



**60th MSAC Meeting
28 November 2013**

PBAC referral relevant to Applications 1362 and 1363 – KRAS/RAS testing under MBS item 73330 for access to cetuximab/panitumumab

Summary of consideration and rationale for MSAC's advice

MSAC noted that the applicant (Merck Serono) had withdrawn its Application 1362 for *KRAS* mutation testing under MBS item 73330 for access to cetuximab in the first-line setting of metastatic colorectal cancer (mCRC). This corresponded to a withdrawal of the co-dependent submission to the 6-8 November 2013 Pharmaceutical Benefits Advisory Committee (PBAC) meeting for cetuximab in the first-line setting of mCRC. MSAC also noted that an assessment report had not yet been received to enable consideration of Application 1363 for *RAS* mutation testing under MBS item 73330 for access to panitumumab in the first-line setting of mCRC.

However, MSAC undertook a preliminary consideration of these matters in response to a referral from the 6-8 November 2013 PBAC meeting which raised several matters for MSAC consideration in relation to the emerging data on variable treatment effect of panitumumab and cetuximab associated with a broader range of *RAS* mutations than the exon 2 mutation currently detected with *KRAS* mutation testing. Specifically, PBAC had sought advice from MSAC and the sponsor companies (Merck Serono for cetuximab and Amgen for panitumumab) regarding the need for wider *RAS* mutation testing (and other mutation testing) to better select patients.

MBS item 73330 was created following December 2010 MSAC advice to fund testing of tumour tissue from a patient with metastatic colorectal cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to Kirsten ras (*KRAS*) gene mutation status for access to cetuximab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Testing is of codons 12 and 13 on exon 2 and is conducted in the context of a quality assurance program. Prior to listing on the MBS, *KRAS* mutation testing was available in two specialised laboratories; it is now available in more than 12 NATA-accredited pathology centres across Australia.

As indicated by PBAC in its referral, extended analyses of the PRIME randomised trial of first-line panitumumab published by Douillard et al in the September 2013 issue of the New England Journal of Medicine raised concerns that other activating *RAS* mutations beyond *KRAS* mutations in exon 2 may also be negative predictive biomarkers for anti-EGFR therapy (e.g., panitumumab and cetuximab). The additional activating mutations occurred in 16% of PRIME participants and were found as *KRAS* mutations outside exon 2 and *NRAS* mutations on exons 2, 3 and 4. These analyses contributed to a safety-related change in the TGA-approved indication for panitumumab for the treatment of patients with *RAS* wild-type (rather than *KRAS* wild-type) mCRC as first-line combination therapy.

The results of similar analyses in mCRC are becoming available from the PEAK randomised trial of panitumumab as combination therapy and from the OPUS, (**redacted information**)

and FIRE 3 randomised trials of cetuximab as combination therapy. Other emerging analyses in mCRC are coming from the Piccolo (panitumumab as combination therapy), CAPRI (cetuximab as combination therapy), Study 408 (panitumumab as monotherapy), and Consortium (cetuximab as combination therapy) studies.

MSAC identified four questions which needed to be addressed:

- Is the identified effect of *RAS* mutation status (in predicting a reduced treatment effect) operating as a class effect across anti-EGFR antibodies, i.e., does it similarly affect both panitumumab and cetuximab?
- Is this effect consistent irrespective of the chemotherapy partner with the anti-EGFR antibody, including anti-EGFR antibody used as monotherapy?
- Is this effect consistent across all lines of therapy, noting that there are more clearly effective alternatives to anti-EGFR antibodies in earlier lines of therapy which may affect the consequences of this effect for an assessment of the health benefits and harms comparing anti-EGFR antibody based therapies with these alternative therapy options?
- What is the full spectrum of mutations which predict a reduced treatment effect of anti-EGFR antibodies, e.g., *HRAS*, *BRAF*, *PIK3CA* mutations and others?

MSAC also sought an update on how regulatory agencies in Australia, Europe, Canada and the United States of America were responding to the emerging evidence and the evidentiary basis they were relying on for any regulatory changes.

Similarly, MSAC sought an update on whether and how pathology laboratories were modifying their testing strategies in response to the emerging evidence. Relevant information in this update would include identifying:

- what additional tests are being conducted
- what order testing is occurring
- whether mutation load is being estimated
- with what consequence for MBS billing practice (e.g., is item 73330 being billed on multiple occasions to look for *KRAS* mutations beyond exon 2?) and
- at what additional cost.

This information (and the rationale for these changes) is needed to identify the most cost-effective way of covering these additional genes, such as:

- in a cascade of testing given that *KRAS* and *NRAS* mutations are mutually exclusive
- using multiplex testing
- mutation screening for multiple genes followed by confirmation of specific gene mutations
- some other approach?

MSAC considered that the emerging evidence indicated that maintaining the status quo means that some patients with mCRC are unnecessarily being exposed to side effects and reduced treatment outcomes. MSAC therefore considered that the review of the evidence and its consequences should be conducted as a matter of urgency.

Accordingly, MSAC requested that the sponsors of panitumumab (Amgen) and cetuximab (Merck Serono) provide the requested information in submissions to be assessed via the Evaluation Sub-Committee. MSAC further requested that TGA be requested to provide updated advice for MSAC consideration alongside its consideration of these submissions.

MSAC recalled that these requests were consistent with its December 2010 advice to review the MBS funding of *KRAS* mutation testing two years after it started. MSAC also requested that the sponsors provide a plan for providing timely updates on new molecular data which may alter the testing requirements for the anti-EGFR antibodies.

MSAC's advice to the Minister

MSAC has not yet finalised its advice to the Minister. As a matter of urgency, MSAC seeks further information from the sponsors, Amgen and Merck Serono, and from the TGA, on matters related to re-defining the appropriate biomarker testing in metastatic colorectal cancer to guide treatment with cetuximab and panitumumab. On the basis of this information, MSAC intends to be in a position to update its advice to the Minister to optimise mutation testing in this context.

Summary

The selection of patients with metastatic colorectal cancer for treatment with panitumumab or cetuximab is currently guided by pathology testing to ensure that their cancer does not have a particular *KRAS* gene mutation which predicts reduced effectiveness to these medicines. Emerging evidence suggests that other gene mutations are also likely to predict reduced effectiveness and so that mutation testing should be extended. As a matter of urgency, MSAC is requesting information to advise on the MBS funding arrangements which would optimise the mutation testing performed for these patients.