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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CONCLUSIONS

- In patients with advanced or metastatic ESCC, adding LBL-007 to TIS and CT demonstrated comparable ORR with TIS and CT, which is consistent with historical data in this patient population
- PFS was numerically longer with the addition of LBL-007
- A trend toward improved PFS and ORR in the small subgroups of patients with PD-L1 low expression or LAG-3 high (≥10%) expression indicated the need for specific biomarker identification
- The safety profile of LBL-007 plus TIS and CT was manageable and consistent with the known profiles of the individual agents

INTRODUCTION

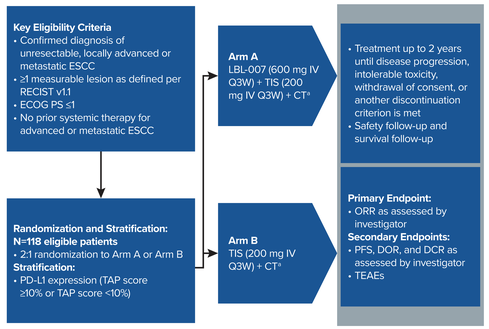
- Esophageal squamous cell carcinoma (ESCC) accounts for approximately 90% of esophageal cancer cases worldwide,[1] and is associated with poor clinical outcomes, with a 5-year survival rate of only 5.4% for patients with distant metastases[2]
- Tislelizumab (TIS), a humanized IgG4 anti-programmed cell death protein-1 (PD-1) monoclonal antibody (mAb), in combination with platinum-based chemotherapy (CT), is approved as first-line treatment for advanced or metastatic ESCC
- Lymphocyte activation gene-3 (LAG-3) is an immune checkpoint protein that is co-expressed with PD-1 on tumor-infiltrating T cells and has been shown to be upregulated in anti-PD-1 resistant tumors;[3-5] thus, co-inhibition of LAG-3 and PD-1 may enhance antitumor responses
- LBL-007 is a novel, fully human anti-LAG-3 IgG4 mAb developed for the treatment of solid tumors
- In this phase 2 study, efficacy and safety of LBL-007 with TIS and CT in patients with unresectable, locally advanced or metastatic ESCC, regardless of baseline programmed cell death protein-ligand 1 (PD-L1) status is being assessed

METHODS

Trial Design

- This was a phase 2, randomized, active-controlled, open-label trial (NCT06010303; **Figure 1**)

Figure 1. Study Design



[a]The CT doublet consisted of either cisplatin + 5-fluorouracil (5-FU) or cisplatin + paclitaxel.
Abbreviations: DCR, disease control rate; DOR, duration of response; ECOG PS; Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, overall response rate; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TAP, tumor area positivity; TEAE, treatment-emergent adverse event.

Analysis and Statistical Methods

- The intent-to-treat (ITT) analysis set included all randomized patients and was used for all efficacy analyses
- The safety analysis set included all patients who received ≥1 dose of any component of study treatment and was used for the safety analysis
- Efficacy was assessed by the investigator per RECIST v1.1
- Descriptive statistics were used to summarize the demographic, disease characteristic, efficacy, and safety data
- No statistical hypotheses were planned for this exploratory study
- PD-L1 expression was determined centrally by TAP score, which was evaluated based on visual estimation of positive tumor cells (TCs) and tumor-associated immune cells (ICs) by the VENTANA PD-L1 (SP263) assay
- LAG-3 expression was retrospectively determined by IC score, defined by the percentage of positive ICs over the total tumor area

RESULTS

Baseline Characteristics and Patient Disposition

- As of the data cutoff date of May 30, 2025, 118 patients were randomized (Arm A: n=78; B: n=40; **Table 1**)
- Median study follow-up (range) time was 12.5 (0-18.5) months in Arm A and 11.5 (0.4-18.8) months in Arm B

Table 1. Baseline characteristics (ITT analysis set)

	Arm A (n=78)	Arm B (n=40)	Total (N=118)
Median (range), age, years	61.5 (44-80)	65.5 (46-80)	63.5 (44-80)
Sex, n (%)			
Male	67 (85.9)	35 (87.5)	102 (86.4)
Female	11 (14.1)	5 (12.5)	16 (13.6)
ECOG PS, n (%)			
0	25 (32.1)	13 (32.5)	38 (32.2)
1	53 (67.9)	27 (67.5)	80 (67.8)
Race, n (%)			
Asian	78 (100.0)	40 (100.0)	118 (100.0)
Chinese	64 (82.1)	30 (75.0)	94 (79.7)
Korean	10 (12.8)	5 (12.5)	15 (12.7)
Thai	4 (5.1)	5 (12.5)	9 (7.6)
Baseline PD-L1 TAP score, n (%)			
≥10%	17 (21.8)	9 (22.5)	26 (22.0)
<10%	61 (78.2)	31 (77.5)	92 (78.0)
Patients with metastatic disease at study entry, n (%)	69 (88.5)	32 (80.0)	101 (85.6)
Number of metastatic sites at study entry, n (%)			
0	9 (11.5)	8 (20.0)	17 (14.4)
1	29 (37.2)	15 (37.5)	44 (37.3)
2	23 (29.5)	11 (27.5)	34 (28.8)
≥3	17 (21.8)	6 (15.0)	23 (19.5)
Backbone chemotherapy regimen, n (%)[a]			
Cisplatin + paclitaxel	62 (79.5)	31 (77.5)	93 (78.8)
Cisplatin + 5-FU	15 (19.2)	9 (22.5)	24 (20.3)

[a]Includes patients who received at least 1 treatment regimen.

Efficacy Results

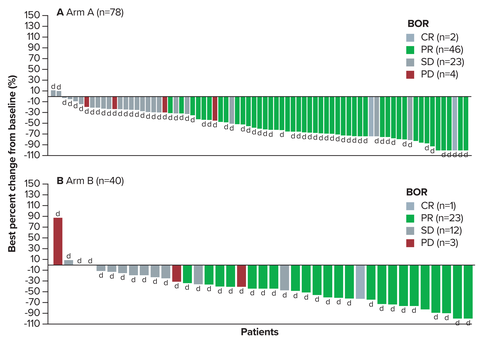
- Confirmed ORR (95% confidence interval [CI]) was 61.5% (49.8-72.3) in Arm A and 60.0% (43.3-75.1) in Arm B (**Table 2**)
- Best overall response (BOR) in both treatment arms was complete response (CR), which was observed in 2 patients (2.6%) in Arm A and 1 patient (2.5%) in Arm B (**Figure 2**)
- Median PFS (mPFS) was numerically longer in Arm A (**Table 2**; **Figure 3**)

Table 2. Efficacy Results (ITT Analysis Set)

	Arm A (n=78)	Arm B (n=40)
Primary endpoint		
ORR, n (%)	48 (61.5)	24 (60.0)
95% CI[a]	49.8-72.3	43.3-75.1
BOR, n (%)		
CR	2 (2.6)	1 (2.5)
PR	46 (59.0)	23 (57.5)
SD	23 (29.5)	12 (30.0)
PD	4 (5.1)	3 (7.5)
NE	3 (3.8)	1 (2.5)
Secondary endpoints		
DCR, n (%)	71 (91.0)	36 (90.0)
95% CI[a]	82.4-96.3	76.3-97.2
Median DoR, months[b]	7.2	7.3
95% CI	5.7-12.3	4.1-NE
Median PFS, months	8.2	6.9
95% CI	5.7-9.2	5.6-8.2

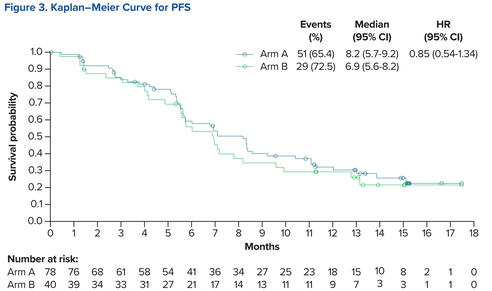
CR and PR were confirmed per RECIST v1.1. BOR of NE included patients with no postbaseline response assessment or assessment as NE per RECIST v1.1. Only patients with BOR of CR or PR confirmed per RECIST v1.1 were included in the DOR analysis, and percentages were based on the number of responders.
[a]The 95% CI was estimated using the Clopper–Pearson method. [b]Medians and other quartiles were estimated by the Kaplan–Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.
Abbreviations: NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 2. Waterfall Plot



d indicates the patient discontinued treatment.

Figure 3. Kaplan–Meier Curve for PFS



Number at risk:

Arm A	78	76	68	61	58	54	41	36	34	27	25	23	18	15	10	8	2	1	0
Arm B	40	39	34	33	31	27	21	17	14	13	11	11	9	7	3	3	1	1	0

HR and 95% CIs were estimated using a Cox regression model stratified by PD-L1 expression status.
Abbreviation: HR, hazard ratio.

- Subgroup analyses of mPFS and ORR by PD-L1 or LAG-3 baseline expression levels are presented in **Table 3**
  - In patients with PD-L1 low expression (PD-L1 <5%), Arm A showed numerically longer mPFS compared with Arm B (8.31 months vs 5.72 months; HR 0.76 [0.43-1.34])
  - No clear association of LAG-3 expression with clinical benefit was noted in Arm A vs Arm B, except numerically longer mPFS (8.31 months vs 5.98 months; HR 0.37 [0.09-1.51]) and higher ORR (78.6% vs 50.0%) in patients with LAG-3 ≥10% expression

Table 3. mPFS and ORR for Arm A vs Arm B, by PD-L1 or LAG-3 baseline expression levels

		Arm A	Arm B	PFS HR (95%CI)
PD-L1 ≥5%	**mPFS** (events)	**6.01** mo (17/24)	**7.13** mo (11/14)	
	ORR (n)	66.7% (16/24)	78.6% (11/14)	
PD-L1 <5%	**mPFS** (events)	**8.31** mo (34/54)	**5.72** mo (18/26)	
	ORR (n)	59.3% (32/54)	50.0% (13/26)	
PD-L1: TAP score				0 0.5 1 1.5 2 2.5 estimate (95% CI) Tisle+LBL+Chemo Tisle+Chemo
		Arm A	**Arm B**	**PFS HR (95%CI)**
LAG-3 ≥5%	**mPFS** (events)	**6.77** mo (25/36)	**6.93** mo (12/16)	
	ORR (n)	58.3% (21/36)	62.5% (10/16)	
LAG-3 <5%	**mPFS** (events)	**8.31** mo (25/40)	**6.87** mo (17/23)	
	ORR (n)	65.0% (26/40)	56.5% (13/23)	
LAG-3 ≥10%	**mPFS** (events)	**8.31** mo (8/14)	**5.98** mo (4/6)	
	ORR (n)	78.6% (11/14)	50.0% (3/6)	
LAG-3: IC% / tumor area				0 0.5 1 1.5 2 2.5 estimate (95% CI) Tisle+LBL+Chemo Tisle+Chemo

Safety/Tolerability Profile

- The addition of LBL-007 to TIS and CT was generally well tolerated with a safety/tolerability profile comparable to combination of TIS and CT (**Table 4**)
- The incidence and severity of immune-mediated adverse events (imAEs) were comparable between the two arms, with no unexpected safety/tolerability signals with addition of LBL-007

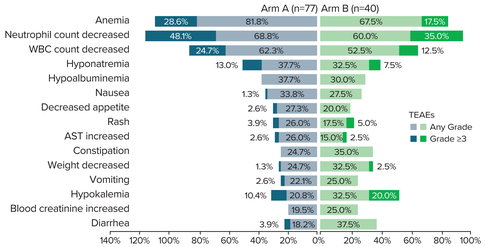
Table 4. Overall Safety Summary (Safety Analysis Set)

	Arm A (n=77)	Arm B (n=40)
Any TEAE, n (%)	77 (100.0)	40 (100.0)
Grade ≥3	66 (85.7)	31 (77.5)
Serious	40 (51.9)	18 (45.0)
Leading to treatment discontinuation	23 (29.9)	11 (27.5)
Leading to treatment modification	60 (77.9)	30 (75.0)
Leading to death	2 (2.6)	2 (5.0)
Any immunotherapy treatment-related TEAE, n (%)	63 (81.8)	27 (67.5)
Grade ≥3	34 (44.2)	12 (30.0)
Serious	20 (26.0)	9 (22.5)
Leading to death	1 (1.3)	2 (5.0)
Any imAE, n (%)	40 (51.9)	20 (50.0)
Grade ≥3	11 (14.3)	6 (15.0)
Serious	9 (11.7)	6 (15.0)
Leading to death	0 (0.0)	1 (2.5)
Any IRR, n (%)	7 (9.1)	2 (5.0)
Grade ≥3	2 (2.6)	0 (0.0)

AEs were graded for severity using CTCAE (version 5.0).
Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; IRR, infusion-related reaction.

- The most common TEAEs (**Figure 4**) were anemia (81.8% in Arm A; 67.5% in Arm B), neutrophil count decreased (68.8% in Arm A; 60.0% in Arm B), and white blood cell count decreased (62.3% in Arm A; 52.5% in Arm B)

Figure 4. Any Grade TEAEs in ≥25% of Patients (Safety Analysis Set)



AEs were classified based on MedDRA (version 27.0). AEs were graded for severity using CTCAE (version 5.0).
Patients with multiple events for a given preferred term and multiple preferred terms within a system organ class were counted once at the Preferred Term and System Organ Class levels, respectively.
Abbreviations: AST, aspartate aminotransferase; WBC, white blood cell.

REFERENCES

1. Abnet CC, et al. *Gastroenterology.* 2018;154:360-373.
2. Surveillance, Epidemiology, and End Results Program (SEER) Program. Accessed November 4, 2025. https://seer.cancer.gov/statfacts/html/esoph.html.
3. Gettinger S, et al. *Cancer Discov.* 2017;7:1420-1435.
4. Hanna GJ, et al. *JCI Insight.* 2018;3:e98811.
5. Johnson DB, et al. *JCI Insight.* 2018;3:e120360.

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DISCLOSURES

YB has nothing to disclose.

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