Published in final edited form as:

Curr Opin Urol. 2015 November ; 25(6): 586–596. doi:10.1097/MOU.0000000000000213.

Immunotherapies for bladder cancer: a new hope

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Abstract

Purpose of review—We review recent data on immunotherapies for bladder cancer and discuss strategies to maximize the antitumor effect of immunotherapy in solid tumors.

Recent findings—Anti-programmed death ligand 1 has shown promise in advanced bladder cancer. Clinical trials of immune checkpoint inhibitors as monotherapy or in combination are underway. Here we review strategies for enhancing antitumor immunity using immunomodulating agents or combination treatments that may increase tumor response.

Summary—Combining immune checkpoint inhibitors with other treatment modalities may lead to the development of new treatment strategies in advanced bladder cancer; however, identifying predictive biomarkers is essential for appropriate patient selection.

Keywords

advanced bladder cancer; combination therapy; immunotherapy; programmed death ligand-1;
tumor-infiltrating lymphocytes

INTRODUCTION

Survival rates for patients with muscle-invasive or metastatic bladder cancer have not improved in the past 15 years [1], highlighting the urgent need for new strategies for bladder cancer therapy. Comprehensive genomic profiling has improved our understanding of mutational processes in bladder cancer and revealed potential therapeutic target genes and pathways [2,3[■]]. However, the US Food and Drug Administration (FDA) has not approved a new medication for the treatment of advanced bladder cancer in over 20 years.

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Conflicts of interest

There are no conflicts of interest.

Bladder cancer was the first disease for which the FDA approved an immunotherapy in 1990: intra-vesical administration of bacillus Calmette-Guérin (BCG) in nonmuscle-invasive bladder cancer (NMIBC) [4–6]. Clinical evidence has shown that intravesical BCG after transurethral resection of bladder tumor (TURBT) is superior to TURBT alone or TURBT and intravesical mitomycin C in preventing recurrence in NMIBC [7–9]. Although the exact mechanism of action of BCG immunotherapy is not yet fully understood, it has been demonstrated that BCG induces an orchestrated cellular immune response, including T-cell sensitization, macrophage activation, and cytokine production, resulting in tumoricidal activity [6,10].

Today, cancer immunotherapy is entering a new era. Immune checkpoint inhibitors have demonstrated significant clinical activity in melanoma and other solid tumors, including bladder cancer [11–13,14■,15■]. Ongoing clinical trials in bladder cancer are investigating the safety and efficacy of immune checkpoint blockades and other immune therapies. Here we provide an overview of recent clinical trials of immunotherapies in bladder cancer and other solid tumors, strategies that may enhance immunity, as well as the role of predictive biomarkers in patient selection for immunotherapy.

CLINICAL TRIALS OF IMMUNE CHECKPOINT INHIBITORS IN BLADDER CANCER AND OTHER SOLID TUMORS

Cytotoxic T-lymphocyte-associated protein 4

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a molecule that negatively regulates T-cell activation, is expressed on activated CD4⁺ and CD8⁺ T cells [16]. Engagement of CD80/CD86 on antigen-presenting cells (APCs) with CTLA-4 inhibits T-cell activation and proliferation [17]. CTLA-4 is constitutively expressed on Tregs and plays a critical role in their immunosuppressive function [18]. Ipilimumab is a fully human monoclonal antibody (mAb) that targets CTLA-4 and was approved for unresectable/metastatic melanoma in 2011 [19]. Carthon *et al.* [20] conducted a phase I trial of ipilimumab in patients with NMIBC who were candidates for radical cystectomy. Nine of 12 patients remained disease free during a median 20-month follow-up after surgery. The study showed increased CD4⁺-high inducible T-cell costimulator (ICOS)^{hi} and CD8⁺ICOS^{hi} T cells in tumor tissue and blood vessels after ipilimumab.

Programmed cell death protein 1/programmed death ligand 1

Malignant tumors can disrupt immune checkpoint pathways as a mechanism of immune evasion [21,22]. Programmed cell death protein 1 (PD-1) is an immune checkpoint receptor expressed on CD4⁺ and CD8⁺ T cells, Tregs, B cells, and natural killer (NK) cells [23]. Programmed death ligand 1 (PD-L1, B7-H1) and PD-L2 (B7-DC) are ligands of PD-1. PD-L1, more widely expressed than PD-L2, is expressed on T cells, B cells, macrophages, and dendritic cells [24], and also by many types of tumors, including bladder cancer. Interferon (IFN)- γ , interleukin-4, and interleukin-10 have been shown to upregulate PD-L1 expression [25,26]. Macrophages and dendritic cells mainly express PD-L2 [27]. IFN- γ , interleukin-4, and Toll-like receptor ligands increase PD-L2 expression on dendritic cells and macrophages [27]. The binding of PD-1 with PD-L1/PD-L2 suppresses CD4⁺ and CD8⁺ T-cell functions.

Furthermore, interaction of PD-1 with its ligands is involved in immune evasion by urothelial cancer [28[■]]. Inman *et al.* [29] evaluated PD-L1 expression in 280 high-risk urothelial bladder cancer tumors by immunohistochemistry (IHC) and reported PD-L1 expression in 7% of pathologic stage Ta, 16% of pT1, 23% of pT2, 30% of pT3/4, and 45% of carcinoma in-situ tumors. PD-L1 expression positively correlated with high-grade tumors and tumor-infiltrating lymphocytes (TILs) and was associated with BCG failure in the subset of high-risk NMIBC, suggesting that the PD-1/PD-L1 pathway may be an effective therapeutic target for the treatment of bladder cancer. A phase I trial of pembrolizumab in patients with high-risk NMIBC refractory/intolerant of BCG is ongoing (NCT02324582). Large clinical trials in other solid tumors have demonstrated the durable activity of PD-1/PD-L1 inhibitors, which are now changing the standard of care for some tumor entities [30–32].

Several single-agent trials with PD-1/PD-L1 inhibitors are ongoing in both locally advanced and metastatic bladder cancer (NCT02108652, NCT01848834, and NCT01375842). To date, two phase I trials of immunotherapies in advanced bladder cancer have been reported. The anti-PD-L1 antibody MPDL3280 [14[■]] showed an overall response rate of 25%, and pembrolizumab, an anti-PD-1 antibody [33[■]], showed an overall response rate of 24% (Table 1) in a PDL⁺-enriched population. In addition to the promising and durable responses seen with these immunotherapies, the toxicity profile for each was favorable compared with standard cytotoxic treatments (Table 2). Randomized phase III trials of MPDL3280A and pembrolizumab in the second-line setting compared with chemotherapy are ongoing (NCT02302807 and NCT02256436).

OTHER IMMUNE TARGETS IN EARLY PRECLINICAL OR CLINICAL DEVELOPMENT

B7 homolog 3

B7 homolog 3 (B7-H3), a potent inhibitor of T-cell activation, is another emerging target for immunotherapy of bladder cancer [28[■]]. B7-H3 is broadly expressed on T cells, NK cells, APCs, osteoblasts, fibroblasts, and epithelial cells [50], and is overexpressed in multiple tumors [51–54]. B7-H3 inhibits T-cell proliferation and reduces secretion of IFN- γ and tumor necrosis factor- α [55]. A phase I study of MGA271, an Fc-optimized humanized mAb, is ongoing in patients with refractory cancers, including urothelial carcinoma, that express B7-H3.

OX40

OX40 (CD134) is a costimulatory molecule transiently expressed on activated T cells after antigen recognition [56]. OX40 engagement by ligands present on dendritic cells promotes antigen-specific T-cell expansion, survival of T cells, and IFN- γ production by T cells [57–59]. OX40 signaling may inhibit interleukin-10 production by Tregs as well as Treg function [60]. A phase I clinical trial of a murine agonistic antihuman OX40 mAb in patients with advanced cancer showed an acceptable toxicity profile and tumor regression in 12/30 patients [61[■]]. In this study, anti-OX40 antibody also increased proliferation of peripheral CD4⁺ and CD8⁺ T cells and increased endogenous tumor-specific immune responses.

Clinical trials of agonistic anti-OX40 antibody in patients with advanced or metastatic solid tumors, including bladder cancer, are ongoing (NCT02219724 and NCT02221960).

CD40

CD40 is primarily expressed on not only APCs such as dendritic cells, but also monocytes, B cells, and tumors [62–64]. CD40-CD40L interaction in dendritic cells plays a critical role in generating antigen-specific cytotoxic T-lymphocytes (CTLs). Preclinical studies in bladder cancer models have shown that agonistic anti-CD40 antibody may suppress tumor growth and metastases [65,66,67]. In a phase I trial of an agonistic immunoglobulin G (IgG)1 chimeric anti-CD40 antibody in patients with CD40-expressing solid tumors resistant to conventional therapy, 15/29 patients had stable disease with tolerable toxicities [68].

BIOMARKERS FOR IMMUNE CHECKPOINT INHIBITORS

Although recent clinical trials have revealed that immune checkpoint inhibitors have activity against several tumors [11–13,14,15], not every patient will respond. Biomarkers that can identify patients most likely to benefit from immune checkpoint inhibitors and other immunotherapies are urgently needed to guide precision cancer therapy.

Programmed death ligand 1 detection by immunohistochemistry

In the MPDL3280 bladder cancer study, PD-L1 status of the tumor and infiltrating immune cells was used to assess treatment response. However, PD-L1 is a dynamic biomarker dependent on IFN- γ and other cytokines upregulating PD-L1 on both tumor and immune cells. As PD-L1 status can change by treatment or disease progression, evaluating PD-L1 expression at a single time point in order to select patients for therapy is not optimal. Patients with PD-L1-negative tumors or immune-infiltrating cells can still have radiologic response to immune checkpoint blockade.

Tumor-infiltrating lymphocytes as biomarkers

Accumulating evidence has revealed the crucial role of the tumor microenvironment in promoting tumor progression and response to anticancer therapy, significantly affecting patient prognosis [22,69,70]. A tumor microenvironment infiltrated by T cells may be a potential biomarker for clinical benefit from immunotherapy [71,72]. The presence of TILs has been shown to correlate with improved clinical outcome in many cancer types, including bladder [73,74].

One of the therapeutic mechanisms of immune checkpoint inhibitors is to enhance the function of TILs and augment antitumor immunity within the tumor microenvironment [21]. Thus, the presence of TILs can also be an indicator of response to immune checkpoint blockade and, conversely, a lack of TILs may be a marker for poor response to immunotherapy.

Sharma *et al.* [75] reported intratumoral CD8⁺ TILs correlated with improved disease-free survival in patients with muscle-invasive bladder cancer (MIBC). Notably, CD8⁺ TILs had no influence on disease-free survival among patients with NMIBC. In a multivariate

analysis, the presence of CD8⁺ TILs was a significant indicator of overall survival (OS) in patients with bladder cancer.

A positive correlation has been found between ipilimumab treatment and the frequency of CD4⁺ T cells expressing ICOS, which is one of the markers of T-cell activation [20,76]. This phenomenon was also observed in a phase I study of localized bladder cancer [20]. Carthon *et al.* [20] studied ICOS expression on T cells in tumor tissues after two doses of ipilimumab and found that ICOS^{hi}CD4⁺ or CD8⁺ T-cell levels were significantly higher compared with untreated tumor tissues after two doses of tremelimumab 10 mg/kg, suggesting that monitoring ICOS levels on TILs may be a pharmacodynamic marker of anti-CTLA-4 antibody therapy in bladder cancer.

Somatic mutations as biomarkers

To eliminate cancer cells, the immune system must recognize them as nonself [77]. Antigen expression in cancer cells differs from normal cells because of genetic and epigenetic variations. Somatic mutations produce neoantigens and generate neo-epitope-specific T cells [78–80]. Neoantigen-specific T-cell responses play a critical role in antitumor responses [79–82]. A recent study revealed that immune checkpoint inhibitors target mutant tumor antigen-specific T cells [83]. Rizvi *et al.* [84] used whole-exome sequencing of nonsmall cell lung cancer (NSCLC) tumors treated with pembrolizumab to reveal the relationship between the number of mutations in a tumor and response to pembrolizumab. The study demonstrated that a higher non-synonymous mutation burden in tumors was associated with improved objective response, durable clinical benefit, and progression-free survival (PFS). Using whole-exome sequencing in melanoma patients treated with CTLA-4 blockade (ipilimumab or tremelimumab), Snyder *et al.* [85] identified candidate tumor neoantigens for each patient and validated a neoantigen signature associated with a strong treatment response for each patient. This study revealed that mutational load is associated with degree of clinical benefit, suggesting that monitoring mutations in tumor cells may provide a predictive biomarker of response to immune checkpoint therapies. Recent genome-wide expression and sequencing studies have demonstrated that bladder cancer has a high mutational burden [3]. In addition, bladder cancer responds to immune checkpoint blockade [14].

These studies demonstrate a concerted effort to identify predictive biomarkers of response to immune checkpoint inhibition, with no accurate result as yet [86]. Further studies are needed to find reliable and consistent biomarkers predictive of response to immunotherapy.

ENHANCING ANTITUMOR IMMUNITY

Immunomodulatory chemotherapy

Chemotherapy agents used in metastatic bladder cancer include cisplatin, methotrexate, gemcitabine, and doxorubicin [87]. Lesterhuis *et al.* [88] showed that platinum-based chemotherapeutics such as cisplatin downregulate expression of PD-L2 on both human dendritic cells and tumor cells, resulting in enhanced tumor antigen-specific proliferation and T-helper type 1 cytokine secretion, as well as enhanced recognition of tumor cells by T

cells. In a study reported by Alva *et al.* [89], mean PD-L1 expression was significantly higher in post-chemotherapy tumor specimens from patients with MIBC treated with carboplatin/cisplatin and gemcitabine. Gemcitabine can increase human leukocyte antigen (HLA) class I expression on cancer cells [90]. It also enhances cross-presentation of tumor antigens to tumor-specific CD8⁺ T cells *in vivo* [91] and kills myeloid-derived suppressor cells [92], suggesting that gemcitabine may promote antitumor T-cell responses.

Immunogenic cell death

Some conventional chemotherapeutics such as doxorubicin, cyclophosphamide, and oxaliplatin induce immunogenic cell death that stimulates tumor-specific immune responses [93,94]. A subset of drugs stimulates cancer cells to release specific damage-associated molecular patterns, which can act as danger signals and accentuate the immunogenicity of cancer cells. Damage-associated molecular patterns bind to receptors expressed on the surface of APCs, promote engulfment of dying cancer cells, including tumor-associated antigens, and trigger maturation of APCs. As a result, APCs can elicit a tumor-specific immune response and long-lasting immunologic memory.

Immunomodulatory targeted drugs

Recent studies suggest that the therapeutic efficacy of several targeted drugs is partially mediated by the host immune system [69]. TRC105 is a human/murine chimeric anti-CD105 (endoglin) IgG1- χ mAb. CD105 is essential in normal vascular development and tumor angiogenesis [95,96]. Anti-CD105 mAb binds to human CD105, inhibiting angiogenesis and tumor growth. The CD105 protein is a TGF- β coreceptor expressed on CD4⁺ T cells, activated monocytes, and macrophages [97–99]. TGF- β plays an important role in Treg induction [100,101]. In recent studies, TRC105 antibody decreased Treg levels in metastatic castration-resistant prostate cancer and advanced or metastatic urothelial carcinoma (NCT01090765 and NCT01328574, respectively) [102].

A phase II study in metastatic urothelial carcinoma recently reported the immunomodulatory effect of cabozantinib [103], a multiple tyrosine kinase inhibitor that primarily targets MET and vascular endothelial growth factor receptor 2. Patients with metastatic urothelial carcinoma treated with cabozantinib, who had low levels of Tregs at baseline, had an improved clinical response ($P=0.014$) and OS ($P=0.0078$). Interestingly, cabozantinib treatment decreased levels of Tregs and expression of CTLA-4 on Tregs. A multi-institutional phase I trial combining cabozantinib and nivolumab with or without ipilimumab in metastatic urothelial carcinoma is currently under way at the National Cancer Institute (NCT02308943).

Radiation therapy

In addition to the direct cytotoxic effects on cancer cells, recent studies suggest that host immune responses may contribute to the therapeutic efficacy of ionizing radiation as well as cancer cell intrinsic mechanisms in immunocompetent hosts [104]. Sublethal irradiation of cancer cells increases sensitivity to antigen-specific CTLs [105]. There are several effects of radiation that might enhance immune response, including local production of proinflammatory anaphylatoxins (C3a and C5a) [106] and immunogenic cell death induction

that generates a long-range bystander, or abscopal, effect [104,107–109], which has been correlated with induction of IFN- γ -producing T cells [110,111]. These findings suggest that the combination of radiation and immunotherapy may have a synergistic antitumor effect [112–114].

OTHER TARGETS FOR IMMUNOTHERAPY OF BLADDER CANCER

Adoptive cell transfer

Adoptive cell transfer (ACT) is a promising approach to cancer treatment [115,116] that involves three steps: collection of circulating lymphocytes or TILs; selection/modification/expansion/activation of collected immune cells *ex vivo*; and readministration of the cell product to patients, most often in combination with immunostimulatory agents [117]. A phase II study of ACT in metastatic solid tumors, including bladder cancer, is ongoing at the National Cancer Institute (NCT01967823). This ACT therapy targets the cancer-testis antigen NY-ESO-1 [118]. Anti-NY-ESO-1 murine T-cell receptor (TCR) gene-engineered lymphocytes are transferred after lymphodepleting conditioning using cyclophosphamide and fludarabine. Another phase I/II ACT study in metastatic cancer, including bladder cancer, expressing MAGE-A3 is currently open (NCT02111850). *HLA-DP*04:01/04:02*-restricted anti-MAGE-A3 TCR gene-engineered lymphocytes are transferred into cancer patients after lymphodepleting conditioning.

Oncolytic viruses

An oncolytic virus is a nonpathogenic viral strain that specifically infects cancer cells and triggers cancer cell death [119]. A phase II/III study of intravesical therapy of an oncolytic adenovirus that expresses granulocyte-macrophage colony-stimulating factor (CG0070) in patients with carcinoma in situ of the bladder or with NMIBC with carcinoma in situ who have failed BCG therapy is ongoing to evaluate safety and efficacy (NCT01438112).

Cancer vaccines

Cancer vaccines can elicit a tumor-specific immune response. Recombinant tumor antigens, tumor antigen-derived peptides, or genetically engineered and irradiated cancer cell lines are administered to cancer patients together with immunostimulatory agents known as adjuvants, which potentially promote dendritic cell maturation or antigen presentation [120]. Several trials of cancer vaccines are currently under way in bladder cancer, including the vaccine HS-410, currently in a phase I/II study in patients with NMIBC after TURBT (NCT02010203), and a DEC-205-NY-ESO-1 fusion protein vaccine with or without the mammalian target of rapamycin inhibitor rapamycin, in a phase I study in patients with NY-ESO-1-expressing solid tumors, including metastatic bladder cancer (NCT01522820).

Antibody/cytokine fusion

ALT-801 is a bifunctional fusion protein comprising interleukin-2 linked to a single-chain TCR domain that recognizes a peptide epitope (aa264–272) of the human p53 antigen presented on cancer cells in the context of *HLA-A*02:01* [121]. Two phase I/II studies of ALT-801 are ongoing: a trial of ALT-801 in combination with gemcitabine in patients with

NMIBC who have failed BCG therapy (NCT01625260), and a trial of ALT-801 in combination with gemcitabine and cisplatin in MIBC (NCT01326871).

COMBINATION THERAPY

Combination therapy that targets different pathways of tumorigenesis has been used to maximize antitumor effects without overlapping toxicity [122]. Immune checkpoint inhibitors interfere with interactions between CTLA-4 and CD80/86, PD-1 and PD-L1, T-cell immunoglobulin mucin-3 and galectin-9, and lymphocyte activation gene 3 (LAG-3) and major histocompatibility complex class II. Treatment with PD-1 antibody increases antitumor activity when combined with therapeutic anti-T-cell immunoglobulin mucin-3 antibodies [123] or anti-LAG-3 antibodies [124] compared with monotherapies. Recent results from a phase I study in patients with stage III or IV melanoma suggest that combination therapy with blockades of CTLA-4 and PD-1 may be more effective than either agent alone [13]. In this study, concurrent combination therapy with ipilimumab and nivolumab achieved an overall objective response rate that was 40% higher than the rate achieved by either agent alone or in sequence, but increased grade ≥ 4 adverse events from 6% with nivolumab alone [48] to 53% with the combination of ipilimumab and nivolumab [13]. A phase I/II study in advanced or metastatic solid tumors, including bladder cancer, is investigating the safety and efficacy of nivolumab in combination with ipilimumab (NCT01928394).

Conventional chemotherapies and targeted agents stimulate host antitumor immunity, suggesting that these nonimmunotherapeutic drugs may facilitate the activity of cancer immunotherapy [69,93,125]. Clinical studies combining ipilimumab and paclitaxel/carboplatin in advanced NSCLC and extensive small-cell lung cancer have reported the efficacy of combining CTLA-4 antibody and chemotherapy [126,127]. In these studies, phased ipilimumab (placebo + paclitaxel/carboplatin followed by ipilimumab + paclitaxel/carboplatin), but not concurrent ipilimumab, improved immune-related PFS or PFS compared with control (paclitaxel/carboplatin with placebo). These studies suggest that exposure to chemotherapy before CTLA-4 antibody therapy may enhance antitumor immune response. In patients with metastatic urothelial carcinoma, a phase II trial of gemcitabine, cisplatin, and ipilimumab in the first-line setting is ongoing (NCT01524991). A number of trials of PD-1/PD-L1 blockade in combination with other drugs, including anti-LAG-3 antibody (NCT01968109), anti-CD40 agonistic antibody (NCT02304393), MEK inhibitor (NCT01988896), 4-1BB agonistic antibody (NCT02179918), anti-KIR antibody (NCT01714739), and IDO1 inhibitor (NCT02178722), are under way in patients with advanced urothelial cancer.

Radiation has been demonstrated to induce immunogenic modulation and exert antitumor effects by activating antitumor immunity [104,105,114,128], suggesting that the combination of immunotherapy and radiation may provide synergistic antitumor activity. Clinical trials of that combined immunotherapy with immune checkpoint blockade and radiation are ongoing [129].

We can hypothesize from available data that combining immunotherapy with radiation, chemotherapy, ACT, or immune checkpoint inhibitors may achieve greater clinical benefit than single therapies. However, combination therapies that include immune checkpoint inhibitors may increase treatment-related toxicities. It is hoped that ongoing combination studies will contribute to our understanding of the additive and synergic effects of certain classes of agents and PD-1/PD-L1 inhibitors.

CONCLUSION

Unlike standard chemotherapy or targeted agents, immune checkpoint inhibitors and other immunotherapies work by enhancing the capacity of the immune system to attack tumors. Recent clinical studies of immune checkpoint inhibitors have produced promising results. Many more trials are ongoing or in development in bladder cancer (Fig. 1).

Future directions in immunotherapy of bladder cancer

In the near future, immunotherapies may provide new therapeutic options for the treatment of bladder cancer. In addition, accumulating evidence suggests that using immunotherapeutic agents in combination with cytotoxic chemotherapy, targeted therapy, or radiotherapy may lead to synergistic or additive antitumor activity in advanced bladder cancer [130]. Chemotherapy or targeted agents not only directly act on tumor cells but can also have immunomodulatory activities, making them ideal for combination strategies. Finally, predictive biomarkers that can identify patients likely to benefit from immunotherapies will help to guide precision cancer treatment.

Acknowledgements

The authors would like to thank Bonnie L. Casey for editorial assistance in the preparation of this article.

Financial support and sponsorship

This work was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, National Institutes of Health.

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KEY POINTS

- Immune checkpoint inhibitors have shown promising results in advanced bladder cancer.
- Accumulating evidence shows that combining immunotherapy with other modalities such as chemotherapy, radiation therapy, and targeted therapies has a synergistic effect and may lead to the development of new cancer treatments.
- There is a need to identify and implement predictive biomarkers to aid the selection of appropriate patients for immunotherapy.
- The dynamic nature of PD-L1 status makes it an unreliable biomarker for patient selection.
- Owing to the emerging data that reveal better antitumor responses in tumors with greater numbers of TILs, these cells may play a role in patient selection for immunotherapy.

FIGURE 1.
Checkpoint clinical trials in bladder cancer, ongoing and in development.

Table 1.

Comparison of two studies of immune checkpoint inhibitors in bladder cancer

Author	Powles <i>et al.</i> [14]	Plimack <i>et al.</i> [33]
Phase	I expansion	Ib
Medication	MPDL3280A (anti-PD-L1)	Pembrolizumab (anti-PD-L1)
No. of patients/no. evaluable	68/67	33/29
At least two previous chemotherapies	48 (72%)	15 (45%)
Stage of disease	4	4
Metastases: liver	22	7
ORR	17 (2 CR + 15 PR) (25%)	7 (3 CR + 4 PR) (24%)
Ongoing response at last follow-up	16/17	6/7
SD	21 (31%)	4 (14%)
Biomarker	IHC, PD-L1	IHC, PD-L1
Median follow-up (months)	4.2 months (IHC 2/3); 2.7 months (IHC 0/1)	11 months
Drug administration/duration	15mg/kg IV Q3W, 16 cycles or 1 year	10 mg/kg IV Q2W ^a
Total AEs	39 (57%)	20 (61%)
Grade 3 AEs	3 (4%)	
>Grade 3 AEs	0	4 (12%)
Nephrotoxic AEs	0	0
Decrease in size of primary lesion	33 (49%)	16 (55%)
PFS	24 weeks (IHC 2/3); 8 weeks (IHC 0/1)	37 weeks
OS (months)	-	9.3
Males	48 (71%)	23 (70%)

AE, adverse event; CR, complete response; IHC, immunohistochemistry; IV, intravenous; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease.

^a At the discretion of the investigator, patients who received pembrolizumab for 24 weeks and for at least two treatments beyond confirmed complete response may discontinue therapy. Patients who experience progression may be eligible for up to 1 year of additional pembrolizumab if no other anticancer therapy was received. If clinically stable, patients are to remain on pembrolizumab until progressive disease is confirmed on a second scan performed 4 weeks later.

Table 2.

Safety profiles of immune checkpoint inhibitors in studies in various cancers

Tumor type	Author	Study phase	Patient no.	Treatment	Tumor marker	Overall AEs	Grade 3 AEs	Nephrotoxic AE	Grade 3 nephrotoxic AEs
Solid	Topalian <i>et al.</i> [11]	I	296	Nivolumab (anti-PD-1)	PD-L1 expression	41%	14%	NR	NR
Melanoma	Weber <i>et al.</i> [34]	I	90	Nivolumab (anti-PD-1)	PD-L1 expression	NR	5.6%	0	0
Solid	Brahmer <i>et al.</i> [12]	I	207	Anti-PD-L1	NA	39%	9%	0	0
Melanoma	Hamid <i>et al.</i> [35]	I	135	Lambrolizumab (anti-PD-1)	NA	79%	13%	2%	1% (RF)
Melanoma	Robert <i>et al.</i> [32]	I	173	Pembrolizumab (anti-PD-1)	NA	82%	12%	0	0
Melanoma	Robert <i>et al.</i> [36]	I	834	Pembrolizumab (q2, q3w) vs ipilimumab (anti-CTLA-4)	NA	79.5%/72.9%/73%	13.3%/10.1%/19.9%	0/0.4%/0.4%	0/0/0.4%
Hodgkin's lymphoma	Ansell <i>et al.</i> [37]	I	23	Nivolumab	PD-L1 /2±	78%	22%	NR	NR
Melanoma	Dummer <i>et al.</i> [38]	II	540	Pembrolizumab 2 vs 10 mg/kg	NA	NR	11 %/14%	NR	NR
Melanoma	Long <i>et al.</i> [39]	I	418	Nivolumab	PD-L1 ±	NR	12%	NR	NR
Melanoma	Postow <i>et al.</i> [40]	I	142	Nivolumab+ ipi vs ipi	PD-L1 ±	91 %/93%	54%/24%	3.1 %/2.1 %	1 %/0%
Melanoma	Eggermont <i>et al.</i> [41]	III	951	Ipi vs placebo	NA	98.7%/91 %	55.4%/26.1 %	NR	NR
Solid tumor	Herbst <i>et al.</i> [15]	I	277	Anti-PD-L1	PD-L1 ±	70%	12.6%	NR	NR
Lung (squamous)	Rizvi <i>et al.</i> [42]	II	117	Nivolumab	PD-L1 expression	74%	17%	NR	NR
NSCLC	Gettinger <i>et al.</i> [43]	I	129	Nivolumab	NA	41.1%	4.7%	3.1%	0
Renal cell carcinoma	Motzer <i>et al.</i> [44]	II	168	Nivolumab 0.3/2/10 mg/kg	PD-L1 expression	75%/67%/78%	5%/17%/13%	2%/0/2%	0
Melanoma	Weber <i>et al.</i> [45]	III	268	Nivolumab	PD-L1 expression	67.5%	9%	NR	NR
Follicular lymphoma	Westin <i>et al.</i> [46]	II	32	Pidilizumab (anti-PD-L1)	NA	NR	0	0	0
Diffuse large B-cell lymphoma	Armand <i>et al.</i> [47]	II	66	Pidilizumab	NA	96%	58%	3% (RF)	3% (RF)
Melanoma	Topalian <i>et al.</i> [48]	I	107	Nivolumab	NA	84.1%	22.4%	2.8% (2 RF, 1 AIN)	0
Melanoma	Hodi <i>et al.</i> [19]	III	540	Ipi + gp100 vs ipi	NA	98.4%/96.9%	45.5%/45.8%	NR	NR
Head and neck cancer	Seiwert <i>et al.</i> [49]	Ib	60	Pembrolizumab	PD-L1 +	78.3%	55%	NR	NR
Bladder	Powles <i>et al.</i> [14]	I	67	MPDL3280A (anti-PD-L1)	PD-L1 ±	57%	4%	0	0
Bladder	Plimack <i>et al.</i> [33]	Ib	29	Pembrolizumab (anti-PD-1)	PD-L1 ±	61%	12%	0	0

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AE, adverse event; AIN, acute interstitial nephritis; ipi, ipilimumab; NA, not applicable; NR, not reported; NSCLC, nonsmall cell lung cancer; PD-L1, programmed death ligand-1; RF, renal failure.