The therapeutic landscape of advanced melanoma

Erika Richtig

Received: 29 January 2020 / Accepted: 10 March 2020 / Published online: 15 April 2020
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Summary The therapeutic landscape of advanced and metastatic melanoma has changed dramatically in the last ten years. Targeted therapies as well as checkpoint inhibitors and oncolytic viruses have launched a broad revolution within this field. First presented at ASCO 2011, changes in melanoma treatment giving “light at the end of the tunnel” have also changed the treatment of many other tumor entities. So oncologists all over the world can offer their patients these treatment options with higher efficacy than we ever had. But despite all optimism we are still losing about half of our patients with metastatic melanoma along the way. In this short review the therapeutic landscape of advanced melanoma is described.

Keywords Melanoma · Checkpoint inhibitor · Targeted therapy · Oncolytic virus · Brain metastasis

Immune checkpoint inhibitors

Programmed cell death protein (PD-1) inhibitors are nowadays the backbone of most melanoma treatments, in many cases as the first-line treatment option. Pembrolizumab and nivolumab in treatment-naïve patients show overall survival of over 40% at 5 years. Better data were presented for the combination of the cytotoxic T-lymphocyte-associated Protein (CTLA)-4 antibody in combination with nivolumab at ESMO 2019 in Barcelona by James Larkin et al. [1]. In this study unresectable or metastatic melanoma patients were randomized 1:1:1 in the first arm of ipilimumab three milligram per kilo-

gram every 3 weeks in combination with nivolumab one milligram per kilogram for four doses followed by nivolumab three milligram per kilogram every 2 weeks. The second arm was nivolumab three milligram per kilogram every 2 weeks with ipilimumab-matched placebo and the third arm was ipilimumab three milligram per kilogram every 3 weeks for four doses with nivolumab-matched placebo. Overall survival for those patients treated with ipilimumab and nivolumab at the 5-year follow-up were 52% compared to nivolumab 44% and ipilimumab 26%, giving a hazard ratio of 0.83. The median progression-free survival (PFS) for ipilimumab and nivolumab was 11.5 months, nivolumab 6.9 months and ipilimumab 2.9 months. Patients with BRAF-mutated melanoma (V600) performed even better with overall survival rates of 60% in the ipilimumab and nivolumab arm at the 5-year follow-up compared to nivolumab (46%) and ipilimumab (30%). In BRAF wild-type patients the difference between the study arms were less giving overall survival of 48% for ipilimumab and nivolumab patients compared to 43% for nivolumab patients and 25% for ipilimumab patients. The improved overall survival of ipilimumab and nivolumab was independent of baseline PDL-1 expression and baseline LDH levels. The best overall response rates for ipilimumab and nivolumab was 58% followed by nivolumab 45% and ipilimumab 19%. In the intent-to-treat (ITT) population median duration of response was not reached in either the ipilimumab and nivolumab arm or in the nivolumab arm. A higher proportion of patients were alive and treatment free at 5 years in the nivolumab and ipilimumab arm (74%) compared to nivolumab (58%) and ipilimumab (45%).

The KEYNOTE-006 study answered the question about the outcome of the patients treated with pembrolizumab for 2 years where the treatment was stopped at this time point. These follow-up data

E. Richtig (✉)
 Department of Dermatology, Medical University of Graz,
 Auenbruggerplatz 8, 8036 Graz, Austria
erika.richtig@medunigraz.at

after 2 years after cessation of treatment were presented at ASCO 2018 by Georgina Long et al. showing that a high percentage patients with complete remission remained in complete remission. Over 80% of patients with a partial remission remained in partial remission and even more than 50% of patients with a stable disease remained stable after stopping treatment. These data were amended by the 5-year follow-up data by Robert C et al. [2].

The results regarding salvage therapy after failure from anti PD-1 single agent treatment were presented by Weichenthal et al. at ASCO 2019. The study showed that ipilimumab and nivolumab after failure of PD-1 treatment had 19% objective remissions and 44% disease control rates. These results were comparable to the re-challenge of BRAF and MEK inhibitors with 22% objective remissions and 50% disease control rates. Other treatment options (e.g., chemotherapy, T-VEC) showed better objective remissions and disease control rates than ipilimumab monotherapy [3].

Ongoing combination studies with PD-1 antibodies in combination with LAG-3 antibodies, NKTR 214 and other checkpoint inhibitors are focusing on better response rates and less toxicity.

Brain metastases

Brain metastases are a frequent problem in metastatic melanoma patients as melanoma is one of the most frequent tumors that metastasize to the brain. BRAF and MEK inhibitors as well as checkpoint inhibitors have been shown to cross the blood–brain barrier and to be able to achieve fascinating response rates. Thus, whole-brain radiation treatment has become less frequent giving space to stereotactic radiotherapy—in some cases applied only to “stimulate the immune system” before systemic treatment. Long-term outcomes from the randomized phase II study of nivolumab or nivolumab plus ipilimumab in patients with melanoma brain metastases were presented at ESMO 2019 by Georgina Long [4]. In asymptomatic patients intracranial response was achieved in 51% of patients in the nivolumab and ipilimumab arm and 20% in the nivolumab arm. In treatment-naïve patients response rates were even better in the nivolumab and ipilimumab arm (59%). The median intracranial progression-free survival was 5.4 months for nivolumab and ipilimumab compared to 2.5 months for nivolumab. Symptomatic patients showed median PFS of 2.6 months but only 6% intracranial responses. Overall survival rates achieved after 3 years in the nivolumab and ipilimumab arm are 49% compared to 42% in the nivolumab arm and 19% in the nivolumab arm with symptomatic patients. Intracranial and extracranial responses were mostly concordant. Interestingly activity of nivolumab plus/minus ipilimumab was low after BRAF/MEK inhibitors, after multiple modality therapies and in

patients with leptomeningeal/symptomatic intracranial melanoma.

Targeted therapies

Targeted therapies with BRAF and MEK inhibitors show impressing tumor responses in a short time and are used in patients where quick response is urgently needed.

The 5-year analysis of dabrafenib plus trametinib in patients with BRAF V-600 mutated melanoma was presented at ASCO 2019 by Paul Nathan (pooled analysis of Combi-v and Combi-d) [5]. The 5-year PFS was 19% (median PFS 11.1 months). In patients with normal LDH levels PFS at 5 years was 25% compared to 8% in patients with elevated LDH levels. The 5-year overall survival was 45%. Patients with normal LDH levels achieved 43% and patients with normal LDH and at less than 3 organ sites showed even 54% overall survival (Robert et al. [2]). At ASCO 2019, Liszkay et al. presented the 4-year data of the Columbus study with encorafenib and binimetinib [6]. Overall survival of the combination with 450 mg encorafenib and binimetinib was 39% compared to 25% of vemurafenib; progression-free survival was 25% of the Combo450 versus 12% vemurafenib.

Different triple combinations with BRAF and MEK inhibitors in combination with anti-PD-1 and anti-PDL-1 antibodies are still under investigation. Updated efficacy and safety from parts 1 and 2 of combi-i study (anti-PD-1 antibody spartalizumab in combination with dabrafenib and trametinib in previously untreated patients with advanced BRAF V600-mutant melanoma) were described by Georgina Long et al. in a poster presentation at ASCO 2019 [7]. More than 40% of patients treated with spartalizumab + dabrafenib + trametinib had confirmed complete responses, ongoing at the time of data cut-off in 67% (10 of 15) of patients. Of the patients with CR, 20% (3 of 15) had elevated baseline LDH levels. The median PFS was 23.7 months and 10.7 months in patients with elevated baseline LDH levels. Grade ≥ 3 AEs occurred in 78% of patients, and AEs leading to discontinuation of all 3 study drugs occurred in 6 (17%) patients.

Data of a phase III randomized study presented at ESMO 2019 comparing cobimetinib and atezolizumab versus pembrolizumab did not meet its primary endpoint of PFS [8]. The combination of cobimetinib plus atezolizumab did not demonstrate an improvement in PFS compared to pembrolizumab monotherapy in patients with BRAF V-600 wild-type locally advanced or metastatic melanoma.

T-VEC

Oncolytic viruses aim to selectively infect tumor cells and are able to lyse them without harming normal tissues. Talimogene laherparepvec (T-VEC) is

based on a HSV-1 virus and is licensed for stage IIIB, IIIC and IV M1a with no bone, brain, lung or other visceral metastases. The Optim study comparing T-VEC intralesional to subcutaneous GM-CSF (stage IIIB–IVM1c melanoma) showed durable response rates and best overall responses of T-VEC with 40.5% compared to 2.3% in the GM-CSF arm in the subpopulation leading to approval in stage IIIB/IIIC and IV M1a. At ESMO 2019 Middleton et al. presented a poster with a retrospective analysis of OPTiM assessed T-VEC in patients with unresectable AJCC 7 stage IIIB/C melanoma who had locoregional disease, including intralymphatic local, satellite, and regional cutaneous/subcutaneous metastases as the site of first recurrence following primary surgery [9]. T-VEC versus GM-CSF led to objective response rates of 56% vs 1%, CR rates of 24% vs 0%, and durable response rates of 34% vs 0%. Median overall survival was not reached with T-VEC versus 25 months with GM-CSF. The locoregional subpopulation experienced higher T-VEC efficacy versus the entire study population.

Take home messages

Checkpoint inhibitors, targeted therapies and T-VEC as oncolytic virus have dramatically changed the therapeutic landscape of locally advanced and metastatic melanoma. Despite these advances, the choice of which best treatment option for the individual patient still remains with the treating physician.

Funding Open access funding provided by Medical University of Graz.

Conflict of interest E. Richtig declares speakers fees, congress supports, and honoraria for advisory boards from Almirall, Amgen, AstraZeneca, BMS, GSK, MSD, Merck, Novartis, Pierre Fabre, Roche, and Sanofi.

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