

Nivolumab + Ipilimumab for the first line treatment of renal cell carcinoma: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2021

Abstract

Purpose

To compare the predicted and actual utilisation of nivolumab + ipilimumab for the first-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 + Ipilimumab was PBS listed on 1 March 2019 for the first-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 2021 Q2 there were 1,579 patients receiving PBS treatment for RCC, of these 472 received 2nd line nivolumab. The second most common treatment is first-line nivolumab, with 312 patients being treated in 2021 Q2.
- For ipilimumab, in both Years 1 and 2 after listing there were slightly more patients than predicted. However there were slightly less prescriptions than predicted because the prescriptions per patient were less than predicted. This can be explained by the estimates assuming that all patients will complete the induction phase (i.e. 4 prescriptions). Figure 9 shows that 38% of patients received less than the full course of 4 ipilimumab scripts.

- For nivolumab in the first line setting, there were 32% and 67% more patients than expected in Years 1 and 2 respectively. In Year 1 there were more nivolumab patients (442) than ipilimumab patients (395). This can be explained by the results of the drug initiation sequence analysis (Table 4) which shows that over the period from the listing of first-line nivolumab (1 March 2019) to the end of June 2021 there were 91 patients that were supplied only first-line nivolumab (maintenance phase) prescriptions. This pattern of use was outside the PBS restrictions. Some of these may have been grandfathering patients who failed to be allocated the specific PBS item code for such patients. In Year 2 an additional factor that could explain the more than expected number of patients was the presence of continuing patients from Year 1. These had not been factored into the estimates.
- For nivolumab, there were 75% and 76% less scripts per patient than expected in Years 1 and 2 respectively. This is mainly due to the overestimation of the average length of treatment in the submissions and final agreed estimates. A second factor is the shift from 2 to 4 weekly dosing after the 1 September 2019 restriction change. A third factor was the incorrect use of PBS item codes where some patients who initiate first-line nivolumab + ipilimumab treatment used 2nd line nivolumab treatment items for their first-line maintenance treatment (see Table 4).

Purpose of analysis

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

DUSC requested this analysis at its June 2021 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 the number of treated patients was higher than estimated and considered a predicted versus actual review should be undertaken.

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

Background

Nivolumab + ipilimumab was PBS listed on 1 March 2019 for the first-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 second-line treatment of advanced or metastatic clear cell variant RCC following first-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 second-line treatment for RCC on 1 June 2018.

On 1 March 2019 nivolumab in combination with ipilimumab was listed on the PBS as a first-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 second-line treatment if they have first-line TKI treatment.

Pharmacology

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>

Nivolumab is a protein which helps the immune system to attack and destroy cancer cells.² It is a human anti PD-1 monoclonal antibody which inhibits the programmed death 1 (PD-1) receptor from binding to its ligands (PD-L1 and PD-L2) on tumour cells, reactivating cytotoxic T lymphocytes and anti-tumour immunity.³

Ipilimumab is also a protein which helps the immune system to attack and destroy cancer cells. It binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) resulting in an enhanced T-cell mediated immune response which leads to tumour cell death.³

Therapeutic Goods Administration (TGA) approved indications

Nivolumab is indicated for the treatment of ⁴;

- Melanoma
 - as monotherapy and in combination with ipilimumab.
- Non-Small Cell Lung Cancer (NSCLC)
 - as monotherapy and in combination with ipilimumab.
- Malignant Pleural Mesothelioma (MPM)
 - in combination with ipilimumab.
- 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)
- Oesophageal Squamous Cell Carcinoma (OSCC)

Ipilimumab is indicated for the treatment of ⁵;

- Melanoma
 - as monotherapy and in combination with nivolumab.
- Non-Small Cell Lung Cancer (NSCLC)
 - in combination with nivolumab.
- Malignant Pleural Mesothelioma (MPM)
 - in combination with nivolumab.

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

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

⁴ OPDIVO® (NIVOLUMAB). Australian Approved Product Information. Bristol-Myers Squibb Australia Pty Ltd. Approved 11 January 2016, updated 11 May 2021. Available from <https://www.tga.gov.au/product-information-0>

⁵ YERVOY® (IPILIMUMAB). Australian Approved Product Information. Bristol-Myers Squibb Australia Pty Ltd. Approved 27 June 2011, updated 10 May 2021. Available from <https://www.tga.gov.au/product-information-0>

- 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.

Dosage and administration

Induction / Combination Phase: The recommended dose of nivolumab in the combination phase is 3 mg/kg administered intravenously over 30 minutes every 3 weeks for the first 4 doses in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes. This should be followed by nivolumab monotherapy therapy in the single-agent / maintenance phase (see below).

Single-agent / Maintenance Phase: The recommended dose of nivolumab in the single agent phase administered intravenously over 30 minutes is 3 mg/kg every 2 weeks or 240 mg every 2 weeks or 480 mg every 4 weeks.

Following the last dose of the combination of nivolumab and ipilimumab, the first dose of nivolumab monotherapy should be administered after 3 weeks when using 3 mg/kg or 240 mg or 6 weeks when using 480 mg. Treatment with nivolumab in the single-agent phase 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 August 2021)

Tables 1A & 1B shows the PBS listings of nivolumab and ipilimumab for first-line treatment of Stage IV clear cell variant RCC.

Table 1A: PBS listings of nivolumab for first-line treatment of RCC

Item	Name, form & strength, pack size	Treatment Phase	Date of listing	Max. amount	Rpts	DPMA*	Brand name and manufacturer
11626X	Injection concentrate for I.V. infusion 100 mg in 10 mL & 40 mg in 4 mL	Maintenance treatment – Private Hospital	1/3/2019	480 mg	11	\$10,235.25	Opdivo® Bristol-Myers Squibb Australia Pty Ltd
11627Y		Induction treatment – Private Hospital		360 mg	3	\$7,708.27	
11636K		Induction treatment – Public Hospital		360 mg	3	\$7,562.58	
11642R		Maintenance treatment – Public Hospital		480 mg	11	\$10,054.68	

Table 1B: PBS listings of ipilimumab for first-line treatment of RCC

Item	Name, form & strength, pack size	Treatment Phase	Date of listing	Max. amount	Rpts	DPMA*	Brand name and manufacturer
11628B	Injection concentrate for I.V. infusion 50 mg in 10 mL	Induction treatment – Public Hospital	1/3/2019	120 mg	3	\$16,964.04	Yervoy® Bristol-Myers Squibb Australia Pty Ltd
11644W		Induction treatment – Private Hospital		120 mg	3	\$17,241.35	

Source: the PBS website. *Special Pricing Arrangements apply. These items are listed in the Efficient Funding of Chemotherapy (EFC) section of the PBS Schedule.

Restriction

Nivolumab has Authority Required (STREAMLINED) listings for induction and maintenance treatment.

Stage IV clear cell variant renal cell carcinoma (RCC)

Treatment Phase: **Induction treatment**

Clinical criteria:

- The condition must not have previously been treated,
AND
- The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC),
AND
- Patient must have a WHO performance status of 2 or less,
AND
- The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition.

Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks. The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

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.

A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: <https://www.mdcalc.com/imdc-international-metastatic-renal-cell-carcinoma>.

One point is assigned for each of:

- (i) a time of diagnosis to systemic therapy of less than 1 year
- (ii) a Karnofsky Performance Status of less than 80%
- (iii) a haemoglobin less than the lower limit of normal
- (iv) a corrected calcium level greater than the upper limit of normal
- (v) a neutrophil count greater than the upper limit of normal

(vi) a platelet count greater than the upper limit of normal

Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.

Favourable IMDC risk is a score of 0.

Intermediate IMDC risk is a score of 1 to 2.

Poor IMDC risk is a score of 3 to 6.

Document any IMDC risk score assessment in the patient's medical records.

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

Special Pricing Arrangements apply.

Caution

Combination treatment with ipilimumab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.

Treatment Phase: **Maintenance treatment**

Clinical criteria:

Patient must have previously received of up to maximum 4 doses of PBS-subsidised combined therapy with nivolumab and ipilimumab as induction for this condition,
AND

- The treatment must be as monotherapy for this condition,

AND

- Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug 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. The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

Note

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

Special Pricing Arrangements apply.

Ipilimumab has Authority Required (STREAMLINED) listings for induction and maintenance treatment.

Stage IV clear cell variant renal cell carcinoma (RCC)

Treatment Phase: **Induction treatment**

Clinical criteria:

- The condition must not have previously been treated,

AND

- The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC),

AND

- Patient must have a WHO performance status of 2 or less,

AND

- The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction therapy for this condition.

Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks. The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

Note & Caution: same as for nivolumab induction treatment (see above)

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

Changes to listing

There were two PBS items for grandfather patients for both nivolumab (11631E – Public Hospital & 11635J – Private Hospital) and ipilimumab (11641Q – Public Hospital & 11647B – Private Hospital) that started on 1 March 2019 and ceased on 30 September 2020. These items were for a patient who had received less than 4 doses of combined therapy with ipilimumab and nivolumab as induction therapy for this condition prior to 1 March 2019 and patients who received monotherapy with nivolumab as maintenance for this condition prior to 1 March 2019. See Appendix B for details of these restrictions.

The nivolumab second-line RCC listing changed in authority approval level (Authority Required to Streamlined) for initial and continuing prescriptions on 1 September 2019. First-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 first-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, except the first-line induction treatment items 11627Y and 11636K.

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 2018 PBAC

The PBAC decided not to recommend nivolumab in combination with ipilimumab (NIVO+IPI) for the first-line treatment of Stage IV clear cell variant renal cell carcinoma (RCC) in patients at intermediate to poor prognostic risk. The PBAC acknowledged the high clinical need for effective first-line therapies, especially in patients who are categorised as being at poor prognostic risk. However, the PBAC considered that the incremental survival and quality of life benefits were overestimated in the economic model presented, and that the incremental cost-effectiveness ratio (ICER) was uncertain and unacceptably high. The PBAC considered that a price reduction would be required to bring the estimated ICER into an acceptable range. The submission was not considered by DUSC.⁶

November 2018 PBAC

The PBAC recommended extending the Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing of NIVO+IPI to include the first-line treatment of Stage IV clear cell variant RCC in patients at intermediate to poor prognostic risk. The PBAC considered that the resubmission's revised economic model parameters, utilisation estimates and risk-sharing arrangement helped to address many of its previous concerns. However, the PBAC advised that a price reduction would be required to bring the estimated ICER into an acceptable range. The submission was a minor resubmission and consequently was not considered by DUSC.⁷

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.

⁶ <https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2018-07/Nivolumab-ipilimumab-psd-july-2018>

⁷ <https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2018-11/Nivolumab-And-Ipilimumabpsd-november-2018>

- 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.⁸

DUSC considered a predicted vs. actual utilisation analysis of nivolumab for second-line treatment of RCC June 2020 meeting. The key findings were:

- 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 second-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 appeared to have not used a TKI before initiation of second-line nivolumab. Such use is outside the PBS restriction which requires a patient to fail prior TKI treatment.
- The most common treatment switch for patients who had second-line RCC treatment is from nivolumab to cabozantinib.
- The median and mean length of treatment (including breaks and date of death (DoD) adjustment) with second-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 December 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 second-line nivolumab treatment was 1.69 years (20.3 months) and the mean was 1.47 years (17.6 months).

For details of this DUSC consideration refer to the Public Release Document from the June 2020 DUSC meeting.⁹

⁸ <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/pazopanib-sunitinib/pazopanib-sunitinib>

⁹ <https://www.pbs.gov.au/pbs/industry/listing/participants/public-release-docs/2020-06/nivolumab-for-the-treatment-of-renal-cell-carcinoma>

Methods

The report examines the use of nivolumab + ipilimumab for the first-line 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 June 2021 (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

As these analyses use date of supply prescription data, there may be small differences compared with publicly available Services Australia PBS date of processing data¹⁰ 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.

Results

Analysis of drug utilisation

Prescription utilisation

¹⁰ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <https://www.servicesaustralia.gov.au/organisations/about-us/reports-and-statistics/statistical-information-and-data-0/medicare-statistics/pharmaceutical-benefits-schedule-statistics>

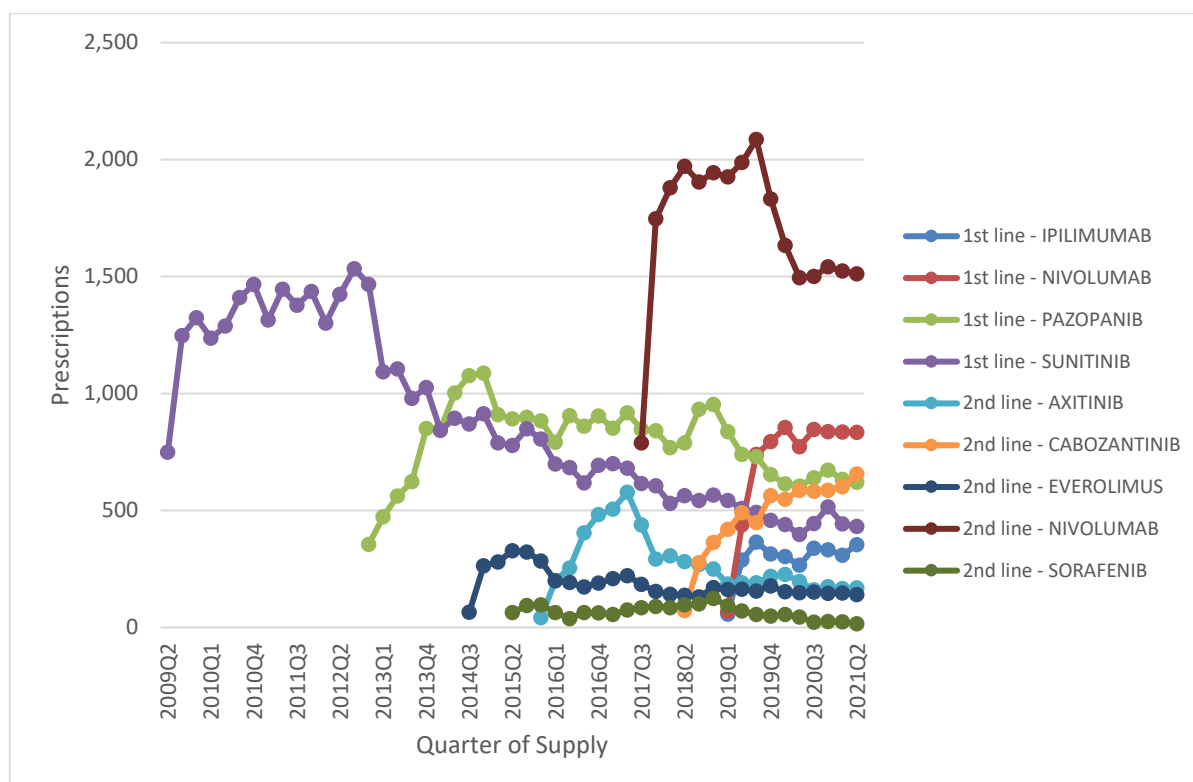


Figure 1: Prescriptions for the treatment of RCC by line of therapy and drug

Note: Nivolumab + Ipilimumab for first-line RCC was PBS listed on 1 March 2019

Figure 1 shows that second-line nivolumab has the most prescription utilisation in the RCC treatment market. 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.

First-line nivolumab is the second most utilised medicine in the market. Utilisation of first-line ipilimumab is not as high as first-line nivolumab because combination treatment is only required for induction treatment which lasts 12 weeks (4 doses at 3 weekly intervals). After this, in the maintenance phase, nivolumab is prescribed as monotherapy.

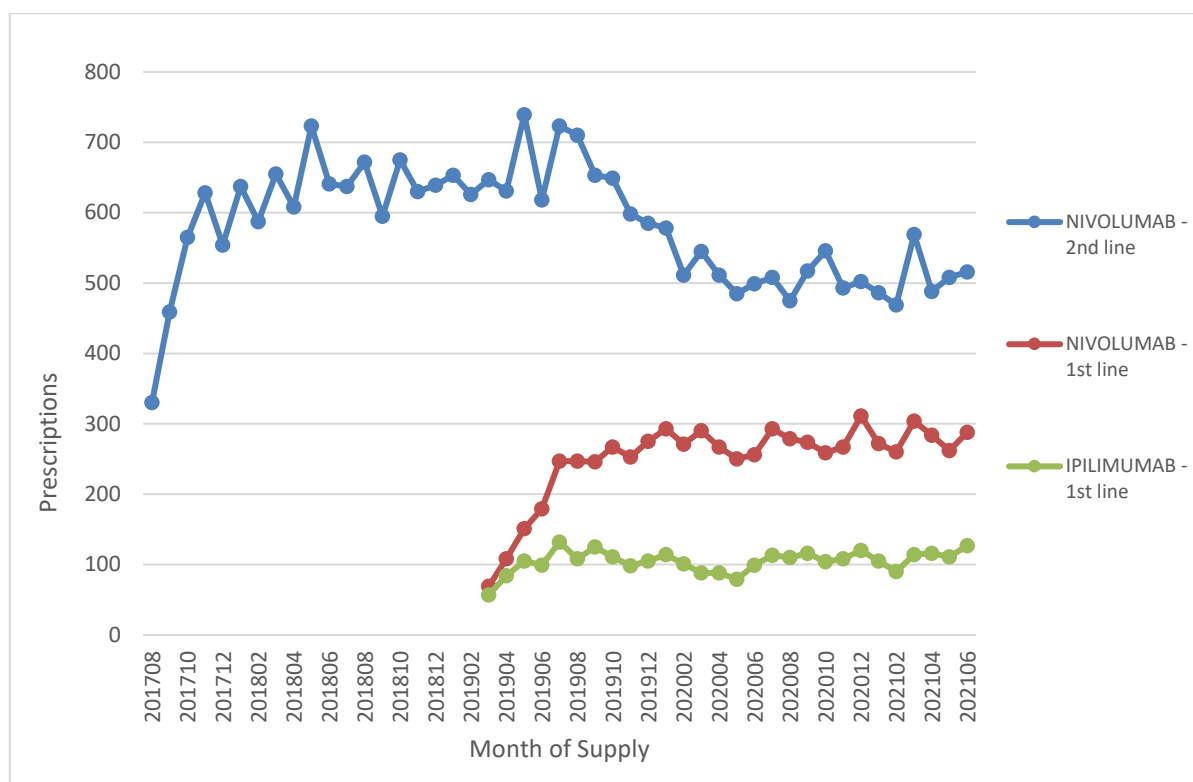


Figure 2: Nivolumab and ipilimumab prescriptions for RCC by line of therapy

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 first-line treatment on 1 March 2019;
- the extension the first- & second-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 first- & second-line on 1 September 2019.

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. The utilisation of first-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 second-line initial and continuing prescriptions on 1 September 2019. First-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.

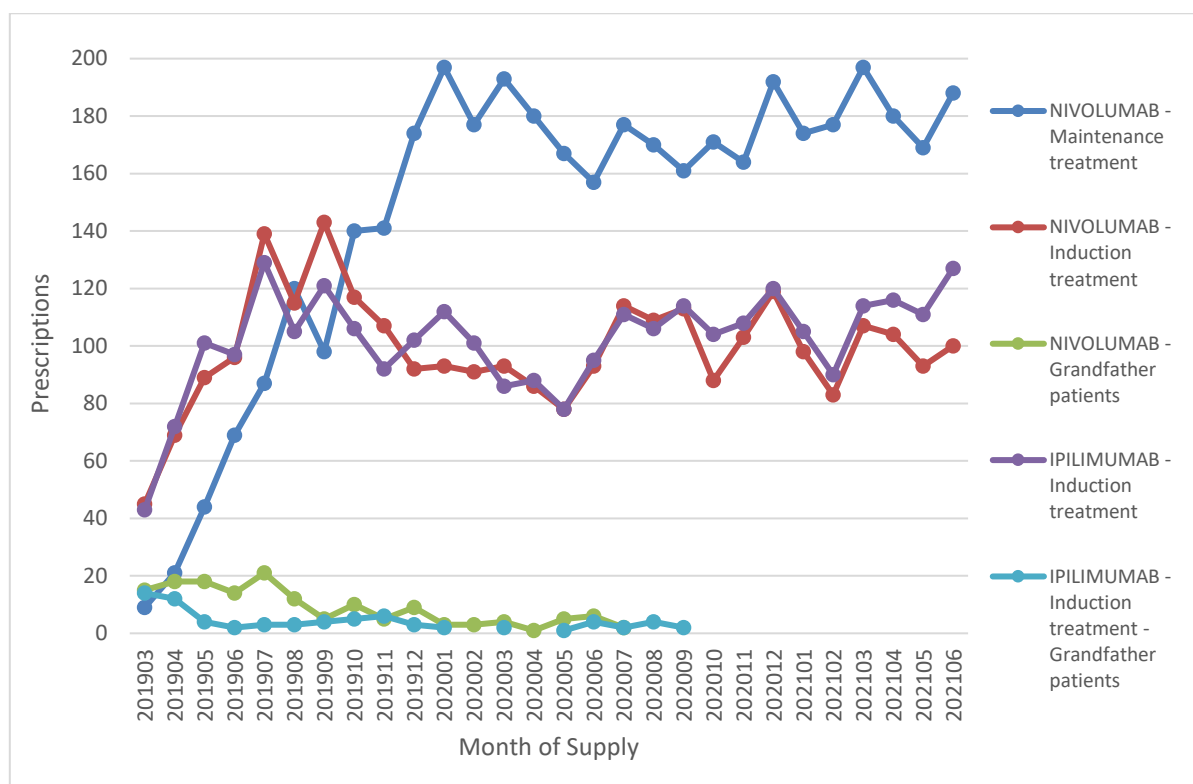


Figure 3: Nivolumab and ipilimumab prescriptions for first-line RCC by treatment phase

Figure 3 shows the extent of utilisation for grandfathering and the expected close match between the number of prescriptions for nivolumab and ipilimumab in the induction phase.

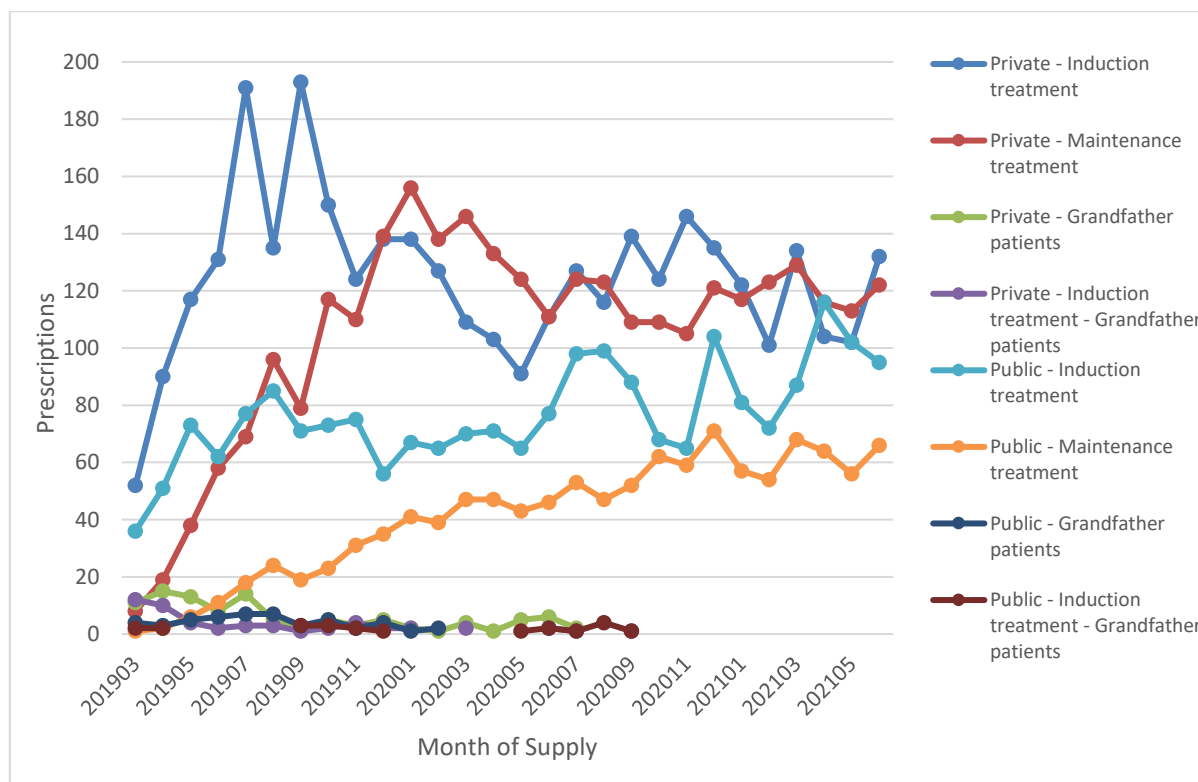


Figure 4: Nivolumab and ipilimumab prescriptions for first-line RCC by hospital type and treatment phase

Figure 4 shows that utilisation was initially greater in the private hospital settings and utilisation in the public hospital setting has been steadily increasing.

Patients

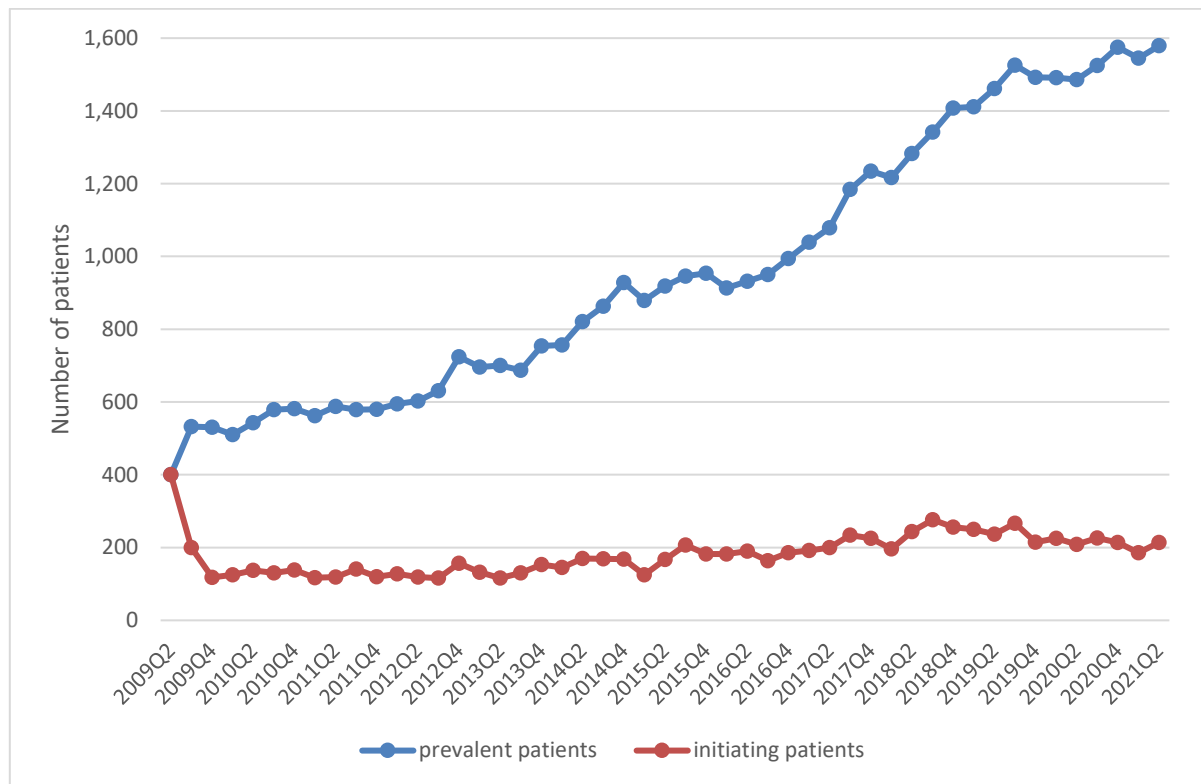


Figure 5: Initiating and prevalent patients for the PBS treatment of RCC

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

Figure 5 shows the number of patients initiating treatment for RCC gradually increased until 2018 Q3 and has slowly decreased since then.

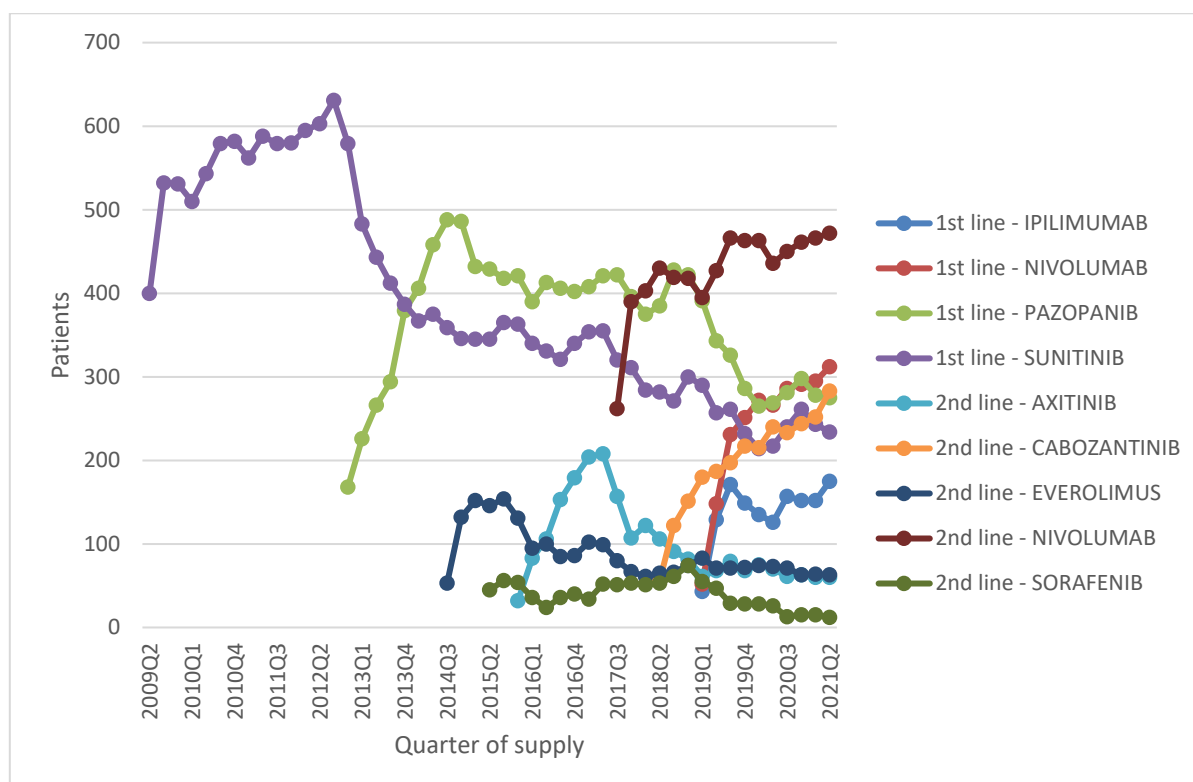


Figure 6: Prevalent patients for the treatment of RCC by line of therapy and drug

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

In Figure 6:

- Second-line nivolumab was (as at 2021 Q2) the most utilised treatment, followed by first-line nivolumab and then 2nd line cabozantinib.
- First-line nivolumab looks to be mainly replacing first-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.

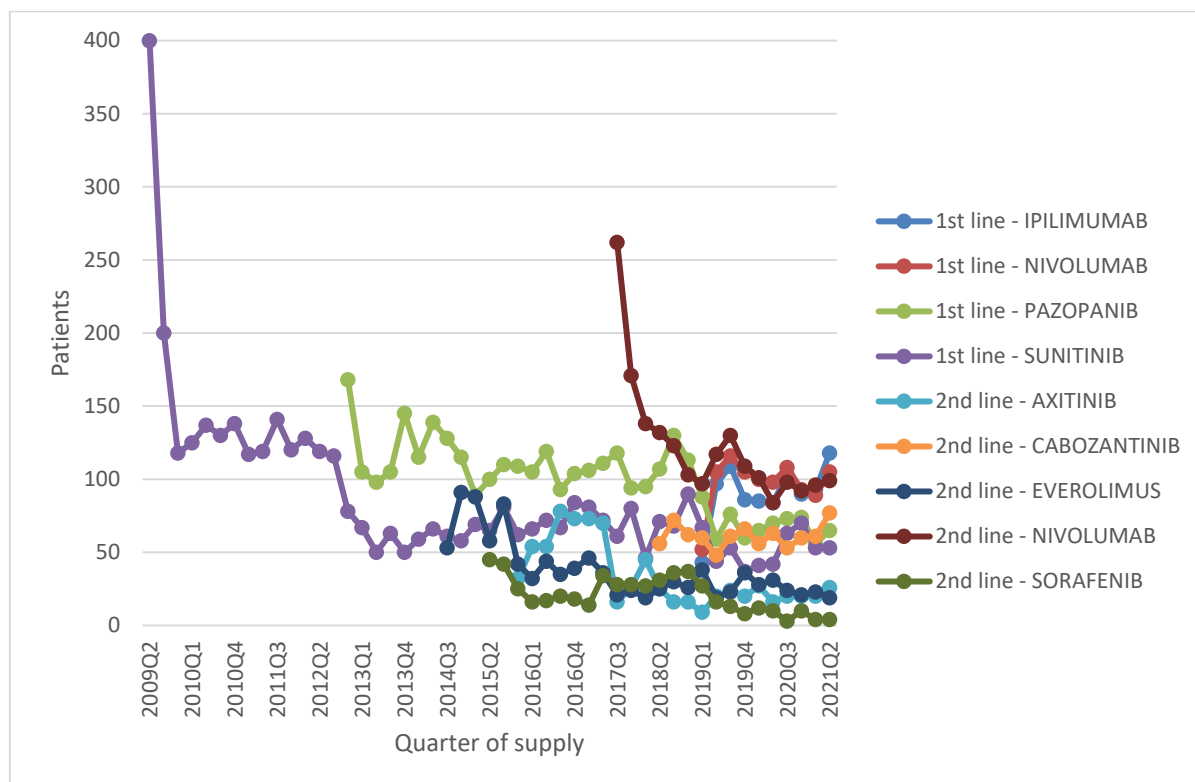


Figure 7: Initiating patients for the treatment of RCC by line of therapy and drug

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

Figure 7 shows that currently (as at 2021 Q2) first-line nivolumab and ipilimumab and 2nd line nivolumab are the two most commonly initiated treatments. As expected the number of patients initiating first-line nivolumab and first-line ipilimumab are similar.

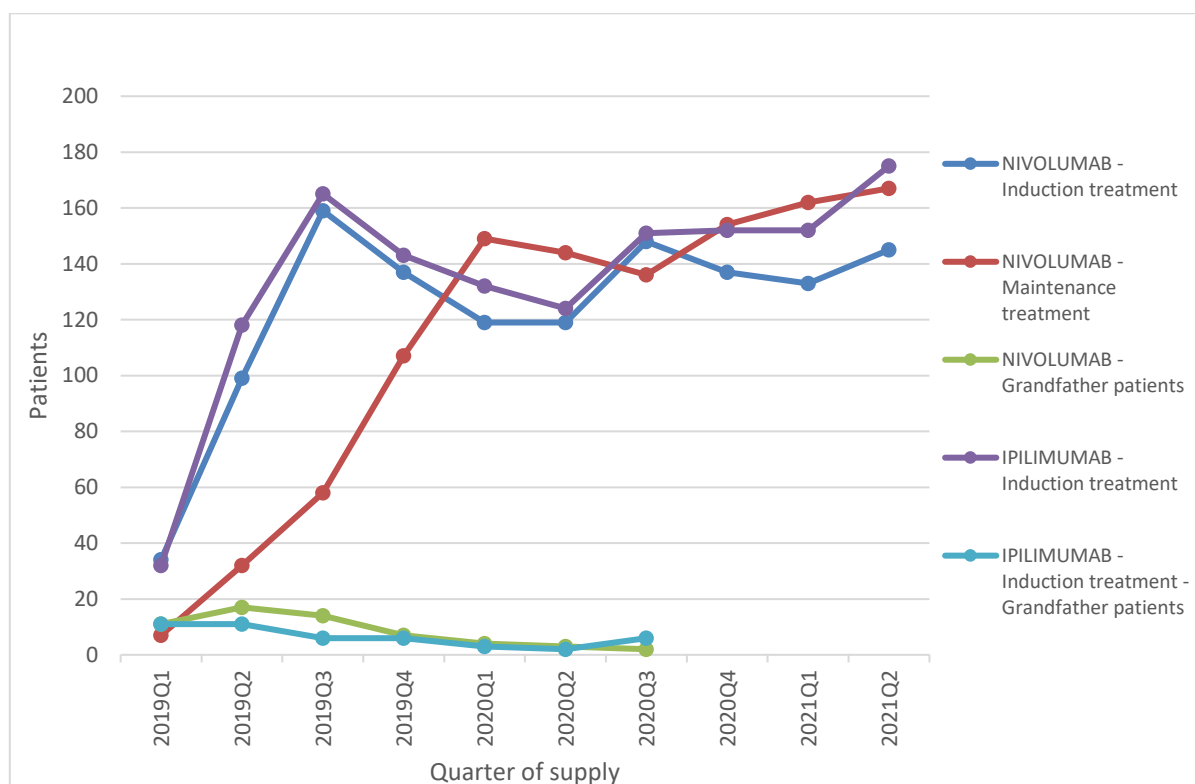


Figure 8: Prevalent patients for the first-line nivolumab and ipilimumab by treatment phase

Note: Patients can be prevalent to (i.e. supplied) more than one drug in a quarter. Patients are counted in the first treatment phase they have in a quarter

There is a slight discrepancy between the number of patients prevalent to nivolumab and ipilimumab induction treatment. This will be investigated further in a patient level medicine sequence analysis later in the report.

Analysis of predicted versus actual utilisation

Table 3: Predicted vs Actual analysis of nivolumab + ipilimumab for first-line RCC

		Year 1	Year 2
		Mar 19 to Feb 20	Mar 20 to Feb 21
Ipilimumab			
Treated patients (PBS & RPBS)	Predicted (P)	335	344
	Actual (A)	395	404
	% Difference (A-P)/P	18%	17%
Prescriptions	Predicted (P)	1,339	1,376
	Actual (A)	1,239	1,220
	% Difference (A-P)/P	-7%	-11%
Prescriptions per patient	Predicted (P)	4.0	4.0
	Actual (A)	3.1	3.0
	% Difference (A-P)/P	-22%	-25%
PBS + RPBS expenditure	Predicted (P)		
	Actual (A)		
	% Difference (A-P)/P	-36%	-41%
Nivolumab			

Treated patients (PBS & RPBS)	Predicted (P)	335	344
	Actual (A)	442	573
	% Difference (A-P)/P	32%	67%
Prescriptions	Predicted (P)	8,033	8,254
	Actual (A)	2,606	3,278
	% Difference (A-P)/P	-68%	-60%
Prescriptions per patient	Predicted (P)	24.0	24.0
	Actual (A)	5.9	5.7
	% Difference (A-P)/P	-75%	-76%
PBS + RPBS expenditure	Predicted (P)		
	Actual (A)		
	% Difference (A-P)/P	-75%	-62%

The predicted figures in the above table are the final estimates agreed with the sponsor after the November 2018 PBAC recommendation.

In Table 3, for ipilimumab the actual number patients was 18% and 17% more than predicted in Years 1 and 2 respectively. For nivolumab the actual number of patients was 32% and 67% more than predicted in Years 1 and 2 respectively. As this is combination therapy, one might expect the number of patients treated with nivolumab and ipilimumab to be the same in Year 1. However there are slightly more nivolumab patients (442) than ipilimumab patients (395). The reason for this may be grandfathered patients who already completed the induction phase prior to starting PBS nivolumab in the maintenance phase. This will be investigated in a sequence analysis later in this report.

Both medicines have lower than expected prescriptions and expenditure in both years. This is due to the lower than expected prescriptions per patient. This will be investigated in the "Distribution of number of prescriptions in 12 months after initiation" analysis and the "Dose distribution of first-line nivolumab infusions" analysis later in this report. The assumption that patients will get 24 prescription per year is based on a fortnightly dosing regimen in the maintenance phase. However many patients changed to the monthly regimen when it became available on 1 September 2019.

In Study CA209214, the pivotal trial in the submission to the July 2018 PBAC, the median duration of study therapy for NIVO + IPI was 7.85 months in all treated subjects and 7.37 months for intermediate/poor risk patients (p 66 of submission). This was estimated from Kaplan-Meier curves and not limited to 12 months follow-up and so the actual treatment time of 6.1 months in a 12 month period calculated in this report (see treatment time analysis in Figure 12) is not dissimilar to that reported in the pivotal trial.

The reason the submission used a much longer estimated length of treatment was (p66):

"It is acknowledged that given the extent of patients still continuing on treatment in Study CA209214 (20.8%), it is likely that the average duration of therapy has not reached sufficient maturity, with the exception of ipilimumab which was only administered in the induction phase for a maximum of 4 cycles. Consequently, the modelled duration of therapy for nivolumab and sunitinib from the economic model (refer to Section 3) is used to determine the cost per patient that is applied financial estimates (refer to Section 4)."

Page 187 to the submission stated;

“the mean extrapolated value from the economic evaluation minus the induction phase (assumed this was equivalent to IPI) was applied in the financial estimates (34.3 - 3.6 = 30.7 infusions). As the mean duration of NIVO + IPI exceeds one calendar year the number of infusions applied per patient was spread over 1-3 years depending on date of initiation.”

The submission then applied a “half-year correction” to allow for patients initiating through the year. The minor submission to the November 2018 PBAC made adjustments to the time horizon of the economic model and the duration of therapy. Page 10 to the minor submission states;

the Sponsor has adjusted the financial estimates to account for the potential additional costs in clinical practice associated with patients who experience adverse events during NIVO+IPI induction and go on to receive nivolumab monotherapy, rather than discontinue as was required by the trial protocol. In Study CA209214, 13.4% of patients discontinued NIVO+IPI during the induction phase due to drug toxicity. The revised financial estimates apply an increased cost of NIVO maintenance infusions per patient (13.4% increase to the modelled mean duration of maintenance therapy from the economic evaluation) to proxy the proportion of patients in Study CA209214 who discontinue NIVO+IPI during the induction phase but may go on to receive NIVO monotherapy in clinical practice.

Page 13 further states;

Several changes in assumptions have impacted the estimated cost of NIVO+IPI to PBS/RPBS between the July 2018 Major submission and the revised base case. While an increase in the number of patients (grandfather restriction, 2020 listing) and duration of maintenance therapy (30.7 to 33.06 respectively) were key drivers for the 14% increase in infusions over the forecast period, this was outweighed by the reduction in the proposed price (NIVO 100mg: [REDACTED]; IPI 50mg: [REDACTED]) culminated in a 7.4% reduction in total costs to the PBS/RPBS for Year 1 to Year 6.

Since the submission assumed fortnightly doses, this translates to a mean length of maintenance therapy of $33.06 \times 2 = 66$ weeks, for a total length of therapy of 78 weeks (including 12 weeks of induction therapy). This is an average of 18 months of therapy which is very different to the median value of 7.85 months from the clinical trial.

In the final agreed estimates, instead of having a patient’s 18 month treatment carry over from their initiating year to the next, a simplified approach was taken where all initiating patients were deemed to have had 4 induction and 20 fortnightly maintenance nivolumab prescriptions in the year they initiated and none in subsequent years. The reasons for this simplified approach are not recorded. As shown in the Predicted vs Actual analysis (see Table 3), even though this simplified estimate was less than that specified in the November

2018 minor submission, it was still a large overestimate of nivolumab prescriptions per patient.

Other analyses:

Distribution of number of prescriptions in 12 months after initiation

This analysis investigates the discrepancy between the predicted and actual prescriptions per patient shown in Table 3. The predicted prescriptions per patient are based on the number of prescriptions expected in the year(s) from patient initiation, not in the year(s) since listing of the medicines for this indication. Thus a more valid comparison may be to the number of prescriptions in the 12 months after patient initiation.

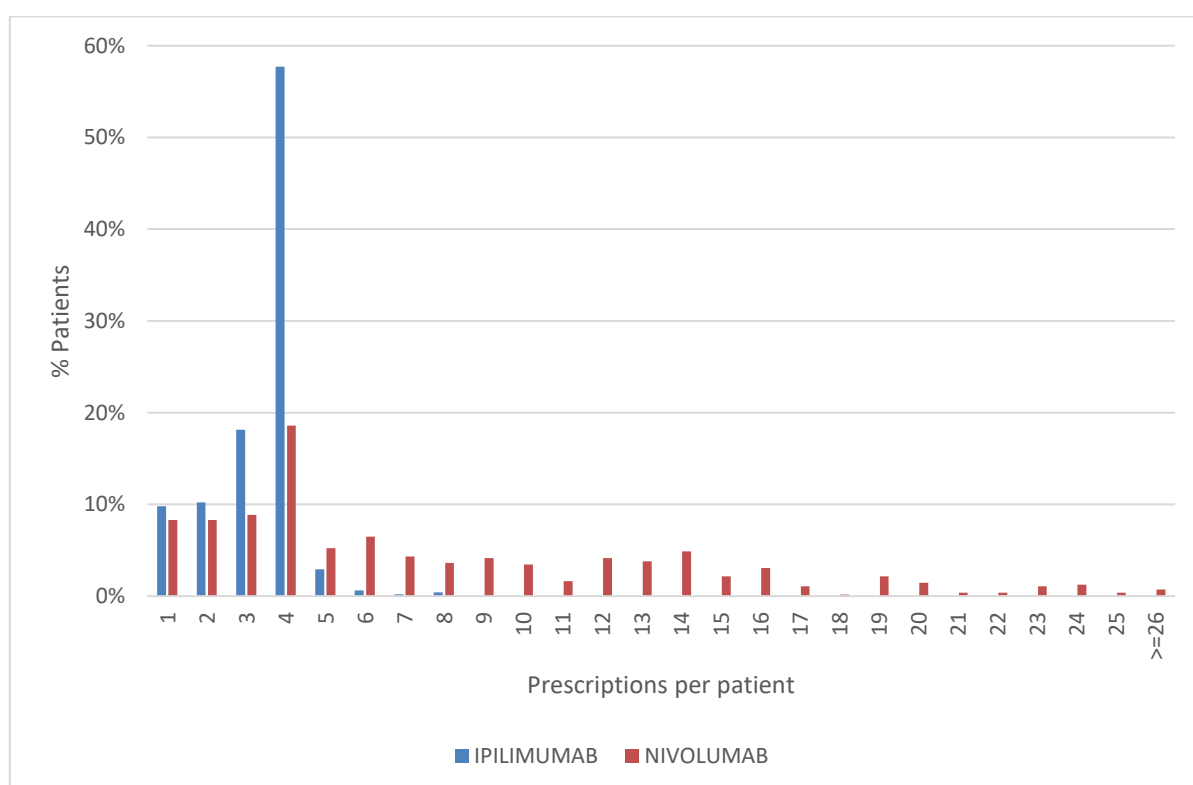


Figure 9: Distribution of prescriptions per patient in 12 months after initiation to each medicine for first-line treatment.

Figure 9 shows the prescriptions per patient in 12 months after initiation to each medicine for first-line treatment for all patients who have at least 12 months follow up in the data (i.e. patients initiating from March 2019 to the end of June 2020). There were 480 ipilimumab initiating patients who had a mean and median of 3.4 and 4 prescriptions respectively. This is close to the expected value of 4 prescriptions for induction treatment. There were 554 nivolumab initiating patients who had a mean and median of 7.8 and 6 prescriptions respectively. This is a lot less than the expected 24 prescriptions, consisting of 4 induction and 20 maintenance. These figures imply that on average there was only $7.8 - 4 = 3.8$ maintenance prescriptions instead of the expected 20. Even allowing for the

introduction of monthly treatment in September 2019 which reduced the number of expected maintenance prescriptions to as low as 10 for patients who started maintenance treatment after September 2019 and took up the monthly treatment option. The relative frequency of the fortnightly and monthly options will be examined in the analysis below.

Dose distribution of first-line nivolumab infusions

The nivolumab restriction for first-line maintenance treatment 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 prior to 1 September 2019, 1 year post (i.e. 1 September 2019 to 31 August 2020) and the remainder (1 September 2020 to 30 June 2021) post this change.

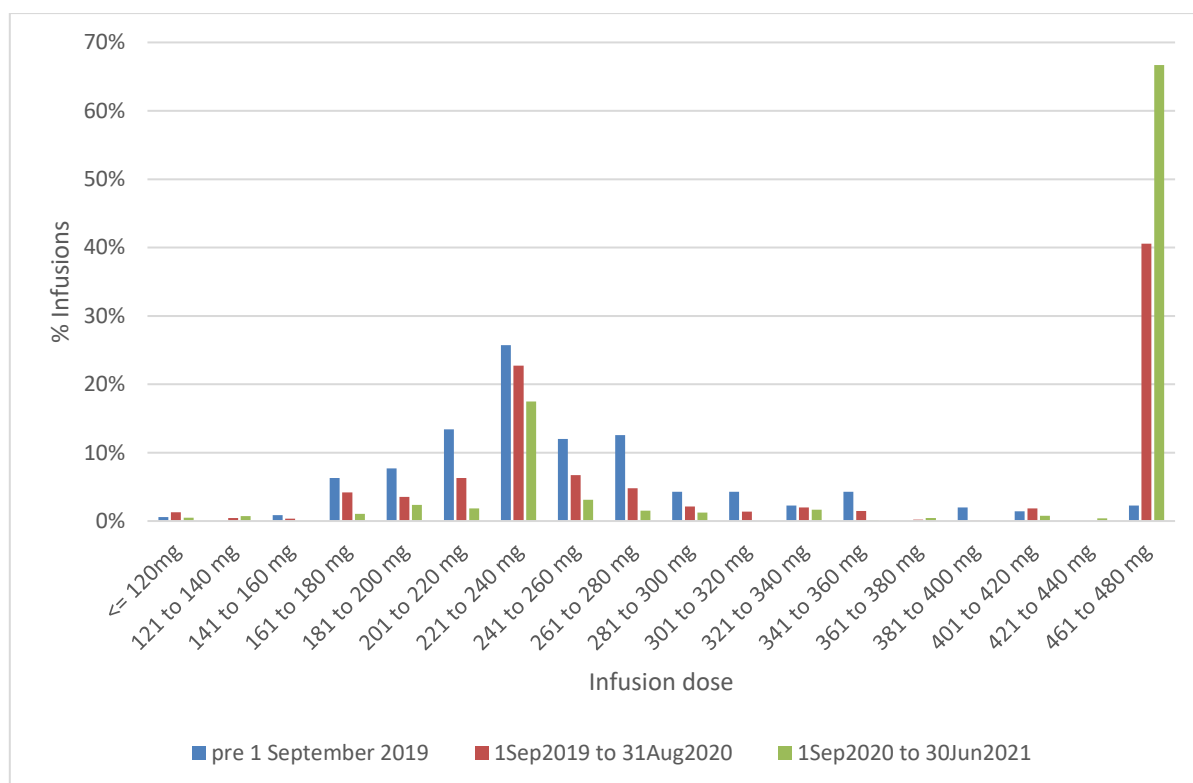


Figure 10: Dose distribution of first-line nivolumab maintenance infusions for pre & post restriction change.

Note: each infusion is supplied on a separate prescription

Figure 10 shows that there was a large shift to the flat 480mg 4 weekly dosing after the restriction change. In the most recent period, approximately 67% of nivolumab maintenance infusions have been 480mg. The doses not 480 mg or in the 221 to 240mg range would be for the weight-based 3 mg/kg every two weeks dosing. Those in the 221 to 240mg range could be for either the weight based dosing or flat 240mg 2 weekly dosing. It should be noted at each 480mg dose covers double the period of treatment of the other doses, so it is more dominant as a percentage of treatment than Figure 10 suggests.

The equivalent dose distribution graphs for induction treatment for both ipilimumab and nivolumab do not show much variation across these periods because the restriction change

did not apply to these items and so these are not presented in this report. The median and mean doses for induction ipilimumab in the most recent period (1 September 2020 to 30 June 2021) were 80 and 83.5mg respectively. The median and mean doses for induction nivolumab in the most recent period (1 September 2020 to 30 June 2021) were 240 and 251mg respectively.

Drug initiation sequence for first-line nivolumab patients

Table 4 shows the drug initiation sequence for all initiators to first-line nivolumab or ipilimumab treatment. This includes all prescriptions indicated for RCC from 1 May 2009 (the listing of sunitinib for RCC) to the end of June 2021. This captures any treatment for RCC before or after first-line nivolumab or ipilimumab treatment.

Table 4: Drug initiation sequences for first-line nivolumab or ipilimumab patients

Drug initiation sequence	Patients	% Patients	Ranking
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd)	183	16.3%	1
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, nivolumab, Maintenance	125	11.1%	2
1st line, nivolumab, Maintenance	91	8.1%	3
1st line, ipilimumab, Induction -> 2nd line, nivolumab(sd)	81	7.2%	4
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 2nd line, nivolumab	67	6.0%	5
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, sunitinib	28	2.5%	6
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, pazopanib	24	2.1%	7
1st line, nivolumab, Induction -> 1st line, ipilimumab, Induction	23	2.0%	8
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, nivolumab, Maintenance -> 2nd line, nivolumab	18	1.6%	9
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, nivolumab, Maintenance -> 1st line, sunitinib	17	1.5%	10
1st line, nivolumab, Induction	15	1.3%	11
1st line, nivolumab, Induction -> 1st line, ipilimumab, Induction -> 1st line, nivolumab, Maintenance	14	1.2%	12
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, nivolumab, Maintenance -> 1st line, pazopanib	13	1.2%	13
1st line, ipilimumab, Induction -> 2nd line, nivolumab(sd) -> 1st line, nivolumab, Maintenance	12	1.1%	14
1st line, nivolumab, Induction -> 1st line, ipilimumab, Induction -> 2nd line, nivolumab	11	1.0%	15
1st line, ipilimumab, Induction -> 2nd line, nivolumab(sd) -> 1st line, sunitinib	10	0.9%	16
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, pazopanib -> 2nd line, cabozantinib	9	0.8%	17
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 2nd line, cabozantinib	8	0.7%	18
1st line, ipilimumab, Induction	8	0.7%	19
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, sunitinib -> 2nd line, cabozantinib	8	0.7%	20
1st line, pazopanib -> 2nd line, nivolumab -> 1st line, nivolumab, Maintenance	7	0.6%	21
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 2nd line, nivolumab -> 1st line, nivolumab, Maintenance	7	0.6%	22
2nd line, nivolumab -> 1st line, ipilimumab, Induction	7	0.6%	23
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, nivolumab, Maintenance -> 2nd line, cabozantinib	6	0.5%	24
1st line, sunitinib -> 1st line, nivolumab, Induction -> 2nd line, nivolumab	<=5	<=0.4%	25
1st line, ipilimumab, Induction -> 1st line, nivolumab, Maintenance(sd)	<=5	<=0.4%	26
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, nivolumab, Maintenance -> 1st line, pazopanib -> 2nd line, cabozantinib	<=5	<=0.4%	27
1st line, sunitinib -> 2nd line, nivolumab -> 1st line, nivolumab, Maintenance	<=5	<=0.4%	28
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 1st line, nivolumab, Maintenance -> 1st line, sunitinib -> 2nd line, cabozantinib	<=5	<=0.4%	29
1st line, ipilimumab, Induction -> 1st line, nivolumab, Induction(sd) -> 2nd line, nivolumab -> 1st line, sunitinib	<=5	<=0.4%	30
Other	303	26.9%	
Total	1,125	100%	

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

Table 4 shows that the most common initiation sequence was first-line nivolumab + ipilimumab both supplied on the same day (16.3%). The 2nd most common was the same as the first and followed by first-line nivolumab maintenance treatment (11.1%). The 3rd most common was first-line nivolumab maintenance treatment only (8.1%). This is outside the restriction, except if this is a grandfathered patient (see Appendix B for the grandfathering restrictions). In this is the case then the grandfathering PBS item should have been used rather than the regular maintenance treatment item. The 4th (7.2%), 5th (6.0%) and 9th (1.6%) most common show the incorrect use of 2nd line nivolumab items rather than the first-line induction and maintenance items.

This use of incorrect PBS item codes would explain some of the less than expected number of actual nivolumab prescriptions per patient (see Table 3 and Figure 9) as these analyses only counted first-line nivolumab prescriptions. To investigate the size of this effect, the distribution of the number of prescriptions in 12 months after initiation was re-calculated with 2nd line nivolumab scripts included for all patients that initiated first-line nivolumab or ipilimumab.

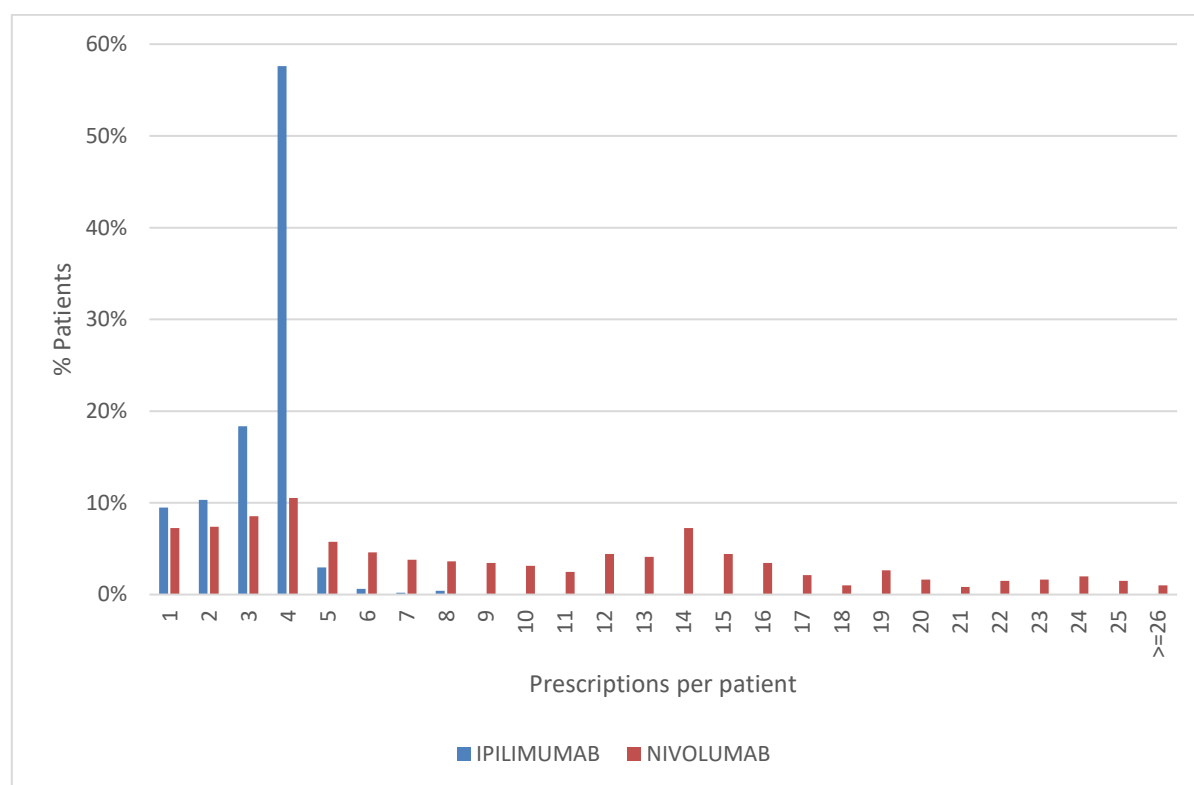


Figure 11: Distribution of prescriptions per patient in 12 months after initiation to each medicine for first-line treatment.

Note: Second-line nivolumab scripts also included

Comparing Figure 11 to Figure 9 shows that the inclusion of the second-line nivolumab scripts has increased the number of nivolumab scripts per patient after initiating first-line therapy. The peaks at 14 and 24 scripts would correspond to patients who are still on treatment at the end of 12 months and are using 4 & 2 weekly dosing respectively for their maintenance treatment. The mean and median number of nivolumab scripts per patient

has increased to 9.6 and 8 respectively (up from 7.8 and 6 when 2nd line nivolumab was not included). It is still difficult to compare these numbers to the predicted 24 nivolumab scripts per patient (see Table 3) because the predicted maintenance scripts were assumed to be 2 weekly dosing, whereas the actuals are a mixture of 2 and 4 weekly dosing. To enable this comparison the prescriptions were converted to treatment time based on allocating 3 weeks to induction treatment prescriptions (both ipilimumab and nivolumab), 4 weeks to nivolumab prescriptions that have a dose of 480 mg and 2 weeks to all other dose nivolumab prescriptions (i.e. both weight based and 240mg flat dose infusions have a frequency of 2 weeks).

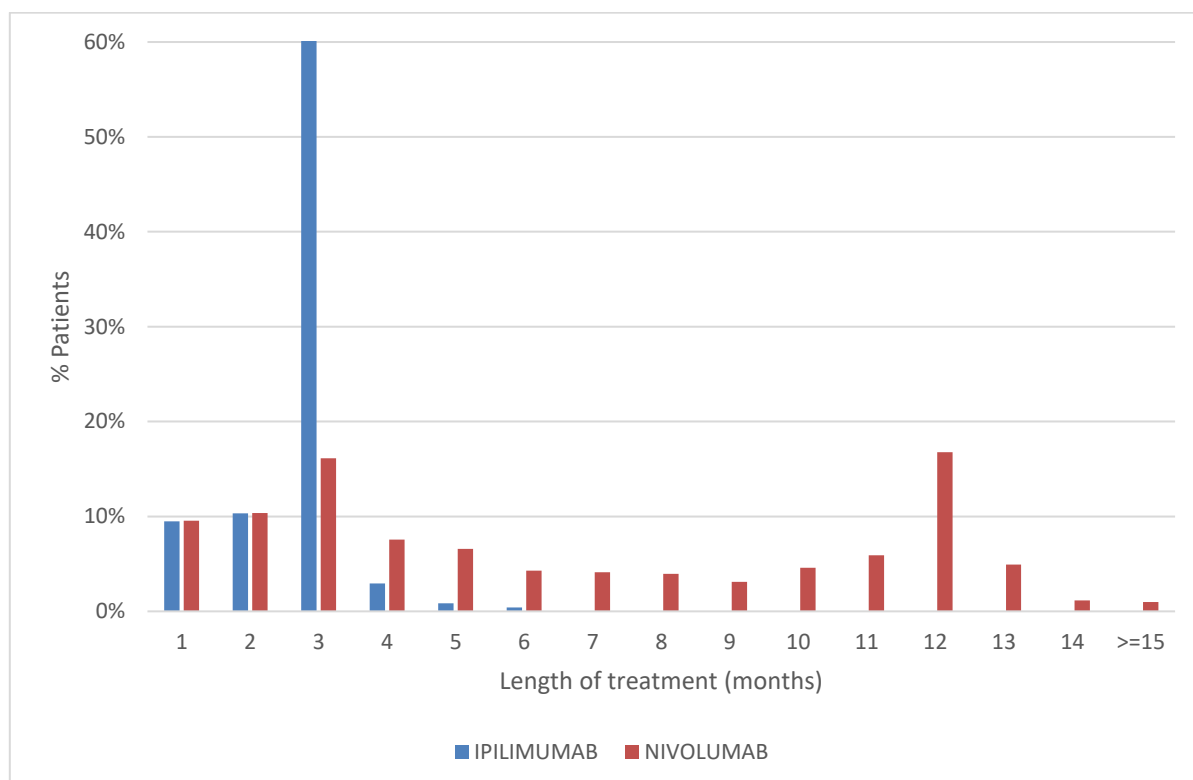


Figure 12: Distribution of treatment time per patient in 12 months after initiation to each medicine for first-line treatment.

Note: 2nd line nivolumab scripts also included

Treatment time in weeks was converted to months and rounded up to the nearest month for Figure 12. The mean and median treatment times were 27 weeks (6.1 months) and 21 weeks (4.8 months). The predicted 24 prescriptions per patient, implied a mean treatment time of 12 months (the 4 induction scripts would take 12 weeks and the 20 maintenance scripts would take 40 weeks, a total of 52 weeks). That is, all patients would still be on treatment 12 months after initiation. Thus the actual mean treatment time for nivolumab (6.1 months) was approximately half of the predicted.

Discussion

Second-line nivolumab is the most common PBS treatment for RCC. In 2021 Q2 there were 1,579 patients receiving PBS treatment for RCC, of these 472 received second-line nivolumab. The second most common treatment is first-line nivolumab, with 312 patients being treated in 2021 Q2.

For ipilimumab, in both Years 1 and 2 after listing there were slightly more patients than predicted. However there were slightly less prescriptions than predicted because the prescriptions per patient were less than predicted. This can be explained by the estimates assuming that all patients will complete the induction phase (i.e. 4 prescriptions). Figure 9 shows that 38% of patients received less than the full course of 4 ipilimumab scripts.

For nivolumab, there were 32% and 67% more patients than expected in Years 1 and 2 respectively. In Year 1 there were more nivolumab patients (442) than ipilimumab patients (395). This can be explained by the results of the drug initiation sequence analysis (Table 4) which shows that over the period from the listing of first-line nivolumab (1 March 2019) to the end of June 2021 there were 91 patients that were supplied only first-line nivolumab (maintenance phase) prescriptions. This pattern of use was outside the PBS restrictions. Some of these may have been grandfathering patients who failed to be allocated the specific PBS item code for such patients. In Year 2 an additional factor that could explain the more than expected number of patients was the presence of continuing patients from Year 1. These had not been factored into the estimates.

For nivolumab, there were 75% and 76% less scripts per patient than expected in Years 1 and 2 respectively. This is mainly due to the overestimation of the average length of treatment in the submissions and final agreed estimates. A second factor is the shift from 2 to 4 weekly dosing after the 1 September 2019 restriction change. A third factor was the incorrect use of PBS item codes where some patients who initiate first-line nivolumab + ipilimumab treatment used second-line nivolumab treatment items for their first-line maintenance treatment (see Table 4).

Actions undertaken by the DUSC Secretariat

The report was provided to the sponsor of nivolumab and ipilimumab.

DUSC consideration

DUSC considered that:

- *The various restriction changes made on 1 September 2019 did not materially impact the utilisation of nivolumab + ipilimumab.*
- *The predicted number of patients in the final agreed estimates turned out to be reasonably accurate.*
- *Actual prescription numbers for nivolumab were less than predicted. This could be explained by a number of factors including:*
 - *A move from fortnightly to monthly dosing (and prescriptions) after this was allowed by a restriction change on 1 September 2019.*
 - *Inaccurate application of PBS item numbers. Further analysis revealed that there was some use of second- line nivolumab treatment items for first-line maintenance treatment and these prescriptions were not counted in the actuals of the predicted versus actual comparison for first-line nivolumab.*
 - *Surviving population not yet mature.*
- *The report should be modified to not say that length of treatment was overestimated.*

DUSC noted the actual prescriptions per patient in Years 1 and 2 after listing are often less than that estimated in submissions and final agreed estimates. This may indicate a need for more guidance on the method(s) of translating from estimated patients treated to estimated prescription utilisation in the PBAC Guidelines and the Utilisation and Cost Model Workbook for PBAC Submissions User Manual.

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.

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References

Please use Vancouver style. A citation style guide is available at http://jppr.shpa.org.au/lib/pdf/reference_citation_guide.pdf.

Appendices

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	Phase*	Item code	Hospital type*	Form & 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	first-line	Induction treatment	11628B	Public	Injection concentrate for I.V. infusion 50 mg in 10 mL
			11644W	Private	Injection concentrate for I.V. infusion 50 mg in 10 mL
		Induction treatment - Grandfather patients	11641Q	Public	Injection concentrate for I.V. infusion 50 mg in 10 mL
			11647B	Private	Injection concentrate for I.V. infusion 50 mg in 10 mL
NIVOLUMAB	first-line	Grandfather patients	11631E	Public	Injection concentrate for I.V. infusion 100 mg in 10 mL
			11635J	Private	Injection concentrate for I.V. infusion 100 mg in 10 mL
		Induction treatment	11627Y	Private	Injection concentrate for I.V. infusion 100 mg in 10 mL
			11636K	Public	Injection concentrate for I.V. infusion 100 mg in 10 mL
		Maintenance treatment	11626X	Private	Injection concentrate for I.V. infusion 100 mg in 10 mL
			11642R	Public	Injection concentrate for I.V. infusion 100 mg in 10 mL
	2nd line		11150W	(blank)	Injection concentrate for I.V. infusion 100 mg in 10 mL
			11157F	(blank)	Injection concentrate for I.V. infusion 100 mg in 10 mL
			11159H	(blank)	Injection concentrate for I.V. infusion 100 mg in 10 mL
			11160J	(blank)	Injection concentrate for I.V. infusion 100 mg in 10 mL

PAZOPANIB	first-line		02029T	(blank)	Tablet 200 mg (as hydrochloride)
			02030W	(blank)	Tablet 400 mg (as hydrochloride)
			02034C	(blank)	Tablet 200 mg (as hydrochloride)
			02035D	(blank)	Tablet 400 mg (as hydrochloride)
			02201W	(blank)	Tablet 400 mg (as hydrochloride)
			02232L	(blank)	Tablet 200 mg (as hydrochloride)
			11252F	(blank)	Tablet 200 mg (as hydrochloride)
			11261Q	(blank)	Tablet 400 mg (as hydrochloride)
SORAFENIB	2nd line		10226F	(blank)	Tablet 200 mg (as tosilate)
			10242C	(blank)	Tablet 200 mg (as tosilate)
SUNITINIB	first-line		09417P	(blank)	Capsule 12.5 mg (as malate)
			09418Q	(blank)	Capsule 25 mg (as malate)
			09419R	(blank)	Capsule 50 mg (as malate)
			09420T	(blank)	Capsule 12.5 mg (as malate)
			09421W	(blank)	Capsule 25 mg (as malate)
			09422X	(blank)	Capsule 50 mg (as malate)
			10459L	(blank)	Capsule 37.5 mg (as malate)
			10504W	(blank)	Capsule 37.5 mg (as malate)

* only populated for first-line nivolumab and ipilimumab

Appendix B: PBS Restrictions for grandfathering items

There were two PBS items for grandfather patients for both nivolumab (11631E – Public Hospital & 11635J – Private Hospital) and ipilimumab (11641Q – Public Hospital & 11647B – Private Hospital) that started on 1 March 2019 and ceased on 30 September 2020. The restriction text for these items was:

Ipilimumab

Stage IV clear cell variant renal cell carcinoma (RCC)

Treatment Phase: Induction treatment - Grandfather patients

Clinical criteria:

- **Patient must have received less than 4 doses of combined therapy with ipilimumab and nivolumab as induction therapy for this condition prior to 1 March 2019, AND**
- The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prior to initiating non-PBS-subsidised induction therapy with nivolumab and ipilimumab, AND
- Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised induction therapy with nivolumab and ipilimumab, AND
- The condition must not have previously been treated prior to initiating non-PBS-subsidised induction therapy with nivolumab and ipilimumab, AND
- The treatment must be in combination with PBS-subsidised-treatment with nivolumab as induction for this condition, AND

- Patient must not have developed disease progression while being treated with combined therapy with ipilimumab and nivolumab as induction for this condition.

A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks. The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

Nivolumab

Stage IV clear cell variant renal cell carcinoma (RCC)

Treatment Phase: Grandfather patients

Clinical criteria:

Patient must have received less than 4 doses of combined therapy with ipilimumab and nivolumab as induction therapy for this condition prior to 1 March 2019; OR

Patient must have received monotherapy with nivolumab as maintenance for this condition prior to 1 March 2019, AND

The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prior to initiating non-PBS-subsidised induction therapy with nivolumab and ipilimumab, AND

Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised induction therapy with nivolumab and ipilimumab, AND

The condition must not have previously been treated prior to initiating non-PBS-subsidised induction therapy with nivolumab and ipilimumab, AND

Patient must not have developed disease progression while being treated with combined therapy with ipilimumab and nivolumab as induction for this condition; OR

Patient must not have developed disease progression while being treated with monotherapy with nivolumab as maintenance for this condition, AND

The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition; OR

The treatment must be as monotherapy as maintenance for this condition.

Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks. Maintenance treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks. A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.