Highlights in melanoma

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The introduction of immune checkpoint inhibitors and the combined use of BRAF and MEK inhibitors dramatically changed the treatment landscape of advanced melanoma over the last decade. The success of these agents in the advanced setting formed the basis to also evaluate these drugs in less advanced disease stages. During ESMO 2018 updates were given on the adjuvant use of dabrafenib and trametinib in resected stage III melanoma patients. In addition to this, results were presented on the use of immune checkpoint inhibitors in the neo-adjuvant setting. In the advanced melanoma setting, the most important data came from the four-year survival update of the CheckMate 067 trial and the presentation of the Keynote-022 study, in which the immune checkpoint inhibitor pembrolizumab was used in combination with dabrafenib and trametinib in the first-line treatment of BRAF-mutation positive advanced melanoma.

EARLY STAGE MELANOMA

SUSTAINED RELAPSE FREE SURVIVAL BENEFIT WITH ADJUVANT DABRAFENIB-TRAMETINIB IN RESECTED, STAGE III, BRAF-MUTANT MELANOMA

Two randomised, phase III clinical trials, COMBI- and COMBI-v, showed that treatment with dabrafenib + trametinib improved the overall survival (OS) in patients with unresectable or metastatic melanoma harbouring a *BRAF*$^{V600E/V600K}$ mutation. Whether the therapy improved survival in stage III (resectable) melanoma was assessed in the COMBI-AD trial. In COMBI-AD, 870 patients with resected, *BRAF*-mutant stage III melanoma were randomised to receive dabrafenib + trametinib or placebo. As reported last year, the primary analysis of this trial showed a 3-year relapse-free survival (RFS) rate of 58% with the combination therapy and 39% with placebo (HR[95%CI]: 0.47[0.39-0.58], p< 0.001).[1] The analyses presented at ESMO 2018 included updates on RFS and distant metastasis-free survival (DMFS) with extended follow-up. The analysis occurred after a median follow-up of 44 months, 11 months longer than the follow-up for the primary analysis. At 4-years, the RFS rate with dabrafenib + trametinib was 54% as compared to 38% with placebo. The updated analysis revealed a HR for RFS of 0.49 (95%CI: 0.40-0.59).[2] The DMFS rate at 4 years was 67% with the combination therapy *vs.* 56% with placebo (HR[95%CI]: 0.53[0.42-0.67]). In addition, cure-rate modelling indicated that a higher proportion of patients is estimated to be free of relapse long-term with dabrafenib + trametinib than with placebo (estimated cure rates 54% *vs.* 37%). Finally, a biomarker analysis showed that genetic alterations in the MAPK pathway were not associated with clinical outcome or with response to therapy. In contrast, immune gene expression evaluation did identify signatures that were strongly prognostic for RFS. In both the combination and placebo arms, a high interferon-gamma signature predicted a prolonged RFS. Combining interferon-gamma gene signature with tumour mutation burden (TMB) further increased the prognostic power. In the placebo arm, a high interferon-gamma signature and high TMB were associated with the best RFS, whereas low interferon gamma and a low TMB was associated with the worst RFS. The other combinations fell in between. Repeating the analyses

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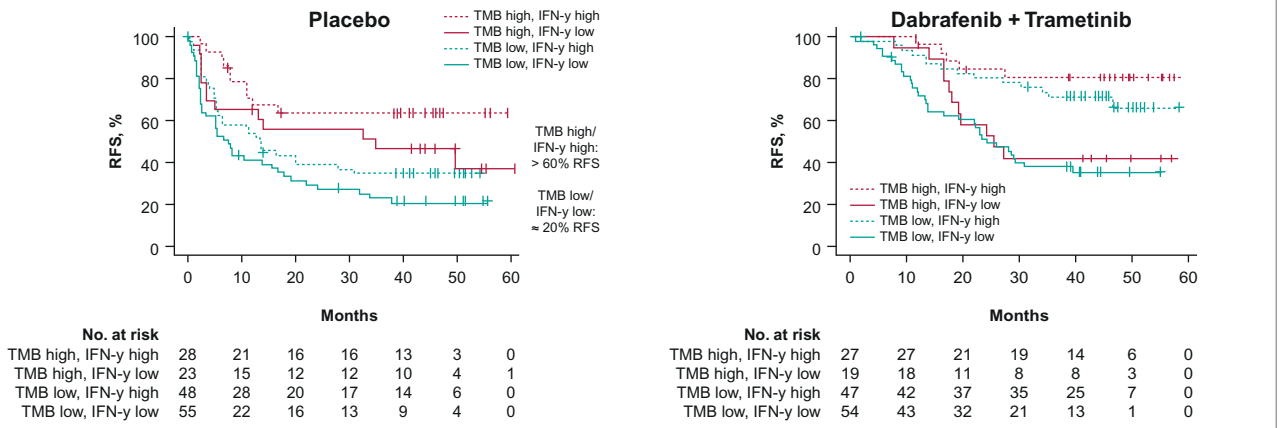

FIGURE 1. High TMB adds positive prognostic value to immune gene signatures in the placebo arm of COMBI-AD. In the dabrafenib-trametinib arm, interferon gamma gene signature identified patients with a longer RFS, independently of the TMB status.[2]

for the combination arm, the investigators found that prognosis was driven more by the interferon gamma. However, in comparisons with the placebo group, dabrafenib + trametinib prolonged three of the four combinations of TMB and interferon gamma. Only the high TMB/low interferon-gamma combination was not associated with an improved RFS with the combination (*Figure 1*).[2]

NEOADJUVANT POTENTIAL OF IMMUNE CHECKPOINT INHIBITORS: RESULTS OF THE OPACIN-NEO TRIAL

In the previous phase Ib OpACIN study, neoadjuvant ipilimumab plus nivolumab provided a pathological response rate (pRR) of 78%, and none of the patients who achieved a pathologic response in that trial has relapsed to date. Unfortunately, toxicity was high in this trial, with 90% of patients experiencing grade 3/4 immune related adverse events (irAEs). This forced investigators to evaluate alternative dosing regimens that could preserve this high response rate while minimising toxicity. The subsequent multicentre phase II, OpACIN-neo trial randomly assigned 86 patients with resectable macroscopic stage III melanoma (1:1:1) to receive standard therapy comprising 2 doses of ipilimumab at 3 mg/kg plus nivolumab at 1 mg/kg every 3 weeks (arm A), or 2 doses of ipilimumab at 1 mg/kg plus nivolumab at 3 mg/kg every 3 weeks (arm B), or to receive 2 doses of ipilimumab at 3 mg/kg every 3 weeks followed immediately by 2 doses of nivolumab at 3 mg/kg every 2 weeks (arm C). Eligible patients were required to have one or more measurable lymph node metastases (RECIST v1.1), no in-transit metastases within the last 6 months, and normal LDH levels. A complete lymph node dissection was scheduled at week 6. The primary endpoints were grade ≥3 irAEs within the first 12 weeks, radiologic RR according to RECIST v1.1, and pRR, which was defined as less than 50% of viable tumour cells.[3]

At a median follow-up of 7.7 months, the Data Safety Monitoring Board recommended early closure of arm C due to toxicity. Grade ≥3 irAEs had occurred in 40%, 20%, and 50% of patients in arms A, B, and C, respectively. The radiologic and pathologic response was also lowest in arm C; the radiologic RR was 60%, 60%, and 42%, and the pRR was 80%, 77%, and 68% in arms A, B, and C, respectively. A pathological complete response (pCR) was achieved by 47% of patients in arm A, 57% in arm B, and by 23% of patients in arm C. None of the patients achieving a pathologic response relapsed. In contrast, relapse has been reported in 9 of 21 patients demonstrating no pathologic response (pNR). Two deaths occurred in in arm A; one patient without a pathologic response died of melanoma and one pCR patient died due to complications after experiencing immune-related encephalitis at 9.5 months following the initiation of therapy.

Data from the OpACIN-neo study led the investigators to conclude that the arm B combination of neoadjuvant ipilimumab at 1 mg/kg plus nivolumab at 3 mg/kg resulted in less toxicity than the standard dosing regimen. Furthermore, the high response rate was preserved with this regimen.

MANAGING RECURRENCE AFTER ADJUVANT ANTI-PD1 THERAPY IN HIGH-RISK RESECTED MELANOMA

Anti-PD1 immunotherapy prolongs the RFS when used as adjuvant therapy in high-risk resected melanoma. To date,

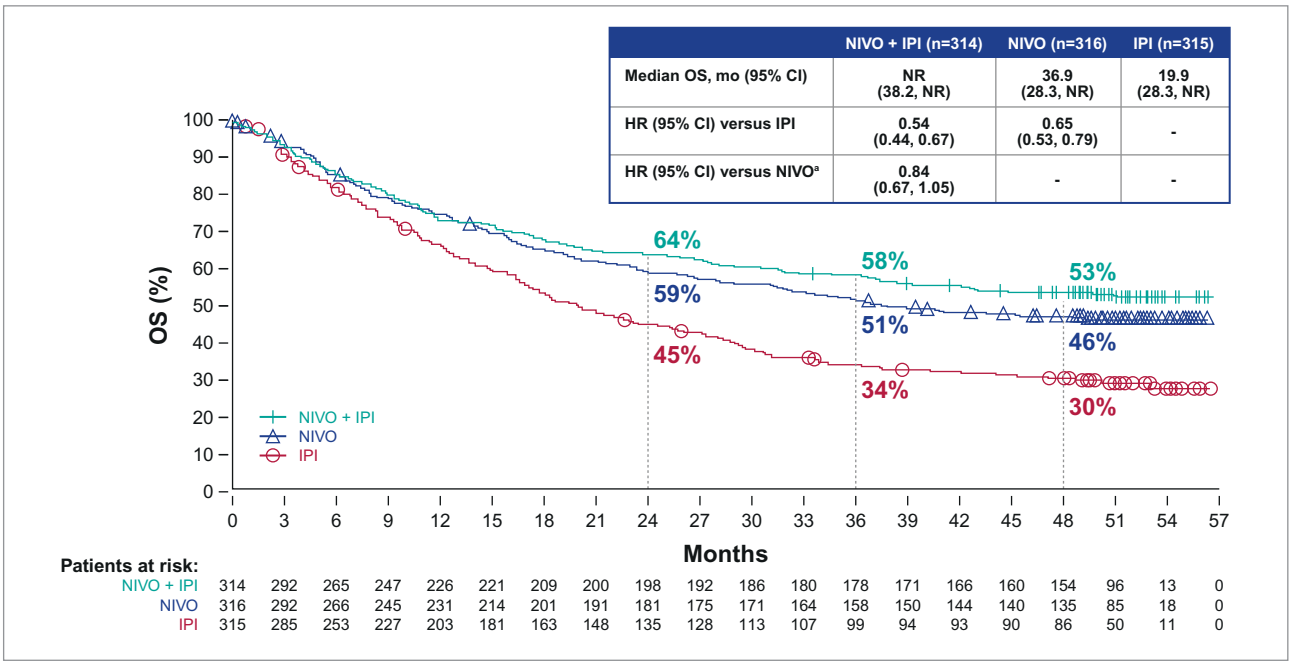

FIGURE 2. Updated four-year OS in the phase III CheckMate 067 study.[6,7]

detailed data on the nature and management of recurrences following adjuvant anti-PD1 therapy are lacking. To address this question, Owen *et al.* looked at the characteristics of 36 patients with resected stage III/IV melanoma who received adjuvant anti-PD1-based therapy and had a melanoma recurrence. Eighteen of these relapses were locoregional only, 12 relapsed at a were distant site only and in 6 patients the relapse was both distant and locoregional. Six of these 36 patients died, 4 have disease progression after subsequent therapy and 22 are in response to their current management (61%) (including 10 patients treated with local therapy for locoregional recurrence). The remaining 4 patients did not reach their first assessment on systemic therapy yet.[4]

These data are the first to demonstrate the utility of salvage therapy for patients who progress early despite adjuvant anti-PD1. These early results also suggest that this is a challenging group that will likely require multimodal treatment.

ADVANCED MELANOMA

FOUR-YEAR OS DATA WITH NIVOLUMAB PLUS IPILIMUMAB: UPDATES FROM CHECKMATE 067

The phase 3 CheckMate 067 trial randomly assigned 945 patients with previously untreated, unresectable, stage III or IV melanoma with known *BRAF* status to receive nivolumab plus ipilimumab, nivolumab plus placebo, or ipilimumab plus placebo. The co-primary endpoints were PFS and OS. Previously reported results from CheckMate067 demonstrated that the first-line combination of nivolumab and ipilimumab or nivolumab alone substantially improved ORR, PFS and OS compared with ipilimumab for advanced melanoma.[5] During ESMO 2018, four-year data of this trial were presented (and simultaneously published in the Lancet Oncology).[6,7] The combination therapy and the nivolumab plus placebo regimens continued to show improved survival outcomes compared with ipilimumab plus placebo with a minimum follow-up of 48 months among the intention-to-treat population. The median OS was still not reached for nivolumab plus ipilimumab (95%CI: 38.2 months-not reached) as compared to 36.9 months with nivolumab plus placebo and 19.9 months with ipilimumab alone (*Figure 2*). The median PFS of 11.5 months seen with nivolumab-ipilimumab was significantly longer than the 6.9 median seen with nivolumab (HR[95%CI]: 0.79[0.65-0.97]) and the 2.9 months median PFS achieved with ipilimumab monotherapy (HR[95%CI]: 0.42[0.35-0.51]).[6,7] The median treatment-free interval of patients who discontinued study therapy was 15.4 months in the combination arm as compared to 1.7 and 1.9 months with nivolumab and ipilimumab monotherapy, respectively. At four years of follow-up, 71% of the surviving patients in the nivolumab plus ipilimumab arm was free of treatment as compared to 50% with nivolumab alone and 39% with ipilimumab monotherapy.

Treatment-related adverse events (TRAEs) occurred most frequently in the nivolumab plus ipilimumab arm. The rate of grade 3/4 TRAEs was 59%, 22%, and 28% with the combination, nivolumab, and ipilimumab, respectively. The most common grade 3 TRAEs were diarrhoea with the combination therapy and with nivolumab alone and colitis in the ipilimum-

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Sustained relapse free survival benefit with adjuvant dabrafenib-trametinib in resected, stage III, *BRAF*-mutant melanoma.**
2. **Neoadjuvant ipilimumab at 1 mg/kg plus nivolumab at 3 mg/kg results in less toxicity than the standard dosing regimen, while preserving a high response rate.**
3. **Four-year survival data of CheckMate 067 confirm the superiority of nivolumab-ipilimumab over nivolumab and ipilimumab alone in the 1st line treatment of advanced melanoma**
4. **Combining pembrolizumab with dabrafenib and trametinib leads to a numerical survival advantage at the cost of added toxicity. These findings require phase III validation.**

ab group. There were 4 treatment-related deaths, 2 of which occurred in the combination arm as a result of cardiomyopathy and liver necrosis, 1 in the nivolumab arm due to neutropenia, and 1 in the ipilimumab arm due to colon perforation. None of these deaths occurred since the 3-year update.[5-7]

COMBINING IMMUNE CHECKPOINT INHIBITION WITH DABRAFENIB/TRAMETINIB IN THE FIRST-LINE TREATMENT OF *BRAF*-MUTANT ADVANCED MELANOMA

Pembrolizumab in combination with dabrafenib (D) and trametinib (T) demonstrated promising antitumor activity and acceptable tolerability in phase 1 of the KEYNOTE-022 trial. In part 2 of this trial, 120 patients with treatment-naïve $BRAF^{V600E/K}$-mutant, stage III/IV melanoma were randomly assigned to pembrolizumab (2 mg/kg Q3W) + D (150 mg BID) + T (2 mg QD) or placebo + D + T. The primary endpoint of the study was PFS, with ORR, duration of response (DoR) and OS as secondary objectives. The median PFS with pembrolizumab + D + T was 16 months, which was longer than the 10.3 months seen in the control arm (HR[95%CI]: 0.66[0.40-1.07]; p= 0.04287). However, this difference did not reach statistical significance. Looking at pre-defined subgroups it appeared that particularly male patients, patients with an ECOG PS of 1 and patients with a baseline LDH >1.1x the upper limit of normal (ULN) benefited from the combination. Adding pembrolizumab to D + T did not lead to an improved ORR (63.3% *vs.* 71.7%). However, looking at the change in target lesion size from baseline revealed that more patients had a reduction in the lesion size of 60% or more in the pembrolizumab arm (63% *vs.* 51%). Responses with pembrolizumab + D + T were also more durable than responses in the control arm: median DoR 18.7 *vs.* 12.5 months.[8] The OS rate at 12 months was 79% with the pembrolizumab containing regimen as compared to 73% with placebo + D + T.

Combining the three drugs did come at the cost of added toxicity. The incidence of grade 3/4 adverse events was 67% with the three-drug combination as compared to 45% with D + T. Adverse events led to discontinuation of all three drugs in 25% of patients in the pembrolizumab + D + T arm *vs.* 15% in the control arm. Grade 3/4 TRAEs were reported in 57% of patients in the pembrolizumab arm *vs.* 27% with D + T. [8]

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