Chapter 18
Anti-CTLA-4 Ab

Takuto Tokudome

Abstract Ipilimumab (MDX-010, BMS-734016) is a fully human monoclonal immunoglobulin (IgG1) specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T cells as a negative regulator of T-cell activation. Two phase III clinical studies (MDX010-20 and CA184-024) of ipilimumab have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively (Hodi FS et al., N Engl J Med 363:711–723, 2010; Robert C et al., N Engl J Med 364:2517–2526, 2011). Ipilimumab (Yervoy™) has been approved for clinical use in advanced melanoma in over 40 countries as the first immune checkpoint inhibitor to show overall survival benefit in patients with advanced melanoma. From the experiences in both clinical development and clinical use of ipilimumab in more than 18,000 patients, some unique features of ipilimumab such as response patterns, durability of response, long-term survival benefit, immune-related adverse events (irAEs), and their management have been recognized. Challenges that contribute to the further development of ipilimumab are currently underway, including combination therapies and biomarker research.

Keywords Ipilimumab • CTLA-4 • Immune checkpoint inhibitor • Advanced melanoma • Durability of response • Long-term survival benefit • Immune-related adverse events (irAE)

18.1 Introduction

In 1970, Bretscher et al. proposed the two-signal model in which activation of T cells requires both a signal involving antigen-specific stimulation via T-cell receptor (TCR) (signal 1) and a costimulatory signal (signal 2) for the first time [1]. In subsequent decades, the engagement of CD28 by B7 (CD80 or CD86) molecules became widely understood as one of the dominant costimulatory signals as signal

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2, and, in addition, the presence of negative costimulatory (co-inhibitory) signals that inhibit T-cell activation such as human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4 or CD152) and programmed death-1 (PD-1 or CD279) were established [2, 3].

In 2011, an anti-CTLA-4 monoclonal antibody (mAb), ipilimumab (Yervoy™), was approved for clinical use in advanced melanoma as the first immune checkpoint inhibitor based on the two phase III clinical studies [4, 5]. Other immune checkpoint inhibitors such as PD-1 are currently being developed for various types of cancer. Advances in understanding the mechanisms regulating T-cell activation have allowed the development of better strategies for the immunotherapy of cancers.

18.2 Cytotoxic T Lymphocyte-Associated Antigen 4 (CTLA-4)

CTLA-4 was discovered as the fourth in a series of gene products identified in a subtractive cDNA library produced from activated CTLs in 1987 (hence CTL activation gene number 4, or CTLA-4) [6]. CTLA-4 is an activation-induced T-cell surface molecule that also binds B7, but with greater affinity than CD28 [7].

CTLA-4 ligation downregulates T-cell responses. Several studies have demonstrated that, in vitro, soluble anti-CTLA-4 mAb enhanced T-cell responses, whereas directly cross-linking CTLA-4 results in blockade of cell cycle progression, diminished cytokine expression, and decreased proliferation [8–11]. Blockade of CTLA-4/B7 interactions prevents induction of peripheral T-cell tolerance upon vaccination with peptides under tolerogenic conditions, suggesting that CTLA-4 is involved in the induction of anergy [12].

The observation that CTLA-4 knockout mice suffer a fatal lymphoproliferative disorder supports the idea that CTLA-4 functions as a key negative regulator of T-cell responses [13–15]. However, blockade of CTLA-4 function by the antibody does not lead to any detectable nonspecific T-cell activation or proliferation, although the antibody can augment autoimmune responses in mice prone to specific autoimmune disease [16]. Using anti-CTLA-4 mAb, CTLA-4 blockade enhanced rejection of B7-transfected tumors and induced rejection of unmodified tumor cells and immunity to rechallenge in a T-cell-dependent mechanism [17].

Blockade of CTLA-4 interaction with its ligands also enhances host responses against bacteria and parasites and limits viral spread in human immunodeficiency virus-infected T cells in vitro [18–20].

In addition to being expressed on activated effector T cells, CTLA-4 is constitutively expressed on the surface of regulatory T cells. CTLA-4 blockade can also reduce regulatory T-cell function, which may lead to an increase in antitumor immune response [21, 22]. Anti-CTLA-4 mAb may selectively deplete regulatory T cells at the tumor site, leading to an increase in the intratumoral effector/regulatory T-cell ratio which drives tumor cell death [23–25].

18.3 Anti-CTLA-4 Antibodies

18.3.1 Ipilimumab (Yervoy™)

Ipilimumab (MDX-010, BMS-734016) is a fully human monoclonal immunoglobulin (IgG1) antibody with a half-life of approximately 14 days. The mechanism of action for ipilimumab is interference of the interaction of CTLA-4, expressed on a subset of activated T cells, with B7 molecules on antigen-presenting cells (APCs). This results in tumor antigen-specific T-cell proliferation and activation due to blockade of the inhibitory modulation of T-cell activation and thereby is believed to inhibit tumor growth (Fig. 18.1) [26].

Currently, ipilimumab (Yervoy™) has been approved for clinical use in advanced melanoma in over 40 countries as the first agent to show overall survival

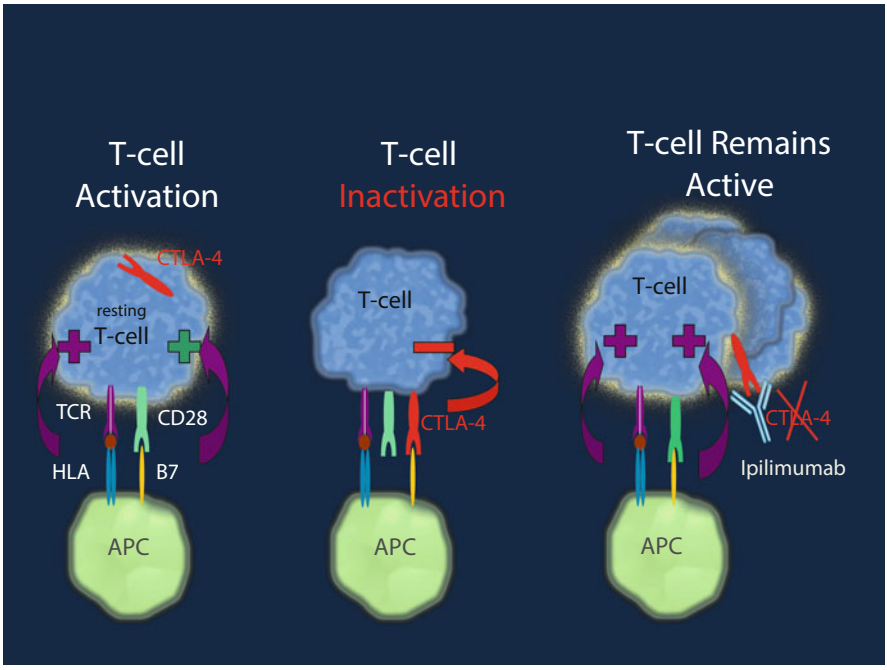


Fig. 18.1 Ipilimumab MOA. The two key signals between APCs and T cells that are required for T-cell activation are (1) the tumor-specific antigen is presented (as a peptide on major histocompatibility complex [MHC] molecules) to the T-cell receptor and (2) a B7-costimulatory signal is delivered to the CD28 receptor. This leads to proliferation of activated T cells with the capacity to attack and kill antigen-bearing tumor cells. Subsequently, as part of a negative feedback loop, CTLA-4, a high-affinity inhibitory receptor, is expressed on activated T cells and blocks the B7-costimulatory signal, which disrupts the integrity of the immunological synapse, reduces cytokine production, and slows T-cell proliferation. With CTLA-4 blockade by ipilimumab, the negative feedback loop is interrupted, and tumor-specific T-cell activation and proliferation are potentiated and thereby are believed to inhibit tumor growth

(OS) benefit in patients with advanced melanoma. As a CTLA-4 immune checkpoint inhibitor, ipilimumab is being developed for use in the treatment of various types of cancer, including prostate cancer and lung cancer.

18.3.2 Tremelimumab

Tremelimumab (CP-675,206) is another CTLA-4 immune checkpoint inhibitor (a fully monoclonal immunoglobulin [IgG2] antibody with a half-life of approximately 22 days) that is being investigated for several tumor types including advanced melanoma. In the early phase studies, tremelimumab showed promising antitumor activity in patients with advanced melanoma [27]. However, a phase III study of tremelimumab was halted after interim analysis failed to show OS benefit compared with standard therapy although the results showed favorable outcomes with tremelimumab therapy [28].

18.4 Clinical Development of Ipilimumab

The clinical development of ipilimumab was initiated in 2000 by Medarex Inc. (MDX), which started a joint development program with Bristol-Myers Squibb (BMS) in 2004. BMS and MDX (acquired by BMS in 2009) have cosponsored an extensive clinical development program for ipilimumab, encompassing more than 18,000 patients in several cancer types in completed and ongoing studies, as well as a compassionate use program. The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

In melanoma, two completed phase III studies (MDX010-20 and CA184-024) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively (data will be showed later in this chapter) [4, 5]. In 2010, a biologics license application (BLA) for ipilimumab was filed with the US Food and Drug Administration (FDA) and European Medical Agency (EMA) for approval in patients with advanced melanoma, primarily based on the MDX010-20 results (ipilimumab 3 mg/kg) on efficacy and safety. Ipilimumab (Yervoy™) has been approved for clinical use in advanced melanoma in over 40 countries including the USA (March, 2011), the EU (July, 2011), and Australia (July, 2011) as the first agent to show OS benefit in patients with advanced melanoma. Currently, ipilimumab is designated as category 1 anticancer treatment option for advanced melanoma in the National Comprehensive Cancer Network (NCCN) guideline and used regardless of BRAFV600 mutation. Also, both the NCCN and European

Society for Medical Oncology (ESMO) recommend ipilimumab for use in advanced melanoma, regardless of whether the patients have received treatment in the past or are treatment naïve [29, 30].

For prostate cancer, a completed phase III study (CA184-043) evaluated ipilimumab in patients with metastatic castration-resistant prostate cancer (mCRPC) who had progressed during or following docetaxel. Eligible patients were randomized to a single dose of bone-directed radiotherapy, followed by either ipilimumab 10 mg/kg or placebo. This study did not meet its primary endpoint of OS although the hazard ratio (HR) of 0.85 showed a favorable trend for ipilimumab [31]. A second phase III study evaluating ipilimumab 10 mg/kg versus placebo in patients with chemotherapy-naïve mCRPC with no visceral metastases is underway (CA184-095, NCT01057810).

For lung cancer, a completed large phase II study (CA184-041) has investigated the addition of ipilimumab to carboplatin and paclitaxel using two different schedules (concurrent and phased) in patients with non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). A concurrent group consisted of four cycles of chemotherapy with ipilimumab followed by two chemotherapy cycles with a placebo. A phased group consisted of two chemotherapy cycles followed by four chemotherapy cycles with ipilimumab. The phased, but not the concurrent schedule, demonstrated activity in both NSCLC and SCLC, including significant improvement of immune-related progression-free survival (irPFS) and a favorable trend for OS improvement [32, 33]. Currently, the efficacy and safety of ipilimumab in a phased schedule with carboplatin and paclitaxel is being investigated in a phase III study in patients with squamous NSCLC (CA184-104, NCT01285609). The efficacy and safety of ipilimumab in a phased schedule with etoposide and platinum in patients with extensive disease (ED) SCLC are also being investigated in an ongoing phase III study (CA184-156, NCT01450761).

In Japan, clinical development of ipilimumab started in 2010 with a phase I study (CA184-113) to evaluate the safety of ipilimumab combined with carboplatin and paclitaxel in Japanese patients with NSCLC. The study confirmed that ipilimumab 3 and 10 mg/kg doses administered in combination with carboplatin and paclitaxel were tolerable in Japanese patients, and safety and pharmacokinetics were similar compared to non-Japanese patients [34]. For melanoma, a Japanese phase II study of ipilimumab at 10 mg/kg in combination with DTIC in chemotherapy-naïve patients with advanced melanoma (CA184-202) was conducted; however, this study was discontinued due to high incidence of severe liver toxicity (currently under publication). Another phase II study of ipilimumab monotherapy at 3 mg/kg in patients with advanced melanoma (CA184-396, NCT01990859) is underway. Except for melanoma, ipilimumab is currently being developed for NSCLC, SCLC, and gastric cancer in Japan.

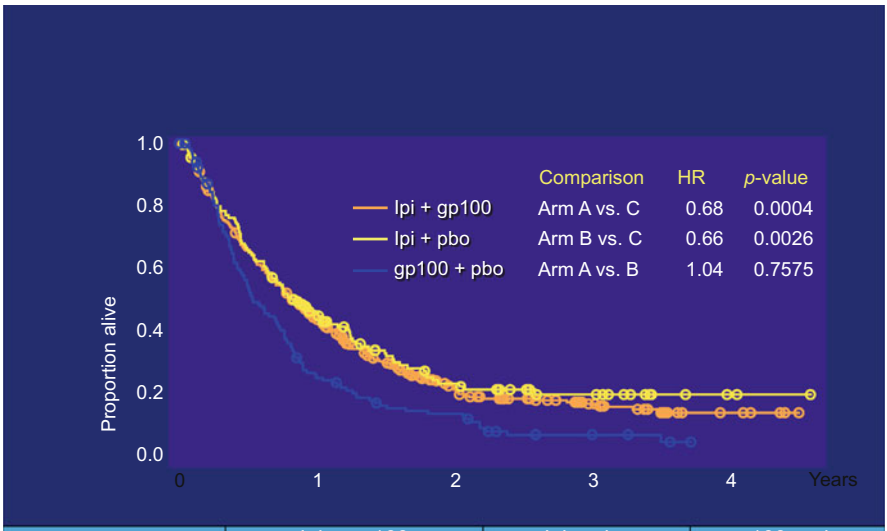
18.5 Clinical Studies on Melanoma

18.5.1 Phase III Study in Previously Treated Advanced Melanoma (MDX010-20)

The first phase III study (MDX010-20) was conducted in 676 patients with melanoma previously treated with chemotherapy. The primary endpoint of this study was to compare the OS of the groups of ipilimumab (3 mg/kg) plus peptide vaccine, gp100 ($n = 403$), ipilimumab alone ($n = 137$), and gp100 alone ($n = 136$) in a 3:1:1 ratio. Median survival was 10 months in the combination group and 10.1 months in the ipilimumab-alone group, as compared with 6.4 months in the gp100-alone group, indicating a statistically significant prolongation of OS in both comparisons (HR 0.68 and 0.66, respectively) (Fig. 18.2) [4]. No difference was observed in OS between the combination group and the ipilimumab-alone group, which suggests that it is appropriate to administer ipilimumab alone instead of coadministering gp100.

The 1-year survival rate in the combination group, the ipilimumab-alone group, and the gp100-alone group was 44 %, 46 %, and 25 %, respectively, and the 2-year survival rate 22 %, 24 %, and 14 %, respectively. Of responders in the ipilimumab-alone group, 60 % (9/15) showed response duration of more than 2 years, and there were patients in whom best overall response (BOR) improved from partial response (PR) or stable disease (SD) to complete response (CR), or from SD to PR, after 24 weeks of the first administration of ipilimumab. The survival benefit of ipilimumab in this study was observed across all relevant subgroups, including age, gender, race, metastasis stage, Eastern Cooperative Oncology Group (ECOG) performance status (PS), baseline LDH level, prior use of immunotherapy, prior use of IL-2, response to prior systemic therapy, and demographic region.

Immune-related adverse events (irAEs) occurred in approximately 56.8–59.5 % in the ipilimumab groups (the combination group and the ipilimumab-alone group) compared with 31.8 % in the gp100-alone group. Common irAEs in the combination group, the ipilimumab-alone group, and the gp100-alone group, respectively, were gastrointestinal (GI) tract (28.2 %, 31.1 %, 14.4 %), skin (42.0 %, 38.9 %, 16.7 %), liver (3.1 %, 2.1 %, 3.8 %), and endocrine (7.6 %, 3.4 %, 1.5 %). Common grade $\geq$3 irAEs were GI irAE (colitis and diarrhea), which were reported in 3–5 % in the ipilimumab groups. Most frequent drug-related AEs leading to discontinuation were diarrhea (1.5 %, 2.6 %, 0 %) and colitis (2.3 %, 2.4 %, 0 %). Of the 12 drug-related deaths in the ipilimumab groups, seven were associated with an irAE, of which four were due to GI perforation [35].

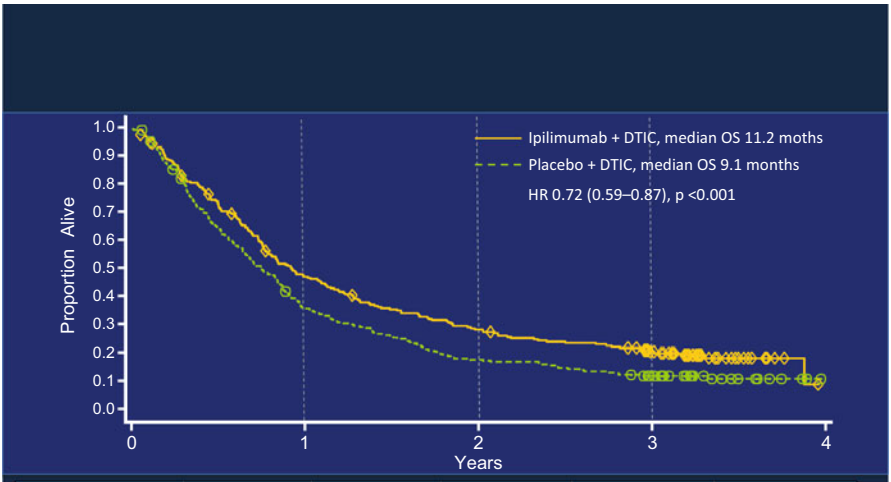


Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Fig. 18.2 Overall survival study MDX010-20. Kaplan-Meier survival curves were similar among the three groups during approximately 4 months after the treatment start, after which the curves started to divert from one another, showing a more favorable OS in ipilimumab 3 mg/kg + gp100 group and in ipilimumab 3 mg/kg group compared with gp100 group. Compared with the risk of death in gp100 group, the risk decreased by 32 % in the ipilimumab 3 mg/kg + gp100 group (hazard ratio = 0.68 [95 % CI: 0.55, 0.85], $p = 0.0004$) and by 34 % in the ipilimumab 3 mg/kg group (hazard ratio = 0.66 [95 % CI: 0.51, 0.87], $p = 0.0026$), with differences being statistically significant in both treatment groups. In contrast, no difference in the risk of death was observed between the ipilimumab 3 mg/kg + gp100 group and ipilimumab 3 mg/kg group (hazard ratio = 1.04 [95 % CI: 0.83, 1.30] $p = 0.7575$). The median OS was 9.95 months (95 % CI: 8.48, 11.50) in ipilimumab 3 mg/kg + gp100 group, 10.12 months (95 % CI: 8.02, 13.80) in ipilimumab 3 mg/kg group, and 6.44 months (95 % CI: 5.49, 8.71) in gp100 group

18.5.2 Phase III Study in Untreated Advanced Melanoma (CA184-024)

Another phase III study (CA184-024) was conducted in 502 chemotherapy-naïve patients with melanoma. The primary endpoint of this study was to compare the OS in the combination group (ipilimumab 10 mg/kg plus DTIC, $n = 250$) and the DTIC-alone group ($n = 252$). Median survival was 11.2 months in the combination group and 9.1 months in the DTIC-alone group (HR 0.72; 95 % CI = 0.59–0.87), indicating 28 % decrease in the risk of death with combined use of ipilimumab. The best overall response rate (BORR) was 15.2 % (38/250) in the combination group and 10.3 % (26/252) in the DTIC-alone group. The median duration of response in



Estimated Survival Rate	1 Year	2 Year	3 Year	*4 Year	*5 Year
Ipilimumab + DTIC n=250	47.3	28.5	20.8	19.0	18.2
Placebo + DTIC n=252	36.3	17.9	12.2	9.6	8.8

Fig. 18.3 Overall survival study CA184-024. The hazard ratio between the two groups was 0.72 (95 % CI: 0.59, 0.87, $p = 0.0009$), showing a significant hazard reduction (by 28 %) of death in ipilimumab + DTIC group compared with DTIC monotherapy group. Kaplan-Meier survival curves were similar between the two groups up to approximately 4 months after the treatment start, after which the curves started to divert from each other, showing a significantly beneficial effect of ipilimumab + DTIC on OS compared with DTIC monotherapy. Median OS was 11.2 months (95 % CI: 9.4, 13.6) in ipilimumab + DTIC group and 9.1 months (95 % CI: 7.8, 10.5) in DTIC monotherapy group

those patients who achieved an objective response (CR and/or PR) was 19.3 months in the combination group ($n = 38$) and 8.1 months in the DTIC-alone group ($n = 26$). In the combination group and the DTIC-alone group, the 1-year survival rate was 47.3 % and 46 %, the 2-year survival rate was 28.5 % and 17.9 %, the 3-year survival rate was 20.8 % and 12.2 %, and the 4-year survival rate was 19.0 % and 9.6 %, respectively (Fig. 18.3) [5, 36].

IrAEs were reported in 75.7 % in the combination group compared with 30.7 % in the DTIC-alone group. Grade $\geq$3 irAEs were reported for 37.2 % in the combination group compared with 2.4 % in the DTIC-alone group. Common irAEs in the combination group and the DTIC-alone group, respectively, were the GI (35.6 % vs. 16.7 %), skin (42.9 % vs. 10.4 %), liver (36.8 % vs. 6.0 %), and endocrine (2.8 % vs. 0.8 %). Common grade $\geq$3 irAEs were liver irAEs (ALT/AST increased), which were reported in 27.9 % in the ipilimumab group and 2.0 % in DTIC-alone group. Grade $\geq$3 GI irAEs were reported in 5.7 % in the combination group and 0 % in DTIC-alone group. No GI perforation was reported in this study.

Common toxicities associated with DTIC (e.g., nausea, vomiting, and myelosuppression) were not increased in the combination group compared to the DTIC-alone group. Most frequent drug-related AEs leading to discontinuation were AST increased (17.0 %) and AST increased (16.6 %). The incidence of drug-related deaths was 0.4 % ($n = 1$) in the DTIC-alone group, and no drug-related deaths were observed in the combination group [35].

18.5.3 Adjuvant Therapy

For patients with earlier stage melanoma, two phase III studies are currently being conducted.

One phase III study (CA184-029) demonstrated that ipilimumab 10 mg/kg ($n = 475$) significantly improved recurrence-free survival (RFS) compared with placebo ($n = 476$) for patients with stage III melanoma who are at high risk of recurrence following complete surgical resection. A 25 % reduction in the risk of recurrence or death was observed (HR 0.75; 95 % CI = 0.64–0.90). At 3 years, an estimated 46.5 % of patients treated with ipilimumab were free of disease recurrence compared to an estimated 34.8 % of patients on placebo. The median RFS was 26.1 months for ipilimumab vs. 17.1 months for placebo, with a median follow-up of 2.7 years. Grade $\geq$3 irAEs in the ipilimumab and placebo groups, respectively, were the GI (15.9 % vs. 0.8 %), liver (10.6 % vs. 0.2 %), endocrine (8.5 % vs. 0 %), and skin (4.5 % vs. 0 %). The incidence of drug-related death in the ipilimumab group was 1.1 % ($n = 5$, GI perforation in two patients), and no drug-related deaths were observed in the placebo group. Of the patients who began treatment with ipilimumab, 48.8 % discontinued treatment due to drug-related AEs as compared with 1.7 % in the placebo group [37].

Another phase III study (NCT01274338) in the adjuvant setting is underway to investigate ipilimumab at doses of 3 mg/kg and 10 mg/kg, or high-dose interferon alfa-2b in patients with high-risk stage III or resectable stage IV melanoma.

18.6 Unique Features of Ipilimumab

18.6.1 Patterns of Response

The unique immune-based mechanism of action of ipilimumab is reflected in the clinical patterns of antitumor activity in some patients.

Ipilimumab impacts tumor cells indirectly, and measurable clinical effects emerge after the immunological effects. Tumor infiltration with lymphocytes and the associated inflammation is likely the cornerstone of the effect of ipilimumab and can manifest in various patterns of clinical activity leading to tumor control. In

some cases, inflammation may not be noted by radiological examination, and objective response is observed with the first tumor assessment in a manner seen in patients receiving other types of anticancer treatments. In other cases, response may be preceded by an apparent increase in initial tumor volume and/or the appearance of new lesions, which may be mistaken for tumor progression on radiological evaluations [38]. Notably, the effects of immune activation appear to persist after discontinuation of treatment, leading to continued tumor shrinkage in some cases, durable response or stable disease, and long-term survival.

Therefore, in patients who are not experiencing rapid clinical deterioration, confirmation of progression is recommended, at the physician's discretion, to better understand the prognosis as well as to avoid unnecessarily initiating potentially toxic alternative therapies in patients who might be benefiting from treatment. Immune-related response criteria (irRC) were developed based on these observations to systematically categorize novel patterns of clinical activity and are currently being prospectively evaluated in clinical studies [39].

18.6.2 Durability of Response and Long-Term Survival Benefit

One of the hallmarks of ipilimumab efficacy is durability of response.

In the phase III study (MDX010-20), response duration was longer than 2 years in 60.0 % (9/15) of responders in the ipilimumab-alone group and 17.4 % (4/23) of responders in the ipilimumab plus gp100 group. Twelve out of these 13 responders had ongoing responses at the time of the primary analysis, with their response duration ranging from 26.5 to 44.4 months at censoring. A total of three patients in the ipilimumab groups maintained the response for more than 3 years (all ongoing at the primary analysis). None of the patients in the gp100-alone group remained in response at the 2-year time point [4].

In another phase III study (CA184-024), the response rate was 15.2 % in the combination group (ipilimumab plus DTIC) compared with 10.3 % in the DTIC-alone group, indicating that tumor reduction in the former group was not much greater than in the latter group. However, the duration of response in the combination group was 19.3 months, which was more than double the duration in the DTIC-alone group (8.1 months) [5].

Five-year survival rates from this study showed further long-term benefit of ipilimumab in treatment-naïve patients with advanced melanoma. The 5-year OS rates were 18.2 % for combination and 8.8 % for DTIC alone. The rates are similar to the previously reported 3-year OS rates (20.8 % in the combination group, 12.2 % in DTIC-alone group) and 4-year OS rates (19.0 % in the combination group, 9.6 % in the DTIC-alone group), suggesting that OS plateaus at the 3-year mark and the antitumor effect of ipilimumab may persist for one to several years [40].

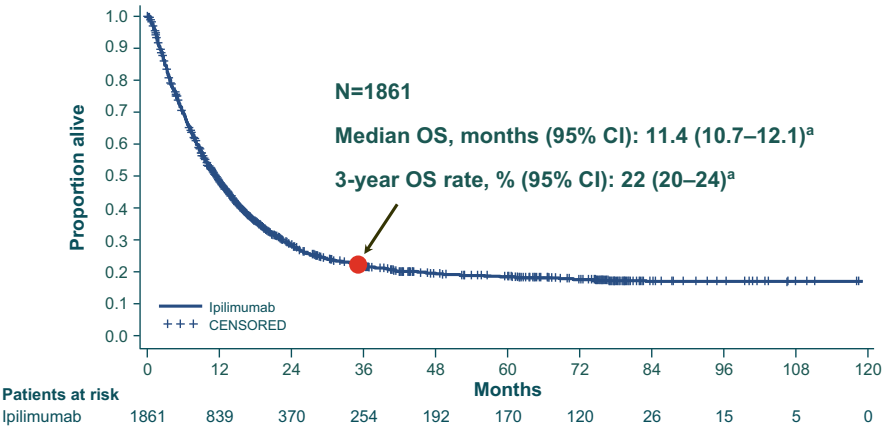


Fig. 18.4 Pooled OS data from melanoma. In a pooled analysis of 12 studies, an OS plateau starts at approximately 3 years with follow-up of up to 10 years in some patients

The long-term survival benefit with ipilimumab beyond 3 years is also supported by a long-term follow-up from a pooled analysis of 12 prospective and retrospective ipilimumab melanoma studies for which OS data are available ($N = 1{,}861$). A total of 254 patients have a minimum follow-up of 3 years. The OS plateau appears at year 3 in previously untreated ($N = 604$) and treated ($N = 1{,}257$) patients (26 % and 20 %, respectively) with longest OS up to year 7 and 10, respectively (Fig. 18.4) [41]. The durability of ipilimumab survival benefit against melanoma has also been confirmed in other clinical studies [42].

18.6.3 Immune-Related Adverse Events (irAEs) and Management of irAEs

The unique immune-based mechanism of action of ipilimumab is also reflected in the safety profile.

The safety profile of ipilimumab has been described by immune-related AEs (irAEs), which are defined as (1) AEs that are related to ipilimumab, (2) are consistent with an inflammatory process, and (3) alternative etiologies (e.g., tumor progression, infections, and other medications) can be excluded.

IrAEs primarily involve the GI tract (e.g., diarrhea, colitis), skin (e.g., pruritus, rash), and less frequently, the liver (e.g., transaminase elevations), endocrine glands (e.g., hypophysitis with hypopituitarism, hypothyroidism, or adrenal insufficiency), and nervous system (e.g., motor neuropathy, sensory neuropathy). The majority of these irAEs initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab.

IrAEs are generally manageable using symptomatic or immunosuppressive therapy as recommended through management algorithm which was developed based on the irAE safety experience across the ipilimumab clinical program. According to the algorithm, irAEs are managed with either symptomatic therapy for mild to moderate irAEs (grades 1–2), systemic corticosteroids for severe irAEs (grade 3 or higher), or other immunosuppressants (e.g., infliximab, mycophenolate mofetil [MMF]) for steroid-unresponsive GI or liver irAEs, as appropriate. Upon irAE improvement, corticosteroids should be tapered gradually over at least 1 month. In general, moderate irAEs are managed by withholding ipilimumab, while ipilimumab should be permanently discontinued for severe irAEs [35, 43, 44].

Early diagnosis and treatment intervention for inflammatory events can help prevent the occurrence of complications, such as GI perforation. Patients should be assessed for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy, and clinical chemistries (including liver and thyroid function tests) should be evaluated at baseline and before each dose of ipilimumab. Serological, immunological, imaging, and biopsy with histology data should be used to support the diagnosis of irAEs.

18.6.4 Skin irAE

The most common skin irAEs by ipilimumab are rash and pruritus with a highest incidence of approximately 50 % at all grades. Most cases are mild to moderate in severity, and the incidence of grade 3 or higher skin irAEs based on the pooled data of the monotherapy with ipilimumab at a dose of 10 mg/kg was 3 % [42]. Skin irAEs usually resolve with symptomatic therapy (topical emollients, antihistamines, etc.) or topical steroids. Two cases of fatal drug-related toxic epidermal necrolysis (TEN) was reported in clinical studies of ipilimumab [35].

18.6.5 Gastrointestinal (GI) irAE

The most common site for ipilimumab-induced GI irAE is the lower GI tract, and the most common presentation is mild to severe diarrhea or colitis with occasional bloody stools. In some cases, diarrhea occurs as mild and then worsens. The incidence of grade 3 or higher GI irAEs based on the pooled data was 12 % [42]. GI irAEs generally resolve by systemic corticosteroids; however, during the early phase of clinical development when steroid therapy was not adequately recommended and used, fatal cases of GI perforation were reported in melanoma studies [35]. Delay in corticosteroid treatment may be associated with a poor outcome for patients with high-grade diarrhea.

18.6.6 Liver irAE

Patients receiving ipilimumab may develop elevations in liver function tests (LFTs), mainly ALT/AST increased (T-Bil elevation is rare), generally in the absence of clinical symptoms. Most of inflammatory hepatitis responded to high-dose corticosteroids (IV route recommended). The incidence of grade 3 or higher liver irAEs based on the pooled data of ipilimumab monotherapy was 7 % [45]; however, grade 3 or higher ALT/AST increased was observed in approximately 30 % of the patients in the phase III study in combination with DTIC (CA184-024) [5]. Also, one phase I combination study with vemurafenib (simultaneous concomitant therapy) was discontinued due to the high incidence of liver toxicity (CA184-161, NCT01400451) [46]. LFTs should be routinely assessed and reviewed prior to administration of each dose of ipilimumab.

18.6.7 Endocrine irAE

The most common endocrine irAEs are hypophysitis and hypopituitarism. Secondary adrenal insufficiency, hypothyroidism or thyroiditis, and, less commonly, other endocrinopathies such as diabetes mellitus may occur. Most patients with hypopituitarism presented with nonspecific complaints such as appetite loss, fatigue, headache, hypotension, etc. Some patients with hypopituitarism can demonstrate enlarged pituitary glands based on brain MRI. Low adrenocorticotropic hormone (ACTH), low cortisol, abnormal (mostly low) thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) are the most common abnormalities in clinical laboratory test. Symptoms of hypopituitarism and other endocrine toxicities were generally controlled with corticosteroid and appropriate hormone replacement; however, some laboratory abnormalities (TSH, ACTH) can be persisted for long periods of time. The endocrine irAEs are least common (6 % at any grade based on the pooled data) and slower onset, but require more time for resolution than other irAEs [45].

18.6.8 Neurological irAE

Neurological manifestations in patients treated with ipilimumab may include motor and/or sensory neuropathy. Fatal Guillain-Barre syndrome (GBS) and cases of myasthenia gravis (MG) were reported in clinical studies of ipilimumab [35].

Approximate onset time and course of each irAE are shown in Fig. 18.5 [45].

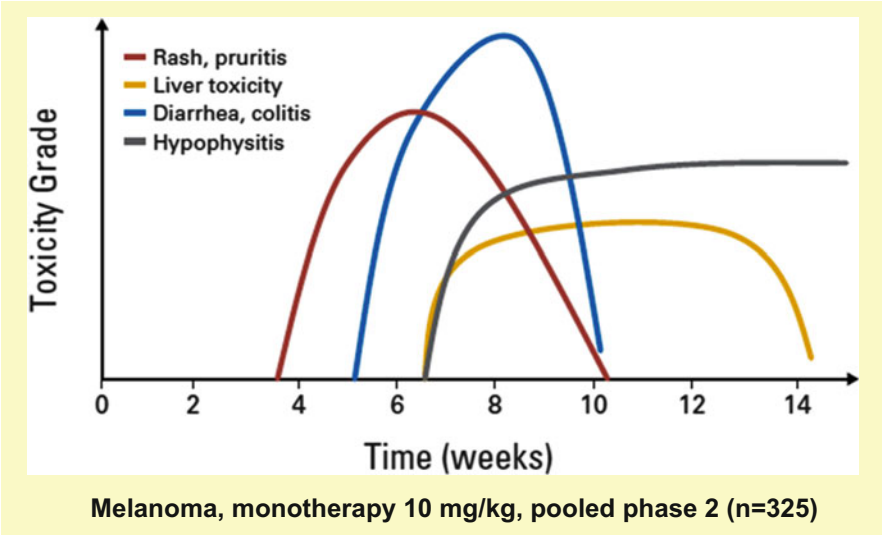


Fig. 18.5 irAE onset time and course

18.7 Challenges for the Future

18.7.1 Optimum Dose of Ipilimumab

The two pivotal phase III studies (MDX010-20, CA184-024) showed comparable median OS and long-term OS outcomes (1- and 2-year survival rates); however, the combination study (CA184-024, ipilimumab 10 mg/kg plus DTIC) has not been approved due to high incidence rates of severe liver toxicities (grade 3 or higher) [4, 5].

The current approval dose of ipilimumab is 3 mg/kg monotherapy. Three doses of ipilimumab (0.3 mg/kg, 3 mg/kg and 10 mg/kg) as a monotherapy were compared in a phase II study (CA184-022), and this study demonstrated dose-dependent efficacy (BORR, 0 %, 4.2 %, 11.1 %) and safety (grade 3 or higher irAEs, 0 %, 7 %, 25 %), suggesting that 10 mg/kg monotherapy was tolerable and more efficacious than 3 mg/kg monotherapy [47].

For the purpose of determining the optimum dose of ipilimumab monotherapy for advanced melanoma, one phase III study requested by FDA to compare ipilimumab 3 mg/kg vs. 10 mg/kg monotherapies in patients with advanced melanoma is ongoing (CA184-169, NCT01515189).

18.7.2 Combination Therapy

In the clinical development of ipilimumab for the treatment of advanced melanoma, several combination studies have been investigated.

As described earlier, the combination of ipilimumab with DTIC in the phase III study (CA184-024) developed approximately 30 % of severe liver toxicities, and the combination with peptide vaccine (gp100) in another phase III study (MDX010-20) failed to show the superiority to ipilimumab monotherapy [4, 5].

For patients with BRAF-mutated advanced melanoma, a phase I combination study with vemurafenib discontinued due to ALT/AST increased (CA184-161, NCT01400451), whereas a phase I combination study with dabrafenib did not show liver toxicity [47, 48]. The Society for Immunotherapy of Cancer (SITC) has recently described the sequential use of ipilimumab and BRAF inhibitors in the consensus statement, suggesting that ipilimumab should be given first for BRAF-mutated patients with good PS, and a BRAF inhibitor should be considered when the disease is progressing rapidly or when PS is poor [49].

At present, combined use with a PD-1 immune checkpoint inhibitor (nivolumab) is most likely to become the best combination partner for ipilimumab for the treatment of advanced melanoma. A phase I combination study demonstrated remarkable synergistic antitumor effect with tolerable safety profile in advanced melanoma (CA209-004, NCT01024231). The ORR of the initial 53 patients who received concurrent therapy was 41 % ($n = 22$). Long-term follow-up showed that 42 % of the patients had $\geq$80 % tumor reduction by week 36, and the 1-year and 2-year OS rates were 85 % and 79 %, respectively, with a median OS of 40 months and a median PFS of 27 weeks [50, 51]. Currently, two late-stage studies are underway to investigate the combination therapy of ipilimumab plus nivolumab vs. either agent alone in patients with advanced melanoma (NCT01844505, NCT01927419). This combination therapy has also shown promising antitumor activity in other tumor types, including renal cell carcinoma [52].

Combinations of ipilimumab with several forms of immunotherapy such as granulocyte macrophage colony-stimulating factor (GM-CSF) [53], oncolytic viral vaccines [54], dendritic cells (DCs) [55, 56], and indoleamine 2,3-dioxygenase (IDO) [57] for advanced melanoma have been recently reported. Some clinical case reports of ipilimumab combined with radiation therapy for melanoma have been recently reviewed [58, 59].

18.7.3 Biomarkers

Although the two phase III studies (MDX010-20 and CA184-024) indicated that ipilimumab contributes to prolongation of OS in patients with advanced melanoma, only 20–30 % of patients can enjoy the survival benefit. In addition, time of onset of antitumor effect is relatively long for ipilimumab. It is essential to find predictive

biomarkers that can identify patients for whom clinical efficacy of ipilimumab can be expected at the initiation of therapy.

Retrospective analyses of several studies have suggested that there is significant correlation between safety (irAEs) and efficacy [60, 61]. Several biomarkers, including absolute lymphocyte count (ALC) [62, 63], sustained inducible T-cell co-stimulator (ICOS) [64], T-cell responses to tumor antigen NY-ESO-1 [65], myeloid-derived suppressor cells (MDSC) [66], and vascular endothelial growth factor (VEGF) [67], have been reported to be associated with clinical benefit from ipilimumab. Further prospective studies will be needed to establish the significance of these biomarker candidates. By biopsy evaluation in the tumor microenvironment, forkhead box P3 (FOXP3) and indoleamine 2,3-dioxygenase (IDO) have been reported to be correlated with clinical efficacy [68]. Expression of immune-related genes has also been reported to be a predictor of clinical efficacy in tumor microenvironment [69].

More recently, immunogenic neoantigens identified by tumor exome sequencing have been suggested to be a potentially important predictive biomarker for ipilimumab [70, 71].

18.8 Conclusion

An anti-CTLA-4 monoclonal antibody (mAb), ipilimumab (Yervoy™), was approved for clinical use in advanced melanoma as the first immune checkpoint inhibitor. From the abundant clinical experiences, unique features of ipilimumab such as response patterns, durability of response, long-term survival, irAEs, and its management have been identified. Future challenges including combination therapies and biomarker research are ongoing to maximize clinical benefit of ipilimumab.

References

1. Bretscher P et al (1970) A theory of self-nonself discrimination. Science 169:1042–1049
2. Lenschow DJ et al (1996) CD28/B7 system of T-cell costimulation. Annu Rev Immunol 14:233–258
3. Ishida Y, Agata Y, Shibahara K et al (1992) Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J 11:3887–3895
4. Hodi FS et al (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711–723
5. Robert C et al (2011) Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 364:2517–2526
6. Brunet JF, Denizot F, Luciani MF et al (1987) A new member of the immunoglobulin superfamily – CTLA-4. Nature 328:267–270
7. Collins AV et al (2002) The interaction properties of costimulatory molecules revisited. Immunity 17:201–210

8. Kearney ER, Walunas TL, Karr RW et al (1995) Antigen-dependent clonal expansion of a trace population of antigen- specific CD4+ T cells in vivo is dependent on CD28 costimulation and inhibited by CTLA-4. J Immunol 155(3):1032–1036
9. Krummel MF et al (1995) CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 182(2):459–465
10. Krummel MF et al (1996) Superantigen responses and co-stimulation: CD28 and CTLA-4 have opposing effects on T cell expansion *in vitro* and *in vivo*. Int Immunol 8(4):519–523
11. Walunas TL et al (1994) CTLA-4 can function as a negative regulator of T cell activation. Immunity 1(5):405–413
12. Perez VL, Van Parijs L, Biuckians A et al (1997) Induction of peripheral T cell tolerance in vivo requires CTLA-4 engagement. Immunity 6:411–417
13. Chambers CA et al (1997) Lymphoproliferation in CTLA-4-deficient mice is mediated by costimulation-dependent activation of CD4+ T cells. Immunity 7(6):885–895
14. Tivol EA et al (1995) Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity 3(5):541–547
15. Waterhouse P et al (1995) Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. Science 270(5238):985–988
16. Egen JG, Kuhns MS, Allison JP (2002) CTLA-4: new insights into its biological function and use in tumor immunotherapy. Nat Immunol 3:611–618
17. Yang YF, Zou JP, Mu J et al (1997) Enhanced induction of antitumor T-cell responses by cytotoxic T lymphocyte-associated molecule-4 blockade: the effect is manifested only at the restricted tumor-bearing stages. Cancer Res 57(18):4036–4041
18. McGaha T, Murphy JW (2000) CTLA-4 down-regulates the protective anticryptococcal cell-mediated immune response. Infect Immun 68(8):4624–4630
19. Gomes NA, Barreto-de-Souza V, Wilson ME et al (1998) Unresponsive CD4+ T lymphocytes from Leishmania chagasi-infected mice increase cytokine production and mediate parasite killing after blockade of B7-1/CTLA-4 molecular pathway. J Infect Dis 178(6):1847–1851
20. Riley JL, Schlienger K (2000) Modulation of susceptibility to HIV-1 infection by the cytotoxic T lymphocyte antigen 4 costimulatory molecule. J Exp Med 191(11):1987–1997
21. Read S et al (2006) Blockage of CTLA-4 on $CD4^+$ $CD25^+$ regulatory T cells abrogates their function in vivo. J Immunol 177(7):4376–4383
22. Wing K (2008) CTLA-4 control over $Foxp^{3+}$ regulatory T cell function. Science 322:271–275
23. Selby et al (2013) Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T. cells. Cancer Immunol Res 1:32–42
24. Simpson et al (2013) Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. J Exp Med 210:1695
25. Liakou et al (2008) CTLA-4 blockade increases IFNγ-producing $CD4^+ICOS^{hi}$ cells to shift the ratio of effector to regulatory T cells in cancer patients. Proc Natl Acad Sci U S A 105:14987–14992
26. Korman AJ, Peggs KS, Allison JP (2006) Checkpoint blockade in cancer immunotherapy. Adv Immunol 90:297–339
27. Camacho LH, Antonia S, Sosman J et al (2009) Phase I/II trial of tremelimumab in patients with metastatic melanoma. J Clin Oncol 27:1075–1081
28. Ribas A, Kefford R, Marshall MA et al (2013) Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol 31:616–622
29. National comprehensive cancer network clinical practice guidelines in oncology melanoma, version 3.2014
30. Dummer R, Hauschild A, Guggenheim M et al (2012) Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 23(Supplement 7): vii86–vii91

31. Kwon ED et al (2014) Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 14:700–712
32. Lynch TJ et al (2046) Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non–small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 30(17):2012
33. Reck M et al (2013) Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive disease small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 24:75–83
34. Nokihara H Phase 1 study of ipilimumab in combination with paclitaxel/carboplatin in patients with non-small cell lung cancer. Presented at: IASLC 15th world conference on lung cancer
35. Ipilimumab Investigator Brochure Ver.16.
36. Maio M, Bondarenko I, Robert C et al Four-year survival update for metastatic melanoma patients treated with ipilimumab plus dacarbazine on phase III study CA184-024. ESMO 2012, Abstract 1127
37. Eggermont AM et al (2014) Ipilimumab versus placebo after complete resection of stage III melanoma: initial efficacy and safety results from the EORTC 18071 phase III trial. ASCO 2014, LBA9008
38. Saenger YM et al (2008) The heterogeneity of the kinetics of response to ipilimumab in metastatic melanoma: patient cases. Cancer Immun 8:1
39. Wolchok JD et al (2009) Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 15:7412–7420
40. Maio M et al (2013) Survival analysis with 5 years of follow-up in a phase III study of ipilimumab and dacarbazine in metastatic melanoma. Oral presentation ESMO 2013, Abstract 3704
41. Schadendorf D, Hodi FS, Robert C et al (2013) Late breaking abstract: pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma. ECCO Amsterdam, LBA24
42. Prieto PA et al (2012) CTLA-4 blockade with ipilimumab: long term follow-up of 177 patients with metastatic melanoma. Clin Cancer Res 18:2039–2047
43. YERVOY™ (ipilimumab) immune-mediated adverse reaction management guide. Available at: https://www.hcp.yervoy.com/pages/index.aspx. Accessed 9 Oct 2014
44. Giuseppina DVS et al (2014) Onco Targets Ther 7:203–209
45. Weber JS et al (2012) Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 30:2691–2697
46. Ribas A, Hodi FS, Callahan M et al (2013) Hepatotoxicity with combination of vemurafenib and ipilimumab. N Engl J Med 368:1365–1366
47. Wolchok JD et al (2010) Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicenter, phase II, dose-ranging study. Lancet Oncol 11:155–164
48. Puzanov I, Callahan MK, Linette GP et al (2014) 1 study of the BRAF inhibitor dabrafenib (D) with or without the MEK inhibitor trametinib (T) in combination with ipilimumab (Ipi) for V600E/K mutation-positive unresectable or metastatic melanoma (MM). J Clin Oncol 32 (suppl 5S):abstr 2511
49. Kaufman HL, Kirkwood JM, Hodi FS et al (2013) The Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma. Nat Rev Clin Oncol 10:588–598
50. Wolchok JD et al (2013) Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 369:122–133
51. Sznol M, Kluger HM, Callahan MK et al (2014) Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO 4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). J Clin Oncol 32(suppl 5S):abstr LBA9003

52. Hammers HJ, Plimack ER, Infante JR et al (2014) Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC). J Clin Oncol 32(suppl 5S):abstr 4504
53. Hodi FS, Lee SJ, McDermott DF et al (2014) Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: a randomized clinical trial. JAMA 312 (17):1744–1753
54. Puzanov I, Milhem MM, Andtbacka RHI et al (2014) Primary analysis of a phase 1b multicenter trial to evaluate safety and efficacy of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB–IV melanoma. J Clin Oncol 32 (suppl 5S):abstr 9029
55. Dhodapkar MV, Sznol M, Zhao B et al (2014) Induction of antigen-specific immunity with a vaccine targeting NY-ESO-1 to the dendritic cell receptor DEC-205. Sci Transl Med 6:232ra51
56. Neyns B, Wilgenhof S, Corthals J et al (2014) Phase II study of autologous mRNA electroporated dendritic cells (TriMixDC-MEL) in combination with ipilimumab in patients with pretreated advanced melanoma. J Clin Oncol 32(suppl 5S):abstr 3014
57. Gibney GT, Hamid O, Gangadhar TC et al (2014) Preliminary results from a phase 1/2 study of INCB024360 combined with ipilimumab (ipi) in patients (pts) with melanoma. J Clin Oncol 32 (suppl 5s):abstr 3010
58. Barker CA, Postow MA, Khan SA et al (2013) Concurrent radiotherapy and ipilimumab immunotherapy for patients with melanoma. Cancer Immunol Res 1:92–98
59. Barker CA et al (2014) Combinations of radiation therapy and immunotherapy for melanoma: a review of clinical outcomes. Int J Radiat Oncol Biol Phys 88:986–997
60. Lutzky J, Wolchok J, Hamid O et al (2009) Association between immune-related adverse events and disease control or overall survival in patients with advanced melanoma treated with 10 mg/kg ipilimumab in three phase II clinical trials. J Clin Oncol 27:abstr 9034
61. Downey SG, Klapper JA, Smith FO et al (2007) Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res 13:6681–6688
62. Berman DM et al (2009) Association of peripheral blood absolute lymphocyte count (ALC) and clinical activity in patients with advanced melanoma treated with ipilimumab. J Clin Oncol 27:15s
63. Postow MA, Chasalow SD, Yuan J et al (2013) Pharmacodynamic effect of ipilimumab on absolute lymphocyte count (ALC) and association with overall survival in patients with advanced melanoma. J Clin Oncol 31(suppl):abstr 9052
64. Tang DN, Shen Y, Yuan J et al (2013) Increased frequency of ICOSt CD4 T cells as a pharmacodynamic biomarker for anti-CTLA-4 therapy. Cancer Immunol Res 1:229–234
65. Yuan J et al (2011) Integrated NY-ESO-1 antibody and CD8+ T-cell responses correlate with clinical benefit in advanced melanoma patients treated with ipilimumab. Proc Natl Acad Sci U S A 108:16723–16728
66. Kitano S, Postow M, Yuan J et al (2012) Myeloid derived suppressor cell quantity prior to treatment with ipilimumab at 10 mg/kg predicts for clinical benefit and improved overall survival in patients with metastatic melanoma. J Clin Oncol 30, (suppl; abstr 2518)
67. Yuan J, Zhou J, Dong Z et al (2014) Pretreatment serum VEGF is associated with clinical response and overall survival in advanced melanoma patients treated with ipilimumab. Cancer Immunol Res 2:127–132
68. Hamid O et al (2011) A prospective phase II trial exploring the association between tumor microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. J Transl Med 9:204
69. Ji RR et al (2012) An immune-active tumor microenvironment favors clinical response to ipilimumab. Cancer Immunol Immunother 61:1019–1031

70. van Rooij N, van Buuren MM, Philips D et al (2013) Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol 31:e439–e442
71. Charen AS, Makarov V, Merghoub T et al (2014) The neoantigen landscape underlying clinical response to ipilimumab. J Clin Oncol 32(suppl 5S):abstr 3003