Mr Tim Irish

Vice Chair

National Institute for Clinical Excellence,

2nd Floor

2 Redman Place

London

E20 1JQ

4th August 2021

Dear Mr Irish

**Appeal against NICE FAD Avelumab for maintenance treatment of locally advanced or metastatic urothelial cancer after platinum–based chemotherapy (ID3735)**

As a UK Uro Oncologist with 17 years’ experience as an NHS consultant specialising in the treatment of bladder cancer, and as the Secretary of the British Uro Oncology Group, I would like to appeal personally and on behalf of the British Uro Oncology Group against the FAD for the above Single Technology appraisal on a number of grounds.

1. ***In making the assessment that preceded the recommendation NICE has failed to act fairly/exceeded its powers***.

I was an independent expert at the initial appraisal meeting- however was subsequently excluded- like Fight Bladder Cancer representing patient voices, from the second appraisal meeting.

The opinions of patients and clinicians were ignored by NICE in its refusal to allow a stopping rule. UK Uro Oncologists routinely discuss potential reasons for future stopping of treatment as part of any initial discussion with a patient at the start of any course of immune check point inhibitors. These reasons would include disease progression, toxicity and the maximum duration of treatment. In the registration JAVELIN 100 trial < 5 % of patients remained on Avelumab at 24 months. Patient representatives at the Appraisal strongly felt that the concept that a stopping rule would be “unethical for clinicians and unfair on patients” is flawed and is out-with both patient and clinicians experience. Patients and clinicians voiced the opinion that access to maintenance Avelumab with a maximum duration of two years would benefit far more patients than the small number who could conceivably feel disadvantaged at stopping at 24 months. These opinions were disregarded.

In addition, the failure to allow a stopping rule for Avelumab was not consistent with NICE’s own FAD on second line Atezolizumab, another immune checkpoint inhibitor (TA 525) based on the ImVIGOR 211 trial , where there was in fact no maximum duration of treatment in the trial protocol but was imposed by NICE. In a further FAD, the TA492 (Atezolizumab for untreated PDL-1 positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable) a maximum of 24 months duration of treatment was mandated. In addition NICE’s appraisal of Pembrolizumab in advanced/metastatic urothelial cancer (TA692) again applied a stopping rule. The Committee stated the fact that in other tumour types Avelumab has no stopping rule applied in other cancers. This is irrelevant for NICE’s review of its benefit in urothelial cancer and consistency of approach for check point inhibition in urothelial cancer has failed.

1. *The recommendation is unreasonable in the light of evidence submitted to NICE.*

The above referenced TA492 was deemed to have met End of Life criteria. Whilst the TA492 patient group itself are not the receiving first line chemotherapy as in JAVELIN 100, the comparator arm of JAVELIN 100 clearly documents the prognosis of patients treated with placebo post chemotherapy as 14.3 months from initiation of chemotherapy, falling well within the standard EOL criteria. NICE itself has utilised both median and mean life expectancy in this patient group in other appraisals and its decision to focus on mean rather than median in this group unfairly biases against a fraction of long term survivors.

The NIHR study LAMB investigated the use of maintenance lapatinib after chemotherapy in an identical patient population in the UK of advanced/metastatic urothelial cancer, and documented a median Overall survival of 12.0 months in the placebo arm, and 12.6 in the lapatinib group (N =446 for the trial). Only 30 percent of patients in this study were able to go on to receive second line chemotherapy and this is in keeping with other studies.

In JAVELIN 100, Overall survival remained significantly better in the group treated with maintenance Avelumab despite greater numbers receiving subsequent treatment in the control use (61.7%) with 43.7% subsequently receiving Immunotherapy. It is against the published data to assume that all patients progressing after first line platinum based chemotherapy will have the option to access second line immune checkpoint inhibitors. Some will progress rapidly (as seen in the initial number of patients already failed at time of 3 months scan in JAVELIN 100) and never be fit enough for further treatment.

The life expectancy of patients with advanced bladder cancer is well documented in the references submitted to the Panel and is from Global Phase 2 and 3 data, 9.5 to 16.3 months. This is in keeping with clinical experience.

The Evidence Review Group’s base case prediction of overall survival of 27.8 months is completely out with UK clinical experience and the experience of patients. NICE’s ERG on TA525 assumed a mean survival of 12 months, improved by second line Atezolizumab by a further 8 months for the 1 in 5 patients who respond to this treatment. If one assumes that every second line patient was suitable for, received and responded to Atezolizumab (a highly implausible scenario in real life), the maximum mean survival would be 22 months.

In conclusion, the UK Uro Oncology community would ask NICE to reconsider their decision based on the factors listed above, to approve its use, to implement a stopping rule, and to accept that advanced urothelial cancer patients in this setting meet End of Life Criteria. In addition, NICE’s reviews in the arena of advanced urothelial cancer have been few in number over the last 20 years emphasising the importance of maintenance Avelumab in extending life and prolonging quality of life and allowing equity of access to life extending treatments in urothelial cancer as with any other cancer. Advanced/metastatic Urothelial cancer has few options. The use of chemotherapy in this setting is 20 years old and there have been few new treatments.

We would also wish to avoid an effective post code lottery if other review bodies such as the SMC deem that EOL criteria have been met

Yours faithfully

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Consultant Clinical Oncologist & Honorary Clinical Professor

Secretary, British Uro Oncology Group

Independent Clinical Expert NICE first appraisal (ID 3735)