24.8	24.0	17.4	21.4	12.6
Drug-related AEs leading to discontinuation	18.1	12.5	12.3	7.2	9.1	4.9

a) extended follow-up category included events that occurred up to 100 days after last dose of study therapy (rather than the usual adverse event definition, that is within 30 days).

The safety profiles of immunotherapy and chemotherapy are different and for the most part mutually exclusive. Immunotherapy treated patients reported a predominance of immune mediated AEs, whilst chemotherapy treated patients reported more myelosuppression and nausea.

The most common AEs seen in patients treated with nivolumab + ipilimumab, nivolumab monotherapy, or chemotherapy in the CheckMate-227 trial are summarised in Table 8 using clinically relevant term groupings from the approved Food and Drug Administration (FDA) label (see Table 9).[14]

[14] United States Prescribing Information (USPI) for Opdivo (nivolumab) injection, for intravenous use, FDA; first approval 2014, available from the FDA website.

Table 8: Study CA209227 (CheckMate-227 trial) Part 1, most common treatment-emergent adverse events (at least 10% in any group) in patients treated with nivolumab + ipilimumab, nivolumab or chemotherapy

	Nivolumab + ipilimumab (Arm B + D, N = 576)		Nivolumab (Arm A, N = 391)		Chemotherapy (Arm C + F, N = 570)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Fatigue	44	6	40	3.8	42	4.4
Rash	34	4.7	21	1.5	10	0.4
Decreased appetite	31	2.3	23	1.3	26	1.4
Musculoskeletal pain	27	1.9	26	1.8	16	0.7
Diarrhoea/colitis	26	3.6	22	1	16	0.9
Dyspnoea	26	4.3	25	3.6	16	2.1
Cough	23	0.2	24	0	13	0
Hepatitis	21	9	16	6	10	1.2
Nausea	21	1	18	0.5	42	2.5
Pruritus	21	0.5	11	0	3.3	0
Constipation	18	0.3	15	0.5	27	0.5
Pyrexia	18	0.5	14	0.3	11	0.4
Hypothyroidism	16	0.5	9	0.3	1.2	0
Oedema	14	0.2	6	0.3	12	0.5
Arthralgia	44	6	40	3.8	42	4.4
Pneumonia	34	4.7	21	1.5	10	0.4
Vomiting	31	2.3	23	1.3	26	1.4
Headache	27	1.9	26	1.8	16	0.7
Abdominal pain	26	3.6	22	1	16	0.9
Hyperthyroidism	26	4.3	25	3.6	16	2.1

Table using data adapted from the United States Prescribing Information (USPI) for Opdivo (nivolumab) injection, for intravenous use, FDA; first approval 2014, available from the FDA website.

Table 9: Adverse event terms that were considered as clinically relevant groups by the Delegate

Group	Preferred Term
Fatigue	Fatigue and asthenia
Rash	Autoimmune dermatitis, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, granulomatous dermatitis, rash generalized, drug eruption, dyshidrotic eczema, eczema, exfoliative rash, nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, toxic skin eruption
Musculoskeletal pain	Back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, and pain in extremity
Diarrhoea/colitis	Colitis, colitis microscopic, colitis ulcerative, diarrhoea, enteritis infectious, enterocolitis, enterocolitis infectious, and enterocolitis viral
Dyspnoea	Dyspnoea and dyspnoea exertional
Cough	Cough and productive cough
Hepatitis	Alanine aminotransferase increased, aspartate aminotransferase increased, autoimmune hepatitis, blood bilirubin increased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatitis, hepatitis E, hepatocellular injury, hepatotoxicity, hyperbilirubinaemia, immune-mediated hepatitis, liver function test abnormal, liver function test increased, transaminases increased
Pruritus	Pruritus and pruritus generalised
Hypothyroidism	Autoimmune thyroiditis, blood thyroid stimulating hormone increased, hypothyroidism, primary hypothyroidism, thyroiditis, and tri-iodothyronine free decreased
Oedema	Eyelid oedema, face oedema, generalised oedema, localised oedema, oedema, oedema peripheral, and periorbital oedema
Pneumonia	Atypical pneumonia, lower respiratory tract infection, lower respiratory tract infection bacterial, lung infection, organising pneumonia, pneumonia, pneumonia adenoviral, pneumonia aspiration, pneumonia bacterial, pneumonia klebsiella, pneumonia influenzal, pneumonia viral
Abdominal pain	Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness
Hyperthyroidism	Contains blood thyroid stimulating hormone decreased, hyperthyroidism, and tri-iodothyronine free increased

Table using data adapted from the United States Prescribing Information (USPI) for Opdivo (nivolumab) injection, for intravenous use, FDA; first approval 2014, available from the FDA website.

Table 10: Study CA209227 (CheckMate-227 trial) Part 1, immune mediated adverse events and other events of special interest that occurred within 100 days of last study drug dose in patients treated with nivolumab + ipilimumab, nivolumab or chemotherapy

	Nivolumab + ipilimumab (Arm B + D) N = 576) n (%)		Nivolumab (Arm A; N = 391) n (%)		Chemotherapy (Arm C + F) N = 570) n (%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hypothyroidism/thyroiditis	81 (14.1)	4 (0.7)	33 (8.4)	1 (0.3)	1 (0.2)	0
Hyperthyroidism	50 (8.7)	0	15 (3.8)	0	2 (0.4)	1 (0.2)
Adrenal insufficiency	27 (4.7)	13 (2.3)	3 (0.8)	1 (0.3)	0	0
Pancreatitis	6 (1.0)	4 (0.7)	0	0	0	0
Diabetes mellitus	6 (1.0)	5 (0.9)	2 (0.5)	2 (0.5)	0	0
Hypophysitis	20 (3.5)	9 (1.6)	4 (1.0)	0	0	0
Uveitis	2 (0.3)	0	0	0	0	0
Encephalitis	2 (0.3)	2 (0.3)	0	0	0	0
Myocarditis	2 (0.3)	2 (0.3)	0	0	0	0
Myositis	2 (0.3)	1 (0.2)	2 (0.5)	2 (0.5)	1 (0.2)	0
Myasthenic syndrome	1 (0.2)	1 (0.2)	0	0	0	0
Rhabdomyolysis	1 (0.2)	1 (0.2)	0	0	0	0

Deaths

Table 11 summarises deaths in Part 1 of the CheckMate-227 trial. In addition to the fatal AEs considered attributable to study drug toxicity by the investigators, three additional fatal events are considered attributable to nivolumab + ipilimumab by the Delegate based on the case narratives (see Table 12). A higher rate of fatal AEs was seen in the nivolumab + ipilimumab arm compared to either nivolumab or chemotherapy monotherapy.

Table 11: Study CA209227 (CheckMate-227 trial) Part 1, summary of deaths in patients treated with nivolumab + ipilimumab, nivolumab or chemotherapy

Deaths	Nivolumab + ipilimumab (Arms B + D) (N = 576)	Nivolumab (Arm A) (N = 391)	Chemptherapy (Arms C + F) (N = 570)
Total, %	64.6	69.1	78.1
Due to:			
Underlying disease, %	52.8	56.0	63.9
Study drug toxicity, n (%) fatal events	11 (1.9) myocarditis, acute tubular necrosis, pneumonitis, pneumonitis, pneumonitis, pneumonitis, shock, cardiac tamponade, hyperglycaemia*, multi-system organ failure*, renal failure*	2 (0.5) pneumonitis, neutropenia/sepsis	6 (1.1) sepsis, sepsis, multiple brain infarctions, interstitial lung disease, thrombocytopenia, febrile neutropenia/sepsis
Unknown, %	2.4	3.1	4.7
Other, %	8.0	9.5	8.4

*Considered attributable to nivolumab + ipilimumab by the Delegate based on the case narratives (see Table 12).

Table 12: Study CA209227 (CheckMate-227 trial) Part 1, fatal adverse events in the nivolumab + ipilimumab arm not considered related to study treatment by the sponsor but considered attributable to study treatment by the Delegate

Fatal event	Narrative	Delegate comments
Fatal event 1, hyperglycaemia	A 61-year old male presented to hospital with nausea, vomiting, and weight loss on Day 147 (14 days after the 10th infusion of nivolumab and the 4th infusion of ipilimumab) and was admitted to the intensive care unit with Grade 4 hyperglycaemia with a glucose level of 459 mg/dL (baseline 112 mg/dL; range 70-110). WBC count, BUN, and creatinine were also elevated. On Day 154 the patient's condition worsened and he required mechanical ventilation; study therapy was discontinued. On Day 155 the patient died.	This patient did not have a past medical history of diabetes. It is unlikely that the glucose elevation was due to an infectious cause given the magnitude of glucose elevation and lack of fever. Given the known safety profile of nivolumab plus ipilimumab, immune-mediated diabetes mellitus is a possible cause of this death.

Fatal event	Narrative	Delegate comments
Fatal event 2 multi-system organ failure	A 77-year old female developed Grade 4 AST, ALT and bilirubin elevations on Day 337 with AST 1601 U/L (range 0-40), ALT 1092 U/L (range 0-40) and total bilirubin 150.5 umol/L (range 0-25.7), considered to be related to study therapy. The patient's most recent doses of nivolumab and ipilimumab were on Day 321. On Day 358 , the event term was amended to hepatitis and was downgraded to Grade 3, related to study therapy. No additional details were provided. On Day 375 the investigator reported an SAE of multiple organ failure resulting in death. The investigator reported the multi- system organ failure as unrelated to study drug. The sponsor made several attempts to obtain further information, but were unable to, due to withdrawal of consent except overall survival (OS) follow up.	Given the temporal relationship of the end-organ failure to the treatment-related hepatitis, it is not possible to rule out a causative role of nivolumab and ipilimumab in this fatal event.

Fatal event	Narrative	Delegate comments
Fatal event 3, renal failure	A 57-year-old male was hospitalised for Grade 4 renal failure on Day 213, 15 days after the patient's 15th infusion of nivolumab and 43 days after the 5th dose of ipilimumab. The patient presented with 'psychomotor agitation' and laboratory tests revealed a creatinine of 13 mg/dL (range 0.7-1.2) and urea of 223 mg/dL (range 18-55). Previous creatinine on Day 198 was 0.83 mg/dL and urea was 51.8 mg/dL. At Baseline, creatinine was 0.99 mg/dL (normal range: 0.7-1.2), and urea was 21.4 mg/dL. The patient was treated with cefoperazone/ sulbactam and dexamethasone. On Day 214, the patient developed heart failure, was intubated and placed on mechanical ventilation; however, the patient did not respond to resuscitative measures and died due to renal failure that day. The investigator was asked by the sponsor why the subject's death was felt to be not related to study therapy, and responded that the immunotherapy was very well tolerated for all 15 nivolumab administrations and all 5 ipilimumab administrations; the creatinine level was between normal ranges, so a causal relationship between the high level of creatinine at the time of death, and nivolumab or ipilimumab was not considered.	None of the concurrent medications the patient was taking (cyanocobalamin, folic acid, perindopril) are known to cause renal failure. Treatment-related nephritis can't be ruled out as the cause of renal failure in this fatal event, given the known safety profile of nivolumab + ipilimumab.

WBC = white blood cell (count); BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; OS = overall survival.

Toxicity in the elderly

The withdrawal European Public Assessment Report (EPAR);[11] included further information on the safety profile in older patients:

'The analysis of the safety profile of nivolumab + ipilimumab according to age (< 65 years, 65 to 74 years, 75 to 84 years and > 85 years) shows higher rates of drug-related AEs of Grade 3 to 4 in patients between 75 to 84 years (75 to 84: 43.9%; < 65: 32.0%; 65 to 74: 31.2%). Discontinuations due to drug-related AEs (29.8% versus 17.0% versus 16.5%) were also higher in this subgroup of very elderly patients.'

Risk management plan

There was no requirement for a risk management plan evaluation for a submission of this type.[15]

[15] The sponsor must still comply with routine product vigilance and risk minimisation requirements.

Risk-benefit analysis

Delegate's considerations

Good clinical practice

The TGA is reliant on confirmation of adherence to ICH;[16]-defined GCP from major international regulatory agencies to ensure that clinical trials are of adequate conduct to allow confident regulatory interpretation of the data.

The initial concern that triggered inspection was around protocol revisions being affected by interim results. However, the documentation from EMA indicates that the GCP inspection team had broader concerns regarding study quality in the CheckMate-227 trial. Despite the sponsor's stance that these concerns are not relevant because patient-level data is preserved and source data as captured in the electronic case report form (eCRF) is reliable, the EMA concluded:

'The critical GCP findings indicate that the overall quality of the study is poor and, as a consequence, it is not possible to obtain assurance that the data and reported results are credible and accurate.'

In contrast, separate GCP inspections conducted by Japan and the USA were non-eventful and an indication has been approved in the USA based on the OS data from Part 1a.

Clinical issues

The following discussion focusses on the risk-benefit profile, under the assumption that the trial data can be interpreted with an acceptable level of confidence despite the EMA's concerns over trial quality.

In the CheckMate-227 trial, early crossing of the Kaplan-Meier OS curves demonstrates that there is a survival detriment for patients treated with nivolumab + ipilimumab compared to chemotherapy during the first few months of therapy.

The current standard-of-care therapies, for example, nivolumab + ipilimumab + chemotherapy,[17] are not associated with this risk of worse early mortality (see Figure 4).

[16] The **International Council for Harmonisation** of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and the pharmaceutical industry. It makes recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.

[17] Nivolumab 360 mg every three weeks plus ipilimumab 1 mg/kg every six weeks plus two cycles of platinum-based chemotherapy every three weeks.

Figure 4: Study CA209-9LA (CheckMate-9LA trial) Kaplan-Meier curve for overall survival with nivolumab + ipilimumab + chemotherapy versus chemotherapy

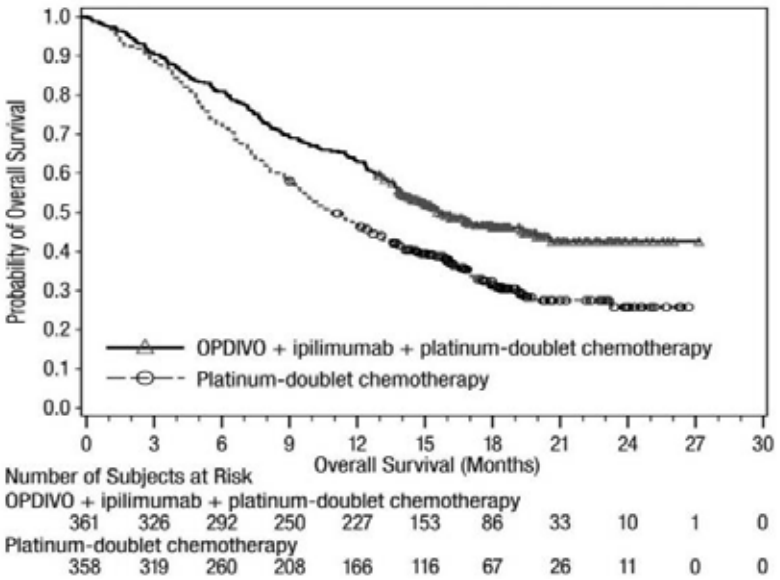


Table adapted from Figure 7 of the current Australian Product Information for Opdivo nivolumab, dated 13 July 2020, Available from the TGA website.

Opdivo (nivolumab) + ipilimumab + chemotherapy group: nivolumab 360 mg IV every 3 weeks + ipilimumab 1 mg/kg IV every 6 weeks + platinum-doublet chemotherapy every 3 weeks for 2 cycles.

Chemotherapy (monotherapy) group: platinum-doublet chemotherapy every 3 weeks for 4 cycles. Patients with non-squamous NSCLC in the control arm could receive optional pemetrexed maintenance therapy.

In response to the second round of TGA clinical evaluation, the sponsor states:

'While the potential risk factors for early detriment with a chemo-free regimen observed in Study CA209227 are not known, the risk of rapid disease progression is likely higher in subjects with symptomatic disease, highly metastatic to multiple organs and/or worst performance status, who may need a rapid disease control that could be achieved with chemotherapy. Conversely, asymptomatic patients with less aggressive tumor or with limited tumor lesions and good performance score may be able to benefit from a nivolumab + ipilimumab chemo-free regimen, while chemotherapy could be a second line option in patients with subsequent disease progression.'

There is no way to determine a priori which patients are at risk of early death with nivolumab + ipilimumab treatment compared to a platinum-doublet chemotherapy-containing protocol. Attempts at identifying the group of patients who are subject to a survival detriment with immunotherapy-alone regimens have found some trends but have been non-definitive.[18] The sponsor's suggestion that nivolumab + ipilimumab would have a positive risk-benefit balance in a subgroup of patients with less aggressive tumour or with limited tumour lesions and good performance score, with a plan to use chemotherapy as a second-line option in case of disease progression, is speculative and has not been substantiated.

The sponsor infers that nivolumab + ipilimumab would have a positive risk-benefit balance if considered as a chemotherapy-free treatment option. There are no direct data to

[18] Mulkey, F. et al. Analysis of Early Mortality in Randomized Clinical Trials Evaluating Anti-PD-1/PD-L1 Antibodies: A Systematic Analysis by the United States Food and Drug Administration (FDA), *J Clin Oncol*, 2019; 37 (15 suppl): 2516-2516.

support the use of nivolumab + ipilimumab in patients seeking to avoid chemotherapy or to minimise toxicity as no such patients were enrolled in the CheckMate-227 trial.

The safety profile of nivolumab + ipilimumab indicates significant toxicity. The incidence of adverse reactions that were serious, high grade, fatal, late-onset (up to 100 days after treatment cessation) or led to treatment modification or discontinuation were all higher with nivolumab + ipilimumab compared to platinum-doublet chemotherapy. The risk of serious drug-related adverse reactions was doubled with nivolumab + ipilimumab compared to chemotherapy. The median age of lung cancer diagnosis in Australia is around 71 years. The safety profile in Australian clinical practice may be worse than that observed in the CheckMate-227 trial, in which the median age was 64 and all patients were considered suitable candidates for chemotherapy treatment.

The risk of early mortality for a poorly defined group of patients and the toxicity profile of nivolumab + ipilimumab render the risk-benefit profile of nivolumab + ipilimumab for the proposed usage negative.

Proposed action

While a decision is yet to be made, at this stage the Delegate is not inclined to approve either of these two applications.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. ***Please discuss how a 1:1:1 randomisation scheme led to the randomisation of 10 subjects to Arm D and 10 subjects to Arm F in CheckMate-227, prior to any subjects being randomised to Arm E.***

In Part 1b of the CheckMate-227 study, for subjects with PD-L1 non-expressing tumors, the original protocol (29 May 2015) was designed to randomise subjects 1:1:1 to one of three arms:

- Nivolumab 3 mg/kg every two weeks with ipilimumab 1 mg/kg every six weeks (Arm D)
- Nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every three weeks x four, followed by nivolumab 240 mg every two weeks (Arm E)
- Platinum doublet chemotherapy (Arm F)

Following the presentation of CheckMate-012 efficacy results at the World Conference on Lung Cancer (8 September 2015), evaluating different doses and schedules of the nivolumab + ipilimumab combination, the decision was made to drop Arm E. This was because data indicated that in NSCLC, nivolumab 3 mg/kg was more effective than 1 mg/kg (both when combined with ipilimumab). A letter to the investigators was sent on 11 September 2015 informing them that Arm E will be closed. At that time, only one subject had been randomised (26 August 2015) into Part 1a, and no subjects had been randomized into Part 1b. Only one site had been activated for enrolment.

The sponsor created a new 1:1 randomisation schedule for Arms D and F of Part 1b pending the addition of a replacement arm for Arm E. As only one investigational site had been opened at this time, the decision was made to allow sites that had approved the protocol to start to enrol subjects. However, those sites in which the protocol had not yet been approved were advised to wait for the amendment before submitting it to their institutional review board (IRB)/ethics committee (EC).

The protocol was amended on 21 October 2015 (Amendment 9) to add a treatment arm with nivolumab + chemotherapy (Arm G) for patients with PD-L1 < 1% (Part 1b) and

randomisation would occur 1:1:1 between Arms D, F, and G. The new randomisation programming was implemented in the interactive randomisation technology (IRT) on 29 January 2016. Sites that had approved this revised protocol were able to randomise subjects to all treatment arms (A, B, C, D, F, and G). Sites with approval of the original protocol but yet to receive approval of revised protocol were able to randomise subjects only to Arms A, B, C, D, and F. For this reason, there was a slight imbalance in the number of subjects randomised to the arms in Part 1b, since Arm G was added several months after the original protocol, replacing Arm E, which was dropped at the very beginning of the study.

This clarification is also represented in the protocol amendments timeline captured in the Delegate's Overview [adapted and shown above as Table 4 under Section: Submission overview; Clinical; Study CA209227, Protocol amendments]. In addition to reproducing this table, the sponsor submitted the following information in their pre-ACM response to the Delegate's question:

- 11 September 2015: Dear Investigator Letter sent informing Arm E would be closed.
- 29 January 2016: new randomisation programming implemented.

  Sites that had approved revised protocol were able to randomise subjects to all treatment arms (Arms A, B, C, D, F and G).

  Sites yet to receive approval of revised protocol were able to randomise subjects only to Arms A, B, C, D, and F

Advisory Committee considerations[19]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the delegate

1. Please comment on Good Clinical Practice in CheckMate-227 and regulatory interpretation of the results.

The ACM noted that the primary analysis in the CheckMate-227 trial shows an improvement in survival for the PD-L1 > 1% population. However, the ACM expressed several concerns with the design and results of the CheckMate-227 trial.

The ACM considered the various protocol amendments that occurred during the CheckMate-227 trial, and expressed apprehension about whether the interim analysis might have influenced the subsequent protocol amendments. The ACM also advised that the treatment landscape in which the trial was designed has changed over time, and that the control arm used in the trial is no longer the standard of care. The ACM expressed concern that the design of the trial does not allow for a comparison of nivolumab with nivolumab + ipilimumab, thus the benefit of adding ipilimumab is uncertain. Considering

[19] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

that there are increased toxicities observed with combination therapy, this presents a significant risk.

Taking these concerns into consideration, the ACM advised that the benefit-risk balance is negative.

2. Would you recommend treatment with nivolumab + ipilimumab as first line therapy to any patient with previously untreated, advanced NSCLC that did not contain a driver mutation (EGFR or ALK) and had a tumour PD-L1 expression score of > 1%?

If so, please describe the clinical scenario(s) in which you envision this could be an appropriate choice of therapy.

The ACM advised that is was not clear where nivolumab + ipilimumab would fit in the treatment landscape for NSCLC, and would not recommend treatment with this combination in the scenario described in the question. The ACM discussed whether this particular combination therapy would benefit patients with PD-L1 expression 1 to 49% who do not want to be on chemotherapy, and agreed single agent therapy would likely be preferable for this group of patients, due to the toxicity associated with the combination therapy. The ACM advised that patients with chronic obstructive airways disease could potentially benefit from the combination therapy.

Conclusion

The proposed indication considered by the ACM was:

> *Opdivo in combination with ipilimumab is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumors express PD-L1 (≥ 1%) as determined by a validated test and with no EGFR or ALK genomic tumour aberrations.*
>
> *Yervoy/Winglore in combination with nivolumab is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumors express PD-L1 (≥ 1%) as determined by a validated test and with no EGFR or ALK genomic tumour aberrations.*

The ACM agreed that Opdivo and Yervoy/Winglore had an overall negative benefit-risk profile for the proposed indication as the evidence submitted did not satisfactorily establish the efficacy and safety of the product.

In providing this advice, the ACM acknowledged the difficulty of conducting long term studies where the treatment space is rapidly evolving, however, the concerns with the conduct of the pivotal trial mean that the benefit-risk profile is unfavourable for this combination therapy.

Outcome

The sponsor withdrew their submissions on 24 December 2020 before a decision had been made by the TGA.

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