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INVITED REVIEW ARTICLE

Recent advances in therapeutic strategies for unresectable or metastatic melanoma and real-world data in Japan

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Abstract
New therapeutic strategies including immunotherapy and selective molecular target inhibitors have brought about a new era in the treatment of patients with advanced melanoma. In Japan, the immune checkpoint inhibitors ipilimumab, nivolumab and pembrolizumab, the BRAF inhibitor (BRAFi) vemurafenib, dabrafenib and MEK inhibitor (MEKi) trametinib have been available for the treatment of unresectable and metastatic melanoma. The BRAFi + MEKi combination shows high response rates (60–70%) and rapid response induction associated with symptom control, with a progression-free survival of 12 months. Nivolumab and pembrolizumab offer moderate response rates (30–40%) and long survival (3- to 5-year survival: 30–50%). In Japan, treatment options for the first-line setting frequently include nivolumab or pembrolizumab monotherapy and BRAFi + MEKi combinations (for patients with BRAF-mutant melanoma). Ipilimumab is included in the second-line setting, and the nivolumab + ipilimumab combination has not been approved yet in Japan. Although these medications have demonstrated impressive efficacy, the clinical trials and real-world data have shown that the clinical benefit is not fully satisfactory. We have to carefully manage a new class of adverse events due to these medicines. Moreover, biomarkers are emerging with which we can identify a population that would experience more benefits without severe adverse events.

Keywords Melanoma · Japan · Immune checkpoint inhibitors · BRAF inhibitors · MEK inhibitors · Biomarker

Introduction

Malignant melanoma has been resistant to radiation therapy and cytotoxic chemotherapy. The overall response rate (ORR) of dacarbazine, which had been a key drug for treating advanced melanoma, were 10–20% and less than 5%, respectively. Moreover, combination chemotherapy showed no survival benefit compared with dacarbazine monotherapy. The unsatisfactory clinical effects in the treatment of advanced metastatic melanoma did not change for decades. In the last few years, anti-programmed cell death 1 (PD-1) antibodies, anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi) have dramatically increased the ORR and elongated the overall survival (OS) of patients with advanced melanoma (Fig. 1). A retrospective multicenter analysis from Switzerland showed that the 1-year survival of advanced melanoma patients was 69% for checkpoint inhibitors, 50% for targeted therapies, 85% for checkpoint inhibitor plus targeted therapy and 38% for standard chemotherapy [1]. This article will review the recent advanced therapies for unresectable metastatic malignant melanoma using real-world data from Japan.

Melanoma in Japan

Incidence and epidemiology

The incidence of skin cancer is rapidly increasing in Japan (Fig. 1). The number of cases of and number of deaths from skin cancer in 2016 were 26,000 and 1700, respectively (Fig. 2) [2]. This increase is most likely due to the aging demographic of the Japanese population. Although melanoma is a rare neoplasm in Japan that is initially diagnosed in approximately 1500 patients per year, 40% of all patients who die of skin cancer have melanoma. The crude mortality rates of melanoma per million population (male/female)

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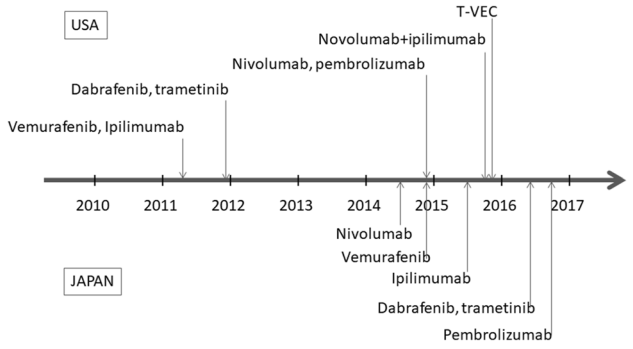

Fig. 1 Approval timeline for advanced melanoma

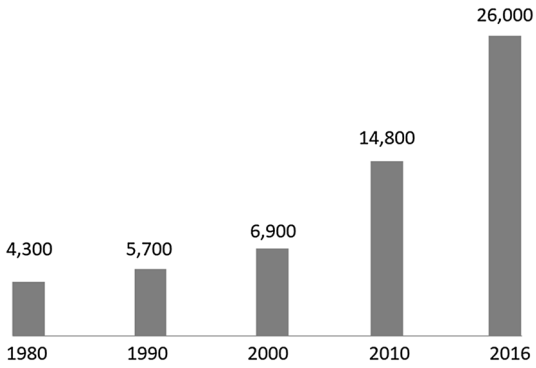

Fig. 2 Incidence of skin cancer per year in Japan (National Cancer Center, Center for Cancer Control and Information Services)

in Japan increased from 3.40/2.98 in 1999 to 5.68/5.33 in 2014 [3].

Clinical characteristics of Japanese melanoma patients

The foot is the most prevalent site in Japanese patients, occurring in 30% of cases, followed by the trunk in 15%, the head and neck in 14%, the hand in 12%, lower limb in 9%, mucosal in 9%, upper limb in 4% and uveal in 1% ($n = 2978$, 2005–2013, Japanese Skin Cancer Society) [4]. Acral lentiginous melanoma is the most common type in Japanese patients, occurring in 42% of cases, followed by superficial spreading melanoma in 20%, nodular melanoma in 10% and lentigo maligna melanoma in 8%. The 5-year survival rates according to the AJCC-TNM classification in Japanese patients are as follows: stage 1A, 96%; IB, 92.1%; IIA, 85%; IIB, 80%; IIC, 614.6%; IIIA, 74%; IIIB, 58%; IIIC, 39%; IV, 21% ($n = 2978$) [4]. The prognoses for Japanese patients with melanoma at each stage are similar to those in western countries. However, the frequency of Tis, stage I, II, III, IV and unclassified in Japanese patients is 17, 20, 24, 22, 11 and 7%, respectively. The frequency of stage III and IV is 33%, which is much higher than the 13% in the USA (SEER, http://seer.cancer.gav/) [4].

Genetics in Japanese melanoma patients

In 2005, Curtin et al. reported that the *BRAF* mutation [which belongs to the mitogen-activated protein kinase (MAPK) family], was highly detected in patients with melanoma without chronic sun-induced damage (CSD) [5]. Subsequent studies showed that V600E, which is the most common genotype of mutant *BRAF*, was especially closely associated with non-CSD, although V600K was closely associated with CSD [6]. The clinicopathologic characteristics have also been examined in other studies of patients with a *NRAS* or *KIT* mutation. The *NRAS* mutation was frequently observed in melanomas on the sun-exposed skin of older patients, and it was reported that the *KIT* mutation could be associated with acral, mucosal and CSD melanomas [7, 8]. In the most recent genetic data for Caucasian melanoma patients, 94% of melanoma patients had the *BRAF, NRAS* or *NF-1* mutations [9].

BRAF, NRAS and *KIT* mutations were detected in 30.4, 12.3 and 12.9% of Japanese patients, respectively [10]. Compared with the wild type, *BRAF* V600E was significantly associated with younger age (median 50 years) and was frequently detected in lesions of the scalp (80%), trunk (72.0%), extremities (56.7%) and neck (44.4%), while it was least prevalent in lesions of the face (22.2%), nail (12.5%), palm or sole (8.9%) and mucosa (0%). *NRAS* mutations were prevalent in the face (33.3%) and palm or sole (20.0%), and the median age of these patients was 70.5 years [10, 11]. *KIT* mutations were observed in the nail apparatus (25%), palm or sole (15.6%) and mucosa (18.2%). The median age of the patients with a *KIT* mutation was 63.0 years. The clinical characteristics associated with *BRAF, NRAS* and *KIT* mutations in Japanese patients were basically consistent with those in Caucasians except for the higher frequency of *BRAF* mutations in the scalp and neck.

BRAFi and MEKi

The advances in molecular analyses of melanomas have contributed to the development of novel therapies including BRAFi and MEKi. The combination of BRAFi and MEKi demonstrated improved progression-free survival (PFS) and OS over BRAFi monotherapy in randomized phase 2 and 3 trials in patients with *BRAF* V600E/K-mutant unresectable or stage IV metastatic melanoma] [12, 13]. In a recent analysis of a randomized, double-blind, phase 3 trial of the combination of dabrafenib and trametinib versus dabrafenib monotherapy (dabrafenib plus placebo), the median PFS was 11.0 versus 8.8 months [hazard ratio (HR) 0.67; 95% confidence interval (CI) 0.53–0.84; $P = 0.0004$], the median OS

was 25.1 versus 18.7 months (HR 0.71; 95% CI 0.55–0.92; $P = 0.0107$), and the 2-year survival rate was 51 versus 42% [13]. The most recent report of long-term outcomes in patients who received the combination of dabrafenib and trametinib showed 5-year survival rate and PFS values of 28 and 13%, respectively [14].

The combination has been associated with a reduction in hyper proliferative skin lesions (e.g., squamous cell carcinoma, keratoacanthoma) compared with BRAFi monotherapy [13]. However, the frequency and severity of several adverse events (AEs) appear to be higher than with monotherapy: pyrexia (59 versus 33%), chills (32 versus 17%), diarrhoea (31 versus 17%), vomiting (26 versus 15%), and peripheral oedema (22 vs 9%).

In the post-marketing data (real-world data) from Japan, the AEs involving vemurafenib were consistent with previous reports [15]. However, the incidence of cutaneous squamous carcinoma was much lower than in Caucasians: 1% (1/95). This might be associated with Japanese subjects being more resistant to sun damage compared to Caucasians. Skin rash was most prevalent in severe AEs, and almost all such eruptions occurred in patients who had been previously treated with nivolumab. Because dabrafenib and trametinib were just approved in April 2016 in Japan, the post-marketing data have not been published yet.

Immune checkpoints inhibitors

Nivolumab was approved as the first immune check point inhibitor in June 2014 in Japan, followed by ipilimumab in June 2015 and pembrolizumab in September 2016 (Fig. 1). The approval of these medicines has dramatically improved the clinical outcomes for patients with advanced melanoma. An anti PD-L1 antibody, avelumab, was approved only for Merkel cell carcinoma in September 2017 in Japan. Because the *BRAF* mutation is detected in only one-third of Japanese patients, immunotherapy with antibodies targeting CTLA-4 and PD-1 play important roles in the treatment of advanced melanoma patients in Japan.

Ipilimumab

In the first phase III trial, the median OSs in patients receiving ipilimumab plus gp100 and ipilimumab alone were 10.0 and 10.1 months, respectively, versus 6.4 months in those who received gp100 alone [16]. The 1-year survival rate for the ipilimumab-alone group was 45.6%, which was higher than previously reported for any other regimens in patients with advanced melanoma. In a second phase III trial randomized to ipilimumab plus dacarbazine versus dacarbazine alone, the median OS was superior in the ipilimumab group (HR for death was 0.72, $P < 0.001$) [17]. The most recent pooled analysis of long-term survival data from phase II and phase III trials demonstrated that the median OS was 11.4 months and the 3-year survival rate was 22%. Interestingly, the survival curve began to plateau after 3 years and remained flat until 10 years [18]. The long tail in the survival curve could be characteristic of cancer immune therapy. In addition, because ipilimumab blocks normal immune regulation, an immune reaction could occur not only in tumor tissues but also in normal organs. The frequently observed immune-related adverse events (irAEs) included skin rash, colitis, pneumonitis, hepatitis and thyroiditis. A systematic review and meta-analysis of irAE associated with ipilimumab showed that the overall incidences of all-grade irAEs and high-grade irAEs were 72 and 24%, respectively [19]. Death due to irAEs occurred in 0.86% of patients.

In Japan, ipilimumab has been administered after nivolumab failure because the combination of nivolumab and ipilimumab has not been approved, and two-thirds of patients are negative for the BRAF mutation. However, the clinical effect of ipilimumab after nivolumab was limited (ORR 3.6%) and associated with a high frequency of severe irAEs (grade 3–4: 70%) [20].

PD-1 blockades

PD-1 is an inhibitory receptor expressed by activated T cells that down-modulates effector functions. A phase II trial of the anti-PD-1 antibody nivolumab showed that the median OS in nivolumab-treated patients (62% with two to five prior systemic therapies) was 16.8 months, and the 1- and 2-year survival rates were 62 and 43%, respectively [21, 22]. Pembrolizumab produced durable responses in patients with ipilimumab-refractory advanced melanoma with an ORR of 26% [23].

Subsequent phase III trials that compared anti-PD-1 antibodies with ipilimumab showed the superiority of anti-PD-1 antibodies over ipilimumab. The Checkmate-067 study was a randomized phase III trial of ipilimumab monotherapy compared to nivolumab monotherapy or the combination of nivolumab and ipilimumab in patients with advanced melanoma [24]. The ORR was 43.7% with nivolumab compared to 19.0% with ipilimumab. A longer PFS (HR 0.57; $P < 0.001$) and lower toxicity were seen with nivolumab monotherapy. KEYNOTE-006 was a phase III trial comparing standard ipilimumab to pembrolizumab at 10 mg/kg every 2 or 3 weeks in patients with melanoma [25]. The ORR was similar for both pembrolizumab schedules (33.7, 32.9%) but higher than the ORR with ipilimumab (11.9%). The six-month PFS rates were 47.3, 46.4, and 26.5%, respectively. The rate of severe treatment-related adverse events was lower in patients receiving pembrolizumab compared to ipilimumab.

In Japan, nivolumab was approved for advanced melanoma as the first anti-PD-1 antibody in July 2014, followed

by pembrolizumab in September 2016. The interim results of post-marketing surveillance (real-world use) in Japan were reported in the 33rd Annual Meeting of the *Japanese Skin Cancer Society*, Akita, June 30, 2017 (Uhara H, Kiyohara Y, Tsutida T, et al.). The number of patients was 991, the median age was 68.0 (15–93) and the male-to-female ratio was 51:49. The site of the primary tumor was the skin including the acral regions in 56% of cases and mucosal in 32% of cases. The median number of doses was 6 (1–24). The reasons for the withdrawal of nivolumab were progression of disease in 39%, AE in 11% and death in 9%. All irAEs and severe irAEs were reported in 57 and 16% of cases, respectively. The frequently observed irAEs included thyroiditis (24%), hepatitis (19%), infusion reaction (10%), colitis and/or diarrhea (5%) and pneumonitis (5%). The median OS was 394 days in all cases, while the OS was not reached in cutaneous melanoma including acral melanoma, and was 345 days in mucosal melanoma cases. Outside the occurrence of rare events, fulminant type 1 diabetes mellitus, myalgia graves, myositis, adrenal failure, carditis, thrombocytopenia and anemia were reported as severe irAEs [26–31]. irAEs should be managed according to the guidelines. It should be noted that irAEs are different from stereotypical ordinal autoimmune disorders which specialists in each organ routinely manage.

Combination of nivolumab and ipilimumab

The combination of ipilimumab and nivolumab is the most recent advance in melanoma therapy, although it has not been approved in Japan. A randomized control trial comparing the combination to monotherapy with nivolumab or ipilimumab showed that the combination was superior to the monotherapy despite the presence of more severe irAEs [32]. At a minimum follow-up of 36 months, the median OS had not been reached in the combination group and was 37.6 months in the nivolumab group, as compared with 19.9 months in the ipilimumab group. The 3-year survival rate was 58% in the combination group and 52% in the nivolumab group, as compared with 34% in the ipilimumab group. Treatment-related AEs of grade 3 or 4 occurred in 59% of the patients in the combination group, in 21% of those in the nivolumab group, and in 28% of those in the ipilimumab group.

A single-arm phase 2 study of the combination of ipilimumab and nivolumab in Japanese patients with previously untreated melanoma ($n = 30$) showed that the disease control rate was higher at 73.3%, but the ORR, at 30.3% (CR 3.3%), was lower compared with compared with that in the previous phase III study (Kiyohara Y, Takenouch T, Uhara H, et al., #380P, ESMO Asia 2017). The clinical types of the patients enrolled in this study included 40% of mucosal and 23% of acral melanomas. It is unclear whether the genetic status of mucosal and acral melanoma, as distinct from UV-related cutaneous melanoma, could result in a lower response [33]. Grade 3–4 AEs were observed in one-third of the patients, and AEs leading to drug withdrawal were observed in one-quarter of the patients.

Treatment for brain metastasis

Brain metastasis is the event coinciding with the worst prognosis. The median survival after the occurrence of new metastasis during combination therapy with dabrafenib and trametinib was 4 months with brain metastasis and 10 months with metastasis in a location other than the brain [34]. Brain metastasis as the worst prognostic factor was reflected in the newest AJCC staging (8th edition, 2017) and a new category (M1d: brain metastasis) was added in the M classification. The intracranial ORR and CR rate of brain metastasis for the combination therapy of dabrafenib and trametinib were 44–59 and 0–1%, respectively [35]. The median PFS and OS were 4.2–7.2 and 10.1–24.3 months, respectively. The intracranial ORR was not influenced by the type of BRAF mutation, symptom, previous therapy and size of brain metastasis. However, the response was not durable.

Promising results have been demonstrated with the combination of nivolumab and ipilimumab for asymptomatic patients with melanoma brain metastases who had not received prior local therapy in the brain. The combination showed an intracranial response rate of 46% with a CR rate of 17%, and the median intracranial PFS was not reached (the median follow-up was 17 months) [36]. The combination of immune checkpoint inhibitors and stereotactic radiosurgery appeared to prolong OS [37].

Adjuvant therapy

The role of adjuvant systemic therapy in treating completely resected melanoma has been studied in numerous trials. However, the improvement of OS has not been consistent in high-dose IFN-alpha-2b and pegylated IFN-alpha-2b.

Ipilimumab 10 mg/kg has been evaluated in randomized phase III trials compared to a placebo (EORTC 18071) [38]. Ipilimumab was approved by the FDA because it showed an improved median recurrence-free survival of 26.1 months with ipilimumab compared to 17.1 months with a placebo (HR 0.75). However, a high frequency of severe irAEs including five treatment-related deaths was observed, and the usefulness of this treatment has not yet been conclusively shown.

Most recently, an adjuvant setting study comparing ipilimumab 10 mg/kg to nivolumab 3 mg/kg in stage IIIB, IIIC, or IV melanoma was reported [39]. Nivolumab showed significantly longer recurrence-free survival with a lower rate of grade 3 or 4 adverse events than ipilimumab (the

12-month rate of recurrence-free survival was 70.5% in the nivolumab group and 60.8% in the ipilimumab group).

A study comparing the combination of dabrafenib and trametinib to a placebo showed that the adjuvant use of combination therapy resulted in a significantly lower risk of recurrence in patients with stage III melanoma than did a placebo [40]. The estimated 3-year rate of relapse-free survival was 58% in the combination-therapy group and 39% in the placebo group; the 3-year survival rate was 86% in the combination-therapy group and 77% in the placebo group.

New strategy

Multiple novel therapies have been studied in clinical trials. Talimogene laherparepvec (T-VEC), already approved by the FDA, is an oncolytic modified herpes simplex virus expressing GM-CSF, which is injected directly into the tumor. HF10 is an oncolytic herpes simplex virus-1 without engineered deletions in the genomic structure [41]. These oncolytic viruses are being investigated in clinical trials in combination with immune checkpoint inhibitors. A recent study showed that ORR was significantly higher with the combination of T-VEC and ipilimumab versus ipilimumab alone (52 vs 23%) [42]. Interestingly, responses were not limited to injected lesions.

Another immunotherapy target for combination strategies is indoleamine 2,3-dioxygenase 1 (IDO1), which converts tryptophan to kynurenine, leading to immune suppression in tumors. Promising results have been demonstrated with the combination of the IDO1 inhibitor epacadostat (INCB024360) and ipilimumab or pembrolizumab in patients with advanced melanoma.

Biomarkers

The identification of a population that would experience much greater benefits without severe adverse events is necessary to establish the use of BRAFi, MEKi, anti-PD-1 and anti-CTLA-4 antibodies.

For BRAFi and MEKi, lactate dehydrogenase (LDH) and the number of metastatic organs are the most important factors associated with the clinical effect. The 3-year survival rate for the combination of dabrafenib and trametinib reached 62% in the most favorable subgroup (normal LDH and < 3 organ sites with metastasis) versus only 25% in an unfavorable subgroup (elevated LDH) [43]. Mutation analysis of *BRAF* in circulating tumor DNA (ctDNA) and tumor cells provide genetic information that can monitor treatment responses [44, 45].

The clinical response or irAE to the treatment with anti-PD-1 and anti-CTLA-4 antibodies could be associated with the following: the expression of PD-1/PD-L1, CD8+ tumor-infiltrating lymphocytes (TIL), T cell repertoire (PD-L1, granzyme A, and HLA-A), mutational burden, the presence of neoantigens, the absolute lymphocyte and absolute neutrophil counts before treatment [46–50]. Freeman demonstrated that some irAEs of nivolumab, namely rash (HR 0.423) and vitiligo (HR 0.184), correlated with statistically significant OS differences in patients with metastatic disease [51].

Conclusion

The introduction of immune checkpoint inhibitors and BRAF/MEK inhibitors has produced a new era in the treatment of patients with advanced melanoma. Moreover, novel therapies such as oncolytic viruses and IDO-1 inhibitors are coming. We have to carefully manage a new class of adverse events that result from these medicines. Biomarkers are emerging to identify a population that will experience much greater benefits without severe adverse events.

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Compliance with ethical standards

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