Durvalumab

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Approved indications: urothelial carcinoma, non-small cell lung cancer

Imfinzi (AstraZeneca)
vials containing 120 mg or 500 mg concentrate for dilution
Australian Medicines Handbook section 14.2.1, Antineoplastic antibodies

Some tumours evade detection by the immune system by expressing a molecule called programmed cell death ligand 1 (PD-L1). This interacts with the programmed cell death 1 (PD-1) receptor on the surface of T cells to suppress the immune response. Inhibiting these immune checkpoints therefore enables the T cells to recognise the tumour cells and attack them. Immune checkpoint inhibitors are being used in a variety of cancers including melanoma, non-small cell lung cancer and urothelial carcinoma.[1]

Durvalumab is a genetically engineered monoclonal antibody to PD-L1. It blocks the interaction of PD-L1 and PD-1, enabling T-cell activation.

The antibody concentrate is diluted then infused intravenously over an hour every two weeks. A steady state is reached after 16 weeks. The antibody is cleared with a half-life of 18 days. No dose adjustment is needed for renal or hepatic impairment, but durvalumab has not been studied in patients with severe kidney impairment.

In urothelial cancer durvalumab is being studied as a second-line drug. A phase I/II trial enrolled patients with inoperable or metastatic transitional-cell bladder carcinoma who had progressed on, or been ineligible for, other therapies. In a group of 61 patients 19 had received three or more previous therapies. After a median follow-up of 4.3 months there was an objective response in 13 patients (based on the RECIST criteria). The response rate was highest in patients with tumours expressing PD-L1.[2]

A later report on the same trial evaluated 191 patients with a median follow-up of 5.8 months. There were 34 objective responses including seven complete responses. Again, the response rates were higher in patients with greater PD-L1 expression. The median progression-free survival was 1.5 months. Although the data are incomplete, overall survival was 20 months in those with high PD-L1 expression and 8.1 months in other patients.[3] As almost all the patients had been previously treated with carboplatin or cisplatin, the Australian approval of durvalumab specifies that there must have been disease progression during or following platinum-containing chemotherapy.

For non-small cell lung cancer, durvalumab has been studied in a phase III trial. The patients had unresectable, locally advanced cancer (Stage III) and had been treated with chemotherapy and radiation. Infusions of durvalumab were given to 473 patients and 236 were given a placebo. After a median follow-up of 14.5 months there was an objective response in 28.4% of the durvalumab group and 16% of the placebo group. There was a significant difference in progression-free survival (16.8 months vs 5.6 months).[4] This translated into improved overall survival in a later analysis.

After a median follow-up of 25.2 months, the 24-month overall survival rate was 66.3% with durvalumab and 55.6% with placebo. The median time to metastasis or death was 28.3 months with durvalumab and 16.2 months with placebo. The degree of PD-L1 expression did not appear to influence the outcome significantly. Patients under 65 years old had a greater reduction in the risk of death than older patients.[5] Reflecting the trial population, the Australian approval for this indication specifies that the cancer must not have progressed following platinum-based chemoradiotherapy.

Immune checkpoint inhibitors, such as durvalumab, can cause a wide range of immune-mediated adverse reactions. These include colitis, endocrinopathies, hepatitis, nephritis, pneumonitis and rashes.[1] Depending on the severity of these reactions, treatment may have to be postponed or stopped.

Common adverse effects in the treatment of urothelial cancer and non-small cell lung cancer include fatigue, decreased appetite, diarrhoea, fever and nausea. In the phase III trial 15.4% of the durvalumab group discontinued therapy because of adverse events compared with 9.8% of the placebo group.[5]

Durvalumab adds to the range of immune checkpoint inhibitors available to treat non-small cell lung cancer. It has also been approved for urothelial carcinoma, but the results of the single-arm study[3] need to be confirmed. Like other members of the class, durvalumab is being studied in other cancers and in combination with other drugs such as tremelimumab. Whether any durvalumab regimen has an advantage over other immune checkpoint inhibitors in particular patients remains to be seen.

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.