Immune modulation for cancer therapy

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Background: Immune modulation in cancer refers to a range of treatments aimed at harnessing a patient’s immune system to achieve tumour control, stabilisation, and potential eradication of disease. A novel therapeutic drug class called immune checkpoint-blocking antibodies modulate T-cell pathways that regulate T cells and have the potential to reinvigorate an antitumour immune response. Ipilimumab was the first FDA-approved immune checkpoint antibody licensed for the treatment of metastatic melanoma (MM) and blocks a checkpoint molecule called cytotoxic T-lymphocyte antigen 4 (CTLA-4).

Methods: Herein we review the preclinical and clinical development of ipilimumab. We outline the mode of action of these agents and other immune checkpoint inhibitors, the management of their toxicities, and how to adequately assess response to treatment.

Results: As a result of these data, a number of other antibodies that block novel checkpoint molecules including programmed death-1 (PD-1), and corresponding ligands such as programmed death ligand-1 (PD-L1) are under preclinical and clinical development, and have demonstrated activity in multiple tumour types.

Conclusions: This review will summarise the mechanism of action and clinical development of immune checkpoint antibodies, as well as lessons learned in the management and assessment of patients receiving these agents.

During immune surveillance, the host provides defense against foreign antigens, while ensuring it limits activation against self-antigens (Page et al, 2014). Immune checkpoints are cell surface molecules that serve as endogenous regulators of the immune response, limiting autoimmunity by mediating co-inhibitory signalling pathways (Nirschl and Drake, 2013). In cancer, these pathways are important in the tumour microenvironment and draining lymph nodes, leading to a state of T-cell exhaustion, thereby allowing tumour escape from immune surveillance, and unchecked tumour growth. Monoclonal antibodies (mAbs) that target immune checkpoints either antagonise co-inhibitory immunologic pathways or activate co-stimulatory pathways. These immune checkpoint antibodies are clinically active in a variety of malignancies, including those not traditionally classified as immunogenic, such as non-small-cell lung cancer (NSCLC).

The prototypical immune checkpoint mAb, and first to be approved by the FDA, is ipilimumab (Yervoy, Bristol-Myers Squibb, New York, NY, USA). Ipilimumab is a fully human antibody that targets cytotoxic T-lymphocyte antigen 4 (CTLA-4; Hodi et al, 2003) and was approved for metastatic melanoma (MM) based upon two phase III studies demonstrating an improvement in overall survival (OS; Hodi et al, 2010; Robert et al, 2011). After the initial clinical development of this agent, agents modulating other novel immune checkpoint molecules and their ligands have been identified, such as programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), lymphocyte activation gene-3, T-cell immunoglobulin mucin protein-3, GITR, and CD-137 (Figure 1) among others (Page et al, 2014). This article will summarise the underlying mechanisms by which immune checkpoint mAbs elicit an antitumour effect, as well as outline the preclinical and clinical development of both single agent and combination immune modulation with checkpoint antibodies.

ANTI-CTLA-4 ANTIBODIES

Preclinical studies with CTLA-4. CTLA-4 is a molecule expressed on the surface of CD-4 and CD-8 T cells as well as CD25 +
FOXP3+ T-regulatory cells, and is a member of the CD28/ 
immunoglobulin superfamily (Avogadri et al., 2011). CTLA-4 
competes with CD28 to bind to its ligands B7–1 (CD80) and B7–2 
(CD86) on antigen-presenting cells (APCs). CTLA-4 generates 
an inhibitory signal that blocks a T-cell response. An anti-CTLA-4 
antibody was first studied in transplantable tumour models of 
colon carcinoma (51B1H10), fibrosarcoma (Sa1N and CSA1M), 
ovarian cancer (OV-HM), and prostate cancer (TRAMPC1; Yang 
et al., 1997). In these models, primary shrinkage of tumours was 
observed in response to the mAb, and recurrence was not seen at 
the time of tumour rechallenge.

**Anti-CTLA-4 agents: ipilimumab and tremelimumab.** Ipi-
umab was first tested in MM in a phase I trial of 17 patients and 
demonstrated two durable partial responses at a starting dose of 
3 mg kg\(^{-1}\) \(\text{Tchekmedyian et al., 2002}\). A dose–response relation-
ship was established in a double-blind phase II trial at three dose 
levels of 0.3, 3, or 10 mg kg\(^{-1}\), administered every 3 weeks for 
four doses, followed by 12-weekly maintenance therapy. 
A response rate (RR) of 11% and a median OS of 14 months 
for four doses, followed by 12-weekly maintenance therapy. 
A median duration of response of 36 months was seen 
with or without gp100 peptide vaccine, \(\text{vs} \) the gp100 peptide 
 vaccine alone (Hodi et al., 2010; Robert et al., 2011). 
The first trial compared ipilimumab at a dose of 3 mg kg\(^{-1}\) \(\text{vs} \) with or without gp100 peptide vaccine, \(\text{vs} \) the gp100 peptide 
 vaccine alone (Hodi et al., 2010). The median OS in the ipilimumab 
and ipilimumab/gp100 groups was 10.1 \(\text{vs} \) 10.0 months, respec-
tively, compared with 6.4 months with gp100 alone, with a hazard 
 ratio (HR) of 0.68, \(P < 0.001\). In the first-line setting, ipilimumab/ 
dacarbazine was compared with dacarbazine/placebo, at an 
 ipilimumab dose of 10 mg kg\(^{-1}\), followed by maintenance 
ipilimumab or placebo every 12 weeks. This trial demonstrated 
an improvement in the median OS for the combination arm (11.2 
months \(\text{vs} \) 9.1 months; Robert et al., 2011). In this study, the 
number of long-term survivors exceeded the number of patients 
with objective responses (ORs), with survival rates in the 
ipilimumab/dacarbazine group at 1 year of (47.3% \(\text{vs} \) 36.3%), 2 
years (28.5% \(\text{vs} \) 17.9%), and 3 years (20.8% \(\text{vs} \) 12.2%; HR for death, 
0.72; \(P < 0.001\)). Responses were durable, with a median duration 
of response of 19.3 months with the combination and 8.1 months 
with dacarbazine alone. These observations suggest that immune- 
based therapies may generate a sustained antitumour effect in a 
subset of patients, long after completion of active therapy. Of 
patients re-induced on the original ipilimumab/gp100 trial, 19% 
\((n = 6/31)\) of patients exhibited an OR, with an additional 48% 
\((n = 15/31)\) achieving stable disease (SD; Hodi et al., 2010).

**Ipilimumab** has also been evaluated in other cancers, with 
responses observed in both renal cell carcinoma (RCC) and 
NSCLC (Yang et al., 2007; Lynch et al., 2012). A three-arm phase II 
study in NSCLC evaluated concurrent, phased, and sequential 
ipilimumab combined with carboplatin and paclitaxel in patients 
with stage IV NSCLC (Lynch et al., 2012). This trial demonstrated 
a benefit in immune-related progression-free survival, defined later 
in this review. A subset analysis of this study benefit in patients 
with squamous cell carcinomas of the lung, leading to a large phase 
III study (NCT01285609).

A second antibody against CTLA-4, tremelimumab (MedImm-
une LLC, Gaithersburg, MD, USA), is a human immunoglobulin 
G2 (IgG2) monoclonal antibody (Ribas et al., 2007). Ribas et al. 
(2013) reported a phase III trial of tremelimumab vs investigator’s 
choice of chemotherapy in MM, at a dose of 15 mg kg\(^{-1}\) every 
3 months. A median duration of response of 36 months was seen 
with tremelimumab vs 14 months with combination chemotherapy 
\((P = 0.0011)\); however, no OS benefit was observed. This finding 
can potentially be explained by the exclusion of patients with an 
elevated lactate dehydrogenase level, crossover of patients to 
 ipilimumab, as well as possible suboptimal dose and schedule.

**ANTI-PD-1/PD-L1 ANTIBODIES**

**Preclinical studies with the PD-1/PD-L1,2 pathway.** The PD-1/ 
PD-L1,2 pathway is a second inhibitory immune checkpoint 
pathway, mediated by the transmembrane molecule PD-1 (CD279) 
found on the surface of T lymphocytes, B lymphocytes, and 
monocytes (Keit et al., 2008). PD-1 binds to PD-L1 and PD-L2, 
which are expressed on APCs and other cells, including tumour 
and normal tissues. Upon ligation to PD-L1/2, PD-1 suppresses 
downstream phosphoinositide 3-kinase (PI3K) and Akt signalling 
via an immunoreceptor tyrosine-based inhibitory motif. In 
contrast, CTLA-4 signalling inhibits Akt independent of PI3K(- 
 Parry et al., 2005). These two pathways therefore bring about 
similar effects but by different mechanisms.

**Anti-PD-1 agents: nivolumab, MK3475 and pidilizumab.** The 
first anti-PD-1 mAb to be clinically evaluated was nivolumab 
(BMS-936558), a human monoclonal immunoglobulin (Ig) G4 
antibody. Results from a Phase Ib study of nivolumab reported 
activity in MM, RCC and NSCLC (Topalian et al., 2012). Objective 
response rates (ORRs) in these diseases were 28% \((n = 26/94)\), 24% 
\((n = 4/17)\), and 18% \((n = 14/76)\) respectively. The median duration 
of response was 74 weeks, with a median OS of 9.6 months in the

Figure 1. Targets of antibody immune modulators (Page et al., 2014). Targets of antibody immune modulators. (A) Targetable members of the 
CD28/CTLA-4 immunoglobulin superfamily include cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), 
B- and T-cell attenuator (BTLA), lymphocyte activation gene 3 (LAG3), and inducible T-cell costimulator (ICOS). (B) Targetable members of the 
tumour necrosis factor (TNF) superfamily include CD40, OX40, CD137/4-1BB, glucocorticoid-induced TNFR-related protein (GITR), and CD27. 
(C) Programmed cell death 1 ligand 1 (PD-L1). (D) Killer inhibitory receptor (KIR). (E) T-cell Ig and mucin-containing domain 3 (TIM3).
patients with heavily-pretreated NSCLC. Nivolumab monotherapy at a dose of 3 mg kg\(^{-1}\) is currently being studied in phase III clinical trials in MM, RCC and NSCLC (Table 1). Successful re-induction with nivolumab has been described in a patient with melanoma who achieved a partial response (PR), followed by a period of SD for 16 months off treatment (Lipsen et al., 2013).

A second humanised monoclonal IgG4 anti-PD-1 antibody, MK-3475 (Merck, Sharpe and Dohme, Whitehouse Station, NJ, USA), was deemed safe at 1 mg kg\(^{-1}\), 3 mg kg\(^{-1}\), and 10 mg kg\(^{-1}\) dose levels administered every 2 weeks in a phase I study, with no maximum tolerated dose (MTD) identified (Patnaik and Tolcher, 2012). This agent was subsequently studied in both first-line and ipilimumab-pretreated patients with MM, at dose levels 2 and 10 mg kg\(^{-1}\) administered every 2 or 3 weeks. Identical immune-related responses by immune-related response criteria (irRC), detailed later in this review, were 56% in both first-line and ipilimumab-pretreated patients at 10 mg kg\(^{-1}\) given every 2 weeks (Hamid et al., 2013). A phase II trial of this agent at two dose levels in comparison to chemotherapy, is currently in accrual (NCT01704287), as well as a phase III study in advanced MM compared to ipilimumab (NCT01866319).

In hematologic malignancies, the anti-PD-1 antibody pidilizumab (CT-011) demonstrated a ORR of 66% (n = 19/32) when combined with rituximab in relapsed follicular lymphoma (Westin et al., 2014). An ORR of 51% was also seen in a phase II study of 35 patients with measurable disease after autologous stem-cell transplant for diffuse large B-cell lymphoma (n = 18/35) (Armand et al., 2013). This agent is currently being studied in MM, malignant gliomas, RCC and combination with chemotheraphy in advanced colorectal cancer (NCT01435369, NCT01952769, NCT01441765, NCT00890305).

### Anti-PD-L1 agents: BMS-936559 and MPDL3280A

The first anti-PD-L1 mAb to be clinically evaluated was BMS-936559. Brahmer and colleagues reported a phase I study of this agent in multiple tumour types, including 75 patients with NSCLC and 52 with MM (Brahmer et al., 2012). The ORR 17% of patients with MM was 17% (n = 9/52), 12% in RCC (n = 2/17), 10% in patients with NSCLC (n = 5/49). No MTD was found, and 9% of patients sustained grade 3/4 AEs. MPDL3280A is a second human mAb against PD-L1, and contains an engineered Fc portion that targets PD-L1. In a phase I trial of MPDL3280A administered to patients with MM, RCC and NSCLC, RR's were 29%, 22% and 15% respectively (Hamid and Lawrence, 2012). Table 1 outlines current phase III trials with nivolumab and other agents targeting the PD-L1/PD-L1.2 pathway, in a number of tumour types. Additional PD-L1-directed agents such as MEDI-4736 are being evaluated in the phase I setting.

### TOXICITIES WITH IMMUNE CHECKPOINT ANTIBODIES

The spectrum of AEs associated with immune checkpoint antibodies are termed immune-related AEs (irAE's). The underlying pathophysiology relates to the immune-based mode of action of these agents, leading to T-cell inflammatory infiltration of solid organs, and increased serum inflammatory cytokines (Fecher et al., 2013). irAEs observed with ipilimumab appear to be dose-dependent, and range in severity from mild to fatal, and in onset from slow to sudden, but generally appear late, 8–10 weeks after initiation of therapy (Weber et al., 2012). Medical management is aimed at correctly identifying the irAE, grading based on the National Cancer Institute common toxicity criteria of AEs, and initiating early treatment with supportive care or immunosuppressive medications, typically corticosteroids. AEs with ipilimumab and tremelimab are dermatitis (pruritus, rash), enterocolitis, endocrinopathies (hypophysitis, thyroiditis), liver enzyme abnormalities, and uveitis (Page et al., 2011). irAEs including mild fatigue, rash, diarrhea, and colitis have been described with anti-PD-1 agents, although AEs seem to be less common than those seen with anti-CTLA-4 antibodies (Gangadhar and Vonderheide, 2014). A rare but potentially fatal inflammatory pneumonitis was observed in 2–4% of cases, and led to three treatment-related deaths in the original phase I study of nivolumab (Topalian et al., 2012). In the phase I study of MK-3475 in MM, 13% of patients developed grade 3/4 irAEs, and 4% developed mild (grades 1–2) pneumonitis (Hamid et al., 2013). MPDL3280A had a 30–40% incidence of grade 3/4 AEs including hyperglycaemia, nephritis, and fatigue, but no cases of grade 3–5 pneumonitis were reported (Hamid and Lawrence, 2012). Toxicities may vary across tumour types, possibly explained by heterogeneity of antigen expression and resulting autoreactivity.

Management algorithms have emerged for irAE’s, such as inflammatory diarrhea/colitis and uniformly begin with elimination of potential infectious etiologies. Grade I diarrhea is managed with oral hydration, an American Dietary Association colitis diet, and loperamide (Weber et al., 2012). Diarrhea of grade 2 or greater can be managed with oral budesonide, oral corticosteroids, intravenous methylprednisolone, and occasionally infliximab (Fecher et al., 2013). Colitis-associated mortality is associated with management delays, failure to withhold ipilimumab, and an inadequate anti-diarrheal regimen. The use of effective management algorithms have reduced life-threatening complications, with bowel perforations now occurring in < 1% of patients.

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**Table 1. Current phase III trials investigating antibodies that target the PD-1/PD-L1,2 pathway**

| Agents | NCI Identifier | Cancer type | Setting | Phase | n | Primary end point |
|--------|----------------|-------------|---------|-------|---|------------------|
| Nivolumab vs Everolimus | NCT01668784 | Pre-treated or metastatic RCC | Pre-treated or first-line | III | 822 | Overall survival |
| Nivolumab vs Nivolumab + Ipilimumab vs Ipilimumab | NCT01844505 | Metastatic melanoma | First-line | III | 917 | Overall survival |
| Nivolumab vs Dacarbazine | NCT01721772 | Metastatic melanoma | First-line | III | 410 | Overall survival |
| MK-3475 (2 dose levels) vs Ipilimumab | NCT01866319 | Metastatic melanoma | Pre-treated or first-line | III | 645 | Overall survival (Progression-free survival) |
| MPDL3280A | NCT01846416 | NSCLC (PD-L1 +) | First-line | II | 130 | Response rate |
| MPDL3280A vs Docetaxel | NCT01903993 | NSCLC | Platinum pre-treated | II | 180 | Response rate |

**Abbreviations:** NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma.
ASSESSING RESPONSE TO IMMUNOTHERAPEUTICS

Antitumour responses with immunotherapies are heterogeneous: responses may be mixed or delayed, lesions may enlarge before shrinking, lesions may remain stable or slowly regress over time. These responses can be potentially explained by T-cell activation and tumoral infiltration by immune cells, as well as intra-patient heterogeneity of tumour-host interactions. These observations led a group of colleagues to propose the ‘immune-related response criteria (irRC)’ for evaluating response to immunotherapeutic agents. These criteria are based on the rationale that immunotherapies generate an antitumour effect with response kinetics distinct from cytotoxic chemotherapy (Wolchok et al, 2009). The irRC thus recommends interval imaging at least 4 weeks apart to aid in the confirmation of asymptomatic progression. Owing to these response patterns, patients who experience clinically insignificant progression often continue therapy until progression is confirmed on subsequent imaging.

Intriguing clinical effects with immune checkpoint antibodies and radiation therapy have also been observed. The abscopal effect refers to tumour regression occurring outside an irradiated field, when a patient is receiving immunomodulatory therapy (Postow et al, 2012). The underlying mechanism is thought to be due to the stimulation of antigen release by local inflammation at the site of radiotherapy. The combination of radiation plus immunotherapy is being prospectively studied (NCT01703507, NCT01497808, NCT01565837, and NCT01689974).

BIOMARKERS TO IMMUNE CHECKPOINT MOLECULES

As only a subset of patients treated with immune checkpoint antibodies experience durable and long-term disease control, predictive biomarker development has become a priority. The absolute lymphocyte count (ALC) is a potential pharmacodynamic biomarker for ipilimumab, with the ALC at 7 weeks following therapy. ALC and baseline absolute eosinophil count have also been associated with improved survival in patients with advanced melanoma (Delyon et al, 2013; Schindler and Postow, 2013). Variations in IHC technique, cancer type, and radiation therapy have also been observed. The abscopal effect refers to tumour regression occurring outside an irradiated field, when a patient is receiving immunomodulatory therapy (Postow et al, 2012). The underlying mechanism is thought to be due to the stimulation of antigen release by local inflammation at the site of radiotherapy.

The combination of ipilimumab and nivolumab was recently evaluated in a phase I trial in MM, demonstrating a RR of 53% at the MTD, with all responding subjects in this cohort achieving a >80% decline in tumour burden at 12 weeks (Wolchok et al, 2013). The combination was safe; however, there were more frequent (53%) grade 3/4 AE than with either agent as monotherapy. Other mAb combinations are currently being investigated, and are detailed in Table 2. Another strategy is to combine checkpoint agents with other standard or investigational anticancer therapies including radiotherapy, cytotoxic chemotherapy, targeted therapies, or vaccine/cytokine therapy. However, the combination of ipilimumab + BRAF inhibitor vemurafenib produced significant hepatotoxicity, requiring termination of a phase I trial. (Ribas et al, 2013) A study of dabrafenib and trametinib with ipilimumab is ongoing and trials of targeted therapies with PD-1 pathway-blocking drugs are about to be initiated in MM.

Table 2. Current clinical trials investigating combinations of immune checkpoint inhibitors

| Agents                          | NCI Identifier       | Cancer Type               | Phase | n  | Primary end points          |
|---------------------------------|----------------------|---------------------------|-------|----|-----------------------------|
| MED4736 + Tremelimumab          | NCT02000947          | NSCLC                     | Ib    | 156| Safety MTD                 |
| Anti-LAG-3 (BMS986016) + Nivolumab | NCT01968109        | Multiple solid tumours    | I     | 168| Safety MTD                 |
| Anti-IL2 (BMS982470) + Nivolumab | NCT01629758        | Multiple solid tumours    | I     | 165| Safety MTD                 |
| Anti-Kir (Lirilumab) + Nivolumab | NCT01714739        | Multiple solid tumours    | I     | 150| Safety MTD                 |
| Nivolumab vs Nivolumab + Ipilimumab | NCT01928394       | Gastric SCLC              | I/II  | 160| Objective response rate     |
| Nivolumab + Sequential Ipilimumab | NCT01783938        | Metastatic melanoma       | II    | 100| Safety                      |

Abbreviations: GEJ = gastroesophageal junction; KIR = killer-cell immunoglobulin-like receptor; LAG-3 = Lymphocyte-activation gene 3; MTD = maximum tolerated dose; NCI = National Cancer Institute; NSCLC = non-small cell lung carcinoma; SCLC = small cell lung carcinoma; TNBC = triple negative breast cancer.

COMBINATORIAL APPROACHES

The combination of ipilimumab and nivolumab was recently evaluated in a phase I trial in MM, demonstrating a RR of 53% at the MTD, with all responding subjects in this cohort achieving a >80% decline in tumour burden at 12 weeks (Wolchok et al, 2013). The combination was safe; however, there were more frequent (53%) grade 3/4 AE than with either agent as monotherapy. Other mAb combinations are currently being investigated, and are detailed in Table 2. Another strategy is to combine checkpoint agents with other standard or investigational anticancer therapies including radiotherapy, cytotoxic chemotherapy, targeted therapies, or vaccine/cytokine therapy. However, the combination of ipilimumab + BRAF inhibitor vemurafenib produced significant hepatotoxicity, requiring termination of a phase I trial. (Ribas et al, 2013) A study of dabrafenib and trametinib with ipilimumab is ongoing and trials of targeted therapies with PD-1 pathway-blocking drugs are about to be initiated in MM.
NOVEL IMMUNE CHECKPOINT MOLECULES

New agents that attempt to target other immunomodulatory receptors on T cells and other immune cells are in development (Figure 1). Agonists of co-stimulatory molecules on B and T cells such as CD-137, OX40, and glucocorticoid-induced TNFR-related protein (GITR) are in clinical development (Mallett et al, 1990). A phase I study of an OX40 agonist in advanced solid tumours demonstrated tumour shrinkage of at least one metastatic lesion in 12 out of 30 subjects after one cycle of therapy (Curti et al, 2013). A humanised anti-GITR mAb (TRX518) also enhances co-stimulation in human lymphocytes in vitro, and is being studied in a dose-escalation trial (NCT1239134). CD-137/4-1BB is a third co-stimulatory mediator present on activated T cells, with corresponding ligands on activated B cells, and APCs (Lin et al, 2008). Agonist mAbs for CD137 enhance the co-stimulatory signal on T cells and such mAbs against CD137 have entered clinical trials in haematologic malignancies and others (urelumab: NCT01471210, NCT01775631; FF-05082566: NCT01307267).

CONCLUSION

Preliminary studies of CTLA-4, PD-1, and PD-L1-blocking antibodies show clear evidence of clinical activity, proving that immune checkpoint modulation is a viable emerging treatment modality across malignancy types, even in cancers not traditionally viewed as amenable to immunotherapy. However, because responses are confined to a subset of treated subjects, future development will focus upon rational combinatorial approaches and predictive biomarker discovery.

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