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MELANOMA

Time for adjuvant vemurafenib?

After complete resection, the standard-of-care procedure for stage IIC–III melanoma, most patients have a high risk of disease recurrence. Vemurafenib, a BRAF inhibitor with proven effectiveness in patients with advanced-stage or metastatic melanoma harbouring *BRAF*^{V600}, has now been tested in the adjuvant setting in the BRIM8 trial.

The intention-to-treat population was divided into two cohorts of patients with *BRAF*^{V600}-positive melanoma, who received either vemurafenib or placebo. Cohort 1 included patients with stage IIC–IIIB disease (157 patients in each arm). All of the patients in cohort 2 had stage IIIC disease: 93 patients received vemurafenib and 91 patients received placebo.

The primary end point was disease-free survival (DFS). In cohort 2, median DFS was 23.1 months (95% CI 18.6–26.5 months) in the vemurafenib group versus 15.4 months (95% CI 11.1–35.9 months) in the placebo group (HR 0.80). At 1 year, DFS was higher in the vemurafenib arm compared with placebo (78.9% versus 58%), but 2-year DFS was similar (46.3% versus 47.5%). Therefore, the primary end point was not met. In cohort 1, median DFS was not reached with vemurafenib (95% CI not estimable (NE)), and 36.9 months (21.4 months–NE) with placebo (HR 0.54). DFS was 84.3% and 66.2% in the vemurafenib and placebo groups at 1 year, respectively, and 72.3% versus 56.5% at 2 years.

In cohort 2, median distant metastasis-free survival (DMFS) was 37.2 months (95% CI 22.1 months–NE) versus 30.7 months (24.5 months–NE) for vemurafenib and placebo, respectively (HR 0.91). In cohort 1, median DMFS was not reached in either treatment group. Regarding toxicities, most adverse events were grade 1–2 and manageable (affecting 104 of 247 patients receiving vemurafenib and 182 of 247 patients receiving placebo, in both cohorts). Grade 3–4 adverse events occurred in 141 of 247 patients in the vemurafenib group and 37 of 247 patients in the placebo group. The most common event was basal cell carcinoma, which affected eight patients in each arm.

Taken together, the results of the BRIM8 trial show that vemurafenib reduces the risk of disease recurrence in patients with stage IIC–IIIB *BRAF*^{V600}-positive melanoma. However, this result could not be considered statistically significant because the primary end point was not met in the cohort including patients with stage IIIC disease.

Until 2017, the only options in the adjuvant setting for patients with stage IIC–III melanoma were interferon-α or the anti-CTLA-4 monoclonal antibody ipilimumab. Pivotal studies have been performed in the past few years in this disease setting to solve this unmet need. In 2017, the publication of CheckMate 238 and COMBI-AD resulted in the FDA approvals of nivolumab and dabrafenib plus trametinib, respectively. Whether vemurafenib becomes another treatment option, perhaps in combination with a MEK inhibitor and/or adding a neoadjuvant phase in the treatment plan, needs further investigation.

Diana Romero

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FURTHER READING Killock, D. Drug therapy: moving on up — from stage IV into stage III. *Nat. Rev. Clin. Oncol.* **14**, 647 (2017) | Sidaway, P. Melanoma: neo/adjuvant BRAF/MEKi improves outcomes. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/nrclinonc.2018.23 (2018)