Durvalumab for the management of urothelial carcinoma: a short review on the emerging data and therapeutic potential

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Abstract: Urothelial carcinoma (UC) is the second most frequent urogenital malignancy with high incidence in the United States and Europe. Despite poor prognosis, new treatments have emerged with great efficacy and safety such as immune checkpoint inhibitors. Durvalumab, an anti Programmed Death Ligand 1, has been given breakthrough in UC in 2017 in patients who have disease progression during or following platinum-containing chemotherapy or who have disease progression <12 months after neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Food and Drug Administration approval was given on the results of the Phase I/II study of MEDI 4736. In this article, we will review available data on durvalumab in the treatment of locally advanced and metastatic UC and discuss therapeutic potential.

Keywords: immunotherapy, PD-L1 inhibitor, durvalumab, urothelial carcinoma, bladder cancer

Introduction

Urothelial carcinoma (UC) also known as transitional cell carcinoma is the ninth most common cancer worldwide with 430,000 new cases and 165,000 deaths in 2012. In Europe, the incidence is high with 151,297 new cases in 2012 and 52,411 deaths. Despite the poor prognosis of the disease and the 30% rate of muscle-invasive carcinoma at diagnosis, treatment has remained the same for decades. The cornerstone of metastatic or unresectable disease was platinum-based chemotherapy. The combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) regimen has been considered for first-line therapy in fit patients for 30 years with objective response rates (ORR) around 50%–70%. The association of gemcitabine and cisplatin (GC) has been compared to M-VAC in a Phase III study, showing no improvement in overall survival (OS; M-VAC 14.8 months vs GC 13.8 months), but the study was not powered enough to show equivalence between the two regimens. However, the better safety profile led to an approval of GC as an equivalent of M-VAC. These chemotherapy regimens are tailored for fit patients with good performance status (PS) and adequate renal function. However, 25%–50% of patients with UC are not eligible for cisplatin-based therapies because of age-related comorbidities and epidemiology of the disease. UCs are immunogenic tumors with a high mutational load that can be targeted by immunotherapy.

Moreover, intravesical Bacille Calmette–Guerin, an immunotherapy, has been used since 1990 to reduce recurrence in nonmuscle-invasive bladder cancer. Several immune checkpoint blockers have been given breakthrough in UC since 2016 with promising results (Table 1). In this review, we will focus on the use of durvalumab, an anti Programmed Death Ligand 1 (PD-L1) in UC.
### Table 1 Immune checkpoint blockers with FDA breakthrough approval

| Drugs            | Trial               | Setting                                      | Patients | Results (ITT)                                                                 | Grade 3–4 AE |
|------------------|---------------------|----------------------------------------------|----------|-------------------------------------------------------------------------------|--------------|
| Atezolizumab     | Phase III IMvigor-211 NCT023002807 | Second-line post platinum therapy            | n=931    | OS: 11.1 months vs 10.6 months ORR: 13% vs 13%                                | 20%          |
| Pembrolizumab    | Phase III KEYNOTE-045 NCT02256436   | Second-line post platinum therapy            | n=542    | OS: 10.3 months vs 7.4 months ORR: 21% vs 11%                                | 15%          |
| Nivolumab        | Phase II Checkmate-275              | Second-line post platinum therapy            | n=270    | OS: 8.7 months ORR: 20%                                                        | 18%          |
| Avelumab         | Phase IB               | Post chemotherapy                            | n=44     | ORR: 18%                                                                      | 8%           |

**Abbreviations:** AE, adverse event; FDA, Food and Drug Administration; ITT, intention to treat population; ORR, objective response rate; OS, overall survival.

### Durvalumab

Durvalumab (Imfinzi™, MEDI 4736) is a fully human immunoglobulin G1k monoclonal antibody against PD-L1, which is being developed by Astra Zeneca for cancer treatment (Figures 1 and 2). PD-L1 binds to programmed cell death-1 (PD-1) and CD80 (B7-1) receptors, resulting in inhibition of T-cell function. A broad range of human tumors upregulate PD-L1, evading immune surveillance and antitumor T-cell responses. Durvalumab binds to PD-L1 with high affinity and specificity, blocking its interactions with PD-1 and CD80, resulting in enhanced activation of T-cells against tumor cells (TCs). It does not bind to PD-L2.

Durvalumab is given every 2 weeks intravenously at 10 mg/kg over 60 minutes. Pharmacodynamics parameters showed a concentration-dependent inhibition of PD-L1 in an anti-CD3-based T-cell activation assay and a mixed lymphocyte reaction assay. Exposure to durvalumab increases dose-proportionally at C3 mg/kg in cancer patients, with steady-state levels observed at around 16 weeks. Durvalumab clearance decreases over time but is not considered clinically relevant; the geometric mean terminal half-life of durvalumab is around 17 days. The pharmacokinetics of durvalumab are not affected by age (19–96 years), body-weight (34–149 kg), sex, race, tumor type, PS, levels of albumin, lactate dehydrogenase, creatinine or soluble PD-L1, mild or moderate renal impairment (creatinine clearance 60–89 and 30–59 mL/minute, respectively) or mild hepatic impairment (bilirubin ≤ upper limit of normal [ULN] and AST > ULN or bilirubin >1.0–1.5 times ULN and any AST). No data are available in severe renal or hepatic impairment.

### Efficacy and safety in UC

Durvalumab was evaluated in a Phase I/II study in all solid tumors (Table 2). Subjects received durvalumab 10 mg/kg every 2 weeks until disease progression, unacceptable toxicities, or a maximum duration of 12 months. After the treatment course, patients were offered a retreatment course of another 12 months. The initial 20 patients were enrolled regardless of PDL-1 expression. PD-L1 was defined as positive if either ≥25% of TC or ≥25% of immune cells (IC) expressed PD-L1. In UC patients, most of them (93.4%) had received ≥1 prior lines of platinum-based chemotherapy, 29.5% had liver metastases.

In the expansion phase with a cohort of 182 patients with UC, the ORR was 31.0% (95% CI, 17.6–47.1) overall in the...
42 response-evaluable patients. The ORR was 46.4% in the PD-L1-positive subgroup and 0% in the PD-L1-negative subgroup, and disease control rate at 12 months was 57.1% and 28.6%, respectively. Patients showed rapid and durable response. Median follow-up of response-evaluable patients was 6.5 months (range, 0.8–14.8 months). The median time to response was 6.3 weeks (95% CI, 5.6–12.1 weeks) in the 13 responding patients, and median duration of response has not been reached (range, 4.1+ to 49.3+ weeks). The updated results showed an ORR of 17.8% (34/191; 95% CI, 12.7–24.0), including seven complete responses. The ORRs were 27.6% (n=27; 95% CI, 19.0–37.5) in PD-L1 high patients and 5.1% (n=4; 95% CI, 1.4–12.5) in PD-L1 low or negative patients. Median time to response was 1.41 months (range, 1.2–7.2). Median duration of response in the as-treated population had not been reached at data cutoff (range, ≥0.9 to ≥19.9 months). The median OS was 18.2 months (95% CI, 8.1–not estimable) in the as-treated population and 20.0 months (95% CI, 11.6–not estimable) and 8.1 months (95% CI, 3.1–not estimable) in PD-L1 high and low or negative patients, respectively. The OS rates at 6, 9, and 12 months were 64% (95% CI, 56–71), 57% (95% CI, 47–66), and 55% (95% CI, 44–65), respectively, in the as-treated population.

Durvalumab showed manageable safety profile. Grade 3 or 4 treatment-related adverse events (AEs) occurred in 6.8% of the patients. Treatment-related AEs leading to death occurred in 2 of 191 patients (1.0%) with one autoimmune hepatitis and one pneumonitis. Regarding adverse
events of special interest (AESIs), they occurred in 34.6% and were mostly grade 1 or 2. Their cumulative incidence seemed to plateau at around 32 weeks. Almost 5% experienced treatment-related grade 3/4 AESIs (hepatic and skin events).^17^ Based on these first results, the Food and Drug Administration (FDA) granted accelerated approval to durvalumab in May 2017 for patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or who have disease progression at 12 months after neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

**Biomarkers and companion test**

Finding robust biomarkers that could help select patients who will benefit from immunotherapy is one of the main challenges with immune checkpoint blockers. Mutational burden and high clonal neoantigens have shown great correlation with efficacy of diverse anti-PD-L1/PD-1 and anti-CTLA4 drugs.\(^\text{18,19}\) PD-L1 expression was one of the first biomarkers investigated in multiple tumor types.\(^\text{20–22}\) In the Phase I/II trial of durvalumab, PD-L1 testing was required. PD-L1 status was determined using a companion test Ventana 2P263 assay. Tumor was considered PD-L1 high with expression on ≥25% of either IC or TC. The first 20 patients were enrolled regardless of their PD-L1 status but subsequent patients were required to have 5% of PD-L1 expression on TCs.\(^\text{16}\) FDA approval was also granted with the companion test as a complementary diagnostic for the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded UC tissue. At ASCO 2018, the results of PD-L1 expression in TC or IC on the outcomes of OS, PFS, objective response rate (ORR), best percentage tumor change, and tumor shrinkage 15 months after last subject randomization were presented. Both tumor-infiltrating ICs and TC PD-L1 were linked to higher ORR, and PD-L1 tumor-infiltrating ICs were associated with better survival in patients treated with durvalumab. Remarkably, PD-L1 tumor-infiltrating ICs had a higher impact on response to durvalumab than PD-L1 TC, demonstrating a significant association with OS, PFS, ORR, and tumor shrinkage. The results of this study for patients treated with durvalumab for bladder cancer suggest that a cutoff/algorithm using PD-L1 TC 25%/PD-L1 tumor-infiltrating IC 25% (TC25%/IC25%) provides optimal predictive value based on efficacy and prevalence of the biomarker (HR = 0.46; 90% CI: 0.33–0.64).\(^\text{23}\)

**Future perspectives**

Durvalumab is currently under investigation in combination with other agents such as tremelimumab (anti-CTLA4) in various tumor types (Table 3). First results were presented at ASCO 2018 for the combination of durvalumab and tremelimumab in patients with localized, high-risk, muscle-invasive bladder carcinoma who are ineligible for cisplatin-containing chemotherapy due to decreased renal function, neuropathy, hearing loss, or heart failure (NCT02812420). Patients received durvalumab (1,500 mg) plus tremelimumab (75 mg) on weeks 1 and 5 and then underwent surgery at weeks 9–11. Twelve patients were enrolled and six completed radical cystectomy; three (50%) had pathologically complete response; one (17%) did not respond; two (33%) had upstaging of disease. Only 1 of 12 patients developed grade 3 immune-related toxicity. These promising results showed interesting potential of using immune checkpoint blockers as a neoadjuvant therapy, and results of larger studies are awaited.\(^\text{24}\)
In the first-line setting, the DANUBE trial is ongoing in UC testing the combination of durvalumab and tremelimumab. Results of this Phase III trial will be presented soon and hopefully showed increased response rate. Many questions remain on how to better select patients and also improve the number of patients who will benefit from immune checkpoint blockers.

Main perspectives are thus combination therapies with either other immune checkpoint blockers, epigenetic drugs, chemotherapy or radiation therapy and hopefully find robust biomarkers to increase response rate (Table 3). One option is possibly to combine immune checkpoint blockers and the other option is to adapt treatment based on biomarkers. This

### Table 3  Ongoing studies with durvalumab in UC

| Drugs | Trial | Setting | Status |
|-------|-------|---------|--------|
| Durvalumab ± tremelimumab | DANUBE NCT02516241 Phase III | First line | Ongoing |
| Durvalumab + tremelimumab | NITIMIB NCT03234153 Phase I | Neoadjuvant Muscle-invasive, high-risk, ineligible for cisplatin-based chemotherapy | Ongoing |
| Durvalumab ± tremelimumab + radiation therapy | NCT03601455 Phase II | Unresectable, locally advanced, or metastatic urothelial bladder cancer ineligible or refusing chemotherapy | Recruiting Nov 2018 |
| Durvalumab ± tremelimumab + MVAC | NEMIO NCT03549715 Phase I/II | Neoadjuvant muscle-invasive UC | Not yet recruiting |
| Durvalumab ± BCG Durvalumab ± radiation therapy | ADAPT-BLADDER NCT03317158 Phase I/II | BCG-relapsing UC of the bladder | Ongoing |
| Durvalumab | NCT02901548 Phase II | BCG-relapsing UC of the bladder | Ongoing |
| Durvalumab + olaparib | NEODURVARIB NCT03534492 Phase II | Neoadjuvant bladder carcinoma | Not yet recruiting |
| Durvalumab + BCG vs BCG alone | POTOMAC NCT03528694 Phase III | BCG naive nonmuscle-invasive bladder carcinoma | Ongoing |
| Durvalumab + olaparib | BAYOU NCT03459846 Phase II | First-line in platinum-ineligible unresectable stage IV UC | Ongoing |
| Durvalumab + Vicinium | NCT03258593 Phase I | BCG-relapsing UC of the bladder | Ongoing |
| Durvalumab + tremelimumab vs SoC | DUTRENEO NCT03472274 Phase II | Neoadjuvant bladder carcinoma | Not yet recruiting |
| AZD4547 vs Durvalumab vs AZD4547 + Durvalumab vs Durvalumab + Olaparib vs Durvalumab + AZD1775 vs Durvalumab + Vistusertib | BISCAY NCT02546661 Phase Ib | Muscle-invasive bladder cancer (urothelial) who have progressed on prior treatment | Ongoing |
| Durvalumab with radiotherapy then adjuvant Durvalumab | DUART NCT02891161 Phase I/II | Bladder cancer (T2–4, N0–2, M0) | Ongoing |
| In situ vaccination with tremelimumab and IV Durvalumab + toll-like receptor agonist PolyICLC (TLR3 agonist) | NCT02643303 Phase I/II | Bladder cancer | Ongoing |
| Durvalumab + tremelimumab | NCT02812420 Phase II | Muscle-invasive, high-risk UC ineligible for cisplatin-based neoadjuvant chemotherapy | Ongoing |
| Durvalumab + SoC; Durvalumab + tremelimumab + SoC; SoC | NILE NCT03682068 Phase III | Unresectable or metastatic UC | Ongoing |

**Abbreviations:** BCG, Bacille Calmette–Guerin; SoC, standard of care chemotherapy; UC, urothelial carcinoma.
is the purpose of the BISCY trial (NCT02546661), which is
designed to combine Durvalumab with other targeted therapies
according to biomarkers. This Phase Ib study is a multiam
trial and is evaluating the combination of durvalumab with
AZD4547 (selective inhibitor of the FGFR1, 2, and 3 tyrosine
kinases), Olaparib, AZD1775 (WEE1 inhibitor), Vistusertib
(mTOR inhibitor), or AZD9150 (STAT3 inhibitor) in
patients with UC who have progressed after prior treatment.

Phase III trials are also ongoing in other tumor types, in
first, second, and third line in Non-small-cell lung cancer
(NSCLC; PEARL NCT03003962, MYSTIC NCT02453282,
ARCTIC NCT02352948, PACIFIC NCT02125461) and
in Head and Neck Squamous Cell Carcinoma (KESTREL
NCT02551159, EAGLE NCT02369874).

Very few data are available in older patients with only
subgroup analysis and no geriatric data to better character-
ize the population. However, the incidence of cancer is
increasing in that population. There is a tremendous need for
evidence-based medicine data in that population, to better
adapt treatment strategies. Indeed, compared with conven-
tional cancer therapies, immunotherapy offers a better safety
profile with <10% of severe toxicities and is therefore an
attractive option in older patients.

Due to the low toxicity profile, the revolution of immune
cancer therapy might especially be of great interest in the
older population. Nevertheless, at the moment, there is few
evidence of efficacy and tolerance of these drugs in the
geriatric population. At the same time, a decline of both
adaptive and innate immunity is observed with increasing
age. This phenomenon, called immunosenescence (IS),
is responsible for poor response to vaccination and increased
susceptibility to infections.

Additionally, increased prevalence of autoimmune
disease which is linked with an increase of autoantibodies
is observed in older patients. Especially, in older cancer
patients, modification of both the IC phenotype (mainly T cell
compartment), the immune microenvironment and intracell-
ular communication are the main reasons for dysfunctional
immune responses.

IS is also associated with a state of chronic low-grade
inflammation called inflammaging, responsible for altered
level of cytokines. All these reasons urged us to analyze
efficacy and toxicity of anti PD-L1 therapy.

Therefore, studies with durvalumab in patients with vari-
ous solid tumors including UC, aged >70 years old incorpo-
rating geriatric data to assess safety and efficacy are ongoing.
Moreover, it was recently suggested that a subgroup of
patients presents a deleterious acceleration of their cancer
disease, defined as hyperprogression in different tumor
types such as lung cancers and head and neck cancers.

Several biological hypotheses may explain why PD1/PD-L1
blockade may paradoxically lead to this phenomenon, including,
expansion of PD1+ Tregs, compensatory T-cell exhaustion,
modulation of protumor immune subsets, activation of aber-
rant inflammation, or activation of an oncogenic pathway.
Prospective trials are warranted to validate this new concept.

Improving patient selection for immuno-oncology trials
and real-life setting is an active area of research to better iden-
tify, in particular, fast progressors. Massard et al developed a
tool (FastProgIO) predicting 12-week life expectancy using a
multivariate regression method in patients with NSCLC and
UC treated with durvalumab ± tremelimumab and compared
it to existing published scores (Royal Marsden Hospital
prognostic score [RMH], Gustave Roussy Immune Score
[GRIM], lung immune prognostic index [LIPI]). The
performance was assessed by time-dependent true positive
rate (TPR) and false positive rate (FPR). FastProgIO includes
neutrophils, AST, alkaline phosphatase, and hemoglobin as
the predictive markers. At 12 weeks, the TPR for FastProgIO
was 73%, (90% CI: 67%–80%) vs 69%, 65%, and 41% for
RMH, GRIM, and LIPI, respectively. Furthermore, the FPR
of FastProgIO (11%, 90% CI: 9.3%–13%) was comparable
to LIPI (10%), but better controlled than RMH and GRIM
(20% and 17%). This score needs to be further validated but
can be an interesting option to better select patients eligible
for immune-oncology trials.

Finally, new patterns of response to immune checkpoint
blockers need to be further investigated and described to
improve our understanding of immune checkpoint blockers
and improve patient care.

**Conclusion**

Durvalumab is a safe and effective therapeutic option in UC
and was granted FDA approval in May 2017 based on the
results of the Phase I/II trial. Questions remain about the
optimal therapeutic strategies in UC with the breakthrough
of several anti-PD-I and anti-PD-L1 recently and new treat-
ments such as FGFR inhibitors. Answers may emerge with the
recent molecular characterization of muscle-invasive bladder
cancer. Robertson et al identified five expression subtypes
that may be sensitive to different treatments. This charac-
terization may help practitioners to find optimal strategies
for patients. Moreover, results of trials testing combination
therapies with immune checkpoint blockers are awaited.
Treatment landscape of UC is moving forward, and new
therapeutic options will be available in the upcoming future.
Disclosure
The authors report no conflicts of interest in this work.

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