Advanced Melanoma

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Therapeutic options for treating advanced melanoma are progressing rapidly. Until 6 years ago, the regimen for treating advanced melanoma mainly comprised cytotoxic agents such as dacarbazine, and type I interferons. Since 2014, anti-programmed cell death 1 (PD1) antibodies have become recognized as anchor drugs for treating advanced melanoma with or without additional combination drugs such as ipilimumab. In addition, BRAF kinase inhibitors in combination with MEK kinase inhibitors are among the most promising chemotherapeutic regimens for treating advanced BRAF-mutant melanoma, especially in patients with low tumor burden. Since anti-PD1 antibodies are widely applicable for the treatment of both BRAF wild-type and mutated advanced melanomas, several clinical trials for drugs in combination with anti-PD1 antibodies are ongoing. This review focuses on the development of the anti-melanoma therapies available today, and discusses the clinical trials of novel regimens for the treatment of advanced melanoma.

metastatic melanoma BRAF inhibitors MEK inhibitors immune checkpoints inhibitors combination therapy

1. Introduction

Until 2014, regimens for the treatment of advanced melanoma mainly comprised cytotoxic agents such as dacarbazine (DTIC) and cytokines (e.g., type I interferon (IFN), high-dose interleukin (IL)-2, etc.) [1][2][3][4][5][6]. Since 2014, anti-programmed cell death 1 (PD1) antibodies (Abs) have become recognized as anchor drugs for the treatment of advanced melanoma, with or without additional combination drug such as ipilimumab [7][8]. In addition, v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors in combination with mitogen-activated protein kinase kinase (MEK) inhibitors are among the most promising chemotherapeutic regimens for the treatment of advanced *BRAF*-mutant melanoma, especially among patients with a low tumor burden [9][10]. Since anti-PD1 Abs are widely applicable to the treatment of both *BRAF* wild-type and mutated advanced melanoma, several clinical trials for drugs combined with anti-PD1 Abs are ongoing.

2. Clinical Use of ICIs in the Treatment of Advanced Melanoma

2.1. Efficacy of Anti-PD1 Antibody Monotherapy against Advanced Melanoma

To date, two different anti-PD1 Abs (nivolumab and pembrolozumab) are available for advanced melanoma treatment [7][8]. Since estimated 5-year OS and 5-year PFS of nivolumab monotherapy for *BRAF*-wild-type advanced melanoma were comparable to those of nivolumab plus ipilimumab (N + I) combination therapy [7], nivolumab monotherapy was considered as a first-line immunotherapy for *BRAF*-wild-type advanced cutaneous melanoma [11]. Five-year OS rate was 44% and 5-year PFS rate was 29% in the nivolumab monotherapy group [7] (Table 1). The ORR of nivolumab monotherapy was 43.7% (95% CI 38.1–49.3%) in a Caucasian population [8], but lower in a Japanese population (34.8%; 95% CI 20.8–51.9%) [12]. The ORR of nivolumab monotherapy in a Japanese population was again much lower than that in a Caucasian population according to post-marketing surveillance analysis in Japan (22.2%) [13]. Notably, the most common subtype of melanoma in Japan was acral lentiginous melanoma (ALM) (40.4%) [14], while the ratio of ALM in a non-Hispanic, white-skinned population in the United States was much lower (1%) [15]. A previous report also suggested that the ORR of anti-PD1 Abs for ALM and mucosal melanoma was lower in a Caucasian population [16]. Taken together, since the ORR of anti-PD1 Abs for advanced ALM in Japanese population was 16.6%, and the PFS and OS for the study cohort were 3.5 months and 18.2 months, respectively [17], the efficacy of anti-PD1 Abs monotherapy for advanced melanoma in the Japanese population was lower than that in the Caucasian population.

Table 1. Firstline therapy recommended by National Comprehensive Cancer Network (NCCN) guideline 2020.4.

Protocol	Efficacy	Median OS (95% CI)	5-Year OS	Median PFS (95% CI)	5-Year PFS	Reference
nivolumab monotherapy	43.7%	36.9 M	44.0%	11.5 M	29.0%	[7]
pembtolizumab monotherapy	36.0%	32.7 M	38.7%	8.4 M	23.0% (4-year)	[18]
N + I combination therapy	57.6%	60 M	52.0%	6.9 M	36.0%	[7]
D + T combination therapy	68.0%	25.9 M (22.6–31.5)	34.0%	11.1 M (9.5–12.8)	19.0%	[19]
V + C combination therapy	70.0%	22.3 months (20·3–N.E.)		12.3 M (9.5–13.4)		[20]
E + B combination therapy	64.0%	33.6 M (24.4–39.2)		14.9 M (11.0–20.2)		[21]
A + V + C combination therapy	66.3%	N.E. (2 years)		16.1 M (11.3–18.5)		[22]

N.E.: not estimable; N + I: nivolumab + ipilimumab; D + T: dabrafenib + trametinib; V + C: vemurafenib + cobimetinib; E + B: encorafenib + binimetinib; A + V + C: atezolizumab + V + C.

Monotherapy with pembrolizumab, another anti-PD1 Ab for advanced melanoma, should also be considered as a first-line immunotherapy for advanced cutaneous melanoma [18][23]. The ORR of pembrolizumab was 37% in melanoma patients taking pembrolizumab every 2 weeks and 36% in melanoma patients taking pembrolizumab every 3 weeks [18]. In a Japanese population, the ORR was 24.1% (95% CI 10.3–43.5%) for cutaneous melanoma and 25.0% (95% CI 3.2–65.1%) for mucosal melanoma [24]. Median OS and median PFS were 32.7 months (95% CI 24.5–41.6 months) and 8.4 months (95% CI 6.6–11.3 months), respectively [23]. The 5-year OS rate was 38.7% (95% CI 34.2–43.1%), and the 48-month PFS rate was 23.0% (95% CI 19.1–27.1%) in the pembrolizumab group [23], suggesting that both 5-year OS and 4-year PFS were comparable to those of nivolumab monotherapy.

Since the efficacies of N + I combination therapy or ipilimumab monotherapy as a second-line immunotherapy are low [25][26], determining the efficacy of nivolumab monotherapy before tumor progression is important. Moreover, the incidence of SAE is much higher in N + I combination therapy groups compared to nivolumab monotherapy groups. For these reasons, biomarkers for predicting the efficacy of nivolumab monotherapy have been under investigation [27]. For example, serum LDH levels should be taken into accounts before selecting immunotherapy [7][28]. Indeed, subgroup analysis from the CheckMate 067 (NCT01844505) trial confirmed a correlation of efficacy of nivolumab monotherapy with serum LDH levels, and suggested that nivolumab monotherapy should also be considered as a first-line immunotherapy for advanced cutaneous melanoma in patients with normal LDH levels [7]. In addition, a pre-clinical study suggested that an increased baseline neutrophil-lymphocyte ratio combined with normal serum LDH correlated significantly with the efficacy rate of nivolumab according to multivariate analysis [28]. These reports suggested the significance of serum LDH to predict the efficacy of nivolumab monotherapy. In addition, subgroup analysis of the CheckMate 067 (NCT01844505) trial also suggested that tumor PD-L1 expression alone was not predictive of efficacy outcomes [7], although other previous reports suggested that PD-L1 expression on melanoma cells can represent a biomarker for predicting the efficacy of anti-PD1 Abs [27][29][30].

More recently, TAM-related factors (soluble (s)CD163, CXCL5, (Chemokine (C-C motif) ligand (CCL)19 and CCL26)) could be predictive biomarkers for anti-PD1 Abs monotherapy [31][32][33][34]. In future, these predictive markers might be taken into accounts in combination with conventional markers, such as *BRAF* mutation, before selecting the protocol for immune therapy.

2.2. Efficacy of N + I Combination Therapy against Advanced Melanoma

N + I combination therapy is currently the most effective therapy for advanced melanoma [7][8], and is recommended as a first-line immunotherapy for the treatment of advanced melanoma [11]. The ORR to N + I combination therapy was higher than that to nivolumab monotherapy (57.6% (95% CI 52.0–63.2%) vs. 43.7% (95% CI 38.1–49.3%)) [8] (Table 1). The percentage of patients showing complete response was higher in the N + I combination group (11.5%) than in the nivolumab monotherapy group (8.9%) [8]. Notably, among patients with elevated LDH levels and high tumor burden, 5-year OS rate was much better with N + I combination therapy (38%) than with nivolumab monotherapy (28%). Five-year PFS rate was also improved with N + I combination therapy (28%) compared to nivolumab monotherapy (18%) among patients with elevated LDH levels and high tumor burden [7]. Indeed, a recent case report described a patient with advanced melanoma and 7 metastatic organs

successfully treated using N + I combination therapy in the real world [22] Subgroup analysis of the CheckMate 067 trial revealed the utility of N + I combination therapy for the *BRAF*-mutated advanced melanoma group [7]. Indeed, the 5-year OS rate was much improved in the N + I combination group (60%) than in the nivolumab monotherapy group (46%) among patients with tumors with *BRAF* mutations [7]. Five-year PFS rate was also improved with N + I combination therapy (38%) compared to with nivolumab monotherapy (22%) among patients with tumors showing *BRAF* mutations. Notably, these 5-year OS and PFS rates were comparable to those of D + T combination therapy [19]. Since the efficacy of BRAF/MEK inhibitors among patients with elevated LDH levels is limited [19], N + I combination therapy could be a first-line immunotherapy for *BRAF*-mutated advanced melanoma with high tumor burden.

2.3. Other ICIs Related Protocol

Recent NCCN Clinical Practice Guidelines for cutaneous melanoma also recommended anti-PD-L1 antibodies in combination with BRAF/MEK inhibitor [35]. Gutzmer et al. reported the efficacy of atezolizumab plus V + C (A + V + C) combination therapy for unresectable $BRAF^{V600}$ mutation-positive melanoma [36]. Although ORR of A + V + C combination therapy (66.3% (95% CI; 60.1–72.1)) was similar to V + C combination therapy (65.0% (95% CI; 58.7–72.1)), median PFS favored in A + V + C combination group (16.1 months (95%; CI 11.3–18.5)) compared with V + C combination therapy (12.3 months (95% CI; 10.8–14.7) (HR 0.85; 95% CI 0.67–1.07; log-rank $p = 0.16$)).

Talimogene Laherparepvec (T-vec) should also be taken into accounts for the treatment of advanced melanoma in combination with or without ICIs [37][38]. As Chesney et al. reported, the ORR of T-vec plus ipilimumab (39%) was higher than that of ipilimumab (18%) (odds ratio: 2.9 (95% CI; 1.5 to 5.5; $p = 0.002$)) in patients with advanced melanoma with prior therapy [38]. In another report, T-vec monotherapy was evaluated [38]. For patients with stage IV-M1a melanoma, the effect of T-VEC on DRR was higher than that of control cohort (recombinant GM-CSF) (24.0% vs. 0%). For patients with stage IV-M1b or -M1c disease, however, the effects of T-VEC on DRR and OS were small and not statistically significant [38].

2.4. Immune-Related AEs (irAEs)

As described above, anti-PD-1 Abs significantly prolong survival in patients with metastatic melanoma, and co-administration with ipilimumab leads to further improved outcomes [7][8]. However, co-administration of nivolumab and ipilimumab and sequential administration of nivolumab and ipilimumab with a planned switch leads to a high frequency of irAEs among patients with advanced melanoma [7][8][39]. Indeed, safety profiles from the CheckMate 067 trial revealed that the incidence of treatment-related SAE was higher with N + I combination therapy (55.0%) than with nivolumab monotherapy (16.3%) [8]. Among these, the incidence of treatment-related colitis, hepatitis and skin rash was 5 to 10 times much higher with N + I combination therapy than with nivolumab monotherapy [8]. Moreover, several reports have suggested that AEs caused by ICIs correlate with better response among melanoma patients [31][40][41][42]. For example, Kobayashi et al. reported that melanoma patients who developed pituitary dysfunction induced by ICIs display better OS than patients without this irAE [40]. Schadendorf et al. reported that the ORR to N + I combination therapy was higher in patients who discontinued because of irAEs

during the induction phase than in patients who did not discontinue [41]. Since absolute serum levels of sCD163 were significantly increased in patients who developed AEs [42], and serum levels of sCD163 were also significantly increased in melanoma patients who responded to nivolumab monotherapy [31], irAEs caused by ICIs might correlate with the efficacy of nivolumab. Indeed, serum levels of sCD163 in a patient with isolated ACTH deficiency caused by nivolumab were increased with good response to nivolumab monotherapy [40]. These reports suggest that several subtypes of irAEs caused by ICIs might correlate with better response in melanoma patients.

The correlation between human leukocyte antigen (HLA) subtypes and several irAEs caused by ICIs has been investigated in various studies [43][44][45][46][47][48][47,75,76,77,78,79]. For example, Fujimura et al. reported two cases of advanced melanoma patients who possessed HLA-DRB1*04:05, which is strongly associated with VKH disease, developing VKH-like uveitis after sequential administration of nivolumab and D + T combination therapy [43]. In other report, Magis et al. reported that in acute type I diabetes, 80% of patients (4/5) possessed HLA-DRB01*03 or *04 subtypes, which are known to increase type 1 diabetes risk in the general population [41]. Kambayashi et al. also reported a case of severe demyelinating neuropathy in an advanced melanoma patient treated with N + I combination therapy, who showed HLA-DQB1 polymorphisms (DQB1*040101 and *060401) [46]. More recently, Yano et al. reported that HLA-DR15, which is reported to correlate with autoimmune disease via IL-17 regulation, could be a predictive marker for ICI-induced secondary adrenal insufficiency [47]. Since both IL-17 and sCD163 reportedly correlate with autoimmune skin diseases such as bullous pemphigoid [48], psoriasis [49] and alopecia areata [50], and these autoimmune skin diseases were occasionally induced by ICIs in melanoma patients [51][52][53], HLA genotyping before treatment may help to avoid the incidence of irAEs by ICIs.

3. Future Perspectives

Since both BRAF/MEK inhibitors and ICIs could obtain the resistance [54][55][56][57], several pre-clinical studies had performed before the clinical studies on going today. For example, Corre et al. reported that aryl hydrocarbon receptor (AhR) transcription factor constitutively activates human melanoma cells to induce BRAF inhibitor-resistance genes [58]. In addition, targeting AhR signaling could prevent the induction of the BRAF inhibitor resistance gene in melanoma cells [56]. Another report suggested that resistance to BRAF/MEK inhibitors combined therapy is associated with reactive oxygen species (ROS) activities in human melanoma cell lines, and the administration of a histone deacetylase (HDAC) inhibitor induces selective apoptotic death of drug-resistant tumor cells [54]. Since short-term treatment with the HDAC inhibitor can eliminate cells harboring secondary mutations that induce resistance of BRAF and MEK inhibitors [55], HDAC inhibitors are a possible combined drug for BRAF/MEK inhibitors. Indeed, a phase III trial to evaluate sequential treatment of vorinostat and BRAF inhibitors plus MEK inhibitors in resistant $BRAFV^{600E}$ mutant melanoma is ongoing (NCT02836548).

As described above, ICIs are currently among the most promising methods for inducing long-acting anti-tumor effects [7]. Notably, a recent pre-clinical study suggested possible novel therapies for the treatment of advanced melanoma using therapy combining BRAF/MEK inhibitors and ICIs [59]. Indeed, several phase I/II clinical studies for the treatment of patients with advanced melanoma have been set up according to such preclinical studies (Table 2). For example, a phase I/II study to assess the safety and efficacy of pembrolizumab in combination with

dabrafenib and trametinib for *BRAF*-mutated advanced melanoma is now ongoing (NCT02130466). Since a dose-seeking and efficacy study of pembrolizumab plus vemurafenib and cobimetinib for advanced melanoma is also ongoing (NCT02818023), results from these two independent clinical trials should be compared. In addition, a phase II clinical trial to evaluate sequential administration of BRAF/MEK inhibitors, V + C combination therapy and N + I combination therapy for the treatment of *BRAF*-mutated advanced melanoma is ongoing (NCT02968303). The results of such clinical trials might offer more optimal protocols for *BRAF*-mutated advanced melanoma in the future. Unlike anti-PD1 Abs, ipilimumab is unsuitable for sequential therapy with BRAF inhibitors because of the high frequency of severe hepatotoxicity [54].

Table 2. Clinical trials on going.

Phase	Protocol	Cancer Species	Reference
I/II	pembrolizumab plus D + T	*BRAF*-mutated advanced melanoma	NCT02130466
I	pembrolizumab plus V + C	*BRAF*-mutated advanced melanoma	NCT02818023
II	sequential V + C and N + I	*BRAF*-mutated advanced melanoma	NCT02968303
II	neoadjuvant N + I	macroscopic stage III melanoma	[58]
II	anti-PD1 Abs plus denosumab	stage III/IV melanoma	NCT03620019
III	vorinostat plus BRAFi/MEKi	resistant *BRAF*V^{600E} mutant melanoma	NCT02836548

Several clinical trials for *BRAF*-wild-type advanced melanoma using anti-PD1 Ab-based immunotherapy are ongoing. Among these, Rozeman et al. reported a phase 2 clinical study of N + I combination therapy in a neoadjuvant setting for macroscopic stage III melanoma (OpACIN-neo) [58]. That clinical trial suggested appropriate doses of 1 mg/kg for ipilimumab and 3 mg/kg for nivolumab in a neoadjuvant setting to induce pathological response in a high proportion of patients without SAEs [60]. Indeed, in this dose setting, the ORR was 57% (17/30) and no grade 3–4 AEs were seen in more than one patient each, suggesting that this protocol might be suitable for broader clinical use against stage III melanoma involving lymph nodes [60].

Since a pre-clinical report has suggested that blockade of the receptor of receptor activator of nuclear factor kappa-B (RANK) enhanced the therapeutic effects of ICIs in a B16F10 melanoma model [58], denosumab might be suitable for treating advanced melanoma [61]. Indeed, based on such pre-clinical studies, a phase II study to assess the efficacy of anti-PD1 Abs (nivolumab or pembrolizumab) in combination with denosumab for stage III/IV melanoma is now underway (NCT03620019). In other pre-clinical studies, IFN-β also enhanced the therapeutic effects of anti-PD1 Abs in a B16F10 melanoma model by recruiting cytotoxic CD8+ T cells to tumor sites [62][63].

According to those pre-clinical studies, a phase 1 clinical trial had already been performed [64]. According to that clinical trial, the efficacy of anti-PD1 Abs might be improved without severe irAEs in future [54][64].

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