NEW DRUGS

New drugs

Nivolumab

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Approved indications: melanoma, non-small cell lung cancer

Opdivo (Bristol-Myers Squibb)
vials containing 10 mg/mL as concentrate
Australian Medicines Handbook section 14.2

The immune system contains checkpoints which attenuate the immune response to prevent damage to normal cells. However, the checkpoint pathways may limit the immune response to cancer cells. One of the receptors involved in this immunosuppression is programmed death 1 (PD-1). Ligands of PD-1 produced by certain cancers bind to the PD-1 receptor on T-lymphocytes, inhibiting the ability of the T cells to attack the tumour cells.

Nivolumab is a monoclonal antibody which binds to the PD-1 receptor. This stops the ligands binding to the receptor. By blocking their inhibitory effects on T cells, nivolumab should enhance the immune response to tumours. An initial study in a small number of patients reported tumour responses in colorectal cancer, renal cell carcinoma, non-small cell lung cancer and melanoma.[1]

Melanoma

Existing targeted therapies for advanced malignant melanoma include the BRAF and MEK inhibitors for patients with the BRAF mutation, and the CTLA-4 immune checkpoint inhibitor ipilimumab.[2] There have now been several trials of nivolumab in stage III and IV melanoma.

Monotherapy

In a trial of patients without a BRAF mutation 210 were randomised to receive infusions of nivolumab every two weeks and 208 were randomised to receive infusions of the alkylating agent dacarbazine every three weeks. If tolerated, the treatment continued until the cancer progressed. The median progression-free survival was 5.1 months with nivolumab and 2.2 months with dacarbazine. At one year, the overall survival rate was 72.9% for nivolumab and 42.1% for dacarbazine.[3]

An open-label trial studied monotherapy in patients with advanced melanoma which had progressed despite treatment with ipilimumab. While 272 patients were randomly allocated to infusions of nivolumab, the treating clinicians chose a chemotherapy regimen, such as dacarbazine, for a further 133 patients. An interim analysis of the first 120 patients given nivolumab, with a minimum follow-up of six months, found a greater radiological response. There was a response in 38 (31.7%) of these patients compared with a response in 5 (10.6%) of 47 patients given chemotherapy. Responses were seen in patients with or without the BRAF mutation.[4]

Combination therapy

As nivolumab and ipilimumab have different sites of action they have been studied as a combination treatment for melanoma. One trial randomised 316 patients to nivolumab, 315 to ipilimumab and 314 to both drugs. They were treated until the disease progressed or toxicity became unacceptable. The median progression-free survival was 6.9 months with nivolumab, 2.9 months with ipilimumab and 11.5 months with the combination.[5]

Another trial compared the response rates of the combination to ipilimumab alone in patients whose BRAF mutation status was known. After a minimum follow-up of 11 months, in patients with wild-type tumours, there was a median decrease of 68.1% in tumour volume in the combination group compared with a 5.5% increase in the ipilimumab group. Irrespective of mutation status there was a complete response in 21 (22%) of the 95 patients treated with the combination. None of the 47 patients treated with ipilimumab alone had a complete response. Analysis by mutation status showed that the overall response rate to the combination was 61% (44/72) for patients with wild-type tumours and 52% (12/23) for those with the V600 mutation.[6]

Non-small cell lung cancer

Patients with non-small cell lung cancer have a poor prognosis, especially those with advanced disease which has progressed despite chemotherapy. They usually die within a year. Preliminary investigation found that in previously treated patients given nivolumab 3 mg/kg every two weeks the median overall survival was 14.9 months.[7] This dose was investigated in patients with stage IIIB or stage IV cancer who had previously been treated with platinum-based chemotherapy.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Squamous cell carcinoma

An open-label trial randomised 137 patients to intravenous docetaxel, every three weeks, and 135 patients to nivolumab. The median number of doses given was three for docetaxel and eight for nivolumab. There was a median progression-free survival of 2.8 months with docetaxel and 3.5 months with nivolumab. The median overall survival was 6 months with docetaxel and 9.2 months with nivolumab. At one year, 42% of the nivolumab group were still alive compared with 24% of the docetaxel group.[8]

Non-squamous non-small cell carcinoma

In another open-label trial, 582 patients were randomised to the same regimens of docetaxel or nivolumab. A median of four doses of docetaxel and six doses of nivolumab were infused. Although the median progression-free survival was shorter with nivolumab (2.3 vs 4.2 months), the median overall survival was longer than with docetaxel (12.2 vs 9.4 months). At one year 51% of the nivolumab group and 39% of the docetaxel group were still alive.[9]

Safety

Some of the hazards of intravenously infusing a monoclonal antibody such as nivolumab are predictable. There can be infusion reactions and a wide range of potentially life-threatening immune-related problems. These include pneumonitis, colitis, hepatitis, nephritis and endocrinopathies. Corticosteroids may be required. Treatment with nivolumab may need to be modified or stopped if the patient develops problems such as diarrhoea, rashes or alterations in liver, renal or thyroid function. Common adverse events during the trials were fatigue, nausea, musculoskeletal pain, rash, pruritus and diarrhoea. Nivolumab can also reduce haemoglobin and blood counts. Adverse reactions are likely to be more frequent if nivolumab is given with ipilimumab. The toxicity of this combination resulted in 45% of the patients receiving it for untreated melanoma discontinuing therapy.[6]

Pharmacokinetics

The nivolumab concentrate is diluted and then infused over an hour. Infusions of nivolumab and ipilimumab should not be given at the same time. It is expected that nivolumab will be broken down like other antibodies. Nivolumab has a half-life of about 27 days. Clearance is not affected by mild hepatic or mild–moderate renal impairment. It will be increased if anti-nivolumab antibodies develop.

Conclusion

The trials have shown that nivolumab improves the survival of patients with advanced melanoma and non-small cell lung cancer by a few months (see Table). Other indications are likely to be added. The best use of nivolumab requires further study. For example, how does its effectiveness compare with that of chemotherapy for non-small cell lung cancer? If it is used at earlier stages of treatment, long-term adverse effects may emerge.

Table **Efficacy of nivolumab monotherapy**

Cancer	Treatment	Number of patients	Median progression-free survival (months)	Median overall survival (months)
Previously untreated metastatic melanoma[3]	nivolumab	210	5.1	Not reached‡
	dacarbazine	208	2.2	10.8
Previously untreated advanced melanoma[5]	nivolumab	316	6.9	–
	ipilimumab	315	2.9	–
Previously treated advanced melanoma[4]	nivolumab	272	4.7§	–
	chemotherapy	133	4.2§	–
Advanced squamous cell non-small cell lung cancer[8]	nivolumab	135	3.5	9.2
	docetaxel	137	2.8	6.0
Advanced non-squamous non-small cell lung cancer[9]	nivolumab	292	2.3	12.2
	docetaxel	290	4.2	9.4

‡ after a median follow-up of 8.9 months
§ analysis based on the first 120 patients given nivolumab (47 given chemotherapy)

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Nivolumab is not the first antibody aimed at the PD-1 receptor, as pembrolizumab was marketed in Australia during 2015.[10] Although pembrolizumab requires shorter and less frequent infusions, its efficacy and safety have not been directly compared with nivolumab.

T manufacturer provided the product information

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