



3rd July 2012



Single Technology Appraisal (STA) Melanoma: (BRAF V600E, met) - vemurafenib [ID489] - Appraisal Consultation Document

Please find below my comments on the vemurafenib ACD.

New data

The Committee has recognised that vemurafenib is an active treatment in melanoma, with the majority of patients experiencing a benefit. The BRIM3 data cuts in December 2010, March 2011 and October showed that the hazard ratio (HR) for survival was reducing (i.e benefit less) with longer follow-up. The two explanations explored were cross over of patients failing DTIC to braf inhibitors or other second line therapies, and acquired resistance to vemurafenib limiting its activity. A further unanswered question is whether some patients receiving vemurafenib experience a long term benefit.

A recent update of the BRIM3 data was presented at the Annual Meeting of the American Society of Clinical Oncology in June 2012 (Chapman et al). This was a data-cut taken in February 2012. The relevant findings were

1. This data-cut reported a median PFS benefit of 5.3 months compared to the 3.7 months seen in the December 2010 cut-off.
2. The median overall survival benefit was 3.9 months in February 2012, compared to 3.6 months for the October 2011 cut.
3. There was evidence that the PFS curve was flattening, indicating that less patients were relapsing and suggesting that this may translate in to more long term survivors
4. The complete response rate had increased to 5.6%, compared to 0.9% for March 2011. This indicates that responses may take time to evolve for some patients.
5. There was a significant imbalance in the use of second line therapies. For patients receiving DTIC, 26.5% of subsequently received a braf inhibitor, and a further 22% received ipilimumab. Second line therapy was less common in patients treated with vemurafenib; 18% received ipilimumab and a further 18% received other treatment, likely to be chemotherapy which is largely ineffective.

Taken together, these data suggest that cross over and second line therapy contributed significantly to the reduction in hazard ratio. Furthermore, there is evidence that some patients will get a long term benefit, with a flattening of the PFS survival curve and responses evolving over time. Clinical experience is that confirmed complete responses tend to be durable for a prolonged period of time

There are new data that patients responding to vemurafenib mount an immune response to the tumour (Wilmott et al). Long term survivors in advanced melanoma have previously been confined mainly to patients responding to immunotherapy. This speaks to the possibility of there being long term survivors with vemurafenib, with tumour breakdown resulting in activation of the immune system - acquired resistance to vemurafenib may not be an issue for these patients. Clinical trials combining vemurafenib, a potent antigen releasing agent, followed by ipilimumab as immunotherapy, are now underway.

Modeling long term outcomes

The use of the AJCC staging data to describe the base line for patients is inappropriate. These are results for academic centres and reflect highly selected patients. The results of a number of large international trials consistently report a worse survival for patients receiving DTIC. (Patel et al, Bedekian et al, Middleton et al, Robert et al.)

The separation of advanced melanoma patients into 2 main groups with 80.6% surviving a median of 11 months and 19.4% surviving a median of > 12 years is not supported by clinical experience, with the median survivals reported being above that seen for DTIC in the BRIM3 study and nearly all other published randomised trials.

References

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Wilmott J, Long G, Howle J, et al. Selective braf inhibitors induce marked T-cell infiltration into human metastatic melanoma. Clinical Cancer Research 2012; 18: 1389-94.

With kind regards

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