TILVANCE-301, a Phase 3 Study of Lifileucel Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy Combined With Pembrolizumab (Pembro) vs Pembro Alone in Treatment-Naïve Unresectable or Metastatic Melanoma

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Background

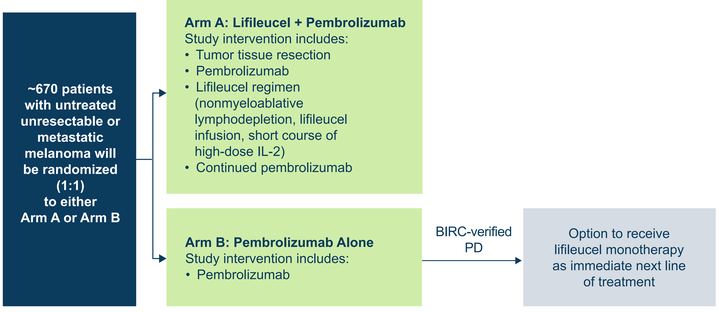
- ICI and targeted therapies have transformed the treatment landscape of advanced (unresectable or metastatic) melanoma; however, most patients receiving frontline ICI experience disease progression within 1 year[1-3]
- Further, 40%–65% of patients have disease that is primary resistant to ICI,[4-6] and 30%–40% of patients have secondary-resistant disease[6-8]
- Novel early-line therapies are needed to improve the rate of deep and durable responses and to increase the proportion of patients with long-term benefit
- Lifileucel, an autologous TIL cell therapy, has demonstrated potentially meaningful clinical activity in patients with advanced melanoma in the post-ICI setting[9,10]
- The combination of lifileucel with pembrolizumab has the potential for enhanced antitumor activity through the addition of PD-1 blockade allowing for optimal engraftment, increased cytotoxicity, and intratumoral expansion of the infused lifileucel product
  - Continued pembrolizumab therapy after lifileucel infusion is expected to perpetuate the antitumor effect
- Earlier-line treatment with lifileucel plus pembrolizumab demonstrated encouraging efficacy in patients with ICI-naïve advanced melanoma in Cohort 1A of the Phase 2 IOV-COM-202 study[11,12]
  - Investigator-assessed ORR of 67%
  - CR rate of 25%

TILVANCE-301 Study Overview

- **TILVANCE-301** (NCT05727904) is a Phase 3, multicenter, randomized, open-label, parallel-group treatment study to assess the efficacy and safety of lifileucel in combination with pembrolizumab compared with pembrolizumab alone in patients with untreated unresectable or metastatic melanoma (**Figure 1** and **Figure 2**)
  - ~670 patients will be randomized 1:1 to either Arm A (lifileucel plus pembrolizumab) or Arm B (pembrolizumab alone)
  - Patients randomized to Arm B who receive pembrolizumab and experience confirmed progressive disease verified by BIRC have the option to receive lifileucel monotherapy as the immediate next line of treatment, and may continue pembrolizumab until start of nonmyeloablative lymphodepletion

Study Design and Treatment Regimen

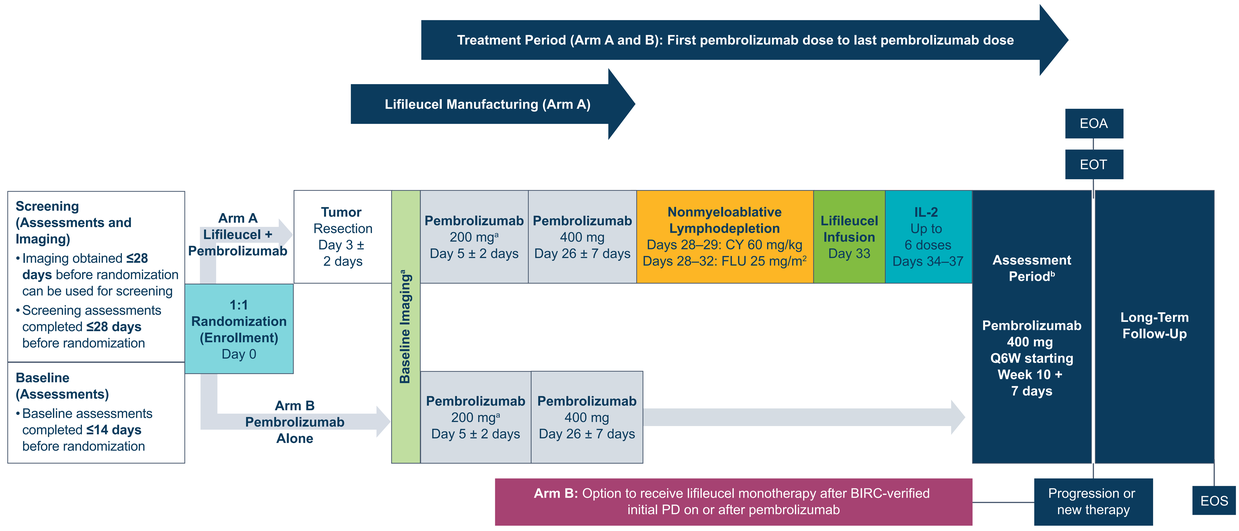
Figure 1. TILVANCE-301 Study Design



Study Endpoints

- **Dual primary efficacy endpoints**
  - BIRC-assessed ORR per RECIST v1.1
  - BIRC-assessed PFS per RECIST v1.1
- **Key secondary efficacy endpoint**
  - OS
- **Additional secondary endpoints**
  - BIRC-assessed CR rate, DOR, EFS per RECIST v1.1
  - Investigator-assessed ORR, PFS, CR rate, DOR, EFS, PFS2 per RECIST v1.1
  - Safety (characterized by severity and seriousness of TEAEs, and relationship to study drug)
- **Exploratory endpoints**
  - In vivo T-cell persistence (unique CDR3 sequences in PBMC over time)
  - 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**

Figure 2. TILVANCE-301 Treatment Schema



[a]Baseline imaging will be obtained prior to first pembrolizumab dose. Both treatment arms have the same schedule for pembrolizumab doses and tumor assessments, with pembrolizumab continued until PD, initiation of a new anti-cancer therapy, CR, or unacceptable toxicity; death; withdrawal of consent; or study completion. [b]First post-treatment tumor assessment is at Week 10 +7 days before the third dose of pembrolizumab in both treatment arms. Assessments are done every 6 weeks until Month 7 ±7 days, then every 12 weeks until PD, planned initiation of a new anti-cancer therapy, unacceptable toxicity, withdrawal of consent, death, or study completion.

Key Eligibility Criteria

Inclusion Criteria

- Histologically or pathologically confirmed diagnosis of Stage IIIC, IIID, or IV unresectable or metastatic melanoma
- Age 18–70 years
  - Patients >70 years of age may be allowed (after discussion with the medical monitor)
- ECOG PS 0 or 1 and estimated life expectancy >6 months
- ≥1 resectable lesion(s) with an estimated minimum diameter of 1.5 cm for lifileucel generation and ≥1 remaining measurable lesion as defined by RECIST v1.1
- Adequate organ function
- Patients of childbearing potential or those with partners of childbearing potential must be willing to practice an approved method of highly effective birth control

Exclusion Criteria

- Melanoma of uveal/ocular origin
- Symptomatic untreated brain metastases
- Prior therapy for metastatic disease or >1 prior line of therapy in any setting
  - Patients completing 1 prior line of neoadjuvant/adjuvant therapy with no progression for ≥6 months are allowed (except for patients with *BRAF V600* mutation receiving ICI alone as prior neoadjuvant/adjuvant therapy)
- Active medical illnesses (eg, systemic infections; seizure disorders; coagulation disorders; other active major medical illnesses of the cardiovascular, respiratory, or immune systems)
- Any form of primary or acquired immunodeficiency (eg, SCID, AIDS)
- Other primary malignancy in the last 3 years
- Allogeneic cell or organ transplant
- Chronic systemic steroid therapy

Abbreviations

AIDS, acquired immunodeficiency syndrome; BIRC, blinded independent review committee; CDR3, complementarity determining region 3; CR, complete response; CY, cyclophosphamide; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; EOA, end of assessment; EOS, end of study; EOT, end of treatment; FLU, fludarabine; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; NMA-LD, nonmyeloablative lymphodepletion; ORR, objective response rate; OS, overall survival; PBMC, peripheral blood mononuclear cell; PD, progressive disease; PD-1, programmed cell death protein-1; PFS, progression-free survival; PFS2, progression-free survival 2; Q6W, every 6 weeks; Q12W, every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SCID, severe combined immunodeficiency; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocyte.

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