ESMO 2017 - Melanoma

Integrating science into oncology for a better patient outcome

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Plenary sessions: Melanoma

Adjuvant dabrafenib plus trametinib significantly lowers risk of death in stage III BRAF V600–mutated melanoma*: Combined dabrafenib plus trametinib as an adjuvant treatment for patients with high-risk BRAF V600-mutated melanoma after surgical resection significantly decreased the risk of death or recurrent disease, according to findings from the phase III COMBI-AD study. (LBA6_PR – Hauschild A, et al.)*

RFS, OS, DMFS, and FFR were all improved with adjuvant dabrafenib plus trametinib compared to placebo

Date: 11 Sep 2017
Topic: Melanoma and other skin tumours / Anticancer agents & Biologic therapy

Combined dabrafenib plus trametinib as an adjuvant treatment for patients with high-risk *BRAF V600*-mutated melanoma after surgical resection significantly decreased the risk of death or recurrent disease, according to findings from the phase III COMBI-AD study presented at ESMO 2017, the Annual Congress of the European Society for Medical Oncology in Madrid, Spain.

Axel Hauschild, University Hospital Schleswig-Holstein, Kiel, Germany and colleagues conducted this trial to develop an adjuvant regimen for patients with melanoma and regional nodal involvement (stage III disease), who are still at a high risk for relapse and death after a complete lymphadenectomy.

The randomised double-blind, placebo-controlled, phase III COMBI-AD trial (NCT01682083) investigated dabrafenib plus trametinib as an adjuvant treatment for patients with high-risk stage III *BRAF V600E/K*-mutated melanoma following complete surgical resection. The trial stratified 870 patients according to *BRAF* mutation (V600E versus V600K) and stage (IIIA versus IIIB versus IIIC); 18% of patients were stage IIIA, 41% IIIB, 40% were IIIC, and 1% of patients had unknown stage disease.

In this study, 438 patients were randomised to receive dabrafenib at 150 mg twice daily plus trametinib at 2 mg once daily, and 432 patients to receive matching placebo for 12 months. The primary endpoint was relapse-free survival (RFS), with secondary endpoints of overall survival (OS), distant metastasis-free survival (DMFS), freedom from relapse (FFR), and safety.

The primary endpoint of relapse-free survival was met

After a median follow up of 2.8 years, the risk of disease recurrence or death was reduced by adjuvant dabrafenib plus trametinib by 53% compared to placebo, hazard ratio [HR] 0.47; 95% confidence interval [CI] 0.39, 0.58.

The median RFS was not reached versus 16.6 months, respectively, with dabrafenib plus trametinib versus placebo ($p < 0.001$). This RFS benefit was consistent across all patient subgroups.

Secondary endpoint also showed a benefit; the hazard ratio for OS was 0.57 in favour of the combination (95% CI, 0.42, 0.79), for DMFS the HR was 0.51 (95% CI 0.40, 0.65), and FFR was HR 0.47 (95% CI 0.39, 0.57).

Forty-one percent of patients had grade 3/4 adverse events (AEs) in the combination arm compared to 14% of patients on placebo. Additionally, 26% of patients in the dabrafenib plus trametinib arm discontinued the trial due to an AE compared to 3% of patients in the placebo arm. The type and severity of treatment-related AEs did not differ from already known toxicities observed in randomised trials for advanced unresectable metastatic melanoma leading to the approval for this stage of melanoma in 2015.

Conclusions

In COMBI-AD, adjuvant therapy with dabrafenib and trametinib was associated with improvements in RFS, OS, DMFS, and FFR, and demonstrated manageable safety in patients with high-risk, resected, stage III, *BRAF* V600E/K–mutated melanoma.

The authors concluded that a combined dabrafenib and trametinib regimen represents a new adjuvant treatment option in this setting.

Alexander Eggermont of the Gustave Roussy Cancer Campus, Villejuif, France who discussed the study results said that dabrafenib/trametinib is convenient oral adjuvant treatment for resected BRAF-mutant melanoma.

Disclosure

This trial was sponsored by Novartis.

Reference

LBA6_PR – Hauschild A, *et al.* COMBI-AD: Adjuvant Dabrafenib (D) Plus Trametinib (T) for Resected Stage III *BRAF* V600E/K–Mutant Melanoma.

Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. NEJM; Published online September 10, 2017. DOI: 10.1056/NEJMoa1708539

BRIM8 data shows benefit with adjuvant vemurafenib in resected BRAFV600 positive melanoma: *Adjuvant vemurafenib provided substantial benefit to patients with completely resected stage IIC-IIIB BRAFV600 positive melanoma at high recurrence risk, where fewer disease-free survival events and distant metastasis-free survival events were observed with vemurafenib compared to placebo. (LBA7_PR – Lewis K, et al.)*

Patients with resected melanoma at high risk of recurrence experienced prolonged DFS with adjuvant vemurafenib over placebo

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Topic: Melanoma and other skin tumours / Anticancer agents & Biologic therapy

Adjuvant vemurafenib provided substantial benefit to patients with completely resected stage IIC-IIIB *BRAF*^{V600} positive melanoma at high recurrence risk, where fewer disease-free survival (DFS) events and distant metastasis-free survival (DMFS) events were observed with vemurafenib compared to placebo, researchers reported during the ESMO 2017, the Annual Congress of the European Society for Medical Oncology in Madrid, Spain.

However, this benefit was not significant in patients with resected stage IIIC melanoma, where a trend towards improved DFS was seen.

Karl Lewis, an associate professor of medicine, Division of Medical Oncology, at the University of Colorado Denver School of Medicine, in Aurora, USA presented results of the BRIM8 trial, which compared adjuvant vemurafenib to placebo in patients with completely resected V600E BRAF-mutated melanoma who had a high risk of recurrence.

BRIM8 was a randomised, double-blind, placebo-controlled, 2-cohort study that placed 498 adult patients with fully resected stage IIC, IIIA, or IIIB melanoma into cohort 1 and patients with stage IIIC melanoma to cohort 2. Both cohorts were randomly assigned to vemurafenib at 960 mg twice daily or placebo for 52 weeks. In cohort 1, patients were also stratified by geographic region and disease stage.

The primary endpoint of BRIM8 was DFS. Secondary objectives included safety, DMFS, and overall survival (OS). A hierarchical analysis of cohort 2 data prior to cohort 1 was prespecified.

Greater DFS seen with vemurafenib at nearly three years of follow-up

As of the clinical cut-off date for the primary analysis, cohorts 2 and 1 had a median follow-up of 34 and 31 months, respectively.

Cohort 2 contained 184 patients with resected stage IIIC melanoma, including 93 patients on adjuvant vemurafenib and 91 patients on placebo. Analysis of the data

revealed a trend towards improved DFS with adjuvant vemurafenib compared to placebo; DFS events occurred in 52 (55.9%) versus 53 (58.2%) of patients, respectively, hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.54, 1.18 (p = 0.2598). The DMFS was similar between treatment arms in cohort 2, HR 0.91 (p = 0.6815).

However, in cohort 1, which included patients with resected stages IIC, IIIA, or IIIB melanoma, adjuvant vemurafenib substantially improved DFS versus placebo. Of the 157 patients in each treatment arm, 45 (28.7%) versus 72 (45.9%) patients receiving vemurafenib versus placebo experienced a DFS event and the median time to event was 'not estimated' versus 36.9 months (95% CI 21, NE), respectively, HR 0.54; 95% CI 0.37, 0.78 (p = 0.0010).

Cohort 1 data for DMFS reflected that of DFS: DMFS events occurred in 21.7% of vemurafenib patients versus 33.1% of placebo treated patients and the median time to DMFS event was not estimated for both groups, HR 0.58 (p = 0.0133).

Subgroup analyses were conducted in cohort 1 by common disease and demographic covariates that showed results that were consistent with the overall analysis.

The OS data are immature for both cohorts.

Both cohorts had a similar exposure to study drug with a median duration of 364.0 days and the median dose intensity was approximately 80% overall.

Patients receiving vemurafenib in cohorts 1 and 2 had a similar incidence of serious adverse events (AEs) of 16.2% and 16.1%, respectively. Cohort 1 showed a slightly higher rate of treatment discontinuation due to a treatment related AEs of 22.7% compared to 15.1% in cohort 2.

Vemurafenib is currently indicated in first line BRAFV^{600} positive advanced melanoma

Current indications for vemurafenib include approval by the European Medicines Agency as a monotherapy or in combination with cobimetinib for the treatment of adult patients with BRAF V600E mutation-positive unresectable or metastatic melanoma and US Food and Drug Administration (FDA) approval for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation as detected by an FDA-approved test.

Conclusions

Although the study did not meet the primary DFS endpoint in patients with stage IIIC disease, adjuvant vemurafenib appeared to be well tolerated and effective in patients with resected stage IIC–IIIB *BRAF*^{V600} positive melanoma.

Overall, the safety profile of adjuvant vemurafenib was consistent with previous data and no new safety signals were observed.

According to the authors, further follow-up is needed to assess OS benefit.

Alexander Eggermont of the Gustave Roussy Cancer Campus, Villejuif, France who discussed the study results said there is unclear future for BRAF inhibition monotherapy in adjuvant melanoma.

Disclosure

This trial was sponsored by F. Hoffmann-La Roche Ltd.

Reference

LBA7_PR – Lewis K, *et al.* BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients (pts) with completely resected, BRAFV600+ melanoma at high risk for recurrence.

Nivolumab bests ipilimumab as adjuvant therapy in resected melanoma: *Patients with stage IIIb/IIIc or stage IV melanoma at high risk of recurrence following complete surgical resection had greater recurrence-free survival with adjuvant nivolumab compared to adjuvant ipilimumab, according to results from the phase III CheckMate 238 study. (LBA8_PR – Weber J, et al.)*

In CheckMate 238, nivolumab demonstrated greater clinical benefit and superior safety compared to ipilimumab in patients with completely resected melanoma at high risk of recurrence

Date: 11 Sep 2017
Topic: Melanoma and other skin tumours / Cancer Immunology and Immunotherapy

Patients with stage IIIb/IIIc or stage IV melanoma at high risk of recurrence following complete surgical resection had greater recurrence-free survival (RFS) with adjuvant nivolumab compared to adjuvant ipilimumab, according to results from the phase III CheckMate 238 study reported at ESMO 2017, the Annual Congress of the European Society for Medical Oncology in Madrid, Spain.

Jeffrey Weber of the Perlmutter Cancer Center, NYU Langone Health in New York, USA presented the first results on behalf of an international research team from the CheckMate 238 trial (NCT02388906), which directly compared nivolumab to ipilimumab in patients with resected stage IIIb/c/IV melanoma at high risk of recurrence.

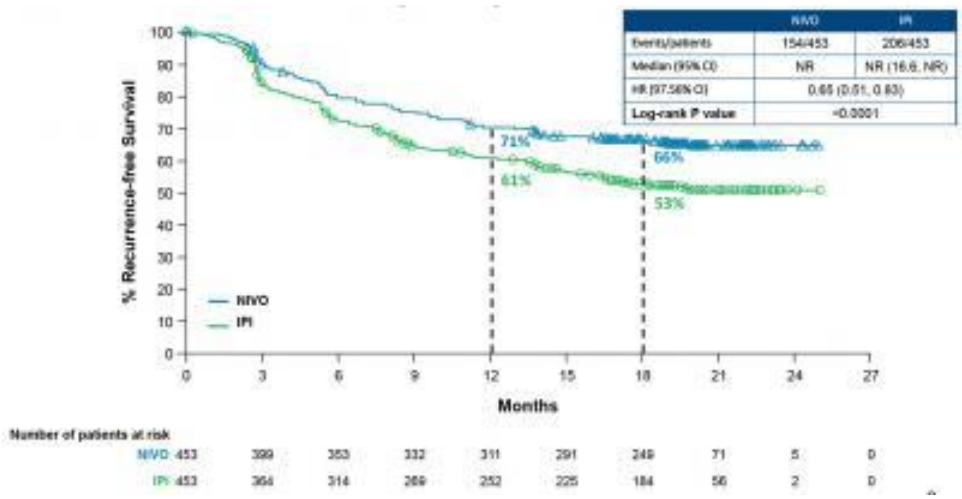
CheckMate 238 is an ongoing phase III, randomised, double-blind study of nivolumab versus ipilimumab in patients greater than 15 years of age who have undergone complete resection of stage IIIb/IIIc or stage IV melanoma. The trial randomised 906 patients, 453 patients per treatment arm, to receive either nivolumab at 3 mg/kg i.v. every two weeks or ipilimumab at 10 mg/kg i.v. every 3 weeks for four doses and every 12 weeks thereafter until documented disease progression or unacceptable toxicity, up to a maximum treatment duration of one year.

The primary endpoint of recurrence-free survival was met in the ongoing study

The primary endpoint in the study was RFS, defined as the time between randomisation and the date of first recurrence or death.

Overall, stage IIIb, IIIc, and IV disease was reported for 34%, 47%, and 19% of patients, respectively. Thirty-two percent of patients had ulcerated primary disease, 48% had macroscopic lymph node involvement, and 42% of patients were positive for the BRAF mutation.

RFS was significantly improved with nivolumab over ipilimumab at a median follow-up of 18.5 months; the 18-month RFS rates were 66.4% versus 52.7%, respectively, hazard ratio [HR] 0.65; 97.56% confidence interval [CI] 0.51, 0.83 ($p < 0.0001$).



CheckMate 238 primary endpoint: RFS.

© Jeffrey Weber.

Median RFS was not reached in either treatment arm.

Findings from prespecified subgroup analyses demonstrated consistent hazard ratios favouring nivolumab

Safety results also favour nivolumab

Fewer grade 3/4 treatment-related adverse events (TRAEs) were observed with nivolumab. Grade 3/4 TRAEs occurred in 14% of patients treated with nivolumab and 46% of patients on ipilimumab.

Study discontinuation due to an adverse event of any grade was reported in 10% of nivolumab and 43% of ipilimumab patients.

The incidence of grade 3/4 immune-related TRAEs for the following organ systems with nivolumab and ipilimumab was: gastrointestinal 2.0% versus 16.8%, hepatic 1.8% versus 10.8%, and skin 1.1% versus 6.0%.

No deaths due to study drug toxicity were reported for nivolumab; however, two (0.4%) patient deaths due to colitis and medullary aplasia occurred in patients more than 100 days after last ipilimumab dose.

Both drugs are currently approved for treatment of advanced melanoma

Nivolumab and ipilimumab are immune checkpoint inhibitors that restore immune anti-tumour activity by different mechanisms. Nivolumab blocks the programmed death 1

(PD-1) receptor and ipilimumab targets the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) molecule on T cells.

Both drugs have demonstrated significant benefit and have been approved for advanced melanoma. Ipilimumab has also been approved in the adjuvant setting for patients with resected stage III melanoma in the United States since 2015, based on results from the phase III international, double-blind EORTC 18071 trial. This trial showed that ipilimumab at a 10 mg/kg dose reduced the risk of recurrence by 25% versus placebo (HR 0.75; 95% CI, 0.64-0.90; $p < 0.002$).[1]

Despite surgical intervention and possible adjuvant treatment, most patients with stage IIIb/IIIc melanoma experience disease recurrence and many progress to advanced disease. By five years, 68% of patients with stage IIIb and 89% of patients with stage IIIc melanoma experience disease recurrence, making development of successful adjuvant therapy a priority in melanoma.

Conclusions

Nivolumab administered as adjuvant therapy significantly improved RFS compared to ipilimumab for patients with stage IIIb/c/IV melanoma at high risk of recurrence.

Nivolumab also demonstrated a superior safety profile.

Reinhard Dummer of the Skin cancer Unit Dermatology, Cancer Center Zürich, University Hospital, Zürich, Switzerland who discussed the study results said that his personal perspective in term of implications for approvals is that in USA, nivolumab will fully substitute the approval of ipilimumab in all stages including stage IIIA in the adjuvant setting and in Europe, nivolumab will be approved for stage IIIB and higher, dabrafenib/trametinib for stage IIIA-IIIC. His personal conclusions in term of surgical and medical management of stage III melanoma are that IFN and ipilimumab are no longer recommended in the adjuvant setting; in clinical trials, these control arms should be discontinued; adjuvant treatment options are nivolumab for all and dabrafenib/trametinib for BRAF mutant patients. He underlined that nessecity of complete lymphnode dissection is questionable and there is a need for urgent investigation. Neoadjuvant therapy is still experimental and must be applied in the context of clinical trials only.

The study results are simultaneously published in The New England Journal of Medicine.

Disclosure

This trial was sponsored by Bristol-Myers Squibb.

Citation

1. Eggermont AM, *et al*. *Lancet Oncol* 2015;16(5):522-530.

Acknowledgement

The co-senior authors for this abstract are Dr. J. Larkin and Dr. P.A. Ascierto.

Reference

LBA8_PR – Weber J, *et al.* Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: a randomized, double-blind, phase 3 trial (CheckMate 238).

Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. NEJM; Published online September 10, 2017. DOI: 10.1056/NEJMoa1709030

ESMO Daily Reporter, September 12, 2017

Late-Breaking Abstract presentations of phase III trial data in yesterday's Presidential Symposium gave exciting new insights into the future of treatment for resected, high-risk melanoma.

One of two studies investigating adjuvant BRAF inhibitor therapy for patients with BRAF V600 mutation-positive melanoma, the COMBI-AD trial, reported that the combination of dabrafenib plus trametinib significantly doubled relapse-free survival (RFS)—the primary endpoint—and improved a number of other endpoints, such as overall survival (OS), distant metastasis-free survival and freedom from relapse, compared with placebo in 870 patients with stage III disease (Abstract LBA6_PR).[1]

In the placebo-controlled BRIM8 trial, disease-free survival benefits with vemurafenib were substantial and significant for stage IIC–IIIB melanoma, but did not reach significance for stage IIIC disease (Abstract LBA7_PR).

During the same session, the CheckMate 238 trial demonstrated that adjuvant nivolumab was more effective than ipilimumab among 906 patients with stage III/IV melanoma after complete resection (Abstract LBA8_PR).[2]

The trial was stopped early due to clear evidence of benefit with nivolumab, which not only significantly improved RFS (hazard ratio [HR] 0.65; $p<0.0001$), but was far better tolerated.

The separate findings that combination dabrafenib–trametinib and nivolumab monotherapy have demonstrated survival benefits in the stage III melanoma setting will undoubtedly be practice changing.

Professor Georgina Long from Melanoma Institute Australia, Sydney, Australia, ommented, "These results are a game changer for the way we manage high-risk resected melanoma. The reduction in risk of recurrence of 35% for adjuvant nivolumab versus ipilimumab, and 53% for dabrafenib plus trametinib versus placebo, were highly significant and are clinically meaningful. Also, we saw an OS benefit with dabrafenib and trametinib, with a 43% reduction in the risk of death."

1. Long GV, et al. N Engl J Med 2017. Sept 10. Epub ahead of print
2. Weber J, et al. N Engl J Med 2017. Sept 10. Epub ahead of print

(View article here)

ESMO 2017 Press Releases

September 11, 2017

ESMO 2017 Press Release: Combination Targeted Adjuvant Therapy Doubles Relapse-free Survival in Stage III Melanoma

ESMO 2017 Press Release: Adjuvant Nivolumab Superior to Ipilimumab in Surgically Resected Stage III/IV Melanoma

Poster Submissions

To view and to learn more about specific topics related to melanoma and other skin cancers, follow this link to the Poster Submissions Visitors Carousel and enter "melanoma" in search. 44 posters are displayed for viewing or download purposes, for example: