ESMO 2014 Congress Scientific Meeting Report – Melanoma and Other Skin Tumours Extract

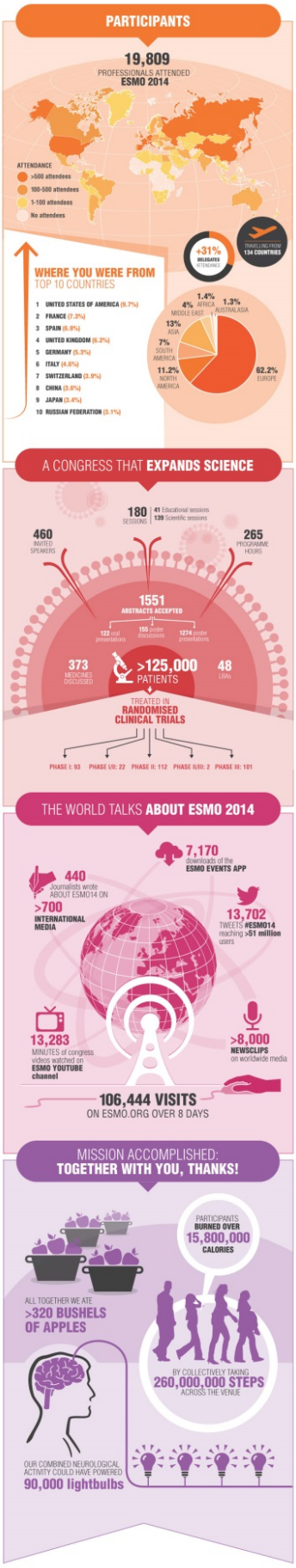
26-30 September 2014

Madrid, Spain

Summary

The European Society for Medical Oncology (ESMO) Congress, held September 26 to 30 in Madrid, Spain, was a record-breaker on nearly all levels. It was resounding success and in a dedicated infographic you can find the congress statistics. A primary emphasis in the scientific programme was placed on precision medicine and how it will change the future treatment landscape in oncology. In addition, a number of scientific presentations were dedicated to cancer immunology and immunotherapy across multiple tumour types. This report is an overview of key scientific presentations made during the congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2014 scientific programme, as well as advances in oncology.

Infographic (right): ESMO 2014 record breaking Congress



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Melanoma and Other Skin Tumours

Results of the COMBI-v randomised, open-label, phase III study in the first-line treatment of patients with unresectable or metastatic cutaneous melanoma

First-line treatment with combination therapy dabrafenib plus trametinib improves OS in comparison with vemurafenib in patients with BRAF V600E/K mutation-positive unresectable or metastatic cutaneous melanoma. The results of a randomised, open-label, phase III, COMBI-v study were presented by Dr Caroline Robert of the Institut Gustave Roussy, Villejuif, France.

Dabrafenib, a BRAF inhibitor and trametinib, a MEK inhibitor demonstrated superior PFS vs. chemotherapy in patients with BRAF V600E/K mutation-positive metastatic melanoma. However, the emergence of disease resistance and development of cutaneous squamous cell carcinoma are associated with BRAF inhibition. Simultaneous inhibition of BRAF and MEK mitigated these effects as shown in the phase I/II study of dabrafenib/trametinib combination vs. treatment with single agent dabrafenib and in the phase III study of dabrafenib/trametinib combination vs. dabrafenib monotherapy with an improvement in ORR, PFS and reduced frequency of cutaneous squamous cell carcinoma.

The COMBI-v phase III study was conducted to establish the superiority of dabrafenib/trametinib combination over vemurafenib with respect to OS in patients with BRAF V600E/K mutation-positive metastatic melanoma.

Patients were randomised 1:1 to receive dabrafenib/trametinib vs. vemurafenib monotherapy as first-line therapy.

Eligible patients were ≥ 18 years old and had an ECOG PS ≤ 1, with histologically confirmed, unresectable stage IIIC or IV, BRAF V600E/K mutation-positive metastatic melanoma. All patients were treatment-naive with no brain metastasis except those treated and stable status longer than 12 weeks. Stratification was according V600E vs. V600K mutation and LDH level.

The primary endpoint was OS; secondary endpoints were PFS, ORR, DoR, and safety.

The study crossover was prohibited.

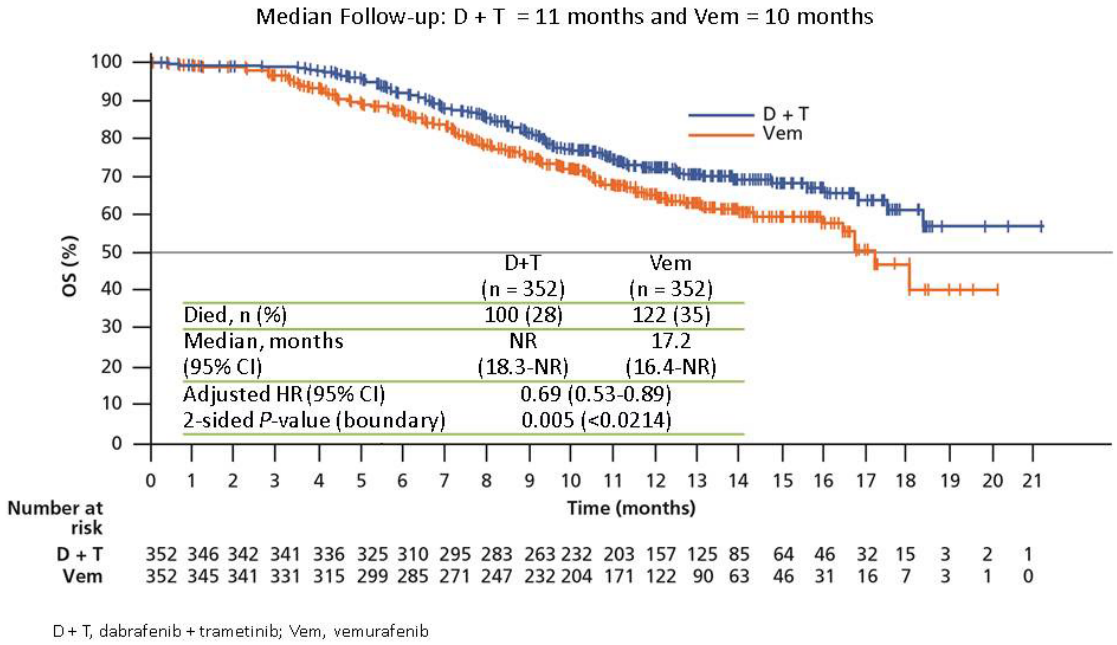
From June 2012 to October 2013, 1644 patients were screened and 704 patients were randomised (352 patients in each arm).

A pre-specified interim OS analysis was planned when 70% (202 of 288) of the total number of expected deaths, required for the protocol-specified final analysis, are observed. The study could be stopped for efficacy if the one-sided p value was < 0.0107. However, due to data entry lag, there were 222 (77%) observed death events at data cut-off.

It was pre-specified that if the Independent Data Monitoring Committee (IDMC) recommends stopping at interim, interim analysis would become the final one.

The IDMC recommended stopping the study based on an interim analysis which demonstrated an OS benefit that crossed the pre-specified efficacy stopping boundary for dabrafenib/trametinib combination. At the time of analysis, the median OS was not reached in the dabrafenib/trametinib arm and 17.2 months in the vemurafenib arm (HR 0.69, p = 0.002). The OS data in subgroup analysis favoured the dabrafenib/trametinib arm.

COMBI-v: Overall Survival



Caption: First-line combination therapy dabrafenib plus trametinib improves OS compared to vemurafenib in patients with BRAF V600E/K mutation-positive melanoma. © Caroline Robert

The PFS was 11.4 vs. 7.3 months in favour of the dabrafenib/trametinib arm (HR 0.56, p < 0.001). Difference in best confirmed RR was 13% among the two study arms, again in favour of dabrafenib/trametinib treatment (p < 0.001). The DoR was 13.8 months in the dabrafenib/trametinib arm and 7.5 months in the vemurafenib arm.

Rates of adverse events were generally similar in both arms and consistent with data from previous trials. However, all grades and grade 3 of arthralgia, rash, alopecia, hyperkeratosis, photosensitivity and skin papilloma were present more among patients treated with vemurafenib. Grade 3 pyrexia was present more in the dabrafenib/trametinib arm.

Among BRAF inhibitor-related adverse events, cutaneous small-cell carcinoma and keratoacanthoma, hyperkeratosis, skin papilloma, hand-foot syndrome, alopecia, photosensitivity plus sunburn, and non-cutaneous malignancy were present more in the vemurafenib arm.

Among MEK inhibitor-related adverse events, decrease in ejection fraction was present more in the dabrafenib/trametinib arm.

Dr Robert concluded that dabrafenib/trametinib vs. vemurafenib resulted in significant improvement in OS for combination treatment with 31% reduction in the risk of death (median OS not reached for combination vs. 17.2 months in the vemurafenib arm) and significant improvement in PFS for combination treatment with 44% reduction in the risk of progression or death (median PFS of 11.4 months for combination vs. 7.3 months for vemurafenib treated patients).

Dr Christian Blank of the The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands, who discussed the study results, said that N-RAS mutation was discovered in 1985, loss of CDKN2 in 1994, PTEN loss in 1997, B-RAF mutation in 2002, CSK4 mutation in 2005, c-KIT mutation in 2006, GNAQ mutation in 2009, and erbB4 mutation in 2009.

Among these genetic changes observed in melanoma, the oncology community was excited with findings from 2009 coming from phase 1 study of BRAF inhibition in advanced melanoma and fast induced responses. After this, he spoke about the rationale for dual targeting of the MAPK pathway.

The observed response rate in the COMBI-v study was 64% with 13% CRs and 51% PRs, SD was observed in 26% of patients. Median PFS was 7.3 months and OS was 17.2 months. COMBI-v confirms improved efficacy for combinations of BRAF inhibitor and MEK inhibitor therapies as compared to single BRAF inhibition in BRAFV600 mutant melanoma. This combination leads to decreased toxicity occurring from paradoxical MAPK pathway activation in BRAF wild-type cells. Dabrafenib and trametinib toxicity is similar to the toxicity observed from single treatment. If the mature data confirm the presented observations BRAF and MEK inhibition would be the new standard targeted therapy in BRAFV600 melanoma.

Dr Blank questioned why gaining 4 months of PFS translated only into 2 months of OS benefit. In addition, he asked what kind of pricing this OS benefit will justify.

The study describes investigational use of dabrafenib/trametinib combination and was funded by GlaxoSmithKline.

Reference

LBA4_PR: COMBI-v: A randomised, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) with vemurafenib (V) as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma

Results of a phase III study of cobimetinib in combination with vemurafenib in previously untreated patients with BRAFV600 mutation-positive melanoma

coBRIM, a phase III, double-blind, placebo-controlled study of vemurafenib vs. vemurafenib plus cobimetinib in previously untreated patients with BRAFV600 mutation-positive unresectable locally-advanced or metastatic melanoma met its primary endpoint. Cobimetinib in combination with vemurafenib significantly improved PFS among patients with BRAFV600-mutant tumours. The results were reported by Prof. Grant McArthur of the Peter MacCallum Cancer Centre, Melbourne, Australia.

Combined inhibition of BRAF and MEK is hypothesised to improve clinical outcomes by preventing or delaying the onset of resistance observed with BRAF inhibitors alone. The most common mechanism of acquired resistance to vemurafenib is MAPK reactivation through MEK. MEK plus BRAF inhibition prevents the development of acquired resistance in preclinical models. Dabrafenib plus trametinib in phase III and vemurafenib plus cobimetinib in phase I/II study improved RRs and PFS in BRAF inhibitor–naive melanoma patients. Reduced incidence of hyperproliferative lesions is seen by blocking paradoxical activation of the MAPK pathway from RAF inhibition.

This randomised phase III study evaluated the combination of the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetinib. Cobimetinib is an oral, small molecule, highly selective, allosteric inhibitor of MEK.

Between January 2013 and January 2014, 495 patients were randomly assigned (1:1) to receive vemurafenib/cobimetinib or vemurafenib/placebo.

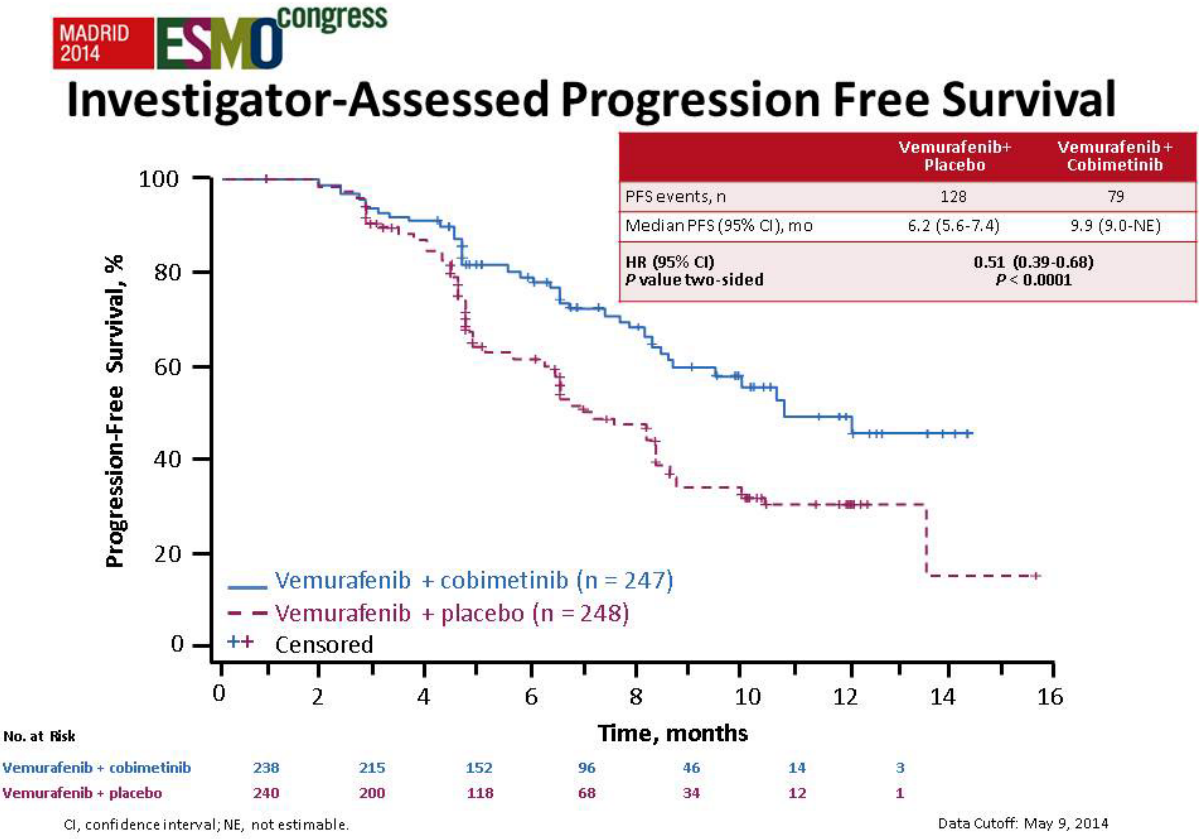
The study eligibility criteria included treatment-naive patients with BRAFV600 mutation–positive (detected by cobas® 4800) unresectable locally-advanced or metastatic melanoma, adequate PS and organ function, and no prior therapy for advanced disease. The treatment was given until disease progression, unacceptable toxicity, or withdrawal of consent. The patients were stratified by geographic region and extent of disease (M1c vs. other).

The primary endpoint was investigator-assessed PFS. Secondary endpoints included OS, ORR, DoR, PFS assessed by Independent Radiology Committee (IRC), safety, pharmacokinetics, QoL assessed by QLQ-C30 and EQ-5.

Statistical assumptions were 95% power to detect an improvement in median PFS from 6 to 11 months (HR 0.55) and 80% power to detect an improvement in median OS from 15 to 20 months (HR 0.75).

Patient characteristics were well balanced, except PS 1 which was slightly higher in the vemurafenib plus placebo arm.

Prof. McArthur reported that median investigator-assessed PFS was 9.9 months with the combination compared with 6.2 months in the control arm (HR 0.51; p < 0.0001).



Caption: The MEK inhibitor cobimetinib in combination with the BRAF-inhibitor vemurafenib improves PFS compared to vemurafenib alone in patients with BRAFV600-mutated melanoma. © Grant McArthur

Investigators-assessed PFS based on key demographic and tumour characteristics were consistent with PFS in the ITT population. The PFS assessed by independent review was comparable with investigator-assessed PFS (11.3 months vs. 6.0 months, HR 0.60, p = 0.0003).

The rate of CR and PR was 68% in the combination arm and 45% in the vemurafenib arm ($p < 0.0001$), including CR in 10% of patients treated with the combination and 4% of patients in the vemurafenib group.

The 9 months OS rate was 81.1% in the combination arm vs. 72.5% in the vemurafenib arm (HR 0.65, p=0.046).

Vemurafenib/cobimetinib combination, compared with vemurafenib alone, was associated with a higher incidence of grade ≥ 3 adverse events (65% vs. 59%). However, there was no difference in the rate of adverse events leading to study drug discontinuation.

The study investigators found a decrease in the occurrence of secondary cutaneous neoplasms with the combination treatment.

The rate of grade 1 and 2 serous retinopathy (includes specific terms chorioretinopathy and retinal detachment) was higher in the cobimetinib/vemurafenib arm, but there were no cases of retinal veinocclusion reported. In the combination arm, there was also higher rate of grade 2 of decreased ejection fraction.

Prof. McArthur concluded that the coBRIM study provides clear and definitive evidence that combined BRAF and MEK inhibition results in improved clinical outcomes. The combination of vemurafenib plus cobimetinib vs. vemurafenib alone resulted in 49% reduction in risk of progression. Interim OS showed a reduction in risk of death of 35%. The study is ongoing to evaluate mature OS.

Prof. McArthur said that the study results are being published simultaneously with the presentation at the ESMO 2014 Congress in the New England Journal of Medicine.

Dr Christian Blank of the The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands, who discussed the study results, congratulated the authors and said that confirmed objective response of 68% as well as CR rate of 10%, PR rate of 58% and SD seen in 20% of patients in the coBRIM study are in line with the results from other dual-MAPK targetting. The resemblance between the arms in the coBRIM study showed a higher ECOG PS 0 rate in vemurafenib and cobimetinib treated patients. The PFS and OS were more favourable in the vemurafenib and cobimetinib arm. However, OS data were immature at the time of presentation.

coBRIM confirms improved efficacy for combinations of BRAF inhibitor and MEK inhibitor as compared to single BRAF inhibition in BRAFV600 mutant melanoma. The combination therapy leads to decreased toxicity occurring from paradoxical MAPK pathway activation in BRAF wild-type cells. Vemurafenib and cobimetinib toxicity is similar to the toxicity observed from single treatment. If the mature data confirm the presented observations, BRAF and MEK inhibition would be the new standard targeted therapy in BRAFV600 melanoma.

The coBRIM study was sponsored by F. Hoffmann-La Roche, Ltd. Cobimetinib is being developed by Genentech, Inc, a member of the Roche Group, under a collaboration agreement with Exelixis.

Reference

LBA5_PR: Phase 3, double-Blind, placebo-controlled study of vemurafenib versus vemurafenib + cobimetinib in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma (NCT01689519)

Results of a phase III randomised study of nivolumab in patients with advanced melanoma after prior anti-CTLA4 therapy

In patients with metastatic melanoma who progressed on or after anti-CTLA-4 therapy and treatment with BRAF inhibitors in the case of BRAF mutation positive disease, nivolumab was well tolerated and showed a higher ORR when compared with investigator's choice chemotherapy. Durable tumour regression was observed in the majority of responders to nivolumab. The results of a phase III randomised, open-label study were presented by Prof. Jeffrey Weber of Lee Moffitt Cancer Center & Research Institute, Tampa, USA.

Effective therapies are needed for patients with melanoma who progress on or after anti-CTLA-4 therapy and a BRAF inhibitor.

Nivolumab is a fully human IgG4 monoclonal antibody that inhibits the PD-1 immune checkpoint protein. In early studies, single-agent nivolumab demonstrated meaningful clinical activity and a manageable safety profile in pretreated patients with advanced melanoma with promising OS rates of 63%, 48%, and 41% observed at 1, 2, and 3 years, respectively.

In this phase III open-label trial, patients with advanced melanoma who progressed on or after anti-CTLA-4 therapy and a BRAF inhibitor in case of BRAF V600 mutation positive disease were randomised 2:1 to receive nivolumab (268 treated patients) or investigator's choice chemotherapy (dacarbazine, or carboplatin plus paclitaxel) (102 treated patients) until progression or unacceptable toxicity. Patients receiving nivolumab may be treated beyond initial progression if considered by the investigator to be experiencing clinical benefit.

Patients were stratified by PD-1 ligand expression status (PD-L1 positive vs. PD-L1 negative/indeterminate; PD-L1 positive status was defined as ≥ 5% tumour cell surface staining cut-off by IHC); BRAF status (BRAF wild-type vs. BRAF V600 mutant); and best overall response to prior anti-CTLA-4 therapy (clinical benefit defined as best overall response that included CR/PR/SD) vs. no clinical benefit (progressive disease).

Exclusion criteria were active brain metastases; prior therapy with anti-PD-1, anti-PD-L1 or anti-PD-L2 antibodies; grade 4 toxicity or use of infliximab to manage adverse events from prior ipilimumab treatment and ocular melanoma.

Co-primary endpoints were ORR by independent radiology review committee and OS. Secondary objectives included to compare PFS of nivolumab to investigator's choice chemotherapy at the time of OS analysis and to evaluate PD-L1 expression as a predictive biomarker for ORR and OS. However, OS analysis had not taken place at the time of interim ORR analysis.

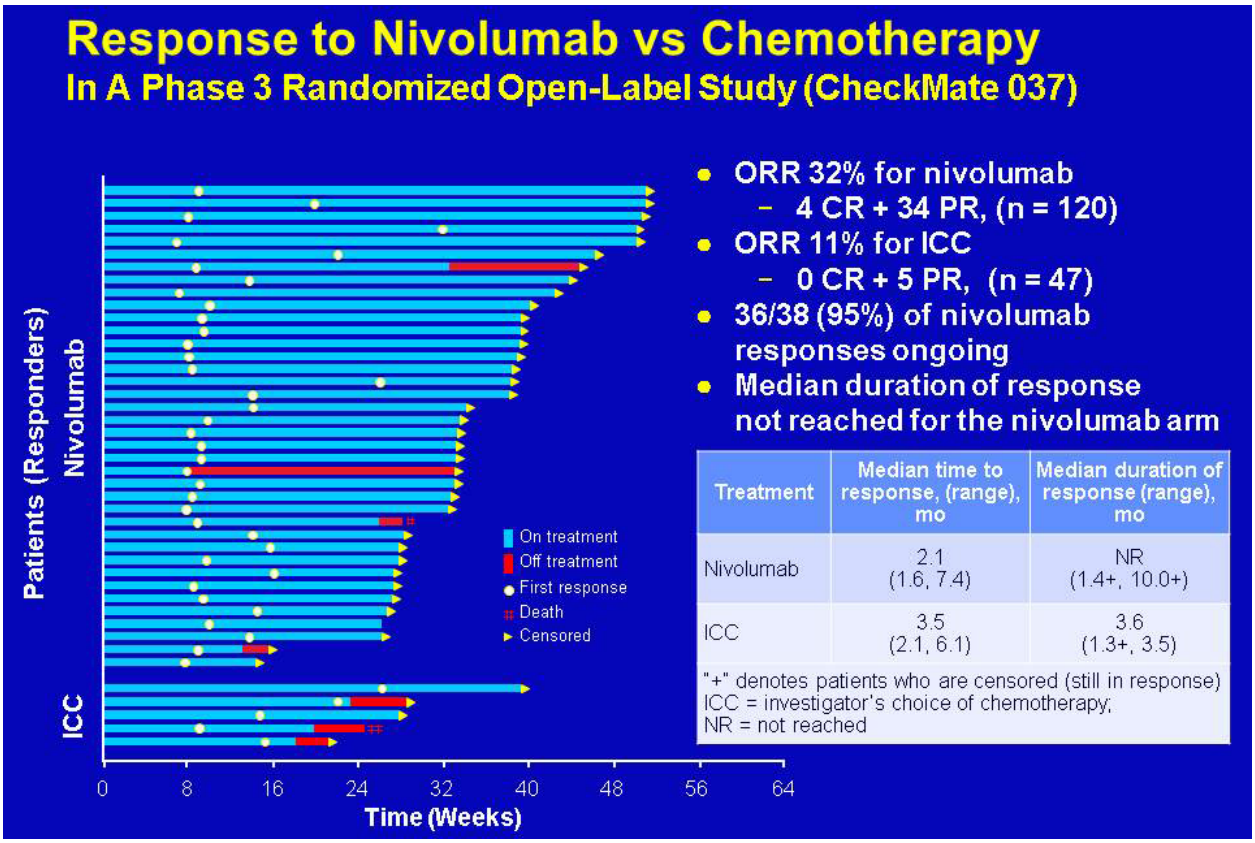
Response according to RECIST v1.1 criteria was assessed 9 weeks after randomisation, followed by 6 week assessments for the first 12 months and then by assessments every 12 weeks.

The ORR was assessed as planned in the first 120 patients treated with nivolumab and 47 patients who received investigator's choice chemotherapy with follow-up of at least 6 months.

Baseline age, sex and metastasis stage were balanced between the arms. However, there were slightly more patients with a history of brain metastasis and elevated LDH in the nivolumab arm.

Median time on therapy was 5.3 months in the nivolumab arm and 2 months in the investigator's choice chemotherapy arm. Disease progression was the most common reason for discontinuation in the nivolumab (43%) and investigator's choice chemotherapy arms (61%).

Confirmed ORR by independent radiology review committee in nivolumab and patients treated with investigator's choice chemotherapy was 32% and 11%, with a median time to response of 2.1 months (range: 1.6, 7.4) and 3.5 months (range: 2.1, 6.1), respectively.



Treatment	Median time to response, (range), mo	Median duration of response (range), mo
Nivolumab	2.1 (1.6, 7.4)	NR (1.4+, 10.0+)
ICC	3.5 (2.1, 6.1)	3.6 (1.3+, 3.5)

"+" denotes patients who are censored (still in response)
ICC = investigator's choice of chemotherapy;
NR = not reached

Caption: Response to nivolumab vs. chemotherapy. © Jeffrey Weber

Median DoR for nivolumab was not reached (range: 1.4+, 10+ months) with 36 (95%) patients being still in response. Median DoR in patients treated with investigator's choice chemotherapy was 3.6 months (range: 1.3+, 3.5) with 4 (80%) patients still in response.

Consistently higher clinical activity was observed for nivolumab vs. investigator's choice chemotherapy regardless of pre-treatment PD-L1 expression status, BRAF mutation status and prior anti-CTLA-4 benefit.

Reduction of ≥50% in target lesion burden occurred in 82% (31/38) of nivolumab responders and 60% (3/5) of responders in the investigator's choice chemotherapy arm. Among nivolumab-treated patients, an additional 10 (8%) patients had immune-related response patterns observed (≥30% reduction in target lesion tumour burden).

Grade 3-4 drug-related adverse events were seen in 9% and 31% of patients treated with nivolumab and investigator's choice chemotherapy, respectively. Discontinuations due to drug-related adverse events of any grade occurred in 2% and 8% of treated patients, respectively. No drug-related grade 3-4 adverse events were reported in ≥2% of nivolumab treated patients. All grade 3-4 drug-related adverse events belonging to the select adverse event categories resolved. Corticosteroids were the most common immunosuppressive medication used.

There were no deaths related to study drug toxicity. One patient in the nivolumab group experienced grade 5 hypoxia, possibly pneumonitis, in the setting of lymphangitic spread and

possible pneumonia; this patient's cause of death was classified by the investigator as 'other' rather than 'study drug toxicity'.

The study authors concluded that in patients with advanced melanoma who have progressed despite anti-CTLA-4 therapy and BRAF inhibitors if BRAF is mutated, nivolumab monotherapy demonstrated superior efficacy to investigator's choice chemotherapy. The majority of nivolumab treatment-related adverse events were of a low grade and manageable using recommended treatment algorithms. Co-primary endpoint (OS) data was pending at the time of presentation.

Dr Ignacio Melero of the Clinica Universitaria de Navarra, Pamplona, Spain, who discussed the study results, said that immunotherapy of cancer is no longer a quixotic goal. In his talk, Dr Melero highlighted the recent approvals of nivolumab in Japan and pembrolizumab in USA for the treatment of advanced melanoma. He further said that chemotherapy might be eliminated as an option in BRAF wild-type disease but the clinical trials are important because the best is yet to come. This is particularly true for combination therapy. In terms of biomarker analysis from tumour biopsy, antigenicity, immunogenicity, immune escape, and T-cell infiltrates should be considered. PD-L1 as single parameter is not good enough, according to Dr Melero. The scenario might be going towards a multiparameter scores (including tumour PD-L1 status). The highest number of mutations in solid tumours is observed in melanoma and NSCLC with lower frequencies in other tumour type and in that regard, melanoma remains at the top of the iceberg.

The study was supported by Bristol-Myers Squibb, Ono Pharmaceutical Company, Ltd. and Dako for collaborative development of the automated PD-L1 IHC assay.

Reference

LBA3_PR: A phase 3 randomized, open-label study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus investigator's choice chemotherapy (ICC) in patients with advanced melanoma after prior anti-CTLA-4 therapy

Randomised, double-blind study of sonidegib (LDE225) in patients with advanced basal cell carcinoma

Prof. Reinhard Dummer of the Universitätsspital Zürich, Switzerland reported that sonidegib demonstrates clinically meaningful tumour shrinkage, sustained responses, and prolonged PFS in patients with advanced basal cell carcinoma. Reduced GLI1 levels vs. baseline were seen in patients with disease control.

The BOLT phase II study, comparing two doses of sonidegib, a hedgehog (Hh) pathway inhibitor, in patients with advanced basal cell carcinoma, met its primary endpoint of ORR ≥30% in both arms in analyses of data collected up to 6 months after randomisation of the last patient. Median follow-up was 13.9 months for data presented at ASCO 2014. Associations of GLI1 (marker of Hh pathway activation) with clinical outcome and updated 12 months efficacy and safety data were presented at ESMO 2014.

Patients with locally advanced basal cell carcinoma (194 cases) not amenable to curative surgery or radiation, or metastatic basal cell carcinoma (36 cases) were randomised 1:2 to receive sonidegib 200 or 800 mg daily. Clinical response was assessed by central review using modified RECIST for locally advanced basal cell carcinoma or RECIST v1.1 for metastatic basal cell carcinoma. Exploratory analyses in a subset of patients (137 with locally advanced basal cell

carcinoma and 13 with metastatic basal cell carcinoma) assessed GLI1 levels in tumour tissue collected at baseline, week 9, and week 17.

GLI1 levels decreased from baseline with both doses at week 9 and 17 ($p < 0.0001$) and in patients with disease control (CR, PR, SD). Median % changes with 200 mg at week 17 by response were −99.47 for CR; −90.79 for PR; −96.58 for SD; +10.19 for PD; and for unknown −94.24. With an additional 6 month follow-up, median exposure duration was 11.0 (200 mg) and 6.6 month (800 mg). Half of patients with locally advanced basal cell carcinoma in the 200 mg arm responded, and tumour responses in both arms were durable.

The safety profile of sonidegib was typical of Hh pathway inhibitors. The 200 mg dose had a better benefit-risk profile. The most common adverse events (200/800 mg) were muscle spasms in 52% of patients in the 200 mg arm and 69% patients in the 800 mg arm, alopecia in 49% patients in the 200 mg arm and 57% patients in the 800 mg arm, and dysgeusia in 41% patients in the 200 mg arm and 60% patients in the 800 mg arm.

The 200 mg dose has been selected for future use based on its more favourable benefit-risk profile.

The study was sponsored by Novartis.

Reference

LBA33: Randomized, double-blind study of sonidegib (LDE225) in patients (pts) with advanced basal cell carcinoma (BCC)

RELATED INFORMATION

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European Cancer Congress 2015 (ECC 2015), Vienna, Austria, 25-29 September 2015.

Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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