Nivolumab for the treatment of non-small cell lung cancer: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

June 2020

Abstract

Purpose

To compare the predicted and actual utilisation of nivolumab for the second line treatment of non-small cell lung cancer (NSCLC) in the first 24 months of Pharmaceutical Benefits Scheme (PBS) listing.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Nivolumab was PBS listed on 1 August 2017 for the second line treatment of NSCLC.

Data Source / methodology

Data were extracted from the Services Australia Supplied Prescription database for the nivolumab items for NSCLC.

Key Findings

- Since PBS listing, 5,331 patients have been supplied nivolumab for NSCLC, and 59% of these initiating patients are male.
- In 2019, 25,816 prescriptions of nivolumab were supplied to 2,327 patients.
- Flat dosing may be changing prescribing, as it appears more people are being supplied higher doses less often in recent months.
- Other immunotherapies (atezolizumab, pembrolizumab and durvalumab) are gaining market share, however 99.6% of patients treated with an immunotherapy for NSCLC have not switched to a second immunotherapy.
- Over 90% of patients treated with nivolumab for NSCLC had at least one prior platinum based chemotherapy supply.

Purpose of analysis

To compare the predicted and actual utilisation of nivolumab for the second line treatment of non-small cell lung cancer (NSCLC) in the first 24 months of Pharmaceutical Benefits Scheme (PBS) listing.

Background

Clinical situation

There are many sub-types of lung cancer. Within non-small cell lung cancer (NSCLC), which accounts for over 80% of lung cancers, there are subtypes based on histology (squamous or non-squamous) and various genetic biomarkers that can direct the treatment course. The relevant genetic biomarkers indicate the presence or absence of driver mutations, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and c-ROS oncogene 1 (ROS1), for which specific inhibitor treatments are available. The presence of a high level of programmed cell death ligand 1 (PD-L1) expression, defined as greater than or equal to 50% of cells, is another molecular characteristic that guides treatment options. Despite this definition, PD-L1 expression is a continuum. There is evidence that PD-L1 or PD-1 protein inhibitors are effective agnostic of PD-L1 expression in various cancer settings.

The immunotherapies nivolumab, pembrolizumab, atezolizumab and durvalumab are PBS-subsidised PD-L1/PD-1 inhibitors for the treatment of advanced lung cancer. For initial treatment of advanced NSCLC without a driver mutation, most guidelines recommend pembrolizumab, with or without chemotherapy depending on the tumour histology, extent of PD-L1 expression, tumour burden and speed of disease progression. Some guidelines suggest nivolumab is an alternative to pembrolizumab in this setting, although this use is not PBS-subsidised.

Nivolumab and atezolizumab are treatment options for patients who have failed platinum-based chemotherapy with cisplatin or carboplatin. Patients who receive pembrolizumab as initial therapy for advanced NSCLC are not eligible to receive another PD-L1 inhibitor in a later line of therapy.

Guidelines (ESMO[1], NICE[2], UpToDate[3,4]) suggest that patients with a driver mutation should first be treated with an inhibitor therapy that targets their specific mutation; e.g. afatinib,

[1] Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann Oncol (2018) 29 (suppl 4): iv192–iv237, https://www.esmo.org/Guidelines/Lung-and-Chest-Tumours/Metastatic-Non-Small-Cell-Lung-Cancer

[2] Lung cancer: diagnosis and management, NICE guideline [NG122] Published date: 28 March 2019, www.nice.org.uk/guidance/NG122

[3] Overview of the initial treatment of advanced non-small cell lung cancer, Author: Rogerio C Lilenbaum, MD, FACP, Literature review current through: Mar 2020. | This topic last updated: Jun 25, 2019. Accessed 2 April 2020 https://www.uptodate.com/contents/overview-of-the-initial-treatment-of-advanced-non-small-cell-lung-cancer

[4] Management of advanced non-small cell lung cancer lacking a driver mutation: Immunotherapy Authors: Matthew Hellmann, MD, Howard (Jack) West, MD, Literature review current through: Feb 2020. | This topic last updated: Mar 05, 2020. Accessed 1 April 2020

erlotinib or gefitinib, possibly followed by osimertinib, for EGFR, ceritinib, alectinib or crizotnib for ALK, and crizotinib followed by ceritinib or brigatinib for ROS1. Following these targeted therapies, patients may be treated with platinum-based chemotherapy. Immunotherapies would only feature in the treatment of these patients after chemotherapy.

Use of immunotherapy earlier in the treatment course (adjuvant and neoadjuvant) is the subject of clinical trials. In time, immunotherapy use in the neoadjuvant and adjuvant settings may reduce use in the advanced setting, although the majority of NSCLC is diagnosed in the advanced stage.

Pharmacology

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb) which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with the ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity. Engagement of PD-1 with PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.[5]

Therapeutic Goods Administration (TGA) approved indications

Nivolumab is TGA approved for:

- Monotherapy for the treatment of locally advanced or metastatic squamous or non-squamous NSCLC with progression on or after prior chemotherapy.
- In combination with ipilimumab and two cycles of platinum-based chemotherapy for first-line treatment of patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations.
- Unresectable or metastatic melanoma.
- Renal Cell Carcinoma (RCC).
- Classical Hodgkin Lymphoma (cHL).
- Squamous Cell Carcinoma of the Head and Neck (SCCHN).
- Urothelial Carcinoma (UC).
- Hepatocellular Carcinoma (HCC).

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https://www.uptodate.com/contents/management-of-advanced-non-small-cell-lung-cancer-lacking-a-driver-mutation-immunotherapy

[5] Opdivo (nivolumab). Australian Approved Product Information. Mulgrave VIC: Bristol-Myers Squibb Australia Pty Ltd. Approved 11 January 2016, updated 9 April 2020. Available from https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01052-1&d=202004201016933

Dosage and administration

The recommended dose of nivolumab for NSCLC as a monotherapy administered intravenously over 30 minutes is 3 mg/kg every 2 weeks or 240 mg every 2 weeks or 480 mg every 4 weeks.

Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

PBS listing details (as at 1 March 2020)

Up to eight repeats are allowed for initial prescriptions, and up to 11 repeats for continuing prescriptions.

Table 1: PBS listing of nivolumab

Item	Name, form & strength, pack size	Max. amount	Rpts	DPMA	Brand name and manufacturer
11143L Private	nivolumab 100 mg/10 mL injection, 10 mL vial nivolumab 40 mg/4 mL injection, 4 mL vial	480 mg	8	$10232.76	Opdivo Bristol-Myers Squibb Australia Pty Ltd
11152Y Private	nivolumab 100 mg/10 mL injection, 10 mL vial nivolumab 40 mg/4 mL injection, 4 mL vial	480 mg	11	$10232.76	
11153B Public	nivolumab 100 mg/10 mL injection, 10 mL vial nivolumab 40 mg/4 mL injection, 4 mL vial	480 mg	11	$10053.46	
11158G Public	nivolumab 100 mg/10 mL injection, 10 mL vial nivolumab 40 mg/4 mL injection, 4 mL vial	480 mg	8	$10053.46	

Source: the PBS website. Note: Special Pricing Arrangements apply.

Restriction (Abridged)

Nivolumab is PBS listed for locally advanced or metastatic non-small cell lung cancer in initiating patients where

- the patient has not received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition,
- has a WHO performance status of 0 or 1,

- the treatment must be the sole PBS subsidised treatment for this condition, and
- the condition must have progressed on or after prior platinum based chemotherapy.

The PBS restriction states that patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen.

For details of the current PBS listing refer to the PBS website.

Date of listing on PBS

Nivolumab was PBS listed for NSCLC on 1 August 2017.

Changes to listing

The advice that "Patients must only receive a maximum of 240 mg every two weeks or 480 mg every four weeks under a weight based or flat dosing regimen" was added to the PBS restriction, and the maximum amount was changed from 360 mg to 480 mg, on 1 September 2019.

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

Separate major submissions for nivolumab for squamous and non-squamous NSCLC were considered by the PBAC in March 2016 and November 2016. A minor re-submission for non-squamous and squamous NSCLC was considered and recommended by the PBAC at its March 2017 meeting.

Non squamous

March 2016

The submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC). The PBAC also considered a concurrent submission to list nivolumab for squamous NSCLC.

The submission was considered by DUSC. The submission took an epidemiological approach to estimate the number of patients with non-squamous NSCLC each year and the proportion of patients eligible for EGFR, TKIs or ALK inhibitors based on the literature. The submission further estimated the proportion of patients treated with each second- or later-line therapies based on expert opinion.

There was considerable uncertainty in the proportions of patients assumed to receive each treatment option, given that they were based on advice from the eight expert members of the sponsor's advisory board. The level of agreement among these advisors was not

reported, nor was any justification provided for the proportions proposed. Consequently, there was substantial uncertainty in the estimated number of patients likely to be treated.

The total cost of nivolumab was likely to be an underestimate since the treatment duration was assumed to be as that observed in the CA209-057 trial. The trial duration was unlikely to be sufficient to capture the full treatment duration. The estimated use and financial implications of nivolumab in the treatment of non-squamous NSCLC are summarised below. The net cost to the PBS/RPBS over five years was estimated to be more than $100 million.

DUSC considered the estimates presented in the submission were overestimated. The main issues were:

- The financial implications to government were overestimated by applying a 'wider' versus 'narrower' definition of NSCLC to estimate the non-squamous NSCLC eligible population (81.7% vs. 74.2%, respectively). The Pre-PBAC Response (p.3) acknowledged that there is uncertainty regarding the true split between squamous and non-squamous NSCLC patients in Australia, noting that "if a narrower definition of NSCLC is used (excluding less common NSCLC subtypes), then the estimate of the proportion of squamous NSCLC patients reduces to 74.2% and net cost to the PBS decreases."
- The duration of nivolumab treatment in practice would likely be longer than the estimate based on Trial 057 due to the early cessation of this trial.
- There was potential for use beyond the restriction: (i) use in earlier lines of therapy; (ii) use in patients with a performance status that is worse than those participating in the key trial (i.e. ECOG >1); and (iii) use beyond disease progression.

The PBAC decided not to recommend that nivolumab be listed in the PBS for the treatment of non-squamous NSCLC on the PBS.

For further details refer to the Public Summary Document from the March 2016 PBAC meeting.

November 2016

The re-submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC).

As for the original submission, the re-submission used an incidence-based approach to estimate the eligible population. This was appropriate.

The main differences between the re-submission and the original submission were:

- The proportion of patients diagnosed with NSCLC who were assumed to have non-squamous histology was reduced from 81.7% to 74.2%, as recommended by DUSC;
- The proposed effective price for nivolumab was reduced;
- The mean number of nivolumab infusions per patient was increased, in line with updated data from trial CA209-057; and

- Drug wastage was included.

The re-submission's estimates for the proportion of patients receiving each treatment option were the same as those in the original submission. The assumptions in the treatment algorithms were based on clinical expert opinion, but there was no detail provided on how the information was elicited or the level of consensus among participants. These assumptions were a major source of uncertainty in the financial estimates and may have underestimated the uptake of nivolumab.

The estimated average cost of nivolumab per patient was uncertain, given:

- The duration of nivolumab treatment in practice may be longer than the estimate based on the 2-year minimum follow-up data from CA209-057, as 9.4% of patients in the trial were still receiving nivolumab;
- The allowance for wastage of nivolumab may have been excessive.

The PBAC previously noted the DUSC's concerns about the potential for use of nivolumab beyond the restriction (paragraph 7.12, 5.07 nivolumab PSD, March 2016 PBAC Meeting). These concerns included the potential for use in earlier lines of therapy, use in patients with a performance status that is worse than those participating in the key trial (i.e. ECOG>1), and use beyond disease progression. The proposed restriction was amended in the re-submission to limit eligibility to patients with a performance score of 0 or 1.

The financial estimates presented in the re-submission may be underestimated, given:

- The uptake of nivolumab is likely be higher than assumed in the re-submission;
- The duration of nivolumab treatment in practice may be longer than the estimate based on trial CA209-057; and
- There is potential for use of nivolumab beyond the restriction. These factors may be offset to some extent by the potentially excessive allowance for wastage of nivolumab.

The PBAC deferred its decision on the listing of nivolumab for the treatment of non-squamous NSCLC as there were concerns regarding the variation in the extent of effectiveness in patients over 75 years, especially given the high ICERs presented in the resubmission and doubts about the ability of the proposed RSA to achieve the sponsor's intended effect on these ICERs.

The PBAC considered that the financial implications presented in the resubmission may be underestimated due to potential leakage beyond the restriction and uncertainty around treatment duration, however considered that an RSA providing an overall cap based on patient numbers as well as the numbers of doses per patient would offer some certainty of the overall costs to the PBS.

For further details refer to the Public Summary Document from the November 2016 PBAC meeting.

Squamous

March 2016

The submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC). The PBAC also considered a concurrent submission to list nivolumab for non-squamous NSCLC.

The submission was considered by DUSC. The submission took an epidemiological approach to estimate the number of patients with squamous NSCLC each year. The submission further estimated the proportion of patients treated with second- and third-line therapies based on expert opinion.

There was considerable uncertainty in the proportions of patients assumed to receive each treatment option, given that they were based on advice from the eight expert members of the sponsor's advisory board. The level of agreement among these advisors was not reported, nor was any justification provided for the proportions proposed. Consequently, there was substantial uncertainty in the estimated number of patients likely to be treated.

The total cost of nivolumab was likely to be an underestimate since the treatment duration was assumed to be that observed in trial CA209-017. The trial duration was unlikely to be sufficient to capture the full treatment duration. The estimated use and financial implications of nivolumab in the treatment of squamous NSCLC are summarised below. The net cost to the PBS/RPBS over five years was estimated to be more than $100 million.

DUSC considered the estimates presented in the submission to be underestimated. The main issues were:

- The financial implications to government may be significantly underestimated by applying a 'wider' versus 'narrower' definition of NSCLC to estimate the squamous NSCLC eligible population (18.3% vs. 25.8%, respectively). The PrePBAC Response (p.3) acknowledged that there is uncertainty regarding the true split between squamous and non-squamous NSCLC patients in Australia, noting that an "increase in cost to the PBS for the squamous NSCLC indication is offset by a reduction in PBS cost for the non-squamous indication."
- The number of eligible patients receiving prior platinum-based chemotherapy was likely to be underestimated by assuming a relatively large proportion (25%) receive single agent chemotherapy instead. There would be an incentive to use doublet chemotherapy over single agents in order to access nivolumab.
- The duration of nivolumab treatment in practice would likely be longer than the estimate based on Trial 017 due to the early cessation of this trial.
- There was potential for use beyond the restriction: (i) use in earlier lines of therapy; (ii) use in patients with a performance status that is worse than those participating in the key trial (i.e. ECOG >1); and (iii) use beyond disease progression.

The PBAC decided not to recommend that nivolumab be listed in the PBS for the treatment of squamous NSCLC on the basis that acceptable cost-effectiveness had not been adequately demonstrated.

The PBAC noted the DUSC's concerns regarding the eligible patient numbers, duration of treatment in practice, and potential risk of use beyond the restriction, and advised that a financial cap would be required to manage these uncertainties.

For further details refer to the Public Summary Document from the March 2016 PBAC meeting.

November 2016

The re-submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC).

This re-submission was not considered by DUSC.

As for the original submission, the re-submission used an incidence-based approach to estimate the eligible population. This was appropriate.

The main differences between the re-submission and the original submission were:

- The proportion of patients diagnosed with NSCLC who were assumed to have squamous histology was increased from 18.3% to 25.8%, as recommended by DUSC;
- The proposed effective price for nivolumab was reduced;
- The mean number of nivolumab infusions per patient was increased, in line with updated data from trial CA209-017; and
- Drug wastage was included.

The re-submission's estimates for the proportion of patients receiving each treatment option were the same as those in the original submission. The assumptions in the treatment algorithms were based on advice from the eight expert members of the sponsor's advisory board. The level of agreement among these advisors was not reported, nor was any justification provided for the proportions proposed. Consequently, there was substantial uncertainty in the estimated number of patients likely to be treated.

The DUSC considered that the number of eligible patients receiving prior platinum based chemotherapy was likely to be underestimated by assuming a relatively large proportion (25%) receive single agent chemotherapy instead. There would be an incentive to use doublet chemotherapy over single agents in order to access nivolumab (paragraph 6.42, 5.06 nivolumab PSD, March 2016 PBAC Meeting).

The average cost of nivolumab per patient was likely to be underestimated, as the duration of nivolumab treatment in practice may be longer than the mean treatment duration observed from the 2-year minimum follow-up data in CA209-017, given that 8% of patients in the trial were still receiving nivolumab.

The PBAC previously noted the DUSC's concerns about the potential for use of nivolumab beyond the restriction (paragraph 7.10, 5.06 nivolumab PSD, March 2016 PBAC Meeting). These concerns included potential use in earlier lines of therapy, use in patients with a performance status that is worse than those participating in the key trial (i.e. ECOG5 >1), and use beyond disease progression (paragraph 6.42, 5.06 nivolumab PSD, March 2016 PBAC Meeting). The proposed restriction was amended in the re-submission to limit eligibility to patients with a performance score of 0 or 1.

- The financial estimates presented in the re-submission may be underestimated, given the following: In the scenario in which nivolumab was available on the PBS, the number of patients receiving prior platinum-based chemotherapy was likely to be underestimated, as there would be an incentive to use doublet chemotherapy over single agents in order to access nivolumab.
- The average cost per patient for nivolumab may be underestimated as the mean duration of nivolumab treatment in practice may be longer than that observed in trial CA209-017.
- There is potential for use of nivolumab beyond the restriction.

The PBAC deferred its decision on the listing of nivolumab for the treatment of squamous NSCLC as there were concerns regarding the variation in the extent of effectiveness in patients over 75 years, especially given the high ICER presented in the resubmission and doubts about the ability of the proposed RSA to achieve the sponsor's intended effect on this ICER. The PBAC requested that the Department hold discussions with the sponsor in order to develop a proposal for a Managed Entry Scheme (MES) to address these concerns.

The PBAC considered that the financial implications presented in the resubmission may be underestimated due to potential leakage beyond the restriction and uncertainty around treatment duration, however considered that an RSA providing an overall cap based on patient numbers as well as the numbers of doses per patient would offer some certainty of the overall costs to the PBS.

For further details refer to the Public Summary Document from the November 2016 PBAC meeting.

Squamous and non-squamous

March 2017

The PBAC recommended the Authority Required (STREAMLINED) listing of nivolumab for the treatment of locally advanced or metastatic, squamous or non-squamous, NSCLC. The PBAC considered that, with its suggested modifications, the risk sharing arrangements proposed by the sponsor adequately addressed concerns regarding the possible variation in the extent of effectiveness in patients 75 years or older, and uncertainties regarding the ICERs presented in the November 2016 submissions, the overall numbers using nivolumab in NSCLC, the risk of leakage of nivolumab outside of the intended restriction, and the duration of nivolumab treatment.

For further details refer to the Public Summary Document from the March 2017 PBAC meeting.

Flat dosing

March 2019

At the March 2019 meeting a minor submission was recommended by the PBAC which requested the addition of two flat dosing regimens to the current 3 mg/kg every two weeks (Q2W) weight based dosing regimen to allow clinicians choice of either:

1. weight-based 3 mg/kg Q2W dosing, or
2. flat 240 mg Q2W dosing, or
3. flat 480 mg Q4W dosing

The minor submission requested that all three dosing regimens be made available for all existing nivolumab PBS listed indications.

For further details refer to the Public Summary Document from the March 2019 PBAC meeting.

Approach taken to estimate utilisation

The March 2017 submission included separate estimates of squamous and non-squamous NSCLC, which were updated from the previous submissions.

The estimates of squamous and non-squamous both took an epidemiological approach. The submissions used incidence data from the AIHW and made assumptions based on a publication from the AIHW.[6] The submissions assumed 87% of newly diagnosed lung cancer is NSCLC, 26% of newly diagnosed NSCLC is squamous NSCLC and 74% is non-squamous NSCLC. The estimates for squamous NSCLC assumed 49.9% of eligible patients would receive platinum doublet chemotherapy, and the estimates for non-squamous NSCLC assumed 53% of eligible patients would receive platinum doublet chemotherapy.

The estimated mean dose per patient was 226 mg for squamous patients and 220 mg for non-squamous patients, calculated from the dosage in the PI and trial using patient weights from the early access program. Both sets of estimates assumed the mean number of nivolumab treatments per patient would be [redacted], which was the mean number of treatments in the trial.

[6] Australian Institute of Health and Welfare & Cancer Australia 2011. Lung cancer in Australia: an overview. Cancer series no. 64. Cat. no. CAN 58. Canberra: AIHW.

Methods

The report examines the use of nivolumab for the treatment of NSCLC. Prescriptions were extracted from the Services Australia prescription database from 1 August 2017.

Consistency of assignment of indication was investigated. All nivolumab items (i.e. for all indications) were extracted from the Services Australia prescription database from 1 May 2016 when nivolumab was first listed for malignant melanoma. An analysis of indication sequence (see Appendix A for details) was then performed to determine the reliability of assigning indication via PBS item code. This analysis showed that 95.8% of patients were treated for one indication. Therefore for this analysis prescriptions were extracted for the item codes for nivolumab for NSCLC only.

These prescriptions were used to analyse overall use, the age and sex of patients, the supplied dose and time to resupply of nivolumab for NSCLC.

Further data was obtained from Services Australia, which listed whether patients had died, and included the date of death if the patient had died. These data were used to analyse the length of treatment and time between last nivolumab prescription and death. As the prescription data were extracted more recently, a smaller number of patients were analysed in this section than in the overall use section. Thirty eight patients included in the date of death data were excluded from analyses because their last nivolumab supply was more than the median time to resupply (14 days) after their recorded date of death or their recorded initiation of nivolumab was after their recorded date of death.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Medicare date of processing data.[7]

Number of doses

The number of doses patients were supplied was calculated for patients who initiated treatment with nivolumab between 1 August 2017 and 31 July 2018, i.e. in the first year of PBS listing.

Length of treatment

The length of treatment was estimated using the Kaplan Meier method for the 5,117 patients included in the Services Australia date of death data. Two ways of measuring length of treatment were undertaken to account for patients stopping nivolumab for periods of time (called a 'break' in therapy). One analysis excluded the time of any breaks in treatment (i.e. reports the total time a patient is actually receiving regular supplies of nivolumab) and the other did not.

[7] PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>.

A patient was deemed to have a break in treatment if the time between two of their supplied prescriptions was more than two times the median time to resupply (i.e. 2 x 14 days), which is an estimated break in treatment of at least one median time to resupply (i.e. 14 days).

A censoring definition was applied in the length of treatment analysis, to account for the end of the data observation period where patients who might be continuing supply appear to stop treatment (because there is no further data for supplies). For patients noted by Services Australia to be alive, a patient was deemed to be continuing treatment at the end of the data period if their last prescription was supplied within two times the median time to resupply of this end date. Otherwise, the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time (14 days) to resupply.

For patients noted by Services Australia to have died, the patient was deemed to have died on treatment if their recorded date of death was earlier than their last prescription plus a median time (14 days) to resupply. The treatment coverage end date was determined to be the date of death, and the patient was censored. Otherwise, the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time (14 days) to resupply.

Use of other immunotherapies for NSCLC

To investigate the NSCLC immunotherapy market and to check for switching within the NSCLC immunotherapy market, prescriptions of atezolizumab, pembrolizumab and durvalumab for NSCLC were extracted from their earliest listing for NSCLC to 31 March 2020.

Prior use of chemotherapy

To investigate the extent of prior use of chemotherapy, prescriptions of cisplatin and carboplatin were extracted from January 2010, to ensure that patients were not classified as being naïve to treatment if they were treated with chemotherapy several years ago. Oxaliplatin was not included as it is not generally listed in clinical guidelines (e.g. in eviQ) as a treatment for NSCLC. The use of cisplatin and carboplatin in patients who were not supplied nivolumab for NSCLC is not presented in the report.

Results

Analysis of drug utilisation

Overall utilisation

Figure 1: Patients and prescriptions of nivolumab for NSCLC

Figure 1 shows that after an initial increase in use following PBS listing, the number of treated patients, initiating patients and supplied prescriptions have been decreasing since the third quarter of 2018.

Of the 79,537 prescriptions dispensed in the dataset, 98.6% had a correct streamlined code recorded. The remaining 1.4% of prescriptions had a missing streamlined code, likely due to an application through the Authority Approvals database for an increased amount.

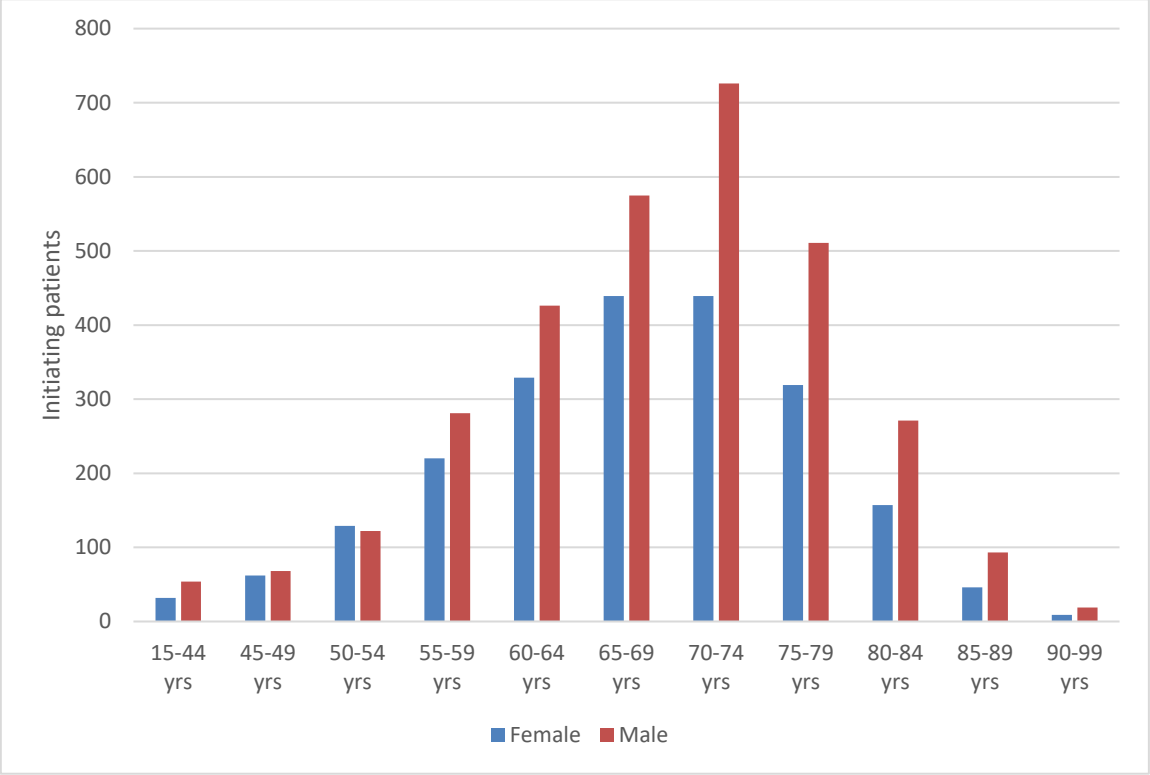

Figure 2: Age and sex of patients at initiation to nivolumab for NSCLC

Figure 2 shows the age and sex of patients at initiation to nivolumab for NSCLC. Patients aged 15 to 44 years old and 90 to 99 years old are grouped because of small patient numbers. More males (3,146) than females (2,181) have initiated treatment since August 2017. In females, the number of patients aged 65 to 69 and 70 to 74 years old are similar, however in males the group with the highest number of patients is the 70 to 74 year old group. Of the patients treated in 2019, 30% were aged 75 or older at their first prescription supplied in 2019.

Dosing of nivolumab

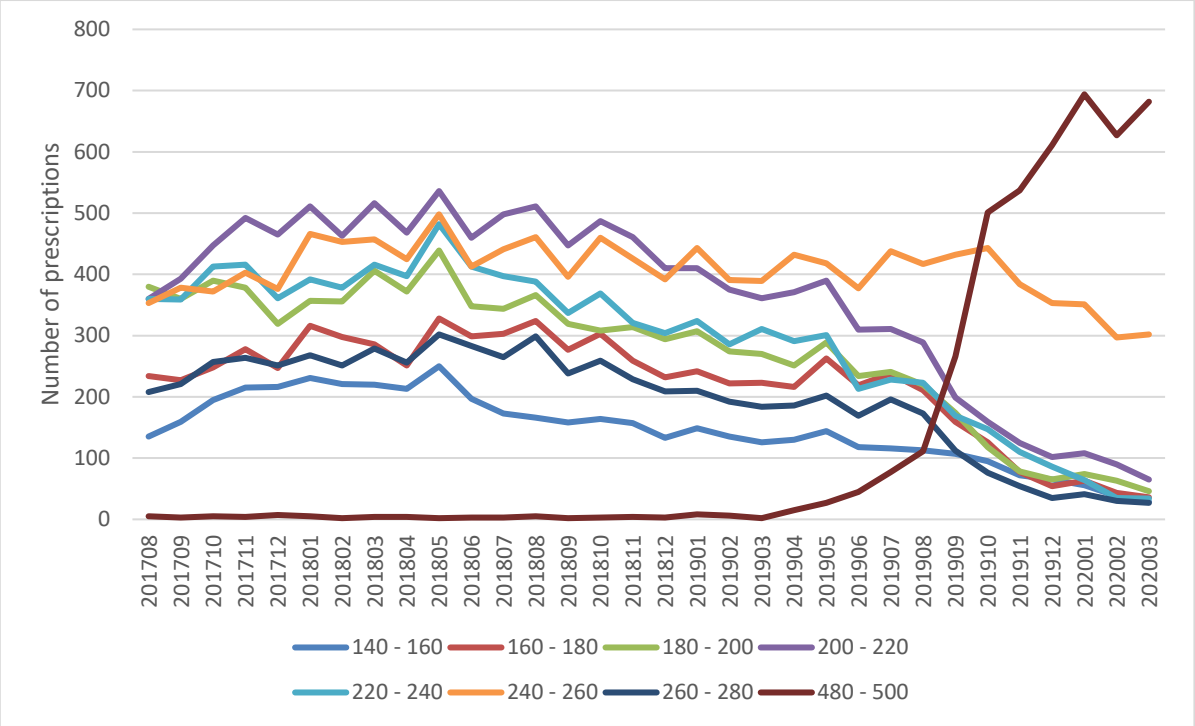

Figure 3: Dispensed dose of nivolumab for NSCLC over time

Note: Top eight results shown. 140 – 160 represents doses ≥ 140 and < 160.

The submission estimated patients would be treated with a mean dose of 222 mg, however the restrictions were amended to allow flat dosing in September 2019. The introduction of flat dosing has increased the use of 240 mg and 480 mg, and decreased doses below and between these amounts. It appears the use of 480 mg began to increase prior to the change in September 2019. Figure 4 below also shows that the mean and median doses per month have increased since the introduction of flat dosing, but the time to resupply has also increased. Note that the time to resupply in the last month of data is probably not reliable.

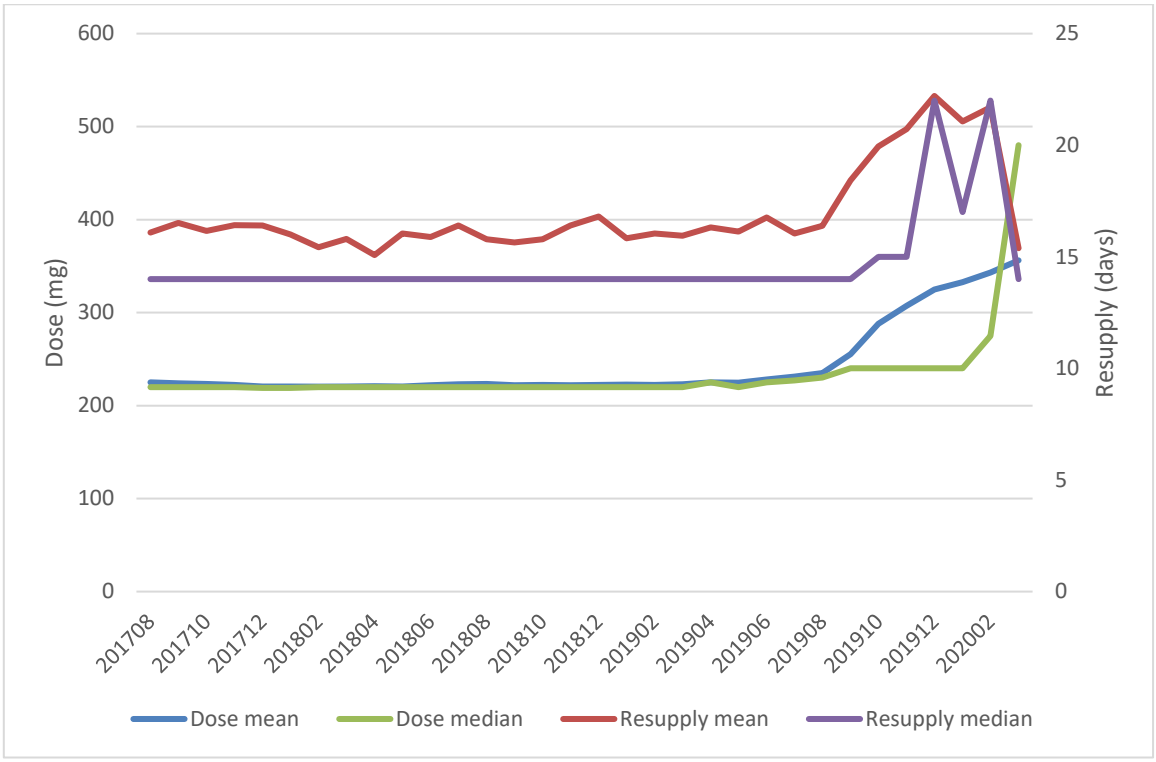

Figure 4: Mean and median dose and time to resupply over time

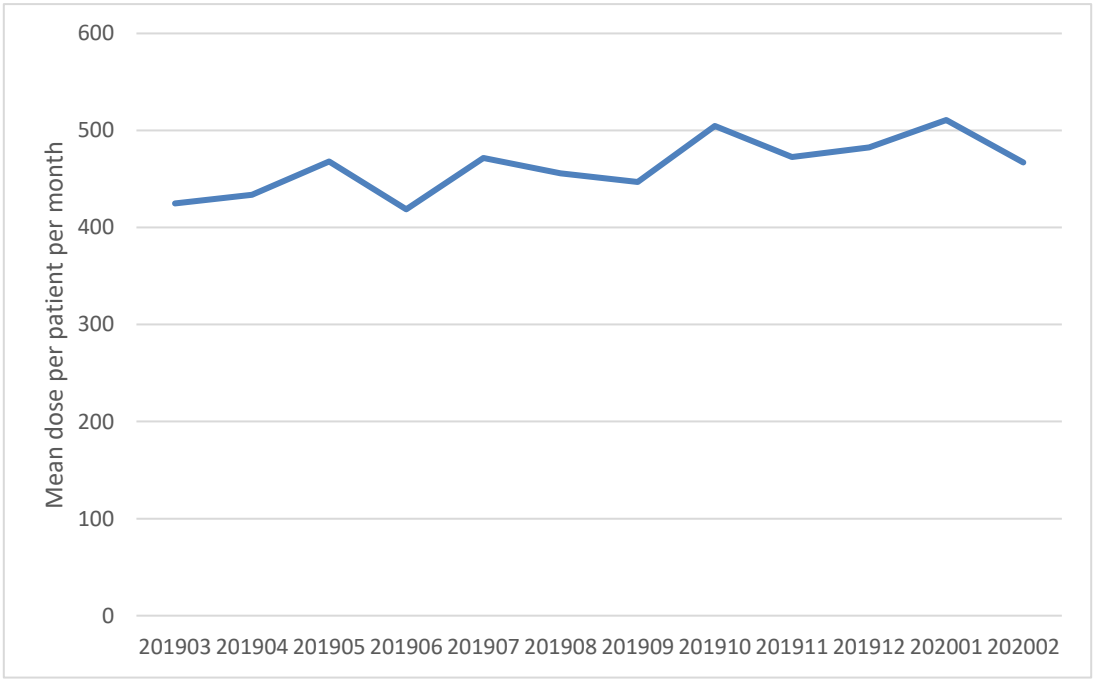

Figure 5: Mean doses per patient six months prior to and following the introduction of flat dosing in September 2019

Figure 5 shows that the total dose of nivolumab supplied to patients per month has remained relatively stable. In the six months prior to the introduction of flat dosing (March to August 2019) the mean dose per patient per month was 445 mg, and the mean dose per patient per month in the six months after the change (September 2019 to February 2020) was 481. The introduction of flat dosing does not appear to have affected the amount of nivolumab supplied to patients per month.

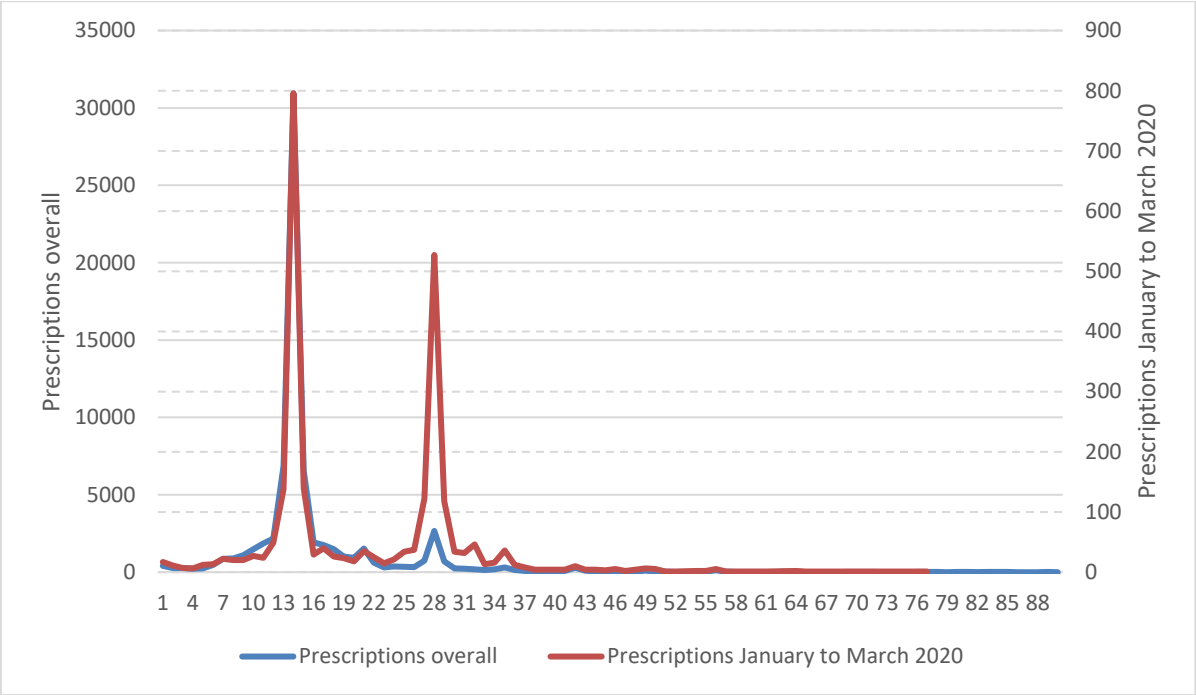

Figure 6: Time between supplies of nivolumab for NSCLC

When all prescriptions for nivolumab for NSCLC were considered, the time to resupply was frequently 14 days. In the most recent quarter of data, the most frequent time to resupply is also 14 days, but the proportion of prescriptions resupplied at 28 days is higher.

Number of doses

For patients who initiated in the first year of PBS listing, the mean number of doses supplied was 18, and the median was 10. There are 3,520 patients included in this analysis, 1,162 (33%) of these patients have died.

Length of treatment

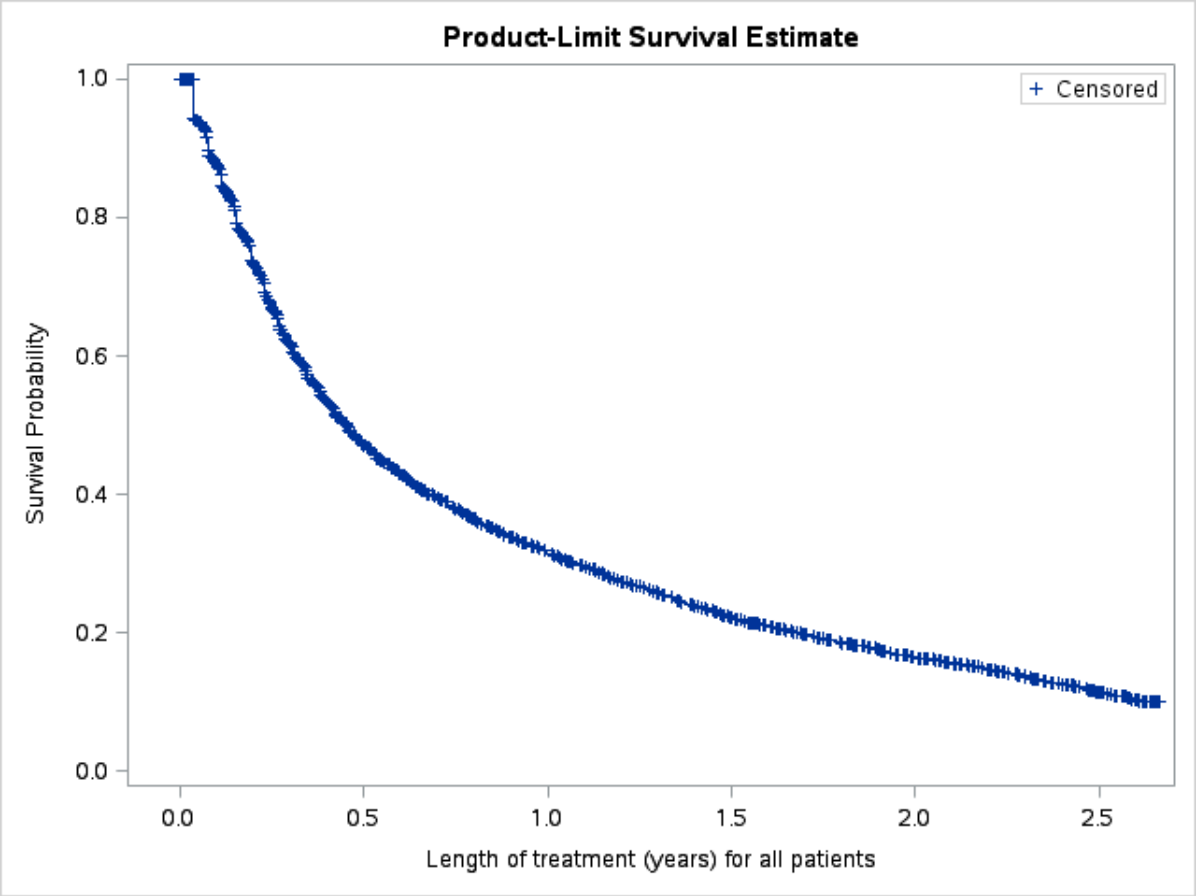

Figure 7: Length of treatment for patients treated with nivolumab for NSCLC

Table 2: Estimate length of treatment from Kaplan Meier analysis

	0-74 years	75+ years	Overall
Number of patients	3,751	1,364	5,115
Censored	974	341	1,315
Mean	314	306	312
Standard error	5.65	9.00	4.80
Median	166.00	168.00	167.00
Median lower limit	154.00	154.00	155.00
Median upper limit	174.00	183.00	173.00

Overall, the median length of treatment was estimated to be 167 days. Patients aged 75 years and older at initiation of nivolumab had a similar estimated length of treatment compared to patients aged 0 to 74.

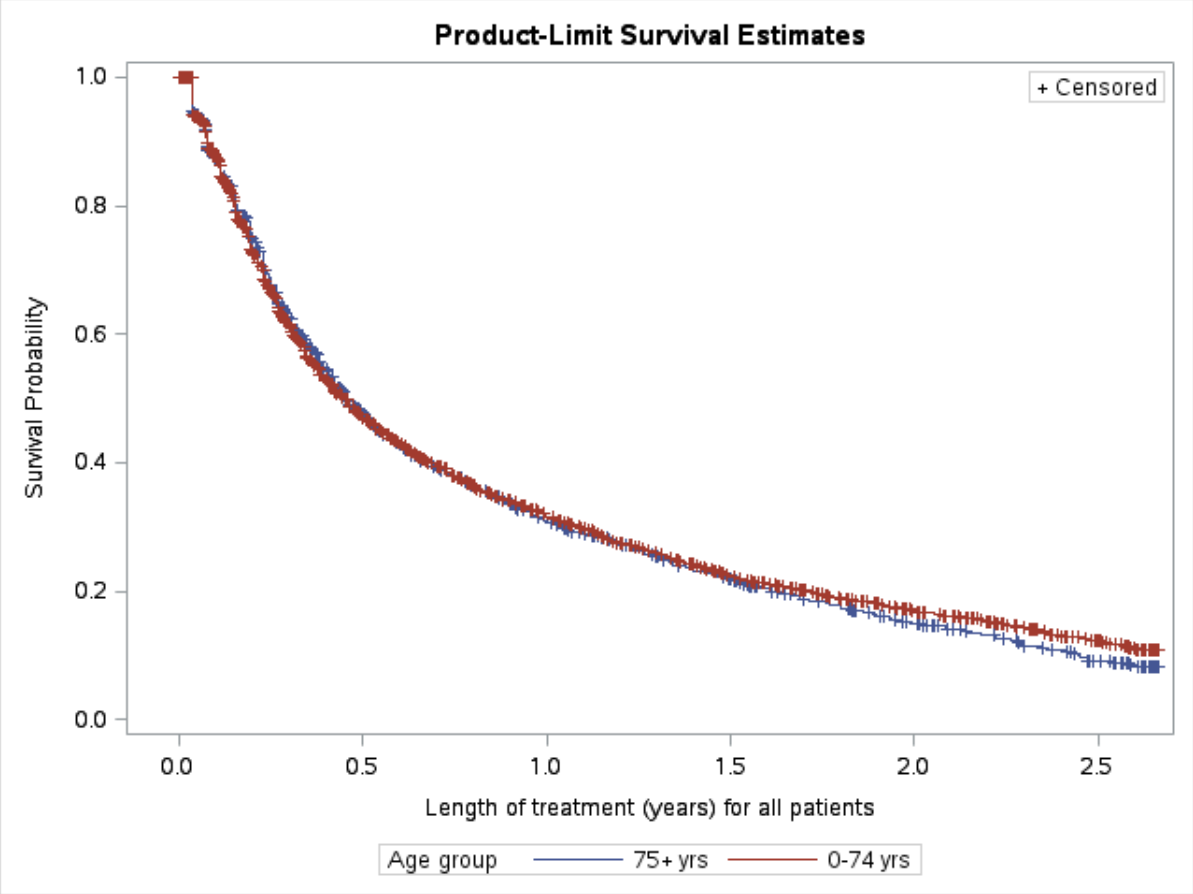

Figure 8: Length of treatment for patients treated with nivolumab for NSCLC, by age

Table 3: Estimate length of treatment (accounting for breaks) from Kaplan Meier analysis

	0-74 years	75+ years	Overall
Number of patients included in the analysis	3,751	1,364	5,115
Censored	974	341	1,315
Mean (days)	280	268	278
Standard error (days)	5.27	8.13	4.46
Median (days)	140.00	153.00	145.00
Median lower limit (days)	133.00	137.00	139.00
Median upper limit (days)	153.00	163.00	154.00

Accounting for breaks reduced the estimated mean length of treatment from 312 to 278 days overall, from 314 to 280 days in patients aged 0 to 74 and from 306 to 268 days in patients aged 75 and older.

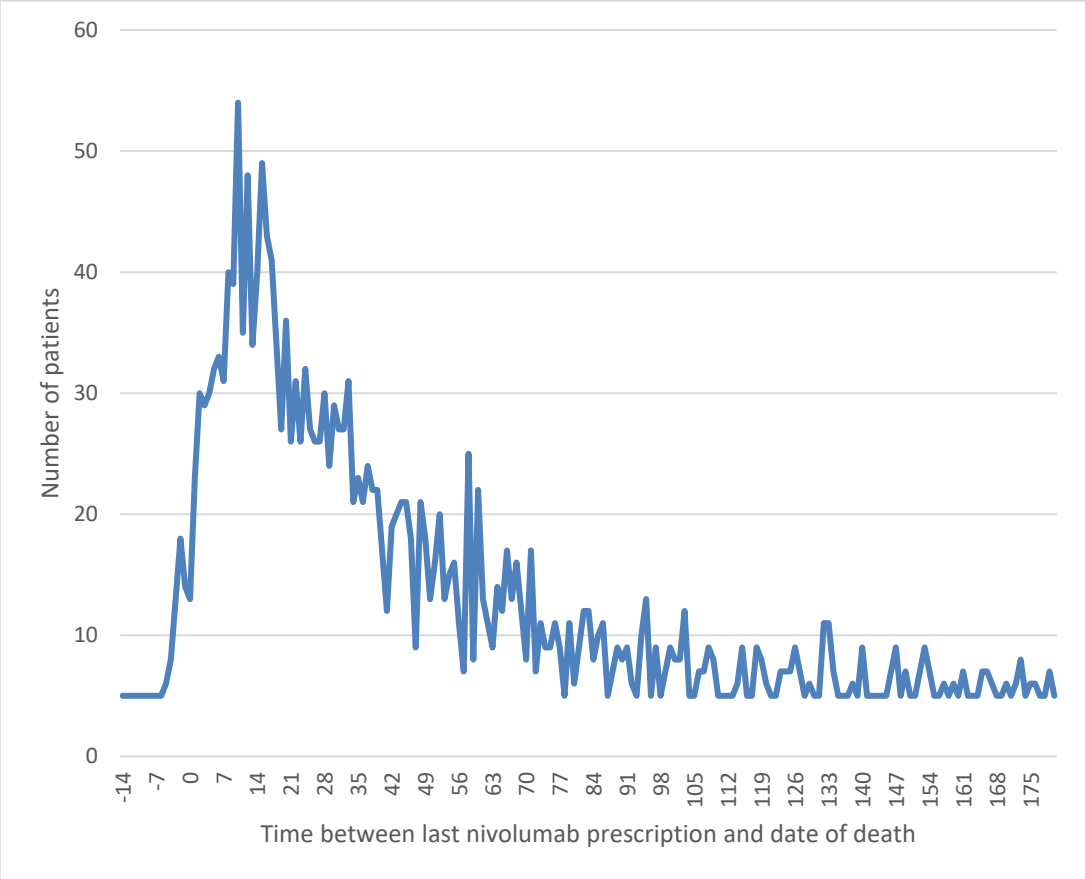

Figure 9: Time between last nivolumab prescription and date of death

Note: Where the number of patients is ≤5, the result is shown as 5. The figure is cut at 180 days although data exists beyond this.

The analysis of time between last nivolumab prescription and date of death excludes patients whose date of death was more than 14 days before their last nivolumab

prescription. The mode time between last nivolumab prescription and date of death was 10 days, with other peaks at 12 days and 15 days.

Use of other immunotherapies for NSCLC

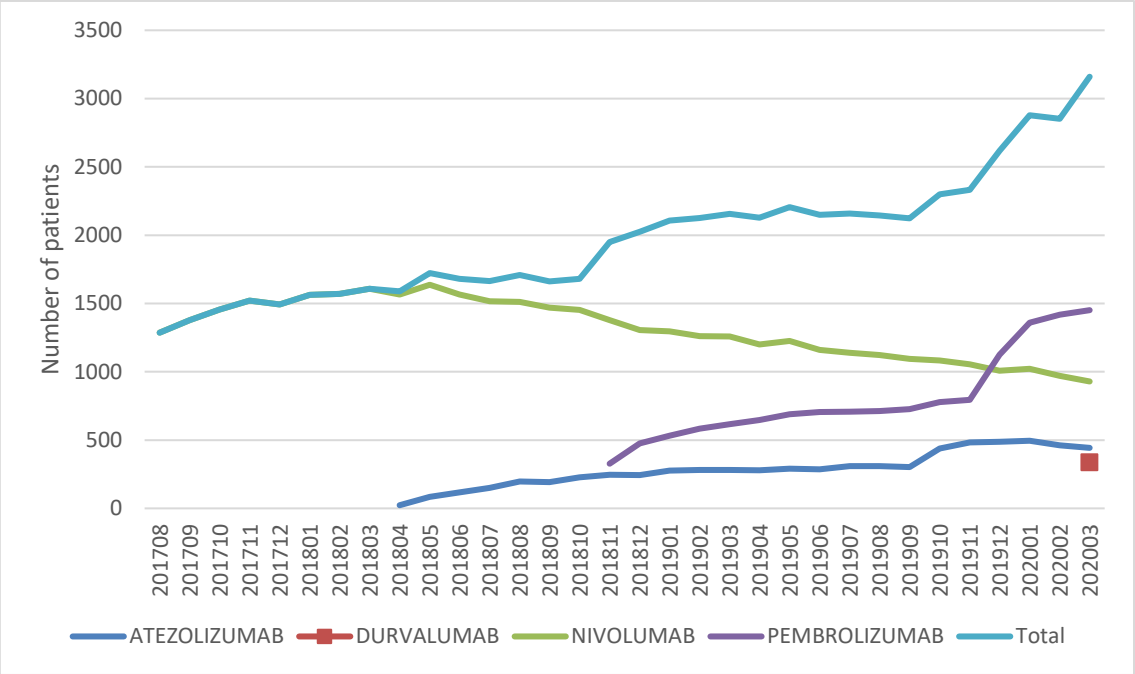

Figure 10: Number of patients treated with immunotherapy medicines for NSCLC

Figure 10 shows the number of patients treated with nivolumab, atezolizumab, pembrolizumab and durvalumab for NSCLC. Atezolizumab was PBS listed in April 2018 and is listed for first and second line NSCLC, which may explain the decrease in use of nivolumab for NSCLC since the third quarter of 2018. Pembrolizumab was PBS listed for NSCLC in November 2018, and is currently the market leader of the immunotherapies for NSCLC. As durvalumab was PBS listed in March 2020 there is only one data point included in the analysis.

Table 4: Switching between immunotherapies for NSCLC

Sequence	Count Patients	Percent of total
NIVOLUMAB	5,294	54.0%
PEMBROLIZUMAB	2,787	28.4%
ATEZOLIZUMAB	1,349	13.8%
DURVALUMAB	336	3.4%
NIVOLUMAB>ATEZOLIZUMAB	25	0.3%
ATEZOLIZUMAB>NIVOLUMAB	6	0.1%
NIVOLUMAB>PEMBROLIZUMAB	≤5	
PEMBROLIZUMAB>ATEZOLIZUMAB	≤5	
ATEZOLIZUMAB>PEMBROLIZUMAB	≤5	
PEMBROLIZUMAB>NIVOLUMAB	≤5	
PEMBROLIZUMAB>DURVALUMAB	≤5	

Table 4 above shows 99.6% of patients treated with immunotherapies for NSCLC have not switched to a second immunotherapy. The switch with the highest number of patients was from nivolumab to atezolizumab but only involved a small number of patients. Of the patients who did switch, no patients switched more than once, and no patients switched from a second immunotherapy back to the original immunotherapy.

Prior use of chemotherapy

For patients treated with nivolumab for NSCLC, Figure 10 shows the number of patients who initiated on nivolumab for NSCLC or a platinum based chemotherapy (cisplatin or carboplatin) by initiation date. Overall, 91.1% of the 5,331 patients who were supplied nivolumab for NSCLC had at least one prior platinum based chemotherapy supply.

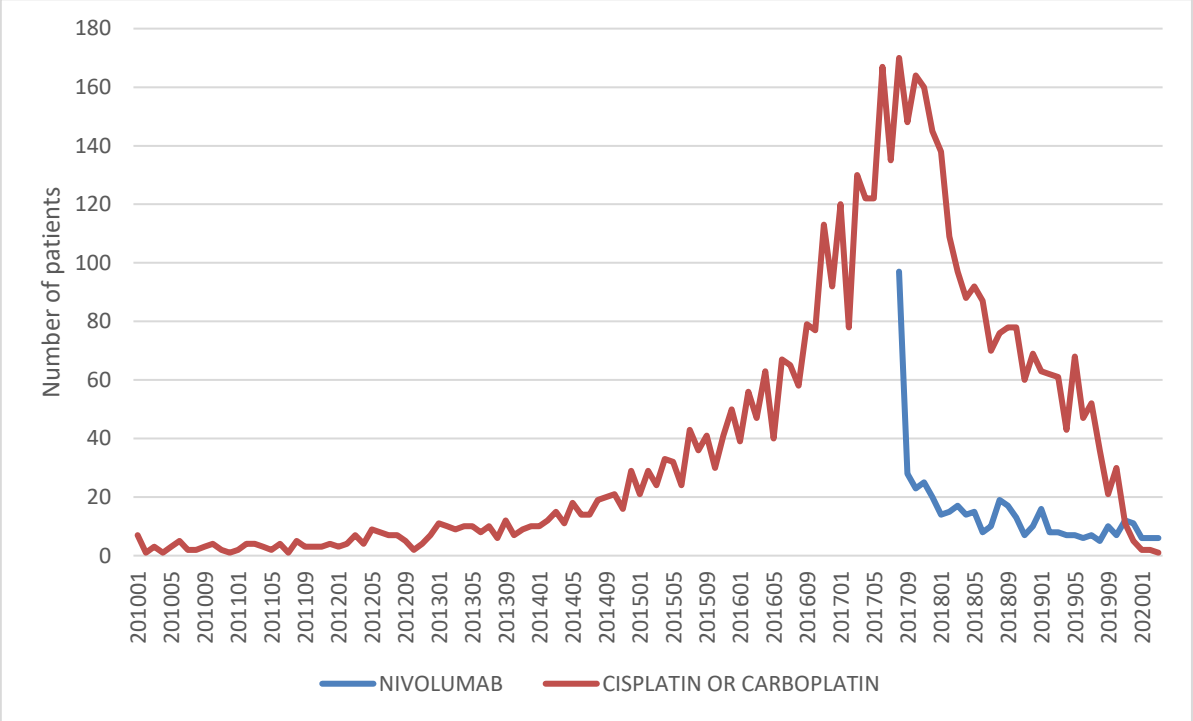

Figure 11: Initiating medicine for patients treated with nivolumab for NSCLC

The number of patients initiated on cisplatin or carboplatin who were then treated with nivolumab gradually increased prior to the listing of nivolumab for NSCLC. The decrease in the number of patients following the listing of nivolumab may be due to the listing of other immunotherapies.

The number of patients who were supplied cisplatin or carboplatin prior to nivolumab in the final three months of the data extraction appears to be low because patients were excluded from the analysis if they have not been supplied nivolumab for NSCLC.

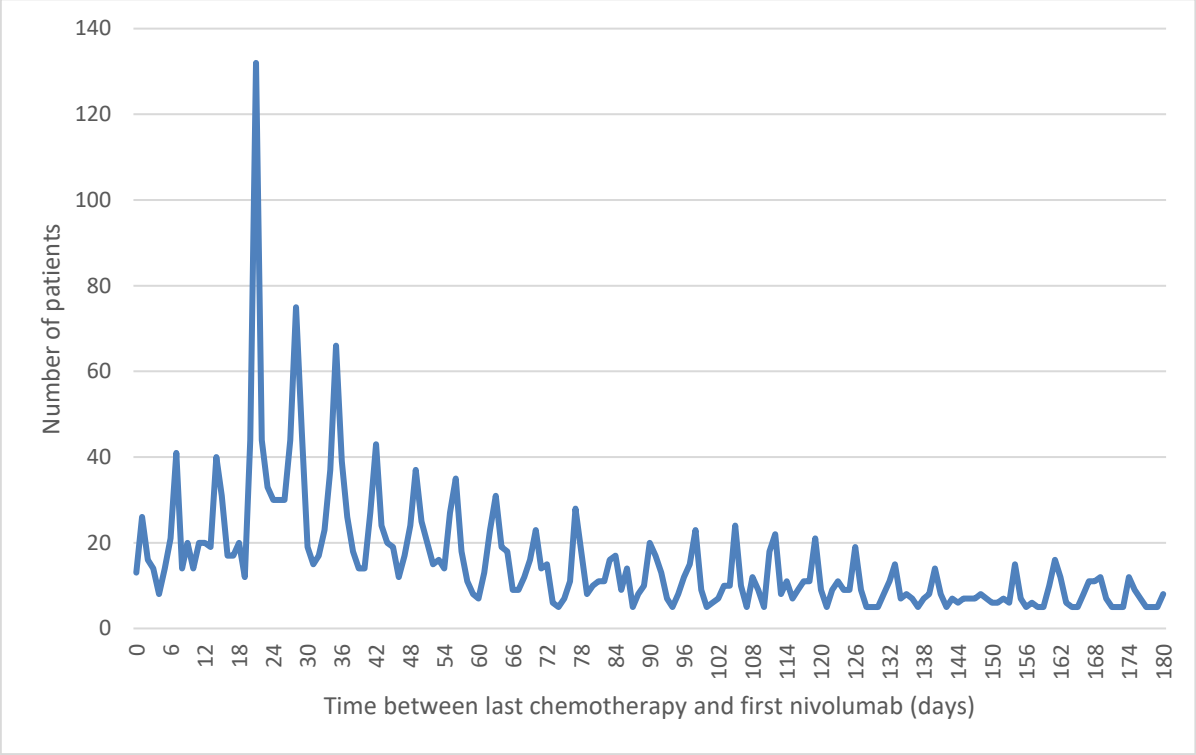

Figure 12: Time between last chemotherapy prescription and first nivolumab prescription

Analysis of actual versus predicted utilisation

The main assumptions outlined in the 'Approach taken to estimate utilisation' section were not changed in the agreed estimates.

Table 5: Predicted versus actual for nivolumab for NSCLC

			Year 1	Year 2	Year 3
			Aug 17 – Jul 18	Aug 18 – Jul 19	Aug 19 – Mar 20
Patients	Nivolumab	Predicted	[redacted]	[redacted]	[redacted]
		Actual	3,524	2635	1,715
		Difference	[redacted]	[redacted]	[redacted]
	Immunotherapies for NSCLC	Predicted	[redacted]	[redacted]	[redacted]
		Actual	3,708	4,634	5,123
		Difference	[redacted]	[redacted]	[redacted]
Administrations	Nivolumab	Predicted	[redacted]	[redacted]	[redacted]
		Actual	35,431	30,832	13,274
		Difference	[redacted]	[redacted]	[redacted]
	Immunotherapies for NSCLC	Predicted	[redacted]	[redacted]	[redacted]
		Actual	35,945	42,314	29,973
		Difference	[redacted]	[redacted]	[redacted]
Dose per administration	Nivolumab	Predicted	221.5	221.5	221.5
		Actual	221.8	223.9	298.8
		Difference	+0.1%	+1.1%	+35%

Note: Year 3 is incomplete (includes eight months of data from August 2019 to March 2020)

Although there appears to be a large overestimate in the number of nivolumab administrations in Year 3, this can likely be attributed to the introduction of flat dosing. This is supported by the dose per administration, which appears to be underestimated in Year 3 of listing.

Discussion

Following an initial rise in use after listing in August 2017, the use of nivolumab for NSCLC has been decreasing since approximately one year after PBS listing. This appears to be largely due to the PBS listings of other immunotherapies, atezolizumab, pembrolizumab and durvalumab for NSCLC. The PBS data does not show a large amount of switching between immunotherapies for NSCLC, which implies the shift in the market is due to patients initiating on more recently listed immunotherapies.

The PBS restriction for nivolumab for NSCLC states that the treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition, and that the condition must have progressed on or after prior platinum based chemotherapy. The analyses suggest the majority of patients are using nivoumab within these limits of the PBS restriction. Of patients treated with immunotherapies for NSCLC, 99.6% have only ever been supplied one therapy, and of the patients supplied nivolumab for NSCLC, over 90% were supplied prior platinum-based chemotherapy. The estimated mean dose per patient of 222 mg appears to have been reasonable prior to the introduction of flat dosing. Prior to the introduction of flat dosing in September 2019, patients were most often supplied a dose less than 240 mg. In recent months, the most commonly supplied dose was 480 mg, and the proportion of prescriptions supplied at 28 days rather than 14 days has increased.

The estimates of use for squamous and non-squamous patients assumed the mean number of nivolumab treatments per patient would be [redacted]. In practice, the mean number of treatments for patients who initiated in the first year of PBS listing was 18.

Actions undertaken by the DUSC Secretariat

The report was provided to the sponsor of nivolumab.

DUSC consideration

DUSC noted the overall treated population has declined, the number of initiating patients has decreased, the number of treated patients has decreased, and the largest decrease was the number of prescriptions supplied per month. DUSC noted that the decrease in prescriptions is due to patients switching to less frequent flat dosing regimens. DUSC agreed that flat dosing appears to be changing prescribing, and commented that patients are not being supplied higher doses per month.

DUSC noted that over 90% of patients treated with nivolumab for NSCLC had at least one prior platinum based chemotherapy supply. However, DUSC commented that 10% patients were supplied nivolumab naïve to platinum chemotherapy, and considered this seemed high and was not expected from a clinical perspective.

DUSC noted the use of fact of death data and that of the 3,520 patients included in the analysis, 1,162 (33%) of these patients had died. DUSC commented that of the patients who

died, a large proportion were supplied their last nivolumab prescription in the month prior to death. DUSC considered this suggests that many patients continue treatment past progression of disease and do not stop treatment prior to death.

DUSC noted that the length of treatment analysis showed that 10% of patients are still on treatment at 2.5 years, 30% are still on treatment after one year, and 50% are treated for more than six months. DUSC noted that in its Pre-Sub-Committee Response the Sponsor suggested it would be useful to know how many patients discontinued in March 2020. DUSC commented that to determine this, data to the end of May would be required, as future prescriptions are required to determine discontinuation.

DUSC noted the sponsor implied that because the length of treatment is similar between the <75 and ≥75 year age groups, the health outcomes of the two groups are similar. DUSC disagreed with this statement, and noted that cessation of treatment does not imply effectiveness. DUSC reiterated that as patients appear to be continuing treatment until close to death and that some patients have long term treatment the assertion that health outcomes between the two cohorts are similar is likely not correct.

DUSC noted that the Sponsor suggested that the presentation of prescriptions of immunotherapy medicines for NSCLC should account for different dosing schedules. The Sponsor noted that these were monthly trends, therefore the number of nivolumab prescriptions on average is two per month while other medicines will have one prescription per month. DUSC noted the figure may be more informative if it displayed the number of patients per month on each treatment (presented as Figure 10 in this report).

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsor's comment

Bristol-Myers Squibb Australia Pty Ltd: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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Appendix A

Consistency of indication

Nivolumab is listed on the PBS for the following indications:

- Locally advanced or metastatic non-small cell lung cancer (NSCLC)
- Recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx (SCC)
- Stage IV clear cell variant renal cell carcinoma (RCC)
- Unresectable Stage III or Stage IV malignant melanoma (MM)

PBS item codes are indication specific and so in theory allocation of an indication to a prescription can be solely based on the PBS item code and does not need to have regard to the restriction code on the corresponding authority approval. The reliability of the PBS item code (i.e. whether or not the correct item code was used) can be checked by analysing the consistency of a patient's indication across time.

The table below show the frequency of indication sequences of nivolumab patients across all their nivolumab prescriptions.

Table A.1: Indication sequences of nivolumab patients

Indication sequence	Rank	Patients	% Patients
NSCLC	1	4,843	52.7%
MM	2	1,955	21.3%
RCC	3	1,482	16.1%
SCC	4	522	5.7%
NSCLC->MM	5	53	0.6%
RCC->NSCLC	6	44	0.5%
NSCLC->RCC	7	31	0.3%
MM->NSCLC	8	28	0.3%
NSCLC->MM->NSCLC	9	20	0.2%
NSCLC->RCC->NSCLC	10	20	0.2%
MM->RCC	11	17	0.2%
NSCLC->SCC	12	17	0.2%
RCC->MM	13	15	0.2%
MM->RCC->MM	14	12	0.1%
RCC->NSCLC->RCC	15	12	0.1%
Other		124	1.3%
Total		9,195	100.0%

Table A.1 shows that 95.7% (sum of the top 4 sequences) of patients have a consistent indication for nivolumab. This indicates that the PBS item code selection is reasonably reliable.