



**57<sup>th</sup> MSAC Meeting  
29-30 November 2012**

**Application 1163 – HER2 testing for trastuzumab**

**Summary of consideration and rationale for MSAC's advice**

*Whom to test?*

MSAC considered that the eligible patient population for HER2 testing would have Stage IV (metastatic) adenocarcinoma of the stomach or gastro-oesophageal junction (metastatic gastric cancer) and that there was no need or basis to further enrich the population eligible for testing.

*When to test?*

MSAC considered that there was no need to consider testing a patient who has not yet reached Stage IV (metastatic) gastric cancer because most patients present with metastatic gastric/gastro-oesophageal cancer, and testing of the metastasis is preferred over testing the primary tumour (see what to test below). The expected turnaround time of five days for the test results is reasonable in the context of the time to decide on treatment for the medical condition.

*What to test?*

MSAC considered that the proposed item descriptor should limit HER2 testing to biopsy or resection specimens, and thus exclude the possibility of testing of cytology specimens, due to the evidence of frequent heterogeneity within a tumour sample and the lack of data to support the use of cytology specimens according to the submission.

Although testing the primary tumour should not be excluded, MSAC considered that testing of the metastasis is preferred over testing the primary tumour because of the acknowledged incidence of heterogeneity of HER2 status within and between tumour samples. As most patients present with metastatic gastric cancer, few patients would be disadvantaged by this preference.

MSAC agreed with the base case scenario in the resubmission and considered that *in situ* hybridisation (ISH) testing for human epidermal growth factor receptor 2 (HER2) in the context of metastatic gastric cancer should only be performed when prerequisite immunohistochemistry (IHC) testing for HER2 overexpression is scored at 2+ or 3+ using scoring guidelines reflecting the approach which was standardised for the key randomised trial of trastuzumab (ToGA). MSAC noted that different scoring systems were required for assessment of HER2 overexpression on resection compared with biopsy specimens. Given the heterogeneity of HER2 overexpression, MSAC considered that IHC was a necessary prerequisite to ISH testing. IHC allowed the pathologist to identify the areas within a tumour which should be examined for HER2 gene amplification by ISH. For this reason, it was important that the same laboratory undertook both IHC and ISH testing. This approach maximised the analytical performance of the overall testing strategy.

MSAC considered that the definition of HER2 “positive” in a PBS restriction for trastuzumab in metastatic gastric cancer should be both (a) either IHC2+ or IHC3+ and then (b) ISH results showing >6 copies of HER2 **and** the ratio of HER2:chromosome 17 being >2. Both ISH criteria need to be fulfilled. This definition of HER2 amplification reduces the rate of false positives by ensuring that there are enough copies of HER2 to be confident of the ratio result and excludes instances where the two copies of chromosome 17 are not seen. It conforms to likely Australian practice based on the approach which was standardised for the ToGA trial. MSAC noted that Australian practice relies on biopsy specimens to a greater extent than resection specimens compared to the ToGA trial, and the likelihood of having a positive HER2 ISH result in the ToGA trial was greater with biopsy specimens than with resection specimens.

To support this preferred approach, MSAC advised that Australian pathology practice should be optimised to ensure HER2 testing for metastatic gastric cancer is limited to laboratories with expertise and back-up by requiring that the one laboratory performs both IHC and ISH testing on the specimen. This centralised approach would also facilitate the collation of data on the IHC score, the HER2 copy number and the ratio of HER2 to chromosome 17. For the purposes of informing future decisions, MSAC considered the collection of these data were highly desirable.

However, MSAC advised that the estimate of trastuzumab incremental effectiveness in the economic evaluation presented to PBAC should reflect the intention-to-treat (ITT) results of the ToGA trial because the Committee considered that pathology practice in Australia could not be optimised to the extent that was achieved for the ToGA trial. For this reason, the subgroup analyses conducted to inform the various scenarios in the application do not form a sufficiently robust basis to support the claimed improvements in the incremental effectiveness of trastuzumab over that shown by the ITT results.

MSAC noted that its preference not to specify a type of ISH test means that an assessment of comparative analytical performance is required across available ISH test options. Silver in situ hybridisation (SISH) is more commonly used in Australia than fluorescence *in situ* hybridisation (FISH), which was the evidentiary standard ISH test used in the ToGA trial. Further, it would be expected that unstained slides of metastatic gastric cancer would be sent to a laboratory, which would usually conduct a SISH test. If this did not resolve the HER2 diagnosis, the specimen would likely be sent to a FISH reference laboratory and be billed as a new episode given the 14-day rule applying in the Pathology Services Table of the MBS.

The applicant’s response to the Joint ESC Report provided reassurance that repeat sampling for HER2 in gastric cancer would not be a common occurrence because between six and eight biopsies would be extracted via one endoscopic procedure and tested at the same time maximising the likelihood of recognising possible heterogeneity in the tumour. MSAC therefore agreed that the re-sampling (new biopsy or new testing of resected tissue) rate would be low. MSAC considered that a re-testing rate of 5% would reasonably reflect the rate of indeterminate results from an initial test, for example, due to marked heterogeneity, and thus requiring referral for FISH or further biopsy. MSAC further considered that repeat testing would not be needed, as HER2 status was not informative for purposes other than determining eligibility for trastuzumab. Specifically, HER2 status was not informative for monitoring response to treatment or disease progression, assessing the development of resistance, concordance testing across multiple tumour sites, or assessing mutation stability over time.

The different ISH test options would also have consequences for the submission's implicit assumption for modelling purposes of 100% sensitivity and 100% specificity for testing as conducted in the ToGA trial, which MSAC considered would overestimate the likely test performance across test options and pathology laboratories in Australia. Despite the absence of an agreed reference standard, MSAC noted that the applicant usefully provided additional information in response to the Joint ESC Report on the issues of both comparative analytical performance of SISH and FISH and the importance of reconstructing the modelled economic evaluation to assess the consequences of reduced sensitivity and specificity. However the comparative analytical performance data were from the ToGA trial rather than Australian data from the GaTHER study (such as that provided in Table 7 of the Joint ESC Report). Further the unevaluated sensitivity analyses in this response could not be assessed because the consequences of worsening sensitivity or specificity should be an increase in incremental costs and a decrease in incremental QALYs gained, as well as an increase in incremental cost per extra QALY gained as reported. In addition, it is not clear whether the response included the corrected number of tests and test cost per treated patient provided in the Supplementary Table of the Joint ESC Report (but also adjusting for a 5% re-testing rate). Overall, MSAC advised that the impact of test uncertainty on overall clinical effectiveness and cost-effectiveness needed to be incorporated in the economic evaluation presented for PBAC consideration.

MSAC considered that the range of uncertainty in the estimate of prevalence was sufficiently reflected in the range across the scenarios presented in the submission based on a simple average across the ToGA prevalence data and the GaTHER prevalence data, with a base case of 18.3% and a range for the sensitivity analyses of 14.0% to 22.7%.

#### *Other considerations*

MSAC agreed that the nominated comparator of usual care without HER2 testing was appropriate, and that a comparison of analytical performance of the alternative ISH test options was also appropriate.

MSAC concluded that the primary co-dependency claim had been established based on a biological argument rather than direct evidence, because no comparative assessment of trastuzumab's effectiveness in HER2 negative patients has been presented. Compared to breast cancer, the biological argument is weak and is not supported to the same extent by *in vitro* data. Nevertheless, it has some plausibility and has been widely accepted elsewhere. Given that between 14% and 23% of patients with metastatic gastric cancer are HER2 positive, this means that trastuzumab would only be eligible for this minority of patients. MSAC also concluded that this co-dependency claim could not be clearly distinguished from the unresolved question of whether HER2 status indicates a different prognosis in gastric cancer. MSAC advised that there were no other purposes for HER2 testing in gastric cancer.

MSAC noted that the considerations above and advice below addressed the matters referred to it by the November 2012 PBAC meeting.

MSAC advised that, in the absence of any reason not to do so, the current MBS fee should apply to any expansion of eligibility for MBS funding of HER2 ISH testing.

## MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of in situ hybridisation (ISH) testing for human epidermal growth factor receptor 2 (HER2) to include metastatic adenocarcinoma of the stomach or gastro-oesophageal junction to help determine eligibility for proposed PBS-subsidised trastuzumab, MSAC deferred the application for the requested MBS item until such time as PBAC makes a decision regarding the corresponding PBS listing of trastuzumab. In doing so, PBAC will take into account responses to the questions it has posed to MSAC and the following advice:

- the proposed MBS item descriptor should indicate a preference for testing the metastasis rather than the primary tumour, noting that most patients present with Stage IV disease in clinical practice, although testing the primary tumour should not be excluded
- the proposed MBS item descriptor should require that HER2 ISH testing in the context of metastatic gastric cancer be performed on the same specimen in the same laboratory and only when prerequisite immunohistochemistry (IHC) testing for HER2 overexpression is scored at 2+ or 3+ using scoring guidelines reflecting the approach which was standardised for the ToGA trial of trastuzumab
- the proposed MBS item should therefore be made a pathologist determinable service to allow HER2 ISH testing to be guided by the “hot spots” revealed by the prerequisite IHC test result (the heterogeneity of IHC staining across a sample of tumour and the difficulty of scanning a slide for positive cells using ISH alone), rather than the pathologist being interrupted to get a referral from a clinician to do so
- the proposed MBS item descriptor should allow any accepted type of ISH testing and should refer to dual probe rather than single probe testing
- the proposed MBS item descriptor should limit HER2 testing to biopsy or resection specimens, and thus exclude the possibility of testing of cytology specimens
- the definition of HER2 test positive in a PBS restriction for trastuzumab in metastatic gastric cancer should be both (a) IHC2+ or IHC3+ and then (b) ISH results based on both >6 copies of HER2 and the ratio of HER2:chromosome 17 being >2
- the economic evaluations and financial analyses presented to PBAC should include a re-sampling (new biopsy or new extraction from resected tissue) rate of 5% to reflect the rate of indeterminate results from the initial test, for example, due to excessive heterogeneity
- the economic evaluations and financial analyses presented to PBAC should include the costs of patient retrieval for re-sampling as required, such as professional attendance fees
- the economic evaluations and financial analyses presented to PBAC need not include any other repeat testing
- the economic evaluations and financial analyses presented to PBAC should include the full costs of testing, such as patient episode initiation and specimen retrieval, storage or enrichment
- the sensitivity analyses of the economic evaluation presented to PBAC should appropriately examine the likely extent of proportions of false positive test results and false negative test results in Australia compared with those of the evidentiary standard because these proportions will have clinical and cost-effectiveness consequences due to the resulting misallocation of treatment
- pathology practice should be optimised to ensure HER2 testing for metastatic gastric cancer is limited to laboratories with expertise and back-up by requiring that the one laboratory performs both the IHC and ISH testing on the specimen

- this centralised approach should also be developed to facilitate the collation of data across standardised reports to the requesting oncologists on the IHC score, the number of HER2 copies and the ratio of HER2 to chromosome 17
- the estimate of trastuzumab incremental effectiveness in the economic evaluation presented to PBAC should reflect the intention-to-treat (ITT) results of the ToGA trial, acknowledging the fact that pathology practice in Australia cannot be optimised to the extent that was achieved for the ToGA trial.

If further relevant matters require reconsideration, MSAC will expedite this process. If PBAC subsequently decides to recommend to the Minister that trastuzumab be listed on the PBS for the treatment of metastatic gastric cancer, MSAC will support an expedited process for reconsideration to align MSAC support for public funding of HER2 ISH testing according to the circumstances recommended by PBAC. The purposes of the reconsideration would be to review the wording of the proposed MBS item descriptor, and consider changes in the estimates of costs to the MBS.