Which checkpoint inhibitor? An embarrassment of riches for bladder cancer

“...checkpoint inhibitors have established themselves in the treatment paradigm of urothelial carcinoma and will likely continue to become more important as we await completion of ongoing clinical trials.”

First draft submitted: 22 March 2017; Accepted for publication: 28 March 2017; Published online: 5 May 2017

Keywords: bladder cancer • checkpoint inhibitor • metastatic urothelial carcinoma

Despite the establishment of intravesical Bacillus Calmette-Guerin (BCG) immunotherapy in nonmuscle invasive urothelial carcinoma (UC) in the 1970s, the treatment paradigm for advanced and metastatic UC has relied on first-line platinum-based systemic chemotherapy to extend survival. This has abruptly changed, however, with the advent of immune checkpoint inhibitors. As a number of clinical trials are reporting positive outcomes in both the first- and second-line setting, a new question has emerged among the treating oncologists: which checkpoint inhibitor should be preferred over others for an individual patient? This is especially challenging given absence of head-to-head comparison data from randomized trials. Herein, we specifically discuss PD-1, or its ligand PD-L1 inhibitors which have published or reported Phase II or III clinical trial data in advanced and metastatic UC: atezolizumab, durvalumab, nivolumab, avelumab and pembrolizumab.

In May 2016, the US FDA approved atezolizumab, a monoclonal antibody directed against PD-L1, for use in advanced UC patients who have progressed on a platinum-based regimen based on data from the IMvigor 210 trial [1]. Following this landmark trial, PD-1 inhibitors: pembrolizumab and nivolumab and PD-L1 inhibitors: durvalumab and avelumab, all showed clinically significant objective response rates (ORR) and progression-free survival in the

second-line setting after progression on platinum-based chemotherapy (Table 1) [2–5]. Nivolumab was recently granted accelerated approval in February 2017. In addition, trials with pembrolizumab and atezolizumab reported significant ORR in the first-line setting for cisplatin-ineligible patients [6,7]. While we anticipate the treatment landscape will likely continue to evolve, recently published data and PD-L1 expression may help guide clinical decisions.

Second-line checkpoint inhibitor therapy

Though randomized trials with other agents are expected to report in the near future, pembrolizumab currently has the most robust evidence supporting its use in the second-line setting as it is the only checkpoint inhibitor studied and proven to extend survival in the Phase III KEYNOTE-045 randomized trial (n = 542) and was compared with active chemotherapy agents (paclitaxel, docetaxel or vinflunine). Regulatory approval is anticipated based on these data. In particular, pembrolizumab improved outcomes regardless of PD-L1 expression [2]. However, atezolizumab was the first agent in this class approved and has particularly robust responses in those with >5% PD-L1 expression of tumor infiltrating immune cells (IC2/3) with ORR 27%. This cohort composed roughly a third of the overall population (100/310 patients) [1]. The full approval by the FDA awaits the results of

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Table 1. Efficacy of PD-1 or PD-L1 inhibitors in advanced bladder cancer.

Checkpoint inhibitor (Study)	Pts	Previous platinum?	Comparator drug	PD-L1 assay (company)	PD-L1 (+) (expression cutoff)	ORR	Time to response (months)	OS (months)
Pembrolizumab [2] (KEYNOTE-045)	542	Yes	Paclitaxel, docetaxel or vinflunine	22C3 pharmDx (Dako North America)	>10% (n = 164)*	All: 21.1 vs 11.4% PD-L1 (+): 21.6 vs 6.7%	2.1	All: 10.3 vs 7.4 PD-L1 (+): 8.0 vs 5.2
Atezolizumab [1] (IMvigor 210)	310	Yes	No	SP142 (Ventana)	IC0: <1% (n = 103) IC1: 1–5% (n = 108) IC2/3: >5% (n = 100)	All: 15% IC0: 8% IC1: 10% IC2/3: 26%	2.1 (95% CI: 2.0–2.2)	All: 7.9 [8]
Nivolumab [3] (CheckMate-275)	265	Yes	No	28–8 pharmDx (Dako North America)	>1% (n = 122) >5% (n = 81)	All: 19.6% PD-L1 (-): 16.1% PD-L1 >1%: 23.8% PD-L1 >5%: 28.4%	1.87 (95% CI: 1.81–1.97)	All: 8.74 PD-L1 (-): 5.95 PD-L1 >1%: 11.3
Atezolizumab [6] (IMvigor 210)	119	No, first-line ^s	No	SP142 (Ventana)	IC0: <1% (n = 39) IC1: 1–5% (n = 48) IC2/3: >5% (n = 32)	All: 19% IC 1/2/3: 19% IC 2/3: 22%	Not published	All: 10.6
Pembrolizumab [9] [†] (KEYNOTE-052)	100/374	No, first-line ^s	No	22C3 pharmDx (Dako North America)	>10% (n = 30)	All: 24% PD-L1 (+): 37%	2.0 [7] (95% CI: 0.2–5.0)	6-month OS: 67% [7]
Nivolumab [10] (CheckMate-032)	78	Yes	No	28–8 pharmDx (Dako North America)	<1% (n = 42) >1% (n = 25)	All: 24.4% PD-L1 (-): 26.2% PD-L1 (+): 24.0%	1.5 (95% CI: 1.2–4.1)	All: 9.7 PD-L1 (-): 9.9 PD-L1 (+): 16.2
Durvalumab [4]	103	Yes	No	SP263 (Ventana)	>25% (n = 61)	PD-L1 (-): 5.1% PD-L1 (+): 31.1%	All: 1.41 PD-L1 (-): 2.05 PD-L1 (+): 1.41	Not published
Avelumab [5]	241	Yes	No	Clone 73–10 (Dako North America)	>5% (n = 81)	PD-L1 (-): 14.7% PD-L1 (+): 25.0%	~2.6	PDL1 (-) 6-month OS: 52.7% PDL1 (+) 6-month OS: 61.2%

*PD-L1 expression included percentage of tumor and infiltrating immune cells with PD-L1 expression.

[†]Data from 2016 European Society for Medical Oncology interim data of 100 patients, a total of 374 have been enrolled.

^sCisplatin-ineligible patients.

IC: Tumor infiltrating immune cell; ORR: Objective response rate; OS: Overall survival; Pt: Patient.

the Phase III trial comparing atezolizumab versus chemotherapy as salvage therapy. CheckMate-275, which led to the approval of nivolumab, evaluated nivolumab in three cohorts: <1%, >1% and >5% tumor PD-L1 expression. Those with >1% PD-L1 expression composed nearly half of the trial population (122/265 patients) and had superior ORR (23.8 vs 16.1%) and overall survival (11.3 vs 5.95 months) compared with the PD-L1 negative population [3]. The greatest differential benefit in ORR for PD-L1 positive versus negative cohort has been seen with durvalumab. Requiring >25% expression, 61 of 103 patients were PD-L1 positive in this trial. Of those, partial or complete responses were seen in nearly a third (ORR 31.1%). Interestingly, only 2 of 39 patients in the PD-L1 negative responded to durvalumab, but both obtained complete response [4]. Durvalumab, and avelumab are still unapproved and while they may receive accelerated approval, there are no Phase III trials in the salvage setting. However, durvalumab is undergoing evaluation in a first-line Phase III trial, and avelumab is undergoing Phase III evaluation as a second-line switch maintenance therapy following first-line platinum-based chemotherapy. Trials are also investigating adjuvant therapy using PD1/PD-L1 inhibitors. Based on these responses across patients harboring PD-L1 high and low expressing tumors, most being durable, for second-line therapy, any of the aforementioned therapies would be appropriate. Given the use of different immunohistochemistry methodologies by the different pharmaceutical companies, it is also difficult to compare outcomes based on PD-L1 expression. One study in the non-small-cell lung cancer literature suggests that three of the four assays accorded on tumor cell immunohistochemistry whereas the fourth showed consistently lower staining [11]. Furthermore, all of the assays demonstrated greater variability of immune cell than tumor cell staining and the authors also concluded that interchanging assays and cutoffs would lead to misclassification of some patients. A recently reported validated nomogram can predict 12-month survival for patients receiving historical agents (such as taxanes) based on five major baseline prognostic factors, and may be useful to interpret results of nonrandomized Phase II trials evaluating PD1/PD-L1 inhibitors [12]. Additionally, all these agents have similar excellent therapeutic index and toxicity profiles, that is, grade ≥ 3 toxicities in approximately 15–20% of patients. Hence, toxicities do not help select one agent over another. Given similar toxicities, and the absence of objective definitive data comparing the multiple PD1 and PD-L1 inhibitors, using an agent based on level of evidence, physician experience and patient convenience (every 3 weeks vs every 2-week infusion) may practically occur in the community. Additionally, there is no evidence for activ-

ity of a different PD1/PD-L1 inhibitor after progressing on one PD1/PD-L1 inhibitor.

First-line checkpoint inhibitor therapy

Trials comparing immunotherapy to conventional platinum-based chemotherapy are ongoing; however, checkpoint inhibitors have shown promising results in the first-line therapy setting in those who are cisplatin-ineligible. In a second cohort of the IMvigor 210 trial, 119 cisplatin-ineligible patients received atezolizumab in the first-line setting. ORR had been seen in 19% of patients with an overall survival of 10.6 months [6]. KEYNOTE-052 is a similar study of 374 patients investigating pembrolizumab in the first-line setting for cisplatin-ineligible patients. An interim analysis of 100 patients reported ORR 24% and an ORR 37% in those with >10% PD-L1 expression [2]. While data have not yet matured, the 6-month overall survival is reported to be 67% [7]. Although none of the drug has obtained FDA approval for the first-line setting, both may be reasonable considerations for the patient who is not eligible for, cannot tolerate or prefers not to receive chemotherapy – particularly those with high PD-L1 expression. Indeed, accelerated regulatory approval of these drugs for the first-line indication may be pursued.

Next steps: assessing PD-L1 expression & understanding the tumor microenvironment

Atezolizumab, durvalumab, nivolumab, avelumab and pembrolizumab all have comparable ORR in UC. The role of neoantigen and mutation burden, T-cell repertoire, IFN- γ signature and intrinsic subtype also needs to be intensively interrogated, since they may all complement PD-L1 expression. Additionally, data indicate that pre-existing CD8(+) T cells expressing PD-1/PD-L1 may be necessary for the activity of PD1/PD-L1 inhibitors [13]. Potentially, the combination of PD-L1 inhibition with targeted agents informed by molecular alterations is a reasonable strategy, as is ongoing in the BISCAY trial. As a surrogate of T-cell presence, it is conceivable that PD-L1 expression is not stagnant and may indicate that a patient would benefit from cytokine or peripheral acting immunotherapies to improve T-cell infiltration either prior to or in combination with PD-1/PD-L1 blockade. While responses are currently only seen in a small minority of patients, better characterization and modification of the tumor microenvironment may improve this. Conversely, the improved median survival with pembrolizumab suggests that the majority of patients may benefit to some extent. Hence, it may be more critical to identify patients who exhibit refractory disease with early progression or those who are prone to severe immune adverse events, in order to avoid employing these agents in such patients. Though we

are still learning how to interpret tumor PD-L1 expression and immune modulation is still in its early stages, checkpoint inhibitors have established themselves in the treatment paradigm of UC and will likely continue to become more important as we await completion of ongoing clinical trials.

Financial & competing interests disclosure

G Sonpavde provides consultancy for Bayer, Sanofi, Pfizer, Novartis, Eisai, Janssen, Amgen, AstraZeneca, Merck, Genentech, Argos, and Agensys; received research support to his institution from Bayer, Onyx, Celgene, Boehringer-Ingelheim,

Merck, Pfizer; and is an author for Uptodate; and a speaker for Clinical Care Options. S Pal provides consultancy for Pfizer, Genentech, Novartis, GlaxoSmithKline, Exelixis, Bristol-Myers Squibb, Medivation, Astellas; and received honoraria from Genentech. N Agarwal provides consultancy to Pfizer, Medivation, Merck, Exelixis, Argos, EMD Serono, and Eisai. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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