

# МЕДИЦИНСКИЕ НАУКИ

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## СОВРЕМЕННЫЕ ИНГИБИТОРЫ КОНТРОЛЬНЫХ ТОЧЕК И ИХ ВОЗМОЖНОСТИ ПРИ ТЕРАПИИ МЕТАСТАТИЧЕСКОГО УРОТЕЛИАЛЬНОГО РАКА

DOI: [10.31618/ESU.2413-9335.2020.6.74.761](https://doi.org/10.31618/ESU.2413-9335.2020.6.74.761)*Тилляшайхов М.Н.,**Камышов С.В.,**Бойко Е.В.*

*Республиканский специализированный  
Научно-практический медицинский центр онкологии и радиологии  
Министерства здравоохранения Республики Узбекистан,  
Ташкент*

## MODERN CONTROL POINT INHIBITORS AND THEIR POSSIBILITIES FOR THE THERAPY OF METASTATIC UROTHELIAL CANCER

*Tillyashaikhov M.N.,**Kamishov S.V.,**Boyko E.V.*

*Republican Specialized  
Scientific and Practical Medical Center of Oncology and Radiology  
of the Ministry of Health of the Republic of Uzbekistan,  
Tashkent.*

### РЕЗЮМЕ

В течение длительного времени химиотерапия являлась основным вариантом лечения метастатической уротелиальной карциномы (mUC). За последний год произошли революционные изменения, связанные с одобрением пяти новых препаратов, нацеленных на блокирование взаимодействия между поверхностным белком Т-лимфоцитов PD-1 и его лигандами PD-L1 и PD-L2, в результате чего происходит активация иммунного ответа организма. Примечательно, что антитело против PD-1 пембролизумаб продемонстрировало увеличение общей выживаемости относительно химиотерапии в рандомизированном исследовании III фазы во второй линии метастатического уротелиального рака. На основании этого исследования пембролизумаб был одобрен к использованию Управлением по контролю за продуктами и лекарствами США (FDA). Ниволумаб (анти-PD-1) также продемонстрировал увеличение общей выживаемости по сравнению с историческим контролем и был одобрен FDA для лечения пациентов с метастатическим уротелиальным раком во второй линии терапии. Аналогично антитела, нацеленные на PD-L1, включая атезолизумаб, дурвалумаб и авелумаб, получили ускоренное одобрение FDA в качестве второй линии лечения метастатического уротелиального рака. Некоторые из этих агентов одобрены в первой линии по результатам II фазы исследования (атезолизумаб и пембролизумаб получили ускоренное одобрение для лечения в первой линии у пациентов, не получавших цисплатин). Несмотря на это, клиническое внедрение биомаркеров с целью селекции пациентов, которые могут иметь максимум преимуществ от назначения препаратов данной группы, а также определения оптимальной последовательности терапии остается крайне важным и требующим дальнейшего изучения вопросом.

### ABSTRACT

For a long time, chemotherapy remained the main treatment option for metastatic urothelial carcinoma (mUC). Over the past year, there have been revolutionary changes associated with the approval of five new drugs aimed at blocking the interaction between the surface protein of T-lymphocytes PD-1 and its ligands PD-L1 and PD-L2, resulting in the activation of the immune response. It is noteworthy that the anti-PD-1 antibody pembrolizumab demonstrated an increase in overall survival relative to chemotherapy in a randomized phase III trial in the second line with mUC. Based on this level 1 evidence pembrolizumab was approved by the US Food and Drug Administration (FDA). Nivolumab (antibody PD-1) also demonstrated an increase in overall survival compared to historical control and was approved by FDA. Likewise, antibodies targeting PD-L1, including atezolizumab, durvalumab and avelumab, received accelerated approval from the FDA as the second line of treatment for mUC. Some of these agents are approved in the first line by the results of phase II study (atezolizumab and pembrolizumab received accelerated approval for first-line treatment in patients not receiving cisplatin). Despite these many endorsements, clinical development of new biomarkers for selection of patients, who can get maximum advantages of immunotherapy and also for development the optimal therapy sequencing still are biggest and critical question for future investigation.

The clinical introduction of biomarkers to determine optimal treatment of patients remains extremely important.

**Ключевые слова:** рак мочевого пузыря, PD-1, PD-L1, иммунотерапия, атезолизумаб, ниволумаб, пембролизумаб, авелумаб, дурвалумаб

**Key words:** bladder cancer, PD-1, PD-L1, immunotherapy, atezolizumab, nivolumab, pembrolizumab, avelumab, durvalumab

In 2017, about 79,000 new cases of bladder cancer and 16,870 deaths from this disease were reported in the United States [1]. Around the world, 168,000 people died of urothelial cancer [2]. In most patients, non-muscularly invasive cancer is primarily detected, and in 30–40%, an invasive disease, which is characterized by a worse course and prognosis. Five-year overall survival at all stages of urothelial cancer ranges from 15 to 20%. With metastatic urothelial carcinoma, despite the treatment, the survival rate over the past 30 years has not changed significantly. And only the emergence of a new class of drugs, whose action is aimed at immune control points (PD - 1 / PD - L1), allowed this indicator to shift in a positive direction [3–5]. Over the past 18 months, five new immuno-oncological drugs have been approved in the second line of therapy for metastatic urothelial cancer. This review provides key insights into FDA-approved anti-PD-1 and anti-PD-L1 drugs for the treatment of advanced and metastatic urothelial cancer and discusses future directions for the development of immunotherapy.

#### IMMUNOTHERAPY IN METASTATIC UROTELIAL CANCER

Five immunotherapeutic agents approved by the FDA for metastatic urothelial cancer showed a comparable second-line response rate (PSR) of 15 to 23% in patients. Atezolizumab, nivolumab, durvalumab and avelumab were approved according to the results of single-group studies evaluating overall survival (OS) and PSR compared with chemotherapy. Pembrolizumab is currently the only drug that has proven effective in metastatic urothelial cancer in a randomized phase III trial. Atesolizumab, registered by the FDA according to the results of the second phase, did not demonstrate its advantage in comparison with standard chemotherapy in the third phase of the randomized clinical trial IMvigor 211.

##### Atezolizumab

Atezolizumab is IgG1, a monoclonal antibody to PD - L1 expressed on tumor cells and on tumor-infiltrating immune cells. PD - L1 interacts with PD - 1 and B7.1 on the surface of T - cells, as a result of which their activity is suppressed. By blocking this interaction, atezolizumab activates T cells, restoring their ability to effectively detect and attack malignant cells. This is the first drug that has received FDA approval [6, 7] from a Phase II study of IMvigor 210, in which patients with metastatic urothelial cancer received 1200 mg of atezolizumab once every 3 weeks [8]. There were two cohorts in this study. Cohort II included patients who progressed with or after platinum-based chemotherapy or within 12 months after previous neoadjuvant or adjuvant therapy. The frequency of objective responses in the general population was 14.8% (CI 11.1–19.3). With a low level of expression of PD - L1 by immune cells (IR) (<5%), the ORR was 9.5%, with a high level of expression of PD - L1 (> 5%), the ORR was higher and amounted to 26%. Based on a 10% response rate (historical control),

the FDA approved the use of atezolizumab in patients who progress after platinum-based therapy or who progress within 1 year after neoadjuvant or adjuvant platinum therapy. The median overall survival of patients receiving the second line of therapy with atezolizumab was 7.9 months (CI 1.7–9.3 m) with a median follow-up of 11.7 months. Continued responses were observed in 38 of 45 patients (84%), which indicated that a significant proportion of patients who responded to treatment had a lasting benefit from the therapy. Another group of this study, cohort I, included patients who had not previously received cisplatin, but received atezolizumab in the first line in this study in the same mode as in cohort II [9]. Most patients in cohort I suffered from renal failure, which interfered with cisplatin administration (70%). The ORR for this cohort of 123 patients was 23%. The median overall survival for the entire cohort was 15.9 months (95% CI: 10.4 months - not evaluated), 21% of patients remained on treatment for more than 1 year. In cohort I, in contrast to cohort II, the PSR score was not dependent on the level of PD - L1 expression (28% with PD - L1 expression level > 5% expression and 21% with PD - L1 expression level < 5%). The median overall survival was also independent of PD - L1 status (12.3 versus 19.1 months for expression > 5% and < 5%, respectively). Based on the fact that the PSA study obtained exceeded the historical control results, the FDA approved the use of atezolizumab in patients with metastatic urothelial cancer who had not previously received cisplatin. The most common adverse events (AEs) during treatment with atezolizumab in cohort I and II were fatigue, diarrhea, and itching. Recently, a randomized trial of phase III of IMvigor 211 (NCT02302807) was published, in which atezolizumab was compared with different chemotherapy regimens. In this study, unfortunately, it was not possible to reach the primary endpoint — an increase in overall survival with atezolizumab therapy compared with chemotherapy. This unexpected result underscores the need for large randomized trials of phase III to confirm the results obtained in studies of phases I – II.

##### Nivolumab

Nivolumab is a fully human monoclonal antibody to PD - 1 (IgG4), blocking the interaction between the PD - 1 receptor and its PD - L1 and PD - L2 ligands. The drug has received accelerated FDA approval as a monotherapy for common inoperable or metastatic urothelial cancer in patients after prior platinum therapy, regardless of their PD-L1 status. Approval was obtained based on the results of a Checkmate 275 Phase II trial. 270 patients received 3 mg / kg nivolumab treatment intravenously every 2 weeks until disease progression or intolerable toxicity [10]. PD-L1 expression was evaluated using the Dako test system (Dako PD-L1 IHC kit) and differed from that in the IMvigor 210 study, which evaluated the expression of PD-L1 immune cells using a different diagnostic antibody and staining method. In the Checkmate 275 study, the frequency of objective responses was 19.6%

compared with the historical response control (10%) with a median time to response of 1.9 months and a median response duration not achieved at the time of the evaluation. Unlike cohort II (IMvigor 210), the ORR increased with increasing expression of PD - L1 in tumor cells

(ORR was 28.4% and 16.1% for PDL1 expression by tumor cells  $\geq 5\%$  and  $< 5\%$ , respectively). The median OS was 11.3 months in patients with PD - L1 expression  $\geq 1\%$  compared with 5.95 months in patients with PD - L1 expression  $\leq 1\%$ . The median overall survival in all patients, regardless of expression level, was 8.74 months. Adverse events of the 3-4th degree of severity associated with the therapy were 18%. The most frequent grade 3-4 AEs noted during treatment with nivolumab were weakness, diarrhea, and pruritus, which occurred in 2% of patients. In February 2017, based on the data from the Checkmate 275 study, nivolumab was approved by the FDA for the treatment of patients with locally advanced or metastatic urothelial cancer who had a progression of the disease during or after receiving platinum-containing chemotherapy regimens. In December 2017, nivolumab was approved in the Russian Federation as monotherapy for patients with advanced inoperable or metastatic bladder cancer.

The effectiveness and tolerability of nivolumab is also being studied in the framework of the open multicenter study of Phase I / II Checkmate 032, where patients with urothelial cancer who previously received at least one previous platinum-containing line of therapy received nivolumab in monotherapy at a dose of 3 mg / kg once every 2 weeks or in combination with ipilimumab (a fully human monoclonal anti-CTLA - 4, IgG 1 monoclonal antibody) in various dose regimens followed by nivolumab monotherapy until progression or intolerant toxicity. The primary criterion for evaluating the effectiveness was the PSM according to RECIST 1.1, and the secondary criteria were PFS, OS, and the safety and duration of the response. As part of the nivolumab monotherapy regimen, 78 patients received treatment. The frequency of objective responses in this cohort was 24.4%. This indicator was not dependent on the level of expression of PD - L1. When combined with ipilimumab, nivolumab was prescribed in the following dose modes: nivolumab 1 mg / kg plus ipilimumab 3 mg / kg or nivolumab 3 mg / kg plus ipilimumab 1 mg / kg, intravenously, every 3 weeks, 4 cycles in a row. Then, patients received only nivolumab at a dose of 3 mg / kg every 2 weeks until disease progression or intolerant toxicity. The highest ORR was obtained in the nivolumab group 1 mg / kg + ipilimumab 3 mg / kg and amounted to 38.5%. Patients treated with the combination of nivolumab 3 mg / kg plus ipilimumab 1 mg / kg achieved an ORR in 26% of cases. Nivolumab monotherapy allowed to achieve a PSR in 24.4% of cases. The promising results of phase II of this study allowed the initiation of phase III of a clinical study to evaluate the effectiveness of this therapy compared to standard chemotherapy for advanced urothelial cancer.

#### **Durvalumab**

Durvalumab - IgG1, a modified human monoclonal antibody to PD - L1, which was approved in May 2017 based on a phase I / II study evaluating 61

patients after progression in the background or after platinum-based chemotherapy with metastatic urothelial cancer [17]. The study also included patients who had a relapse of the disease within 1 year after neoadjuvant chemotherapy. Safety in this study was evaluated in 60 patients, response to therapy in 42. The study used PD-L1 status determination using the Ventana SP263 kit. In order to distribute patients in the PD-L1 status study, a positivity biomarker was used. If tumor or immune cells showed  $\geq 25\%$  staining during immunohistochemistry, then such patients were considered PD - L1 positive, if the severity of staining was  $\leq 25\%$ , then these patients were considered negative in terms of PD - L1 expression [18]. Using this new combination biomarker, patients with negative PD - L1 expression in tumor and immune cells had an ORR of 0% (0 out of 14) compared with an ORR of 46.4% in patients with positive PD - L1 status. The overall response to treatment for the entire cohort was 31%. Recent results from yet another study analyzing 191 patients treated with durvalumab showed an ORR of 17.8%. Moreover, in patients with a high level of PD-L1 expression, the response rate was higher than in patients with a low level of expression (27.6% versus 5.1%) [19]. In May 2017, the FDA approved durvalumab based on the frequency of the objective response and the duration of the response to therapy for patients with locally advanced or metastatic urothelial carcinoma previously treated.

#### **Avelumab**

Avelumab is a fully human monoclonal antibody (IgG1) to PD - L1 that blocks the interaction between PD - 1 and PD - L1, but not PD - 1 and PD - L2. In a single-group study of phase Ib of JAVELIN, in which patients with platinum refractory metastatic urothelial cancer were included, the CVR was 18.2%, and the median OS was 13.7 months [20]. Of the 44 patients included in the study, 20% of patients had reactions associated with drug infusion. After 12 weeks of treatment, there was a trend towards improved survival in patients with high PD-L1 levels. Positive for PDL1 expression in this study, samples were taken in which  $\geq 5\%$  of tumor cells were stained. ORR reached 50% in patients with high levels of PD - L1 expression in tumor cells, compared with ORR equal to 4.3% for low-expressing tumors (cut-off 5%). The latest data, with the inclusion of an additional cohort of 241 patients with platinum refractory metastatic urothelial cancer, demonstrated PSR in 17.6% of cases [21]. The median OS for the total cohort of patients was 7.0 months (CI: 5.6–11.1). Using a similar cut-off of 5% of the expression of PD - L1 by tumor cells, the ORR was 25% versus 14.7% with high and low PD - L1 status, respectively. The most common adverse events associated with treatment with avelumab were reactions to infusion (22.8%) and weakness (12.0%). Based on this study, as well as historical control, the FDA approved avelumab for use in the 2nd line of treatment for patients with locally advanced or metastatic bladder cancer who had previously received chemotherapy using platinum drugs.

#### **COMBINED IMMUNOTHERAPY IN METASTATIC UROTELIAL CANCER**

The results obtained in clinical trials of the combination of nivolumab and ipilimumab in the

treatment of metastatic melanoma [22], non-small cell lung cancer [23] and metastatic kidney cancer have also been confirmed in the treatment of urothelial cancer. Preliminary data from a randomized study of Phase I / II Checkmate - 032 showed good tolerability and efficacy of the combination in 2 modes. In combination with ipilimumab, nivolumab was prescribed in the following dose regimens: nivolumab 1 mg / kg plus ipilimumab 3 mg / kg or nivolumab 3 mg / kg plus ipilimumab 1 mg / kg, intravenously, every 3 weeks, 4 cycles in a row. Then, patients received only nivolumab at a dose of 3 mg / kg every 2 weeks until disease progression or intolerant toxicity. The ORR was 38.5% in the nivolumab group 1 mg / kg plus ipilimumab 3 mg / kg and 26% in the nivolumab group 3 mg / kg plus ipilimumab 1 mg / kg. Nivolumab monotherapy also showed good PSR rates - 24.4% [24]. Given the maximum ORR achieved in combination with nivolumab (1 mg / kg) and ipilimumab (3 mg / kg) compared with nivolumab monotherapy, it is planned to evaluate the effectiveness of the combination of two immunologics in a phase III trial (Checkmate - 901, NCT03036098). The frequency of complete responses was 4% when prescribing a combination in the nivolumab regimen 1 mg / kg plus ipilimumab 3 mg / kg, 3% when applying the nivolumab regimen 3 mg / kg plus ipilimumab 1 mg / kg and 6% when using nivolumab monotherapy. Another phase I study evaluating the safety of the combination of nivolumab, ipilimumab and the tyrosine kinase inhibitor cabosantinib in metastatic urothelial cancer showed good tolerance [25].

A phase III study is also currently underway, involving 525 patients using a combination of durvalumab and tremelimumab compared to the standard first chemotherapy line [26]. A number of other ongoing studies evaluate the effectiveness of various combinations with anti-PD-1 / PD-L1 therapy, including traditional chemotherapy [27, 28], intravesical BCG therapy, IDO inhibitors such as epacadostat [29], CD27 [30], CD137, OX - 40 [31] and CSF1 - R [32].

### CONCLUSIONS

The results of treatment of patients with widespread unresectable or metastatic urothelial cancer immuno-oncological drugs, such as atezolizumab, nivolumab, pembrolizumab, avelumab and durvalumab, have changed the existing paradigm, subsequent prospects and therapeutic approaches to the management of these patients. A deeper understanding of the complex mechanisms of tumor immunology has led to an intensive study of new drug treatment options in this area. The use of the patient's own immune system in the fight against the tumor was a promising therapeutic strategy for extensive tumor damage and can provide long-term survival in certain groups of patients. Monoclonal antibodies to PD - 1 / PD - L1 showed efficacy and safety in all subgroups of patients with urothelial carcinoma, including those with unfavorable prognostic factors. Although immuno-oncological drugs registered in the treatment of advanced urothelial cancer show similar efficacy, it is currently difficult to predict which patients will benefit most from the administration of immune control point blockers. The search for new and more effective

prognostic markers is needed to determine the target patient populations for immunotherapy, as well as further randomized trials to determine the optimal sequences and combinations.

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