Trial in Progress: A Phase 3 Study (TILVANCE-301) to Assess the Efficacy and Safety of Lifileucel, an Autologous Tumor-Infiltrating Lymphocyte (TIL) Cell Therapy, in Combination With Pembrolizumab Compared With Pembrolizumab Alone in Patients With Untreated Unresectable or Metastatic Melanoma

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Background

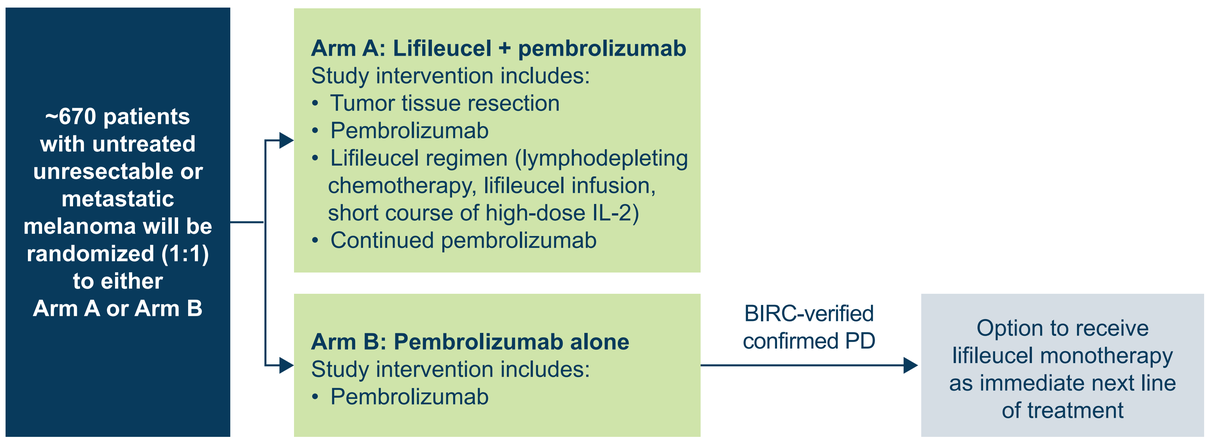
- ICI and targeted therapies have transformed the treatment landscape of advanced (unresectable or metastatic) melanoma; however, most patients receiving frontline ICI progress within a year[1-3]
- Further, 40%–65% of patients have disease that is primary resistant to ICI,[4-6] and 30%–40% of patients 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**)
  - ~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

Study Design and Treatment Regimen

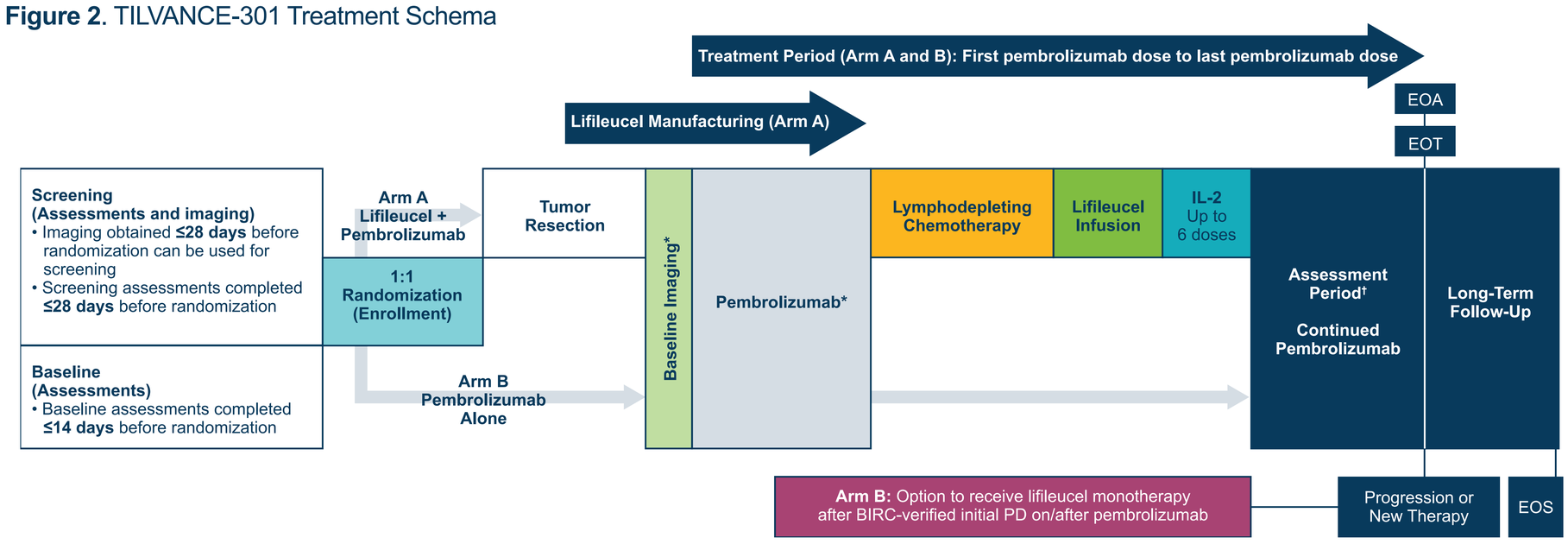
Figure 1. TILVANCE-301 Study Design



Study Endpoints

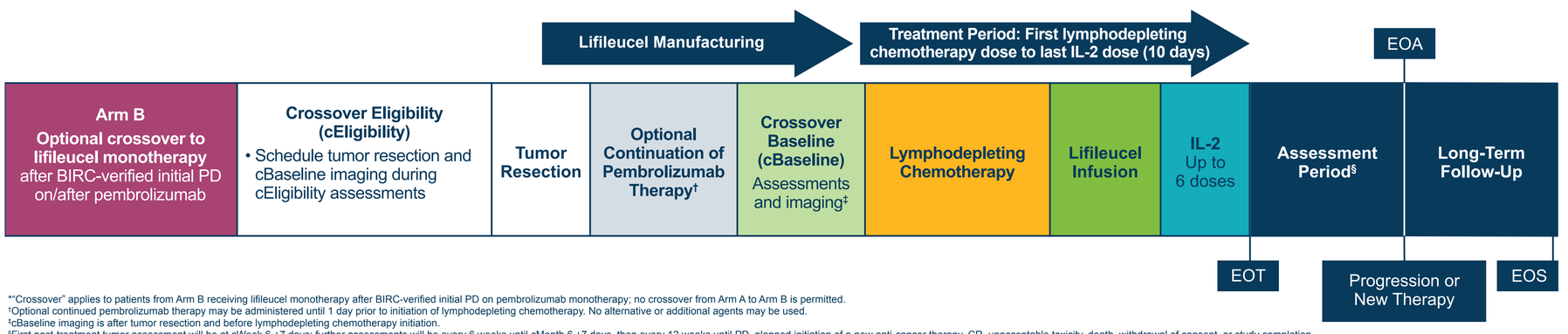
- **Dual primary efficacy endpoints**
  - ORR as assessed by BIRC per RECIST v1.1
  - PFS as assessed by BIRC per RECIST v1.1
- **Key secondary efficacy endpoint**
  - OS
- **Additional secondary endpoints**
  - BIRC-assessed CR rate, DOR, EFS per RECIST v1.1
  - Investigator-assessed ORR, PFS, CR rate, DOR, EFS, PFS2 per RECIST v1.1
  - Safety (characterized by severity and seriousness of TEAEs, and relationship to study drug)
- **The study will enroll globally**

Figure 2. TILVANCE-301 Treatment Schema



*Baseline imaging will be obtained prior to 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.
†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.

Figure 3. Optional Crossover* Schema for Participants in Arm B With Progression on Pembrolizumab Monotherapy



*"Crossover" applies to patients from Arm B receiving lifileucel monotherapy after BIRC-verified initial PD on pembrolizumab monotherapy; no crossover from Arm A to Arm B is permitted.
†Optional continued pembrolizumab therapy may be administered until 1 day prior to initiation of lymphodepleting chemotherapy. No alternative or additional agents may be used.
‡cBaseline imaging is after tumor resection and before lymphodepleting chemotherapy initiation.
§First post-treatment tumor assessment will be at cWeek 6 +7 days; further assessments will be every 6 weeks until cMonth 6 ±7 days, then every 12 weeks until PD, planned initiation of a new anti-cancer therapy, CR, unacceptable toxicity, death, withdrawal of consent, 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) 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

Abbreviations

AIDS, acquired immunodeficiency syndrome; BIRC, blinded independent review committee; cBaseline, baseline for the crossover period; cEligibility, eligibility assessments and imaging for the crossover period; CR, complete response; cWeek, crossover week; 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; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SCID, severe combined immunodeficiency; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocyte.

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