Highlights in melanoma

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ASCO 2019 featured the presentation of several interesting studies in patients with metastatic melanoma. In addition to this, new data in the (neo)-adjuvant setting were presented.

HIGHLIGHTS IN METASTATIC MELANOMA

A Phase III international trial of adjuvant whole brain radiotherapy (WBRT) or observation following local treatment of 1-3 melanoma brain metastases was presented.[1]

As known, patients with stage IV melanoma are at high risk of developing brain metastasis. The risk can go up to 25% within the first year and up to 40% within the first 2 years of disease progression. While surgery and stereotactic radiosurgery (SRS) are highly effective for individuals with a single, or only a few metastases, these patients are at a high risk of developing subsequent new brain metastases. The effect of WBRT *vs.* observation was therefore investigated following local treatment with SRS in patients with 1 to 3 melanoma brain metastases. The primary endpoint was distant intracranial failure within 12 months of randomization. Between 2009 and 2017, 207 eligible, consenting patients from 31 sites across Australia, the United Kingdom and Norway were randomized to receive WBRT (30 Gy in 10 fractions; N= 100) or observation (N= 107) after local treatment. Overall, 61% of patients had a single brain metastasis (mean size, 2 cm) and 67% had extracranial disease. Any form of systemic therapy was permitted during the trial. The median follow-up of the study was 48 months and the treatment completion rate for WBRT was 97%. At 12 months, 50.5% of patients in the observation group (54 of 107 patients) and 42% of patients randomized to radiotherapy (42 of 100 patients) suffered distant intracranial failure (hazard ratio [HR], 1.28; 95% confidence interval [CI], 0.89–1.84; p= 0.16). No differences were observed between the groups in terms of local failure (p= 0.100). Regarding overall survival (OS), 54% of patients in the observation group compared with 58.4% of those in the radiotherapy group were alive at 12 months (log-rank p= 0.89). Patients who received WBRT experienced higher grade 1/2 fatigue (68.2% *vs.* 28.1), nausea (33% *vs.* 15.7%), alopecia (62.4% *vs.* 4.4%), and dermatitis (11.8% *vs.* 0%; all p<0.001) than patients in the observation group. In conclusion, WBRT should no longer be offered to patients with melanoma brain metastases.

At ASCO 2019, data were presented on the efficacy and safety of the combination of nivolumab plus ipilimumab in patients with symptomatic melanoma brain metastases.[2] In this trial, melanoma patients whose disease had spread to the brain were treated with dual PD-1 (nivolumab) and CTLA-4 (ipilimumab) checkpoint immunotherapy, followed by PD-1 immunotherapy alone. Of patients whose metastatic lesions were not active, 54% responded and 63% remained progression-free at the six-month landmark. More than half of all patients are still alive after a median follow-up of almost 21 months. Of the patients whose metastatic tumors were symptomatic, only 22% responded, although half of them saw their tumors completely disappear. Sixty-six percent of the patients in this group survived at least six months, and half the patients survived at least 8.7 months.

ASCO 2019 also featured the presentation of 5-year follow-up data in patients diagnosed with BRAF-V600-mutant metastatic melanomas after a first-line treatment with dabrafenib plus trametinib.[3] These data were the result of a pooled analysis of patients treated with dabrafenib plus trametinib in the phase 3 COMBI-d (*vs.* dabrafenib + placebo, N= 211) and COMBI-v (*vs.* vemurafenib, N= 352) trials. The trials enrolled patients with previously untreated BRAF V600E/K–mutant unresectable or metastatic melanoma. Patients received dabrafenib 150 mg twice daily plus trametinib 2 mg once daily *vs.* either dabrafenib + placebo (COMBI-d) or vemurafenib

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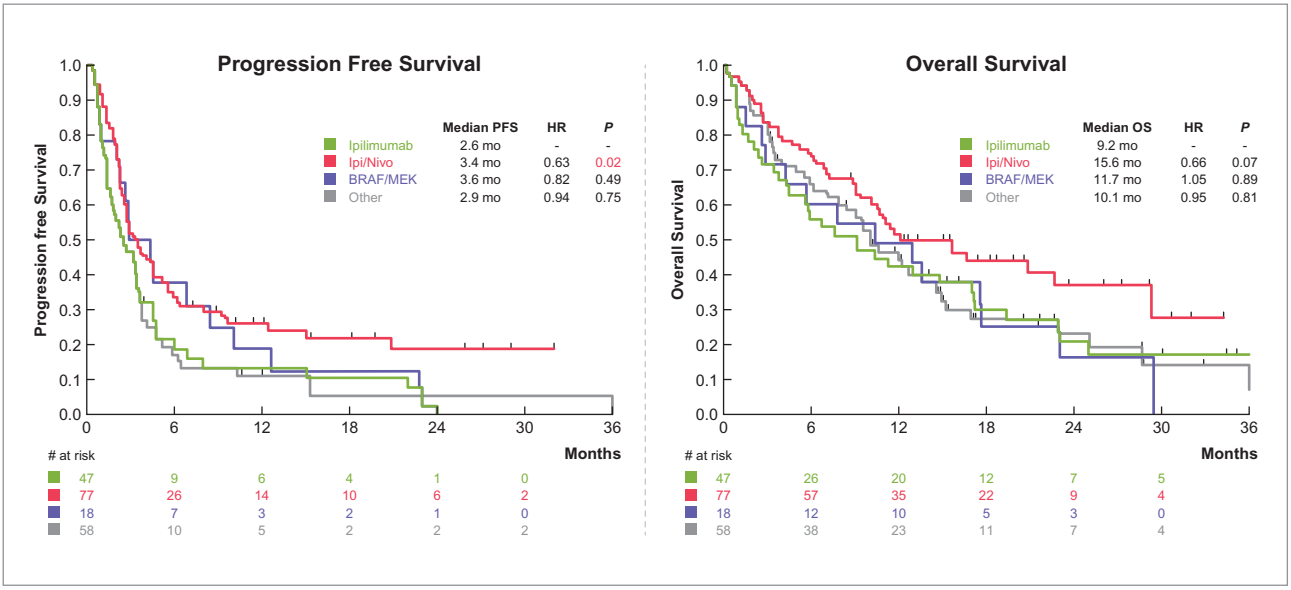

FIGURE 1. Progression Free Survival and Overall Survival with different treatment options after anti-PD-1 failure.[2]

(COMBI-v). This analysis represented the largest data set and longest follow-up in previously untreated patients with *BRAF* V600-mutant unresectable or metastatic melanoma treated with BRAF and MEK inhibitors. Five years out, one-third of patients remained alive following treatment with the dual targeted therapy, and 1 in 5 (19%) remained alive without progression. Patients who achieved a complete response (CR) had the best odds of attaining long-term benefit. Lower baseline tumor burden and less-aggressive tumor biology were associated with prolonged progression-free survival (PFS) and overall survival (OS).

In addition to this, updated results on safety and efficacy from parts 1 and 2 of the COMBI-i study were presented.[4] Encouraging results were obtained with a first-line "triplet therapy" consisting of the PD-1 inhibitor spartalizumab (an anti-PD-1 monoclonal antibody), dabrafenib and trametinib in patients with advanced BRAF V600-mutant melanoma. Of the 36 patients enrolled in the study, 36% had stage IV M1c with elevated levels of lactate dehydrogenase (LDH), and 19% had stage IV M1c with normal LDH levels. "Triplet therapy" resulted in overall response rate (ORR) of 78% by investigator assessment and a CR in 42% (at a median follow-up of 19.9 months). The median duration of response (DoR) was 20.7 months with a 12-month DoR rate of 80.3%. In 10 of the 15 patients with a CR the response was ongoing at the time of the analysis (66.7%). The 12-month PFS rate was 66.7% and the median OS was not yet reached (8 [22%] patients had died, of which 7 had an elevated LDH level at baseline). All patients experienced at least 1 adverse event (AE) of any grade, and serious AEs occurred in 64% of the patients. Pyrexia was the most common AE, occurring in 32 (89%) patients. There were no treatment-related deaths. In all patients, adverse events led to dose adjustments or interruptions. Adverse events led to discontinuation of any study drug in 17 (47%) patients and discontinuation of all 3 study drugs occurred in 6 (17%) patients. Correlative data from the biomarker cohort were presented in a separate poster. All patients had a consistent increase in T-cell inflamed gene expression signature levels from baseline to biopsy at 2 to 3 weeks. At data cut-off, 5 of 22 patients with DNA- and RNA-sequencing data available had a PFS event. Those with a PFS event prior to 12 months had relatively cold tumors at baseline, characterized by low tumor mutational burden values, low T-cell inflamed gene expression signature levels, or high levels of immunosuppressive tumor microenvironment signatures compared with the patients without a PFS event. The global placebo-controlled, randomized part 3 of COMBI-i is currently ongoing.

According to results of exploratory retrospective analyses of patients with advanced melanoma enrolled in clinical studies with immune checkpoint inhibitors, low or undetectable baseline serum levels of the acute phase reactant, C-reactive protein (CRP), and a marker of chronic inflammation that enhances liver production of CRP, interleukin-6 (IL-6), were associated with improved clinical outcomes.[5] The researchers offered a possible rationale for these findings based on investigations of human T cells and dendritic cells from patients with melanoma. Results from this analysis showed a dose-dependent suppression of T-cell and dendritic cell function, decreased generation of antigen-specific T-cells, and inhibition of calcium flux in T-cells (a very early event in T-cell signaling and activation) when CRP levels were higher than 10 µg/

Systemic therapy; responses to first-line and subsequent therapy in evaluable patients (N=92 of 109)

Timing of initial recurrence	Systemic treatment	Best response				
		N	CR/PR	SD	PD	ORR
ON adj-PD1	Ipilimumab +/- anti-PD1	33	**8**	5	20	**24%**
	BRAF/MEKi	23	**18**	5	0	**78%**
	Anti-PD1 + novel agent	9	**1**	1	7	**11%**
	Anti-PD1	6	**0**	1	5	**0%**
OFF adj-PD1	Ipilimumab +/- anti-PD1	5	**2**	0	3	**40%**
	BRAF/MEKi	10	**9**	0	1	**90%**
	Anti-PD1 + novel agent	1	**0**	0	1	**0%**
	Anti-PD1	5	**2**	1	2	**40%**

FIGURE 2. A multicenter analysis of melanoma recurrence following adjuvant anti-PD1 therapy.[7]

mL. Therefore, serum IL-6 and CRP can be used as prognostic factors for checkpoint inhibition.

Treatment patterns and outcome of systemic therapy for patients after anti-PD-1 failure were analyzed by the German ADOReg melanoma registry.[6] Patients fulfilling several inclusion criteria were consecutively included until a number of 200 cases was reached. Treatment patterns of patients after anti-PD-1 (and BRAF-/MEK-inhibitors in BRAF V600mutant melanoma patients) failure differed remarkably. Although lower than reported in treatment naive patients, the combination of ipilimumab and nivolumab appeared more favorable as compared to all other regimens, except for BRAF-/MEK inhibitor re-challenge which produced similar remission rates (*Figure 1*). Chemotherapies, including dacarbazine, are still being used in clinical practice but these data indicate that this therapeutic approach is associated with a poor outcome.

Investigators from the Melanoma Institute Australia looked at stage 3-4 melanoma patients from 16 different institutions who, after their tumors were surgically removed, were treated with PD-1 immunotherapy (nivolumab) to prevent recurrence.[7] More than 800 patients were included in this analysis of whom 83% did not experience a disease recurrence. Among those who did have a recurrence under treatment, a change in treatment was recommended. Among those who experienced recurrence after their treatment ended, some of them responded after re-treatment with PD-1 immunotherapy alone or in combination with CTLA-4 immunotherapy as well as further treatment with targeted therapy against BRAF/MEK (*Figure 2*).

HIGHLIGHTS OF (NEO-)ADJUVANT THERAPY FOR MELANOMA

In another study conducted by the Melanoma Institute Australia and University of Sydney, investigators looked at six trials in which patients with stage 3 melanoma were treated prior to surgery with either PD-1 immunotherapy (nivolumab) or targeted therapy against BRAF/MEK.[8] Of the 184 patients analyzed, 41% had a pathological CR (pCR), meaning that less than 10% of their tumors remained viable prior to surgery. Overall, 65% remained relapse-free for at least two years, including 83% of those who were treated with immunotherapy. Remarkably, of the patients who had a pCR to immunotherapy, none had a recurrence to date.

Investigators at 9 sites in 9 countries enrolled 150 patients (intention-to-treat population) with high-risk resectable stage IIIB-IVM1a melanoma to study Talimogene laherparepvec (T-VEC) as a neo-adjuvant treatment of loco-regionally advanced melanoma.[9] The patients were randomized to immediate surgery or intralesional T-VEC, followed by surgery at week 13. The efficacy analysis included 57 patients who received at least one dose of T-VEC and next had surgery, and 69 patients who had immediate surgery. The safety cohort included 73 patients who received at least one dose of T-VEC, and 69 patients who had immediate surgery. There were no substantial differences in baseline characteristics of both treatment groups. The primary endpoint was relapse-free survival (RFS). In the efficacy analysis, 13 of 57 patients in the T-VEC arm had a pCR. By ITT analysis, the pCR rate was 17.1% (13 of 76) in the T-VEC arm. More patients in the T-VEC arm had R0 resection status (56.1% *vs.* 40.6%; p=

0.082). Rates of R1 resection were 42.1% and 55.1%, and R2 resection rates were 1.8% and 4.3% in the T-VEC and surgery-alone arms, respectively. At 1 year, 33.5% of patients who received preoperative T-VEC plus surgery remained recurrence free, as compared with 21.9% of patients who had surgery only (HR: 0.73; 80%CI: 0.56-0.93; p= 0.048). By ITT analysis, neoadjuvant T-VEC reduced the 1-year recurrence hazard by 27% (80%CI: 0.56-0.93). The median RFS was not reached in any of the treatment groups. Before the start of follow-up, RFS events had occurred in 56.6% of patients in the T-VEC arm (no surgery in 23.7% and lack of R0 resection in 32.3%) and in 60.8% of patients who underwent immediate surgery (5.4%, 55.4%, respectively). After a median follow-up of 20.4 months, the median OS had yet to be reached in either treatment group. More patients randomized to T-VEC were alive at 1 year (95.9% *vs.* 85.8%; HR: 0.47; 80%CI: 0.27-0.82; p= 0.076), but this difference did not reach statistical significance. Treatment-emergent adverse events in the T-VEC arm were consistent with previously reported data. The most commonly observed treatment-emergent adverse events were flu-like symptoms.

The United States Intergroup E1609 conducted a phase III randomized study of adjuvant ipilimumab versus high-dose interferon-α2b for resected high-risk melanoma.[10] In this trial, more than 1,000 patients with a surgically removed high-risk, stage 3-4 melanoma were subsequently treated with CTLA-4 checkpoint immunotherapy (ipilimumab, at one of two dose levels) or interferon-α2b. Compared to the interferon treatment, the lower dose of CTLA-4 immunotherapy was associated with a 22% reduction in the risk of death and a 15% reduction in the risk of recurrence. As such, this regimen performs slightly better than the higher dose of ipilimumab while resulting in less toxicity and allowing more patients to complete their treatment regimen. However, adjuvant therapy with anti-PD-1 antibody therapy (either nivolumab or pembrolizumab) or the combination of dabrafenib plus trametinib in BRAF V600-mutant melanoma patients have replaced both ipilimumab and interferon-a2b as standard of care adjuvant therapy in patients with lymph node melanoma metastases.

The EORTC 18071 study randomized 951 patients with high-risk, stage III, completely resected melanoma to receive ipilimumab (N= 475) or placebo (N= 476).[11] In the initial induction phase of the trial, ipilimumab was administered at 10 mg/kg every 3 weeks for 4 cycles. In a subsequent maintenance phase, ipilimumab was administered at 10 mg/kg every 12 weeks for a maximum of 3 years. Adjuvant ipilimumab resulted in a 25% reduction in the risk of recurrence or death compared with placebo for patients with surgically resected high-risk, stage III melanoma. In this updated analysis, which was conducted after 6.9 years of median follow-up, the estimated 7-year RFS rate was 39.2% (95%CI: 34.5%-43.9%) for ipilimumab compared to 30.9% (95%CI: 26.7%-35.2%) for placebo (HR: 0.75; 95%CI: 0.63-0.88; p< 0.001). At the 6.9-year analysis, 60.0% (95%CI: 55.0%-64.7%) of patients remained alive in the ipilimumab arm compared with 51.3% (95%CI: 46.5%-55.9%) in the placebo group (HR: 0.73; 95%CI, 0.60-0.89; p= 0.002). In 2015, the FDA (but not EMA) approved ipilimumab as an adjuvant therapy for patients with stage III melanoma with pathologic involvement of regional lymph nodes >1 mm who have undergone complete resection including total lymphadenectomy. Since this approval, the PD-1 inhibitor nivolumab was shown to be superior to adjuvant ipilimumab, leading to an FDA and EMA approval for the PD-1 inhibitor in 2017 and 2018 respectively. Overall, 81% of patients in the ipilimumab arm who experienced a recurrence went on to receive a second-line treatment, as compared with 87.3% in the placebo group. The most common subsequent treatments in the ipilimumab and placebo arms, respectively, were surgery (39.6% *vs.* 36.2%), chemotherapy (31.1% *vs.* 32.5%), a *BRAF* inhibitor (25.6% *vs.* 27.6%), or radiotherapy (15.4% *vs.* 19.2%). The trial was conducted before the widespread use of immunotherapy. As such, just 12% of patients received a subsequent PD-1 or PD-L1 inhibitor. The median OS following first recurrence event was 1.8 months in the ipilimumab arm as compared to 1.9 months with placebo (HR: 0.90; 95%CI: 0.74-1.10). The phase III CheckMate-915 trial is comparing nivolumab plus ipilimumab with nivolumab alone after complete resection of stage III or IV melanoma. The study enrolled 1,943 patients, with primary results anticipated in November 2020 (NCT03068455).

Several studies suggested that patients with an immune-related adverse event (irAE) during immunotherapy have better outcomes than those without. It remains uncertain whether these observations can be explained by guarantee-time bias or the role of irAE as an indicator of drug activity. The association between irAEs and RFS in patients was investigated in the double-blind EORTC 1325/KEYNOTE-054 trial.[12] The incidence of irAE in this trial that compared pembrolizumab to placebo in high-risk stage III melanoma was 37.3% in the pembrolizumab arm (N= 509) and 9.0% in the placebo arm (N= 502) (similar in males and females in both arms). The occurrence of an irAE was significantly associated with a longer RFS in the pembrolizumab arm (HR: 0.61, 95%CI: 0.39-0.95, p= 0.03). This was true for both males and females. However, in the placebo arm, no association between irAE incidence and RFS was observed (HR: 1.39, 95%CI: 0.83-2.32, p= 0.21). In a small single center phase II trial, investigators from the Brussels University Hospital (Brussels, Belgium) reported

that adjuvant low-dose regimens of nivolumab with or without low-dose ipilimumab have an acceptable safety profile in patients with resected melanoma macrometastases.[13] The irAE rate and severity was comparable to standard regimens, while also the survival rates resembled those of standard regimens. These regimens could therefore be economically advantageous alternatives for patients without access to standard regimens.

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