Background Novel early-line therapies for advanced (unresectable or metastatic) melanoma are needed to improve the rate of deep and durable responses and increase the proportion of patients with long-term benefit. TILVANCE-301 will evaluate the efficacy and safety of lifileucel autologous TIL cell therapy + pembrolizumab (pembro) in patients with untreated advanced melanoma.

Methods TILVANCE-301 (NCT05727904) is a phase 3, multicenter, randomized, open-label, parallel group study that will randomize ~670 patients (1:1; Day 0) to Arm A: lifileucel + pembro (Day 3: tumor tissue resection for TIL manufacturing; Day 5: pembro 200 mg; Day 26: pembro 400 mg; Day 28–29: cyclophosphamide 60 mg/kg; Day 28–32: fludarabine 25 mg/m²; Day 33: lifileucel; Day 34–37: ≤6 doses of high-dose IL-2; Week 10: pembro 400 mg Q6W) or Arm B: pembro alone (same pembro dosing as Arm A). Patients in Arm B with confirmed progressive disease verified by blinded independent review committee (BIRC) have the option to receive lifileucel monotherapy as immediate next treatment and may continue pembro until start of lymphodepleting chemotherapy.

Eligible adults have histologically confirmed advanced melanoma, ECOG PS 0–1, estimated life expectancy >6 mo, ≥1 resectable lesion to generate lifileucel, and ≥1 remaining measurable lesion. Prior neoadjuvant or adjuvant treatment including immune checkpoint inhibitors may be allowed. Prior therapy for metastatic disease, symptomatic untreated brain metastases, organ allograft or prior cell therapy, uveal/ocular melanoma, and chronic systemic steroid therapy are not permitted.

The dual primary efficacy endpoints are BIRC-assessed (RECIST v1.1) ORR and PFS. Key secondary efficacy endpoint is OS. Additional secondary efficacy endpoints include BIRC-assessed CR rate, DOR, and EFS; investigator-assessed ORR, PFS, CR rate, DOR, EFS, and PFS2; and safety as characterized by severity and seriousness of TEAEs, and relationship to study drug. Exploratory endpoints include in vivo T-cell persistence (unique CDR3 sequences in PBMC over time) and correlative biomarkers (eg, lifileucel phenotypic and functional characteristics; lifileucel, tumor, and PBMC gene expression profiles; tumor mutational landscape).

The study will enroll globally, with initial sites in Europe, North America, and Australia.

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Trial Registration NCT05727904

Ethics Approval The study was approved by the institutional review board at each site and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonization. All patients provided written informed consent.

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