RATIONALE-315: Post hoc Analysis of Event-Free Survival by Surgically Relevant Subgroups Treated With Perioperative Tislelizumab and Neoadjuvant Chemotherapy Versus Neoadjuvant Chemotherapy

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CONCLUSIONS

- Perioperative tislelizumab plus neoadjuvant chemotherapy improved EFS versus neoadjuvant chemotherapy alone in surgical patients with resectable NSCLC regardless of disease stage or surgery type in RATIONALE-315
- Notably, EFS benefit was observed in all disease stage and surgical approach subgroups in surgical patients receiving perioperative tislelizumab plus neoadjuvant chemotherapy versus those receiving neoadjuvant chemotherapy
- These results further support perioperative tislelizumab plus neoadjuvant chemotherapy as an efficacious treatment option with a well-tolerated safety profile in resectable NSCLC

INTRODUCTION

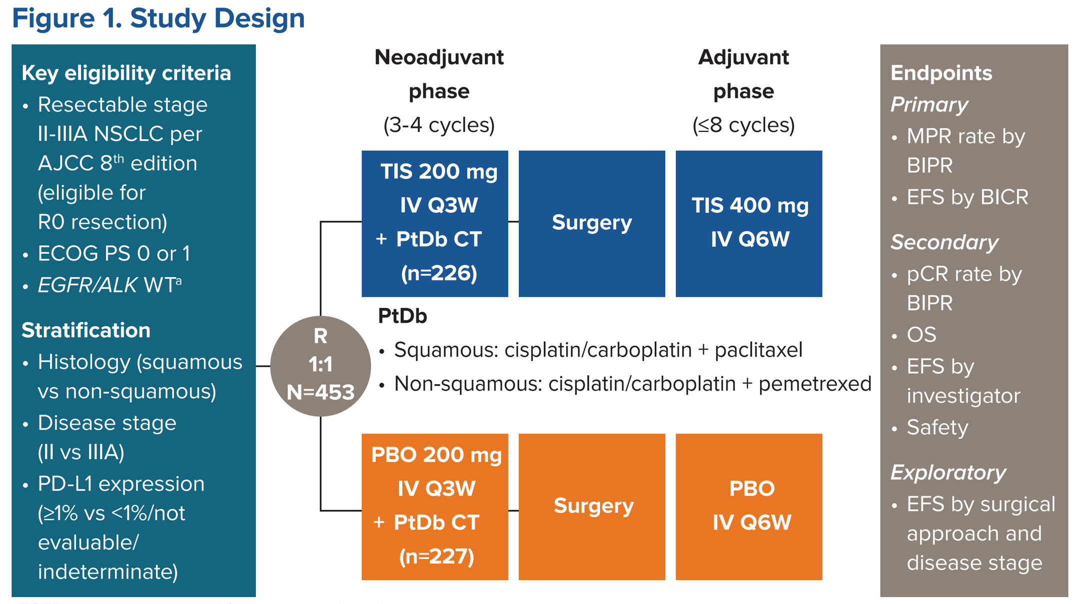
- Surgical resection is frequently used as an early treatment option for resectable non-small cell lung cancer (NSCLC) since complete eradication of disease may be possible,[1,2] but rates of recurrence remain high[3]
  - Additionally, the role of surgery in the era of perioperative immunotherapy plus neoadjuvant chemotherapy is continuously evolving[4]
- RATIONALE-315 (NCT04379635) is a multicenter, randomized, double-blind, placebo-controlled phase 3 trial that compared the efficacy and safety of perioperative tislelizumab or placebo plus neoadjuvant chemotherapy in patients with resectable NSCLC[5]
  - At final analysis (data cut-off: March 7, 2025; median follow-up: 38.5 months), patients in the tislelizumab group had significantly improved overall survival (OS) (hazard ratio [HR]: 0.65; 95% confidence interval (CI): 0.45-0.93; P=.009) and event-free survival (EFS) (HR: 0.58; 95% CI: 0.43-0.79) compared with patients in the placebo group[5]
  - In a previous analysis of RATIONALE-315 (data cut-off: August 21, 2023; median follow-up: 22.0 months), surgical feasibility or completeness were not shown to be impacted when patients with resectable NSCLC were treated with perioperative tislelizumab plus neoadjuvant chemotherapy[6]
- This exploratory analysis reports correlation of EFS with key surgical outcomes to evaluate the benefit of perioperative tislelizumab plus neoadjuvant chemotherapy in surgically relevant subgroups of surgical patients with resectable NSCLC

METHODS

Trial Design

- Patients with resectable stage II-IIIA NSCLC (N=453) were randomized 1:1 to 3-4 cycles of tislelizumab 200 mg or placebo every 3 weeks with neoadjuvant chemotherapy, followed by surgery and ≤8 cycles of adjuvant tislelizumab 400 mg or placebo every 6 weeks (**Figure 1**)
- Primary and key secondary endpoints were reported previously[5,7]
- Exploratory endpoints of surgical outcomes are presented here

Figure 1. Study Design



[a]*EGFR* testing not required for squamous histology.

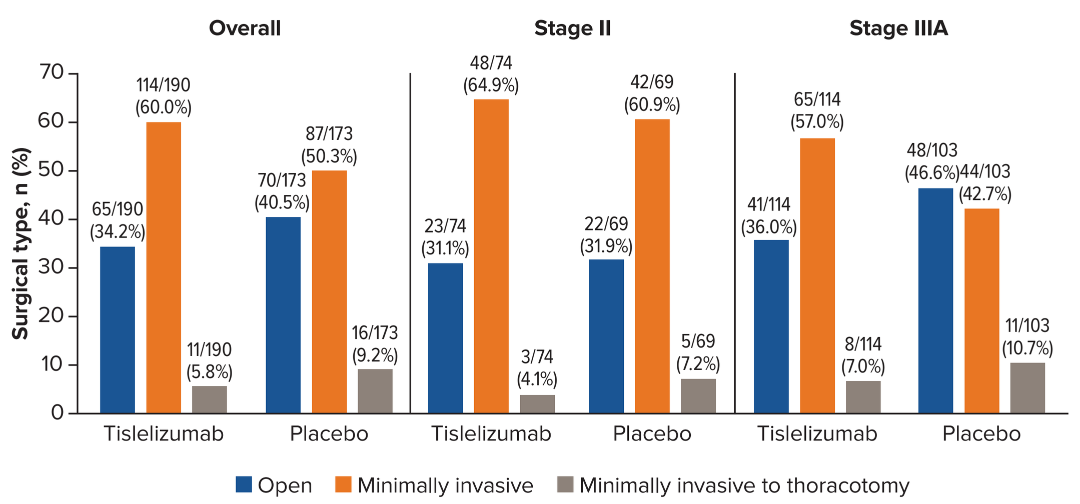
Abbreviations: AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; BIPR, blinded independent pathology review; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IV, intravenous; MPR, major pathological response; NSCLC, non-small cell lung cancer; OS, overall survival; PBO, placebo; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; PtDb CT, platinum-doublet chemotherapy; Q3W, once every 3 weeks; Q6W, once every 6 weeks; R, randomized; R0, pathological complete resection of the primary tumor; TIS, tislelizumab; WT, wild-type.

RESULTS

Patient Disposition

- As of March 7, 2025, 190/226 (86.7%) patients in the tislelizumab arm and 173/227 (76.2%) patients in the placebo arm underwent definitive surgery
  - The number of patients who received each surgical approach in all surgical patients and by disease stage are shown in **Figure 2**
  - Baseline demographics and surgery characteristics were previously presented[6]

Figure 2. Surgery Approach in the Overall Surgical Population and by Disease Stage[a]



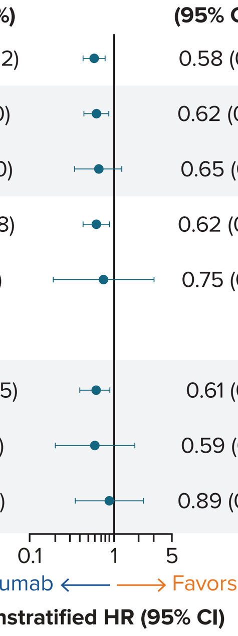
[a]One stage IB and 2 stage IIIB patients were mistakenly enrolled.

Efficacy

- The open and minimally invasive subgroups had sufficient sample size and were selected for EFS analysis
- In the overall patient population, EFS benefit with tislelizumab versus placebo was observed (HR: 0.58; 95% CI: 0.43-0.79) (**Figure 3**)
- In those patients who did (HR: 0.62; 95% CI 0.44-0.88) or did not (HR: 0.65; 95% CI 0.34-1.25) receive surgery, the tislelizumab arm had improved EFS compared with the placebo arm (**Figure 3**)
- Tislelizumab improved EFS versus placebo for surgical patients who had R0 resection (HR: 0.62; 95% CI: 0.43-0.89) and those who had R1 or R2 resections (HR: 0.75; 95% CI: 0.19-3.05; data should be interpreted with caution due to small patient numbers) (**Figure 3**)
- Regardless of surgery type, EFS was improved with tislelizumab versus placebo (**Figure 3**)

Figure 3. EFS by Surgically Relevant Subgroups

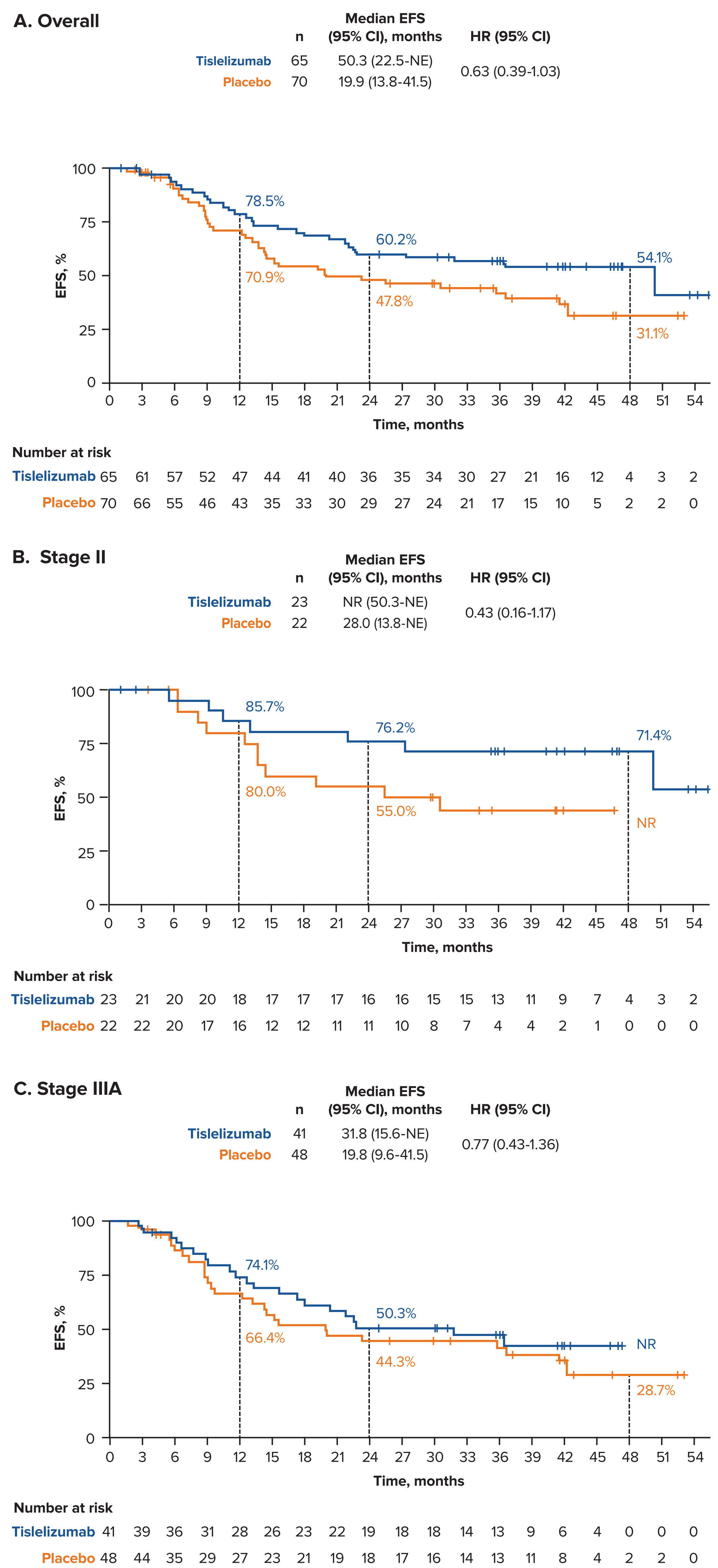
Subgroup		Tislelizumab Events/n (%)	Placebo Events/n (%)	Unstratified HR (95% CI) for EFS
Overall		72/226 (31.9)	98/227 (43.2)	0.58 (0.43-0.79)
Surgery performed	Yes	58/190 (30.5)	71/173 (41.0)	0.62 (0.44-0.88)
	No	14/36 (38.9)	27/54 (50.0)	0.65 (0.34-1.25)
Surgical completeness	R0	53/181 (29.3)	64/161 (39.8)	0.62 (0.43-0.89)
	R1 or R2	3/5 (60.0)	6/11 (54.5)	0.75 (0.19-3.05)
	Unknown[a]	2/4 (50.0)	1/1 (100)	-
Type of surgery[b]	Lobectomy or bilobectomy	44/153 (28.8)	52/135 (38.5)	0.61 (0.41-0.91)
	Pneumonectomy	5/16 (31.3)	9/21 (42.9)	0.59 (0.20-1.79)
	Sleeve lobectomy	9/20 (45.0)	9/16 (56.3)	0.89 (0.35-2.25)



Some subgroups have a wide CI due to small sample size.
[a]HR calculation not performed due to limited sample size within the subgroup.
[b]Two patients (one in treatment and one in control) received surgery other than the three types listed.
Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; R0, pathological complete resection of the primary tumor; R1, macroscopically complete resection of the primary tumor but with microscopic margins; R2, resection with remaining gross tumor.

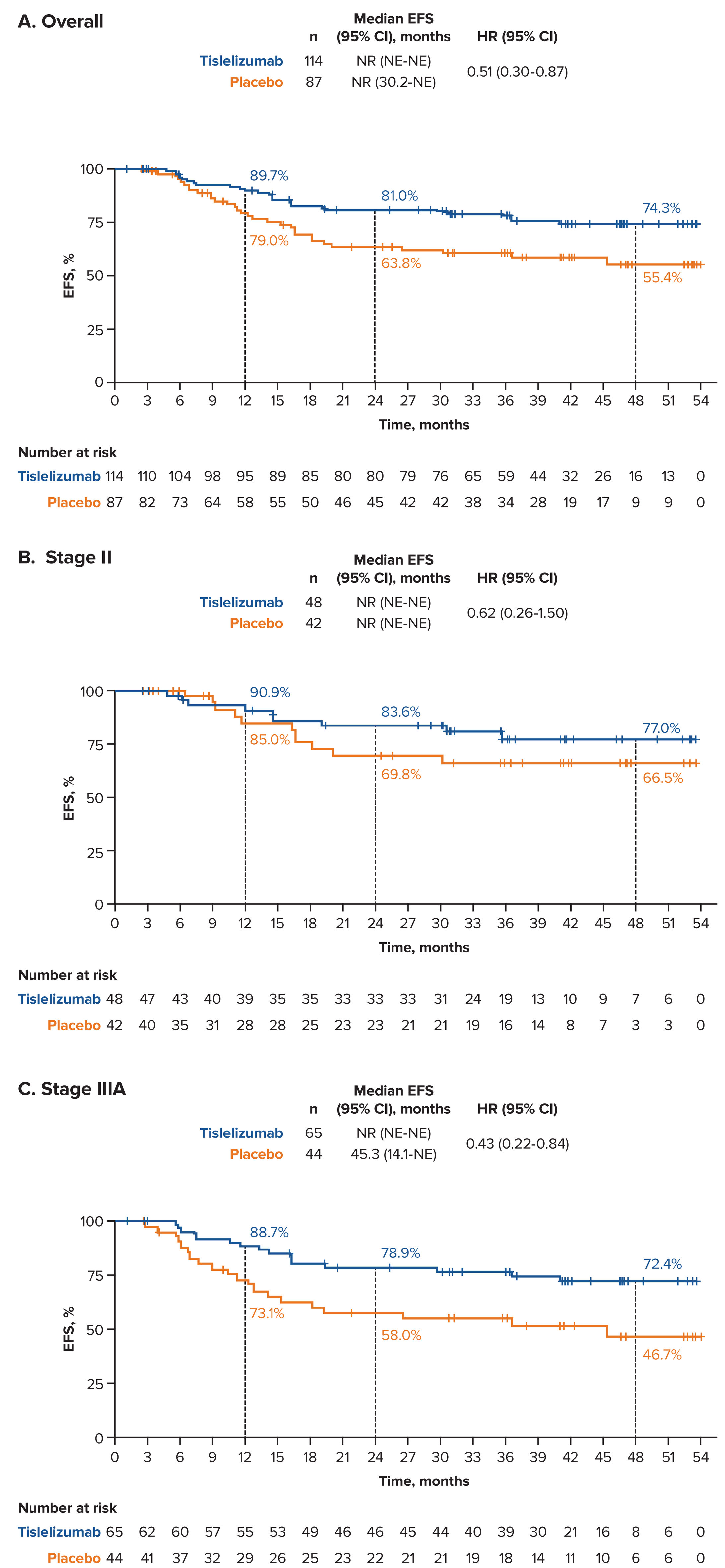
- Patients in the tislelizumab arm who underwent open (**Figure 4**) and minimally invasive (**Figure 5**) surgery (n=179) achieved improved EFS benefit compared with those in the placebo arm (n=157), regardless of disease stage

Figure 4. EFS in Patients who Received Open Surgery



Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; NE, not estimable; NR, not reached.

Figure 5. EFS in Patients who Received Minimally Invasive Surgery



Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; NE, not estimable; NR, not reached.

Safety

- In patients who underwent minimally invasive and open surgery, respectively, grade ≥3 treatment-emergent adverse events occurred in 77.2% and 78.5% of patients in the tislelizumab arm and 71.3% and 81.4% in the placebo arm (**Table 1**)
- In patients who recieved open surgery in the tislelizumab arm versus placebo arm, respectively, grade ≥3 immune mediated adverse events (imAEs) occurred in 4.6% (3/65) versus 5.7% (4/70) of all patients, 4.3% (1/23) versus 4.5% (1/22) in stage II patients, and 4.9% (2/41) versus 6.2% (3/48) in stage IIIA patients
- In patients who underwent minimally invasive surgery in the tislelizumab arm versus placebo arm, respectively, grade ≥3 imAEs were reported in 11.4% (13/114) versus 2.3 (2/87) of all patients, 10.4% (5/48) versus 2.4% (1/42) in stage II patients, and 12.3% (8/65) versus 2.3% (1/44) in stage IIIA patients
- No grade ≥3 imAEs were observed in patients who underwent minimally invasive to thoracotomy surgery in the tislelizumab or placebo arms

Table 1. Summary of TEAEs and imAEs in the Overall Surgical Population and by Disease Stage

	Overall population[a]					
	Tislelizumab (n=190)			Placebo (n=173)		
Event, n (%)	Open (n=65)	Minimally invasive (n=114)	Minimally invasive to thoracotomy (n=11)	Open (n=70)	Minimally invasive (n=87)	Minimally invasive to thoracotomy (n=16)
Any TEAE	65 (100)	114 (100)	11 (100)	70 (100)	87 (100)	16 (100)
Grade ≥3 TEAE	51 (78.5)	88 (77.2)	10 (90.9)	57 (81.4)	62 (71.3)	12 (75.0)
Any imAE	28 (43.1)	48 (42.1)	2 (18.2)	15 (21.4)	14 (16.1)	3 (18.8)
Grade ≥3 imAE	3 (4.6)	13 (11.4)	0	4 (5.7)	2 (2.3)	0
	Stage II[a]					
	Tislelizumab (n=74)			Placebo (n=69)		
Event, n (%)	Open (n=23)	Minimally invasive (n=48)	Minimally invasive to thoracotomy (n=3)	Open (n=22)	Minimally invasive (n=42)	Minimally invasive to thoracotomy (n=5)
Any TEAE	23 (100)	48 (100)	3 (100)	22 (100)	42 (100)	5 (100)
Grade ≥3 TEAE	17 (73.9)	38 (79.2)	3 (100)	20 (90.0)	32 (76.2)	3 (60.0)
Any imAE	14 (60.9)	17 (35.4)	0	5 (22.7)	9 (21.4)	1 (20.0)
Grade ≥3 imAE	1 (4.3)	5 (10.4)	0	1 (4.5)	1 (2.4)	0
	Stage IIIA[a]					
	Tislelizumab (n=114)			Placebo (n=103)		
Event, n (%)	Open (n=41)	Minimally invasive (n=65)	Minimally invasive to thoracotomy (n=8)	Open (n=48)	Minimally invasive (n=44)	Minimally invasive to thoracotomy (n=11)
Any TEAE	41 (100)	65 (100)	8 (100)	48 (100)	44 (100)	11 (100)
Grade ≥3 TEAE	33 (80.5)	49 (75.4)	7 (87.5)	37 (77.1)	29 (65.9)	9 (81.8)
Any imAE	13 (31.7)	30 (46.2)	2 (25.0)	10 (20.8)	5 (11.4)	2 (18.2)
Grade ≥3 imAE	2 (4.9)	8 (12.3)	0	3 (6.2)	1 (2.3)	0

[a]Five patients who were not stage II-IIIA were mistakenly enrolled, and three of them received surgery, so the sum of patients with stage II-IIIa disease may not be equal to the sample size of the entire population.
Abbreviations: imAE, immune-mediated adverse event; TEAE, treatment-emergent adverse event.

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DISCLOSURES

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