Editorial

Evoking durable anti-cancer responses with blocking antibodies to PD-1 and PD-L1

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Inhibitory immune checkpoints play a critical role in regulating the strength and duration of immune responses in order to maintain self-tolerance and prevent autoimmunity (1). Such regulatory mechanisms are typically exploited by tumors as an immune escape mechanism and thereby pose a major obstacle to the induction of clinically relevant anti-cancer immune responses capable of controlling and/or eradicating disease (2). Efforts to safely re-engage endogenous anti-tumor immunity has seen the exciting development of immunotherapeutic antibodies designed to selectively block the interaction of inhibitory receptors with their ligands with the goal of enhancing the anti-tumor activity of T cells. The first antibody of this nature to be successfully trialed in the clinic was ipilimumab (Yervoy, Bristol Myers Squibb, Princeton, NJ) previously known as MDX-010 (Medarex, Princeton, NJ), targeting the immunoregulatory receptor cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) [Reviewed in (3)]. Expressed on activated T cells, CTLA-4 signalling can attenuate T cell function through competing with the co-stimulatory molecule CD28 for its B7-ligands on antigen presenting cells (APC) (4). In 2011 ipilimumab was approved by the US Food and Drug Administration for the treatment of stage IV melanoma and is now being trialed for activity in patients with lung and prostate cancer. Such positive advances of passive cancer immunotherapy into mainstream oncology have been the driving force behind the development of new blocking antibodies to immune checkpoints for cancer therapy and their integration into early phase clinical trials.

The therapeutic promise of antibody mediated blockade of programmed death (PD)-1 for the treatment of cancer has emerged from findings demonstrating that this co-inhibitory receptor, which plays an important role in regulating immune cell exhaustion within peripheral tissue, is commonly expressed on tumor-associated immune infiltrates (3). Tumors are also highly infiltrated by T-regulatory cells that typically express high levels of PD-1, the signalling through which may promote their expansion and/or suppressor activity (5). The most dominant immunosuppressive ligand of PD-1 is Programmed Death-Ligand 1 (PD-L1), which is expressed on both mouse and human tumor cells, and tumor associated stroma and non-transformed immune cells including dendritic cells (DC) (3). Tumor associated expression of PD-L1 has been shown to confer immune resistance and potentially protect tumor cells from T-cell mediated apoptosis (6,7); a phenomenon that can be over-ridden with targeted blocking antibodies to PD-1 or PD-L1 resulting in the induction of enhanced T cell function (2). In cancer patients, PD-L1 expression has been associated with poor outcome (8,9), providing a strong rationale for pursuing the development of inhibitory antibodies to this pathway for cancer immunotherapy.

The much-anticipated findings of two early phase clinical studies trialing the activity and safety of therapeutic antibodies to PD-1 and its ligand PD-L1 in advanced solid cancer were recently published in back-to-back articles in *the New England and Journal of Medicine* (10,11). In the first in-human Phase I study of the fully human IgG4 PD-1 monoclonal antibody in patients with advanced solid tumors (mAb), BMS-936558 (previously known as MDX-1106, BMS, Princeton, NJ), a single-dose regimen was found to be well tolerated and associated with evidence of anti-tumor activity (12). In the recent study by Topalian et al., the anti-tumor activity and safety of this antibody was assessed in a multi-dose Phase I study involving 296 patients with a diverse range of advanced solid cancer (10). The BMS-936558 antibody was administered at 1-10 mg/kg of body weight every 2 weeks over an 8-week treatment cycle, with up to 12 cycles. Of the 296 patients enrolled, 1 in 4 to 1 in 5 patients with melanoma (28%, 26 of 94 patients), non-small-cell lung cancer (18%, 14 of 76 patients) or renal-cell cancer (27%, 9 of 33 patients) had

durable (≥24 weeks), objective (complete or partial) responses (10), as determined by the Response Evaluation Criteria In Solid Tumors (RECIST). Notably, within these patient cohorts, drug-activity was detected in multiple sites of metastases including the liver, lung, lymph nodes and bone. No objective responses were observed in patients with colorectal (19 patients enrolled) or prostate cancer (17 patients enrolled). Given the advanced status of disease in all patients enrolled in this study and the refractive nature of the cancers, the observed activity as well as durability of the responses to BMS-936558, relative to other more conventional therapies, is highly significant.

Interestingly, objective responses were not observed in patient tumors in which tumor-cell expression of PD-L1 was not detected. Of the 42 tumor biopsies taken across all three responding cancer types, 25 were found to be positive for PD-L1 and 36% of these demonstrated an objective response to BMS-936558 therapy (10). Notably, PD-L1 expression is typically up regulated in inflammatory microenvironments in response to proinflammatory cytokines such as IFN-γ and has been suggested to reflect tumor cell adaption to endogenous immune responses (9). Based on this it would be interesting to assess whether PD-L1 expression, particularly in patients in whom objective responses were observed, also correlated with a positive immune score at the initiation of therapy. This preliminary indication that tumors positive for PD-L1 have an increased potential to support an objective response to BMS-936558 drug therapy highlights the potential importance of this immunosuppressive ligand as a predictive biomarker of response; an outcome that may not have been predicted based on preclinical tumor studies in the mouse in which minimal single-agent activity has been reported despite detectably high levels of PD-L1 expression on ex-vivo analysed tumors (13). This disparity may relate to differences in the suppressive barriers that exist within the mouse and human tumor microenvironments and/or the rates with which the disease evolves and/or progresses. Immune suppression associated with prior drug treatments and/or other tumor/host regulatory factors, owing to the advanced nature of the cancers treated in this study, may account for why only a third of the confirmed PD-L1-positive tumors demonstrated an objective response.

The lack of objective responses in all patients with PD-L1-negative tumors raises the question as to whether blocking antibodies to PD-L1 could be a more selective means of disarming this immunosuppressive pathway within tumors. In a companion Phase I study Brahmer JR *et al*., (11) reported on the activity of the BMS-936559 drug, a high affinity fully human PD-L1 specific IgG4 mAb, capable of inhibiting PD-L1 binding to PD-1 as well as CD80 expressed on T cells (and possibly APC); the significance of which is still unclear. In this study, BMS-936559 was administered intravenously at 0.3-10 mg/kg of body weight every 14 days in 6-week cycles for up to 16 cycles. A total of 207 patients with advanced solid cancer were enrolled in the study in which durable (≥24 weeks) objective response rates of 6-17% were induced in a range of different cancer types including melanoma (17%, 9 of 52 patients), renal cell cancer (12%, 2 of 17 patients), non-small cell lung cancer (10%, 5 of 49 patients) and ovarian cancer (6%, 1 of 17 patients) (11). No objective responses have been observed in patients with colorectal (18 patients enrolled) or pancreatic cancer (14 patients enrolled) and no activity of the antibody was evident in patients with gastric (7 patients enrolled) or breast cancer (4 patients enrolled). Notably, the pattern of clinical activity of the BMS-936559 drug was similar to that of the anti-PD-1 mAb used in the Topalian study; however, the frequency of objective responses to the anti-PD-L1 antibody was lower. It will be important to ascertain whether this level of activity correlates with PD-L1 expression on the tumor cells, thus reaffirming the immunosuppressive dominance of tumor cell associated PD-L1.

Collectively the toxicity profiling from both studies would suggest that the PD-1 and PD-L1 targeted antibodies were largely well tolerated. Grade three and four drug associated adverse events, with potential immune-related causes were identified in 14% and 9% of patients, respectively (10,11), however, these appeared to be less severe than that which has been reported for ipilimumab [Reviewed in (14)]. Notably, in the Topalian study 9 of the 296 patients (3%) developed pneumonitis of whom three died due to this drug-related complication. This outcome has raised awareness of the potentially important role that the PD-1/PD-L1 pathway plays in regulating inflammatory responses to pathogenic microbes. Indeed PD-1 deficient mice were reported to have a significantly reduced ability of controlling fatal inflammatory responses in the lung after Mycobacterium tuberculosis infection compared to wildtype mice (15). Notably, M. tuberculosis infected PD-1-/- mice developed severe multifocal necrotic pneumonia. Ultimately, a greater understanding of the role that PD-1/PD-L1 signaling plays in controlling inflammation in the lungs in response to different types of infections will help to identify those patients who may be more susceptible to this drug-related adverse event as well as better manage the condition in future trials.

The question of how best to integrate the use of PD-1/PD-L1 blocking antibodies into mainstream oncology, for the safe and effective treatment of cancer, is a subject of on-going investigation. More extensive histological analysis of patient tumors for PD-L1 expression and immunological assessment of the tumor microenvironment and immune infiltrates of pre- and post-therapy patient biopsies will be the key to identifying viable biomarkers that will ensure optimal clinical application of these immunotherapeutic agents. Ultimately however, the true clinical benefit of these immunotherapeutic agents across a broad range of cancer types will likely be best realised when used in combination with select chemotherapeutics, radiotherapy, HER-2 targeted therapies, anti-CTLA-4 or anti-cancer vaccines, all of which have the capacity to stimulate endogenous anti-tumor immunity. By selectively breaking

down key immunosuppressive barriers within tumors, like that of PD-1, the full therapeutic power of important first-line and experimental anti-cancer therapies will be unleased. Collectively the findings from the Topalian *et al*., and Brahmer *et al*., studies provide strong validation for pursuing the clinical development of blocking antibodies to PD-1 and PD-L1 as part of our increasing immunotherapeutic armament against cancer.

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