

Ipilimumab and dabrafenib: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2015

Abstract

Purpose

To review the predicted versus actual use of ipilimumab and dabrafenib for unresectable melanoma, as requested by DUSC at its June 2014 meeting. The analysis of ipilimumab is a 24 month review; the analysis of dabrafenib is a 12 month review.

Listing on the Pharmaceutical Benefits Scheme (PBS)

- Ipilimumab, PBS listed 1 August 2013
- Dabrafenib, PBS listed 1 December 2013

Ipilimumab and dabrafenib are listed for unresectable Stage III or Stage IV malignant melanoma. For dabrafenib, the condition must have a BRAF V600 mutation and the patient must have a WHO performance status of 2 or less. The condition must not have been treated previously with PBS subsidised therapy; or the patient must have developed intolerance to another BRAF inhibitor of a severity necessitating permanent treatment withdrawal. For continuing treatment, patients must have stable or responding disease. See the PBS website for the full restriction.

Data Source / methodology

Prescription data were extracted from the Department of Human Services (DHS) prescription database for the period August 2013 to April 2015, inclusive.

Key Findings

- Since listing, 2,484 patients have been treated with dabrafenib or ipilimumab. In 2014:
 - 1,642 patients were dispensed at least one prescription of dabrafenib or ipilimumab;
 - 1,467 of these patients were starting treatment with dabrafenib or ipilimumab for the first time. Of these, 712 patients started treatment with dabrafenib and 755 patients started treatment with ipilimumab.
- The number of new patients initiating dabrafenib and ipilimumab per month is similar.

Purpose of analysis

To review the predicted versus actual use of ipilimumab and dabrafenib for unresectable melanoma, as requested by DUSC at its June 2014 meeting. The analysis of ipilimumab is a 24 month review; the analysis of dabrafenib is a 12 month review.

Background

Pharmacology

Ipilimumab is a protein which helps the immune system attack and destroy cancer cells.¹ Dabrafenib can be used to treat melanomas with a mutation in the BRAF gene.²

Therapeutic Goods Administration (TGA) approved indications

Ipilimumab, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma.³

Dabrafenib as monotherapy is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma. Dabrafenib in combination with trametinib is indicated for the treatment of patients with BRAF V600 mutation positive unresectable Stage III or metastatic (Stage IV) melanoma.⁴

Adverse event warning

Ipilimumab is associated with inflammatory adverse reactions resulting from increased or excessive immune activity (immune-related adverse reactions).

Ipilimumab can cause severe and life-threatening immune-related adverse reactions (irARs), including enterocolitis, intestinal perforation, hepatitis, dermatitis (including toxic epidermal necrolysis), endocrinopathy (which may not be reversible), neuropathy, as well as irARs in other organ systems. Early diagnosis and appropriate management are essential to minimise life-threatening complications.³

¹ Yervoy® (ipilimumab) Australian Consumer Medicine Information. Mulgrave: Bristol-Myers Squibb Australia Pty Ltd. March 2015. Available from <<https://www.ebs.tga.gov.au/>>. Accessed 31 August 2015

² Tafinlar® (dabrafenib) Australian Consumer Medicine Information. Sydney: Novartis Pharmaceuticals Australia Pty Limited. July 2015. Available from <<https://www.ebs.tga.gov.au/>>. Accessed 31 August 2015.

³ Yervoy® (ipilimumab) Australian Approved Product Information. Mulgrave: Bristol-Myers Squibb Australia Pty Ltd. 27 June 2011. Available from <<https://www.ebs.tga.gov.au/>>. Accessed 31 August 2015

⁴ Tafinlar® (dabrafenib) Australian Approved Product Information. Sydney: Novartis Pharmaceuticals Australia Pty Limited. 21 August 2013. Available from <<https://www.ebs.tga.gov.au/>>. Accessed 31 August 2015.

Dosage and administration

Table 1: Dosage and administration of ipilimumab and dabrafenib (abridged)

Brand name and sponsor	Product	Dose and frequency of administration
Yervoy® Bristol-Myers Squibb Australia Pty Ltd	Ipilimumab	<p>The recommended dose of ipilimumab is 3mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses. Where there is any withholding of a dose, ipilimumab should be resumed at a dose of 3mg/kg every 3 weeks until administration of all 4 planned doses or 16 weeks from the first administration, whichever occurs earlier.</p> <p>Additional treatment with ipilimumab (re-induction with 4 doses) may be considered for patients who develop progressive disease after prior complete response or partial response or after stable disease lasting longer than 3 months from the first tumour assessment. The recommended re-induction regimen of ipilimumab is 3 mg/kg administered IV over a 90-minute period every 3 weeks for a total of 4 doses as tolerated, regardless of the appearance of new lesions or growth of existing lesions.</p>
Tafinlar® Novartis Pharmaceuticals Australia Pty Limited	Dabrafenib	<p>Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for dabrafenib monotherapy and in combination with trametinib.</p> <p>The recommended dose of dabrafenib used as monotherapy or in combination with trametinib is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg).</p> <p>Treatment should continue until disease progression or the development of unacceptable toxicity.</p>

Source: Yervoy (ipilimumab) Australian approved product information. Mulgrave: Bristol-Myers Squibb Australia Pty Ltd. Approved 27 June 2011, most recent update 9 April 2015.

Tafinlar (dabrafenib) Australian approved product information. Macquarie Park: Novartis Pharmaceuticals Australia Pty Limited. Approved 21 August 2013, most recent update 10 July 2015.

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

Clinical situation

Melanoma is a type of skin cancer. There are three main types of skin cancer that are named after the cells that are affected: squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and melanoma. Melanoma develops from the melanocytes.⁵

Melanoma is the fourth most common cancer diagnosed in Australia⁶, which along with New Zealand has the world's highest incidence rate for melanoma. In Australia in 2011,

⁵ Cancer Council NSW, Woolloomooloo NSW Australia. Available from <http://www.cancercouncil.com.au/melanoma>.

⁶ Cancer Council Australia, Sydney NSW Australia, available from <http://www.cancer.org.au/about-cancer/types-of-cancer/skin-cancer/melanoma.html>

there were 1,544 deaths due to melanoma. Melanoma is the sixth most common cause of cancer death in Australian men and tenth most common in Australian women.

After diagnosis, the first stage of treatment is surgery. Surgery can be curative for thin melanomas and requires that the melanoma be removed with at least 1–2cm of normal skin around it. If the draining lymph nodes are involved they are removed.

Generally, chemotherapy drugs have not been particularly effective in treating melanoma.⁷ In patients with melanoma, chemotherapy is reserved for the patients with metastatic disease.

For some patients with melanoma immunotherapy may be used.⁸ Immunotherapy is the use of medicines to stimulate a patient's own immune system to recognise and destroy cancer cells more effectively.⁹ One example of immunotherapy for melanoma is ipilimumab. Ipilimumab may decrease the effect of immunosuppressants, and immunosuppressants may affect the activity of ipilimumab. Autoimmune disease may be worsened by ipilimumab. Active disease should be controlled before starting patients on ipilimumab.¹⁰

Targeted treatments such as dabrafenib may be used to treat patients with melanomas that have changes (or mutations) in the *BRAF* gene.

⁷ Melanoma Institute Australia, Wollstonecraft NSW Australia. Available from <http://www.melanoma.org.au/understanding-melanoma/treatment-options/>

⁸ Cancer Council Australia, Sydney NSW Australia. Available from <http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-treating-by-stage>

⁹ Cancer Council Australia, Sydney NSW Australia. Available from <http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-treating-immunotherapy>

¹⁰ Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2015, pp. 589-590.

PBS listing details (as at 1 June 2015)

Table 2: PBS listing of ipilimumab

Item	Name, form & strength, pack size	Max. amount	Rpts	DPMA	Brand name and manufacturer
2638W (private hospitals)	IPILIMUMAB ipilimumab 200 mg/40 mL injection, 1 x 40 mL vial	360 mg	3	\$47,585.30	Yervoy Bristol-Myers Squibb Australia Pty Ltd
	IPILIMUMAB ipilimumab 50 mg/10 mL injection, 1 x 10 mL vial				
2643D (private hospitals, grandfathered patients)	IPILIMUMAB ipilimumab 200 mg/40 mL injection, 1 x 40 mL vial	360 mg	2	\$47,585.30	
	IPILIMUMAB ipilimumab 50 mg/10 mL injection, 1 x 10 mL vial				
2641B (public hospitals)	IPILIMUMAB ipilimumab 200 mg/40 mL injection, 1 x 40 mL vial	360 mg	3	\$47,478.28	
	IPILIMUMAB ipilimumab 50 mg/10 mL injection, 1 x 10 mL vial				
2663E (public hospitals, grandfathered patients)	IPILIMUMAB ipilimumab 200 mg/40 mL injection, 1 x 40 mL vial	360 mg	2	\$47,478.28	
	IPILIMUMAB ipilimumab 50 mg/10 mL injection, 1 x 10 mL vial				

Source: the PBS website. Special Pricing Arrangements apply.

Table 3: PBS listing of dabrafenib

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
10003L	DABRAFENIB dabrafenib 75 mg capsule, 120	120	5	\$8,758.87	Tafinlar Novartis Pharmaceuticals Australia Pty Limited
2846T	DABRAFENIB dabrafenib 75 mg capsule, 120	120	3	\$8,758.87	
2954L	DABRAFENIB dabrafenib 50 mg capsule, 120	120	5	\$5,888.15	
2963Y	DABRAFENIB dabrafenib 50 mg capsule, 120	120	3	\$5,888.15	

Source: the PBS website. Special Pricing Arrangements apply.

Restriction

Ipilimumab and dabrafenib are listed for monotherapy in unresectable Stage III or Stage IV malignant melanoma. For ipilimumab, induction treatment must be as monotherapy and the treatment must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks. For re-induction treatment, the patient must have progressive disease after achieving an initial objective response to the most recent course of ipilimumab induction or re-induction treatment, and the treatment must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks.

For dabrafenib, the condition must have a BRAF V600 mutation and the patient must have a WHO performance status of 2 or less. The condition must not have been treated previously with PBS subsidised therapy; or the patient must have developed intolerance to another BRAF inhibitor of a severity necessitating permanent treatment withdrawal. For continuing treatment, patients must have stable or responding disease.

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

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

- Ipilimumab, PBS listed 1 August 2013
- Dabrafenib, PBS listed 1 December 2013
- Trametinib, PBS listed 1 August 2015 – not included in predicted versus actual review

Changes to listing

The listings of ipilimumab for Private Hospital or Private Clinic use was changed from an Authority Required to an Authority Required (STREAMLINED) listing on 1 February 2015.

Current PBS listing details are available from the PBS website.

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

Ipilimumab

Ipilimumab was recommended by the PBAC at its November 2012 meeting. The PBAC recommended ipilimumab for monotherapy in a patient with unresectable Stage III or Stage IV malignant melanoma in the context of high-clinical need and no effective therapies available. The PBAC acknowledged the high clinical need for effective drugs to treat malignant melanoma.

The likely number of patients per year was estimated in the submission to be significantly less than 10,000 in Year 5. The submission's estimated net cost per year to the Government was in the range of \$60 - \$100 million in Year 5.

The PBAC recommended the implementation of a mechanism to verify the anticipated overall survival benefits of ipilimumab in real world clinical practice in Australia and the

negotiation of a suitable risk share agreement with significant rebates in order to manage the risks to Commonwealth financial expenditure in terms of number of patients and dose.

For further details refer to the Public Summary Document from the November 2012 PBAC meeting.

Dabrafenib

Dabrafenib was recommended by the PBAC at its July 2013 meeting.

The PBAC noted that it is difficult to estimate the population size before the relevant data are collected on the prevalence of the BRAF mutation sub-types in the Australian population.

The PBAC noted that there may be some cost offsets for the use of ipilimumab if 30 – 40 % of patients with melanoma are treated with a BRAF inhibitor as first line treatment.

For further details refer to the Public Summary Document from the July 2013 PBAC meeting.

Approach taken to estimate utilisation

Ipilimumab

The ipilimumab submission used an epidemiological approach from mortality of melanoma to estimate utilisation. To estimate the number of patients in Australia with advanced (Stage IIIc and IV) melanoma the sponsor applied 12 month survival data from more than 2,000 patients with advanced melanoma (Korn et al 2008) to AIHW 2007 melanoma mortality data. The sponsor then estimated the proportion of BRAF positive patients to be 48% (Long et al 2011).

Dabrafenib

The dabrafenib submission used an epidemiological approach, and took Australian incidence and mortality rates of melanoma from the Australian Cancer Incidence and Mortality Workbook from the Australian Institute of Health and Welfare (AIHW 2011).

Final agreed estimates

The final agreed estimates between the Department and the sponsors used the age standardised incidence and mortality of melanoma from the AIHW to predicted Australian population from ABS data. After estimating the proportion of patients with stage III and IV unresectable disease, estimates predicted the number of eligible patients to be between 2,000 and 3,000 per year.

The estimated proportion of BRAF mutation positive patients was 45.80%.¹¹

Dabrafenib ██████ of (BRAF positive) patients would have a WHO performance status of 2 or less, and ██████ of those patients would commence dabrafenib. Of the patients treated, it was assumed ██████% would be compliant and the average treatment duration would be ██████ months, using one pack of dabrafenib per month.

The ipilimumab agreed estimates assumed 89.4% of eligible patients would receive first line treatment, and 34% of those patients would be treated with ipilimumab. The proportion of patients who would receive second line treatment was 77%, and 27% of those would receive ipilimumab. The ipilimumab estimates assumed induction patients would receive an average of 3.4 doses, that 6.6% would continue to reinduction treatment, and that these patients would receive an average of 4 doses of ipilimumab.

Previous reviews by the DUSC

The utilisation of dabrafenib and ipilimumab has not been previously reviewed by DUSC. The most recent review by DUSC of a drug to treat metastatic malignant melanoma was fotemustine in September 2006.

Methods

Prescription data were extracted from the Department of Human Services (DHS) prescription database for the supply period August 2013 to April 2015, inclusive. This database contains data on PBS prescriptions submitted to DHS for payment of a PBS/RPBS (R/PBS) subsidy by the Government.

All data were extracted based on the date of supply to the patient. The data differs from that available from the DHS (Medicare) PBS statistics website which is based on the date of processing and is only for subsidised R/PBS prescriptions (under patient co-payment not included).¹²

An analysis of the number of incident and prevalent patients was undertaken using the DHS prescription data. Patient counts were based on de-identified unique patient identification numbers (PINs) from the prescription data. Initiations were identified as the first supply of either dabrafenib or ipilimumab. Where analyses are by drug, a patient who initiates both drugs is counted once for each drug. Patients were identified as being on treatment (prevalent) if they had received at least one dispensing of ipilimumab or dabrafenib in the specified period.

Analyses were undertaken in SAS.

¹¹ MSAC Consideration of Testing for BRAF mutation in patients with advanced melanoma for access to vemurafenib available from [http://www.msac.gov.au/internet/msac/publishing.nsf/Content/284249A4E03C3431CA2578E10017643B/\\$File/PSD%20172%20BRAF%20for%20vemurafenib.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/284249A4E03C3431CA2578E10017643B/$File/PSD%20172%20BRAF%20for%20vemurafenib.pdf), page 10

¹² PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

Results

Analysis of drug utilisation

Overall utilisation

Prescription volume patterns for medicines used to treat melanoma are likely to be driven by the PBS listing dates, access to treatments outside of the PBS, and the difference in the dosage, administration and treatment duration of the medicines. Dabrafenib is taken orally twice daily until disease progression or the development of unacceptable toxicity. Ipilimumab is administered as a course of treatment. The initial course of treatment is referred to as induction, then subsequent treatment is referred to as reinduction. Each course of ipilimumab includes four doses which are administered every three weeks.

Figure 1 shows the monthly number of prescriptions supplied for ipilimumab and dabrafenib.

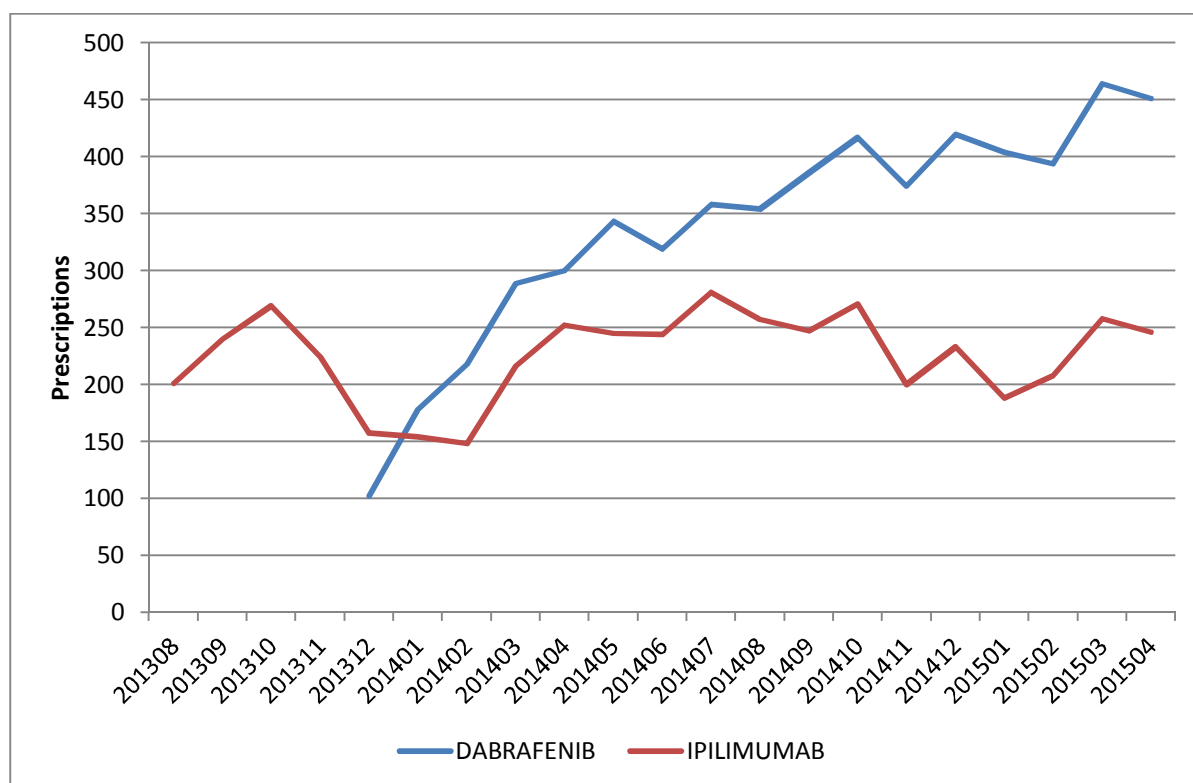


Figure 1: Prescriptions supplied by month for dabrafenib and ipilimumab

The number of prescriptions of ipilimumab increased rapidly the first three months of listing (August to October 2013). The subsequent decline (November 2013 to February 2014) is likely due to patients completing the induction phase of ipilimumab and also due to the availability of dabrafenib through the PBS from 1 December 2013. The subsequent increase and then plateauing of ipilimumab prescriptions (February to April 2014) could be due to patients who received ipilimumab induction moving to reinduction therapy.

However, an analysis of patients who received ipilimumab induction therapy through the PBS shows only 36 patients have received treatment for reinduction (less than 3%). To protect privacy, patient level analyses for reinduction patients have been suppressed in this report, however the treatment these patients received has been included in the overall use of ipilimumab (see Table 4). Due to the small numbers of patients continuing to reinduction treatment, this has negligible effect on the overall treatment patterns. A further reason for the increase in ipilimumab utilisation in early 2014 could be BRAF patients who have received first line dabrafenib (PBS or non-PBS) and have experienced disease progression moving to ipilimumab.

PBS prescription numbers may not represent all treatment of metastatic melanoma in Australia, due to patients being treated with other medicines for melanoma through access programs or clinical trials. For example, there were clinical trials for pembrolizumab and nivolumab during 2013 and 2014, and there were patient access programs for pembrolizumab, trametinib and nivolumab. The patient access programs for pembrolizumab and trametinib finished when these drugs were listed on the PBS in 2015, however the patient access program for nivolumab was still current at the time of reporting.

Analysis of the numbers of patients treated and pathways through treatment provided in the following section shed further light on use of melanoma medicines through the PBS.

Figure 2 below shows the number of patients initiating dabrafenib or ipilimumab, including patients initiating PBS therapy and first time switches.

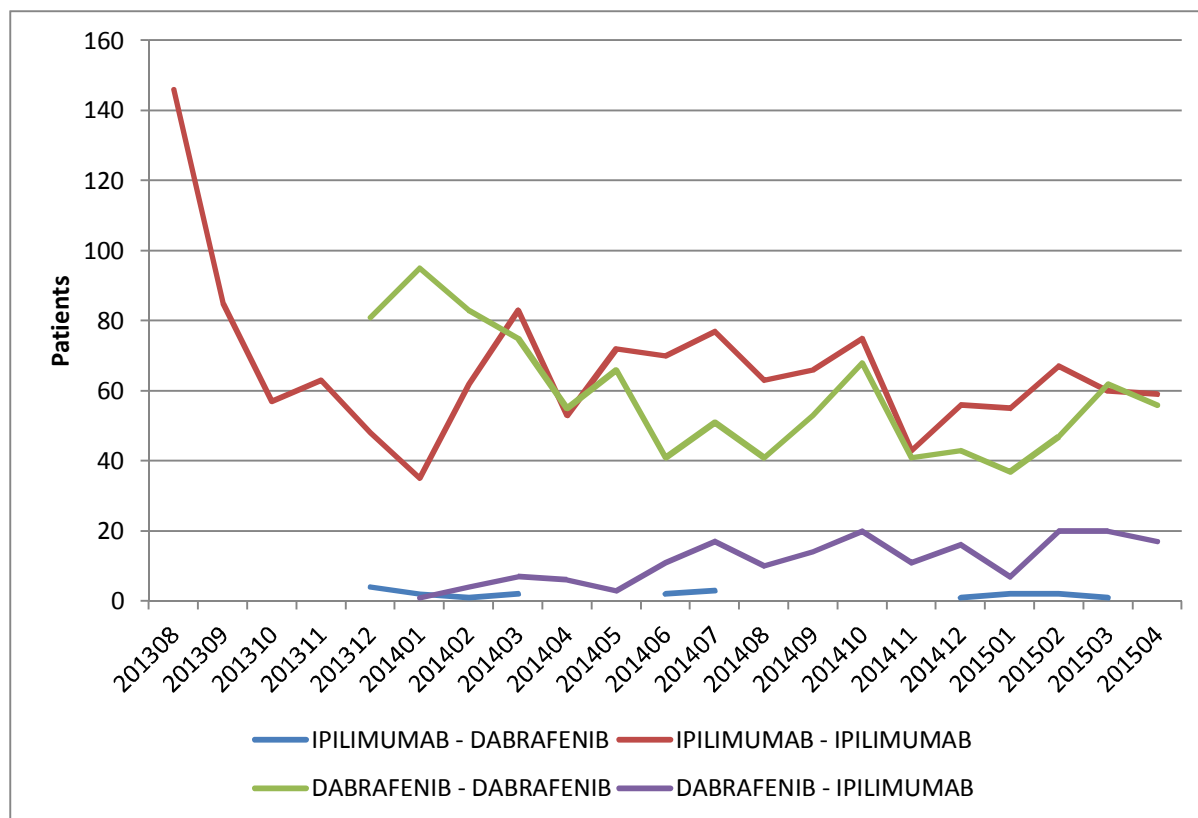


Figure 2: Patients initiating dabrafenib and ipilimumab showing initiation drug, by month

Dabrafenib – Dabrafenib: Patients initiating dabrafenib as their first PBS treatment

Ipilimumab – Ipilimumab: Patients initiating ipilimumab as their first PBS treatment

Dabrafenib – Ipilimumab: Patients who initiated therapy on dabrafenib who are now initiating ipilimumab

Ipilimumab – Dabrafenib: Patients who initiated therapy on ipilimumab who are now initiating dabrafenib

The high number of patients initiating ipilimumab in August 2013 represents accumulated demand for melanoma treatment and movement of patients accessing ipilimumab through the access program or privately to PBS therapy. Similarly, when dabrafenib was listed four months later a high number of patients initiated PBS dabrafenib. The vast majority of dabrafenib use in the first few months was as a first-line PBS therapy, although patients may have received treatment outside of the PBS.

Over time there appears to be a growing number of patients accessing ipilimumab after dabrafenib which may be expected as patients who have the BRAF V600 mutation are more likely to use dabrafenib as first line treatment. The number of patients accessing dabrafenib after initiating therapy with ipilimumab is very low and often zero per month. The low overall number of patients receiving a second line of PBS therapy could be because patients have died, are unsuitable for or choose not to receive further PBS treatment, or are enrolled in clinical trials or access programs.

The number of patients initiating first line PBS therapy with either dabrafenib or ipilimumab are now comparable. This is consistent with the anticipated proportion of patients who are BRAF positive (about 50%) and use of a targeted therapy as first line therapy in this group.

Due to the different regimens of the two medicines, it is difficult to compare the number of prevalent patients considered to be on treatment at any one time. Patients who have finished ipilimumab induction therapy and who have stable disease will not appear in the data until they undergo reinduction.

Patient level analysis

Table 4 below summarises the initiating and treated patients for dabrafenib and ipilimumab by month, and notes the mean and median number of prescriptions that each monthly initiating group had.

For ipilimumab, the mean and median number of prescriptions per patient is between 3 and 4. The data on the number of ipilimumab prescriptions includes both induction and reinduction for all patients (including those grandfathered onto the PBS). As previously mentioned, reinduction data is not presented separately in Table 4 to protect privacy as very few patients undergo reinduction therapy. The data (not shown) indicate that for patients who initiated on an induction code and received reinduction treatment, the mean number of reinduction treatments was 2.47 and the median number was 2.

Dabrafenib patients who initiated dabrafenib between December 2013 and April 2014 have at least 12 months follow-up time to consider the number of prescriptions per patient. The mean and median number of prescriptions per patient initiating dabrafenib in this period is between 6 and 8.

The overall number of patients treated with either dabrafenib or ipilimumab each month appears to have stabilised at between 500 to 600 per month.

Table 4: Number of patients initiated and treated each month with dabrafenib and ipilimumab

Month of supply	Patients dispensed a prescription	Patients initiating ipilimumab or dabrafenib for the first time	Ipilimumab				Dabrafenib			
			Number of new patients in the month	Max follow-up (months)	Number of prescriptions (to max available follow-up)		Number of new patients in the month	Max follow-up (months)	Number of prescriptions (to max available follow-up)	
					Mean	Median			Mean	Median
Aug-13	146	146	146	20	3.30	4				
Sep-13	188	85	85	19	3.51	4				
Oct-13	205	57	57	18	3.23	3				
Nov-13	167	63	63	17	3.10	4				
Dec-13	213	129	48	16	3.33	4	85	16	8.44	8
Jan-14	266	130	36	15	2.89	3	97	15	7.45	6
Feb-14	327	145	66	14	3.18	4	84	14	7.44	7
Mar-14	423	158	90	13	3.32	4	77	13	6.45	6
Apr-14	454	108	59	12	3.36	4	55	12	6.58	5
May-14	490	138	75	11	3.49	4	66	11	6.91	8
Jun-14	499	111	81	10	3.04	3	43	10	6.42	6
Jul-14	536	128	94	9	3.28	4	54	9	6.07	6
Aug-14	522	104	73	8	2.93	3	41	8	6.10	7
Sep-14	538	119	80	7	2.99	3	53	7	5.60	6
Oct-14	558	143	95	6	3.00	3	69	6	5.29	6
Nov-14	515	84	54	5	2.91	3	41	5	5.27	6
Dec-14	533	99	72	4	2.81	3	44	4	4.34	5
Jan-15	522	92	62	3	2.77	3	39	3	3.28	3
Feb-15	535	114	87	2	2.75	3	49	2	2.76	3
Mar-15	599	122	80	1	2.33	2	63	1	1.87	2
Apr-15	584	116	76	0	1.20	1	57	0	1.19	1

Analysis of expenditure

As both ipilimumab and dabrafenib have special pricing arrangements, the expenditure on these drugs available in the public domain does not reflect the actual cost to Government.

Analysis of actual versus predicted utilisation

Ipilimumab

Table 5: Ipilimumab predicted versus actual

	Year 1 (Aug 2013 to July 2014)			Year 2 (Aug 2014 to July 2015)		
	Predicted	Actual	% of predicted	Predicted	Actual	% of predicted
Patients	817	900	+10%	857	731*	-15%
Doses	3,063	2,631	-14%	3,217	2,108*	-34%
Doses / patient	3.75	2.92	-22%	3.75	2.88*	-23%

* 9 months data available, August 2014 to April 2015

The number of predicted patients in Table 5 above is from the ipilimumab submission. The predicted patient numbers in the final agreed estimates were higher than the submission; 1,433 patients in year 1 and 1,492 in year 2. However, these estimates were agreed before dabrafenib was recommended. The total number of patients who initiated either ipilimumab or dabrafenib in the first year of ipilimumab being PBS listed was 1,398.

The mean and median number of actual doses dispensed is less than the predicted number of doses. For many of the initiating groups of patient by initiation month (Table 4) the median is 4 and the mean is between 3 and 3.5. This suggests that although the most common number of doses is 4, some patients are receiving 1 or 2 doses. Reinduction patients are included in these calculations of mean and median doses. However, as there is a very small number reinduction patients, and the mean and median number of reinduction treatments was 2.47 and 2 respectively, the overall median number of treatments has not increased above 4 doses.

The submission predicted 6.6% of induction patients would continue to reinduction. The actual number is less than half of this.

Dabrafenib

Table 6: Dabrafenib predicted versus actual

	Year 1 (Dec 2013 to Nov 2014)		
	Predicted	Actual	% of predicted
Patients	████	765	████
Prescriptions	████	3,638	████
Prescriptions / patient	████	4.76	████

The comparison of predicted and actual use of dabrafenib shows the number of treated patients was an accurate estimate. Table 4 on page 13 suggested the number of prescriptions patients are receiving is approximately 6 to 8, which is lower than estimated based on data available to date. One reason for the difference could be that the submission did not apply a half year correction to the estimate of prescriptions. If this is the reason, it is possible the number of prescriptions will be closer to the predicted number in year 2 as it will include patients who initiated in the first year of listing.

Discussion

Between August 2013 and April 2015, 2,484 patients have been treated with dabrafenib or ipilimumab. In 2014 1,642 patients were dispensed at least one prescription of dabrafenib or ipilimumab; 1,467 of these patients were starting treatment with dabrafenib or ipilimumab for the first time. Of these, 712 patients started treatment with dabrafenib and 755 patients started treatment with ipilimumab.

The number of patients treated with PBS listed melanoma therapies has been similar to the predicted at the time of listing. This should be interpreted in the context that PBS medicine use may not reflect the total number of melanoma patients in Australia, due to some patients being treated with new therapies as part of clinical trials or patient access programs.

The PBS data suggest that the duration of treatment for both ipilimumab and dabrafenib may be shorter than expected. However, for dabrafenib, a longer period of data is required to assess the median duration of treatment. In the case of ipilimumab, the number of doses used, and the extent of reinduction therapy, has been lower than expected. The availability of new therapies may be one factor contributing to this trend. In addition, adverse events associated with ipilimumab may be contributed to lower use of reinduction therapy. At its July 2015 meeting, the PBAC considered correspondence from the South Australian Medicines Evaluation Panel (SAMEP). This correspondence contained South Australian data on the incidence and the costs of treating adverse events associated with ipilimumab treatment since it was listed on the PBS, specifically with regard to the treatment of steroid-refractory ipilimumab-induced colitis. The ratified minutes of the PBAC consideration were provided to DUSC.

DUSC consideration

DUSC noted the use of ipilimumab decreased after the first two months of it being listed on the PBS. DUSC commented this was expected due to the recommended dosing regimen and grandfathered patients completing a course of induction treatment. DUSC also considered that the decline in use may reflect patients ceasing treatment due to adverse events associated with ipilimumab or disease progression. DUSC noted that use of ipilimumab subsequently increased in early 2014. This increase was not accounted for by patients receiving reinduction treatment as the analysis shows the proportion of ipilimumab patients continuing to reinduction therapy is very low. Another reason for the increase may be patients moving from dabrafenib to ipilimumab. Figure 2 shows that only a few patients initiated ipilimumab after PBS subsidised dabrafenib during this time. A likely explanation for the increase in ipilimumab use in early 2014 may be patients moving from targeted therapies provided through clinical trials or access programs to second line ipilimumab through the PBS. The sponsor of dabrafenib suggested that the increase in the number of patients switching from dabrafenib to ipilimumab in early 2014 may be due to the use of targeted therapies such as dabrafenib to elicit a very rapid response in patients (leading to tumour shrinkage), prior to commencement of a slower acting immunotherapy (such as ipilimumab).

DUSC noted the number of patients receiving dabrafenib after ipilimumab is extremely low, and considered that the Authority Required PBS restriction for dabrafenib appears to be limiting use in this group. The sponsor of ipilimumab also considered that the PBS restriction prevents use of BRAFs in the second line setting but based on clinician feedback provided to the sponsor suggested a need to review the PBS listing for the BRAF inhibitors. DUSC recalled that at the March 2015 meeting the PBAC recommended that pembrolizumab should follow progression with appropriate dabrafenib therapy (combined with trametinib after trametinib is listed). This is because a comparison across the available trials suggested greater response rates and prolonged median progression-free survival for these cheaper targeted therapies over the immune therapies. The PBAC was informed at the hearing for pembrolizumab that ongoing trials are comparing different sequence options and that this positioning will be reviewed once these trials are completed.

DUSC noted the number of patients treated with dabrafenib was consistent with the estimated number of patients. However, the overall use of dabrafenib was lower than expected due to patients having shorter durations of therapy than predicted. DUSC noted the comments from the sponsor of dabrafenib which suggested the duration of therapy was lower than expected because:

- the data includes grandfathered patients who received treatment outside of the PBS,
- that patients are likely to be treated with dabrafenib initially to reduce tumour size, and then moved to a slower acting immunotherapy, and
- that the PBS listing of trametinib which occurred 1 August 2015, for use in combination with dabrafenib, is likely to narrow the gap between the expected and actual duration of therapy.

The DUSC requested that a copy of the ratified minutes of the PBAC's consideration of the South Australian Medicines Evaluation Panel report on ipilimumab be circulated to members. This report predominantly considered the rates and costs of ipilimumab-induced colitis. DUSC noted that there have also been reports of hypophysitis in patients treated with ipilimumab.¹³

DUSC noted that the treatment algorithm and evidence base for melanoma is evolving rapidly and it is important to consider utilisation in this context. Overall, DUSC considered that utilisation seems to be moving in accord with best practice guidelines and PBS restrictions. DUSC considered that another analysis should be undertaken 12-24 months after PD-1 inhibitor availability. DUSC considered that switching and cycling analyses will be important in future utilisation estimates.

DUSC actions

The DUSC requested that the report be provided to the PBAC.

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
No comment provided.
- Novartis Pharmaceuticals Australia Pty Limited
No comment provided.

¹³Lam et al. Ipilimumab-induced hypophysitis in melanoma patients: an Australian case series. Internal Medicine Journal Volume 45, Issue 10, pages 1066–1073, October 2015

Disclaimer

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

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

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