PHARMAC
Pharmaceutical Management Agency

10 June 2016

Decision to fund nivolumab (Opdivo) for advanced melanoma

PHARMAC is pleased to announce the approval of an agreement with Bristol-Myers Squibb for the funding of nivolumab (Opdivo) for patients with advanced melanoma. This was the subject of a consultation letter dated 4 May 2016, available on PHARMAC's website.

In summary, the effect of the decision is that:

- Nivolumab (Opdivo) will be fully funded from 1 July 2016 in DHB hospitals for the treatment of patients with unresectable or metastatic (advanced) melanoma, subject to certain clinical criteria being met.

Having considered consultation feedback, we have made some changes to the proposed access criteria to:

- remove the requirement for nivolumab to be administered as monotherapy; and
- allow patients who have had a period of time off treatment, without disease progression, to recommence treatment.

We note that a number of other issues related to the proposed access criteria were raised during consultation. Please see the consultation feedback section for more information regarding these.

Details of the decision

- Nivolumab (Opdivo) will be listed in Section B and Part II of Section H of the Pharmaceutical Schedule from 1 July 2016 at the following prices and subsidies (ex-manufacturer, excluding GST):

Presentation	Pack size	Price and subsidy
Inj 10 mg per ml, 4 ml	1	$1,051.98
Inj 10 mg per ml, 10 ml	1	$2,629.96
Inj 1 mg for ECP	1 mg	$27.62

- A confidential rebate will apply to Opdivo which will reduce its net price to the Funder.
- Nivolumab will be listed as a Pharmaceutical Cancer Treatment only (PCT only – Specialist), meaning that only DHB hospitals will be able to claim for its use.
- Nivolumab will be listed subject to the following restrictions and Special Authority criteria:

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Nivolumab– PCT only - Specialist
Special Authority for Subsidy

Initial Application — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1 Patient has metastatic or unresectable melanoma stage III or IV; and
2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and
3 Nivolumab is to be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles); and
4 Baseline measurement of overall tumour burden is documented (see Note); and
5 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of nivolumab will not be continued beyond 12 weeks if their disease progresses during this time.

Renewal application — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1 Any of the following:
  1.1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
  1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
  1.3 Patient has stable disease according to RECIST criteria (see Note); and
2 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3 No evidence of progressive disease (PD) according to RECIST criteria (see Note); and
4 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5 Nivolumab will be used at a maximum dose of 3 mg/kg every 2 weeks for a maximum of 12 weeks (6 cycles).

Notes:
Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements. Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

Consultation feedback indicated that there are a number of people who are currently receiving a PD1 inhibitor (eg nivolumab or pembrolizumab) who may wish to receive treatment with funded nivolumab from 1 July.

For this to happen a Special Authority waiver will need to be approved by PHARMAC for the patient to be initiated on funded nivolumab. Please see PHARMAC's website which explains how a clinician can apply for a Special Authority waiver.

In order to gain an approval, the applicant would need to demonstrate that the initial Special Authority criteria were met before the patient was initiated on treatment and that any relevant renewal criteria are met.

Feedback received

We appreciate all of the feedback that we received and acknowledge the time people took to respond. All consultation responses received by 26 May 2016 were considered in their entirety in making a decision on the proposed changes. Most responses were supportive of the proposal, and the following issues were raised in relation to specific aspects of the proposal:

Theme	Comment
Several responders noted the importance of funded access to nivolumab for patients who are currently receiving treatment with a PD1 inhibitor or who are receiving (or have previously received) other targeted melanoma treatments.	The Special Authority criteria do not exclude patients who have received prior treatment with PD1 inhibitors or other melanoma treatments. See information above regarding the application process for Special Authority waivers.
One responder considered that access criteria should exclude patients whose disease has progressed on pembrolizumab.	The Special Authority criteria do not exclude patients whose disease has progressed on or after treatment with pembrolizumab or other melanoma treatments; however, the initial Special Authority criteria must be met in order for a patient to commence on funded nivolumab treatment.
Several responders requested clarification on the impacts of the proposal for melanoma patients receiving ACC funded pembrolizumab treatment or claiming compensation from ACC.	As explained above, if such patients wanted to change to PHARMAC funded nivolumab, a Special Authority waiver approval would be required.
One responder considered that combined therapy with privately-funded ipilimumab should not be excluded.	The criteria have been amended to allow for combined therapy.
Several responders requested consideration is given to funding for targeted melanoma treatments such as BRAF and MEK inhibitors.	PHARMAC has received funding applications for BRAF and MEK inhibitor treatments which are under assessment.
One responder considered that the criteria should be amended to allow for interruption in treatment for unrelated reasons including intercurrent illness or travel and for patients on long-term treatment for reasons other than toxicity or progression, and continuation of therapy for patients with oligometastatic CNS disease without systemic progression.	The criteria been amended to allow for patients who have had a period of time off treatment, but no disease progression, to recommence treatment.

Theme	Comment
A number of other issues and requests to amend the Special Authority criteria were raised by responders, including: • to incorporate patients where nivolumab is clinically appropriate but who have no radiologically measurable lesions. • to allow for pseudoprogression; that is, to allow additional treatment time to confirm tumour response in patients who have derived clinical benefit after the first 12 weeks of treatment but who have an equivocal or uncertain tumour response. • concerns regarding the impact of 3-monthly CT or MRI requirements for renewal criteria which may not be appropriate for long-term patients. • concerns that patients with rapidly progressive disease, who are unlikely to benefit from nivolumab treatment are not excluded. • queries around the maximum duration of funded treatment (ie should there be a maximum and what should that be?).	We will be taking further advice from the Cancer Treatments Subcommittee of PTAC on these issues in September 2016. Relevant consultation responses will be provided to the Subcommittee. We note that PHARMAC regularly reviews all its Special Authority criteria and restrictions; this will be the case for the nivolumab listing.
Several responders raised concerns regarding cost and resource implications for DHBs associated with compounding, administration and monitoring of patients receiving nivolumab and the ability for DHB clinical services to deliver the additional services (oncology day-stay and outpatient facilities; specialist medical, nursing, pharmacy, and radiology staff) required within the current funding environment and timeframe.	PHARMAC assessments and economic analysis take into account costs to the health system including costs associated with compounding, administration and monitoring; however we acknowledge that the decision, like many other medicines funding decisions we make, will have financial and resourcing impacts on DHBs over and above the pharmaceutical costs which are funded by PHARMAC.

More information

If you have any questions about this decision, you can email us at enquiry@pharmac.govt.nz.