A phase 2 multicenter umbrella trial assessing tislelizumab ± anti-TIGIT or anti-LAG-3 mAb ± chemotherapy in resectable NSCLC

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ABSTRACT

Introduction: Neoadjuvant chemotherapy plus immunotherapy with adjuvant immunotherapy is the current standard of care for resectable NSCLC. There is an unmet need for additional neoadjuvant regimens containing novel agents that retain efficacy but minimize safety risks. We report results from a phase 2, randomized, open-label, multicenter umbrella trial of neoadjuvant tislelizumab (TIS) monotherapy and TIS-based immunotherapy combinations ± chemotherapy in Chinese patients with resectable NSCLC (NCT05577702).

Methods: Eligible patients had Stage II-IIIA NSCLC without *EGFR* sensitizing mutations or *ALK* rearrangement. Patients with PD-L1 TC ≥50% were assigned to Substudy 1 and randomized to TIS (anti-PD-1; Arm 1A), TIS plus ociperlimab (anti-TIGIT; Arm 1B), or TIS plus LBL-007 (anti-LAG-3; Arm 1C); patients with PD-L1 TC <50% were assigned to Substudy 2 and randomized to TIS and chemotherapy (Arm 2A) or TIS plus LBL-007 and chemotherapy (Arm 2C). Patients received 2-4 cycles of treatment and then surgery. The primary objective was evaluation of major pathological response (MPR) per blinded independent pathology review (BIPR); select secondary objectives were evaluation of the pathological complete response (pCR) per BIPR and feasibility of surgery.

Results: As of February 5, 2025, 121 patients were enrolled. The median number of treatment cycles of TIS or TIS-based immunotherapy combinations was 3, 2, and 2 for 1A, 1B and 1C, and 3 and 2.5 for 2A and 2C, respectively. The overall MPR rates were 64.3% (27/42) for Substudy 1, and 52.1% (25/48) for Substudy 2. Detailed MPR and pCR rates are summarized in the Table. Notably, in the

experimental arms, the MPR rate in patients with non-squamous NSCLC in 1B was 100% (6/6) and in patients with squamous NSCLC with PD-L1 TC <1% in 2C was 75% (9/12). TEAEs were reported in most patients. The three most common treatment-related TEAEs were AST increased, anemia and ALT increased in Substudy 1, and neutrophil count decreased, anemia and WBC count decreased in Substudy 2. An increase in treatment-related Grade ≥3 and serious TEAEs, and immune-mediated AEs were reported for 1B and 1C versus 1A, and 2C versus 2A. Few treatment-related TEAEs leading to surgery withdrawal were reported.

Conclusion: Neoadjuvant TIS as monotherapy or TIS-based immunotherapy combinations in PD-L1 TC ≥50% NSCLC had promising MPR/pCR; the addition of other immunotherapy to neoadjuvant TIS and chemotherapy in PD-L1 TC <50% did not provide additional efficacy benefit. Treatment guided by histology and PD-L1 expression is suggested for future exploration.

Efficacy in Patients Receiving Surgery (Efficacy Evaluable Analysis Set)

	Substudy 1 (PD-L1 ≥50%)			**Substudy 2 (PD-L1 <50%)**	
	Arm 1A (N=20)	**Arm 1B (N=20)**	**Arm 1C (N=20)**	**Arm 2A (N=20)**	**Arm 2C (N=41)**
Overall	n=16	n=14	n=12	n=17	n=31
MPR, n (%)	9 (56.3)	10 (71.4)	8 (66.7)	11 (64.7)	14 (45.2)
pCR, n (%)	6 (37.5)	6 (42.9)	8 (66.7)	7 (41.2)	7 (22.6)
Squamous	n=15	n=8	n=11	n=13 PD-L1 <1%=4 PD-L1 1-49%=9	n=23 PD-L1 <1%=12 PD-L1 1-49%=11
MPR, n (%)	9 (60.0)	4 (50.0)	8 (72.7)	8 (61.5)	14 (60.9)
PD-L1 <1%				2 (50.0)	9 (75.0)
PD-L1 1-49%				6 (66.7)	5 (45.5)
pCR, n (%)	6 (40.0)	1 (12.5)	8 (72.7)	5 (38.5)	7 (30.4)
PD-L1 <1%				2 (50.0)	6 (50.0)
PD-L1 1-49%				3 (33.3)	1 (9.1)
Non-squamous	n=1	n=6	n=1	n=4 PD-L1 <1%=3 PD-L1 1-49%=1	n=8 PD-L1 <1%=4 PD-L1 1-49%=4
MPR, n (%)	0	6 (100.0)	0	3 (75.0)	0
PD-L1 <1%				2 (66.7)	0
PD-L1 1-49%				1 (100.0)	0
pCR, n (%)	0	5 (83.3)	0	2 (50.0)	0

PD-L1 <1%	1 (33.3)	0
PD-L1 1-49%	1 (100.0)	0

Median (range) study follow-up was 10.5 months (1.0-22.3) for Substudy 1 and 9.2 months (0.2-13.0) for Substudy 2.