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Erbitux DHPC Ireland

Direct Healthcare Professional Communication on the importance of establishing wild-type *RAS* (exons 2, 3 and 4 of *KRAS* and *NRAS*) status before treatment with Erbitux® (cetuximab)

Dear Healthcare Professional,

Merck Serono, in agreement with the European Medicines Agency and Irish Medicines Board (IMB) would like to inform you of the following modification of the approved therapeutic indication of Erbitux in metastatic colorectal cancer (mCRC).

Summary

- Evidence of wild-type *RAS* status (exons 2, 3 and 4 of *KRAS* and *NRAS*) is required before initiating treatment with Erbitux. *RAS* (exons 2, 3 and 4 of *KRAS* and *NRAS*) mutational status should be determined by an experienced laboratory using a validated test method.
- Wild type *KRAS* exon 2 status is already required for initiation of treatment with Erbitux, but further data also show that wild type *RAS* as defined above is needed for Erbitux to be active.
- Inferior overall survival (OS), progression-free survival (PFS) and objective response rates (ORR) have been shown in patients with *RAS* mutations (exons 2, 3 and 4 of *KRAS* and *NRAS*) who received Erbitux in combination with FOLFOX4 chemotherapy versus FOLFOX4 alone.
- The contraindication for Erbitux in combination with oxaliplatin-containing chemotherapy (eg FOLFOX4) now includes all patients with mCRC mutant *RAS* (exons 2, 3 and 4 of *KRAS* and *NRAS*) or unknown *RAS* status.

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The product information for Erbitux has been updated in order to communicate this important information (see attached Summary of Product Characteristics).

Background Information

The update of the prescribing information and inclusion of additional *RAS* mutations is based on a retrospective subset analysis of data from a randomised, multicentre phase 2 study (OPUS trial EMR 62202-047) of Erbitux plus FOLFOX4 versus FOLFOX4 alone in patients with previously untreated mCRC. The OPUS trial included 337 patients, of whom 179 patients had wild-type *KRAS* (exon 2) tumor status. The incidence of additional *RAS* mutations in the wild-type *KRAS* exon 2 population was 30.5%.

When patients with additional *NRAS* exon 2, 3 and 4 and *KRAS* exon 3 and 4 mutations were excluded from the *KRAS* exon 2 wild-type population, efficacy outcomes appeared to be improved. Conversely, patients with *RAS* mutations (including and beyond *KRAS* exon 2) who were treated with Erbitux plus FOLFOX4 had inferior survival, PFS and ORR than if treated with FOLFOX4 alone.

The efficacy data generated in this study are summarised in the table below:

Variable/ statistic	***RAS* wild-type population**		***RAS* mutant population**	
	Cetuximab plus FOLFOX4	**FOLFOX4**	**Cetuximab plus FOLFOX4**	**FOLFOX4**
	(N=36)	**(N=46)**	**(N=94)**	**(N=78)**
OS				
months, median	20.7	17.8	13.4	17.8
(95% CI)	(18.2, 26.8)	(12.4, 23.9)	(11.1, 17.7)	(15.9, 24.8)
Hazard Ratio (95% CI)	0.833 (0.492, 1.412)		1.353 (0.954, 1.918)	
p-value	0.4974		0.0890	
PFS				
months, median	12.0	5.8	5.6	7.8
(95% CI)	(7.7, NE)	(4.5, 7.5)	(4.4, 7.4)	(6.7, 9.3)
Hazard Ratio (95% CI)	0.433 (0.212, 0.884)		1.594 (1.079, 2.355)	
p-value	0.0180		0.0183	
ORR				
%	61.1	30.4	36.2	48.7
(95% CI)	(43.5, 76.9)	(17.7, 45.8)	(26.5, 46.7)	(37.2, 60.3)
Odds Ratio (95% CI)	3.460 (1.375, 8.707)		0.606 (0.328, 1.119)	
p-value	0.0081		0.1099	

CI = confidence interval, FOLFOX4 = oxaliplatin plus continuous infusional 5-FU/FA, ORR = objective response rate (patients with complete response or partial response), OS = overall survival time, PFS = progression-free survival time, NE: not estimable

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Safety evaluations revealed no new safety findings attributable to Erbitux when comparing the wild-type *RAS* and mutated *RAS* populations.

The above findings for Erbitux are further supported by recent independent clinical studies that have implicated *RAS* mutations as negative predictive biomarkers of treatment with anti-EGFR therapy in CRC (Douillard et al, 2013, Patterson et al, 2013, Schwartzberg et al, 2013, Seymour et al, 2013, Stintzing et al, 2013).

The approved therapeutic indications for Erbitux have therefore been modified to mitigate the risk of a negative impact on patients with *RAS* mutations beyond *KRAS* exon 2.

Further Information

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

The therapeutic indication will read:

Erbitux is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, *RAS* wild-type metastatic colorectal cancer

- in combination with irinotecan-based chemotherapy,
- in first-line in combination with FOLFOX,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

Call for Reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the online reporting option (preferred method) accessible from the IMB homepage (www.imb.ie). A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost' (see details below). Alternatively, the traditional post-paid 'yellow card' option may also be used.

FREEPOST
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Reports can also be made to Merck Serono Ltd by contacting Merck Serono Medical Information directly on +44 (0)208 818 7373 or by emailing medinfo.uk@merckgroup.com. They can also be contacted should you have any questions or require additional information regarding the use of Erbitux.

Yours sincerely,

Michael Thompson
Medical Director, UK and Ireland

Attached

Erbitux Summary of Product Characteristics dated December 2013

References

Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013;369:1023-34.

Patterson S, Peeters M, Siena S, et al. Comprehensive analysis of KRAS and NRAS mutations as predictive biomarkers for single agent panitumumab (pmab) response in a randomized, phase III metastatic colorectal cancer (mCRC) study (20020408). J Clin Oncol 2013;31 (Suppl; Abstract 3617).

Schwartzberg L, Rivera F, Karthaus M, et al. Analysis of KRAS/NRAS mutations in PEAK: A randomized phase II study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC). J Clin Oncol 2013;31 (Suppl; Abstract 3631).

Seymour MT, Brown SR, Middleton G, et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol 2013;14:749-59.

Stintzing S, Jung A, Rossius J, et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. ESMO 2013, late breaking abstract.