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Treatment with tumor-infiltrating lymphocytes (TIL) versus ipilimumab for advanced melanoma: Results from a multicenter, randomized phase III trial

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Background

Immune checkpoint inhibitors and targeted therapies have greatly improved the outcome of patients (pts) with advanced melanoma. However, as approximately half will not derive durable benefit, a large unmet need for additional treatment options remains. Adoptive cell therapy with TIL is a treatment modality with promising response rates (RR) of 36-70% in pts with advanced melanoma, observed in multiple phase 1/2 trials. To date, no data from phase 3 trials is available to determine the role of TIL in the current treatment landscape.

Methods

In this multicenter, open-label phase 3 trial, pts with unresectable stage IIIC-IV melanoma (7^{th} edition), ≥18 ≤ 75 years, were randomized 1:1 to TIL or ipilimumab (3mg/kg q3wks, max 4 doses). Pts were stratified for $BRAF^{V600}$ mutation status, treatment line and center. Pts randomized to TIL underwent resection of a melanoma lesion (2-3cm) for the *ex vivo* outgrowth and expansion of tumor resident T cells. Infusion of ≥$5x10^9$ TIL was preceded by non-myeloablative, lymphodepleting chemotherapy with cyclophosphamide + fludarabine and followed by high-dose interleukin-2. The primary endpoint was progression-free survival (PFS) per RECIST 1.1. Secondary endpoints were (overall and complete) RR, overall survival (OS) and safety.

Results

In total, 168 pts, the majority (86%) refractory to anti-PD-1 treatment, were randomized to TIL (n=84) or ipilimumab (n=84). With a median follow-up of 33.0 months, median PFS was 7.2 months for TIL (95% CI, 4.2 - 13.1), compared to 3.1 months (95% CI, 3.0 - 4.3) for ipilimumab (HR: 0.50 [95% CI, 0.35 - 0.72]; P<0.001). Overall RR was 49% (95% CI, 38% - 60%) for TIL and 21% (95% CI, 13% - 32%) for ipilimumab, with 20% (95% CI, 12% - 30%) and 7% (95% CI, 3% - 15%) complete responses, respectively. Median OS for TIL was 25.8 months (95% CI, 18.2 - not reached) and 18.9 months (95% CI, 13.8 - 32.6) for ipilimumab (HR: 0.83 [95% CI, 0.54 - 1.27]; P=0.39). Grade ≥3 treatment-related adverse events occurred in all TIL and 57% of ipilimumab pts.

Conclusions

TIL therapy significantly improved PFS compared to ipilimumab in pts with advanced melanoma, the vast majority being anti-PD-1 refractory, making it a possible new treatment option in this pt population.

Clinical trial identification

NCT02278887.

Legal entity responsible for the study

Netherlands Cancer Institute.

Funding

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Disclosure

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