HTA assessments of metastatic urothelial carcinoma treatment in EU countries

Tatyana Benisheva[1,3], Borislav Borissov[3], Dobriana Sidzhimova[1,3] Rumyana Atanasova [3]
[1]Medical University - Sofia, Bulgaria, Faculty of Public Health, [2]Prescriptia EOOD
[3] Bulgarian Association for Drug Information www.badibg.org

OBJECTIVE: Immunotherapy agents (atezolizumab and pembrolizumab) targeting programmed cell death protein-1 (PD-1) and programmed death ligand-1 (PD-L1) for the treatment of metastatic urothelial carcinomas (UC) was approved by the EC in 2018. Following platinum-based chemotherapy, atezolizumab and pembrolizumab have clinical efficacy in patients with metastatic UC with disease progression. These drugs are considered as second-line therapy over single-agent chemotherapy for patients who fail or progress after platinum-based treatment

METHODS:

Documentary Method: Atezolizumab and pembrolizumab for UC were subject to HTA evaluation, in several EU countries: Bulgaria, France, Germany, Ireland, UK - Scotland and UK – England, where clinical data, safety profile and reimbursement parameters were reviewed.

Empirical Method: Several different HTA sources were compared, evaluated and analysed.

RESULTS:

Regarding pemrolizumab n 4 (66%) countries, except Scotland, has a positive HTA assessment. UK-Scotland - SMC first does not recommend it for reimbursement because no robust clinical data had been presented.

Pembrolizumab was accepted with SMC restriction: treatment with pembrolizumab is subject to a two-year clinical stopping rule.

The NCPE in Ireland recommends that pembrolizumab could be considered for UC reimbursement if cost-effectiveness is improved to existing treatments. NICE concluded for pembrolizumab, that extends life by at least 3 months, and meets the criteria for end-of-life treatments and is included in the Cancer Drug Fund.

Regarding atezolizumab two countries (33%) Bulgaria and UK-England recommended it for reimbursement, respectively Positive Drug List and Cancer Drugs Fund.

GBA in Germany required cost/benefit dossier for both UK products in January 2019. The published data from 27 of March 2019 present that there is no added benefit for both products in comparison to ATC. (Table 2) Two countries (33%) (Ireland-NCPE and UK-Scotland - SMC) have not considered atezolizumab for reimbursement (Table 1 and Table 2).

There is no yet HTA assessment, published for UC indication at HAS.

CONCLUSIONS:

The results for both INN at the various HTA authorities in the surveyed EU countries differ due to absence of cost effectiveness or uncertainty of data. (Table1)

Table 1. HTA evaluation for Atezolizumab and Pembrolizumab in UK-England and UK-Scotland

UK - England/ NICE	Atezolizumab	Pembrolizumab
HTA decision from	13 June 2018	25 April 2018
reimbursement	100 %- patient access scheme.	100 % - Cancer Drugs Fund
available on	Atezolizumab is recommended as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if: atezolizumab is stopped at 2 years of uninterrupted treatment or earlier if the disease progresses and the company provides atezolizumab with the discount agreed in the patient access scheme https://www.nice.org.uk/guidance/ta525	Therefore the committee concluded that pembrolizumab was suitable to be recommended for use in for people with locally advanced or metastatic urothelial carcinoma who have had platinum-containing chemotherapy https://www.nice.org.uk/guidance/ta519/chapter/3-Committee-discussion
UK - Scotland/ SME		
HTA decision from	05 October 2018	12 February 2018
reimbursement	**Atezolizumab** is not **recommended** for use within NHS Scotland. In a phase III randomised study of patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy, - there was a small numerical increase in median overall survival for patients treated with atezolizumab compared with chemotherapy. - The submitting company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC. This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting. This advice replaces the second line recommendation for atezolizumab SMC No 1297/18.	**Pembrolizumab** is accepted SMC restriction: treatment with pembrolizumab is subject to a two-year clinical stopping rule. In a phase III study of patients with measurable urothelial carcinoma with progressive disease on or after platinum-based chemotherapy, treatment with pembrolizumab was associated with a statistically significant improvement in overall survival when compared with investigator's choice of single-agent chemotherapy. This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of pembrolizumab. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower. This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.
available on	https://www.scottishmedicines.org.uk/medicines-advice/atezolizumab-tecentriq-2nd-line-uc-fullsubmission-smc2103	https://www.scottishmedicines.org.uk/medicines-advice/pembrolizumab-keytruda-fullsubmission-129118/

Table 2. Time of HTA evaluation for Atezolizumab and Pembrolizumab In Bulgaria, Ireland, France and Germany

SmPC indication	**Atezolizumab** Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC): • after prior platinum-containing chemotherapy, or • who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%	**Pembrolizumab** as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapyand whose tumours express PD-L1 with a combined positive score (CPS)≥10
Bulgaria		
HTA decision from	27.11.2018	Not available
reimbursement	100 % Annex 2 of Positive Drug List https://portal.ncpr.bg/registers/	100 % Annex 2 of Positive Drug List https://portal.ncpr.bg/registers/
HTA - Summary available on Website	http://www.ncphp.government.bg/files/komisa%20zdr.tehn./dokladi/TECENTRIQ-rezume.pdf	Not available
Ireland - NCPE		
decision from	07.06.2019	23.03.2019
reimbursement	A full HTA is not recommended. The NCPE recommends that atezolizumab not be considered for reimbursement at the submitted price. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.	The NCPE recommends that pembrolizumab to be considered for reimbursement for this indication if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.
HTA available on	http://www.ncpe.ie/drugs/atezolizumab-tecentriq-for-urothelial-carcinoma-2l/	http://www.ncpe.ie/drugs/pembrolizumab-keytruda-for-urothelial-carcinoma-2l/
France - HAS		
HTA decision from	7 May 2019	18 October 2019
reimbursement	restriction of the indication to patients with PD-L1-expression tumours - 5% in the treatment of	No data for metastatic urothelial carcinoma in adults found
HTA - available on	https://www.has-sante.fr/jcms/pprd_2982779/fr/tecentriq	https://www.has-sante.fr/jcms/fc_2875171/fr/resultat-de-recherche-antidot-2019?text=urothelial+carcinoma&tmpParam=&opSearch=
Germany-IGWIG		
HTA decision from	27 March 2019	27 March 2019
reimbursement	The company presented no suitable data for the assessment of atezolizumab in the treatment of locally advanced or metastatic urothelial carcinoma in adults for whom cisplatin-containing first-line treatment is unsuitable and whose tumours have a PD-L1 expression ≥ 5%. This resulted in no hint of an added benefit of atezolizumab in comparison with the ACT; an added benefit is therefore not proven.	The company presented no suitable data for the derivation of an added benefit of pembrolizumab as monotherapy in the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a CPS ≥ 10. This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.
HTA available on	https://www.iqwig.de/en/search.1029.html?query_extended=atezolizumab+metastatic+urothelial+carcinoma+after+prior+platinum-containing+chemotherapy&date_from=&date_to=	https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-89-pembrolizumab-urothelial-carcinoma-first-line-benefit-assessment-according-to-35a-social-code-book-v-new-scientific-findings.11472.html

References - all are in the tables

1. Ordinance № 9 from 1 December 2015 for the conditions and rules of the HTA assessment SG97/11December 2015 http://ncphp.government.bg/files/komisa%20zdr.tehn./Naredba_ocenka_zdravni_tehnologii_11_12_2015.pdf (access date 10/10/2018)

2. Ordinance on the Terms, Rules and Procedure for Regulation and Registration of Prices for Medicinal Products, SG no. 40 from 30 April 2013,
last changes and amend. SG no. 62 from 6 August 2019
https://ncpr.bg/images/Naredbi/2019/%D0%9D%D0%A3%D0%9F%D0%A0%D0%A0%D0%A0%D0%A6%D0%A0%D0%9F_6_08_2019.pdf (access date 10/10/2019)