A phase 2 study of LBL-007 (anti-LAG-3) plus tislelizumab (anti-PD-1) and chemotherapy as first-line treatment in patients with unresectable locally advanced/metastatic esophageal squamous cell carcinoma.

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ABSTRACT

Background: Co-inhibition of lymphocyte activation gene-3 (LAG-3) and programmed cell death protein-1 (PD-1) may enhance antitumor responses for patients (pis) with advanced/metastatic esophageal squamous cell carcinoma (ESCC). We evaluated the efficacy and safety of LBL-007, a novel, fully human anti-LAG-3 lgG4 monoclonal antibody (mAb), with tislelizumab (TIS), a humanized lgG4 anti-PD-1 mAb, and chemotherapy (CT) in pis with unresectable, locally advanced/metastatic ESCC, regardless of baseline PD-L1 status.

Methods: In this phase 2, randomized, active-controlled, open-label trial (NCT06010303), pis ;,18 years with ECOG PS ,;1 and no prior systemic therapy were randomized 2:1 to LBL-007 (600 mg IV Q3W) + TIS (200 mg IV Q3W) + CT (Arm A; A) or TIS (200 mg IV Q3W) + CT (Arm B; B); CT was 60-80 mg/m2 cisplatin + 750-800 mg/m2 5-FU or 175 mg/m2 paclitaxel IV Q3W. Primary endpoint was overall response rate (ORR) per investigator-assessed RECIST v1.1. Secondary endpoints were progression-free survival (PFS), duration of response (DoR), disease control rate (DCR), and incidence and severity of treatment-emergent adverse events (TEAEs).

Results: As of May 30, 2025, 118 pis were randomized (A: n = 78; B: n = 40). Median age (range) was 61.5 (44-80) years in A and 65.5 (46-80) in B; 85.9% of pis in A and 87.5% in B were male. Median follow-up (range) was 12.5 (0-18.5) months (mo) in A and 11.5 (0.4-18.8) in B. Confirmed ORR (95% CI) was 61.5% (49.8-72.3) in A and 60.0% (43.3-75.1) in B (Table). Median PFS (95% CI) was 8.2 (5.7-9.2) mo in A and 6.9 (5.6-8.2) in B (HR, 0.85 [95% CI, 0.54-1.34]; P= 0.4753).

The most common TEAEs were anemia (A: 63 [81.8%]; B: 27 [67.5%1), neutrophil count decreased (A: 53 [68.8%]; B: 24 [60.0%1) and WBC count decreased (A: 48 [62.3%]; B: 21 [52.5%1). Grade ;,3 treatment-related TEAEs occurred in 77.9% of pis in A and 65.0% in B. TEAEs led to discontinuation in 23 (29.9%) pis in A and 11 (27.5%) in B, and to death in 2 (2.6%) and 2 (5.0%) pis, respectively. Immune-mediated AEs occurred in 40 (51.9%) pis in A and 20 (50%) in B, and infusion-related reactions in 7 (9.1%) and 2 (5.0%) pis, respectively.

Conclusions: In pis with advanced/metastatic ESCC, adding LBL-007 to TIS+ CT did not improve ORR versus TIS+ CT alone, which was consistent with historical data in this

population. PFS was numerically longer with LBL-007 but not statistically significant. The safety profile of the triplet was manageable and consistent with the known profiles of the individual agents.

Efficacy table

	ArmA n=78	**Arm B** n=40
ORR, n (%) 95% CI	48 (61.5) 49.8-72.3	24 (60.0) 43.3-75.1
Complete response	2 (2.6)	1 (2.5)
Partial response	46 (59.0)	23 (57.5)
Stable disease	23 (29.5)	12 (30.0)
Progressive disease	4 (5.1)	3 (7.5)
Not evaluable (NE)	3 (3.8)	1 (2.5)
DCR, n (%) 95% CI	71 (91.0) 82.4-96.3	36 (90.0) 76.3-97.2
DoR, median, mo 95% CI	7.2 5.7-12.3	7.3 4.1-NE