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Hypofractionated radiotherapy of single tumor lesion increases systemic response rate to pembrolizumab in recurrent or metastatic head-and-neck cancer (R/M-HNSCC): Primary endpoint of the randomized Keynote-717 trial

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Background

Pembrolizumab (P) improves survival in R/M-HNSCC, whereas the response rate is low. Pre-clinical and early clinical studies suggested that radiotherapy (RT) can function as an in-situ vaccine, broadening tumor-specific T-cell repertoires and inducing systemic (abscopal) immune-mediated tumor regression when combined with immune-checkpoint inhibitors.

Methods

Keynote-717 is an investigator-initiated prospective, open-label, randomized phase II trial in adults with R/M- HNSCC. Study inclusion required a PD-L1 CPS ≥ 1 for first line therapy; no PD-L1 threshold for second line therapy. In addition, a tumor lesion (≥ 2ml) amenable to RT plus ≥ 1 additional measurable lesion according to iRECIST criteria was required. Patients were randomized 1:1 to pembrolizumab 200mg q3w (P) or P plus hypofractionated RT (36 Gy in 12 fractions) to a tumor lesion (RT+P). Primary endpoint was overall response rate (ORR) of unirradiated lesions according to iRECIST. Hypothesis was an increase of the ORR from 18 to 36 %, which resulted in a total of 130 patients to be randomized (one-sided p=0.10 and power 80%; intention to treat; ITT). Patients with at least 2 cycles of P were defined as per protocol (PP). Secondary endpoints included duration of response (DOR) and overall survival (OS).

Results

Between 2018 and 2024 a total of 115 patients were randomized in 8 German sites (n=57 RT+P vs. n=58 P). Median follow-up time was 9.3 months. ORR according to iRECIST was 35 % in the RT+P arm versus 22 % in the P arm (OR = 1.87; one-sided p = 0.097, meeting the prespecified phase-II success criterion). In the PP analysis (n=46 RT+P vs. n=54 P) the ORR was 43% for RT+P and 24% for P (OR=2.43; p=0.033). Median DOR was 10.4 months for RT+P vs. 8.3 months for P (log-rank p=0.59). Median OS was 11.4 months and 11.3 months, respectively (HR 1.04, 95 % CI 0.67–1.63). The number of patients with any treatment-related adverse event (trAE) grade 3-4 was 11% for RT+P and 5% for P (no grade 5 trAE).

Conclusions

The trial met the prespecified phase-II efficacy endpoint. Local RT increased the systemic response rate to P. Exploratory analyses revealed no significant effect on OS.

Clinical trial identification

NCT03386357.

Legal entity responsible for the study

Dean of the Medical Faculty of the Friedrich-Alexander University Erlangen-Nürnberg.

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Disclosure

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