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Mature survival and integrated biomarker analyses of the randomised ADMEC-O trial of adjuvant nivolumab in Merckel cell carcinoma

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Background

Adjuvant PD-1 blockade has demonstrated promising activity in resected Merckel cell carcinoma (MCC), but its long-term clinical benefit and the biological determinants of response remain unknown. We report the final clinical and integrated translational analyses of the randomized phase II ADMEC-O trial.

Methods

ADMEC-O (NCT02196961) was an open-label, randomized (2:1), multicentre phase II trial comparing one year of adjuvant nivolumab with observation following complete resection of stage I–IV MCC. The primary endpoint was disease-free survival (DFS). Secondary endpoints included overall survival (OS), safety and health-related quality of life. Exploratory translational analyses integrated histopathology, spatial immune phenotyping, DNA methylation profiling, transcriptomics and T-cell receptor repertoire sequencing to identify prognostic and predictive biomarkers.

Results

A total of 179 patients were randomized. Adjuvant nivolumab resulted in a numerical but not statistically significant improvement in DFS (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.38–1.26), whereas OS was unchanged (HR 0.98, 95% CI 0.43–2.27). Grade 3–4 treatment-related adverse events occurred in 40% of nivolumab-treated patients. Exploratory subgroup analyses suggested greater OS benefit in patients aged ≤65 years. Most immune-related molecular signatures were prognostic but not predictive of treatment benefit. In contrast, mature tertiary lymphoid structures (TLS) emerged as the only biomarker demonstrating evidence of predictive value for adjuvant nivolumab. Spatial analyses showed that TLS comprise functional immune niches supporting antigen presentation, T-cell priming and checkpoint-dependent immune regulation.

Conclusions

Mature follow-up of ADMEC-O showed that adjuvant nivolumab did not significantly improve OS in an unselected population with resected MCC despite a numerical improvement in DFS. Integrated translational analyses identified mature TLS as the leading candidate predictive biomarker for adjuvant PD-1 blockade, supporting biomarker-guided patient selection in future adjuvant MCC trials.

Clinical trial identification

EudraCT 2013-000043-78, NCT02196961.

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Legal entity responsible for the study

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Disclosure

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