PD-L1 blockade for urothelial carcinoma

Josephine Kang and Lorenzo Galluzzi

Department of Radiation Oncology, Weill Cornell Medical College, New York, NY, USA; Sandra and Edward Meyer Cancer Center, New York, NY, USA; Université Paris Descartes/Paris V, Paris, France

In May 2017, the US Food and Drug Administration (FDA) granted accelerated approval to durvalumab (IMFINZI®, from AstraZeneca UK Limited) and avelumab (BAVENCIO®, EMD Serono, Inc.) for use in patients with locally advanced or metastatic urothelial carcinoma who exhibit disease progression during or after standard platinum-based chemotherapy, or demonstrate disease progression within 12 mo of neoadjuvant or adjuvant treatment with platinum-based chemotherapy (sources https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm555930.htm and https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm557162.htm). Durvalumab and avelumab, two fully human IgG1 specific for CD274 (best known as PD-L1), add to the growing panel of immunotherapies available for the treatment of urothelial carcinoma.

Urothelial carcinoma, which encompasses carcinomas of the bladder, ureters and renal pelvis, is the second most common urologic malignancy in the United States, with an estimated 79,000 new cases every year.2 Urothelial malignancies are considered to be highly immunogenic, at least in part owing to their relatively high mutational load.3 In line with this notion, the so-called Bacillus Calmette–Guérin—a live attenuated strain of Mycobacterium bovis that mediates rather non-specific immunostimulatory effects by triggering Toll-like receptor (TLR) signaling—has been used with some success for the intravesical therapy of non-muscle invasive bladder carcinoma.4 Nonetheless, the survival rate of patients with urothelial carcinoma failed to improve significantly over the past 10 y.

First-line therapy for locally advanced or metastatic urothelial carcinoma generally consists of platinum-based chemotherapy.5 Patients who progress during or after first-line chemotherapy are considered to be platinum-refractory, and have historically been offered second-line chemotherapy based on various taxanes. In this setting, response rates ranged from 6% to 28%, with median overall survival of a few months, reflecting a significant need for novel, more effective treatment options.6-8

Immune checkpoint blockers including other PD-L1-targeting agents as well as molecules specific for the PD-L1 receptor programmed cell death 1 (PDCD1, best known as PD-1) have demonstrated promise in several clinical studies involving urothelial carcinoma patients. The Phase II IMvigor 210 study examined the efficacy of atezolizumab (TECENTRIQ®, from Genentech Oncology) in patients with locally advanced or metastatic urothelial carcinoma who progressed after platinum-based chemotherapy. Patients on atezolizumab achieved an objective response rate (ORR) of 15%, and 84% of responses persisted at a median follow-up of 11.7 mo, demonstrating a significantly improved efficacy compared with historical controls.9 Based on these results, atezolizumab received accelerated FDA approval in May 2016 for patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or after platinum-based chemotherapy, or within 12 mo of receiving platinum-based chemotherapy (source https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm501878.htm). In this setting, tumor-infiltrating immune cells were assessed for PD-L1 expression using the SP142 immunohistochemical assay (from Ventana Medical Systems, Inc.), but PD-L1 levels did not influence the ability of atezolizumab-treated patients to achieve the primary end point of the study (improved overall response rate as compared with historical controls).9

Soon thereafter, equally encouraging results were obtained from the Phase II Checkmate 275 trial, which assessed the efficacy of the PD-1-targeting agent nivolumab (OPDIVO®, from Bristol-Myers Squibb), in patients with locally advanced or metastatic urothelial carcinoma who exhibited disease progression or recurrence after platinum-based chemotherapy. An ORR of 19.6% was achieved, responses were as durable as those achieved by atezolizumab, and clinical benefits were documented irrespective of PD-L1 expression by tumor-infiltrating immune cells (28.4% ORR with PD-L1 expression > 5% versus 16.1% ORR with PD-L1 expression <1%; both significant).10 These findings drove the accelerated approval of nivolumab by the US FDA for use in this patient subset on 2017, February 2nd (source https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm539646.htm). Similarly, the open-label Phase III KEYNOTE-45 trial demonstrated superior ORR for metastatic urothelial cancer patients with progression after platinum-based chemotherapy receiving the anti-PD-1 agent pembrolizumab (KEYTRUDA®, from Merck and Co.) versus...
investigator’s choice chemotherapy with taxanes or vinca alkaloids (21% versus 11% ORR, respectively). This resulted in FDA breakthrough therapy designation and priority review status, with targeted action date of 2017, June 14th.

Around the same time, durvalumab was granted breakthrough therapy designation by the FDA for patients with locally advanced or metastatic urothelial bladder cancer who progressed after platinum-based chemotherapy (https://www.astrazeneca.com/media-center/press-releases/2016/Durvalumab-granted-Breakthrough-Therapy-designation-by-US-FDA-for-treatment-of-patients-with-PD-L1-positive-urothelial-bladder-cancer-17022016.html). This decision was based upon the results of the Phase II/II Study 1108, demonstrating a promising 31% ORR in patients with PD-L1-expressing urothelial bladder carcinoma, which were first released at the 2016 American Society of Clinical Oncology (ASCO) meeting. Updated efficacy data was presented at the 2017 ASCO Genitourinary Cancers Symposium, pointing to a remarkable 20.4% ORR in all evaluable patients (n = 103), and 31.1% ORR in patients with PD-L1-expressing tumors. Of note, durable clinical responses were documented irrespective of PD-L1 expression levels, as median duration of response was not yet reached at a median follow-up of 7.3 mo. Median overall survival was 14.1 mo at time of data cut-off, which was significantly longer than historical controls. A majority of patients had visceral metastases, and 35% of them had received at least two prior chemotherapy regimens. Overall, durvalumab was well-tolerated, and only three patients had to discontinue treatment due to adverse events. The most commonly noted adverse events were fatigue, arthralgia, constipation, reduced appetite and nausea. PD-L1 expression was evaluated using the SP263 immunohistochemical assay (from Ventana Medical Systems, Inc.), with 25% or more PD-L1 staining in neoplastic or immune cells considered to be positive. On 2017, May 1st, the US FDA granted accelerated approval to durvalumab for use in patients affected by locally advanced or metastatic urothelial bladder carcinoma with disease progression during or following platinum-based chemotherapy, or with disease progression within 12 mo of neoadjuvant or adjuvant treatment with platinum-based chemotherapy. The SP263 PD-L1 assay received simultaneous regulatory approval (https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm559303.htm).

About a week later, on 2017 May 9th, avelumab received accelerated approval by the FDA for the same disease indication (https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm557162.htm). This decision was based on the results of the open-label, single arm, multi-center JAVELIN trial, demonstrating an ORR of 13.3%. On 2017 May 10th, the Phase III IMvigor 211 study (designed to confirm data from the Phase I/II IMvigor 210 study) was reported to be unable to achieve primary end point (improved overall survival compared with chemotherapy) (source http://www.roche.com/media/store/releases/med-corr-2017-05-10.htm), but full details of this study are not available until later this year.

Moving forward, as an increasing number of immunotherapies become available as second-line treatment of locally advanced or metastatic urothelial carcinoma, it will be essential to develop optimal assays to monitor PD-L1. Robust PD-L1 expression by malignant or tumor-infiltrating immune cells has been correlated with increased likelihood of response to PD-1-targeting agents among patients with metastatic urothelial cancers. However, objective clinical responses have also been documented for tumors containing low PD-L1 levels, similar to second-line systemic therapy. Interestingly, PD-L1 expression levels did not necessarily correlate with responses in the KEYNOTE 045 study, perhaps suggesting that additional biomarkers should be considered to properly predict clinical responders. Exploratory analyses performed on the data from the IMvigor 210 study suggest that mutational load and The Cancer Genome Atlas subtyping (cluster 1) may predict for response independently of PD-L1 expression. It will be important to identify additional biomarkers that properly identify patient subsets that are less likely to respond to single-agent PD-1 or PD-L1 blockade, and considerable efforts in this direction are underway. Such patients may indeed obtain clinical benefit from combinatorial regimens involving additional immunotherapeutics, chemotherapy or radiation therapy.

Disclosure of potential conflicts of interest
JK declares no conflicts of interest. LG provides remunerated consulting to OmniSEQ (Buffalo, NY, US).

References
1. Buque A, Bloy N, Aranda F, Castoldi F, Eggermont A, Cremer I, Fridman WH, Fucikova J, Galon J, Marabelle A et al. Trial watch: Immunomodulatory monoclonal antibodies for oncological indications. Oncoimmunology 2015; 4:e1008814; PMID:26137403; https://doi.org/10.1080/2162402X.2015.1008814
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67:7-30; PMID:28055103; https://doi.org/10.3322/caac.21387
3. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankini AV, Bignell GR, Bolli N, Borg A, Borresen-Dale AL et al. Signatures of mutational processes in human cancer. Nature 2013; 500:415-21; PMID:23945592; https://doi.org/10.1038/nature12477
4. Iribarren K, Bloy N, Buque A, Cremer I, Eggermont A, Fridman WH, Fucikova J, Galon J, Spiek R, Zitvogel L et al. Trial watch: Immuno-stimulation with Toll-like receptor agonists in cancer therapy. Oncoimmunology 2016; 5:e1088631; PMID:27141345; https://doi.org/10.1080/2162402X.2015.1088631
5. Board PATE. PDQ Bladder Cancer Treatment. Bethesda, MD: National Cancer Institute.
6. Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, Curiel RE, Obasaju CK, Wang Y, Nicol SJ, Kaufman DS. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. J Clin Oncol 2006; 24:3451-7; PMID:16849761; https://doi.org/10.1200/JCO.2002.20.4.937
7. Vaughn DJ, Broome CM, Hussain M, Gutheil JC, Markowitz AB. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol 2002; 20:937-40; PMID:11844814; https://doi.org/10.1200/JCO.2002.20.4.937
8. Balar AV, Necchi A, Bignell GR, Bolli N, Borg A, Borresen-Dale AL et al. The safety and efficacy of single-agent pemetrexed in platinum-resistant advanced urothelial carcinoma: A large single-institution experience. Oncologist 2015; 20:508-15; PMID:25845990; https://doi.org/10.1634/theoncologist.2014-0354
9. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O’Donnell PH, Balmanoukian A, Lorig Y et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre,
10. Sharma P, Retz M, Sieker-Radtke A, Baron A, Necchi A, Bedke J, Plimack ER, Vaena D, Grimm MO, Bracarda S et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. Lancet Oncol 2017; 18:312-22; PMID:28131785; https://doi.org/10.1016/S1470-2045(17)30065-7

11. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, Vogelzang NJ, Climent MA, Petrylak DP, Choueiri TK et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017; 376:1015-26; PMID:28212060; https://doi.org/10.1056/NEJMoia1613683

12. Massard C, Gordon MS, Sharma S, Rafii S, Wainberg ZA, Luke J, Curiel TJ, Colon-Otero G, Hamid O, Sanborn RE et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol 2016; 34:3119-25; PMID:27269937; https://doi.org/10.1200/JCO.2016.67.9761

13. Powles T, O’Donnell PH, Massard C, Arkenau H, Friedlander TW, Holmes C, Lee JL, Ong M, Sridhar SS, Vogelzang NJ et al. Updated efficacy and tolerability of durvalumab in locally advanced or metastatic urothelial carcinoma. Journal of Clinical Oncology 35, no. 6_suppl (February 2017) 286-286; https://doi.org/10.1200/JCO.2017.35.6_suppl.286

14. Heery CR, O’Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, Lamping E, Oyelakin I, Marte JL, Lepone LM et al. Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): A phase 1a, multicohort, dose-escalation trial. Lancet Oncol 2017; 18:587-98; PMID:28373007; https://doi.org/10.1016/S1470-2045(17)30239-5

15. Sharma P, Callahan MK, Bono P, Kim J, Spiliopoulou P, Calvo E, Pilpai RN, Ott PA, de Braud F, Morse M et al. Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): A multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. Lancet Oncol 2016; 17:1590-8; PMID:27733243; https://doi.org/10.1016/S1470-2045(16)30496-X

16. Paluch BE, Glenn ST, Conroy JM, Papanicolau-Sengos A, Bshara W, Omilian AR, Brese E, Nesline M, Burgher B, Andreas J et al. Robust detection of immune transcripts in FFPE samples using targeted RNA sequencing. Oncotarget 2017; 8:3197-205. PMID:27911273; https://doi.org/10.18632/oncotarget.13691