Chapter 10
Ipilimumab in Melanoma: An Evergreen Drug

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Introduction

Ipilimumab is a fully human monoclonal antibody (IgG1κ) that activates the immune system by targeting the cytotoxic T-lymphocyte antigen 4 (CTLA-4), a co-receptor with inhibitory properties expressed by T lymphocytes. CTLA-4 is physiologically involved in maintaining self-tolerance. When T lymphocytes are activated through recognition of an antigen exposed on the surface of the antigen-presenting cells (signal 1) and the interaction between the CD28 co-stimulatory receptor and the CD80 and CD86 molecules (signal 2), they start expressing CTLA-4 on their surface. CTLA-4 has greater affinity for the CD80 and CD86 molecules than CD28 and displace their interaction, eliciting an inhibitory signal to the T cell rather than an activating one (see Fig. 10.1) [1]. CTLA-4 is also a target gene of the Forkhead box P3 transcription factor (FOXP3), which is a crucial factor in the genesis of regulatory T-cell lineage [2]. The role of CTLA-4 and the function of regulatory T cells are closely related. In fact, subjects harboring the homozygous mutation in FOXP3 suffer from an autoimmune X-linked hereditary syndrome, known as IPEX, with clinical manifestations of polyendocrinopathy and enteropathy [3]. These signs and symptoms are similar to some of the most frequent immune-related adverse events observed in patients treated with anti-CTLA-4 antibodies [4]. Therefore, the inhibition of CTLA-4 is a therapeutic strategy based both on the enhancement of the T

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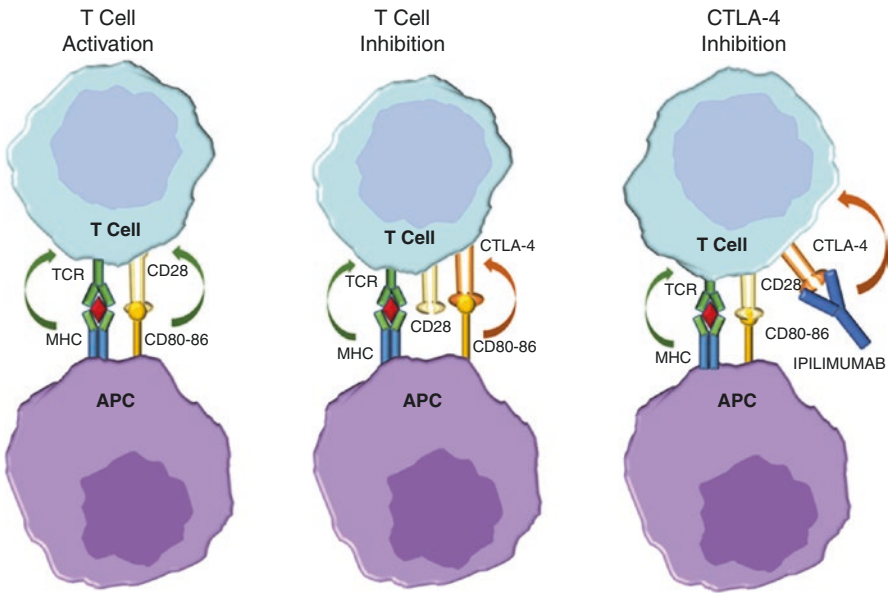

Fig. 10.1 Mechanism of action of ipilimumab. CTLA-4 is an inhibitory molecule present on T cells: during the interaction between antigen-presenting cells and lymphocytes, CTLA4 competes with co-stimulatory signals and interrupts T-cell priming. By blocking CTLA-4, the inhibitory effect on the priming phase is released leading to unrestricted T-cell activation

effector lymphocytes and the inhibition of regulatory T-cell lymphocytes. The anti-CTLA-4 tremelimumab and ipilimumab were the first fully humanized anti-CTLA-4 antibodies that underwent clinical testing, and, in 2011, ipilimumab 3 mg per kilogram (IPI3) every 3 weeks for 4 administrations was the first immune-checkpoint inhibitor which received the FDA approval for the treatment of a solid tumor, after the results of the MDX010–20 phase 3 trial in patients with advanced melanoma [5].

The purpose of this chapter is to report the most relevant results of ipilimumab from selected clinical trials and real world studies, to discuss how the introduction of ipilimumab into clinical practice challenged the evaluation of tumor response and management of toxicity, and to discuss the role of ipilimumab in the era of anti-PD-1 agents.

Ipilimumab as Single Agent for the Treatment of Advanced Melanoma

In the MDX010–20 phase 3 trial, patients with pretreated advanced melanoma were randomized in a 3:1:1 ratio to receive either ipilimumab plus gp100 (403 patients), ipilimumab alone (137 patients), or gp100 alone (136 patients). Ipilimumab was administered with or without gp100 at a dose of 3 mg per kilogram of body weight

for up to four treatments (induction); patients who derived a benefit but ultimately had progressive disease (PD) could receive reinduction therapy, consisting of other 4 ipilimumab infusions. The primary endpoint was overall survival (OS). The median OS was 10.0 and 10.1 months among patients receiving ipilimumab plus gp100 or ipilimumab alone, respectively, as compared with 6.4 months among patients receiving gp100 alone. Severe (grade 3–4) immune-related adverse events (irAEs) occurred in 10–15% of patients receiving ipilimumab, and 7 patients died due to an immune-related toxicity [5]. The most common autoimmune side effects included skin rash, endocrine deficiencies, and colitis. In the ipilimumab-alone group, the overall response rate (ORR) was 10.9%, with a disease control rate (DCR) of 28.5%. Despite the small absolute benefit in terms of median OS and the low response rate, analyses of survival showed that 2-year OS was 21.6–23.5% in patients who received ipilimumab as compared with 13.7% for gp100 alone, which is clinically significant [5] (Table 10.1). Based on the results of this study, ipilimumab 3 mg/kg every 3 weeks for a total of 4 administrations received the approval by the regulatory agencies for the treatment of metastatic melanoma.

Ipilimumab was found to stimulate a dose-dependent effect on both clinical activity and toxicity [6, 15], leading to the investigation of higher doses in further studies (Tables 10.1 and 10.2). In the randomized, phase 2 CA184–022 clinical trial, 217 patients with previously treated advanced melanoma were randomly assigned to receive ipilimumab at either a dose of 10 mg/kg, 3 mg/kg, or 0.3 mg/kg every 3 weeks for four administrations followed by maintenance therapy every 3 months. The primary endpoint was best ORR, which was 11.1% for 10 mg/kg and 4.2% for 3 mg/kg, while no objective responses were achieved with 0.3 mg/kg. The dose-dependent effect on clinical activity was also noted in terms of toxicity, with irAEs of any grade being observed in 70%, 65%, and 26% of patients who received the doses of 10 mg/kg, 3 mg/kg, and 0.3 mg/kg, respectively. No grade 3–4 gastrointestinal irAEs were observed at the lowest dose, as compared as 16% and 3% for ipilimumab 10 mg/kg and 3 mg/kg, respectively [6]. In the phase 3 study of ipilimumab 10 mg per kilogram plus dacarbazine as a first-line treatment for patients with advanced melanoma, 502 subjects were randomized in a 1:1 ratio to receive either ipilimumab 10 mg per kilogram (IPI10) plus dacarbazine or dacarbazine plus placebo. Patients with stable disease (SD) or an objective response and no toxic effects were eligible to receive maintenance therapy with ipilimumab or placebo every 12 weeks. The primary endpoint was OS, which was significantly longer in the group receiving ipilimumab (11.2 months vs. 9.1 months). Similar to that observed in the MDX010–20 phase 3 trial, despite the difference in terms of median OS was only 2.1 months, the landmark analysis of survival revealed a clinically meaningful long-term benefit, with 20.8% of patients who received ipilimumab being alive at 3 years versus 12.2% in the dacarbazine group. Grade 3–4 adverse events occurred in 56.3% of patients treated with ipilimumab plus dacarbazine, with no drug-related deaths [7].

The efficacy and safety of IPI3 and IPI10 was then directly compared in a randomized phase 3 trial. Median OS was 15.7 months (95% CI 11.6–17.8) for IPI10 compared with 11.5 months (95% CI 9.9–13.3) for IPI3 (hazard ratio 0.84, 95%

Table 10.1 Summary of results of selected clinical trials with ipilimumab as single agent or in combination with other drugs for the treatment of patients with advanced melanoma. Only data for treatment regimens including ipilimumab are reported

Name of study, first author and date of publication	Study design	Treatment regimen	Median OS (months)	Median PFS (months)	Overall response rate (%)	2-year OS (%)	3-year OS (%)	Grade 3–4 irAEs (%)
MDX010–20, Hodi 2010 [5]	Phase 3	IPI3 every 3 weeks for 4 cycles	10.0–10.1	2.76–2.86	6–11	22–24	NA	10–15
CA184–022, Wolchok 2010 [6]	Phase 2	IPI10 every 3 weeks for 4 cycles, followed by IPI10 every 3 months	11.4	NA	11	30	NA	18
		IPI3 every 3 weeks for 4 cycles, followed by IPI3 every 3 months	8.7	NA	4	24	NA	5
		IPI0.3 every 3 weeks for 4 cycles, followed by IPI0.3 every 3 months	8.6	NA	0	18	NA	0
CA184–024, Robert 2011 [7]	Phase 3	IPI10 plus DTIC every 3 weeks for 4 cycles, followed by DTIC	11.2	NA	15	29	21	38
CA184–169, Ascierto 2017 [8]	Phase 3	IPI10 every 3 weeks for 4 cycles	15.7	2.8	15	39	31	34
		IPI3 every 3 weeks for 4 cycles	11.5	2.8	12	31	23	18
CheckMate-064, Weber 2016 [9]	Phase 2	NIVO→IPI	Not reached	NA	56	NA	NA	63
		IPI → NIVO	16.9	NA	31	NA	NA	50
CheckMate-069, Hodi 2016 [10]	Phase 2	IPI3 + NIVO1	Not reached	Not reached	59	64	NA	54
		IPI3 every 3 weeks for 4 cycles	Not reached	3.0	11	54	NA	20
CheckMate-067, Wolchok 2017 [11] Larkin 2019 [12]	Phase 3	IPI3 + NIVO1	Not reached (>60.0)	11.5	58	64	58	59
		IPI3 every 3 weeks for 4 cycles	19.9	2.9	19	45	34	28
CheckMate-511, Lebbé 2019 [13]	Phase 3b/4	IPI3 + NIVO1	Not reached	8.94	51	NA	NA	48
		IPI1 + NIVO3	Not reached	9.92	46	NA	NA	34
Keynote-029, Long 2017 [14]	Phase 1b	Pembrolizumab 2 mg/kg plus IPI1 every 3 weeks for four cycles, followed by pembrolizumab 2 mg/kg every 3 weeks	Not reached	Not reached	61	NA	NA	27

IPI1 + NIVO3 nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four cycles, followed by nivolumab 3 mg/kg every 2 weeks; *IPI3 + NIVO1* nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four cycles, followed by nivolumab 3 mg/kg every 2 weeks; *IPI → NIVO* IPI3 every 3 weeks for 4 cycles, followed by NIVO3 every 2 weeks for 6 doses, followed by NIVO3 maintenance therapy every 2 weeks; *NIVO→IPI* NIVO3 every 2 weeks for 6 doses, followed by IPI3 every 3 weeks for 4 cycles, followed by NIVO3 maintenance therapy every 2 weeks

Table 10.2 Summary of safety with different doses of ipilimumab as single agent or in combination with anti-PD-1

Treatment regimen	Grade 3–4 irAEs (%)	Discontinuation rate due to any grade irAEs (%)	Studies
Iplimumab 0.3 mg/kg	0	2	CA184–022 [6]
Iplimumab 3 mg/kg	5–28	5–19	MDX010–20 [5], CA184–022 [6], CA184–169 [8], CheckMate-069 [10], CheckMate-067 [12] [11]
Iplimumab 10 mg/kg	18–34	11–31	CA184–022 [6], CA184–169 [8]
Iplimumab 10 mg/kg + dacarbazine	38	36	CA184–024 [7]
Iplimumab 3 mg/kg + nivolumab 1 mg/kg	48–59	33–39	CheckMate-069 [10], CheckMate-067 [11], CheckMate-511 [13]
Iplimumab 1 mg/kg + nivolumab 3 mg/kg	34	24	CheckMate-511 [13]
Pembrolizumab 2 mg/kg + Iplimumab 1 mg/kg	27	26	Keynote-029 [14]

CI 0.70–0.99), but more treatment-related serious adverse events occurred in patients who received the higher dose (37% versus 18%) [8]. Despite the impact on OS, which is particularly appreciated in terms of chance of long-term survival (3-year OS was 31% for IPI10 versus 23% for IPI3), the higher dosage of ipilimumab did not receive the FDA approval for the treatment of advanced melanoma, partly due to the upcoming results of anti-PD-1 agents, which took the place of ipilimumab as the first-line immunotherapy for metastatic melanoma patients [16, 17].

Long-Term Efficacy and Effectiveness

Despite the impact of ipilimumab on clinical activity outcomes such as ORR and progression-free survival (PFS) was not meaningful (Table 10.1), long-term follow-up demonstrated its great efficacy and effectiveness in at least a subset of patients. In a pooled analysis of long-term survival data from phase 2 and phase 3 trials of ipilimumab in advanced melanoma, among 1.861 patients, median OS was 11.4 months (95% CI, 10.7 to 12.1 months), but the survival curve began to plateau around year 3, with follow-up of up to 10 years. Three-year survival rates were 22%, 26%, and 20% for all patients, treatment-naive patients, and previously treated patients, respectively. Including data from the expanded access program, median OS was 9.5 months (95% CI, 9.0 to 10.0 months), with a plateau at 21% in the survival curve beginning around year 3, demonstrating the effectiveness of ipilimumab in an unselected population [18]. In the 5-year analysis of the phase 3 study with IPI10 plus dacarbazine versus dacarbazine plus placebo, 5-year OS was 18.2% for the experimental arm and 8.8% for the control [19]. The long-term chance for

survival in the chemotherapy group was higher as compared with historical data [20], probably due to a subset of patients who received ipilimumab after PD with chemotherapy.

Efficacy, Clinical Activity, and Safety of Re-induction

Some data suggested that re-induction upon disease progression in patients who derived a clinical benefit from the induction treatment with ipilimumab may be a valid approach to overcome immune tolerance in selected patients. Disease-control was regained in 48–75% of patients receiving re-induction in clinical trials and expanded access programs, and ORR ranged from 12% to 38%, with no toxicity concerns, as the incidence of treatment-related AEs observed during retreatment was similar to that observed during induction [5, 21, 22]. However, the sample size was too small for retreatment to be worth regulatory agencies approval, and further evaluation of this strategy in randomized clinical trials was not necessary due to the anti-PD-1 agent's breakthrough.

Clinical Activity of Ipilimumab in Patients with Brain Metastases

The incidence of brain metastases in melanoma patients is common and associated with poor prognosis [23]. Evidence of intracranial tumor responses after ipilimumab treatment was reported in both clinical trials and real world experiences (Table 10.3) [24–28]. Despite that, survival outcomes remained poor, especially in patients receiving corticosteroids due to brain metastases symptoms [23, 27].

The Evaluation of Antitumor Response to Ipilimumab

Conventional response criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST), were developed based on data from cytotoxic chemotherapy trials and are not always appropriate to assess the activity of immunotherapy. Indeed, ipilimumab may achieve tumor regression and obtain long-lasting disease control even after an initial increase in tumor burden or appearance of new lesions, which would be defined as PD by conventional criteria. Therefore, immune-related response criteria were developed to assess the specific antitumor effects of immune-checkpoint inhibitors: by such criteria, the appearance of new lesions or initial increase in tumor burden is not assessed as PD and must be confirmed through a subsequent tumor assessment [29]. Responses and SD assessed by immune-related criteria were observed in an additional 10% of metastatic melanoma patients treated

Table 10.3 Summary of results of phase 2 clinical trials and selected real world studies

Author and date of publication	Study design and number of patients with brain metastases	Treatment regimen	Median OS (months)	Median PFS (months)	Overall response rate	Overall intracranial response rate	Symptoms due to brain metastases
Heller 2011 [24]	Retrospective analysis of IPI10 EAP ($N = 165$)	IPI10	NA	1-year OS: 20%	NA	NA	0%
Weber 2011 [25]	Retrospective analysis of a phase 2 study ($N = 12$)	IPI10	14.0	NA	NA	NA	NA
Di Giacomo 2012 [26]	Phase 2 ($N = 20$)	IPI10 plus fotemustine	12.7	3.4	40%	NA	0%
Margolin 2012 [27]	Phase 2 ($N = 72$)	IPI10	3.7–7.0[a]	1.3–2.7[a]	5–10%[a]	5–16%[a]	100–0%[a]
Queirolo 2014 [28]	Retrospective analysis of the Italian IPI3 EAP ($N = 146$)	IPI3	4.3	3.1	12%	NA	0%

EAP expanded access program, *IPI3* ipilimumab 3 mg/kg, *IPI10* ipilimumab 10 mg/kg, *NA* not available, *OS* overall survival, *PFS* progression-free survival
[a]Symptomatic and asymptomatic patients, respectively

with ipilimumab and were associated with improved survival [29]. Immune-related criteria have been improved and updated over time. In 2017, a consensus guideline was developed and published by the RECIST working group for the use of RECIST version 1.1 criteria in cancer immunotherapy trials [30]. This guideline, named iRECIST, describes a standard approach to tumor assessment in patients with advanced solid tumors treated with immunotherapy, to warrant consistent design and to facilitate the collection of data. The most relevant difference between conventional RECIST 1.1 and iRECIST is the definition of immune-related unconfirmed progressive disease (iUPD), which is defined on the basis of RECIST 1.1 principles, but requires confirmation at a subsequent tumor assessment: if PD is not confirmed, the sum of diameters of target lesions is reset so that iUPD needs to occur again and then be confirmed by further tumor growth for immune-related confirmed progressive disease to be defined. This allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified [30].

The Management of Immune-Related Adverse Events

The introduction of immune-checkpoint inhibitors in clinical practice was a new challenge not only for the evaluation of antitumor response, but also because a new class of treatment-related adverse events emerged. Indeed, unlike chemotherapy, immune-checkpoint inhibitors can induce a spectrum of toxicities of autoimmune pathogenesis, namely irAEs. Due to the autoimmune pathogenesis, the milestone for the management of irAEs is corticosteroids therapy. Despite the immunosuppressive properties of corticosteroids, especially at higher doses, their use for the management of toxicities did not seem to affect the effectiveness of ipilimumab [31]. The corticosteroid dosages, routes of administration, and duration of tapering depend on the type and severity of the irAEs. In corticosteroid-refractory cases, other immunomodulatory agents such as infliximab (an anti-TNFα agent) and vedolizumab ($\alpha_4\beta_7$ integrin inhibitor) must be used in case of colitis, mycophenolate in case of hepatitis, myositis, bullous dermopathies, lupus, nephritis, interstitial lung disease, while plasmapheresis and immunoglobulin infusions are more commonly employed in case of neurotoxicity (in particular Guillain–Barré-like syndromes) [31]. The majority of severe toxicities, with the exception of dermatologic and endocrine irAEs, require permanent ipilimumab discontinuation [31–33]. Temporary treatment suspensions are generally required for grade 2 irAEs, with the exception of skin rash and asymptomatic endocrine events [31–33]. Toxicities involving the endocrine glands are treated with substitute hormones rather than corticosteroids [31–33]. Guidelines for the management of immune-mediated toxicities have been developed and improved over time. The most recent guidelines are those provided by The National Comprehensive Cancer Network (NCCN) [31], the European Society for Medical Oncology (ESMO) [32], and the American Society of Clinical Oncology (ASCO) [33].

Besides the use of immunomodulatory agents, other key factors are early recognition of irAEs and a proper baseline assessment. The history of autoimmune

diseases must be collected to anticipate possible flares, and laboratory tests and physical examination should be performed before each ipilimumab infusion [34].

The clinical activity as well as toxicity of anti-CTLA-4 immunotherapy was proven to be dose-dependent [6, 8] (Table 10.2), unlike immunotherapy with anti-PD-1 [31, 35]. Moreover, immunotherapy with anti-CTLA-4 is associated with a higher rate of grade 3–4 irAEs (24% in a recent meta-analysis) [36], as compared with patients who received anti-PD-I drugs (5–8%) [37]. In patients receiving the combination of IPI3 and nivolumab 1 mg/kg (NIVO1) the rate of severe toxicities was as high as nearly 50% [17], while the reverse dosage was associated with grade 3–4 irAEs in 33.9% of patients [13].

Ipilimumab in Combination with Targeted Therapy

Strong evidence supports the notion that MAPK kinase-targeted therapy has immunomodulatory properties and enhances immune activation [38], hence clinical trials investigating the combination of ipilimumab with targeted therapy were initiated. However, the first attempt combining BRAF inhibitor vemurafenib with ipilimumab failed due to severe toxicities [39]. In the first cohort, vemurafenib 960 mg bid was administered as a single agent for 1 month, followed by the combination with ipilimumab; dose-limiting toxicities (DLTs) of grade 3 elevations in aminotransferase levels developed in four patients 2–5 weeks after the first infusion of ipilimumab in combination with vemurafenib. In the second cohort, vemurafenib 720 mg bid was given upfront in combination with ipilimumab: among the first four patients who received such regimen, elevations in aminotransferase levels (grade 3 in two patients and grade 2 in one patient) developed within 3 weeks after starting ipilimumab [39].

The safety of combination therapy of ipilimumab with BRAF inhibitor dabrafenib with or without MEK inhibitor trametinib was also halted due to severe treatment-related AEs. In the group of patients receiving ipilimumab plus dabrafenib and trametinib, among seven patients, two developed colitis followed by intestinal perforation [40].

The pursue of a combination regiment with BRAF and MEK inhibitors was abandoned, as new combination approaches were made possible with the more manageable anti-PD-1 agents, which were proven to be safe even in combination with BRAF plus MEK inhibitors [41].

Ipilimumab in Combination with Anti-PD-1 Drugs

In 2015, the results of the CheckMate-069 phase 2 trial [10] led to accelerated FDA approval of a combination of ipilimumab plus nivolumab for patients with BRAF wild-type, advanced melanoma (Table 10.1). After the results of the CheckMate-067 phase 3 trial, ipilimumab plus nivolumab was granted accelerated approval in January 2016 to include patients with BRAF-mutant melanoma [17]. In this phase

3 clinical study, a total of 945 treatment-naive patients with advanced melanoma were randomly assigned 1:1:1 to receive either nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 doses then nivolumab 3 mg/kg every 2 weeks (IPI3 + NIVO1), or nivolumab 3 mg/kg every 2 weeks + ipilimumab-matched placebo, or ipilimumab 3 mg/kg every 3 weeks for 4 doses + nivolumab-matched placebo. The primary endpoints were PFS and OS. Notably, the study was not designed for a formal statistical comparison between the combination group and the nivolumab monotherapy group. The 5-year update showed a PFS of 36%, 29%, and 8%, in the nivolumab + ipilimumab, nivolumab alone, and ipilimumab arms, respectively, with a 5-year OS of 52%, 44%, and 26% [12]. However, these results were obtained at the cost of higher toxicity. In fact, 59% of patients who received nivolumab + ipilimumab had grade 3–4 AEs, versus 23% and 28% in the nivolumab and ipilimumab arms, respectively. The most frequent grade 3–4 AEs leading to treatment discontinuation were diarrhea and colitis for all groups [11, 12, 17].

In order to overcome the difficulty of the higher rate of severe toxicity of the IPI3 + NIVO1, the KEYNOTE-029 phase 1b trial was conducted to evaluate the anti-PD-1 pembrolizumab + low-dose ipilimumab (1 mg/kg) for four cycles every 3 weeks, followed by pembrolizumab alone. An incidence of grade 3–4 irAEs of 27% was observed with this combination, numerically lower than that observed in CheckMate-067 trial with IPI3 + NIVO1. Treatment was permanently discontinued due to a treatment-related AE in 14% of patients. The ORR was 61%, and 1-year estimates for PFS and OS were 69% and 89%, respectively [14]. A similar approach was also investigated in the CheckMate-511 study, which was a phase 3b/4 trial conducted to assess if NIVO3 + IPI1 had a lower incidence of grade 3–5 AEs than the approved NIVO1 + IPI3 regimen. The incidence of treatment-related G3-G5 AEs in the two arms, primary endpoint of the study, was significantly lower in the NIVO3 + IPI1 arm compared with NIVO1 + IPI3 (34% vs. 48%; $p = 0.006$) [13]. Despite the study was not designed to demonstrate the non-inferiority of NIVO3 + IPI1 to NIVO1 + IPI3 in terms of clinical activity, in descriptive analyses ORR was 45.6% for NIVO3 + IPI1 *versus* 50.6% for NIVO1 + IPI3, with a median PFS of 9.9 and 8.9 months in the NIVO3 + IPI1 and NIVO1 + IPI3 arms, respectively [13].

Ipilimumab in Sequence with Anti-PD-1 Drugs

Concurrent administration of the immune-checkpoint inhibitors nivolumab and ipilimumab has shown greater efficacy than either agent alone, albeit with a higher rate of severe treatment-related adverse events [17]. The randomized phase 2 trial CheckMate-064 was designed to assess whether sequential administration of nivolumab followed by ipilimumab with a planned switch, or the reverse sequence, could maximize efficacy while maintaining an acceptable toxicity profile [9]. One hundred and forty patients were randomized 1:1 to receive, in the induction period, nivolumab 3 mg/kg every 2 weeks for 6 doses, followed by ipilimumab 3 mg/kg

every 3 weeks for 4 cycles (NIVO→IPI cohort), or the reverse sequence (IPI → NIVO cohort). In the continuation phase, all patients were treated with nivolumab 3 mg/kg every 2 weeks until PD or unacceptable toxicity. Primary endpoint was the incidence of G3–5 AEs until the end of the induction period [9]. At week 25, the incidence of grade 3–5 AEs in the two groups was similar: 50% for NIVO→IPI and 43% for IPI → NIVO. No treatment-related deaths occurred. The most common grade 3–4 irAEs was colitis (15% in patients receiving NIVO→IPI and 20% in those treated with the IPI → NIVO sequence). Types and frequencies of AEs leading to discontinuation during the whole study were similar between groups (37% for the NIVO→IPI sequence versus 33% for IPI → NIVO); the most frequent irAEs leading to treatment permanent discontinuation were colitis, increased AST/ALT, and diarrhea. In terms of clinical activity and efficacy, the overall response rate at week 25 was higher for patients who received NIVO→IPI as compared with the reverse IPI → NIVO sequence (41% versus 20%), and more patients in the NIVO→IPI cohort were alive at 1 year than in the IPI → NIVO cohort (76% versus 54%) [9].

Biomarkers

Ipilimumab achieves a great clinical benefit in a small proportion of melanoma patients, highlighting the strong need to investigate predictive biomarkers. Despite that, no validated predictive biomarker has been identified yet to select patients who derive a benefit from such treatment.

Several blood biomarkers have shown their prognostic role, including baseline and post-treatment changes in leukocyte counts [42–46], lactate dehydrogenase [43–45, 47, 48], C-reactive protein [45, 47], and soluble CTLA-4 [49], but the retrospective and non-randomized nature of most studies, the small sample sizes, short follow-up time, and variability in the investigated biomarkers did not allow to properly assess their predictive potential [50]. In the largest study assessing the relevance of leucocyte counts in patients receiving ipilimumab for advanced melanoma, the derived neutrophil-to-lymphocyte ratio [absolute neutrophil counts/(white cell counts—absolute neutrophil counts)] and baseline absolute neutrophil counts were found to be associated with risk of death and progression, with higher values being associated with increased risk [42]. However, the role of such indexes as predictive biomarkers was not further investigated in clinical studies.

The investigation of CTLA-4 gene polymorphisms has also shown a promising biomarker to select patients with a higher chance of response to ipilimumab and long-term survival. In a multicenter study on 173 patients who received ipilimumab for advanced melanoma within the Italian Expanded Access, an association of CTLA-4 gene variants with response to therapy and long-term survival was found in subjects carrying the −1577G/G or CT60G/G genotypes [51]. Moreover, the CTLA-4 gene variant −1661A > G was found to be associated with a higher risk of endocrine irAEs [52].

Despite various biomarkers being correlated with improved response rate and long-term survival upon treatment with ipilimumab, their predictive value remains unclear so far, as most of these biomarkers are also well known as prognostic markers [50].

Adjuvant Setting

In 2015, after a significant impact on recurrence-free survival (RFS) was observed in the EORTC 18071 phase 3 trial for patients with completely resected high-risk stage III melanoma, IPI10 was approved for this indication by the FDA only. CA 184–029 (EORTC 18071) is a randomized phase 3 clinical trial which compared the anti-CTLA-4 agent ipilimumab 10 mg/kg every 3 weeks for four cycles, followed by maintenance doses every 3 months for up to 3 years versus placebo, in patients with resected stage III melanoma (excluding lymph node metastasis ≤1 mm in patients with stage IIIA melanoma, and excluding subjects with in-transit metastases for stage IIIB/IIIC). The 5-year RFS was 41% vs. 30% in the ipilimumab and placebo arms, respectively (HR for recurrence or death: 0.76; 95% CI 0.64 to 0.89). Ipilimumab also gave an advantage in terms of DMFS: 48% of patients were alive and metastasis-free at 5 years in the experimental arm versus 39% for placebo (HR for distant metastasis or death: 0.76; 95% CI 0.64 to 0.92) [53, 54]. Moreover, OS was significantly longer in the ipilimumab group (HR for death: 0.72; 95% CI 0.58 to 0.88), with 65% of patients treated with ipilimumab being alive at 5 years vs. 54% in the placebo arm. The subgroup analysis emphasized the superiority of ipilimumab in the ulcerated primary population and in patients with ≥3 involved lymph nodes [53, 54]. Despite these encouraging efficacy results, ipilimumab was associated with severe toxicities. Grade 3–4 irAEs were observed in more than 50% of patients, and 5 patients died (1.1%) in the intervention arm due to immune-related toxicities (3 colitis, 1 myocarditis, 1 Guillain–Barré syndrome) [53]. Of 471 patients who started ipilimumab, 240 patients (51%) discontinued treatment due to treatment-related adverse events. Due to the unacceptable toxicity profile, adjuvant ipilimumab at 10 mg/kg has not been approved in Europe, but received FDA approval only.

The EORTC 18071 had no active comparator in the control arm. In the E1609 study, the safety and efficacy of ipilimumab 10 mg/kg or 3 mg/kg was compared with high dose interferon in patients with resected stage IIIB, IIIC, and IV M1a/M1b melanoma. Treatment with ipilimumab 3 mg/kg improved OS compared with high-dose interferon (HR: 0.78; 95% CI 0.61 to 1.00), while ipilimumab 10 mg/kg showed only a trend toward improvement in OS (HR 0.88; 95% CI 0.69 to 1.12) that was not statistically significant. The study was not powered for the comparison between the two doses of ipilimumab; however, exploratory analyses of OS and RFS with ipilimumab 3 mg/kg and 10 mg/kg suggested that low-dose ipilimumab was at least as effective as high-dose ipilimumab. Additionally, more patients in the ipilimumab 10 mg/kg group experienced a grade 3 or higher treatment-related AE than those who received ipilimumab 3 mg (58% and 37%, respectively), and more

patients discontinued treatment due to an AE of any grade (54% with ipilimumab 10 mg/kg and 35% with ipilimumab 3 mg/kg). Eight patients treated with high-dose ipilimumab died to an AE considered at least possibly related to study treatment compared with 3 patients treated with low-dose ipilimumab [55, 56]. Based on the results of the E1609 study, in cases where adjuvant treatment with ipilimumab still represents an option, ipilimumab 3 mg/kg seems to have an advantage over the approved dosage of ipilimumab 10 mg/kg.

In advanced disease, ipilimumab was outperformed in terms of both efficacy and safety by the anti-PD-1 agents nivolumab and pembrolizumab [16, 17], and their efficacy was then investigated in the adjuvant setting. In the CheckMate-238 randomized phase 3 clinical trial, patients with resected stage IIIB, IIIC, and IV melanoma were randomized to receive either nivolumab 3 mg/kg every 2 weeks for a year or ipilimumab 10 mg/kg every 3 weeks for four cycles and then every 12 weeks for up to a year. At a median follow-up of 36 months, patients receiving nivolumab had superior RFS compared with patients on ipilimumab for an HR of 0.68 (95% CI, 0.56–0.82). At 3 years, 58% of patients were free of relapse in the nivolumab group as compared with 45% for ipilimumab [57]. Nivolumab was superior to ipilimumab regardless of PD-L1 expression, disease stage, and BRAF mutation status [58, 59]. Most importantly, severe treatment-related AEs were significantly lower in patients treated with nivolumab compared with ipilimumab (14% vs. 46%, respectively); treatment was discontinued because of any AE in less than 10% of patients who received the anti-PD-1 agent compared with 43% of patients receiving ipilimumab [59]. Similar to that observed in patients with advanced melanoma, nivolumab was shown to be both more effective and better tolerated than ipilimumab also in the adjuvant setting. Exploratory biomarkers, such as tumor interferon-gamma gene expression signature, tumor mutational burden, tumor CD8+ T-cell infiltration, and myeloid-derived suppressor cell levels, correlated with RFS with both nivolumab and ipilimumab, highlighting their role as prognostic but not predictive biomarkers [57].

In the ongoing CheckMate-915 trial, a randomized phase 3 study evaluating nivolumab plus ipilimumab at a very low dose (1 mg/kg every 6 weeks) versus nivolumab alone for the adjuvant treatment of patients with resected stage IIIB/C/D or stage IV melanoma, the combination treatment failed to provide a statistically significant benefit for the co-primary endpoint of RFS in patients whose tumors expressed PD-L1 < 1% (Bristol-Myers Squibb Press Release, Wednesday, November 20, 2019; https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-announces-update-checkmate-915-opdivo-niv). The study will continue to assess the other co-primary endpoint of RFS in the intent-to-treat population.

The combination of ipilimumab with nivolumab was also assessed in another adjuvant trial for patients with resected stage IV melanoma. In the randomized, placebo-controlled, phase 2 trial IMMUNED, patients with stage IV melanoma with no evidence of disease after surgery or radiotherapy were randomized 1:1:1 to receive either nivolumab plus ipilimumab (1 mg/kg of nivolumab every 3 weeks plus 3 mg/kg of ipilimumab every 3 weeks for four doses, followed by 3 mg/kg of nivolumab every 2 weeks), nivolumab monotherapy (3 mg/kg every 2 weeks), or

placebo. The HR for recurrence for nivolumab plus ipilimumab versus placebo was 0.23 (97.5% CI, 0.12–0.45), and for nivolumab versus placebo was 0.56 (0.33–0.94). In the nivolumab plus ipilimumab group, RFS was 75% and 70% at 1 and 2 years, respectively, versus 52% and 42% for nivolumab monotherapy, and 32% and 14% for placebo. However, severe irAEs were reported at a rate as high as 71% in the combination group, as compared to 27% with nivolumab as a single agent [60]. The results of this study highlight the possible role of combination treatment in patients with melanoma at a very high risk of recurrence, such as resected stage IV, but regimens with lower dosages of ipilimumab could be preferred to decrease the risk of severe and potentially fatal toxicities.

Neoadjuvant Setting

Patients with high-risk resectable stage III/IV melanoma have poor outcomes even after adjuvant treatments [61]. A strong rationale supports the use of immune-checkpoint inhibitors in the neoadjuvant rather than the adjuvant setting, as the presence of the tumor and associated tumor-infiltrating lymphocytes might result in a stronger antitumor immune response. In fact, in the OpACIN trial, the use of neoadjuvant immunotherapy was associated with a greater increase of tumor-resident T-cell clones in peripheral blood compared with adjuvant immunotherapy [62]. Despite that, anti-PD-1 as a single agent did not achieve a sufficient rate of pathological complete responses to be worth further investigation in the neoadjuvant setting [63, 64]. The combination of IPI3 with NIVO1, which is the regimen currently approved in the advanced setting, had a high clinical activity at the cost of a very high rate of severe toxicities [62, 64, 65]. Thus, based on the results of the studies conducted so far, the best immunotherapy regimen to be further investigated in the neoadjuvant setting seemed to be IPI1 plus NIVO3, which achieved similar results than those obtained with IPI3 plus NIVO1 in terms of clinical activity, but with a lower rate of toxicities [65].

The Role of Ipilimumab in the Era of Anti-PD-1 Drugs

Ipilimumab is currently employed in combination with nivolumab as an upfront treatment in patients with advanced melanoma, regardless of the presence of a BRAF mutation. In patients who received previous treatment with a single-agent anti-PD-1 drug, ipilimumab still has a role as a subsequent treatment, with similar safety and clinical activity as that observed in clinical trials with anti-PD-1 naïve patients. However, no prospective clinical trials exist in this setting, and data are still scarce and mostly of retrospective nature [66–68]. The results of two studies recently presented at ASCO 2020 suggest that in single-agent anti-PD-1 resistant patients, the addition of ipilimumab to the anti-PD-1 treatment may be more effective than

ipilimumab alone [69, 70]. Despite that, the use of ipilimumab is not indicated by the regulatory agencies in this setting. Ipilimumab should not be administered neither before nor after anti-PD-1 agents with a planned switch (without evidence of PD), as investigated in CheckMate-064 trial, due to a similar rate of severe toxicities as observed with concurrent administration but with lower activity [9].

In patients with high-risk, resected melanoma, IPI10 should not be considered an option anymore, due to the higher toxicity and lower efficacy than anti-PD-1 agents, as highlighted in CheckMate-238 study [59], and BRAF plus MEK inhibitors in BRAF-mutant patients [71]. In fact, even if a direct comparison between ipilimumab and BRAF and MEK inhibitors does not exist, the overlapping results in terms of RFS of the placebo arms in both studies facilitate cross-trial comparison [53, 71]. The preliminary results of CheckMate-915 clinical trial showed that very low doses of ipilimumab (1 mg/kg every 6 weeks) in combination with nivolumab may not be superior to anti-PD-1 alone in patients with PD-L1 expression <1% [press release], while the IMMUNED study suggested that IPI3 + NIVO1 may have a role for the adjuvant treatment of resected stage IV melanoma, despite toxicity concerns [60].

Finally, even if it has not received an indication by the regulatory agencies yet, low-dose ipilimumab in combination with nivolumab (IPI1 + NIVO3) may have an important role as a neoadjuvant treatment for clinically positive stage III melanoma, as single-agent nivolumab did not provide sufficient pathological responses to be a valuable option in this setting [62, 64, 65, 72].

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