Combination approaches and anti-PD1 therapies: the focus of new research at ESMO and SMR

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Research into the treatment of melanoma is continuing to progress, and both the European Society of Medical Oncology (26–30 September, Madrid, Spain) and the Society of Melanoma Research (13–16 November, Zurich, Switzerland) 2014 annual meetings provided important updates in this field. Areas of particular focus included combinations of a BRAF inhibitor with a MEK inhibitor (COMBI-v and CoBRIM trials) and new data on anti-PD1 therapies (nivolumab and pembrolizumab). Overall, the data reported at these two meetings again suggest that melanoma is perhaps the most dynamic field of oncology, with continuing advances in management of the disease that may improve outcomes for patients in clinical practice.

The approval of four different classes of new therapies (the anti-CTLA-4 agent, ipilimumab; BRAF inhibitors [BRAFi]; MEK inhibitors [MEKi]; and the anti-PD-1 drugs, pembrolizumab and very recently nivolumab) in the last few years has revolutionized melanoma management, with the disease becoming a paradigm of drug development for other types of cancer. Research into the treatment of melanoma is continuing to progress, and both the European Society of Medical Oncology (ESMO, 26–30 September, Madrid, Spain) and the Society of Melanoma Research (SMR, 13–16 November, Zurich, Switzerland) 2014 annual meetings provided important updates in this field.

Adjuvant anti-CTLA4 therapy

In the adjuvant setting, the EORTC 18071 trial randomized 951 high-risk patients who had undergone complete resection of stage III cutaneous melanoma to ipilimumab or placebo [1]. The study met its primary end point with

relapse-free survival of 26.1 months for the ipilimumab arm compared with 17.1 months with placebo (hazard ratio [HR]: 0.75; 95% CI: 0.64–0.90; $p = 0.0013$). Despite a high percentage of patients (42%) with severe (grade 3–4) adverse events (AEs) in the ipilimumab group, no overall impact on health-related quality of life was observed. All AEs were treated according to well-known algorithms for the management of ipilimumab-associated immune-related AEs.

BRAFi

In the treatment of advanced disease, an update of the BREAK-3 Phase III trial that compared dabrafenib with dacarbazine in 250 *BRAF*-mutated patients was reported [2]. At a median follow-up of 2 years, the median overall survival (OS) was 20 months (95% CI: 16.8–24.4) in the dabrafenib arm versus 15.6 months (95% CI: 12.7–21.2) in the dacarbazine arm. A total of 45% of patients in the dabrafenib arm were still alive. Ten percent of dabrafenib-treated patients

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were still on treatment without progression while 9% had treatment beyond progression for more than 7 months. Significantly, 72% of patients on dabrafenib treatment without progression had a low baseline tumor burden. This characteristic was also previously described in a Phase I study of vemurafenib in which patients with a tumor burden less than 11.5 cm had a median OS of 27.1 months compared with 12 months in patients who had a tumor burden more than 11.5 cm [3]. Similarly, data reported for the Italian cohort of patients enrolled in the vemurafenib Expanded Access Program showed that patients with M1a and M1b stage disease (limited disease) had a better outcome than patients with a higher tumor burden (visceral disease or with elevated lactate dehydrogenase) [4]. At a median follow-up of 11.5 months, median OS was 12.9 months in patients with stage M1c disease but was not yet reached for patients with M1a and M1b stage.

The BREAK-3 study also provided further evidence in support of the finding from the BREAK-2 Phase II study of dabrafenib that the presence of circulating free DNA harboring the *BRAF*^{V600E} mutation (cfDNA^{*BRAF*^{V600E}}) is related to a worse overall response rate (ORR) and progression-free survival (PFS) [5]. In the Break-3 study, 44% of patients still on treatment with dabrafenib without progression had no detectable levels of cfDNA^{*BRAF*^{V600E}} [2].

BRAFi combination approaches

Also at ESMO, for the first time, the results of three important Phase III studies in advanced melanoma were reported in a presidential symposium, two of which involved combination approaches in *BRAF*-mutated patients. These were the COMBI-v study of dabrafenib plus trametinib versus vemurafenib and the CoBRIM study of vemurafenib plus cobimetinib versus vemurafenib alone.

The combination of a BRAFi with a MEKi represents a very promising strategy for patients with mutated *BRAF*^{V600} melanoma. In the USA, this combination was approved based on the results of a Phase I–II study of combined treatment with dabrafenib, a BRAFi and the MEKi, trametinib, in which PFS was 9.4 months compared with 5.8 months with dabrafenib monotherapy [6]. In another Phase III trial, the COMBI-d study of dabrafenib plus trametinib versus dabrafenib alone, median PFS was 9.3 months in the combination group and 8.8

months in the dabrafenib only group (HR for progression or death in the combination group: 0.75; 95% CI: 0.57–0.99; *p* = 0.03) [7]. The positive outcomes seen with dabrafenib monotherapy in this study may be attributed the inclusion of a high proportion of patients (about 70%) with normal lactate dehydrogenase levels, with these patients recognized to have an increased benefit from BRAFi treatment. However, the efficacy of dabrafenib monotherapy in this trial had the effect of somewhat reduce enthusiasm for the combined approach.

Because of this, there was much expectation for the results of the COMBI-v trial. In this study, 704 patients with advanced *BRAF*^{V600E/K} mutation-positive melanoma were randomized to first-line therapy with a combination of dabrafenib plus trametinib or vemurafenib monotherapy [8]. In a preplanned interim analysis after a median follow-up of 11 months, the primary end point of median OS was not reached in the dabrafenib plus trametinib arm but was 17.2 months with vemurafenib (HR: 0.69; 95% CI: 0.59–0.89; *p* = 0.002). Based on this analysis, the study was stopped early on the recommendation of the Independent Data Monitoring Committee. In addition, median investigator-assessed PFS was 11.4 versus 7.5 months (HR: 0.56; 95% CI: 0.46–0.69; *p* < 0.001) and the ORR was 64 versus 51%, with combination therapy and vemurafenib, respectively.

In the CoBRIM trial, previously untreated *BRAF*^{V600} mutation-positive patients with unresectable locally advanced or metastatic melanoma (*n* = 495) were randomized to receive vemurafenib plus cobimetinib or vemurafenib alone [9]. As in the COMBI-v study, patients receiving the combination therapy had significantly longer investigator-assessed median PFS than those receiving monotherapy (9.9 vs 6.2 months; HR: 0.51; 95% CI: 0.39–0.68; *p* < 0.001). Comparable results for PFS were observed when assessed by independent review (11.3 vs 6.0 months; HR: 0.60; 95% CI: 0.45–0.79; *p* < 0.001). ORR was 68% in the combination arm and 45% with vemurafenib alone. OS data are not yet mature. However, at a median follow-up of 7.3 months (range 0.5–16.5 months), HR for death was 0.65 (95% CI: 0.42–1.00; *p* = 0.046).

The effect of these two studies may be to change the standard of treatment for melanoma patients with the *BRAF*^{V600} mutation from monotherapy to combined BRAFi and MEKi

therapy. Efficacy of the two combinations, with regard to ORR, PFS and OS, was very similar (Table 1). However, safety profiles differed, with a higher occurrence of pyrexia (53%), nausea (35%), vomiting (29%) and hypertension (26%) with the dabrafenib plus trametinib combination, and more diarrhea (56%), fatigue (32%), photosensitivity (28%) and liver toxicity (16%) with the vemurafenib plus cobimetinib combination. These differences confirm previous observations of monotherapy with dabrafenib or vemurafenib.

Another combination approach presented at ESMO was encorafenib (LGX818), a BRAFi, plus LEE011, a CDK 4/6 inhibitor [10]. In a Phase I study, 28 patients with advanced melanoma harboring the *BRAF*^{V600} mutation (BRAFi naive or pretreated) received different dosages of encorafenib plus LEE011. Seven percent of patients reported a partial response and 46% reported stable disease. Treatment was well tolerated and showed activity, although this seems inferior to that observed with BRAF plus MEK inhibition. LEE011 is currently being assessed as part of a triple combination with encorafenib and binimetinib, an MEH inhibitor (NCT01543698).

Anti-PD1 treatments

At both meetings, interesting data on anti-PD1 therapies were reported (Table 2). At ESMO, the third study presented as part of the presidential symposium was the first Phase III trial with an anti-PD-1, the CA209–037 study of nivolumab versus investigator's choice of chemotherapy. In this study, 405 patients with advanced melanoma who had failed treatment with ipilimumab were randomized (2:1) to nivolumab or investigator's choice chemotherapy (dacarbazine or carboplatin plus paclitaxel) until progression or unacceptable toxicity [11]. The co-primary end points were ORR and OS, although OS data

were not available at the time of this analysis. In the nivolumab arm, the central review assessed response was 32% (95% CI: 24–41) for the nivolumab arm compared with 11% (95% CI: 4–23) with chemotherapy. Median duration of response had not been reached. Treatment-related AEs of grade 3–4 severity were reported for 9% of patients in the nivolumab arm and 31% in the chemotherapy arm.

Responses were evaluated according to the RECIST 1.1 criteria; however, it is notable that 8% of patients experienced progression using these criteria (progression in nontarget lesions, clinical progression or occurrence of new lesions) but subsequently had a reduction in target lesions of more than 30%. This demonstrates that the unconventional immune-related response previously observed for ipilimumab therapy [12] can also happen with nivolumab. As such, the use of immune-related response criteria should be considered in addition to the classic RECIST criteria when evaluating response to nivolumab.

In additional CA209–037 study data presented at the SMR congress, ORR was assessed in predefined subgroups [13]. ORR was higher in the nivolumab arm compared with chemotherapy in patients irrespective of whether PD-L1 positive (44 vs 9%) or PD-L1 negative (20 vs 13%). Although response to nivolumab therapy was higher in PD-L1 positive patients, a good proportion of PD-L1 negative patients also responded to treatment. ORR was 34% with nivolumab and 11% with chemotherapy in *BRAF* wild-type patients, and 23% with nivolumab and 9% with chemotherapy in *BRAF*-mutant patients. In patients with M1c stage disease, ORR in the nivolumab group was 28% compared with 11% in the chemotherapy group.

In addition to this pivotal Phase III study, updated data from a Phase I trial of nivolumab in

Table 1. Comparison of the efficacy of two different BRAF inhibitors plus MEK inhibitor combinations.

	ORR	Median PFS (months) investigator assessed	HR for disease progression	Median OS	HR for death	Median follow-up (months)
Dabrafenib/ trametinib	64%	11.4 (range 9.9–14.9)	0.56 (95% CI: 0.46–0.69) p < 0.001	NR (range 18.3–NR)	0.69 (95% CI: 0.59–0.89) p < 0.002	11
Vemurafenib/ cobimetinib	68%	9.9 (range 9.0–NR) 11.3 [†] (range 8.5–NR)	0.51 (95% CI: 0.39–0.68) p < 0.001 0.60 [†] (95% CI: 0.45–0.79) p < 0.001	NR	0.65 (95% CI: 0.42–1.00) p = 0.046	7.3 (range 0.5–16.5)

[†]Independent review assessed.

HR: Hazard ratio; NR: Not reached; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival.

Type of study	Main end point	ORR	Median PFS (months)	HR for disease progression	Median OS	HR for death	Median follow-up (months)
Keynote 002 study							
Advanced melanoma patients who progressed after ipilimumab treatment	PFS [†]	PEM 2 mg/kg: 21% PEM 10 mg/kg q3w vs ICC: 25% ICC: 4%	5.4 [‡] 5.8 [‡] 3.6 [‡]	0.57 [§] (95% CI: 0.45–0.73) p < 0.0001 0.50 [§] (95% CI: 0.39–0.64) p < 0.0001	NR	NR	10
CA209-037 study							
Advanced melanoma patients who progressed after ipilimumab treatment	Phase III two arms trial: NIV 3 mg/kg q3w vs ICC	NIV: 32% ICC: 11%	NR	NR	NR	NR	Analysis performed in the first 120 NIV with ≥6 months of follow-up
CA209-066 study							
Untreated advanced melanoma BRAF wild-type	Phase III two arm trial: NIV 3 mg/kg q3w vs D	NIV: 40% D: 14%	5.1 2.2	0.43 (95% CI: 0.34–0.56) p < 0.0001	Not reached 10.8	0.42 (99.79% CI: 0.25–0.73) p ≤ 0.0001	NIV: 8.9 D: 6.8

[†]The study allowed cross-over from chemotherapy to pembrolizumab.

[‡]This data represents the mean PFS.

[§]Pembrolizumab 2 mg/kg q3w vs chemotherapy.

[¶]Pembrolizumab 10 mg/kg q3w vs chemotherapy.

D: Dacarbazine; HR: Hazard ratio; ICC: Investigator's choice chemotherapy; NIV: Nivolumab; NR: Not reported; ORR: Overall response rate; OS: Overall survival; PEM: Pembrolizumab; PFS: Progression-free survival; q3w: Every 3 weeks.

ipilimumab-naïve patients with metastatic melanoma confirmed findings previously presented at ASCO this year, with an ORR of 32% observed for all treated patients and an ORR of 40% for the cohort of patients treated with the 3 mg/kg dosage selected for Phase III studies [14]. The 1-, 2-, 3- and 4-year OS rates were 63, 48, 42 and 32%, respectively [15].

An update on a Phase IB study with pembrolizumab included an additional cohort of 244 patients (both ipilimumab-naïve and those previously treated with ipilimumab) who were randomized to one of two dosing schedules (10 mg/kg every 3 weeks [q3w] or 10 mg/kg every 2 weeks) [16]. Overall, no differences were reported between schedules in terms of ORR, PFS or OS or between ipilimumab-naïve and pretreated patients.

Further data on pembrolizumab were reported at the SMR congress, from the KEYNOTE 002 Phase II study of two different dosage of pembrolizumab versus chemotherapy. In this study, patients with advanced melanoma who progressed on ipilimumab treatment (≥2 cycles) were randomized to pembrolizumab at different dosage (2 mg/kg q3w and 10 mg/kg q3w) or investigator's choice chemotherapy (paclitaxel plus carboplatin, paclitaxel alone, carboplatin alone, dacarbazine or temozolomide) [17]. The primary end point was PFS and the study allowed the cross-over from the chemotherapy arm with subsequent randomization to the two different pembrolizumab dosages. The median PFS was 2.9 months in both the pembrolizumab arms and 2.7 months in the chemotherapy arm. Mean PFS was 5.4 months with pembrolizumab 2 mg/kg, 5.8 months with pembrolizumab 10 mg/kg arm and 3.6 months with chemotherapy. The PFS rate was 34, 38 and 16%, respectively, at 6 months, and 24, 29 and 8%, respectively, at 9 months. HR was 0.57 (95% CI: 0.45–0.73; p < 0.0001) for the pembrolizumab 2 mg/kg arm and 0.50 (95% CI: 0.39–0.64; p < 0.0001) for the pembrolizumab 10 mg/kg arm. ORR was 21, 25 and 4% for pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg and chemotherapy, respectively. Median duration of response was not yet reached for the two pembrolizumab arms but was 37 weeks with chemotherapy. There were no statistical differences in terms of PFS, ORR and duration of response between the two different dosage schedules of pembrolizumab. Pembrolizumab was well tolerated with a safety profile consistent with data

previously reported in the Phase I trial. These data confirm the efficacy of pembrolizumab in the treatment of melanoma and support the choice of the 2 mg/kg q3w schedule approved by the US FDA.

Another study of particular importance reported at SMR was the CA209-066 Phase III trial for first-line treatment of patients with *BRAF* wild-type advanced melanoma with nivolumab or dacarbazine [18]. Further detail on the study has been eagerly anticipated since a press release in June of this year announcing that the trial had been stopped early following an analysis by the independent Data Monitoring Committee that showed evidence of superior OS in patients receiving nivolumab compared with the dacarbazine arm. In this study, median OS was not reached for nivolumab and was 10.8 months for dacarbazine. The 1-year survival rate was 73% for nivolumab versus 42% for dacarbazine and there was a 58% decrease in the risk of death for patients treated with nivolumab (HR: 0.42; 99.79% CI: 0.25–0.73; $p < 0.0001$). Median PFS was 5.1 months with nivolumab and 2.2 months with dacarbazine (HR: 0.43; 95% CI: 0.34–0.56; $p < 0.0001$). ORR was also significantly higher for nivolumab than dacarbazine (40 vs 14%, $p < 0.0001$). Complete responses were observed in 7.6% of nivolumab-treated patients compared with just 1% of patients treated with dacarbazine.

This survival advantage with nivolumab was observed in both PD-L1 positive and PD-L1 negative patients. Median OS was not reached in either PD-L1 subgroup in the nivolumab arm, while in the dacarbazine arm median OS was slightly longer in the PD-L1 positive subgroup (12 vs 10 months). The safety profile of nivolumab in this study confirmed observations from previous studies. Fewer patients had treatment-related Grade 3/4 AEs with nivolumab than dacarbazine (11.7 vs 17.6%), with most of these being managed using established safety algorithms, and there were also fewer treatment discontinuations with nivolumab (6.8 vs 11.7%).

Finally, the combination of nivolumab plus ipilimumab was shown to be effective independent of patients *BRAF* and PD-L1 status in a Phase I trial (CA209-004) that confirmed results reported at ASCO earlier this year. Patients receiving concurrent ipilimumab plus nivolumab achieved an ORR of 40% with 17% being complete responses [19]. In a sequentially treated cohort, the ORR was 44% with 6% of patients having a complete response. The 1-year and 2-year OS rates for all patients were 85 and 79%, respectively, while in patients with the dose selected for the Phase III study, the 1-year and 2-year OS rates were 94 and 88%. However, this exceptionally good efficacy was accompanied by grade 3–4 AEs being reported for 64% of patients, although there was no new safety signal and immune-related AEs could generally be managed by following guidelines.

To conclude, important clinical trial data reported at ESMO and SMR again suggest that melanoma is the most dynamic field of oncology, with rapid progress being made in the development of new and effective compounds that can impact on the management of patients with melanoma in clinical practice. With the discovery of the ‘fantastic four’ of ipilimumab, BRAFi, MEKi and anti-PD-1 agents, the prognosis of this disease has been deeply revised. In particular, novel combination approaches together with positive outcomes with anti-PD1 therapy offer new opportunities to improve outcomes for our patients.

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