Dr Rima Makarem

Interim Vice-Chair

National Institute for Health and Care Excellence

10 Spring Gardens

London, SW1A 2BU

01 May 2020

Dear Dr Makarem

***Re: MSD Appeal of Final Appraisal Document - Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum - containing chemotherapy [ID1536] (CDF guidance review of TA519)***

Thank you very much for your final scrutiny letter dated 29 April 2020.

As requested, please find enclosed the following:

* A document containing extracts from the following papers in TA525 and TA520 which are of relevance to Ground 1a.1 in MSD’s appeal:
  + TA525 –3rd set of committee papers (specifically pages 28-29, concerning the additional analyses submitted by the company [pages 2-3 of the additional analyses submitted by Roche]);
  + TA520 – 1st set of committee papers (specifically pages 552-553 [pages 112-113 of the ERG report]);

As requested, the extract document complies with the following specification:

* Less than 15 pages in length at 10 point font
* Contains only verbatim extracts from documents that were before or generated by the committee in TA525 or 520 (and no summary or argument based on those extracts)
* Ellipsis marked in the usual way, without change the meaning of any extract
* For each extract, states precisely where the extract is taken from, and includes a hyperlink to the relevant document on the NICE website (which is for the convenience of NICE staff in confirming the accuracy and context of the extract)

We thank you for agreeing to ask that NICE includes the enclosed document in the appeal papers.

Yours sincerely

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XXXXXXXXXXXXX

**Extract document**

***Extracts from papers in TA525 and TA520***

**TA525: Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum containing chemotherapy**

3rd set of Committee Papers [ID1327], published on NICE website on 17th May 2018

(https://www.nice.org.uk/guidance/ta525/documents/committee-papers-3)

Pages 28-29 of the 3rd set of Committee Papers (Pages 2-3 of the Additional analyses submitted by Roche)

***“Additional analyses***

*Consistent with the appraisal atezolizumab in second-line NSCLC in [ID970], we provide additional analyses*

*incorporating a 2-year treatment stopping rule and a range of treatment benefit duration scenarios; either with*

*a lifetime treatment effect (Table 2) or a treatment effect duration cap (at 3 or 5 years following treatment*

*discontinuation; Table 3 - Table 4) for atezolizumab, to reflect the committee-preferred assumptions in [ID970].*

*In all scenarios presented, atezolizumab is cost-effective compared to taxane therapies. Table 3 reflects the set*

*of committee-preferred assumptions for atezolizumab in second-line NSCLC in [ID970], i.e. 2-year treatment*

*stopping rule and 3-year treatment effect duration cap.*

*…*

***New company base case***

*Whilst we consider that there is a lack of clinical evidence to demonstrate that imposing a treatment stopping*

*rule is of benefit to patients in the long-term, we acknowledge that existing recommendations from NICE for*

*other immunotherapies have incorporated a treatment stopping rule, and so has the committee-preferred*

*analysis for atezolizumab in second-line NSCLC in [ID970]. The inclusion of such a stopping rule in this appraisal,*

*together with the new PAS, would enable patients with metastatic urothelial cancer after platinum-based*

*chemotherapy [ID1327] with access to atezolizumab. Given the inadequacy of current treatment options in this*

*indication, access to atezolizumab, even with the implementation of a 2-year stopping rule, would represent a valuable and radically different treatment option compared to taxane chemotherapy.”*

**TA520: Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after**

**chemotherapy**

1st set of Committee Papers [ID970], published on NICE website on 3rd August 2017

(https://www.nice.org.uk/guidance/ta520/documents/committee-papers)

Pages 552-553 of the 1st set of Committee Papers (Pages 112-113 of the ERG report)

*“****Duration of treatment effect***

*The company has assumed a lifetime duration of treatment effect for atezolizumab, this results in a lower*

*mortality rate for patients who received atezolizumab versus docetaxel or nintedanib+docetaxel for the duration of the model. The NICE Appraisal Committee raised concerns during TA42815 (Pembrolizumab for treating PDL1positive NSCLC after chemotherapy) relating to the duration of treatment effect (after treatment had ended) associated with receiving an immunotherapy. Consequently, the ERG looked to cap the duration of treatment effect of atezolizumab at 3 years in line with the (TA42815) Committee’s view on what could be considered a reasonable duration of treatment effect.*

*Whilst the company model allows the duration of treatment effect to be fixed, the approach that is used to stop*

*the treatment effect in the model is simplistic. If the duration of treatment effect is set to be ‘x’ months in the*

*model, then the hazard rate for atezolizumab is set to be equal to docetaxel at ‘x’ months after the start of the*

*model. Any patients that stop atezolizumab in month ‘t’ will have a duration of treatment effect for atezolizumab of x-t. This means the duration of treatment effect of atezolizumab in the model varies for patients and is not fixed and underestimates the true duration of treatment effect for atezolizumab of ‘x’ months if this is believed to exist in reality.*

*For example, if duration of treatment effect for atezolizumab is actually 3 years, then, in the model, setting the*

*duration of treatment effect to 3 years would mean the duration of treatment effect of atezolizumab would be*

*2.5 years for a patient who stopped treatment after 6 months, but zero for a patient who is still on treatment at 3 years. The method used in the model for dealing with duration of treatment effect for atezolizumab*

*underestimates OS for atezolizumab if a treatment effect of 3 years actually exists and 36 months is entered into the model as the duration of treatment effect. Without restructuring the model, which is beyond the remit of the ERG, it is not possible to implement a more sophisticated approach to modelling the duration of treatment effect.*

*Taking the company model limitations into account but still attempting to implement a 3-year duration of*

*treatment effect, the ERG set the company model duration of treatment effect to 5 years. As 8.5% of patients are predicted by the company’s TTD extrapolation to be receiving atezolizumab at 2 years, this means that for those patients, if they are alive at 5 years, the duration of treatment effect will still be less than 3 years even though the duration of treatment effect is set to 5 years in the company model. However, patients who stopped*

*treatment before 2 years and are still alive at 5 years will have a greater than 3 year treatment effect.*

*On balance, whilst there is no accurate way within the company model to set the duration of treatment effect*

*for atezolizumab to 3 years, the ERG, therefore, considers that setting the company model duration of treatment effect to 5 years rather than 3 years probably produces more accurate ICERs per QALY gained if the real duration of treatment effect for atezolizumab is actually 3 years.”*