REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Tecentriq

1200 mg - 20 ml concentrate for solution for infusion x 1 vial

atezolizumab

Therapeutic indication(s)	As monotherapy, indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%.
Start/end date of procedure	19.07.2019 – 20.12.2019
Final decision	To add a therapeutic indication in Annex 2 of the Positive Drug List (PDL) for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF beyond the value of the rendered medical services.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Tecentriq

Health problem

The therapeutic options for patients with locally advanced or metastatic urothelial carcinoma (UC) are limited, patients are usually elderly and have comorbidities. Practice shows that there is a need for more efficacious and better tolerable treatments.

Urothelial carcinomas include carcinomas of the bladder, ureter and renal pelvis, urethra, which occur in a ratio of 50:3:1. The main risk factor for UC is smoking, with the risk of developing cancer being 2.6 times higher in smokers than in non-smokers. Patients treated with chemotherapy or radiation therapy are at increased risk of developing UC.

A significant proportion of patients are considered unsuitable for cisplatin treatment. For these patients alternatives are gemcitabine and carboplatin-based therapies, considered to be less effective but being the only alternatives. Hence, some patients with advanced UC do not receive first-line treatment.

PD-L1 is expressed on tumor cells and tumor-infiltrating immune cells (IC), and is a transmembrane protein that plays an important role in blocking the antitumor immunological cycle. Binding of PD-L1 to the PD-1 and B7.1 (CD80) receptors inhibits T-cell activation, proliferation and secretion of cytotoxic mediators and thus inhibits the destruction of tumor cells.

Patients eligible for first-line treatment with atezolizumab monotherapy should have PD-L1 expression ≥ 5% on immune cells from archival or fresh tumor tissues, established through specific immunohistochemical validated test (SP 142 Ventana).

Epidemiological data

UC is the ninth most common malignancy, being the seventh most common carcinoma in men and the 17th most common carcinoma in women worldwide. The risk of developing UC is more than four times higher in men than in women (WCRF).

In Bulgaria, according to the Bulgarian Cancer Registry, the frequency is 40.1/100,000 for men and 11.9/100,000 for women. The prevalence is 9850 for men and 3475 for women. The mortality rate is 13.7/100,000 for men and 3.7/100,000 for women. The epidemiological picture remains incomplete - in Bulgaria about 5% are patients whose disease has progressed to stage IV. Also, about ¼ of patients with locally advanced or metastatic UC will not receive

first-line treatment. About 20% of patients are considered unsuitable for first-line cisplatin treatment.
The stages of the UC are determined according to the TNM classification. UC can be categorized as non-invasive (stage I) or invasive (stages II through IV). Stages III and IV include locally advanced or metastatic disease.

In Bulgaria, according to expert estimates, about 20% of patients are considered unsuitable for treatment with cisplatin, and another about 25% are not expected to receive first-line therapy for various reasons. Treatment regimens that do not include cisplatin are often not well tolerated (most patients require dose reduction or discontinuation due to toxicity).

Efficacy data

A clinical trial evaluating the efficacy and safety of atezolizumab was cited - IMvigor 210 (NCT02108652) - Phase 2, a global, multicenter, single-arm, two-cohort study, estimating the therapeutic efficacy of atezolizumab in patients with locally advanced and metastatic UC. Number of patients participating in the study - 438.

End point:
The primary endpoint is ORR. Secondary endpoints: PFS, DOR (IRF score according to RECIST v1.1 and investigator score according to modified RECIST ‡); ORR, DOR and PFS (investigator assessment according to RECIST v1.1); OS and 1-year OS; and safety, tolerability, pharmacokinetics (PKs) and the presence of Anti-Therapeutic Antibodies (ATAs). The end date of data collection for the primary therapeutic efficacy analysis is 5 May 2015 for Cohort 2 and 14 September 2015 for Cohort 1.

Therapeutic efficacy (Cohort 1) NCT02108652
In the primary analysis performed when the last patient enrolled in the study was followed for a minimum of 24 weeks, the median duration of the follow-up period was 8.5 months.

In the population with all patients, a clinically significant ORR was found, assessed by IRF according to RECIST v1.1 - 19.3%.

In the updated analysis, the median OS was 15.9 months (95% CI: 10.4 months, not subject to assessment); The 1-year frequency of OS is 57.2% (48.2, 66.3).

Median duration of therapeutic response was not achieved at the end of follow-up. The lower limit of 95% CI is 30.4 months, so the duration of the response is likely to be longer.

Tumor load

Monitoring of the tumor load in patients who achieved the best response with stable disease (e.g. non-responders according to RECIST v.1.1) shows that with long-term use of atezolizumab, disease control was maintained and tumor load decreased despite progression according to RECIST. These data suggest that the time the tested drug had been administered is a better indicator of clinical benefit than progression according to RECIST.

Subgroup analysis (Cohort 1) NCT02108652

In Cohort 1, a clinically significant and sustained response was observed in the IC2/3, IC1/ 2/3, IC0, IC1 and IC0/1 subgroups. There are no confirmed results for OS (OS rate 49.6%). No median duration of response was achieved in any of the subgroups.

Safety data

The safety profile of atezolizumab is favorable. The majority of treatment-related adverse reactions (ADR) are grade 1 and 2, and the immune-related are easily managed. The safety profile is consistent with data already published for this INN, pertaining to other tumor sites and is more favorable than chemotherapy. For example, gemcitabine + carboplatin resulted in treatment discontinuation in 21% of patients with reported high haematological toxicity (neutropenia), compared with 8% with discontinuation of atezolizumab and no reported cases of neutropenia.

No loss in glomerular filtration was observed with atezolizumab (most patients in IMvigor 210 cohort 1 had renal impairment).

The safety data from this study show that the most common ADR (in over 10% of patients) are fatigue, diarrhea and itching. Immune-mediated ADR have been reported in 12% of patients.

Summary of the safety profile

The safety data for atezolizumab as monotherapy are based on pooled data from 3,178 patients with different tumor types. The most common adverse reactions (> 10%) were fatigue (35.9%), decreased appetite (25.5%), nausea (23.5%), cough (20.8%), dyspnea (20.5%), pyrexia (20.1%), diarrhea (19.7%), rash (19.5%), back pain (15.3%), vomiting (15.1%), asthenia (14.5%), arthralgia (13.9%), musculoskeletal pain (13.1%), pruritus (12.6%) and urinary tract infection (11.6%).

Data on comparators

The approved indication for first-line treatment of patients with UC focuses on the use of atezolizumab only in a small and difficult-to-treat group of patients who are not eligible for the gold standard treatment, namely cisplatin-based therapy. In addition, these patients should have a PD-L1 expression ≥ 5%. Based on international and national recommendations, in these patients the main therapeutic alternatives that are expected to be partially or completely replaced by the new technology are the combination of **gemcitabine + carboplatin** and **pembrolizumab**.

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions, intended for the health care systems of other countries

Health technology assessments for atezolizumab in patients with advanced or metastatic UC who are not eligible for cisplatin-based chemotherapy have been published in England (NICE, 2017), Germany (IQWIG, 2018) and Sweden (TLV, 2018). The assessments are positive and the drug therapy is being reimbursed in these countries.

Applied analysis

Presented as alternatives are the combination of gemcitabine + carboplatin, which is the most commonly used in such patients, and pembrolizumab, which is reimbursed in Bulgaria for the specific group of patients (unsuitable for first-line treatment with cisplatin-based therapy).

The following methods have been applied:

- for comparison to gemcitabine + carboplatin, a cost-utility analysis (CUA) was applied, showing the benefits in long-term QALY and LYG and showing the incremental ratio for both.
- A cost-effectiveness analysis (CEA) was applied for comparison with pembrolizumab, with the data coming from clinical trials of the compared alternatives. PFS results were used for the two technologies compared.

The perspective is that of the paying institution – the NHIF. The selected time horizon is lifelong - 20 years, long enough to properly reflect all the important differences in the results - life expectancy and long-term therapeutic outcomes, as well as costs. Results and costs have been discounted by 3.5%.

Cost-benefit analysis results comparing atezolizumab to gemcitabine + carboplatin

A cost-benefit analysis found that atezolizumab compared to gemcitabine + carboplatin alternative was cost-effective, providing more health benefits (LYG and QALY) at a higher cost. The conducted sensitivity analysis shows that when the benefits and costs ranged within ± 20%, the probability of atezoluzumab being cost-effective is over 68%.

Results from the cost-effectiveness analysis comparing atezolizumab to pembrolizumab

The cost-effectiveness analysis of atezolizumab versus pembrolizumab shows that atezolizumab dominates, i.e. there are greater benefits and lower costs compared to pembrolizumab.

The results of the analyses show that atezolizumab is a cost-effective technology in the treatment of patients considered ineligible for cisplatin treatment and whose tumors have a PD-L1 expression ≥ 5%.

No subgroup analysis was performed.

Costs

Costs presented in the analysis include costs for atezolizumab technology, for gemcitabine + carboplatin alternative, for pembrolizumab alternative, for treatment administration, costs related to ADR, with the expected average duration of treatment of less than one year (about 4 months) for all analyzed technologies.

Budget impact analysis

The budget impact analysis was performed with reference to pembrolizumab as a major alternative to be completely or partially displaced by the new technology. It is also the only other alternative approved by EMA with an indication for the target group of patients. The costs of hospital therapy administration and ADR mangement are considered to be the same and have been excluded from the analysis.

The perspective of the budget impact analysis is that of the paying institution – the NHIF. The time horizon of the analysis is 5 years. The number of patients eligible for treatment with the new alternative is expected to be 13 patients in the first year, increasing to 35 patients in the fifth year.

The inclusion of atezolizumab in the PDL as a first-line treatment of patients will lead to a reduction in the payer's budget during each of the five years of the analysis, without taking into account risk-sharing agreements and patient access schemes. A one-way sensitivity analysis has been performed, confirming the main conclusions.

Conclusion

Tecentriq (atezolizumab) as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC) in patients considered ineligible for treatment with cisplatin and whose tumors have a PD-L1 expression ≥ 5%. The efficacy and safety of atezolizumab in the target population were demonstrated in the clinical trial IMvigor 210 Cohort 1.

The results show the achievement of the primary endpoint ORR (total response rate/objective response rate), which is statistically and clinically significant in both the general population (ITT) and the subgroups of patients, distributed according to PD-L1 expression.
The secondary endpoints PFS, OS and DOR also achieved statistical significance of the results.

The safety profile of atezolizumab is favorable. It is consistent with data already published for this INN, pertaining to other tumor locations.

The results of the budget impact analysis show that inclusion of atezolizumab in the PDL for the treatment of first-line mUC patients will lead to a reduction in the payer's budget during each of the five years of the analysis.