

Nivolumab for the treatment of renal cell carcinoma: 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 renal cell carcinoma (RCC) 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 2nd line treatment of Stage IV clear cell variant renal cell carcinoma.

Data Source / methodology

Data were extracted from the Services Australia Supplied Prescription database for all PBS items that have an RCC restriction. The Services Australia Authority Approvals database was used to determine the treatment indication when the PBS item code was not indication specific.

Key Findings

- Second line nivolumab is the most common PBS treatment for RCC. In 2019 Q4 there were 1,493 patients receiving PBS treatment for RCC, of these 463 received 2nd line nivolumab.
- In both Year 1 and 2 after listing there was approximately 50% more patients than predicted. However there were less prescriptions than predicted because the prescriptions per patient were approximately half that predicted.
- 18.4% of patients appear to have not used a TKI before initiation of 2nd line nivolumab. This is outside the PBS restriction which requires a patient to fail prior TKI treatment.
- The most common treatment switch for patients who had 2nd line RCC treatment is from nivolumab to cabozantinib.

- The median and mean length of treatment (including breaks and date of death (DoD) adjustment) with 2nd line nivolumab was 5.6 and 9.9 months respectively. This is consistent with predicted mean and median of 5.54 and 9.52 months respectively.
- The date of death analysis revealed that 42.0% of patients that had 2nd line nivolumab treatment had died by the end of the analysis period (31/12/2019). 71.8% of patients were deemed to have stopped treatment by the end of the analysis period, of these 9.9% had died on treatment, 48.6% had stopped treatment before death and 41.4% had stopped treatment and were still alive.
- The majority of patients (55%) that died had their last nivolumab prescription within the last 3 fortnights (infusions are generally fortnightly) before death. This may indicate that some patients were treated beyond disease progression, which is outside the PBS restriction.
- The median overall survival from the start of 2nd line nivolumab treatment was 1.69 years (20.3 months) and the mean was 1.47 years (17.6 months).

Purpose of analysis

To compare the predicted and actual utilisation of nivolumab for the 2nd line treatment of renal cell carcinoma (RCC) in the first 24 months of Pharmaceutical Benefits Scheme (PBS) listing.

DUSC requested this analysis at its February 2020 meeting. It is a routine DUSC utilisation analysis of a PBS listing when there is at least 24 months of prescription data available. DUSC noted that the actual number of patients treated in 2018 was higher than predicted and requested that date of death data be used to identify instances of treatment cessation due to death.

The report also examines the use of nivolumab for the treatment of RCC in the context of the whole RCC treatment market.

Background

Nivolumab was PBS listed on 1 August 2017 for the 2nd line treatment of Stage IV clear cell variant renal cell carcinoma.

Clinical situation

Renal cell carcinoma (RCC) is a form of kidney cancer that arises from the cells of the renal tubule, and accounts for up to 90% of primary renal neoplasms. Clear cell variants accounts for 70-80% of all RCC cases¹.

The 1 August 2017 PBS listing of nivolumab was for 2nd line treatment of advanced or metastatic clear cell variant RCC following 1st line treatment with a tyrosine kinase inhibitor (TKI). At that time of listing nivolumab was an alternative to everolimus, axitinib and sorafenib. After listing, cabozantinib was also listed as a 2nd line treatment for RCC on 1 June 2018.

On 1 March 2019 nivolumab in combination with ipilimumab was listed on the PBS as a 1st line treatment of Stage IV clear cell variant RCC in patients meeting the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria¹. Patients are still eligible for nivolumab in 2nd line treatment if they have 1st line TKI treatment.

Pharmacology

Nivolumab is a protein which helps the immune system to attack and destroy cancer cells². It is a human anti PD-1 monoclonal antibody which inhibits the programmed death 1 (PD-1)

¹ Nivolumab and ipilimumab (renal cell carcinoma) PBAC July 2018 public summary document, <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-07/Nivolumab-ipilimumab-psd-july-2018>

² OPDIVO® (NIVOLUMAB). Consumer Medicine Information. July 2019. Available from <https://www.tga.gov.au/consumer-medicines-information-cmi>

receptor from binding to its ligands (PD-L1 and PD-L2) on tumour cells, reactivating cytotoxic T lymphocytes and anti-tumour immunity.³

Therapeutic Goods Administration (TGA) approved indications⁴

Nivolumab is indicated for the treatment of;

- Melanoma
- Non-Small Cell Lung Cancer (NSCLC)
- Renal Cell Carcinoma (RCC)
 - in combination with ipilimumab, is indicated for the treatment of patients with intermediate/poor-risk, previously untreated advanced renal cell carcinoma.
 - 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)
- Squamous Cell Carcinoma of the Head and Neck (SCCHN)
- Urothelial Carcinoma (UC)
- Hepatocellular Carcinoma (HCC)

Dosage and administration⁴

The recommended dose of nivolumab for RCC 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)

Table 1 shows the PBS listings of nivolumab for 2nd line treatment of Stage IV clear cell variant RCC. Table A.1 in Appendix A shows the PBS listings for 1st line treatment of Stage IV clear cell variant RCC. These are shown for completeness, but are not the focus of the report.

³ Australian Medicines Handbook Online. <https://amhonline.amh.net.au/chapters/immunomodulators-antineoplastics/non-cytotoxic-antineoplastics/antineoplastic-antibodies/nivolumab>

⁴ OPDIVO® (NIVOLUMAB). Australian Approved Product Information. Bristol-Myers Squibb Australia Pty Ltd. Approved 11 January 2016, updated 14 November 2019. Available from < <https://www.tga.gov.au/product-information-pi>.>

Table 1: PBS listings of nivolumab for 2nd line treatment of Stage IV clear cell variant RCC

Item	Name, form & strength, pack size	Treatment Phase	Date of listing	Max. amount	Rpts	DPMA*	Brand name and manufacturer
11150W	Injection concentrate for I.V. infusion 100 mg in 10 mL	Initial treatment – Public Hospital	1/08/2017	480 mg	8	\$10,053.46	Opdivo® Bristol-Myers Squibb Australia Pty Ltd
11160J	Injection concentrate for I.V. infusion 100 mg in 10 mL	Continuing treatment – Public Hospital	1/08/2017	480 mg	11	\$10,053.46	Opdivo® Bristol-Myers Squibb Australia Pty Ltd
11159H	Injection concentrate for I.V. infusion 100 mg in 10 mL	Initial treatment – Private Hospital	1/08/2017	480 mg	8	\$10,232.76	Opdivo® Bristol-Myers Squibb Australia Pty Ltd
11157F	Injection concentrate for I.V. infusion 100 mg in 10 mL	Continuing treatment – Private Hospital	1/08/2017	480 mg	11	\$10,232.76	Opdivo® Bristol-Myers Squibb Australia Pty Ltd

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

Restriction

Nivolumab has Authority Required (STREAMLINED) listings for initial and continuing treatment.

Stage IV clear cell variant renal cell carcinoma (RCC)

Treatment Phase: Initial Treatment

Clinical criteria:

- The treatment must be the sole PBS-subsidised therapy for this condition,
AND
- Patient must have a WHO performance status of 2 or less,
AND
- Patient must have progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) following prior treatment with a tyrosine kinase inhibitor; OR
- Patient must have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal,
AND
- Patient must not have 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.

The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

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.

Note

In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.

Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows:

Complete response (CR) is disappearance of all target lesions.

Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.

Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.

Stable disease (SD) is small changes that do not meet above criteria.

No increase in the maximum number of repeats may be authorised.

Treatment Phase: Continuing treatment

Clinical criteria:

- Patient must have previously received PBS-subsidised treatment with this drug for this condition,
- AND
- Patient must not have developed disease progression while being treated with this drug for this condition,
- AND
- The treatment must be the sole PBS-subsidised therapy for this condition.

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.

Note

No increase in the maximum number of repeats may be authorised.

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

Changes to listing

On 1 March 2019 the listing of nivolumab was extended to use in 1st line therapy (in combination with ipilimumab for the induction phase).

The nivolumab 2nd line listing had a change in Authority approval level (Authority Required to Streamlined) for initial and continuing prescriptions on 1 September 2019. 1st line prescriptions for induction and grandfathering were Streamlined Authority from listing on 1 March 2019 (this applies to both nivolumab and ipilimumab). The maintenance phase of 1st line treatment, which only includes nivolumab, was Authority Required from listing on 1 March 2019 and became Streamlined on 1 September 2019

On 1 September 2019, the following sentence was added to the restriction of all nivolumab PBS listings.

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.

In addition the Maximum Amount was changed from 360 mg to 480 mg. This was in response to a minor submission to the March 2019 PBAC requesting 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 every two weeks dosing, or
2. flat 240 mg every two weeks dosing, or
3. flat 480 mg every four weeks dosing

Current PBS listing details are available from the PBS website.

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

July 2016 PBAC

The PBAC decided not to recommend that nivolumab be listed in the PBS for the treatment of advanced or metastatic clear cell variant renal cell carcinoma (RCC) based on an unacceptably high and uncertain incremental cost-effectiveness ratio (ICER) at the requested effective price. The PBAC also noted that the relevant TGA delegate's overview was not yet available for its consideration⁵.

November 2016 PBAC

The PBAC did not recommend the listing of nivolumab for the treatment of advanced or metastatic clear cell variant renal cell carcinoma (RCC) on grounds of unfavourable and uncertain cost-effectiveness. The PBAC considered that the benefit of treatment with nivolumab was uncertain and likely overestimated and that the proposed risk sharing arrangement would not address this uncertainty⁶.

March 2017 PBAC

After lodging its major resubmission in November 2016, the sponsor then lodged a resubmission-addendum in December 2016 and a financial-addendum in January 2017 for consideration at the March 2017 PBAC meeting.

The PBAC recommended the listing of nivolumab, on the basis that it be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) for the treatment of Stage IV clear cell variant renal cell carcinoma

⁵ <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-07/files/nivolumab-psd-july-2016.pdf>

⁶ <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-11/files/nivolumab-rcc-psd-november-2016.pdf>

(RCC) in patients who have progressed according to Response Evaluation Criteria in Solid Tumours (RECIST) following 1st line treatment with a tyrosine-kinase inhibitor (TKI). The PBAC was satisfied that nivolumab provides, for some patients, a significant improvement in efficacy and reduction in toxicity over everolimus⁷.

The PBAC discussed how to deal with pseudo-progression, where progression appears to occur (using the RECIST criteria) in the first few months of treatment however the patient can subsequently have a response to treatment if it is continued.

The continuing phase restriction has the criterion;

- Patient must not have developed disease progression while being treated with this drug for this condition;

However the possibility of pseudo-progression was dealt with by adding the following note to the initial phase criteria;

- In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.

This is the same approach that was taken for the listing of nivolumab for melanoma. It should be noted that the restriction stopping rule is still intended to be based on the RECIST criteria, but allowing them to be modified for early pseudo-progression⁷.

For further details refer to the Public Summary Documents referenced in the above text.

Previous reviews by the DUSC

DUSC considered a predicted vs actual utilisation analysis of pazopanib and sunitinib for RCC at its June 2014 meeting. Sunitinib and pazopanib were PBS-listed for RCC on 1 May 2009 and 1 October 2012, respectively. The key findings were:

- Following the PBS listing of sunitinib, more patients started treatment for RCC than originally predicted.
- The number of new patients who started treatment with either pazopanib or sunitinib for RCC each year was stable at approximately 500 (from 2010 to 2013 inclusive).
- Following the PBS listing of pazopanib, the number of prevalent patients receiving either pazopanib or sunitinib increased from approximately 600 patients in the 12-month period prior to listing to approximately 700 patients in the 12-month period after listing.
- The number of prescriptions for sunitinib were lower than originally expected, indicating that patients treated with sunitinib received fewer prescriptions per year than originally estimated.

⁷ <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2017-03/files/nivolumab-rcc-psd-march-2017.pdf>

- The number of prescriptions for pazopanib were more than double that expected in the first year of listing. Pazopanib appeared to be substituting for sunitinib, with sunitinib prescriptions decreasing after the PBS listing of pazopanib.

For details of the DUSC consideration of sunitinib and pazopanib refer to the Public Release Document from the June 2014 DUSC meeting.

Methods

The report examines the use of nivolumab for the treatment of RCC in the context of the whole RCC treatment market.

Prescriptions were extracted from the Services Australia prescription database for all PBS items that have an RCC restriction (48 items, see Appendix A, Table A.1) from 1 May 2009 (the listing date for sunitinib, the first medicine listed with an RCC restriction) until the end of December 2019 (based on date of supply). Of these items there were four everolimus items (10131F, 10132G, 10133H & 10135K) that had other indications in addition to RCC. For these items, prescriptions were classified as for treatment of RCC or not, based on the Services Australia Authority approval database restriction code or the Streamlined Authority code in the prescription database

In addition, consistency of assignment of indication was investigated for nivolumab. This involved extracting all nivolumab items (i.e. for all indications) from the Services Australia prescription database from the 1 May 2016 when nivolumab was first listed (for malignant melanoma) until the end of December 2019 (based on date of supply). An analysis of indication sequence (see Consistency of indication section for details) was then performed to determine the reliability of assigning indication via PBS item code.

As these analyses use date of supply prescription data, there may be small differences compared with publicly available Services Australia PBS date of processing data⁸ which only includes subsidised PBS and Repatriation PBS (R/PBS) prescriptions (i.e. prescriptions under the patient co-payment are not included). The Services Australia prescription database data used in this report includes under co-payment prescriptions from 1 April 2012.

Length of treatment

The duration of treatment analysis used the Kaplan Meier (aka Product-Limit) method to determine the length of treatment for patients on nivolumab and other medicines for RCC. Two ways of measuring length of treatment were undertaken. One excluded any breaks in treatment and the other did not. A break in treatment was defined as a gap of more than 3 times the median time to resupply (also known as Standard Coverage Days (SCD)) between

⁸ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

supplies, which was an estimated break in treatment of at least 2 times the median time to resupply.

A patient was deemed to be continuing treatment (classified as censored in the Product-Limit method) at the end of the data period (i.e. the end of December 2019) if their last prescription was within 3 x SCD days of this end date (the value of SCD depends on the medicine being analysed, see Table 8 for details). Otherwise the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus 1 x SCD or the end of the data period, whichever was later.

Date of death data was sourced from Services Australia for all patients that had been treated with nivolumab. Analyses of length of nivolumab treatment used the date of death to adjust the coverage end date and the censoring status for patients who died on treatment. A patient was deemed to have died on treatment if DoD < last supply date + SCD. That is, if the last coverage end date based on the above method (i.e. using prescriptions only) was greater than the date of death, then the coverage end date was changed to the date of death, otherwise it remained unchanged. In addition the censoring scheme was changed so that patients who died on treatment were censored (i.e. deemed to be continuing treatment).

Proxy for Date of Death (DoD)

The availability of the date of death data made it possible to validate a proxy for date of death based on PBS prescriptions only.

The DoD proxy was estimated by first measuring the time to next supply for all prescriptions (i.e. all medicines, not just the one of interest in this report) supplied to the RCC patients in this report. The phrase “next supply” is used rather than “resupply” to clarify that the supply is not necessarily for the same drug or strength. It was established that the median time to next supply was 8 days and that 99.4% of scripts had a next supply within 90 days. Thus a patient was estimated to have died if they had no supply of any prescription in the 90 days after their last prescription in the PBS data. If this was the case, the date of death was estimated to be the date of last supply plus 8 days (i.e. the expected number of days to next supply).

Date of death proxies based on PBS data have been calculated by other researchers. Pearson et al. (2012)⁹ used a similar method to this analysis. In addition, they validated the proxy against actual date of death data. A sensitivity analysis indicated that a 90 day or greater delay between a patient’s last prescription and the end of the data period was the best indicator of death compared to shorter and longer delays (i.e. 30, 60 and 180 days).

The above method for estimating a proxy DoD could only detect estimated dates of death up to 8 December 2019. That is, the latest possible proxy DoD would be for a patient whose last script was on 29 November 2019 and had 90 days without a prescription before the end of the data period on 29 February 2020. The estimated DoD for this patient would be

⁹ Mealing NM, Dobbins TA, Pearson S-A. Validation and application of a death proxy in adult cancer patients. *Pharmacoepidemiol Drug Saf* 2012; 21: 742–8.

29 November 2019 + 8 days = 8 December 2019. The DoD data received from Services Australia was complete up until 31 December 2019. Appendix B shows the results of the comparison of proxy DoD and Services Australia DoD.

Results

Analysis of drug utilisation

Prescription utilisation

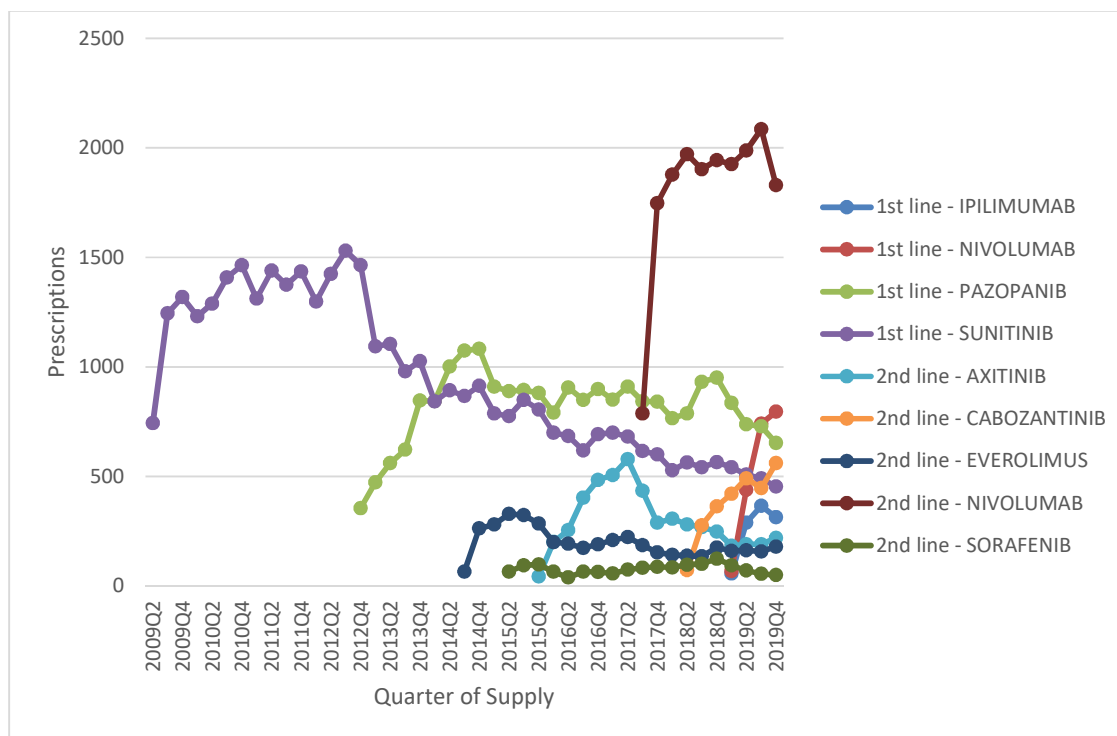


Figure 1: Prescriptions for the treatment of RCC by line of therapy and drug

Note: Nivolumab for 2nd line RCC was PBS listed on 1 August 2017

Figure 1 shows that 2nd line nivolumab has the most prescription utilisation in the RCC treatment market. Relative prescription utilisation differs from the relative number of patients (see Figure 4) because 2nd line nivolumab is supplied twice as frequently (i.e. every 14 days) as most of the other medicines (see Table 8 for details). The decrease in 2nd line nivolumab utilisation in 2019 Q4 is most likely due to the change in restriction on 1 September 2019 that allowed the use of 4 weekly flat dose infusions. Prior to this all infusions had been 2 weekly.

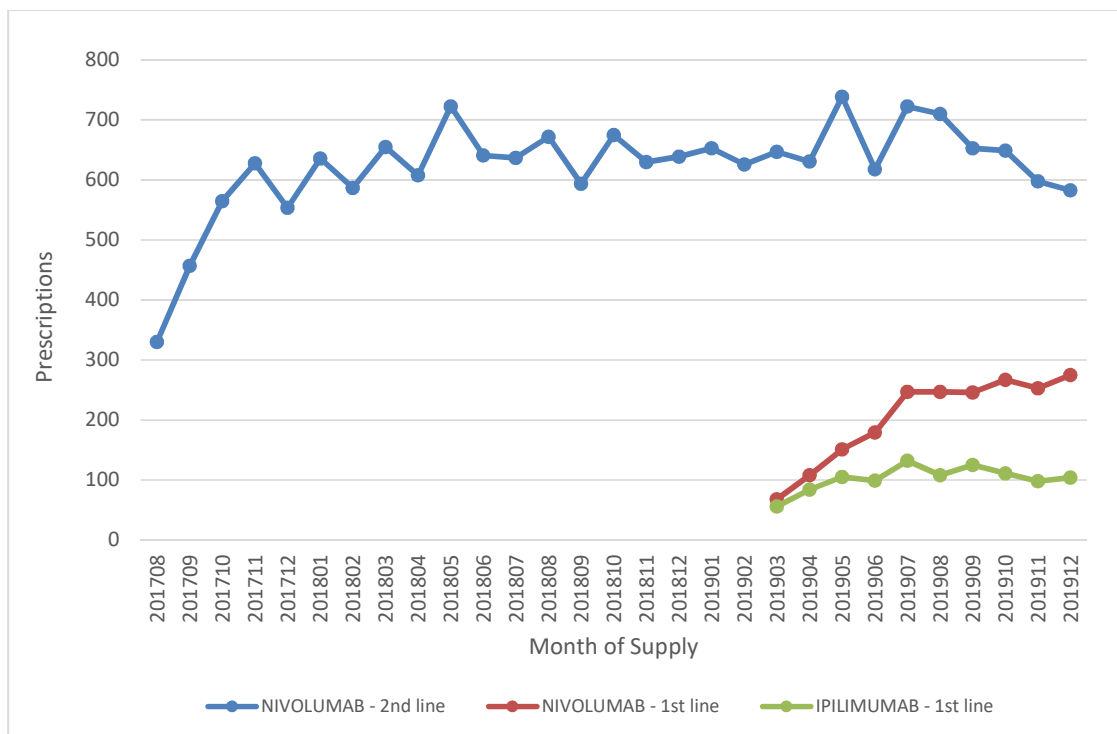


Figure 2: Nivolumab and ipilimumab prescriptions for RCC by line of therapy

Figure 2 uses monthly instead of quarterly data to better discern the influence of three separate changes to listing. These were;

- the extension of nivolumab to 1st line treatment on 1 March 2019;
- the extension the 1st & 2nd line listing to allow use of 4 weekly flat dose infusions on 1 September 2019; and
- the change in authority level (Authority Required to Streamlined) for both 1st & 2nd line on 1 September 2019.

On 1 March 2019 the listing of nivolumab was extended to use in 1st line therapy (in combination with ipilimumab for the induction phase). The predicted versus actual (PvA) analysis later in this report will consider if the 2nd line actuals have been impacted in the 2nd year of listing (i.e. August 2018 to the end of July 2019) by the 1st line listing.

The extension of listing to allow 4 weekly flat dose infusions from 1 September 2019 as an alternative to 2 weekly dosing does seem to have reduced the number of prescriptions for 2nd line nivolumab from that date. For more detail see the section “Dose distribution of 2nd line nivolumab infusions”. The utilisation of 1st line nivolumab does not seem to have been impacted by this change.

The third change to the listing of nivolumab was the change in authority level (Authority Required to Streamlined) for 2nd line initial and continuing prescriptions on 1 September 2019. 1st line prescriptions for induction and grandfathering were Streamlined Authority from listing on 1 March 2019 (this applies to both nivolumab and ipilimumab). The maintenance phase, which only includes nivolumab, was Authority Required from 1 March

2019 and became Streamlined on 1 September 2019. There does not appear to be any obvious increase in utilisation due to the reduction in approval level on 1 September 2019 in either line of therapy. However, any such effect may have been masked by the other two changes to the listing.

Patients

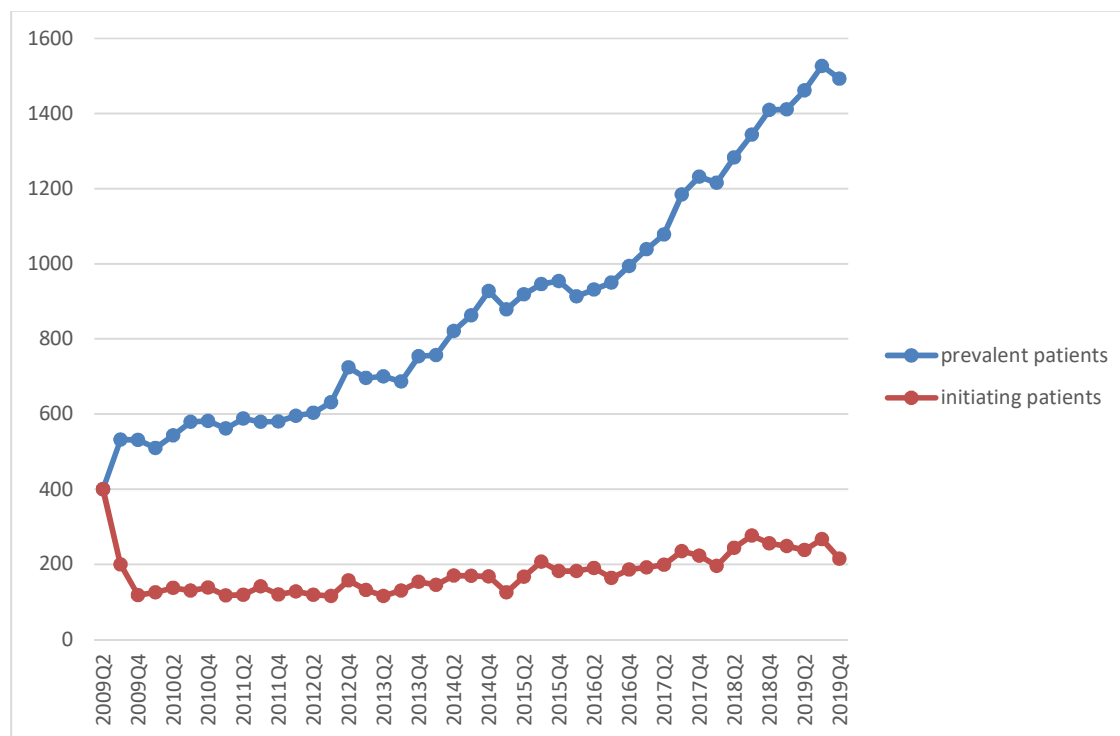


Figure 3: Initiating and prevalent patients for the PBS treatment of RCC

Note: initiating patients have no prior prescription for RCC treatment with any drug

Figure 3 shows the number of patients initiating RCC treatment has been gradually increasing.

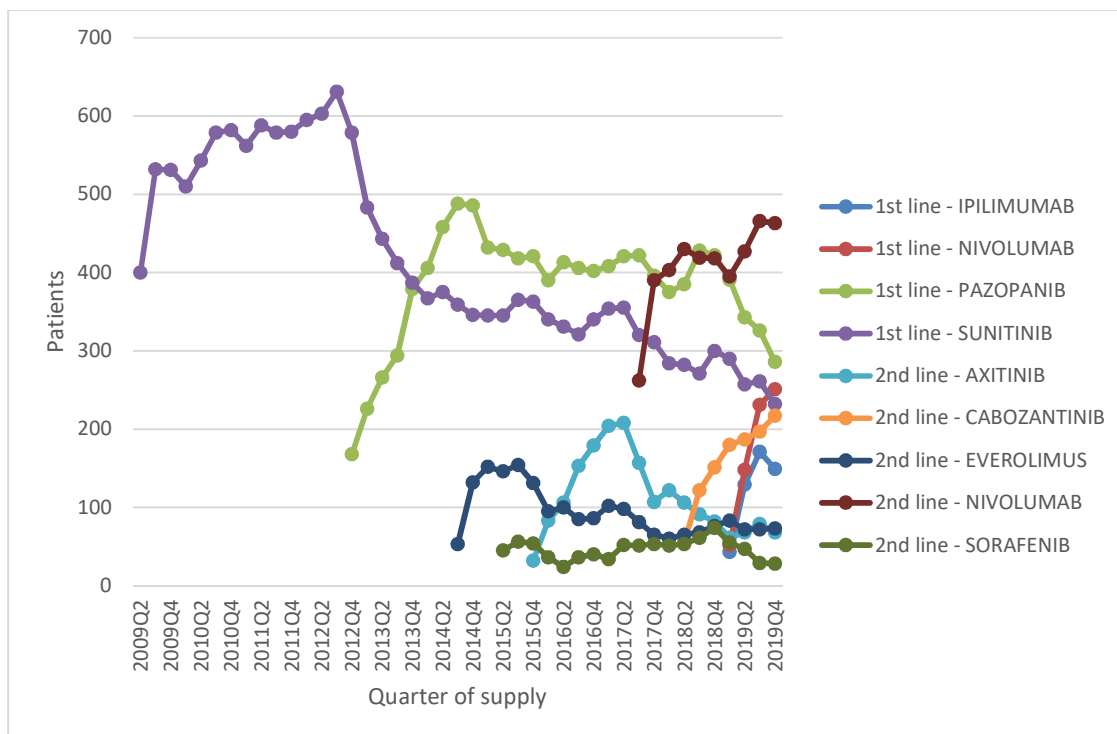


Figure 2: Nivolumab and ipilimumab prescriptions for RCC by line of therapy

Note: patients can be prevalent to (i.e. supplied) more than one drug in a quarter

In Figure 4:

- 2nd line nivolumab was (as at 2019 Q4) the most utilised treatment, followed by 1st line pazopanib and then 1st line nivolumab.
- 1st line nivolumab looks to be mainly replacing 1st line pazopanib.
- 2nd line nivolumab looks to have mainly replaced 2nd line axitinib.
- 2nd line cabozantinib is growing strongly and it looks to have reduced the growth of 2nd line nivolumab after it was listed on 1 June 2018.

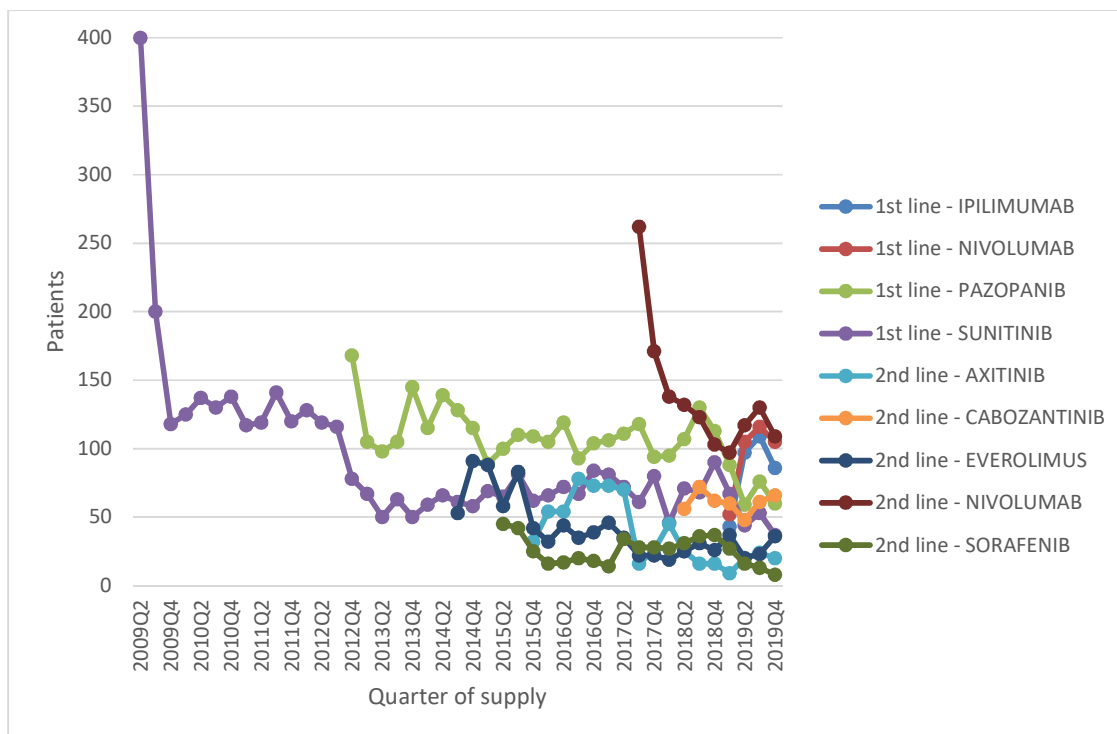


Figure 5: Initiating patients for the treatment of RCC by line of therapy and drug

Note: Patients can initiate more than one drug in a quarter.

Figure 5 shows that currently (as at 2019 Q4) 1st line and 2nd line nivolumab are the two most commonly initiated treatments.

Analysis of predicted versus actual utilisation

Approach taken to estimate utilisation

The re-submission to the March 2017 PBAC was not considered by DUSC. The financial estimates arising from the resubmission-addendum were provided shortly before consideration by the ESC.

The total number of patients likely to be treated with nivolumab over the 5-year forecast period was derived by applying 2nd-line treatment rates to the forecast for the number of patients initiated on TKI therapy each year and factoring in the estimated market share of nivolumab and additional patients to be treated with a 1st line TKI in order to be eligible to receive nivolumab in the 2nd-line setting. Estimated utilisation and subsequent costs to the PBS, including from the financial addendum, are presented in Table 2, including a comparison with the estimates presented in the July 2016 submission.

[illegible]

¹⁰ Table 53 of nivolumab submission to March 2017 PBAC

This PvA analysis only pertains to nivolumab for 2nd line treatment which was listed on 1 August 2017. As shown in Figure 2, the 2nd year of listing (August 2018 to July 2019 inclusive) overlaps by 5 months with the 1st line listing (started 1 March 2019). The final minor resubmission for 1st line listing of nivolumab to the November 2018 PBAC meeting included offsets for reduction in 2nd line nivolumab treatment, however this reduction does not appear to have been significant in the first 5 months (i.e. until the end of July 2019) of listing of 1st line nivolumab. Thus it seems reasonable in the PvA analysis to only include the 2nd line prescriptions for the 2nd year of listing and not attempt to allow for reduction in utilisation due to the 1st line listing.

Table 3: Predicted vs Actual analysis of nivolumab for RCC

		Year 1	Year 2
		Aug 17 to Jul 18	Aug 18 to Jul 19
Treated patients	Predicted (P)	████	████
	Actual (A)	736	757
	% Difference (A-P)/P	████	████
Prescriptions	Predicted (P)	████	████
	Actual (A)	7,021	7,847
	% Difference (A-P)/P	████	████
Prescriptions per patient	Predicted (P)	████	████
	Actual (A)	9.5	10.4
	% Difference (A-P)/P	████	████

Source: Final agreed estimates (P17-10235 PBS Nivolumab RCC vF 20170609.xlsx).

In Table 3 the number of actual treated patients was approximately 50% more than predicted. However the number of actual prescriptions per patient was approximately half of that predicted, resulting in the total number of actual prescriptions being less than predicted.

The predicted number of patients is based on the number of patients initiating 1st line TKI (Source: PBS 10% sample). The estimates then presume that a proportion of these patients will be treated with 2nd line nivolumab and these patients will received █████ infusions in the same year that they initiate treatment. That is, the estimates do not take into account that patients will initiate throughout Year 1 and so some of their course of treatment (████ infusions, taking approximately █████ weeks on average) will be split across Year 1 and 2. That is, there was no “half cycle correction” applied to the prescription estimates and this could be the main reason for the difference in prescriptions per patient.

This report also contains a “2nd line Nivolumab length of treatment” section. This shows that the mean length of treatment (excluding breaks) was █████ months. This is approximately █████ weeks and █████ infusions, which is close to the predicted number of █████ infusions.

In addition the difference between predicted and actual patients may have been less in Year 2 if the predicted patients in Year 2 had included continuing patients from Year 1.

Other analyses:

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 4: 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 4 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. In the patient level analyses to follow, only RCC indicated prescriptions will be included.

Drug initiation sequence for 2nd line nivolumab patients

Table 5 shows the drug initiation sequence for all initiators to 2nd line nivolumab treatment. This includes all prescriptions indicated for RCC from 1 May 2009 (the listing of sunitinib for RCC) to the end of December 2019.

Table 5: Drug indication sequences 2nd line nivolumab patients

Drug initiation sequence	Patients	% Patients	Ranking
1st line, pazopanib -> 2nd line, nivolumab	262	19.0%	1
2nd line, nivolumab	208	15.1%	2
1st line, sunitinib -> 2nd line, nivolumab	183	13.2%	3
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, cabozantinib	67	4.8%	4
1st line, ipilimumab -> 2nd line, nivolumab(sd)	37	2.7%	5
1st line, sunitinib -> 2nd line, nivolumab -> 2nd line, cabozantinib	36	2.6%	6
1st line, pazopanib -> 1st line, sunitinib -> 2nd line, nivolumab	36	2.6%	7
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, nivolumab	36	2.6%	8
1st line, ipilimumab -> 1st line, nivolumab(sd) -> 2nd line, nivolumab	32	2.3%	9
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, nivolumab	31	2.2%	10
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, axitinib	25	1.8%	11
1st line, sunitinib -> 2nd line, axitinib -> 2nd line, nivolumab	23	1.7%	12
1st line, sunitinib -> 2nd line, everolimus -> 2nd line, nivolumab	15	1.1%	13
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, cabozantinib	14	1.0%	14
2nd line, nivolumab -> 2nd line, cabozantinib	13	0.9%	15
1st line, sunitinib -> 2nd line, nivolumab -> 2nd line, axitinib	13	0.9%	16
1st line, sunitinib -> 2nd line, axitinib -> 2nd line, nivolumab -> 2nd line, cabozantinib	10	0.7%	17
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, axitinib	10	0.7%	18
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, axitinib -> 2nd line, cabozantinib	9	0.7%	19
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, nivolumab -> 2nd line, cabozantinib	8	0.6%	20
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, axitinib -> 2nd line, nivolumab	8	0.6%	21
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, everolimus -> 2nd line, nivolumab	7	0.5%	22
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, cabozantinib -> 2nd line, everolimus	7	0.5%	23
1st line, pazopanib -> 2nd line, everolimus -> 2nd line, nivolumab	7	0.5%	24
2nd line, nivolumab -> 2nd line, cabozantinib -> 2nd line, axitinib	6	0.4%	25
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, everolimus	6	0.4%	26
1st line, sunitinib -> 2nd line, cabozantinib -> 2nd line, nivolumab	6	0.4%	27
1st line, pazopanib -> 2nd line, everolimus -> 2nd line, axitinib -> 2nd line, nivolumab	6	0.4%	28
1st line, pazopanib -> 2nd line, cabozantinib -> 2nd line, nivolumab	6	0.4%	29
Other	255	18.5%	
Total	1,382	100%	

Note: sd = same day initiation as prior drug in sequence

The 2nd line nivolumab PBS restriction contains the clinical criterion;

- Patient must have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal

This means a drug initiation sequence should contain a TKI before initiation of 2nd line nivolumab. The 2nd ranked sequence (2nd line, nivolumab only) appears to be treatment

outside this restriction. This is also true for the 15th (2nd line, nivolumab -> 2nd line, cabozantinib) and 25th (2nd line, nivolumab -> 2nd line, cabozantinib -> 2nd line, axitinib) ranked sequences. Including sequences in the “Other” category, there were 254 patients (18.4%) that did not trial a TKI before starting 2nd line nivolumab.

The 5th ranked sequence (1st line, ipilimumab -> 2nd line, nivolumab (same day)) indicates there has been some misallocation of nivolumab PBS item codes, with patients initiating using the 2nd line rather than the 1st line nivolumab item code.

Extent of switching between other 2nd-line listings

Of the 1,382 patients that initiated 2nd line nivolumab, there were 113 that also initiated 1st line ipilimumab. In these instances it is unclear if the nivolumab is really 1st or 2nd line, so these patients were removed from this analysis on the extent of 2nd line switching, leaving 1,269 patients.

Table 6 shows initiation sequences for the 512 patients (40.3% of the 1,269 2nd line nivolumab patients) that have more than one 2nd line treatment (where one must be 2nd line nivolumab).

Table 6: 2nd line nivolumab patients that switched treatment

Drug initiation sequence	Patients	% Patients	Ranking
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, cabozantinib	67	13.1%	1
1st line, sunitinib -> 2nd line, nivolumab -> 2nd line, cabozantinib	36	7.0%	2
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, nivolumab	31	6.1%	3
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, axitinib	25	4.9%	4
1st line, sunitinib -> 2nd line, axitinib -> 2nd line, nivolumab	23	4.5%	5
1st line, sunitinib -> 2nd line, everolimus -> 2nd line, nivolumab	15	2.9%	6
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, cabozantinib	14	2.7%	7
1st line, sunitinib -> 2nd line, nivolumab -> 2nd line, axitinib	13	2.5%	8
2nd line, nivolumab -> 2nd line, cabozantinib	13	2.5%	9
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, axitinib	10	2.0%	10
1st line, sunitinib -> 2nd line, axitinib -> 2nd line, nivolumab -> 2nd line, cabozantinib	10	2.0%	11
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, axitinib -> 2nd line, cabozantinib	9	1.8%	12
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, nivolumab -> 2nd line, cabozantinib	8	1.6%	13
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, axitinib -> 2nd line, nivolumab	8	1.6%	14
1st line, pazopanib -> 2nd line, everolimus -> 2nd line, nivolumab	7	1.4%	15
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, everolimus -> 2nd line, nivolumab	7	1.4%	16
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, cabozantinib -> 2nd line, everolimus	7	1.4%	17
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, everolimus	6	1.2%	18
1st line, pazopanib -> 2nd line, everolimus -> 2nd line, axitinib -> 2nd line, nivolumab	6	1.2%	19
1st line, pazopanib -> 2nd line, cabozantinib -> 2nd line, nivolumab	6	1.2%	20
1st line, sunitinib -> 2nd line, cabozantinib -> 2nd line, nivolumab	6	1.2%	21
2nd line, nivolumab -> 2nd line, cabozantinib -> 2nd line, axitinib	6	1.2%	22
Other	179	35.0%	
Total	512	100%	

Note: sd = same day initiation as prior drug in sequence

The most common 2nd line switch is from nivolumab to cabozantinib. The 2nd most common switch is with axitinib either before or after nivolumab.

The above analysis was repeated with only the requirement that a patient have 2nd line treatment (i.e. not necessarily 2nd line nivolumab treatment). There were 2,885 such patients. Again patients that had been treated with 1st line ipilimumab (n=125) were excluded leaving 2,760. Of these 685 (24.9%) had more than one 2nd line treatment. Initiation sequences for these patients are shown in Table 7.

Table 7: 2nd line patients that switched treatment

Drug initiation sequence	Patients	% Patients	Ranking
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, cabozantinib	67	9.8%	1
1st line, sunitinib -> 2nd line, nivolumab -> 2nd line, cabozantinib	36	5.3%	2
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, nivolumab	31	4.5%	3
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, axitinib	25	3.6%	4
1st line, sunitinib -> 2nd line, axitinib -> 2nd line, nivolumab	23	3.4%	5
1st line, pazopanib -> 2nd line, everolimus -> 2nd line, axitinib	23	3.4%	6
1st line, sunitinib -> 2nd line, everolimus -> 2nd line, axitinib	17	2.5%	7
1st line, sunitinib -> 2nd line, axitinib -> 2nd line, everolimus	15	2.2%	8
1st line, sunitinib -> 2nd line, everolimus -> 2nd line, nivolumab	15	2.2%	9
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, cabozantinib	14	2.0%	10
2nd line, nivolumab -> 2nd line, cabozantinib	13	1.9%	11
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, everolimus	13	1.9%	12
1st line, sunitinib -> 2nd line, nivolumab -> 2nd line, axitinib	13	1.9%	13
1st line, pazopanib -> 2nd line, everolimus -> 2nd line, sorafenib	11	1.6%	14
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, everolimus -> 2nd line, axitinib	11	1.6%	15
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, axitinib	10	1.5%	16
1st line, sunitinib -> 2nd line, axitinib -> 2nd line, nivolumab -> 2nd line, cabozantinib	10	1.5%	17
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, cabozantinib	9	1.3%	18
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, axitinib -> 2nd line, cabozantinib	9	1.3%	19
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, nivolumab -> 2nd line, cabozantinib	8	1.2%	20
1st line, sunitinib -> 1st line, pazopanib -> 2nd line, axitinib -> 2nd line, nivolumab	8	1.2%	21
1st line, pazopanib -> 2nd line, axitinib -> 2nd line, everolimus -> 2nd line, nivolumab	7	1.0%	22
1st line, pazopanib -> 2nd line, everolimus -> 2nd line, nivolumab	7	1.0%	23
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, cabozantinib -> 2nd line, everolimus	7	1.0%	24
1st line, pazopanib -> 2nd line, everolimus -> 2nd line, axitinib -> 2nd line, nivolumab	6	0.9%	25
1st line, pazopanib -> 2nd line, cabozantinib -> 2nd line, nivolumab	6	0.9%	26
2nd line, nivolumab -> 2nd line, cabozantinib -> 2nd line, axitinib	6	0.9%	27
1st line, pazopanib -> 2nd line, nivolumab -> 2nd line, everolimus	6	0.9%	28
1st line, sunitinib -> 2nd line, everolimus -> 2nd line, sorafenib	6	0.9%	29
1st line, pazopanib -> 1st line, sunitinib -> 2nd line, everolimus -> 2nd line, axitinib	6	0.9%	30
1st line, sunitinib -> 2nd line, cabozantinib -> 2nd line, nivolumab	6	0.9%	31
Other	241	35.2%	
Total	685	100%	

Note: sd = same day initiation as prior drug in sequence

The first 5 most common sequences include 2nd line nivolumab and are the same as in Table 6. The most common switches not involving nivolumab are from everolimus to axitinib or vice versa.

Length of treatment

The length of treatment analyses relies on an analysis of number of days between prescriptions (see Methods for details). This analysis has not considered length of treatment for 1st line nivolumab + ipilimumab as these are not the focus of the report and

there are insufficient longitudinal data as this treatment was only listed in March 2019. Thus 1st line nivolumab + ipilimumab prescriptions are excluded from Figure 6 and the following length of treatment analyses.

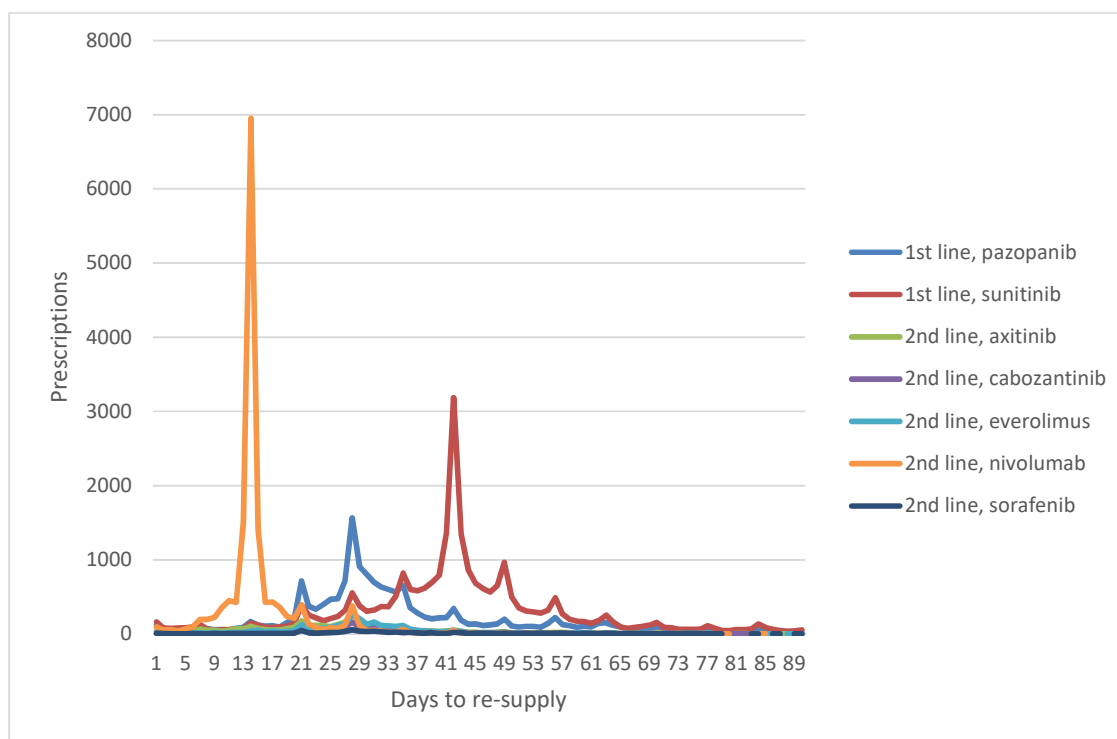


Figure 6: Days to re-supply

Note: Time to re-supply for prescriptions towards the end of the data period were excluded to avoid biasing the distribution towards shorter times.

1st line nivolumab prescriptions are most commonly resupplied after 14 days (median=14 days). This is because it is generally administered every 2 weeks via infusion and is part of the Efficient Funding of Chemotherapy (EFC) S100 Schedule where every infusion is a separate prescription.

1st line pazopanib prescriptions are most commonly resupplied after 28 days (median=32 days). Pazopanib is supplied in packs of 30, 60 or 90 tablets (strengths 200 & 400mg). The recommended dose for the treatment of RCC is 800 mg orally once daily¹¹.

1st line sunitinib prescriptions are most commonly resupplied after 42 days (median=42 days). Sunitinib is supplied a pack of 28 capsules (strengths 50, 37.5, 25 & 50mg). The

¹¹ VOTRIENT® (PAZOPANIB). Australian Approved Product Information. NOVARTIS Pharmaceuticals Australia Pty Limited. Approved 30 June 2010, updated 4 March 2020. Available from < <https://www.tga.gov.au/product-information-pi>.>

recommended dose is 50 mg taken orally once daily for 4 consecutive weeks followed by a 2 week rest period (Schedule 4/2) to comprise a complete cycle of 6 weeks¹².

Table 8: Days to re-supply summary

Treatment	Days to re-supply	
	Mode	Median = Standard Coverage Days (SCD)
1st line, sunitinib	42	42
1st line, pazopanib	28	32
2nd line, nivolumab	14	14
2nd line, axitinib	28	27
2nd line, everolimus	28	29
2nd line, cabozantinib	28	29
2nd line, sorafenib	28	33

The values of SCD in the Table 8 are used in the following length of treatment analyses to determine when breaks in treatment occur (see Methods section for details).

¹² SUTENT[®] (SUNITINIB MALATE). Australian Approved Product Information. Pfizer Australia Pty Ltd. Approved 14 September 2006, updated 31 October 2019. Available from < <https://www.tga.gov.au/product-information-pi>.>

2nd line Nivolumab length of treatment

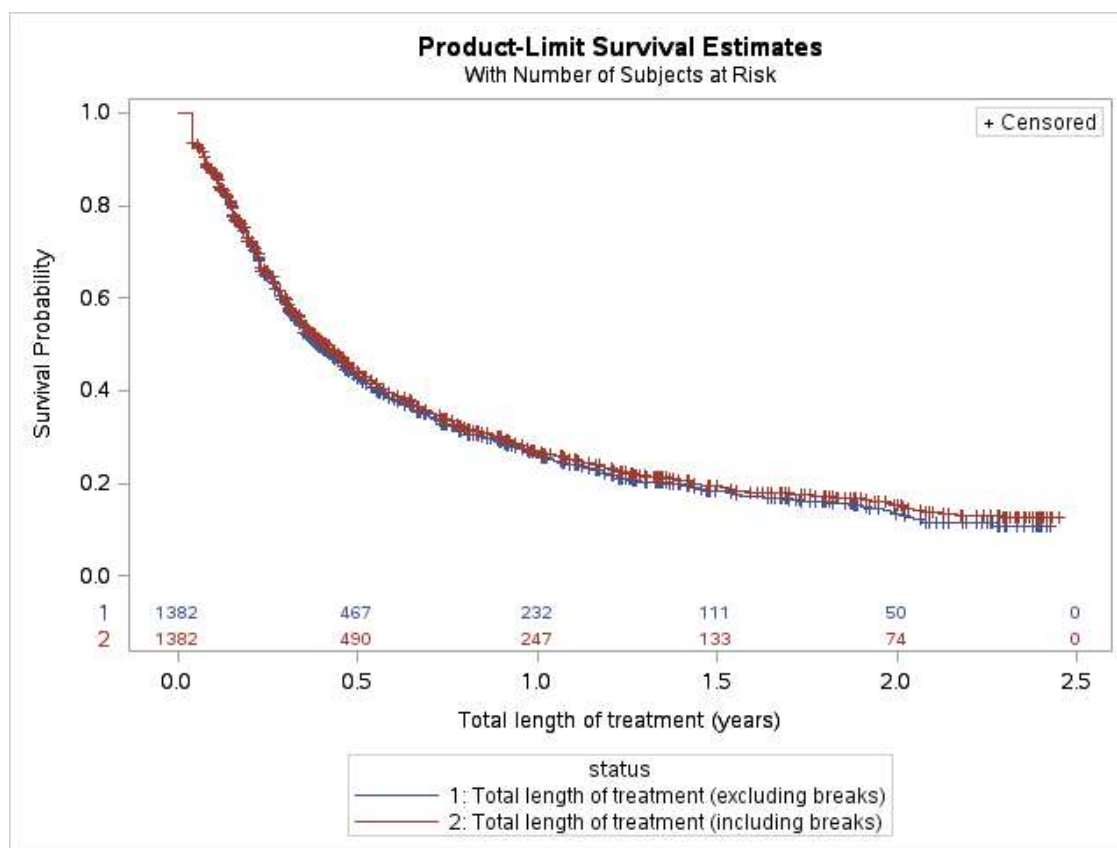


Figure 7: Length of 2nd line nivolumab treatment

The small difference between including and excluding breaks in treatment indicates that breaks in treatment are not common. The median and mean time on treatment from Figure 7 is shown in Table 9

Table 9: Median and mean length of 2nd line nivolumab treatment

	Median	Mean
Total length of treatment (excluding breaks)	0.39 years 4.6 months	0.73 years 8.7 months
Total length of treatment (including breaks)	0.42 years 5.0 months	0.76 years 9.1 months

The mean values of 9.1 months is consistent with the predicted mean of 20.7 infusions which corresponds to 9.5 months. The median of 5.0 months is also consistent with the median of 5.54 months reported in the pivot trial. The large difference between the median and the mean implies that a proportion of people stay on this treatment for a long time. It can be seen from Figure 7 that approximately 15% of patients are predicted to be still on treatment after 2 years.

Length of treatment for first line drugs.

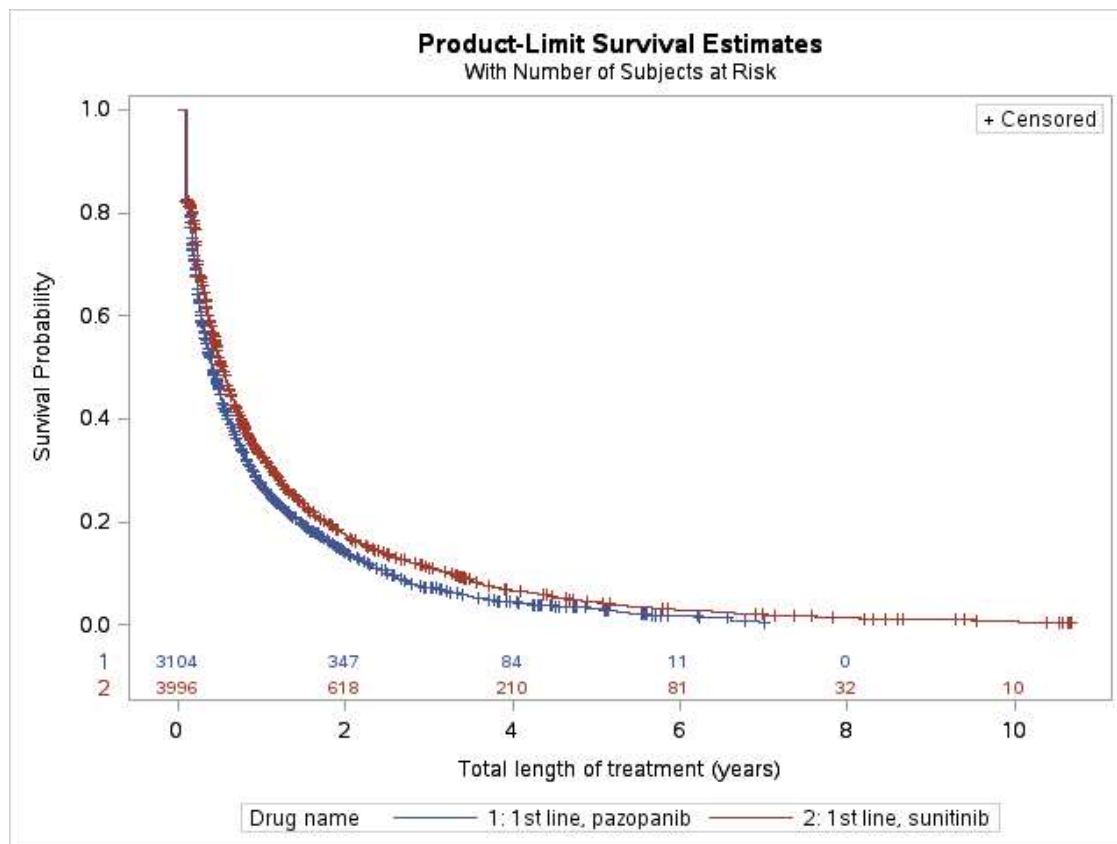


Figure 8: Length of treatment (including breaks) with first line drugs

Summary statistics from Figure 8 are shown in Table 10.

Table 10: Median and mean length of treatment (including breaks)

	Median	Mean
1st line pazopanib	0.41 years 4.9 months	0.94 years 11.3 months
1st line sunitinib	0.53 years 6.4 months	1.19 years 14.3 months

The median length of treatment with sunitinib is slightly more than pazopanib. The mean length of treatment is more than double the median for both medicines, due to there being some very long term patients.

The 2nd line nivolumab estimates were sensitive to the projected 1st line population and assumptions around the proportion failing TKIs. The March 2017 estimates assumed that 85% of patients that initiate a 1st line TKI in a year will seek 2nd line treatment in the same year. Of these it is assumed 90% will be treated with nivolumab. The results from figure 9 are that after 1 year, 73% and 67% of patients have ceased treatment with pazopanib and sunitinib respectively. Thus the proportion failing 1st line TKI therapy was lower than expected in the estimates.

Adjusting Length of Treatment using date of death

Date of death data was sourced from Services Australia for all patients that had been treated with nivolumab. These data were used to adjust the estimated length of nivolumab treatment shown in Figure 7. That is, if the coverage end date based on prescriptions was greater than the date of death, then the coverage end date was changed to the date of death, otherwise it remained unchanged. This effectively meant that the time on treatment would be slightly shorter for patients who had died and whose date of death was within one SCD after their last prescription.

During this analysis it was found that of the 1,382 patients that had 2nd line nivolumab treatment (see Figure 7), 6 patients had an anomalous date of death and were removed from the analysis leaving 1,376. An anomalous date of death was defined as one which was more than one SCD prior to the supply date of a patient's final prescription. If the date of death was less than one SCD prior to a patient's final prescription, it was considered plausible. In this case the final script was considered anomalous and removed from the analysis.

In addition the censoring scheme used for the Kaplan Meier analysis was modified base on the date of death. If a patient was deemed to have died no treatment then they were censored (i.e. deemed to be continuing treatment). The definition of "Died on Treatment" was than the patient died within one SCD after the supply of their last nivolumab prescription. Table 11 shows the status and censoring of the patients in the analysis.

Table 11: Patient status and censoring

Patient status	Original censoring*	DoD adjusted censoring*	Patients	% Patients
Alive not on treatment	0	0	409	29.7
Alive on treatment	1	1	388	28.2
Died on treatment	0	1	98	7.1
Died, but did not die on treatment	0	0	478	34.7
Died, but did not die on treatment **	1	1	3	0.2
Total			1376	100.0

* 1 = Yes, 0 = No

** These patients died close to the end of the data period so were originally deemed to be continuing treatment.

Table 11 shows that that 42.0% (7.1%+34.7%+0.2%) of patients that had 2nd line nivolumab treatment had died by the end of the analysis period (31/12/2019). 71.8% (100% – 28.2%) of patients were deemed to have stopped treatment by the end of the analysis period, of these 9.9% had died on treatment, 48.6% had stopped treatment before death and 41.4% had stopped treatment and were still alive.

Table 12 show a comparison of the original KM length of treatment (i.e. only using prescriptions) with the KM length of treatment;

- using the adjusted time on treatment and the original censoring; and
- using the adjusted time on treatment and the DoD adjusted censoring

Table 12: Estimated total length of treatment (including breaks) with 2nd line nivolumab

Description	Censoring scheme	Median (Days)	Mean (Days)
Estimated length of treatment (LoT) without use of DoD	Original: Only censored if still on treatment at the end of the period	154 days 5.06 months	277 days 9.09 months
Estimated length of treatment (LoT) using DoD and assuming cessation of treatment can be from any cause, including death	Original: Only censored if still on treatment at the end of the period	153 days 5.02 months	276 days 9.05 months
Estimated length of treatment (LoT) in an "immortal world". That is, death is not cessation of treatment	DoD adjusted: Censored if a patients dies on treatment (DoD < last supply + SCD) or still on treatment at the end of the period	170.0 days 5.59 months	300 days 9.86 months

Table 12 shows that the main effect of adjusting for date of death came from changing the censoring scheme. There was a slight reduction in length of treatment when the DoD was used to only adjust the time on treatment. However when the censoring scheme was changed to censor patients who died on treatment then the median and mean length of treatment increased by 11.2% and 8.7% respectively.

The predicted median and mean length of treatment was [REDACTED] and [REDACTED] months respectively (see predicted vs actual section). However it is unclear which censoring scheme was used in the trial to calculate these numbers, so it is unclear which numbers in Table 13 should be compared to the predicted values.

Time from last 2nd line Nivolumab treatment to death

The March 2017 PBAC minutes on nivolumab noted that 46% of patients in the clinical trial were treated with nivolumab beyond RECIST defined progression. The 2nd line nivolumab PBS restriction for continuing treatment contains the clinical criterion;

- Patient must not have developed disease progression while being treated with this drug for this condition.

This analysis looks at the distribution of time from the last 2nd line nivolumab supply to death to estimate if treatment beyond progression was occurring with PBS nivolumab. This analysis only includes patients that have a date of death and for whom 2nd line nivolumab was their last RCC medicine. As noted in the previous section, of the 1,376 2nd line nivolumab patients, 579 (42%) had died on or before 31 December 2019. Of these patients 402 had 2nd line nivolumab was their last RCC medicine. The time from the supply of their last nivolumab prescription to their date of death is shown in Figure 9.

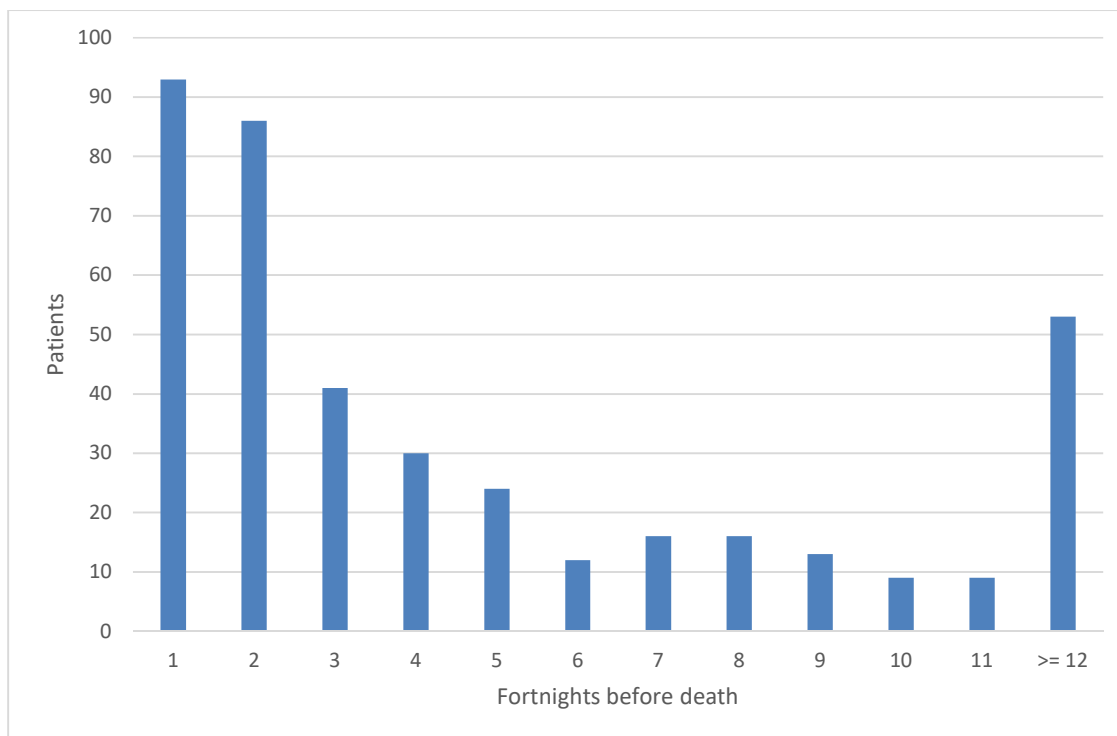


Figure 9: Time from last 2nd line Nivolumab treatment to death

Figure 9 shows that the majority of patients (55%) have their last nivolumab prescription within the last 3 fortnights before death. This may indicate that some patients were treated beyond disease progression.

Overall survival from start of 2nd line nivolumab treatment

The DoD data enabled the analysis of overall survival of patients from the start of 2nd line nivolumab treatment. This analysis was done in a similar way to the length of treatment (including breaks) analysis. For the patients still alive before the 31 December 2019 the survival time is the same as the length of treatment (including breaks) and patients are classified as censored for the Kaplan Meier analysis. For patients with a date of death, the overall survival time is from initiation of 2nd line nivolumab to death and the patients are classified as not censored. This analysis includes those patients that went on to have subsequent treatments.

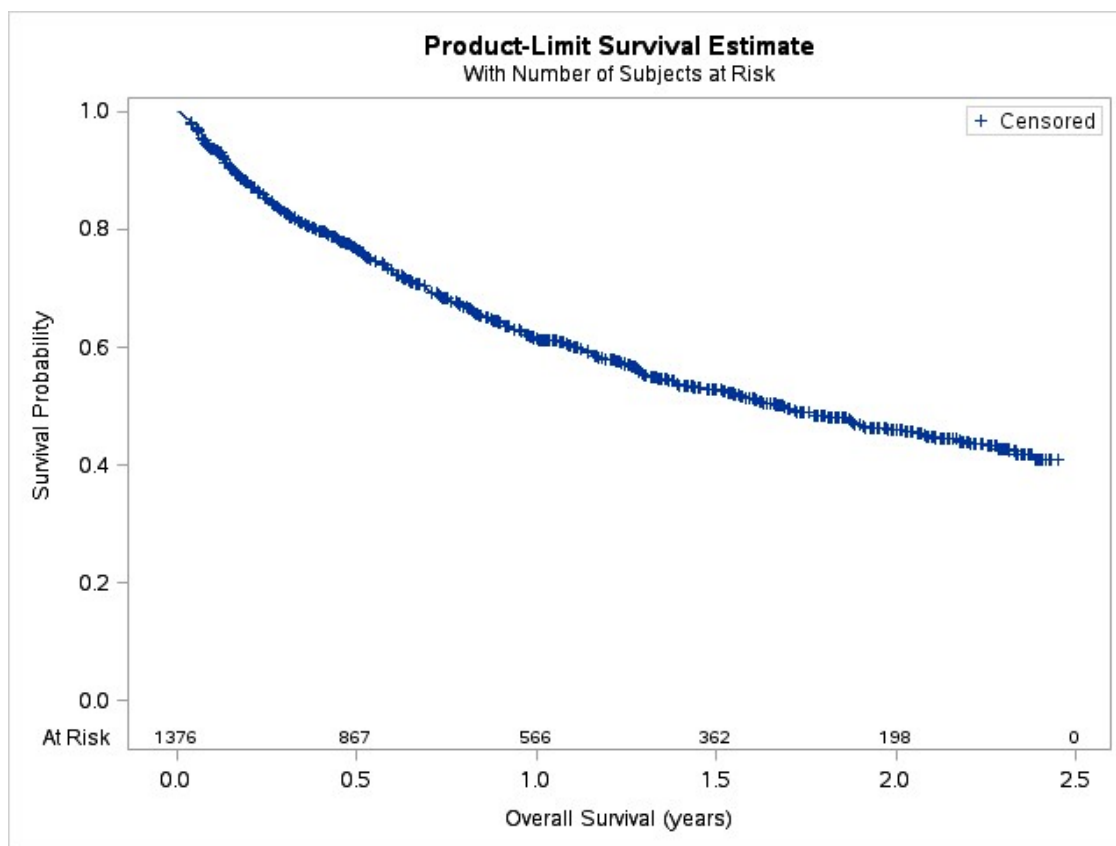


Figure 10: Overall Survival from start of 2nd line nivolumab treatment

In Figure 10 the median overall survival is 1.69 years (20.3 months) and the mean is 1.47 years (17.6 months). In the nivolumab submission to the March 2017 PBAC the overall survival for nivolumab from the pivotal study (CA209025, 11th May 2016 cut-off) was a median of 26.0 months.

Dose distribution of 2nd line nivolumab infusions

The nivolumab restriction was extended on 1 September 2019 to allow a flat 240 mg every two weeks dosing, or a flat 480 mg every four weeks dosing. The results below are presented for the periods pre and post this change.

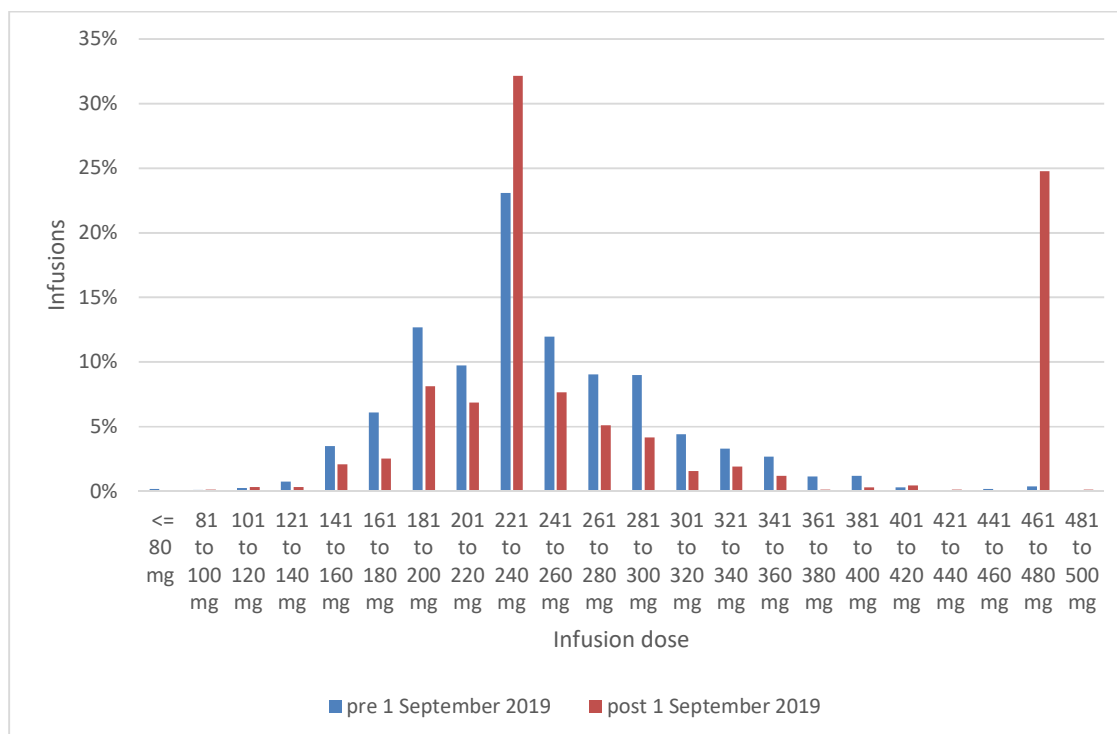


Figure 11: Dose distribution of 2nd line nivolumab infusions pre & post restriction change

Note: each infusion is supplied on a separate prescription

Figure 11 shows that there was a shift in the dose distribution after the restriction change to 240 mg and 480 mg flat dosing. The median doses pre and post 1 September 2019 are both 240 mg. The mean doses pre and post 1 September 2019 are 245 mg and 300 mg respectively. The estimates assumed a mean dose of 240 mg. The mean dose post 1 September 2019 has risen because of the availability of the flat 480mg dosing every four weeks.

Discussion

- Second line nivolumab is the most common PBS treatment for RCC. In 2019 Q4 there were 1,493 patients receiving PBS treatment for RCC, of these 463 received 2nd line nivolumab.
- In both Year 1 and 2 after listing there was approximately 50% more patients than predicted. However there were less prescriptions than predicted because the prescriptions per patient were approximately half that predicted.
- 18.4% of patients appear to have not used a TKI before initiation of 2nd line nivolumab. This is outside the PBS restriction which requires a patient to fail prior TKI treatment.
- The most common treatment switch for patients who had 2nd line RCC treatment is from nivolumab to cabozantinib.
- The median and mean length of treatment (including breaks and DoD adjustment) with 2nd line nivolumab was 5.6 and 9.9 months respectively. This is consistent with predicted mean and median of [REDACTED] and [REDACTED] months respectively.
- The DoD data revealed that 42.0% of patients that had 2nd line nivolumab treatment had died by the end of the analysis period (31/12/2019). 71.8% of patients were deemed to have stopped treatment by the end of the analysis period, of these 9.9% had died on treatment, 48.6% had stopped treatment before death and 41.4% had stopped treatment and were still alive.
- The majority of patients (55%) that have died had their last nivolumab prescription within the last 3 fortnights (infusions are generally fortnightly) before death. This may indicate that some patients were treated beyond disease progression, which is outside the PBS restriction.
- The median overall survival from the start of 2nd line nivolumab treatment was 1.69 years (20.3 months) and the mean was 1.47 years (17.6 months).

DUSC Consideration

DUSC considered that:

- Prevalent patients treated for RCC rose approximately three fold between 2009 and 2019; incident patients almost doubled.
- The introduction of nivolumab increased the second line RCC market substantially.
- The patient numbers were 50% greater than predicted. However, this is likely due to multiple lines of second line therapy, which were not accounted for in the estimates. 40% of patients had at least two second line therapies. Switching in later lines of therapy explains the greater number of patients treated compared to the estimates predicted from a simple market share.

- It is unclear if the restrictions were intended to enable multiple lines of “second line” therapy or if this could be considered beyond restriction. The impact of increasing lines of therapy on the cost-effectiveness is also unclear.
- Prescriptions per patient in each of the first two years after listing were less than predicted. However, the treatment duration analyses show that actual durations were consistent with the estimated duration based on the trial, which indicates that prescriptions are likely to represent predictions in subsequent years (the lower use in years 1 and 2 represents median use. It fails to represent mean use (the factor on which estimates were made) due to the immaturity of the data to each a prevalent mean use.
- Only 7% of nivolumab users died while on therapy, however half of these patients used nivolumab therapy within six weeks of dying, suggesting use beyond progression. The sponsor noted in their Pre-Sub-Committee response that use beyond progression was allowed in the pivotal trial. However, use beyond progression is outside the PBS restriction. DUSC noted that a standard measure of “dying on treatment” was the supply of a prescription within 30 days of death.
- Up to 18% of use appears to be outside of restriction, with use in persons with no prior dispensing history of a tyrosine kinase inhibitor. It is unknown if some of these people received tyrosine kinase inhibitors within trials or privately.

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.

Sponsors' Comments

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.

To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report.

To the fullest extent permitted by law, neither the DoH nor any DoH employee is liable for any liability, loss, claim, damage, expense, injury or personal injury (including death), whether direct or indirect (including consequential loss and loss of profits) and however incurred (including in tort), caused or contributed to by any person's use or misuse of the information available from this report or contained on any third party website referred to in this report.

Appendix A

Table A.1: PBS items that have an RCC restriction

Note: All items are RCC indication specific except those highlighted in **bold italicised text**. For these items prescriptions were classified for RCC or not, based on the authority approval database restriction code or the Streamlined Authority code.

Drug	Line of therapy	PBS item	Form and strength
AXITINIB	2nd line	10539Q	Tablet 1 mg
		10540R	Tablet 5 mg
		10556N	Tablet 5 mg
		10572K	Tablet 1 mg
CABOZANTINIB	2nd line	11360X	Tablet 60 mg
		11367G	Tablet 60 mg
		11368H	Tablet 40 mg
		11369J	Tablet 40 mg
		11371L	Tablet 20 mg
		11374P	Tablet 20 mg
EVEROLIMUS	2nd line	10131F	Tablet 5 mg
		10132G	Tablet 10 mg
		10133H	Tablet 5 mg
		10135K	Tablet 10 mg
		11257L	Tablet 5 mg
		11262R	Tablet 10 mg
IPILIMUMAB	1st line	11628B	Injection concentrate for I.V. infusion 50 mg in 10 mL
		11641Q	Injection concentrate for I.V. infusion 50 mg in 10 mL
		11644W	Injection concentrate for I.V. infusion 50 mg in 10 mL
		11647B	Injection concentrate for I.V. infusion 50 mg in 10 mL
NIVOLUMAB	1st line	11626X	Injection concentrate for I.V. infusion 100 mg in 10 mL
		11627Y	Injection concentrate for I.V. infusion 100 mg in 10 mL
		11631E	Injection concentrate for I.V. infusion 100 mg in 10 mL
		11635J	Injection concentrate for I.V. infusion 100 mg in 10 mL
		11636K	Injection concentrate for I.V. infusion 100 mg in 10 mL
		11642R	Injection concentrate for I.V. infusion 100 mg in 10 mL
	2nd line	11150W	Injection concentrate for I.V. infusion 100 mg in 10 mL
		11157F	Injection concentrate for I.V. infusion 100 mg in 10 mL
		11159H	Injection concentrate for I.V. infusion 100 mg in 10 mL
		11160J	Injection concentrate for I.V. infusion 100 mg in 10 mL
PAZOPANIB	1st line	02029T	Tablet 200 mg (as hydrochloride)
		02030W	Tablet 400 mg (as hydrochloride)
		02034C	Tablet 200 mg (as hydrochloride)
		02035D	Tablet 400 mg (as hydrochloride)
		02201W	Tablet 400 mg (as hydrochloride)
		02232L	Tablet 200 mg (as hydrochloride)

Drug	Line of therapy	PBS item	Form and strength
		11252F	Tablet 200 mg (as hydrochloride)
		11261Q	Tablet 400 mg (as hydrochloride)
SORAFENIB	2nd line	10226F	Tablet 200 mg (as tosilate)
		10242C	Tablet 200 mg (as tosilate)
SUNITINIB	1st line	09417P	Capsule 12.5 mg (as malate)
		09418Q	Capsule 25 mg (as malate)
		09419R	Capsule 50 mg (as malate)
		09420T	Capsule 12.5 mg (as malate)
		09421W	Capsule 25 mg (as malate)
		09422X	Capsule 50 mg (as malate)
		10459L	Capsule 37.5 mg (as malate)
		10504W	Capsule 37.5 mg (as malate)

Appendix B: Comparison of actual Date of Death with PBS Proxy

1. Comparison of patient alive / dead status

There were 9,190 patients that had received a prescription for nivolumab from 1 May 2016 (first listing for nivolumab) to 31 December 2019.

All PBS prescriptions for these patients were extracted from January 2016 to the end of February 2020 and the proxy Date of Death (pDoD) was calculated as per the Methods section. A limitation of the data was that no pDoD could be determined past 8 December 2019.

These data were matched with the Services Australia Date of Death (DoD) data for the same patients. After excluding patients with a DoD after 8 December 2019, there were 8,718 patients remaining in the analysis.

Table B.1: Proxy vs Services Australia (SA) patient status

Patients	Proxy patient status		
SA patient status	Alive	Dead	Total
Alive	4,184	272	4,456
Dead	35	4,227	4,262
Total	4,219	4,499	8,718
% Patients	Proxy patient status		
SA patient status	Alive	Dead	Total
Alive	48.0%	3.1%	51.1%
Dead	0.4%	48.5%	48.9%
Total	48.4%	51.6%	100.0%

Table B.1 compares the proxy patient status (based whether or not a patient has a proxy DoD) with the SA patient status (based whether or not a patient has SA DoD). The agreement rate between the two measures was 96.5% (i.e. 48.0% + 48.5%). Most of the disagreement was where the proxy status = Dead and the SA status = Alive (i.e. 3.1% patients). This disagreement is likely to be due to an error in the proxy status, but not necessarily so. Other possible explanations are;

- late death registrations which will modify the SA status when the data is received by State governments and then flows through to SA.
- a patient no longer accesses PBS (e.g. leaves Australia). In this case their proxy status will become "Dead".

2. Difference between proxy DoD and Services Australia DoD.

For patients where the proxy and SA patient status both are "Dead", the difference between the dates of death in days is summarised in Table B.2.

Table B.2: Days from SA DoD to proxy DoD

Cohort	n	mean	mode	median
Both proxy and SA patient = Dead	4,227	5.4	7	3

The median number of days from the SA DoD to the proxy DoD was 3 days (i.e. proxy DoD was 3 days after SA DoD). If the proxy DoD had been used instead of the SAS DoD in the analyses that required DoD (i.e. Days from last nivolumab prescription to date of death (Figure 10) or Overall Survival from start of 2nd line nivolumab treatment (Figure 11)) then the results would be very similar. For example, the overall median survival was 20.3 months using the SA DoD. If the SA DoD had been used then the median survival would have been less than 3 days longer (as the 3 days extension only applies to the patients who died).

Conclusion

The proxy DoD performed well, scoring 96.5% agreement with the Alive / Dead status from the SA DoD. When both the proxy and SA status measures agreed that the patient was dead, there was only a 3 day median difference in the date of death.

A similar analysis was done previously for sunitinib and everolimus for the treatment of pancreatic neuroendocrine tumours (pNET) in September 2017. The results were very similar (i.e. 96.7% agreement, median and mode difference of 2 and 7 days respectively).

The similarity of the results of the two validation analyses is evidence that the method of calculating a proxy for DoD may be generalisable. It is most likely to be accurate for diseases that are terminal and have a need for some sort of PBS medication (not necessarily the medication used to treat the main disease) up to a patient's death. It is not likely to be accurate for diseases that require acute treatment after which the patient recovers and is well enough to require no other PBS medication. The generalisability may need to be tested further in the future for other conditions.