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Review

The European Medicines Agency review of ipilimumab (Yervoy) for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy: Summary of the scientific assessment of the Committee for Medicinal Products for Human Use

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ABSTRACT

On 13 July 2011 the European Commission issued a marketing authorisation valid throughout the European Union (EU) for ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

Ipilimumab is a monoclonal antibody that specifically blocks the inhibitory signal of cytotoxic T lymphocyte antigen 4 (CTLA-4), resulting in T cell activation, proliferation and lymphocyte infiltration into tumours, leading to tumour cell death. The recommended induction regimen of ipilimumab is 3 mg/kg administered intravenously over a 90 min period every 3 weeks for a total of four doses.

In a phase 3 trial in patients with advanced melanoma, median overall survival for ipilimumab was 10 months versus 6 months for gp100, an experimental melanoma vaccine (Hazard ratio (HR) 0.66; 95% confidence interval (CI): 0.51, 0.87; $p = 0.0026$).

Ipilimumab was most commonly associated with adverse reactions resulting from increased or excessive immune activity. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of ipilimumab. The most common side-effects (affecting more than 10% of patients) were diarrhoea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain. The objective of this paper is to summarise the scientific review of the application leading to approval in the EU. The detailed scientific assessment report and product information, including the summary of product characteristics (SmPC), are available on the European Medicines Agency (EMA) website (www.ema.europa.eu).

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1. Background

About 20% of patients diagnosed with melanoma develop metastatic disease which is associated with a median survival of about 6–9 months.[1–3] Available treatments have included systemic therapy, surgery and radiotherapy. Systemic therapy includes chemotherapy and immunotherapy. Palliative radiotherapy is indicated for symptomatic relief of metastases to brain, bones and viscera. Complete resection of isolated metastases may occasionally achieve long term survival. Chemotherapy with dacarbazine (DTIC) may achieve objective response rates of about 20%, of which less than 5% is complete remission. Higher response rates have been seen using combination chemotherapy; however, no increase in survival has been demonstrated with combination regimens when compared to DTIC alone.[4] Immunotherapy for metastatic melanoma includes interferon-alfa (IFNa) and interleukin 2 (IL-2). The observed response rates for both IFNa and IL-2 are comparable to the responses achieved with DTIC.[5,6] Until recently, no one drug or combination of drugs demonstrated any impact on survival in metastatic melanoma.[7] Recurrent melanoma is resistant to most standard systemic therapy and no effective second line treatments have been available.

On 5 May 2010, the applicant Bristol-Myers Squibb Pharma EEIG submitted an application for marketing authorisation for ipilimumab to the European Medicines Agency (EMA). Ipilimumab is a fully human anti-human cytotoxic T lymphocyte antigen 4 (CTLA-4) (CD152) monoclonal antibody of the IgG1-κ isotype. Ipilimumab binds to human and cynomolgus CTLA-4.

The scientific review was conducted by the Committee for Medicinal Products for Human Use (CHMP). The CHMP recommended the granting of a marketing authorisation for ipilimumab based on a positive benefit-risk balance. Following this review the European Commission issued a marketing authorisation on 13 July 2011 for ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

The detailed scientific assessment report and the most current product information are available on the EMA website (www.ema.europa.eu).

2. Non-clinical aspects and clinical pharmacology

Ipilimumab showed specific binding to activated, but not resting, T cells from the cynomolgus monkey and from humans.

The anti-tumour activity of ipilimumab was tested in a human CTLA-4 transgenic, mouse CTLA-4 knock out mouse. Anti-tumour activity was only seen when ipilimumab was administered at or near the time of the expected peak of the primary (anti-tumour) immune response. The relevance of this study, and other anti-tumour studies conducted using homologous mouse tumour models was considered limited because in all these studies the (blocking) CTLA-4 antibody was administered at the time or shortly after tumour inoculation i.e. at the time of a (primary) immune response against the tumour.

In cynomolgus monkeys, ipilimumab (10 mg/kg) administered concurrently with T cell antigens enhanced the antigen-specific antibody response.

In intravenous repeat-dose toxicology studies in monkeys, ipilimumab was generally well tolerated. Immune-mediated adverse reactions were observed infrequently and included colitis (which resulted in a single fatality), dermatitis and infusion reaction (possibly due to acute cytokine release resulting from a rapid injection rate).

Reproductive and developmental toxicology studies were not performed with ipilimumab. Results of further embryofoetal, pre/post-natal development studies were requested to be submitted post-approval. The effect of ipilimumab on male and female fertility is unknown.

In patients with melanoma who received ipilimumab, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period. In phase 2 studies, this increase was dose-dependent. In the pivotal study MDX010-20, increased ALC throughout the induction dosing period was observed for ipilimumab at 3 mg/kg with or without gp100 but not for gp100 peptide vaccine alone.

The pharmacokinetic profile of ipilimumab was studied in 498 patients with advanced melanoma who received induction doses ranging from 0.3 to 10 mg/kg administered once every 3 weeks for four doses. Cmax, Cmin and AUC of ipilimumab were found to be dose proportional within the dose range examined. Ipilimumab steady state was reached by the third dose administered once every 3 weeks. Ipilimumab clearance increased with increasing body weight and with increasing lactate dehydrogenase (LDH) at baseline; however, no dose adjustment is required for elevated LDH or body weight after administration on an mg/kg basis. No controlled studies have been conducted to evaluate the pharmacokinetics of ipilimumab in the paediatric population or in patients with hepatic or renal impairment.

The use of systemic corticosteroids at baseline, before starting ipilimumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of ipilimumab. However, systemic corticosteroids or other immunosuppressants can be used after starting ipilimumab to treat immune-related adverse reactions.

The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with ipilimumab, patients who require concomitant anticoagulant therapy should be closely monitored.

3. Clinical efficacy

The clinical aspects of the application were supported by one phase 3 pivotal study MDX010-20 and seven supportive phase 1/2 studies, as well as high-level data from a phase 3 study CA184024. Three of the clinical studies (including the pivotal study) evaluated the recommended dose of 3 mg/kg administered once every 3 weeks (q3w) for four doses whereas other studies evaluated ipilimumab at 10 mg/kg.