IRISH MEDICINES BOARD

Cetuximab (Erbitux) - Update on Revised Recommendations for Use and Risk of Infusion-Related Reactions

Overview of revised recommendations for use

Cetuximab* (Erbitux) is a chimeric monoclonal immunoglobulin G1 (IgG1) antibody directed against the Epidermal Growth Factor Receptor (EGFR). Cetuximab is licensed in Ireland and across the EU and is now indicated for the treatment of patients with EGFR-expressing, *RAS* wild-type metastatic colorectal cancer in combination with irinotecan-based chemotherapy, in first-line in combination with Folfox or as a single agent in patients who have failed oxaliplatin and irinotecan-based therapy and who are intolerant to irinotecan.

Following a review of a retrospective subset analysis of data from a randomised, multicentre phase II study, the therapeutic indications for use of cetuximab have been modified[1]. Evidence of wild type *RAS* status (at exons 2, 3, and 4 of *KRAS* and *NRAS*) is required before initiating treatment with cetuximab. RAS mutation status should be determined by an experienced laboratory using a validated test method. Cetuximab combined with oxaliplatin-containing chemotherapy is now contraindicated in people with metastatic colorectal cancer who have mutant *RAS* at these exons or unknown *RAS* status. Further details on the study findings have been highlighted in a direct healthcare professional communication circulated by the company in January 2014, available on the IMB website.

Infusion related reactions (IRR)

A recent EU level review of infusion related reactions for cetuximab has also recommended an update of product information in order to amend administration recommendations and expand on the existing warning related to infusion-related reactions in the course of cetuximab treatment.

IRR constitute a spectrum of symptoms with variable severity, some of which are mild to moderate in intensity, and may be compatible with further therapy. Severe infusion-related reactions, including anaphylactic reactions, may also occur, in some cases with a fatal outcome.

Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Anaphylactic reactions may occur as early as within a few minutes of the first infusion e.g. due to preformed IgE antibodies cross-reacting with cetuximab. These reactions are commonly associated with bronchospasm and urticaria. They can occur despite the use of premedication. Symptoms may also be delayed, occurring up to several hours after the first infusion or with subsequent infusions. It is recommended that patients are warned of the possibility of late onset reactions and should be instructed to contact their physician if symptoms or signs of an infusion-related reaction occur.

Advice to Healthcare Professionals

- A complete medical history should be taken in all patients prior to cetuximab administration, specifically asking about any previous infusion related reactions to another antibody, allergy to red meat, or tick bites, or any results of tests for IgE antibodies against cetuximab.
- All patients should receive premedication with an antihistamine and a corticosteroid at least 1 hour prior to administration of cetuximab.
- The initial dose should be given slowly and the speed of infusion must not exceed 5mg/min. The recommended infusion period is 120 minutes. For subsequent weekly doses, the infusion rate must not exceed 10mg/min and the recommended infusion period is 60 minutes. All vital signs should be closely monitored for at least two hours for the first infusion.
- If during the first infusion, an infusion related reaction occurs within the first 15 minutes, the infusion should be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have IgE antibodies against cetuximab before a subsequent infusion is given.
- If an infusion related reaction (IRR) occurs later during the infusion or at a subsequent infusion, further management will depend on its severity:

- Grade 1: Continue slow infusion under close supervision,
- Grade 2: Continue slow infusion and immediately administer treatment for symptoms,
- Grade 3 and 4: Stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab.

- Mild or moderate infusion-related reactions are very common comprising symptoms such as fever, chills, dizziness or dyspnoea. If a patient experiences a mild or moderate infusion related reaction (IRR) then the infusion rate may be decreased. The lower infusion rate should be maintained in all subsequent infusions.

Key messages

- Product information for cetuximab has been updated to highlight the importance of establishing wild type *RAS* (*KRAS* and *NRAS*) status before treatment of metastatic colorectal cancer.
- Information on cetuximab administration and management of infusion related reactions has also been expanded.

**Cetuximab available in Ireland is called Erbitux. Further details are available at www.imb.ie and www.ema.europa.eu*

1- Tejpar S et al. ASCO-GI, 16-18 January 2014

For further Information see: Letter sent to healthcare professionals in January 2014; cetuximab product information; similar advice issued for panitumimab (Vectibix) in September 2013 (all available at www.imb.ie).