Highlights in melanoma

V. Kruse[1,3,5], L. Brochez[2,3,4,5]

Although immunotherapy for melanoma caught a lot of interest at this year ESMO congress, some interesting new data on targeted therapies were presented as well. We have selected 10 abstracts, which, to our opinion, deserve some extra attention.

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Targeted therapies

In a late breaking abstract, the updated survival data from the COMBI-V trial were presented.[1] The 3 year overall survival (OS) rate for the combination arm (dabrafenib and trametinib) was 45% as compared to 31% for vemurafenib alone. The reported OS from the combination arm is in accordance with the OS achieved in for the combination in the COMBI-D trial. For patients with a normal LDH and < 3 organ metastases (N=141 of in total 352 patients treated in the combination arm) a 3-year OS of 70% and a 3-year progression free survival (PFS) rate of 39% were reported. The safety profile was similar to previous reports. The data suggest that the long-term benefit from TKIs might be larger than what was expected from early trials.

Although *BRAF*/MEK-inhibition has proven to be a valuable treatment option for patients with a metastatic melanoma, there are still some patients, who do not respond to targeted therapy, despite the presence of a *BRAF* mutation. *Yan et al.* addressed this topic, presenting the genomic features of complete responders (CR) versus fast progressors (PD) among patients with $BRAF^{V600}$ mutated metastatic melanoma treated with cobimetinib and vemurafenib *vs.* vemurafenib alone.[2] The authors concluded that certain genes were more frequently altered in either the CR or in the PD group. In patients with PD, genetic alterations in *MITF* were more frequent, while genetic alterations in *NF1* were more frequent in the CR group. No significant difference was observed in frequency of *BRAF* amplifications or *CDKN2A* alterations. Although a super-pooled analysis is warranted before drawing definitive conclusions, these data already provide some interesting information on why some patients respond less than expected to treatment with BRAFi/MEKi.

Abstract 1145P presented data on the analysis of $BRAF^{V600E}$ mutation status, more specifically the concordance of results from circulating tumor DNA (ctDNA) and tissue-based testing.[3] Additionally, the impact on prediction of the clinical course in patients undergoing BRAFi therapy was also discussed. Blood samples from melanoma patients in two independent studies were subjected to plasma testing using the OncoBEAM™ $BRAF^{V600E}$ assay and tissue-based analysis using Sanger sequencing. In total, 205 melanoma patients were evaluated. Overall, results from *BRAF* plasma testing revealed a high degree of concordance with tissue testing in both studies with 89.2% (study 1) and 94% (study 2), respectively. Additionally, 5 of 10 patients originally classified *BRAF*-negative in tumor, tested *BRAF* mutation-positive in plasma. In these cases, secondary malignancies were found to be responsible. Importantly, dynamic changes of *BRAF* mutant ctDNA over time correlated with the clinical course and response to treatment. In fact, a positive *BRAF* plasma test could detect a relapse significantly earlier than classical imaging tech-

[1]Department of Medical Oncology, Ghent University Hospital, [2]Department of Dermatology, Ghent University Hospital, [3]Immuno-Oncology Network Ghent (ION Ghent), Ghent University Hospital, [4]Cancer Research Institute Ghent, Ghent University Hospital, [5]Belgian Association of Dermato-Oncology (BADO)

Please send all correspondence to: Vibeke Kruse MD PhD, Department of Medical Oncology, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium. Telephone: +32 9 332 2692, Fax +32 9 332 62 85, E-mail: Vibeke.kruse@uzgent.be.

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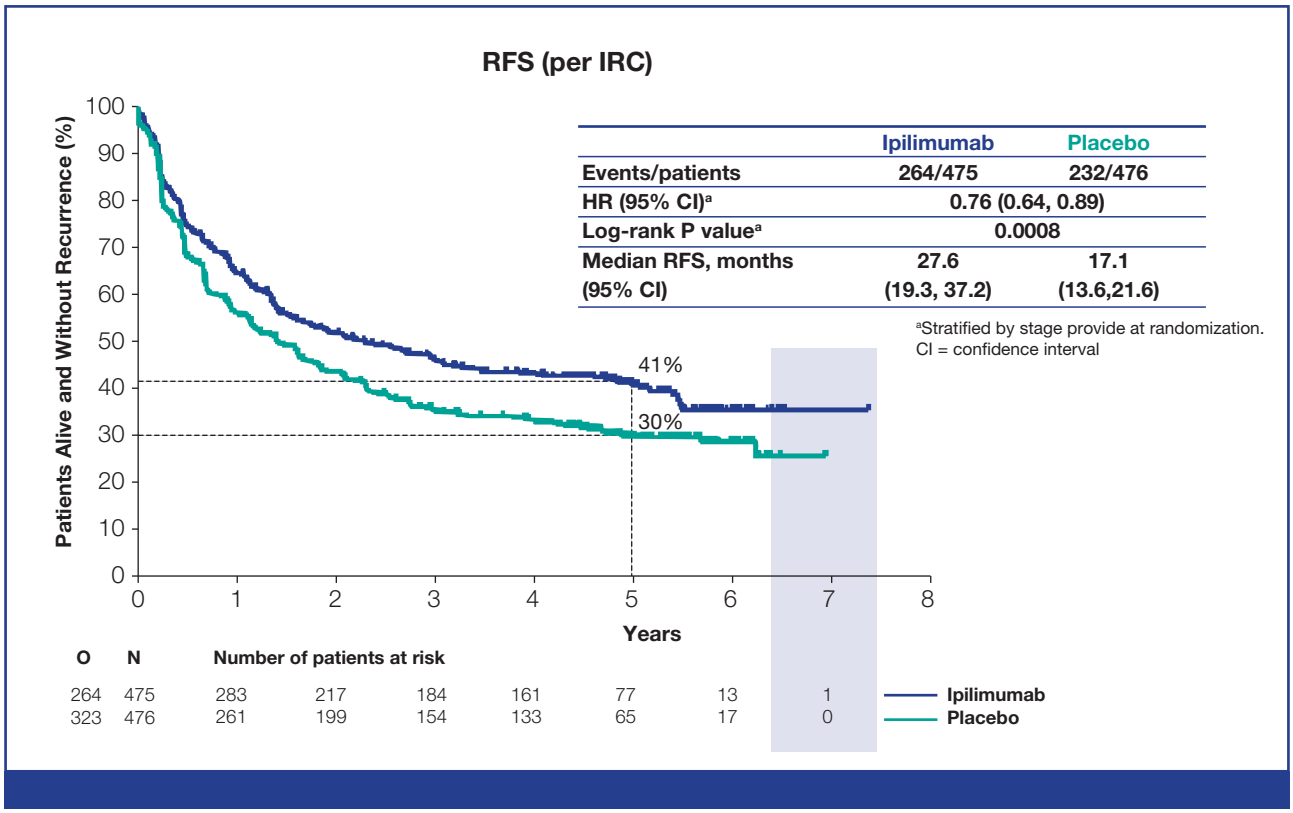

Figure 1. Recurrence free survival in the EORTC 18071-study, assessing adjuvant ipilimumab after complete resection of stage III melanoma.[5]

niques. These results are promising, with a potential new way of evaluating the mutational status. Eventually this technique can also be used in the monitoring of treatment response.

Abstract 1135P discussed the value of re-challenging *BRAF*^{V600}-mutant melanoma patients who previously experienced progression on *BRAF* (+MEK)-inhibition, with dabrafenib plus trametinib.[4] This trial was driven by the hypothesis that acquired resistance could potentially be reversible when *BRAF*-inhibition is withheld for a sufficient period of time. Twenty-five patients with documented disease progression (PD) at least 12 weeks following the last day of dosing of a *BRAF*-inhibitor containing treatment regimen, and who have experienced PD on immunotherapy, were included in this phase II trial. A confirmed PR was documented in 8 patients (32%), stable disease (SD) was observed in 10 patients (40%). The median PFS was 4.8 months, while the median OS was not yet reached. These data suggest a benefit of re-challenging patients previously treated with *BRAF*i (+/- MEKi) and immunotherapy with dabrafenib and trametinib. Although, this combination warrants further investigation in a larger number of patients, the re-introduction of *BRAF*i/MEKi could add a new line of treatment for metastatic melanoma patients.

Immunotherapy

At ESMO 2016, the long awaited results from the EORTC 18071-study with ipilimumab as adjuvant treatment for melanoma were presented as a late breaking abstract.[5] This phase 3 trial evaluated ipilimumab at a dose of 10 mg/kg in patients who had undergone complete resection of stage III melanoma. In total, 951 patients were randomly assigned to receive ipilimumab (N=475 patients) or placebo (N=476) every 3 weeks for four doses, then every 3 months for up to 3 years or until disease recurrence or an unacceptable level of toxic effects occurred. At a median follow-up of 5.3 years, the 5-year rate of recurrence-free survival (RFS) was 40.8% in the ipilimumab group, as compared with 30.3% in the placebo group (*Figure 1*). The rate of OS at 5 years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group. The rate of distant metastasis-free survival (DMFS) at 5 years was also improved in the ipilimumab group compared with the placebo group (48.3% *vs.* 38.9%). Immune-related ad-

verse events (irAEs) of grade 3 or 4 occurred in 41.6% of the patients in the ipilimumab group and in 2.7% of patients in the placebo group. In the ipilimumab group, 5 patients (1.1%) died due to immune-related adverse events. The authors concluded, that ipilimumab at a dose of 10 mg/kg as adjuvant therapy for high-risk stage III melanoma resulted in significantly higher rates of RFS, OS and DMFS than placebo. However, there were more irAE's with ipilimumab than with placebo and this treatment should always be administered with caution.

Another abstract addressed the question on safety and efficacy of anti-PD1 in elderly patients with metastatic melanoma.[6] We believe this abstract is of interest to the daily clinical practice. Comparing patients ≤75 (N= 297) with patients >75 years (N= 38), did not reveal any difference in toxicity, although the two groups were of very different size. Grade III/IV irAE's occurred in 2 patients >75 years of age (14%) and among 16 patients (16%) ≤75 years of age. Furthermore, ORR (overall response rate), PFS and OS were similar for patients ≤75 and >75 years of age (48% *vs.* 34%, 8.7 months *vs.* 4.6 months and 33.5 months *vs.* 48.1 months, respectively). According to these results, anti-PD-1 antibodies are safe and effective in elderly patients, with response rates and toxicity profiles that are similar to what is observed in younger patients.

How to predict response to therapy remains one of the main questions in terms of immuno-oncology. Data were presented on the correlation between baseline characteristics and clinical outcome of patients with advanced melanoma treated with pembrolizumab.[7] The authors found a significant correlation between PFS/OS and PS2, ALC 5xULN and LDH > 1.5ULN. These baseline features were associated with a typical "lower PFS plateau" beyond 30 weeks. Patients with a baseline ALC < 500/mm3 had a PFS and OS < 9 weeks. In patients with ALC >500/mm3 (N= 281), multivariate analysis identified baseline PS2, LDH > 1.5xULN and CRP > 5xULN as independent unfavorable prognostic factors for PFS/OS. In our opinion, these data are highly relevant for the clinical practice.

The value of PD-L1 was also discussed extensively on this year ESMO congress, across various tumor types, including melanoma. PD-L1 is proposed to be one of several biomarkers to evaluate outcome upon PD-1 blockade. In the past, data have demonstrated a higher response rate (ORR) with the combination of ipilimumab and nivolumab in patients with high PD-L1 expression (≥5%). However the median PFS was not affected by the PD-L1 expression. In abstract 1112PD, a pooled analysis of PD-L1 expression as a biomarker for nivolumab plus ipilimumab and nivolumab alone in advanced melanoma was performed.[8] Among patients with PD-L1 expression ≥5%, the median PFS of nivolumab combined with ipilimumab was not reached (NR) and was 22.0 months for nivolumab alone. For patients with low PD-L expression (<5%) the median PFS was 11.1 months for nivolumab plus ipilimumab and 4.9 months for nivolumab. The ORR was higher with nivolumab plus ipilimumab as compared to nivolumab alone, irrespective of the PD-L1 status. The median duration of response was not reached for both subgroups treated with nivolumab plus ipilimumab, and reached 20.8 and 22.3 months with nivolumab in the ≥5% and <5% PD-L1 subgroups, respectively. The frequency and types of treatment-related grade 3-4 adverse events were consistent with earlier reports (combination: 56.5%, nivolumab: 18.2%) and did not differ by PD-L1 expression. While patients with ≥5% PD-L1 tumor expression have better efficacy outcomes, those with <5% PD-L1 expression still benefit from nivolumab plus ipilimumab or nivolumab. As such, it is unlikely that PD-L1 will become a discriminator between anti-PD1 *vs.* anti-PD1 plus anti-CTLA4.

Combination strategies

One of the most promising new combination regimens consisted of the combination of pembrolizumab with the IDO-inhibitor epacadostat.[9] IDO is a tryptophan-catabolizing enzyme that is overexpressed in many cancers, which induces immune tolerance by suppressing T-cell responses. Due to its mechanism of action, IDO1 is associated with a more rapid tumour progression and reduced survival. Furthermore, IDO1 expression exhibits anti-tumour activity through reactivation of effector T-cells and works synergistic with PD-1 blockade. IDO may be a general principle of acquired immune tolerance in cancer, suggesting that IDO checkpoint inhibition might be beneficial in several tumor types. Keynote 037, is a phase 1, dose escalation/expansion study evaluating the combination of pembrolizumab with epacadostat. In total, 62 patient with an advanced solid tumor were involved, including 22 patients with advanced melanoma. Nineteen of 22 patients were treatment-naïve. Eight percent experienced treatment-related AE's that led to discontinuation. An ORR of 58%, a PR of 26% and a DCR of 74% were observed. The re-

Key messages for clinical practice

1. Although immunotherapy is gaining a lot of attention in the treatment melanoma patients, one should not forget the value of targeted therapy. The long-term benefit might be greater than expected in the initial trials. Therefore, the presence of a *BRAF* mutation should always be evaluated at diagnosis of metastatic disease.
2. Gene-signatures may give additional information on response to targeted therapy. These data are interesting, but so far, the value for the daily clinical practice is limited.
3. BRAF plasma testing seems to have a high of concordance with tissue testing. Importantly, BRAF plasma testing allows a significantly earlier detection of relapse than imaging.
4. Re-challenge with BRAFi/MEKi to patients who previously responded to BRAFi containing regimens might provide an additional line of treatment for *BRAF* mutated melanoma patients
5. Ipilimumab 10 mg/kg seems to be a beneficial adjuvant treatment for stage III melanoma patients resulting in higher survival rates. However, this treatment is also associated with a significant risk of developing severe toxicities.
6. Elderly patients can benefit equally from PD1-blockade. Toxicity is the same, but AE management could be more challenging given the risk of significant co-morbidities.
7. PD1 is one of the several markers related to outcome in PD1 blockade. However, it is unlikely that PD1 will become a discriminator between anti-PD1 *vs.* anti-PD1 plus anti-CTLA4.
8. 'Basic' lab values such as ANC, LDH and CRP may serve as prognostic markers in the context of immune-oncology.
9. The IDO inhibitor epacadostat is a relatively new player in the field of immune-oncology, showing promising activity in combination with pembrolizumab.
10. The combination of vemurafenib, cobimetinib and atezolizumab is another innovative treatment strategy, based on data from a phase 1 study. Further investigation is however warranted.

sponses were independent of the PD-L1 status. The median PFS has not been reached yet, with a 6-month PFS of 74% and a 12-month PFS of 57%. These data are promising, suggesting a new valuable treatment strategy. Data from a phase 1 study of the combination of vemurafenib, cobimetinib and atezolizumab in patients (N=30) with a non-resectable stage III/IV and no prior treatment with *BRAF*/MEK or immunotherapy also caught some attention on this year congress.[10] Atezolizumab is humanized engineered monoclonal antibody that targets PD-L1, blocking the interaction with PD-1 and B7.1. The most frequent occurring grade 3-4 AE's were increased ALT (17%), increased AST (13%), increased bilirubin in blood (7%), increased creatinin phosphokinase in blood (7%) and diarrhea (7%). All AE's were manageable and reversible with dose interruption and/or reduction. Among the 29 evaluable patients, the ORR was 83 % (N=24), including 3 CR (10%) and 21 PR (72%). Another 3 patients achieved SD (10%). The results of the triple regimen were promising with an ORR of 83% compared to an ORR of 33% with the atezolizumab single agent regimen.

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