Combination targeted adjuvant therapy doubles relapse-free survival in stage III melanoma

September 11 2017

Combination targeted adjuvant therapy with dabrafenib and trametinib doubles relapse-free survival in patients with stage III BRAF-mutant melanoma, according to late-breaking results from the COMBI-AD trial presented today at the ESMO 2017 Congress in Madrid (1) and published in the *New England Journal of Medicine*. (2)

"There is no standard of care for the adjuvant treatment of stage III melanoma," said the COMBI-AD presenter Axel Hauschild, Professor of Dermatology, University of Kiel, Kiel, Germany. "Interferon is approved for this situation but improves relative relapse-free survival by just 20% compared to placebo."

Previous phase III trials have shown that the combination of dabrafenib and trametinib improved overall survival and progression-free survival, and was well tolerated, in patients with advanced, unresectable metastatic BRAF-mutant melanoma. (3,4)

COMBI-AD is the first clinical trial of targeted therapies for adjuvant treatment of stage III melanoma. All patients had a BRAF mutation - 91% harboured a V600E mutation and 9% had a V600K mutation, which is the typical distribution in clinical practice. Patients had lymph node metastases which had been completely excised. The primary endpoint of the trial was to prolong relapse-free survival.

This double-blind trial randomised 870 patients 1:1 to combination therapy with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib versus matching placebos. Patients were treated for 12 months.

The trial met its primary endpoint. At a median follow-up of 2.8 years, the combination therapy had significantly reduced the risk of disease recurrence or death by 53% compared to placebo (hazard ratio [HR], 0.47; 95% confidence interval, 0.39-0.58). The relapse-free survival benefit with the combination therapy was observed across all patient subgroups.

The combination treatment also showed a benefit in secondary endpoints including overall survival (HR, 0.57), distant metastases-free survival (HR, 0.51) and freedom from relapse (HR, 0.47).

"These are the best results ever shown for an adjuvant treatment in stage III melanomas," said Hauschild. "Combination treatment with dabrafenib and trametinib more than doubled the relapse-free survival time compared to placebo and the improvement in overall survival was impressive, too."

Some 97% of patients on the combination had an adverse event of any kind and 41% had serious (grade 3/4) adverse events, compared to 88% and 14% with placebo, respectively. Around one-quarter (26%) of patients on the combination had to stop treatment due to adverse events versus 3% on placebo.

"The number of treatment discontinuations was a little higher than in trials on stage IV melanoma patients," said Hauschild. "This could be because 90% of patients had no progressive disease and were treated for the scheduled full year. The longer patients receive treatment, the more likely they are to have adverse events. But there were no new toxicities

compared to those already seen in stage IV disease and overall we can say the treatment was well tolerated."

He concluded: "These are practice changing results. The combination of dabrafenib and trametinib is a new and very effective adjuvant treatment option in high-risk melanoma patients."

Commenting on the results, Dr Olivier Michielin, head of Personalised Analytical Oncology, Lausanne, Switzerland, ESMO Melanoma Faculty Coordinator, said: "We have been trying to develop adjuvant therapies for melanoma for many years. Interferon led to minimal benefit and high toxicity and has not been widely adopted. The first revolution was ipilimumab, which improved progression-free survival and overall survival compared to placebo. Presented at the ESMO 2016 Congress, this was the first big breakthrough in the adjuvant setting. The ipilimumab regimen used in that study is, however, fairly toxic."

"Interferon and ipilimumab are both immunotherapies but COMBI-AD is the first trial reporting on the use of targeted therapies in the adjuvant setting for melanoma," continued Michielin. "The improvements in progression-free survival and overall survival are both very significant, making this new treatment an attractive option for patients with BRAF mutations, who constitute around half of the melanoma population. The different toxicity profiles between immunotherapy and the targeted therapies will factor into decisions on which to use."

He concluded: "Both ipilimumab and the combination of dabrafenib plus trametinib have improved overall survival compared to placebo. We now need to determine which adjuvant strategy is best suited for which patient, factoring in also the upcoming results of PD-1 blockade in that setting."

In the same ESMO session, late-breaking results will be presented from

the randomised BRIM8 trial of adjuvant vemurafenib in patients with resected BRAF-mutant melanoma at high risk for recurrence. (5) The drug had previously shown robust clinical activity in BRAF-mutant advanced/metastatic melanoma.

Adjuvant vemurafenib did not improve the primary endpoint of disease-free survival in patients with stage IIIC disease but appeared to be effective and well tolerated in patients with resected stage IIC-IIIB BRAF-mutant melanoma.

More information: References:

1 Abstract LBA6_PR 'COMBI-AD: Adjuvant Dabrafenib (D) Plus Trametinib (T) for Resected Stage III BRAF V600E/K-Mutant Melanoma' will be presented by Dr Axel Hauschild during Presidential Symposium III on Monday, 11 September 2017, 16:30 to 17:45 (CEST) in Madrid Auditorium.

2 Long G.V., Hauschild A., Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. DOI: 10.1056/NEJMoa1708539

3 Robert C, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372(1):30-39. DOI: 10.1056/NEJMoa1412690

4 Long GV, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877-1888. DOI: 10.1056/NEJMoa1406037.

5 Abstract LBA7_PR 'BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients (pts) with completely resected, BRAFV600+ melanoma at high risk for recurrence'

will be presented by Dr Karl Lewis during Presidential Symposium III on Monday, 11 September 2017, 16:30 to 17:45 (CEST) in the Madrid Auditorium.