IASLC 2025 World Conference on Lung Cancer

SEPTEMBER 6-9, 2025 | BARCELONA, SPAIN

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PERIOPERATIVE TISLELIZUMAB FOR RESECTABLE NON-SMALL CELL LUNG CANCER: FINAL ANALYSIS OF RATIONALE-315

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Introduction and Methods

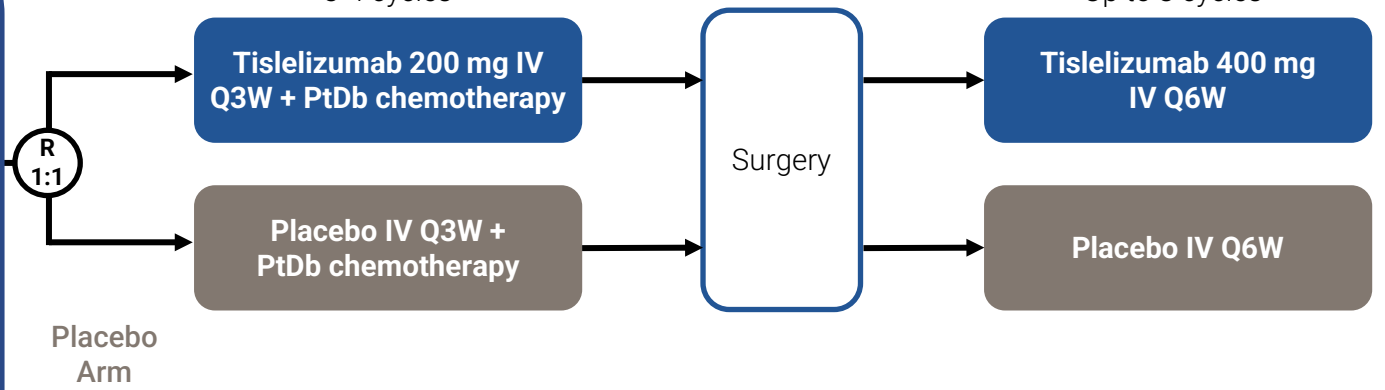
- Previously, RATIONALE-315 (NCT04379635) met its dual primary and key secondary endpoints, demonstrating significant improvements in EFS, MPR rate, and pCR rate with a tolerable safety profile for perioperative tislelizumab plus neoadjuvant platinum-based doublet (PtDb) chemotherapy vs placebo plus neoadjuvant PtDb chemotherapy[1]

Key Eligibility Criteria

- Resectable stage II-IIIA NSCLC[a] (eligible for R0 resection)
- ECOG PS 0 or 1
- *EGFR/ALK* WT[b]

Stratification Factors

- Histology (squamous vs non-squamous)
- Disease stage (II vs IIIA)
- PD-L1 TC expression (≥1% vs <1%/ not evaluable/indeterminate)



PtDb Chemotherapy
- Squamous: cisplatin/carboplatin + paclitaxel
- Non-squamous: cisplatin/carboplatin + pemetrexed

Completed Adjuvant Treatment[d]
- Tislelizumab arm: 115/226 (50.9%) patients
- Placebo arm: 109/227 (48.0%) patients

Primary Endpoints
- BIPR-assessed MPR rate
- BICR-assessed EFS

Key Secondary Endpoint
- BIPR-assessed pCR rate

Other Secondary Endpoints
- OS
- ORR
- BICR-assessed DFS
- Investigator-assessed EFS
- Safety

Data cutoff: March 7, 2025 (median study follow-up: 38.5 months [range: 0.1-57.0]).

The RATIONALE-315 interim analysis publication[1] can be accessed via this QR code.

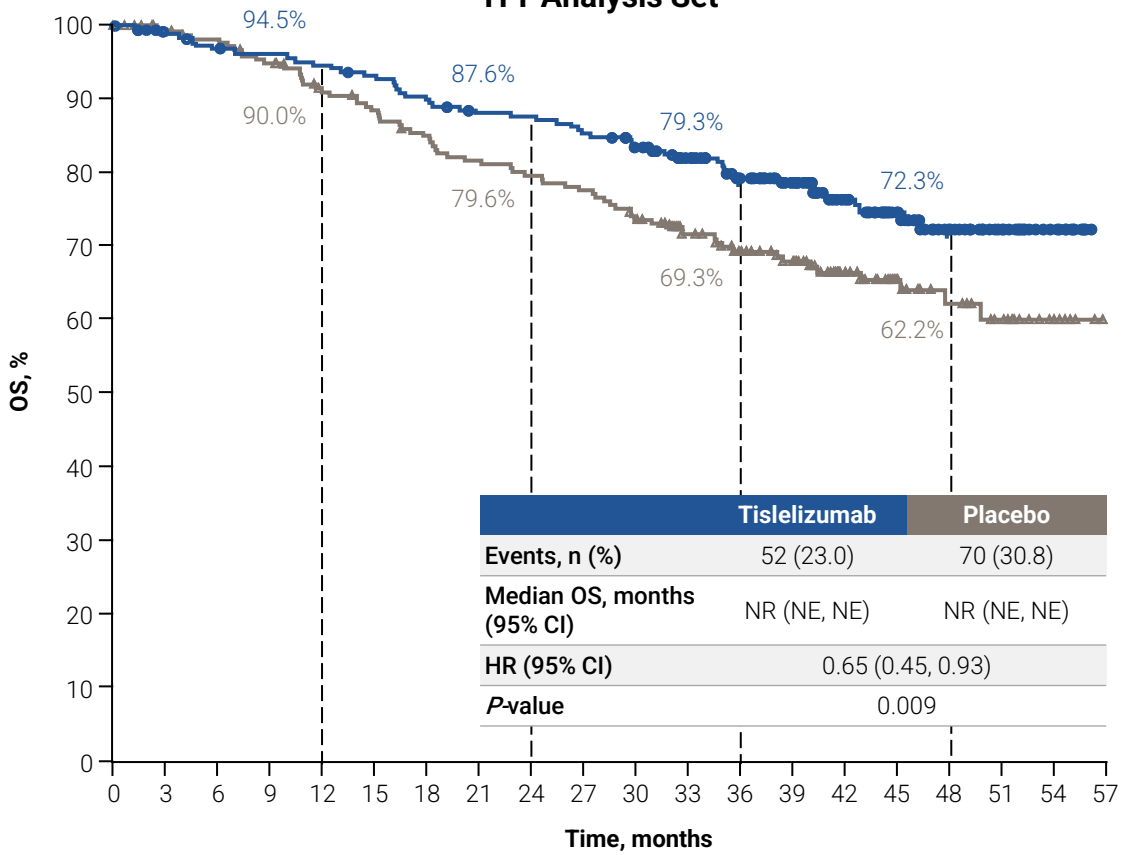
Statistical Considerations
- Overall type I error was strongly controlled at a one-sided α of 0.025
- EFS/OS final analysis was prespecified to occur after approximately 184 EFS events
- The Haybittle–Peto *P*-value boundary for the final OS testing was updated based on the actual number of OS events

[a]Per the 8th edition AJCC staging system. [b]*EGFR* testing was mandatory for non-squamous NSCLC. [c]Adjuvant treatment was only received by patients with an ECOG PS of 0 or 1 and adequate organ function for up to 8 cycles or until disease recurrence/progression, unacceptable adverse events, death occurred, or the patient and/or investigator decided to discontinue study treatment (whichever came first). [d]No patients remained on treatment.
1. Yue D, et al. *Lancet Respir Med.* 2025;13:119-129.

Results: Overall Survival

- Patients in the tislelizumab arm experienced a statistically significant and clinically meaningful improvement in OS vs those in the placebo arm, which was consistent across prespecified and post-hoc subgroups

ITT Analysis Set



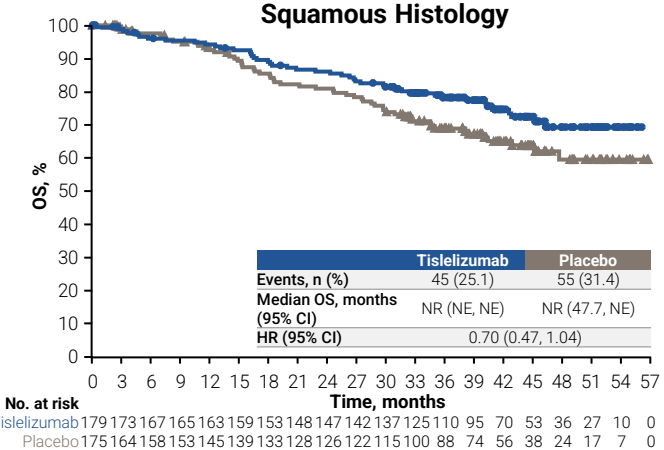
	Tislelizumab	Placebo
Events, n (%)	52 (23.0)	70 (30.8)
Median OS, months (95% CI)	NR (NE, NE)	NR (NE, NE)
HR (95% CI)	0.65 (0.45, 0.93)	
P-value	0.009	

No. at risk

Tislelizumab	226	218	212	209	206	202	195	189	188	183	176	163	143	121	91	69	47	36	15	0
Placebo	227	214	207	199	186	180	172	165	161	157	148	131	117	98	73	51	34	26	9	0

Subgroup Analysis

Squamous Histology

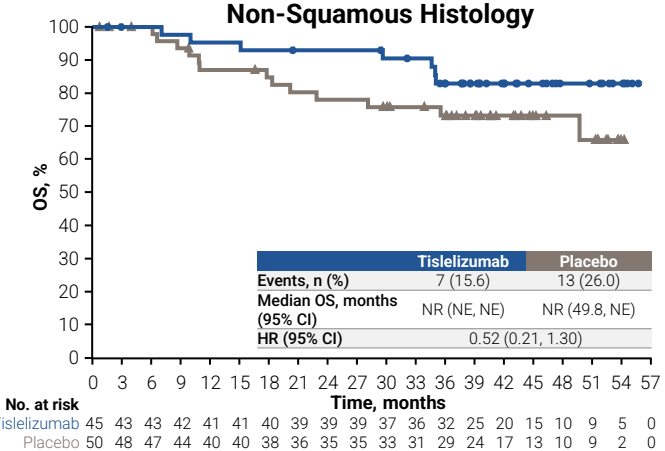


	Tislelizumab	Placebo
Events, n (%)	45 (25.1)	55 (31.4)
Median OS, months (95% CI)	NR (NE, NE)	NR (47.7, NE)
HR (95% CI)	0.70 (0.47, 1.04)	

No. at risk

Tislelizumab	179	173	167	165	163	159	153	148	147	142	137	125	110	95	70	53	36	27	10	0
Placebo	175	164	158	153	145	139	133	128	126	122	115	100	88	74	56	38	24	17	7	0

Non-Squamous Histology

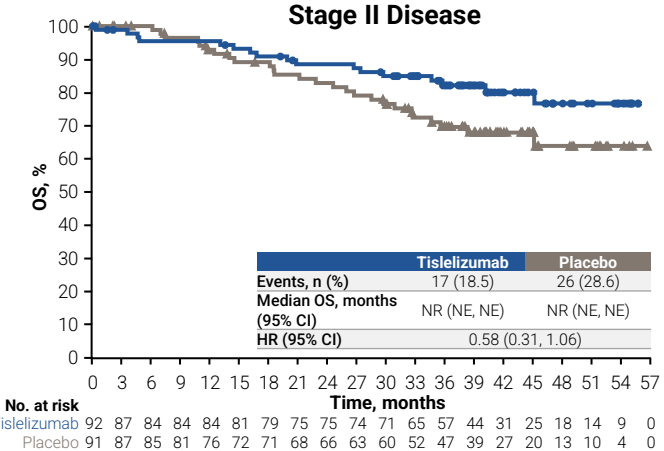


	Tislelizumab	Placebo
Events, n (%)	7 (15.6)	13 (26.0)
Median OS, months (95% CI)	NR (NE, NE)	NR (49.8, NE)
HR (95% CI)	0.52 (0.21, 1.30)	

No. at risk

Tislelizumab	45	43	43	42	41	41	40	39	39	39	37	36	32	25	20	15	10	9	5	0
Placebo	50	48	47	44	40	40	38	36	35	35	33	31	29	24	17	13	10	9	2	0

Stage II Disease

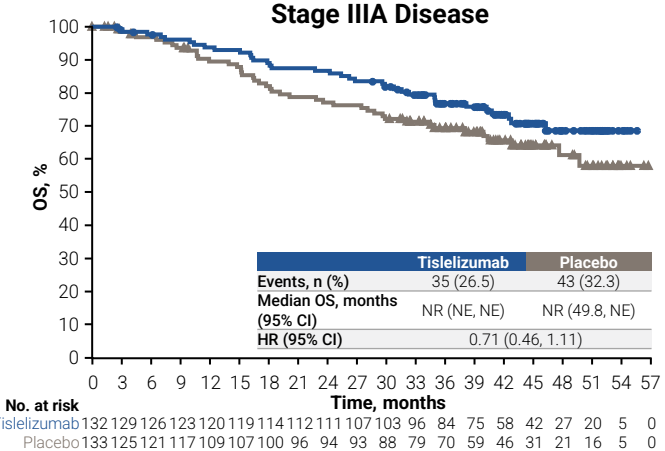


	Tislelizumab	Placebo
Events, n (%)	17 (18.5)	26 (28.6)
Median OS, months (95% CI)	NR (NE, NE)	NR (NE, NE)
HR (95% CI)	0.58 (0.31, 1.06)	

No. at risk

Tislelizumab	92	87	84	84	84	81	79	75	75	74	71	65	57	44	31	25	18	14	9	0
Placebo	91	87	85	81	76	72	71	68	66	63	60	52	47	39	27	20	13	10	4	0

Stage IIIA Disease



	Tislelizumab	Placebo
Events, n (%)	35 (26.5)	43 (32.3)
Median OS, months (95% CI)	NR (NE, NE)	NR (49.8, NE)
HR (95% CI)	0.71 (0.46, 1.11)	

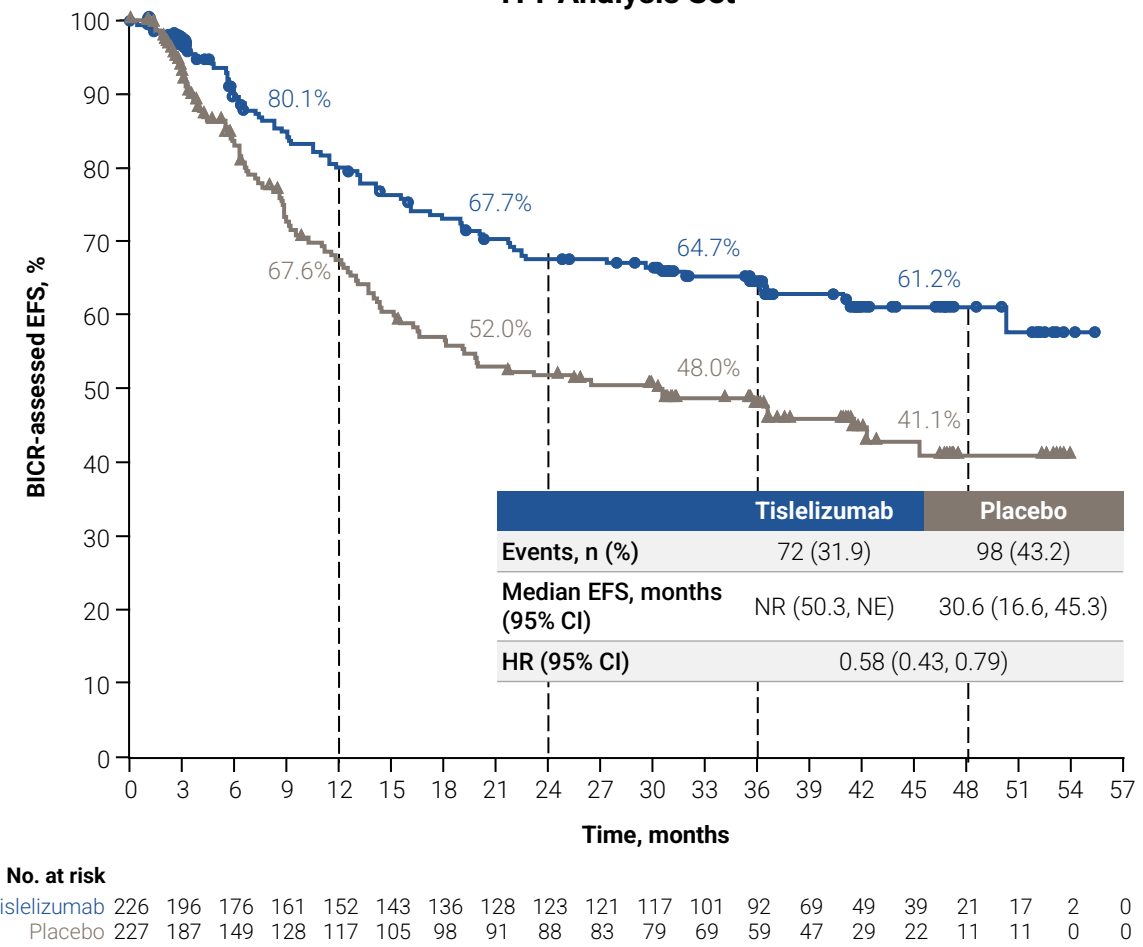
No. at risk

Tislelizumab	132	129	126	123	120	119	114	112	111	107	103	96	84	75	58	42	27	20	5	0
Placebo	133	125	121	117	109	107	100	96	94	93	88	79	70	59	46	31	21	16	5	0

KM curve: Hazard ratios and their 95% CIs were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA), and PD-L1 TC expression (≥1% vs <1%/not evaluable/indeterminate) per interactive response technology. The circle and triangle symbols indicate censored patients. Forest plot: Unstratified hazard ratios and their 95% CIs were estimated using a Cox regression model. The *P*-value boundary of the OS final analysis was 0.024997 (calculated based on 122 OS events).

Results: Event-Free Survival

ITT Analysis Set



	Tislelizumab	Placebo
Events, n (%)	72 (31.9)	98 (43.2)
Median EFS, months (95% CI)	NR (50.3, NE)	30.6 (16.6, 45.3)
HR (95% CI)	0.58 (0.43, 0.79)	

No. at risk

Tislelizumab	226	196	176	161	152	143	136	128	123	121	117	101	92	69	49	39	21	17	2	0
Placebo	227	187	149	128	117	105	98	91	88	83	79	69	59	47	29	22	11	11	0	0

Subgroup Analysis

	Tislelizumab, n/N	Placebo, n/N	Tislelizumab, median (95% CI)	Placebo, median (95% CI)	Hazard ratio (95% CI)
Overall	72/226	98/227	NR (50.3, NE)	30.6 (16.6, 45.3)	0.58 (0.43, 0.79)
Age group					
<65 years	48/143	52/129	NR (41.4, NE)	42.3 (19.2, NE)	0.70 (0.47, 1.03)
≥65 years	24/83	46/98	NR (NE, NE)	18.1 (14.4, 36.5)	0.45 (0.27, 0.74)
Sex					
Male	66/205	93/205	NR (50.3, NE)	25.5 (15.5, 45.3)	0.57 (0.41, 0.78)
Female	6/21	5/22	NR (16.1, NE)	NR (11.2, NE)	0.93 (0.28, 3.08)
ECOG performance status					
0	44/142	61/154	NR (50.3, NE)	41.5 (18.1, NE)	0.62 (0.42, 0.91)
1	28/83	37/73	NR (31.8, NE)	19.2 (12.6, 30.6)	0.52 (0.32, 0.85)
Disease stage at baseline					
II	22/92	33/91	NR (50.3, NE)	NR (18.1, NE)	0.55 (0.32, 0.94)
IIIA	50/132	65/133	NR (36.4, NE)	19.9 (13.1, 41.5)	0.60 (0.41, 0.87)
Histologic subtype					
Squamous	53/179	73/175	NR (50.3, NE)	30.6 (16.6, NE)	0.58 (0.41, 0.82)
Non-squamous	19/45	24/50	NR (19.1, NE)	30.2 (11.1, NE)	0.66 (0.36, 1.21)
PD-L1 TC expression					
<1% (excluding NE/indeterminate)	30/89	35/84	NR (27.4, NE)	30.6 (15.2, NE)	0.70 (0.43, 1.14)
≥1%	39/130	58/132	NR (50.3, NE)	30.6 (15.3, NE)	0.53 (0.35, 0.79)
1%-49%	17/59	35/70	NR (40.9, NE)	18.1 (12.3, NE)	0.41 (0.23, 0.73)
≥50%	22/71	23/62	NR (41.4, NE)	45.3 (18.1, NE)	0.71 (0.40, 1.28)
Smoking status					
Current	14/45	21/52	NR (36.5, NE)	41.5 (15.3, NE)	0.59 (0.30, 1.17)
Former	48/148	63/138	NR (41.4, NE)	19.8 (13.8, NE)	0.57 (0.39, 0.83)
Never	10/33	14/37	NR (16.2, NE)	42.3 (11.2, NE)	0.59 (0.26, 1.33)
Neoadjuvant platinum chemotherapy					
Cisplatin	36/120	56/124	NR (50.3, NE)	35.7 (12.7, NE)	0.53 (0.35, 0.81)
Carboplatin	27/80	33/76	NR (22.7, NE)	23.2 (15.2, NE)	0.62 (0.37, 1.04)
Switched from cisplatin to carboplatin	9/25	9/25	NR (16.2, NE)	NR (8.8, NE)	0.73 (0.29, 1.84)

KM curve: Hazard ratio and its 95% CI were estimated using a Cox regression model stratified by histology (squamous vs non-squamous), disease stage (stage II vs stage IIIA), and PD-L1 TC expression (<1%/not evaluable/indeterminate vs ≥1%) per interactive response technology. The circle and triangle symbols indicate censored patients. Forest plot: Unstratified hazard ratios and their 95% CIs were estimated using a Cox regression model.

Results: Safety Summary

- Perioperative tislelizumab plus neoadjuvant chemotherapy was well tolerated; the safety profile was consistent with the known risks of the individual therapies and interim analyses with no new safety signals identified
- The most frequently reported TRAEs in both the tislelizumab and placebo arms were neutrophil count decreased (any grade, 78.8% vs 78.3%; grade ≥3, 61.5% vs 59.3%) and WBC count decreased (any grade, 63.3% vs 67.3%; grade ≥3, 16.8% vs 14.2%)

Safety Analysis Set

n (%)	Tislelizumab Arm (n=226)	Placebo Arm (n=226)
Patients with ≥1 TRAEs	224 (99.1)	225 (99.6)
Grade ≥3	165 (73.0)	152 (67.3)
Serious	35 (15.5)	20 (8.8)
Leading to death[a]	4 (1.8)	2 (0.9)
Leading to discontinuation of any study treatment	29 (12.8)	21 (9.3)
Leading to dose modification of any study treatment	89 (39.4)	73 (32.3)
Leading to surgery delay[b]	12 (5.3)	4 (1.8)
Leading to surgery cancellation	1 (0.4)	1 (0.4)
Patients with any imAEs	91 (40.3)	41 (18.1)
Grade ≥3	21 (9.3)	7 (3.1)
Serious	24 (10.6)	5 (2.2)
Leading to death[a]	2 (0.9)	0 (0.0)
Leading to tislelizumab/placebo discontinuation	13 (5.8)	0 (0.0)
Leading to tislelizumab/placebo dose modification[c]	29 (12.8)	6 (2.7)
Treated with systemic corticosteroids for imAEs	33 (14.6)	7 (3.1)

[a]Tislelizumab arm (n=1 each): infection, pneumonia, pneumonitis, immune-mediated lung disease. Placebo arm: respiratory hemorrhage, cardiac failure. [b]Defined as when the date of surgery is beyond 6 weeks after the last neoadjuvant treatment dose. [c]Dose modification for tislelizumab/placebo included dose interruption, dose delay, temporary dose discontinuation in the neoadjuvant phase, and infusion rate decrease.
The safety analysis set included all randomised patients who received ≥1 dose of any study drug. AEs were classified based on MedDRA v26.0. AEs were graded for severity using NCI CTCAE v5.0.

Conclusions

- A statistically significant and clinically meaningful benefit in OS was observed with perioperative tislelizumab plus PtDb chemotherapy vs placebo plus PtDb chemotherapy (HR=0.65 [95% CI: 0.45, 0.93]; one-sided *P*-value=0.009)
  - This benefit was consistent across prespecified and post-hoc subgroups
- There were clinically meaningful improvements in EFS, consistent with results from the prespecified and post-hoc subgroups in this analysis and the primary EFS analysis
- Perioperative tislelizumab plus PtDb chemotherapy was well tolerated, and the safety profile was consistent with the known risks of the individual therapies and the profile reported previously
- These final results of RATIONALE-315 further support perioperative tislelizumab plus neoadjuvant PtDb chemotherapy as an efficacious and well-tolerated treatment in patients with resectable NSCLC

Acknowledgments

- The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centres
- We would like to acknowledge all of the investigators who have contributed to the RATIONALE-315 study: Lejie Cao, Chun Chen, Fang Chen, Haiquan Chen, Jun Chen, Qixun Chen, Yuping Chen, Ying Cheng, Jiuwei Cui, Junke Fu, Guang Han, Jian Hu, Mu Hu, Yunchao Huang, Jie Jiang, Jun Li, Lin Li, Qiang Li, Shanqing Li, Yongde Liao, Changhong Liu, Hongxu Liu, Lunxu Liu, Naiquan Mao, Tiejun Ren, Yuping Sun, Lijie Tan, Min Tao, Changli Wang, Wenxiang Wang, Yongsheng Wang, Jun Wu, Ming Wu, Jianping Xiong, Shidong Xu, Fan Yang, Kunpeng Yang, Yue Yang, Min Ye, Bentong Yu, Lanjun Zhang, Lumin Zhang, Peng Zhang, Qiudi Zhang, Yi Zhang, Guofang Zhao, Jian Zhao, Hua Zhong, Kunshou Zhu, and Xibin Zhuang
- This study was sponsored by BeOne Medicines, Ltd.
- Medical writing support was provided by Nivedita Saxena, PhD, of Parexel, and supported by BeOne Medicines

Thank You

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