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A Phase 2 Multicenter Umbrella Trial Assessing Tislelizumab ± Anti-TIGIT or Anti-LAG-3 mAb ± Chemotherapy in Resectable NSCLC

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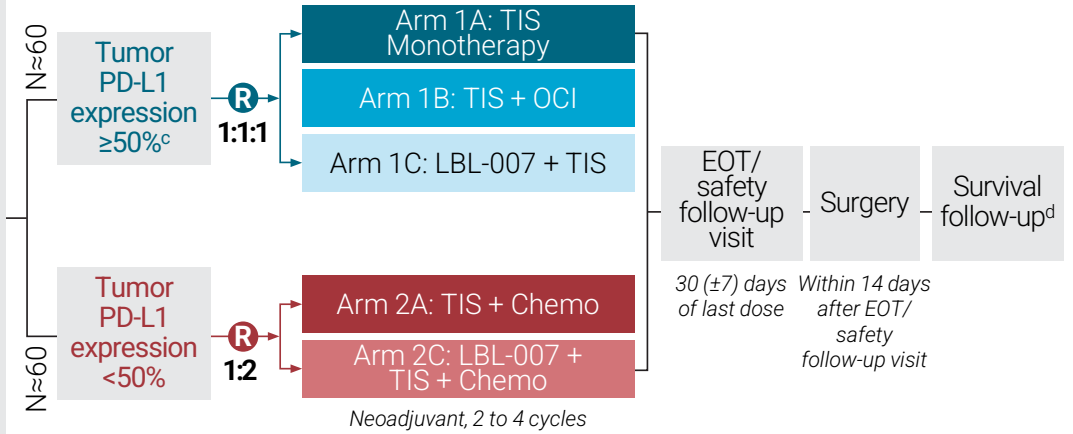
Introduction and Study Design

- Tislelizumab is an anti-PD-1 mAb that is approved as perioperative, first- and second-line treatment for patients with NSCLC in both China and the European Union[1-4]
  - Safety and efficacy of neoadjuvant tislelizumab + chemo followed by adjuvant tislelizumab in resectable NSCLC was investigated in the RATIONALE-315 study (NCT04379635)[5]
- Ociperlimab is a humanized Fc intact IgG1 mAb that binds to TIGIT with high specificity and affinity[6]
- LBL-007 is a novel fully humanized IgG4 mAb that targets LAG-3 and blocks the interaction with its ligands on tumor cells and APCs, restoring T-cell activity[7]

Key eligibility criteria

- ≥18 years
- ECOG PS ≤1
- Stage II-IIIA NSCLC (squamous or non-squamous histology)[a]
- Measurable disease per investigator-assessed RECIST v1.1
- No prior antineoplastic therapy or drug specifically targeting T-cell co-stimulation or checkpoint pathway
- No known *EGFR* sensitizing mutations and/or *ALK* rearrangement[b]



Key Endpoints

- MPR rate assessed by BIPR
- pCR rate assessed by BIPR
- Safety and tolerability
- Percentage of patients who undergo surgical resection

[a]Staging based on the 8th edition of the American Joint Committee on Cancer/Union Internale Contre le Cancer NSCLC staging system. [b]Patients with non-squamous NSCLC must be tested for *EGFR* mutational status at screening. [c]For enrollment, local data with approved PD-L1 assays is acceptable. [d]Tumor assessments should have been conducted per protocol until disease recurrence or progression that precluded definitive surgery, initiation of new anticancer therapy except the prespecified adjuvant therapy, withdrawal of consent, death, loss to follow-up, or study termination by the sponsor, whichever occurred first. Survival status should have been followed per protocol until death, loss to follow-up, or the end of study.

Abbreviations: *ALK*, anaplastic lymphoma kinase; APC, antigen presenting cell; BIPR, Blinded Independent Pathology Review; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; EOT, end-of-treatment; Ig, immunoglobulin; LAG-3, lymphocyte-activation gene 3; mAb, monoclonal antibody; MPR, major pathological response; NSCLC, non-small cell lung cancer; OCI, ociperlimab; pCR, pathological complete response; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand-1; R, randomization ratio; RECIST, Response Evaluation Criteria in Solid Tumors; TIGIT, T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain; TIS, tislelizumab.

1. BeOne Medicines. Press Release. Jan 13, 2021. https://ir.beonemedicines.com/news/china-national-medical-products-administration-approves-tislelizumab-in-combination-with-chemotherapy-in-first-line-advanced-squamous/bafd0e50-64fe-4313-9f63-a58be0fc2c54; 2. BeOne Medicines. Press Release. January 6, 2022. https://ir.beonemedicines.com/news/china-nmpa-approves-tislelizumab-as-second-or-third-line-treatment-for-patients-with-locally-advanced-or/3e337eaa-a5f6-4368-95e0-3e0d35a71254; 3. BeOne Medicines. Press Release. February 26, 2024. https://ir.beonemedicines.com/news/beigene-receives-positive-chmp-opinion-for-tislelizumab-as-treatment-for-non-small-cell-lung-cancer/76c25106-81ac-4654-b382-4ba84e6038f3; 4. BeOne Medicines. Press Release. Aug 27, 2025. https://ir.beonemedicines.com/news/european-commission-approves-tevimbrar-as-neoadjuvantadjuvant-nsclc-treatment-ahead-of-late-breaking-data-presentation-at-wclc/0d7553af-93d0-4616-a02b-ac223e497bca; 5. Yue D, et al. *Lancet Respir Med* 2025;13:119-129; 6. Chen X, et al. *Front Immunol* 2022:13:828319;
7. Yu X, et al. *mAbs* 2019;11:1139-1148.

Baseline Characteristics (ITT analysis set)

	Substudy 1 (PD-L1 ≥50%)			Substudy 2 (PD-L1 <50%)	
	Arm 1A TIS monotherapy (N=20)	Arm 1B TIS + OCI (N=20)	Arm 1C LBL-007 + TIS (N=20)	Arm 2A TIS + chemo (N=20)	Arm 2C LBL-007 + chemo (N=41)
Median (range) age, years	65.5 (47-73)	62.0 (48-76)	62.0 (48-74)	59.5 (48-74)	64.0 (32-82)
Sex, n (%)					
Male	18 (90.0)	19 (95.0)	17 (85.0)	17 (85.0)	31 (75.6)
Female	2 (10.0)	1 (5.0)	3 (15.0)	3 (15.0)	10 (24.4)
ECOG PS, n (%)					
0	9 (45.0)	7 (35.0)	8 (40.0)	9 (45.0)	22 (53.7)
1	11 (55.0)	13 (65.0)	12 (60.0)	11 (55.0)	19 (46.3)
Smoking status, n (%)					
Current	3 (15.0)	1 (5.0)	4 (20.0)	2 (10.0)	5 (12.2)
Former	15 (75.0)	15 (75.0)	12 (60.0)	15 (75.0)	22 (53.7)
Never	2 (10.0)	4 (20.0)	4 (20.0)	3 (15.0)	14 (34.1)
Disease stage at study entry, n (%)					
IIA	4 (20.0)	2 (10.0)	0 (0.0)	0 (0.0)	1 (2.4)
IIB	1 (5.0)	7 (35.0)	7 (35.0)	8 (40.0)	14 (34.1)
IIIA	15 (75.0)	11 (55.0)	13 (65.0)	11 (55.0)	26 (63.4)
IIIB	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Histology					
Non-squamous cell carcinoma	2 (10.0)	6 (30.0)	3 (15.0)	5 (25.0)	12 (29.3)
Squamous cell carcinoma	18 (90.0)	13 (65.0)	17 (85.0)	15 (75.0)	28 (68.3)
Mixed adeno-squamous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Other	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Central lab confirmed PD-L1 expression,[a] n (%)					
≥50%	14 (70.0)	14 (70.0)	15 (75.0)	0 (0.0)	0 (0.0)
1-49%	3 (15.0)	4 (20.0)	3 (15.0)	9 (45.0)	19 (46.3)
<1%	0 (0.0)	0 (0.0)	1 (5.0)	9 (45.0)	21 (51.2)
Unknown	3 (15.0)	2 (10.0)	1 (5.0)	2 (10.0)	1 (2.4)

Data cutoff February 5, 2025.
[a]Assessed by TC score based on Ventana PD-L1 (SP263) assay.
Abbreviations: Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intent-to-treat; OCI, ociperlimab; PD-L1, programmed cell death protein ligand-1; TC, tumor cell; TIS, tislelizumab.

Efficacy Data in ITT Analysis Set and in Patients Who Received Surgery

- Notably, in the experimental arms, the MPR rate in patients with non-squamous NSCLC in Arm 1B was 100% (6/6) and in patients with squamous NSCLC with PD-L1 <1% in Arm 2C was 75% (9/12)
- Tislelizumab demonstrated promising efficacy both as monotherapy in patients with NSCLC with PD-L1 expression ≥50%, and in combination with chemotherapy in patients with PD-L1 expression <50% in the neoadjuvant setting

	Substudy 1 (PD-L1 ≥50%)			Substudy 2 (PD-L1 <50%)	
	Arm 1A TIS monotherapy	Arm 1B TIS + OCI	Arm 1C LBL-007 + TIS	Arm 2A TIS + chemo	Arm 2C LBL-007 + chemo
Patients randomized, n	20	20	20	20	41
MPR, n (%)	9 (45.0)	10 (50.0)	8 (40.0)	11 (55.0)	14 (34.1)
95% CI[a]	23.1-68.5	27.2-72.8	19.1-63.9	31.5-76.9	20.1-50.6
pCR, n (%)	6 (30.0)	6 (30.0)	8 (40.0)	7 (35.0)	7 (17.1)
95% Ci[a]	11.9-54.3	11.9-54.3	19.1-63.9	15.4-59.2	7.2-32.1
Patients who received surgery, n	16	14	12	17	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)
Patients with squamous histology, n	15	8	11	13	23
MPR, n (%)	9 (60.0)	4 (50.0)	8 (72.7)	8 (61.5)	14 (60.9)
pCR, n (%)	6 (40.0)	1 (12.5)	8 (72.7)	5 (38.5)	7 (30.4)
Patients with PD-L1 <1%,[b] n	0	0	0	4	12
MPR, n (%)	--	--	--	2 (50.0)	9 (75.0)
pCR, n (%)	--	--	--	2 (50.0)	6 (50.0)
Patients with PD-L1 1-49%,[b] n	0	0	0	9	11
MPR, n (%)	--	--	--	6 (66.7)	5 (45.5)
pCR, n (%)	--	--	--	3 (33.3)	1 (9.1)
Patients with non-squamous histology, n	1	6	1	4	8
MPR, n (%)	0	6 (100.0)	0	3 (75.0)	0
pCR, n (%)	0	5 (83.3)	0	2 (50.0)	0
Patients with PD-L1 <1%,[b] n	0	0	0	3	4
MPR, n (%)	--	--	--	2 (66.7)	0
pCR, n (%)	--	--	--	1 (33.3)	0
Patients with PD-L1 1-49%,[b] n	0	0	0	1	4
MPR, n (%)	--	--	--	1 (100.0)	0
pCR, n (%)	--	--	--	1 (100.0)	0

Data cutoff February 5, 2025.
The median number of treatment cycles of TIS or TIS-based immunotherapy combinations received were 3, 2, and 2 for Arms 1A, 1B, and 1C, and 3 and 2.5 for Arms 2A and 2B, respectively.
For MPR and pCR, patients without surgery or pathological results were considered as non-responders. [a]The 95% CI was estimated using the Clopper–Pearson method. [b]PD-L1 status at enrolment.
Abbreviations: chemo, chemotherapy; CI, confidence interval; ITT, intent-to-treat; MPR, major pathological response; NSCLC, non-small cell lung cancer; OCI, ociperlimab; pCR, pathological complete response; PD-L1, programmed cell death protein ligand-1; TIS, tislelizumab.

Tislelizumab With Immunotherapy ± Chemotherapy Was Generally Well Tolerated (Safety Analysis Set)

- In Substudy 1, there were no grade ≥3 treatment-related TEAEs reported by >1 patient by preferred term
- In Substudy 2, the most common grade ≥3 treatment-related TEAEs in Arms 2A and 2C, respectively, were neutrophil count decreased (52.6% [10/19] and 47.5% [19/40]), WBC count decreased (10.5% [2/19] and 15.0% [6/40]), and leukopenia (5.3% [1/19] and 10.0% [4/40])
- In general, the imAE profile was acceptable in frequency and severity
  - The most common imAE was rash in 15.0% (3/20) of patients in Arm 1B, 5.0% (1/20) of patients in Arm 1C, 5.3% (1/19) of patients in Arm 2A, and 22.5% (9/40) of patients in Arm 2C, most of which were Grades 1-2

	Substudy 1 (PD-L1 ≥50%)			Substudy 2 (PD-L1 <50%)	
	Arm 1A TIS monotherapy (N=20)	Arm 1B TIS + OCI (N=20)	Arm 1C LB-007 + TIS (N=20)	Arm 2A TIS + chemo (N=19)	Arm 2C LB-007 + chemo (N=40)
Any treatment-related TEAE, n (%)	5 (25.0)	13 (65.0)	11 (55.0)	19 (100.0)	39 (97.5)
Grade ≥3	0 (0.0)	2 (10.0)	2 (10.0)	11 (57.9)	26 (65.0)
Serious	0 (0.0)	2 (10.0)	1 (5.0)	1 (5.3)	13 (32.5)
Leading to surgery withdrawal	0 (0.0)	1 (5.0)	2 (10.0)	0 (0.0)	0 (0.0)
Leading to surgery delay	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.0)
Leading to death	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any imAE,[a] n (%)	0 (0.0)	6 (30.0)	3 (15.0)	2 (10.5)	17 (42.5)
Any IRR,[b] n (%)	0 (0)	0 (0)	0 (0)	1 (5.3)	1 (2.5)

Data cutoff February 5, 2025.
A TEAE is an AE that has an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of the study treatment and during up to 30 days after study treatment discontinuation, or initiation of new anticancer therapy, or prespecified adjuvant treatment, whichever occurs first. AEs were classified based on MedDRA (version 27.0). 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.
[a]imAEs are the immune-mediated AEs occurring from the date of first dose of study drug to 90 days after the last dose of study drug, regardless of whether the patient starts a new anticancer therapy or prespecified adjuvant treatment. imAEs are identified based on BeOne standard process as defined in Immune-Mediated Adverse Event Identification Charter v1.2; imAE CCQ v3.0. [b]IRRs were identified based on investigator's assessment.
Abbreviations: AE, adverse event; chemo, chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse event; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; OCI, ociperlimab; PD-L1, programmed cell death protein ligand-1; TEAE, treatment-emergent adverse event; TIS, tislelizumab; WBC, white blood cell.

Conclusions

- Tislelizumab demonstrated promising efficacy both as monotherapy in patients with NSCLC with PD-L1 expression ≥50%, and in combination with chemotherapy in patients with PD-L1 expression <50% in the neoadjuvant setting
- Although the addition of anti-LAG-3 or anti-TIGIT agents did not significantly enhance the efficacy of tislelizumab ± chemotherapy in either substudy, certain patient subgroups—such as non-squamous NSCLC with PD-L1 expression ≥50% receiving tislelizumab plus TIGIT—may derive additional benefit from these combinations
- Tislelizumab combined with anti-TIGIT or anti-LAG-3 immunotherapy with or without chemotherapy was generally well tolerated with no new safety signals in patients with NSCLC

Abbreviations: LAG-3, lymphocyte-activation gene 3; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand 1; TIGIT, T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain.

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Thank You

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