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The Systemic Management of Advanced Melanoma in 2016

Markus V. Heppt Cecilia Dietrich Saskia A. Graf Thomas Ruzicka Julia K. Tietze Carola Berking

Department of Dermatology and Allergy, Munich University Hospital (LMU), Munich, Germany

Keywords

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Summary

Melanoma is a common type of skin cancer with a high propensity to metastasize. Tyrosine kinase inhibitors targeting the mitogen-activated protein kinase (MAPK) pathway and immune checkpoint blockade have recently revolutionized the management of unresectable and metastatic disease. However, acquired resistance and primary non-response to therapy require novel treatment strategies and combinations. The purpose of this review is to provide a brief and up-to-date overview on the clinical management and current trial landscape in melanoma. We summarize the most pertinent studies on BRAF/MEK inhibitors and blockade of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Although most agents show robust antitumor efficacy as single agents, further improvements have been achieved by the combination of both approved and developing drugs. We discuss ongoing trials and evaluate future approaches that may provide additional efficacy with less toxicity.

Introduction

In the last few years, the therapy for advanced melanoma has been revolutionized by introducing a panel of novel local and systemic treatment approaches. In particular, targeted BRAF mutation status-based therapies with tyrosine kinase inhibitors and immune therapy with ipilimumab or programmed cell death protein 1 (PD-1) inhibitors are now the pillars of a modern and effective treatment (figs. 1 and 2). They have replaced the use of chemotherapy with dacarbazine and other cytotoxic agents in clinical practice. Further improvements could well be achieved by combining therapies that are presently available. In this review article, we summarize the current trials and the state-of-the-art systemic therapies for advanced melanoma.

Targeted Therapy with Kinase Inhibitors (BRAF and MEK Inhibitors)

If the oncogene BRAF harbors activating mutations such as Val600Glu (V600E) or Val600Lys (V600K), targeted therapy with tyrosine kinase-inhibiting substances should be considered in the first- or second-line treatment. Several phase III studies indicate, in a very impressive way, that an upfront combination therapy with inhibitors to BRAF (BRAFi) and MEK (MEKi) is superior to BRAFi monotherapy alone (table 1).

Dabrafenib and Trametinib

The double-blind, randomized phase III study COMBI-d compared dabrafenib and trametinib to dabrafenib alone. In a primary analysis after a median follow-up of 9 months, the combination was superior to monotherapy with a progression-free survival (PFS) of 9.3 and 8.8 months, respectively, and a hazard ratio (HR) for progression or death of 0.75 (95% confidence interval (CI) 0.57–0.99). The objective response rate (ORR) lay at 67% for the combination and at 51% for the monotherapy cohort [1]. A final report on overall survival (OS) was performed when 70% of the intention-to-treat population had died [2]. The median OS was 25.1 months in the dabrafenib plus trametinib group versus 18.7 months in the dabrafenib only group (HR 0.71; 95% CI 0.55–0.92). In the group treated with the combination, 74% and 51% of the patients survived the first and second year under observation.

KARGER

Fax +49 761 4 52 07 14
Information@Karger.com
www.karger.com

Accessible online at:
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Prof. Dr. med. Carola Berking
Department of Dermatology and Allergy
Munich University Hospital (LMU)
Frauenlobstr. 9-11, 80337 Munich, Germany
Carola.Berking@med.uni-muenchen.de

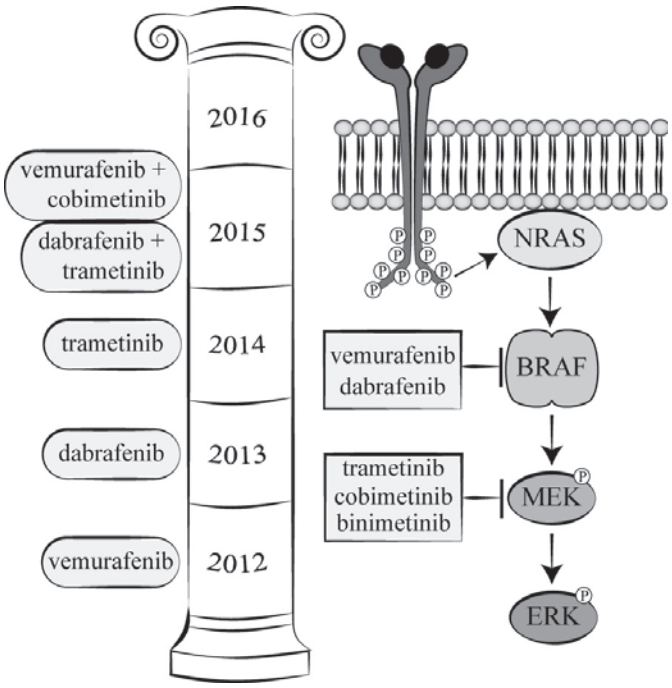

Fig. 1. The mitogen-activated protein kinase (MAPK)-signaling pathway can be induced by activating mutations of receptor tyrosine kinases and mediated through the small guanosine triphosphate (GTP)ase NRAS, the serine/threonine kinase BRAF and the MAPK kinases MEK and ERK. Specific BRAF inactivation can be achieved with the inhibitors vemurafenib and dabrafenib, while cobimetinib, trametinib, and binimetinib block MEK kinase activity. These inhibitors have been approved in single and combination therapy by the European Medicines Agency (EMA) in the years as depicted in the pillar.

The PFS in the combination arm increased further to 11.0 months (HR 0.67; 95% CI 0.53–0.84). The response rates were 69% and 53%, respectively [2]. In addition to objective clinical benefits such as delayed progression or longer OS, patients receiving the combination showed a better health-related quality of life along with significant functional and pain improvements compared with patients receiving monotherapy with dabrafenib. However, some dimensions of the questionnaires such as nausea and vomiting or diarrhea showed a trend of being favorable with dabrafenib only [3]. Recently, a 3-year analysis was presented (with a cut-off date for data of 15 February 2016), revealing a PFS of 22% (dabrafenib plus trametinib) versus 12% (dabrafenib only) and OS of 44% versus 32%. The outcome was best in patients with normal serum lactate dehydrogenase (LDH) and less than 3 affected organ systems at baseline [4]. These data provide the so far longest follow-up on OS in patients receiving BRAFi and MEKi in a phase III trial setting.

The open-label, randomized phase III trial COMBI-v compared dabrafenib and trametinib to vemurafenib as first-line therapy in 704 patients with metastatic melanoma with OS as primary endpoint [5]. The study was prematurely stopped for efficacy based on a positive interim analysis. Median OS was 17.2 months for the vemurafenib only group and was not reached by patients who were treated with the combination. The survival benefit was evident in all specified subgroups except for patients with an Eastern Cooperative Oncology Group (ECOG) score of 1 at baseline. Median

Table 1. Published trials with tyrosine kinase inhibitors in melanoma

Trial	Study design	Treatment arms	Primary endpoint	Previous therapies	ORR	mPFS	OS	AE (> grade 3)
Ribas et. al 2014 (BRIM7) [9]	phase Ib, (dose escalation)	vemurafenib/ cobimetinib (different dosing schedules)	safety	BRAFi, naïve	15% (progression after BRAFi) 87% (naïve)	2.8 months (progression after BRAFi), 13.7 months (naïve)	mOS 8.3 months (progression after BRAFi), not reached (naïve)	higher in naïve patients
Larkin et. al 2014 (coBRIM) [7]	phase III, double blind	vemurafenib/ cobimetinib vs. vemurafenib	PFS	naïve	68% (vemurafenib / cobimetinib), 45% (vemurafenib)	9.9 months (vemurafenib / cobimetinib), 6.2 months (vemurafenib)	9-month OS 81% (vemurafenib / cobimetinib), 73% (vemurafenib)	65% (vemurafenib / cobimetinib), 59% (vemurafenib)
Long et al. 2014 (COMBI-d) [1]	phase III, double blind	dabrafenib/ trametinib vs. dabrafenib	PFS	naïve	67% (dabrafenib / trametinib), 51% (dabrafenib)	9.3 months (dabrafenib / trametinib), 8.8 months (dabrafenib)	6-month OS 93% (dabrafenib / trametinib), 85% (dabrafenib)	35% (dabrafenib / trametinib), 37% (dabrafenib)
Long et al. 2015 (COMBI-d) [2]	phase III, double blind	dabrafenib/ trametinib vs. dabrafenib	PFS	naïve	69% (dabrafenib / trametinib), 53% (dabrafenib)	11.0 months (dabrafenib / trametinib), 8.8 months (dabrafenib)	mOS 25.1 months (dabrafenib / trametinib), 18.7 months (dabrafenib)	32% (dabrafenib / trametinib), 31% (dabrafenib)
Robert et al. 2014 (COMBI-v) [17]	phase III, open label	dabrafenib/ trametinib vs. vemurafenib	OS	naïve	64% (dabrafenib / trametinib), 51% (vemurafenib)	11.4 months (dabrafenib / trametinib), 7.3 months (vemurafenib)	1-year OS 72% (dabrafenib / trametinib), 65% (vemurafenib)	52% (dabrafenib / trametinib), 63% (vemurafenib)

ORR = Overall response rate, PFS = progression-free survival, OS = overall survival, AE = adverse events, mPFS = median PFS, mOS = median OS, BRAFi = BRAF inhibition.

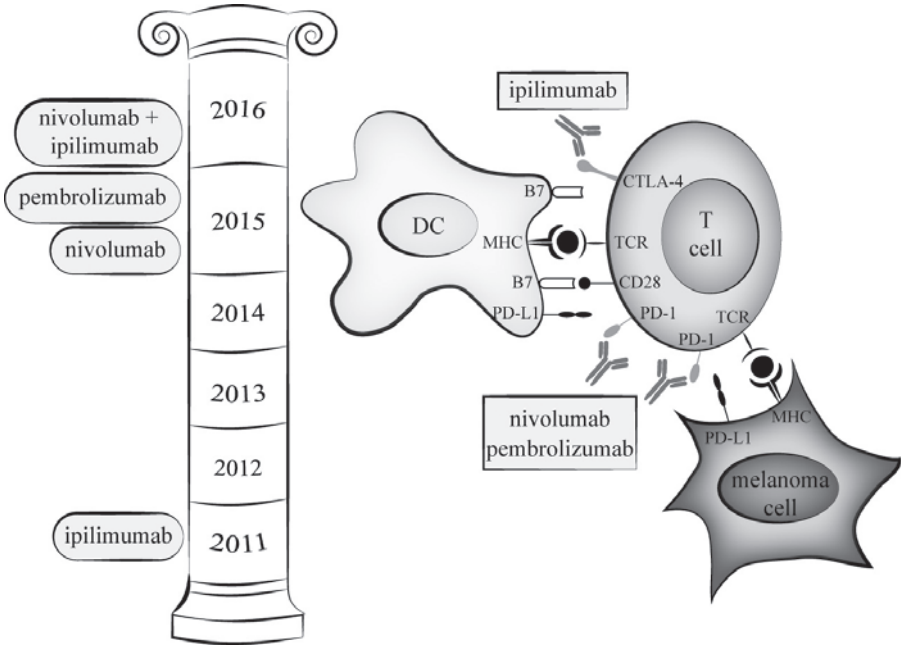

Fig. 2. Blocking cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or programmed cell death protein 1 (PD-1) signaling in tumor immunotherapy. T cells recognize antigens that are presented by dendritic cells (DC) or melanoma cells through the major histocompatibility complex (MHC) with their T-cell receptors (TCR). Several signals regulate T-cell activity. They can be activated through costimulatory B7 molecules binding to CD28, while binding of B7 to CTLA-4 triggers inhibitory signals during the priming phase in lymph nodes. Binding of programmed death ligand 1 (PD-L1) on melanoma cells to PD-1 on T cells results in negative regulation during the effector phase in the peripheral tissue. Thus, T-cell activation can be achieved by antibody-mediated blocking of CTLA-4 with ipilimumab or PD-1 with nivolumab or pembrolizumab. Years in which these antibodies have been approved for melanoma therapy by the EMA are depicted in the pillar.

PFS was 11.4 versus 7.3 months (HR 0.56; 95% CI 0.46–0.69) with best overall response rates of 64% and 51%, respectively [5]. Analogous to COMBI-d, scores for global health and most functional and disease symptoms showed significant improvements in favor of the combination, further underlining that the upfront combination of BRAFi and MEKi is the standard of care for patients with activating BRAFV600 mutations [6].

Vemurafenib and Cobimetinib

The combination of vemurafenib and cobimetinib was approved by the European Medicines Agency (EMA) in December 2015 based on the results of the pivotal coBRIM trial. Patients who had not previously been treated for unresectable or metastatic melanoma received vemurafenib and cobimetinib or vemurafenib plus placebo with investigator-assessed PFS as primary endpoint [7]. The rate of complete or partial responses was 68% for the combination and 45% for the control group. After 9 months of follow-up, survival rates were 81% and 73%, respectively. The median PFS was 9.9 months in the combination group and 6.2 months for vemurafenib monotherapy [7]. After a median follow-up of 14.2 months, PFS further increased to 12.3 and 7.2 months. Vemurafenib plus cobimetinib showed a better ORR (70%) compared to that for vemurafenib plus placebo (50%). Of note, 16% of patients in the combination arm showed complete response. The duration of the response was 13.0 and 9.2 months, respectively. The treatment-related benefits were consistent in every assessed patient subgroup, including patients with BRAFV600E and BRAFV600K mutations [8]. The survival data for the coBRIM were recently updated after a median follow-up of 18.5 months. After 1 year, 75% of patients treated with the combination were alive. The 2-year survival rate was still 48%. Median OS amounted to 22.3 months for the combination as opposed to 17.4 months for vemurafenib only (HR 0.70; 95%CI 0.55–0.90). Even in patients with increased LDH with an unfavorable prognosis, the survival time was significantly better. On the other hand, for the expression of other molecular tumor features, such as the proliferation marker Ki-67 or the tumor-suppressors PTEN, no difference was detected with respect to the OS rate.

Similar results were reported for BRIM7 after an extended follow-up. BRIM7 was initially designed as a dose-escalating phase Ib trial, which formed the basis for the development of the vemurafenib and cobimetinib combination regimen [9]. Included study patients had either previously progressed on vemurafenib or were BRAFi naïve. A striking confirmed response rate of 87% was observed in the latter group with 4 more patients attaining a complete response at cycles 16–25. The median PFS was left unchanged at 13.8 months and the median OS was reached at 28.5 months. After 2 years of follow-up, 61% of patients receiving vemurafenib and cobimetinib were still alive [10].

Binimetinib (MEK162)

Activating mutations of the oncogene NRAS are present in approximately 20% of patients with melanoma. Some studies proposed that the NRAS mutation status is an independent predictor of short survival in stage IV disease [11]. Thus, NRAS-mutated patients are at high risk for disease progression and represent a population with unmet clinical need, in particular after immune checkpoint blockade has failed. Preclinical studies have shown that NRAS-mutated melanoma is sensitive to MEK inhibition [12, 13]. Binimetinib (MEK162), an oral inhibitor of both MEK1 and MEK2, was the first targeted therapy to show antitumor activity in patients with NRAS-mutated melanoma in a phase II trial [14]. This was the rationale for the NEMO trial to test binimetinib in a phase III setting in NRASQ61-mutated melanoma. Patients were randomized at a 2:1 ratio to either binimetinib or dacarbazine. Binimetinib significantly improved PFS over dacarbazine with a me-

dian PFS of 2.8 versus 1.5 months (HR 0.62; 95% CI 0.47–0.80). The response rates in the intention-to-treat population were 15% and 7%, respectively. The median OS was not significantly improved and lay at 11.0 months [4].

Safety and Tolerability

Although in the coBRIM study incidences of severe adverse events in the combination therapy were slightly elevated, other studies and the clinical practice have shown that the safety and the tolerability of both combinations are good. Cutaneous side effects such as the development of palmoplantar hyperkeratosis, squamous cell carcinoma, or hair loss, which frequently occur under BRAFi monotherapy, are found less frequently with the combination due to simultaneous inhibition of MEK [2, 5]. However, nausea, vomiting and diarrhea occur more frequently in the combination regimens. One of the most frequent adverse events of dabrafenib plus trametinib is pyrexia, which has been observed in more than 50% of all cases [1, 5]. On the other hand, with vemurafenib plus cobimetinib, photosensitivity has been observed in 20% of the cases [7]. Moreover, an important effect of MEKi is the reduction of the left ventricle ejection fraction, even to the extent of a clinically manifested heart insufficiency, as well as the development of a central serous retinopathy. Regular cardiac examinations with electrocardiography and trans-thorax echocardiograms should be performed every 3 months as well as an examination of the retina with optical coherence tomography prior to treatment.

Immune checkpoint blockade

Ipilimumab Monotherapy

The antibody ipilimumab, which is directed against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), is administered intravenously for 4 cycles at 3-weekly intervals, in contrast to the PD-1 inhibitors, which are applied as continuous therapy. Pooled data from several phase ll and phase lll trials have recently been collected and analyzed, revealing a median survival time of 11.4 months for ipilimumab monotherapy [15]. Interestingly, the survival curves reach a plateau after 3 years and appear stable even 10 years post treatment. According to the studies that have been published thus far, the response rates of ipilimumab as monotherapy are lower than those with PD-1 inhibitors, and the rate of adverse events is presumably higher. Events such as autoimmune colitis and hypophysitis may require hospitalization and result in irreversible hormone deficiency. Thus, despite its proven long-term efficacy and the limited number of applications, the future of ipilimumab as monotherapy in melanoma is uncertain.

Pembrolizumab Monotherapy

Pembrolizumab is administered intravenously at 2 mg/kg body weight every 3 weeks and can be administered continuously over a period of at least 1–2 years if the response is favorable and the drug well tolerated. However, the optimal treatment duration has not been identified to date [16]. It was first evaluated in the large phase I KEYNOTE-001 study. After a median follow-up duration of 18 months, the response rate was 34% and the median OS 25.9 months. The responses were stable and maintained in 81% of patients, suggesting a high antitumor efficacy in the early stages of drug development [17]. The KEYNOTE-002 study compared 2 dosage schemes of pembrolizumab in comparison to investigator-choice chemotherapy (ICC) in patients who were refractory to ipilimumab or to prior BRAFi. Both dosages of pembrolizumab, 2 mg/kg and 10 mg/kg body weight, were clearly superior to ICC with respect to PFS and tolerability, providing the basis for accelerated approval in advanced melanoma [18]. Pembrolizumab was ultimately compared to ipilimumab in the phase III trial KEYNOTE-006. It was administered at 10 mg/kg body weight in 2 distinct cohorts every 2 and 3 weeks, respectively. The efficacy was similar in both of these groups and significantly higher over ipilimumab with an estimated 6-month PFS of 46–47% compared to 27% (HR 0.58; 95% CI 0.46–0.72). The response rates were 34% (2-week cycle) and 33% (3-week cycle) in comparison to 12% for patients with ipilimumab monotherapy [19]. Regarding safety, pembrolizumab was better tolerated than both chemotherapy (shown in KEYNOTE-002) and ipilimumab (shown in KEYNOTE-006). In 3–7% of patients treatment was discontinued due to severe treatment-related adverse events. The most common events observed with pembrolizumab are fatigue, diarrhea, rash, and pruritus. Immune-related side effects most commonly are hyper- and hypothyroidism, colitis, hepatitis, hypophysitis, and pneumonitis, although virtually any organ system can be affected [19–21].

Nivolumab Monotherapy

Nivolumab is administered intravenously at 3 mg/kg body weight every 2 weeks. The phase III study CheckMate 037 evaluated nivolumab in comparison to ICC as second- or later-line treatment in patients who were refractory to ipilimumab or BRAFi. Confirmed objective responses were reported in 31.7% and 10.6%, respectively [22]. These results were further corroborated in previously untreated patients without a BRAF mutation in the trial CheckMate 066, where nivolumab was compared to dacarbazine as first-line approach. Patients in the nivolumab arm showed a response rate of 40.0% versus 13.9% in the dacarbazine arm. The median PFS was 5.1 and 2.2 months, respectively (HR 0.43; 95% CI 0.34–0.56). After 1 year of follow-up, the survival rates were 73% and 42%, respectively (HR 0.42; 99.8% CI 0.25–0.73). This survival benefit was evident in all pre-specified subgroups including those that were defined by expression of the programmed death ligand 1 (PD-L1), indicating that nivolumab is effective irrespective of PD-L1 expression levels [23]. Recently, updated data have been presented after an observational time of 18.5 months post therapy. After this period of time, the median OS rate had not yet been reached in the nivolumab cohort, whereas it was 11.2 months for dacarbazine (HR 0.43; 95% CI 0.33–0.57). The median PFS further improved to 5.4 months for nivolumab and remained at 2.2 months with chemotherapy (HR 0.42; 95% CI 0.32–0.53). The objective response rates were 42.9% and 14.4%, respectively. The

Table 2. Published trials with PD-1 blockade in melanoma

Trial	Study design	Treatment arms	Primary endpoint	Previous therapies	ORR	mPFS	OS	AE (> grade 3)
Robert et al. 2014 (expansion cohort of KEYNOTE-001) [17]	phase I, open label	pembrolizumab 2 mg/kg Q3W vs. pembrolizumab 10mg/kg Q3W	ORR	ipilimumab	26% (2 mg/kg), 26% (10 mg/kg)	22 weeks (2 mg/kg), 14 weeks (10 mg/kg)	1-year OS 58% (2 mg/kg), 63% (10 mg/kg)	15% (2 mg/kg), 8% (10 mg/kg)
Ribas et al. 2015 (KEYNOTE-002) [18]	phase II, open label	pembrolizumab 2 mg/kg Q3W vs. pembrolizumab 10 mg/kg Q3W vs. ICC	PFS	ipilimumab, BRAFi, MEKi	21% (2 mg/kg), 25% (10 mg/kg), 4% (ICC)	6-month PFS 34% (2 mg/kg), 38% (10 mg/kg), 16% (ICC)	not yet reported	11% (2 mg/kg), 14% (10 mg/kg), 26% (ICC)
Robert et. al 2015 (KEYNOTE-006) [19]	phase III, double blind	pembrolizumab 10 mg/kg Q2W vs. pembrolizumab 10 mg/kg Q3W vs. ipilimumab 3 mg/kg Q3W	PFS, OS	ICC, BRAFi, MEKi	33.7% (pembrolizumab Q2W), 32.9% (pembrolizumab Q3W), 11.9% (ipilimumab)	5.5 months (Q2W), 4.1 months (Q3W), 2.8 months (ipilimumab)	1-year OS 74.1% (pembrolizumab Q2W), 68.4% (pembrolizumab Q3W), 58.2% (ipilimumab)	13.3% (pembrolizumab Q2W), 10.1% (pembrolizumab Q3W), 19.9% (ipilimumab)
Weber et al. 2015 (CheckMate 037) [22]	phase III, open label	Nivolumab 3 mg/kg Q2W vs. ICC	ORR, OS	ipilimumab, BRAFi	31.7% (nivolumab), 10.6% (ICC)	4.7 months (nivolumab), 4.2 months (ICC)	Not yet reported	9% (nivolumab), 31% (ICC)
Robert et al. 2015 (CheckMate 066) [23]	phase III, double blind	Nivolumab 3 mg/kg Q2W vs. DTIC	OS	naïve	40.0% (nivolumab), 13.6% (DTIC)	5.1 months (nivolumab), 2.2 months (DTIC)	1-year OS 72.9% (nivolumab), 42.1% (DTIC)	11.7% (nivolumab), 17.6% (DTIC)
Larkin et. al 2015 (CheckMate 067) [26]	phase III, double blind	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg Q3W vs. nivolumab 3 mg/kg Q2W vs. ipilimumab 3 mg/kg Q3W	PFS, OS	naïve	57.6% (nivolumab plus ipilimumab), 43.7% (nivolumab), 19.0% (ipilimumab)	11.5 months (nivolumab plus ipilimumab), 6.9 months (nivolumab), 2.9 months (ipilimumab)	Not yet reported	55.0% (nivolumab plus ipilimumab), 16.3% (nivolumab), 27.3% (ipilimumab)

PD-1 = programmed cell death protein 1, ORR = overall response rate, PFS = progression-free survival, OS = overall survival, AE = adverse events, Q2(3)W = every 2(3) weeks, ICC = investigator choice chemotherapy, DTIC = dacarbazine, BRAFi = BRAF inhibition, MEKi = MEK inhibition.

2-year OS for patients who received nivolumab was 68.3% for patients with ≥ 5% PD-L1 expression and 54.2% for those with < 5% PD-L1 expression. Treatment-related severe adverse events were observed in 10–13% of patients and comprised fatigue, pruritus, nausea, diarrhea, and rash. Frequent laboratory abnormalities under nivolumab treatment are increased levels of serum lipase and alanine aminotransferase [23].

Ipilimumab plus Nivolumab

Several studies provide strong evidence that a primary combination of CTLA-4 and PD-1/PD-L1 blockade is more effective than the respective monotherapies (table 2). High response rates and improvement of PFS and OS were already evident in 2 early phase trials investigating ipilimumab and nivolumab [24, 25]. However, the pivotal study for this drug combination was the 3-armed phase III trial CheckMate 067 in which 945 treatment-naïve patients with unresectable or metastatic disease were randomized 1:1:1 to nivolumab plus ipilimumab, nivolumab alone, or ipilimumab alone, with PFS and OS as co-primary endpoints [26]. Data on the first parameter have already been published and revealed a response rate of 58% for the combination, 44% for nivolumab alone, and 19% for ipilimumab alone. Median PFS was 11.5, 6.9, and 2.9 months, respectively. The clinical benefit provided by the combination was most evident in patients with PD-L1-negative tumors. However, this high antitumor efficacy was accompanied by a high frequency of severe immune-related adverse events. In the combination cohort, virtually all patients experienced at least 1 side effect, while 57% showed an event of grade 3 or 4. In 39% of all patients the combination therapy had to be stopped due to side effects such as diarrhea with colitis or hepatitis with elevated liver enzymes. However, no treatment-related death occurred in the combination arm of the study, and 85–100% of the severe adverse events were managed successfully and fully reversed with the appropriate therapeutic measures [26].

A post-hoc analysis on patients who discontinued ipilimumab and nivolumab due to severe adverse events in the phase II trial CheckMate 069 was recently presented [27]. After a minimum follow-up of 2 years, median PFS and OS were still not reached in randomized patients receiving ipilimumab and nivolumab and those who discontinued treatment. Thus, the treatment effects of this combination appeared durable with clinical benefit even for patients who discontinue therapy early [27].

Ipilimumab plus Pembrolizumab

The combination of ipilimumab and pembrolizumab has been assessed in the phase I/II trial KEYNOTE-029 for melanoma and renal cell carcinoma. Pembrolizumab was administered at 2 mg/kg body weight every 3 weeks with 4 cycles of ipilimumab at 1 mg/kg body weight. Recent data after a median follow-up of 10 months suggested that this combination was tolerable, as 72% of patients received all 4 doses of ipilimumab and no treatment-related deaths were observed. Severe immune-related adverse events were reported in 25% of patients. The best overall response rate was 57%. However, no phase III trial data are available for pembrolizumab and ipilimumab to date [28].

Triple Combination Therapy

Combining tyrosine kinase inhibitors with immune checkpoint blockade may result in additional synergism. The triplet combination of BRAFi, MEKi, and anti-PD-1 showed high antitumor efficacy in preclinical studies. The phase I/II trial KEYNOTE-022 evaluates the combination of dabrafenib, trametinib and pembrolizumab in BRAFV600-mutated melanoma [29]. The dose-finding part demonstrated a manageable toxicity profile of the approved single-agent doses (dabrafenib 150 mg BID, trametinib 2 mg QID, pembrolizumab 2 mg/kg Q3W). 12 out of 13 patients (92.3%) showed a decrease from baseline in the size of the target lesions. Phase II of this trial is currently further evaluating the safety and efficacy of this triplet combination compared to dabrafenib and trametinib plus placebo [29].

Conclusion

Patients with a BRAFV600 mutation should receive upfront BRAFi and MEKi as first- or second-line therapy. Currently, 2 combination regimens have been approved by the EMA: dabrafenib plus trametinib and vemurafenib plus cobimetinib. They have similar antitumor efficacy but a distinct profile of adverse events. For BRAF mutation-positive patients, the ideal sequence of targeted therapy with kinase inhibitors and immune checkpoint blockade is unclear and depends on the clinical course and individual patient characteristics.

Pembrolizumab and nivolumab show higher response rates compared to ipilimumab and fewer severe immune-related adverse events. However, the optimal treatment duration for these agents has not been defined yet and long-term data are still lacking. Unprecedented efficacy was recently yielded with combined CTLA-4 and PD-1 blockade, although more than half of all treated patients experienced an adverse event of grade 3 or 4. However, no treatment-related deaths were recorded and the events could be adequately managed with close clinical monitoring early immunosuppression.

Disclosure Statement

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