

MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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Targeted Therapy for the Adjuvant Treatment of Stage III *BRAF*-Mutated Melanoma



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H&O What is considered the standard adjuvant treatment for stage III *BRAF*-mutated melanoma?

GL The standard treatment for patients with stage III *BRAF*-mutated melanoma after complete resection of disease varies around the world. In most countries, the standard treatment is observation with close monitoring. In the United States, a standard adjuvant therapy is interferon for 12 months.

H&O What was the basis for undertaking the COMBI-AD study, which appeared in late 2017 in the *New England Journal of Medicine*?

GL We undertook the COMBI-AD study (Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma) because the COMBI-v and COMBI-d trials showed that the combination of dabrafenib (Tafinlar, Novartis) and trametinib (Mekinist, Novartis) significantly improves progression-free survival and overall survival (OS) compared with vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) and dabrafenib, respectively, in patients with stage IV melanoma. A natural follow-up to these findings was to ask whether a period of drug therapy—we chose 12 months—after complete surgical resection of stage III melanoma could reduce the risk for recurrence or development of distant stage IV melanoma.

H&O Could you describe the design of COMBI-AD?

GL In COMBI-AD, patients who had completely resected stage III melanoma with a *BRAF* mutation, either V600E or V600K, were randomly assigned 1:1

Every subgroup benefitted from dabrafenib and trametinib compared with placebo in terms of relapse-free survival.

either to the combination of dabrafenib and trametinib or to placebo tablets daily for 12 months. Patients were monitored regularly, with computed tomography done every 3 months for the first 2 years and at increasing intervals thereafter. The primary endpoints for this study were relapse-free survival and OS. Secondary endpoints included freedom from relapse, survival free of distant metastases, and safety.

H&O What were the results?

GL This trial showed that the estimated 3-year rate of relapse-free survival was 58% with dabrafenib and trametinib vs 39% with placebo—so dabrafenib plus trametinib decreased the risk for recurrence or death by 53% (hazard ratio [HR], 0.47; $P < .001$). Furthermore, an early interim analysis suggested an improvement in 3-year OS with combination therapy vs placebo—86% vs 77%. Although this finding represents a 43% reduction in the risk for death (HR, 0.57; $P = .006$), the P value has not yet crossed the prespecified boundary of significance, which was set at very high levels ($P = .000019$). We plan to perform a fully powered analysis as soon as we accumulate more events and further follow-up data are available. At this early stage, OS appears to be much improved in the drug therapy arm receiving dabrafenib plus trametinib compared with the placebo arm.

H&O Could you discuss the additional data you presented at the Society for Melanoma Research annual meeting?

GL The new data we presented in Brisbane showed that every subgroup benefitted from dabrafenib and trametinib compared with placebo in terms of relapse-free survival. These subgroups included patients with stage IIIA, IIIB, or IIIC melanoma, patients with micrometastases or macrometastases, and those with ulcerated or nonulcerated primary tumors.

H&O What side effects did your study find with dabrafenib/trametinib? Were these what you expected to see?

GL The main side effect of dabrafenib/trametinib was pyrexia, which occurred in 63% of patients. Approximately half of the patients (52%) had 3 or more episodes of fever, which was higher than the number of episodes in the placebo group. This result was not unexpected and was in line with what we see in patients with stage IV disease.

H&O How was fever managed in the study patients?

GL Fever was managed in various ways at different sites around the world. The protocol mandated that the dabrafenib dose would be decreased after several episodes of fever. It also mandated that trametinib would be temporarily discontinued during a febrile episode. However, in our vast experience—both in this study and in prior studies of stage IV melanoma—the

Table. Pyrexia Management and Outcome in Patients Receiving Dabrafenib/Trametinib

| | Dabrafenib/ Trametinib (n=435) | Placebo (n=432) |
|---|--------------------------------------|--------------------|
| <i>Action taken, n (%)^a</i> | | |
| Drug withdrawn | 40 (14)/27 (9) | NA |
| Dose reduced | 86 (29)/18 (6) | NA |
| Drug interrupted | 202 (69)/121 (41) | NA |
| <i>Recovery/resolution, n (%)^a</i> | 289 (99) | 64 (97) |

^a Percentages based on number of patients with pyrexia.

NA, not applicable.

best management appears to be to stop both dabrafenib and trametinib at the first sign of fever or a fever-like syndrome, with resumption of the agents when the patient feels well again. The acute febrile episode can be managed symptomatically with acetaminophen or a nonsteroidal anti-inflammatory drug (Table).

H&O Why did your investigational group use a placebo for the control, rather than interferon or ipilimumab (Yervoy, Bristol-Myers Squibb)?

GL There is no standard adjuvant therapy throughout the world. Interferon is used mainly in the United States, although there are small pockets of use elsewhere. Interferon is associated with a very small benefit in terms of OS; although some patients benefit, it is not clear exactly who those patients are.

Ipilimumab had not yet shown any benefit at the time of the design and commencement of this study. The European Organisation for Research and Treatment of Cancer EORTC 18071 trial of adjuvant ipilimumab had only just completed recruitment. Recruitment for COMBI-AD was completed well before the results for adjuvant ipilimumab had been analyzed. Furthermore, ipilimumab carries significant toxicity. Finally, trials of other checkpoint inhibitors commenced well after COMBI-AD had completed recruitment.

H&O Have any studies compared dabrafenib/trametinib with interferon, ipilimumab, or checkpoint inhibitors?

GL There are no trials in the adjuvant setting comparing dabrafenib/trametinib with interferon, ipilimumab, or checkpoint inhibitors.

H&O What ongoing trials are examining the treatment of patients with stage III *BRAF*-mutated melanoma?

GL Many trials are looking at the adjuvant use of immunotherapies in stage III melanoma, including *BRAF*-mutated melanoma. The KEYNOTE-054 trial from EORTC is comparing pembrolizumab (Keytruda, Merck) vs placebo (NCT02362594). In addition, CheckMate 238 (NCT02388906) is comparing nivolumab (Opdivo, Bristol-Myers Squibb) vs ipilimumab, and CheckMate 915 (NCT03068455) is comparing nivolumab vs nivolumab/ipilimumab.

H&O What is the status of approval of dabrafenib/trametinib for use in patients with stage III disease?

GL The US Food and Drug Administration is currently considering dabrafenib/trametinib for patients with resected stage III melanoma.

Disclosure

Dr Long is a consultant advisor for Amgen, Array, Bristol-Myers Squibb, Idera, Merck/MSD, Novartis, Oncosec, Pierre Fabre, and Roche.

Suggested Readings

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