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Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: Final results regarding distant metastasis-free survival from the EORTC 1325-MG/Keynote 054 double-blinded phase III trial

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Background

We conducted the randomized phase III double-blind EORTC 1325/KEYNOTE-054 trial to evaluate pembrolizumab vs placebo in patients (pts) with resected high-risk stage III melanoma. At a 1.25-year (yr) median follow-up, pembrolizumab improved recurrence-free survival (RFS) (hazard ratio [HR] 0.57, P<0.0001) as compared to placebo (Eggermont, NEJM 2018). This led to the approval of pembrolizumab adjuvant treatment by EMA and FDA.

Methods

Eligible pts included those ≥18 yrs of age with complete resection of cutaneous melanoma metastatic to lymph node(s), classified as AJCC-7 stage IIIA (at least one lymph node metastasis >1 mm), IIIB or IIIC (without in-transit metastasis). Between Aug-2015 until Nov-2016, 1019 pts were randomized to pembrolizumab at a flat dose of 200 mg (N=514) or placebo (N=505) every 3 weeks for a total of 18 doses (⊠1 year) or until disease recurrence or unacceptable toxicity. The 2 main co-primary endpoints were RFS in the intention-to-treat (ITT) overall population and in pts with PD-L1-positive tumors. Secondary endpoints included distant metastasis-free survival (DMFS) in these 2 respective populations. The final DMFS analysis was foreseen when approximately 423 DMFS events (distant metastases or deaths) are reported (⊠87% power to detect a HR of 0.725 in the overall population).

Results

By April 2020, 418 DMFS events were reported. At 3.5 yr median follow-up, pembrolizumab compared with placebo significantly prolonged DMFS in the overall population (3.5-yr DMFS rate: 65.3% vs 49.4%; HR 0.60, 95% CI 0.49-0.73; P<0.0001) and in the PD-L1-positive tumor (N=853; HR 0.61; 95% CI 0.49-0.76; P<0.0001). The impact of pembrolizumab on DMFS was similar in pts with a PD-L1-negative tumor (N=116; HR 0.49, 99% CI 0.24-0.99) and in other subgroups, in particular according to AJCC-7 and -8 staging, and BRAF mutation status. The RFS improvement was confirmed (HR in the ITT population 0.59; 95% CI 0.49-0.70).

Conclusions

At 3.5-yr median follow-up, pembrolizumab adjuvant therapy provided a clinically meaningful improvement in DMFS in resected high-risk stage III melanoma pts.

Clinical trial identification

EudraCT: 2014-004944-37.

Legal entity responsible for the study

Merck & Co., Inc.

Funding

Merck & Co., Inc.

Disclosure

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