Pembrolizumab + Quimioterapia Periadyuvante en Cáncer de Pulmón: de la enfermedad metastásica a estadios precoces

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DECLARATION OF INTERESTS

- **Honoraria:** AstraZeneca, Boehringer-Ingelheim, Amgen, Bayer, Pfizer, Roche, Novartis, Takeda, Sanofi/Regeneron, Merck KGaA, Merck Sharp & Dohme, and Bristol-Myers Squibb.
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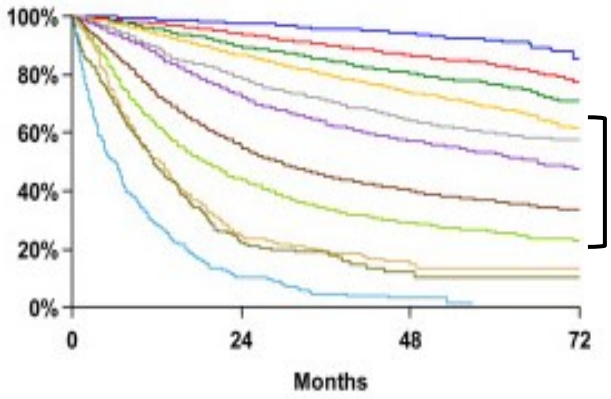
- **Stock Ownership:** None

Localized and locally-advanced NSCLC is a heterogeneous disease with a wide-variable prognosis

- 25–30% of patients with NSCLC present with surgically resectable disease at diagnosis (expected to increase due to LC screening)

Stage Specific Survival in NSCLC, 8th edition staging



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Tumors ≤3 cm, N0

High risk of death: 30% - 75% at 5 years

Usually, systemic therapy offered

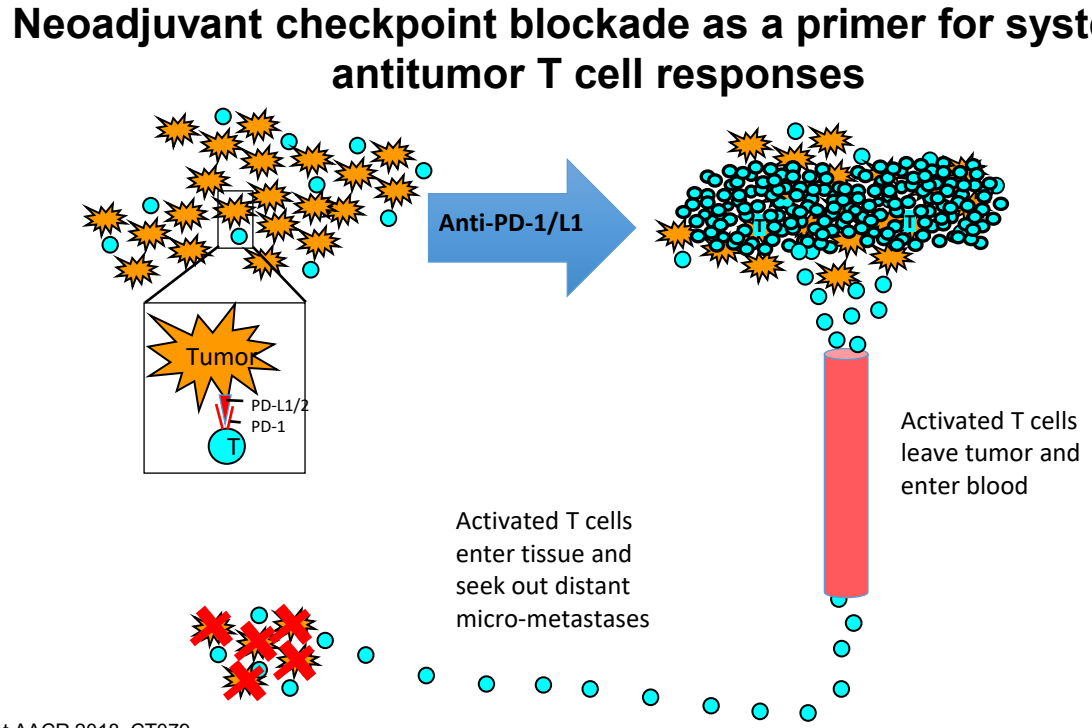
Adjuvant platinum-based chemotherapy is SoC for resected NSCLC over 15 years ago
Similar benefit pre- or post-surgery: ≈5% gain in DFS and OS at 5 years

Journal of Thoracic Oncology, 2016, 39–51;
Vansteenkiste J, et al. Ann Oncol. 2019;30:1244-1253.
Pignon. *J Clin Oncol.* 2008; Felip *J Clin Oncol* 2010
Postmus, *Ann Oncol 2017*, e-update 1 Sept 2021

What is the Best Timing of I-O Treatment Regarding to Surgery in Early-Stage NSCLC?

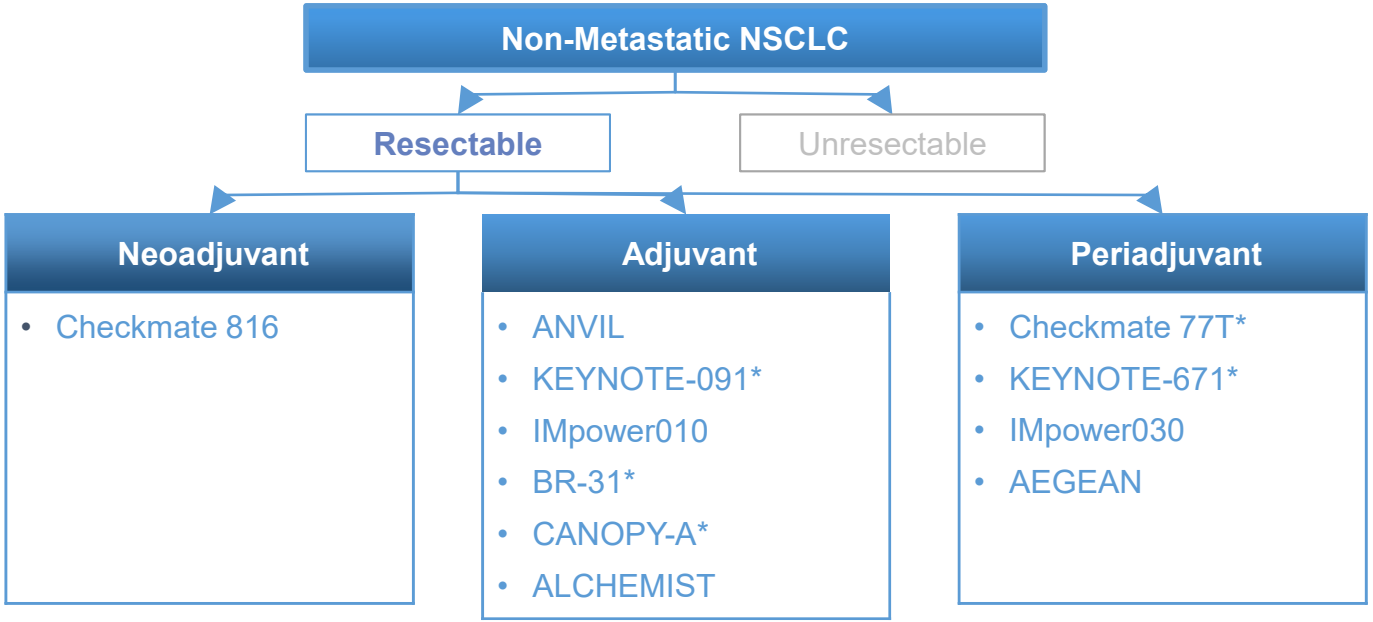
- Before (Neoadjuvant)
- After (Adjuvant)
- Both (Periadjuvant)

Immune system interactions with macroscopic tumor are important for checkpoint inhibitor response



Pardoll D et al. Oral presentation at AACR 2018. CT079.

Overview of stage I-III resectable NSCLC phase 3 trial landscape



*placebo controlled (adjuvant)

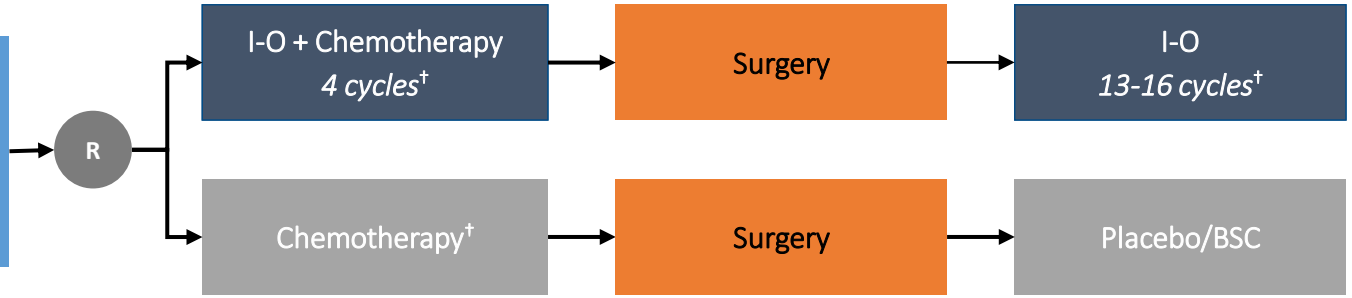
1. Clinicaltrials.gov. NCT02998528. Accessed August 22, 2019. 2. Clinicaltrials.gov. NCT02595944. Accessed August 22, 2019. 3. Clinicaltrials.gov. NCT02504372. Accessed August 22, 2019.
4. Clinicaltrials.gov. NCT02486718. Accessed August 22, 2019. 5. Clinicaltrials.gov. NCT02273375. Accessed August 22, 2019. 6. Clinicaltrials.gov. NCT03447769. Accessed August 22, 2019.
7. Clinicaltrials.gov. NCT04025879. Accessed August 22, 2019. 8. Clinicaltrials.gov. NCT03425643. Accessed August 22, 2019. 9. Clinicaltrials.gov. NCT03456063. Accessed August 22, 2019.
10. Clinicaltrials.gov. NCT03800134. Accessed August 22, 2019. 11. Heymach JV et al. Poster presentation at WCLC 2019. P1.18-02.

Phase 3 periadjuvant trials with I-O in resectable NSCLC

- Checkmate 77T, KEYNOTE-671, IMpower030, AEGEAN

Key Eligibility Criteria

- Stage II-III* resectable NSCLC
- ECOG PS 0–1



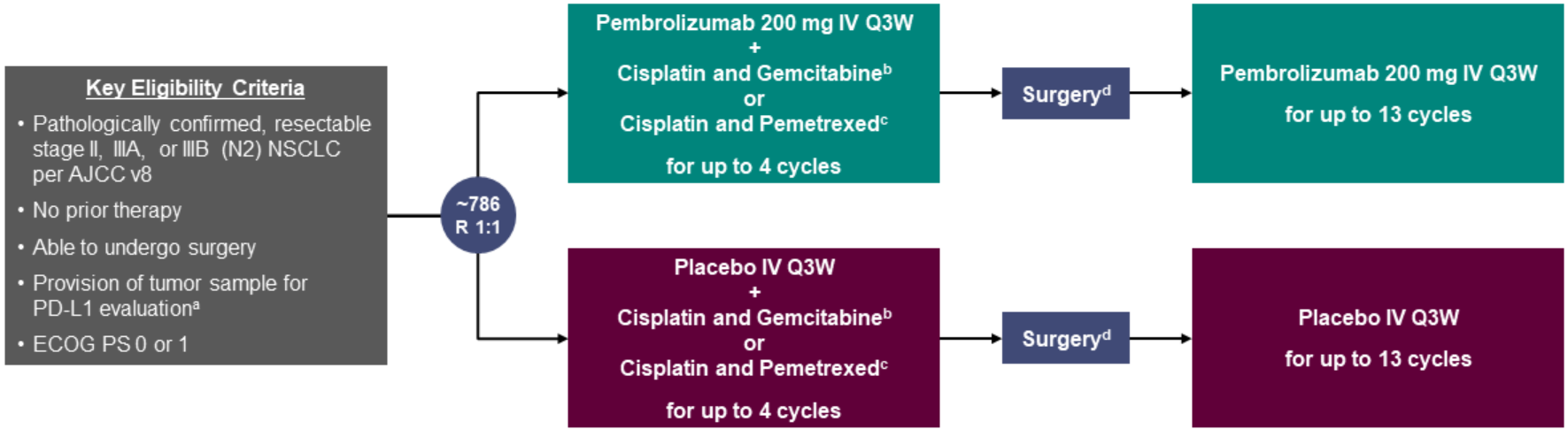
	Checkmate 77T[1]	KEYNOTE-671[2]	IMpower030[3]	AEGEAN[4,5]
I-O agent	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Primary endpoint(s)	EFS	EFS, OS	(MPR), EFS	(MPR), EFS
Results presented	Oct 2023	Jun 2023, Oct 2023	Expected March 2025	April 2023
Stages	II-IIIB‡	II-IIIB‡	II-IIIB‡	IIA-IIIB‡
Target enrollment	461	786	453	(300), 802

Cross-trial comparisons are not intended.

*Stages included differ between trials. †Dosage, timing, duration, and chemotherapy backbones differ between trials; information not available for Checkmate 77T or AEGEAN. ‡Includes stages IIIB patients with N2 disease that is considered resectable.

1. Clinicaltrials.gov. NCT04025879. Accessed August 7, 2019. 2. Clinicaltrials.gov. NCT03425643. Accessed August 7, 2019. 3. Clinicaltrials.gov. NCT034056063. Accessed August 7, 2019. 4. Clinicaltrials.gov. NCT03800134. Accessed August 7, 2019. 5. Heymach JV et al. Poster presentation at WCLC 2019. P1.18-02.

KEYNOTE-671 Study Design
Randomized, Double-Blind, Phase 3 Trial



Stratification Factors
- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease. ClinicalTrials.gov identifier: NCT03425643.

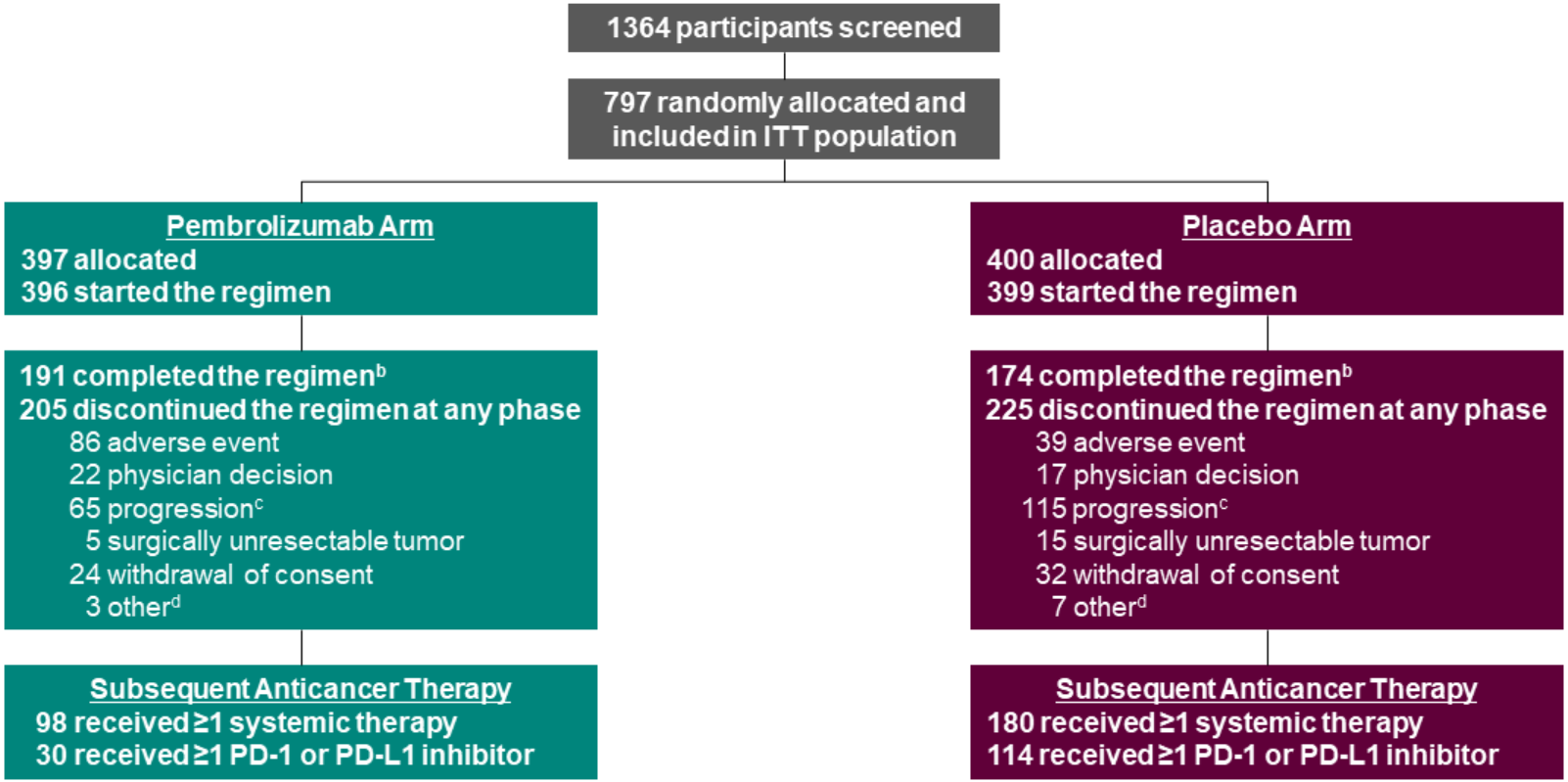
Statistical Considerations

- Analysis populations
  - Efficacy: all randomized participants (ITT)
  - Safety: all randomized participants who received ≥1 dose of study treatment
- Family-wise type I error rate strongly controlled at one-sided alpha level of 0.025 across the EFS, OS, mPR, and pCR hypotheses using the graphical method of Maurer and Bretz[a]
- Interim analysis 2 (IA2)
  - Prespecified to occur after ~416 EFS events observed
  - Final analysis of EFS[b]
  - Interim analysis of OS (significance boundary, one-sided $P = 0.00543$[c])
  - Data cutoff date: July 10, 2023

[a] EFS, OS, mPR, and pCR were tested in a group sequential fashion.
[b] Because statistical significance for EFS was demonstrated at IA1, EFS was not formally tested at IA2.
[c] Based on the actual number of OS events observed.

Treatment Disposition, IA2

Median Follow-Up[a]: 36.6 months (range, 18.8-62.0)



[a] Defined as time from randomization to data cutoff date. [b] Includes participants who discontinued without receiving 4 cycles of neoadjuvant therapy but proceeded to surgery and completed the adjuvant phase. [c] Includes local progression preventing surgery, clinical progression, and progressive disease. [d] Includes non-study anticancer therapy and protocol violation. Data cutoff date for IA2: July 10, 2023.

Baseline Characteristics, IA2

	Pembro Arm (N = 397)	Placebo Arm (N = 400)
Median age (range), years	63 (26-83)	64 (35-81)
Male	279 (70.3%)	284 (71.0%)
Race		
American Indian or Alaska Native	1 (0.3%)	0
Asian	124 (31.2%)	125 (31.3%)
Black or African American	6 (1.5%)	10 (2.5%)
Multiple	3 (0.8%)	10 (2.5%)
White	250 (63.0%)	239 (59.8%)
Missing data	13 (3.3%)	16 (4.0%)
Geographic region		
East Asia	123 (31.0%)	121 (30.3%)
Not east Asia	274 (69.0%)	279 (69.8%)
ECOG PS		
0	253 (63.7%)	246 (61.5%)
1	144 (36.3%)	154 (38.5%)
Histology		
Nonsquamous	226 (59.6%)	227 (56.8%)
Squamous	171 (43.1%)	173 (43.3%)

	Pembro Arm (N = 397)	Placebo Arm (N = 400)
Smoking status		
Current	96 (24.2%)	103 (25.8%)
Former	247 (62.2%)	250 (62.5%)
Never	54 (13.6%)	47 (11.8%)
Clinical stage[a]		
II	118 (29.7%)	121 (30.3%)
IIIA	217 (54.7%)	224 (56.0%)
IIIB	62 (15.6%)	55 (13.8%)
N status[a]		
cN0	148 (37.3%)	142 (35.5%)
cN1	81 (20.4%)	71 (17.8%)
cN2	168 (42.3%)	187 (46.8%)
PD-L1 TPS		
≥50%	132 (33.2%)	134 (33.5%)
1-49%	127 (32.0%)	115 (28.8%)
<1%	138 (34.8%)	151 (37.8%)
Known *EGFR* mutation[b]	14 (3.5%)	19 (4.8%)
Known *ALK* translocation[b]	12 (3.0%)	9 (2.3%)

[a] As determined by imaging and biopsy. [b] *EGFR* mutation and *ALK* translocation status were tested locally per investigator discretion. *EGFR* status was unknown in 272 (68.5%) participants in the pembro arm and 257 (64.3%) in the placebo arm; *ALK* status was unknown in 281 (70.8%) and 259 (64.8%), respectively. Data cutoff date for IA2: July 10, 2023.

KEYNOTE-671: Surgical Details

	Pembrolizumab (n=325)	Placebo (n=317)
In-Study Surgery[a]		
Resected	320 (98.5%)	302 (95.3%)
Complete - R0	299 (92.0%)	267 (84.2%)
Incomplete - R1	17 (5.2%)	31 (9.8%)
Incomplete - R2	4 (1.2%)	4 (1.3%)
Unresected	5 (1.5%)	15 (4.7%)
Surgical procedure		
Lobectomy	256 (78.8%)	238 (75.1%)
Pneumonectomy	37 (11.4%)	39 (12.3%)
Bilobectomy	26 (8.0%)	26 (8.2%)
Exploratory thoracotomy	4 (1.2%)	13 (4.1%)
Other	2 (0.6%)[b]	1 (0.3%)[c]
30-day all-cause mortality	6 (1.8%)[d]	2 (0.6%)[e]

Median follow-up (ITT) = 25.2 months (range: 7.5–50.6). Data cutoff: July 29, 2022.

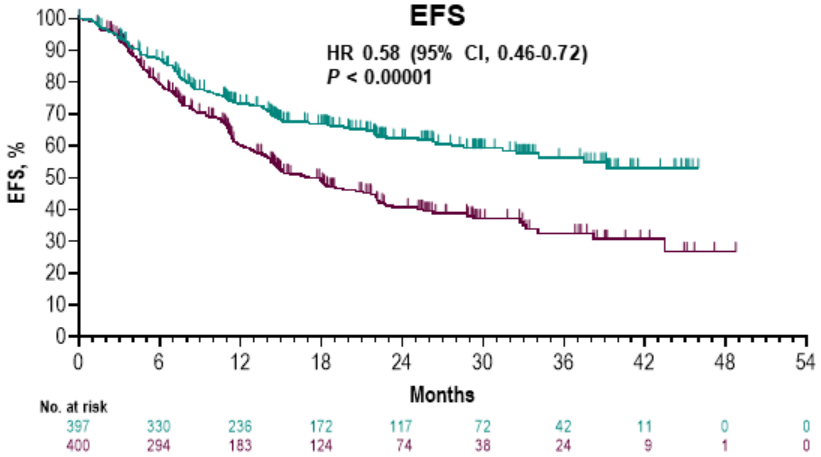
[a]An additional 8 participants in the pembro arm and 7 participants in the placebo arm underwent off-study surgery. [b]Lung segmentectomy (n=1), lung wedge resection (n=1). [c]Lymph node dissection only (planned surgery was lung lobectomy; need for more extensive surgery discovered during surgery, but consent was not granted). [d]Pulmonary embolism (n=2), pulmonary hemorrhage due to arterial injury during surgery (n=1), pulmonary sepsis (n=1), respiratory failure (n=1), and septic shock (n=1). [e]Respiratory failure (n = 1) and pneumonia (n = 1).

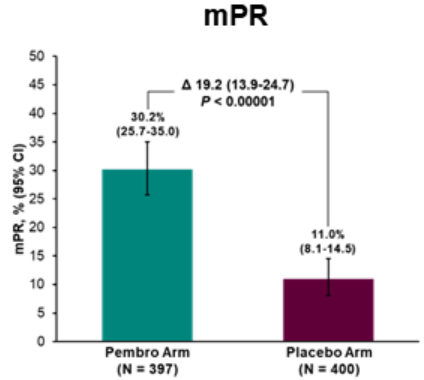
1. Wakelee H et al. *N Engl J Med*. 2023. doi: 10.1056/NEJMoa2302983. **2.** Wakelee H et al. Presented at ASCO 2023. Abstract LBA100.

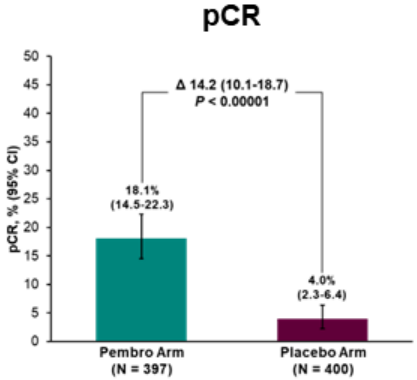
KEYNOTE-671 Results: Interim Analysis 1

Median Follow-Up[a]: 25.2 months (range, 7.5-50.6)

- Neoadjuvant pembrolizumab + chemotherapy followed by surgery and adjuvant pembrolizumab significantly improved EFS, mPR, and pCR compared with neoadjuvant chemotherapy and surgery alone
- AE profile was as expected based on the known profiles of the individual treatment components





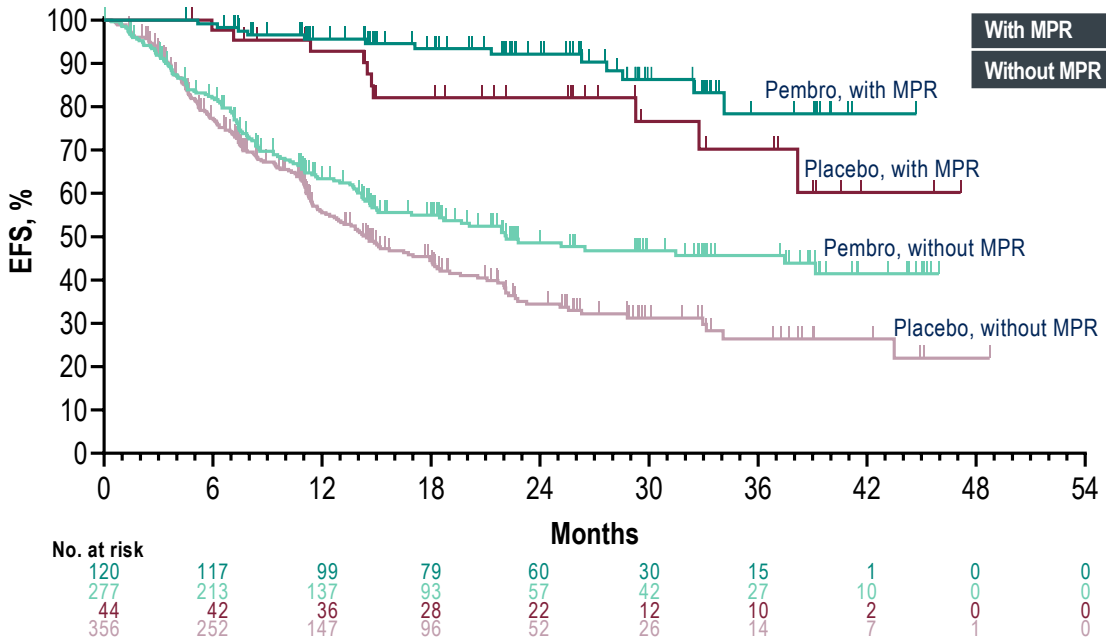


[a] Defined as time from randomization to data cutoff date of July 29, 2022.

Wakelee H et al. *N Engl J Med* 2023;389:491-503.

KEYNOTE-671: EFS by MPR (Exploratory Analysis)

	HR (95% CI)
With MPR	0.54 (0.24–1.22)
Without MPR	0.73 (0.58–0.92)

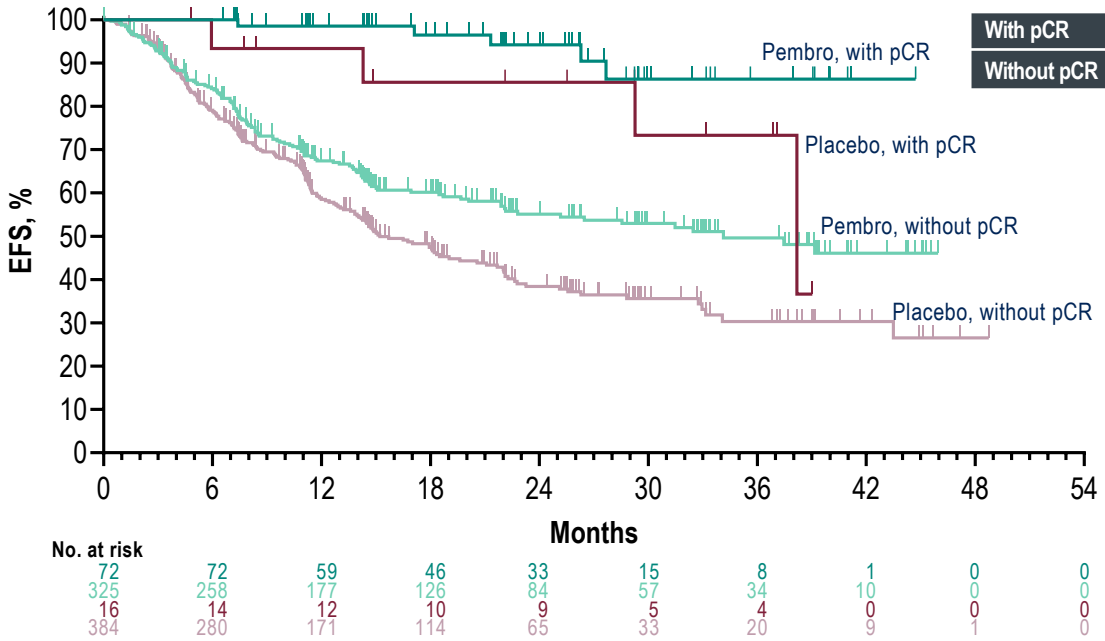


Median follow-up (ITT) = 25.2 months (range: 7.5–50.6). Data cutoff: July 29, 2022.

1. Wakelee H et al. *N Engl J Med*. 2023. doi: 10.1056/NEJMoa2302983. **2.** Wakelee H et al. Presented at ASCO 2023. Abstract LBA100.

Figure adapted from Wakelee H, et al. NEJM. 2023; Online ahead of print, with permission from Massachusetts Medical Society.

KEYNOTE-671: EFS by pCR (Exploratory Analysis)



	HR (95% CI)
With pCR	0.33 (0.09–1.22)
Without pCR	0.69 (0.55–0.85)

Median follow-up (ITT) = 25.2 months (range: 7.5–50.6). Data cutoff: July 29, 2022.

1. Wakelee H et al. *N Engl J Med*. 2023. doi: 10.1056/NEJMoa2302983. **2.** Wakelee H et al. Presented at ASCO 2023. Abstract LBA100.

Figure adapted from Wakelee H, et al. NEJM. 2023; Online ahead of print, with permission from Massachusetts Medical Society.

KEYNOTE-671: Categorization of Events That Contributed to EFS (ITT Population)

n (%)	Pembrolizumab (n=397)	Placebo (n=400)
No event	258 (65.0)	195 (48.8)
Event	139 (35.0)	205 (51.2)
Disease progression or recurrence	94 (23.7)	155 (38.8)
Local disease progression preventing surgery	0	6 (1.5)
Inability to resect the tumor	5 (1.3)	15 (3.8)
Death	40 (10.1)	29 (7.2)

Median follow-up (ITT) = 25.2 months (range: 7.5–50.6). Data cutoff: July 29, 2022.

1. Supplement to Wakelee H et al. *N Engl J Med.* 2023. doi: 10.1056/NEJMoa2302983.

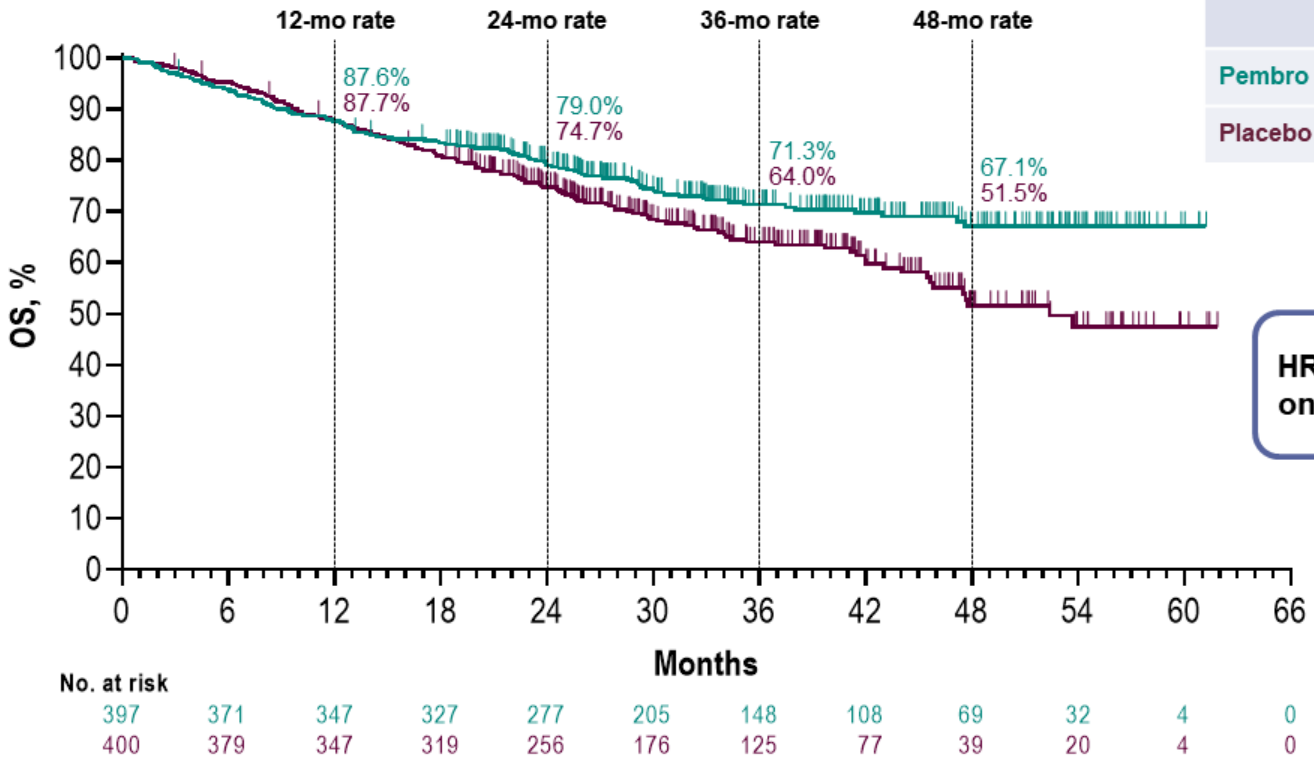
Subsequent Systemic Anticancer Therapy In Participants With Recurrence or PD, IA2

	Pembro Arm (n = 125)	Placebo Arm (n = 208)
Any subsequent systemic therapy[a]	88 (70.4%)	160 (76.9%)
PD-1 or PD-L1 inhibitor-based regimen[b]	27 (21.6%)	104 (50.0%)
Chemotherapy-based regimen	54 (43.2%)	72 (34.6%)
TKI-based regimen[c]	23 (18.4%)	25 (12.0%)
Other	9 (2.7%)	3 (1.4%)

[a] Participants may have received ≥1 subsequent therapy regimen. [b] Includes PD-1 or PD-L1 inhibitors given with or without chemotherapy. [c] Includes TKIs given with or without chemotherapy.
Data cutoff date for IA2: July 10, 2023.

Overall Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)



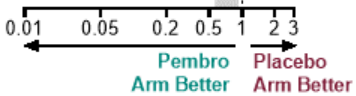
	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

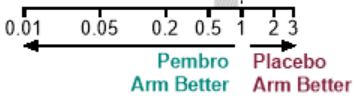
HR 0.72 (95% CI, 0.56-0.93)
one-sided *P* = 0.00517[a]

OS defined as time from randomization to death from any cause. [a] Significance boundary at IA2, one-sided *P* = 0.00543.
Data cutoff date for IA2: July 10, 2023.

Overall Survival in Subgroups, IA2

Subgroup	Events/participants: Pembro Arm	Events/participants: Placebo Arm	Hazard ratio (95% CI)
Overall	110/397	144/400	0.72 (0.56-0.93)
Age			
<65 y	54/221	82/214	0.57 (0.40-0.80)
≥65 y	56/176	62/186	0.96 (0.67-1.38)
Sex			
Female	21/118	30/116	0.69 (0.39-1.20)
Male	89/279	114/284	0.73 (0.55-0.96)
Race			
White	73/250	97/239	0.66 (0.49-0.90)
All others	34/134	39/145	0.93 (0.59-1.48)
Geographic region			
East Asia	32/123	30/121	1.05 (0.64-1.73)
Not east Asia	78/274	114/279	0.63 (0.48-0.85)
Smoking status			
Current	31/96	48/103	0.59 (0.38-0.93)
Former	69/247	87/250	0.76 (0.56-1.05)
Never	10/54	9/47	1.00 (0.41-2.46)
Histology			
Nonsquamous	49/226	64/227	0.73 (0.50-1.06)
Squamous	61/171	80/173	0.71 (0.51-0.99)
Clinical stage			
II	26/118	39/121	0.67 (0.41-1.10)
IIIA	62/217	79/224	0.74 (0.53-1.03)
IIIB	22/62	26/55	0.69 (0.39-1.22)
N status			
cN0	40/148	52/142	0.70 (0.46-1.06)
cN1	21/81	24/71	0.74 (0.41-1.33)
cN2	49/168	68/187	0.74 (0.52-1.07)
PD-L1 TPS			
≥50%	23/132	39/134	0.55 (0.33-0.92)
1-49%	35/127	44/115	0.69 (0.44-1.07)
<1%	52/138	61/151	0.91 (0.63-1.32)
***EGFR* mutation**			
No	20/111	33/124	0.64 (0.37-1.11)
Yes	1/14	5/19	0.24 (0.03-2.03)
Unknown	89/272	106/257	0.75 (0.56-0.99)
***ALK* translocation**			
No	22/104	38/132	0.70 (0.41-1.18)
Unknown	87/281	105/259	0.72 (0.54-0.96)

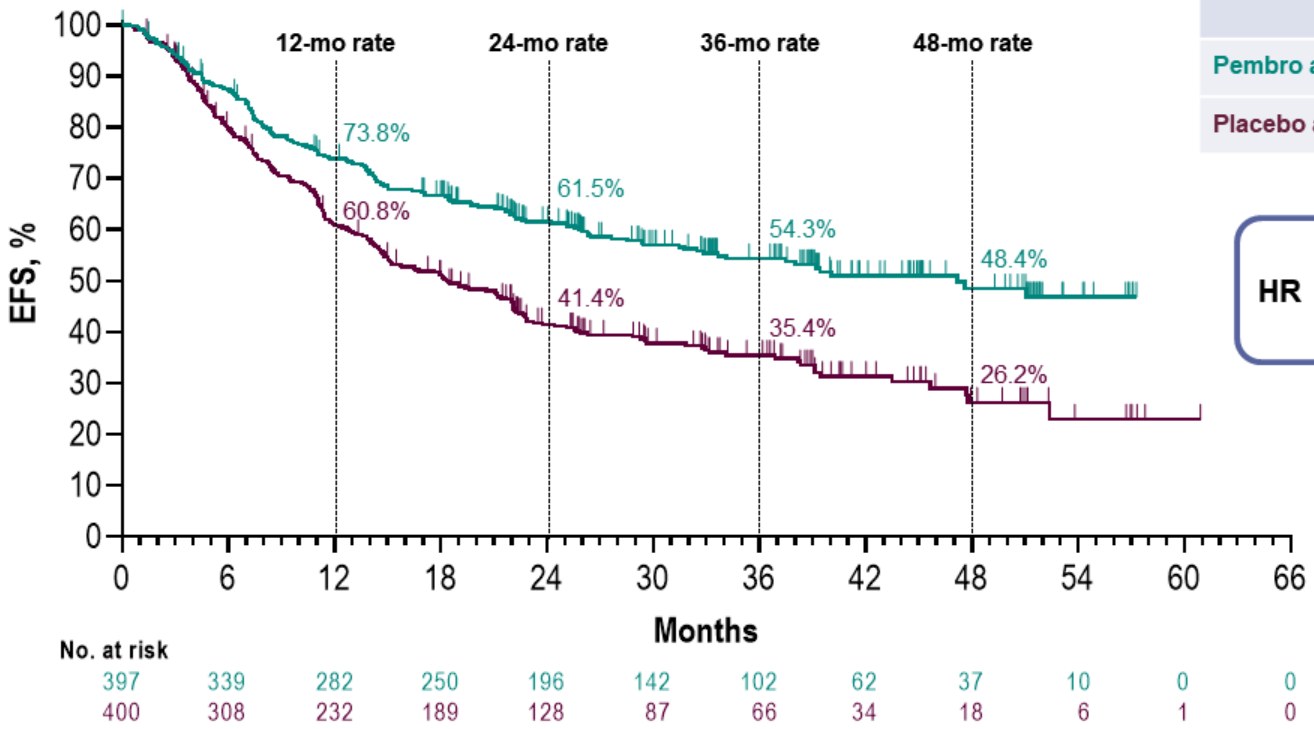




Per the prespecified analysis plan, subgroups with <30 participants are excluded from the forest plot. Subgroups for stage IIIA and IIIB and pN status were post hoc; all other subgroups were prespecified.
Data cutoff date for IA2: July 10, 2023.

Event-Free Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)

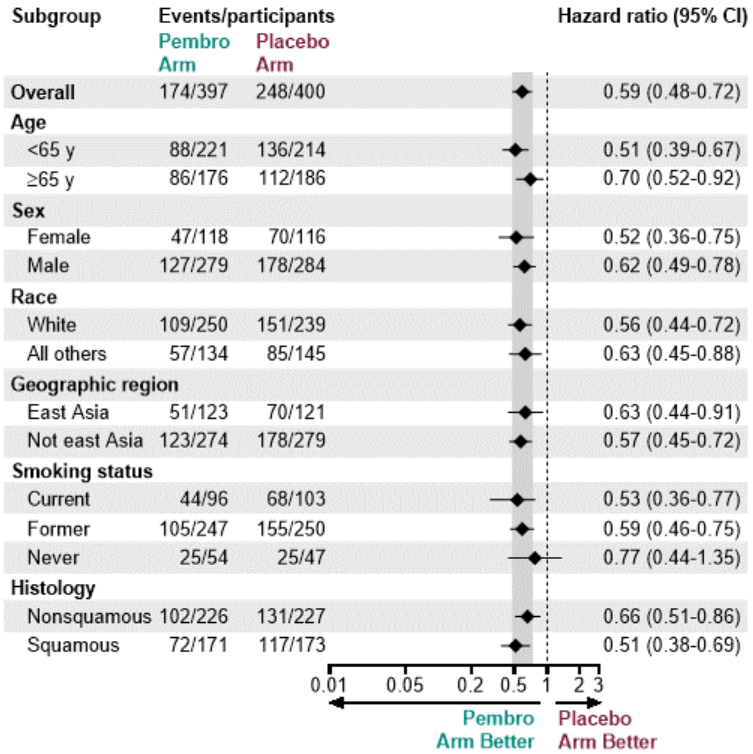


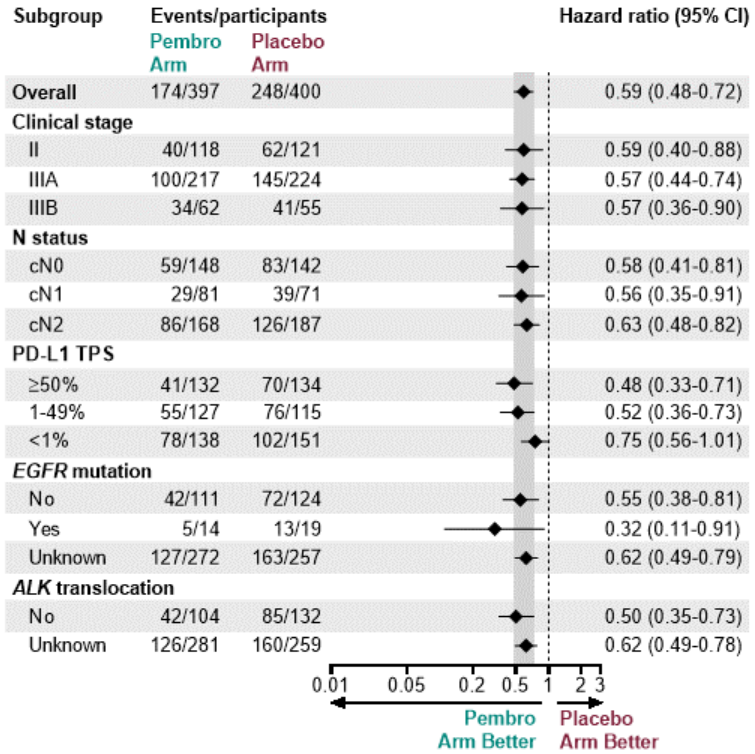
	Pts w/ Event	Median (95% CI), mo
Pembro arm	43.8%	47.2 (32.9-NR)
Placebo arm	62.0%	18.3 (14.8-22.1)

HR 0.59 (95% CI, 0.48-0.72)

EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA2: July 10, 2023.

Event-Free Survival in Subgroups, IA2





Per the prespecified analysis plan, subgroups with <30 participants are excluded from the forest plot. Subgroups for stage IIIA and IIIB and pN status were post hoc; all other subgroups were prespecified.
Data cutoff date for IA2: July 10, 2023.

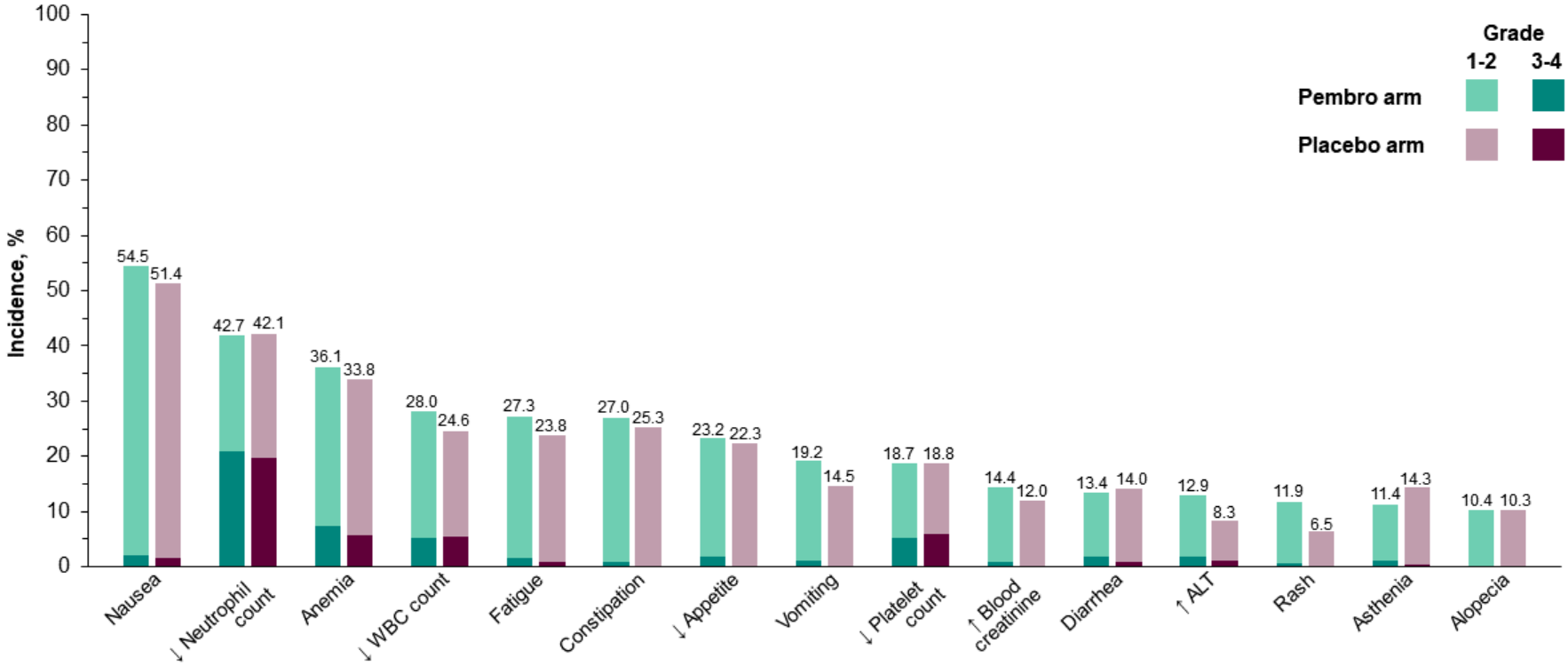
Exposure and AE Summary Across Treatment Phases, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)

	Pembro Arm (n = 396)	Placebo Arm (n = 399)
Exposure		
Study days on pembro or placebo, median (range)	375.5 days (1-728)	337.0 days (1-644)
No. pembro or placebo administrations, median (range)	15 (1-17)	12 (1-17)
Treatment-related AEs[a]	383 (96.7%)	381 (95.5%)
Grade 3-5	179 (45.2%)	151 (37.8%)
Serious	73 (18.4%)	58 (14.5%)
Led to death	4 (1.0%)[b]	3 (0.8%)[c]
Led to discontinuation of all study treatment	54 (13.6%)	21 (5.3%)
Immune-mediated AEs and infusion reactions	103 (26.0%)	36 (9.0%)
Grade 3-5	26 (6.6%)	6 (1.5%)
Serious	24 (6.1%)	6 (1.5%)
Led to death	1 (0.3%)[d]	0
Led to discontinuation of all study treatment	23 (5.8%)	3 (0.8%)

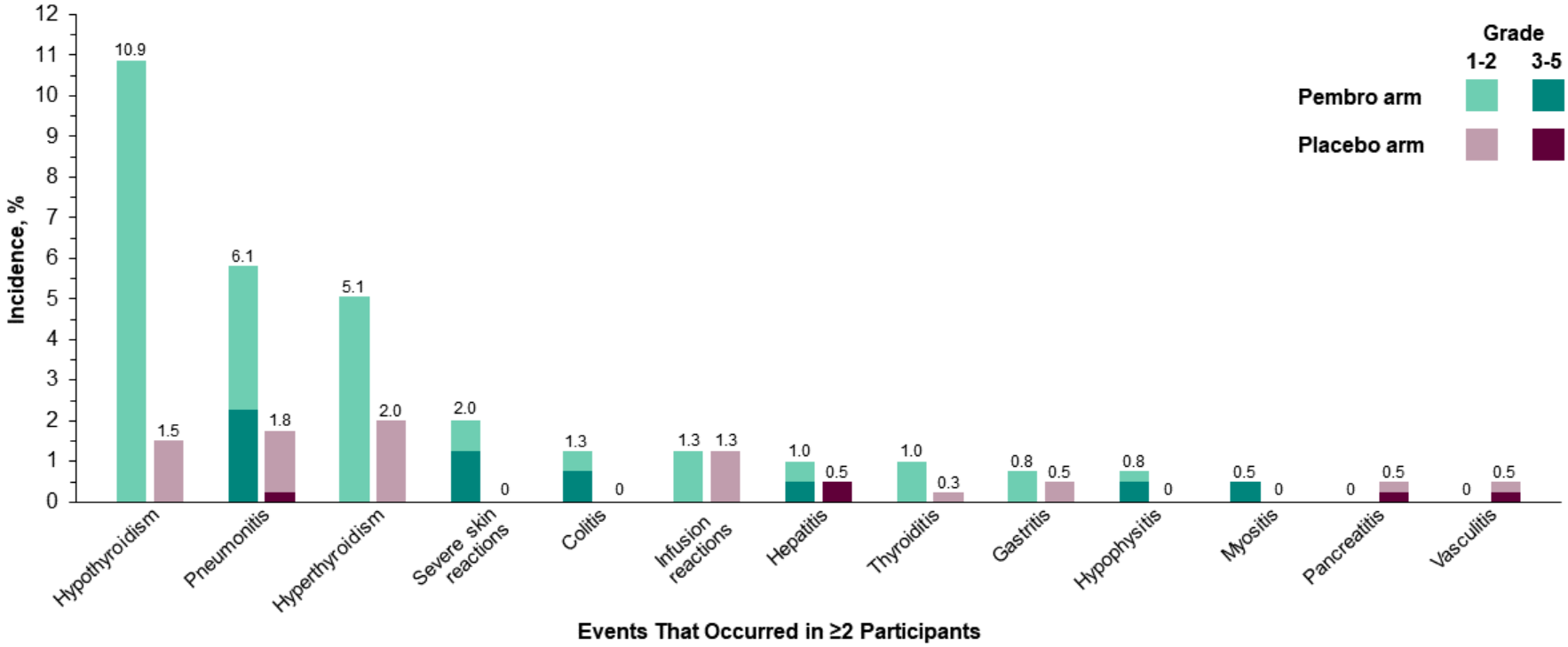
[a] Considered by the investigator to be related to chemotherapy, pembrolizumab, and placebo. [b] AEs leading to death (n = 1 each): atrial fibrillation, immune-mediated lung disease, pneumonia, and sudden cardiac death (no new treatment-related deaths vs IA1). [c] AEs leading to death (n = 1 each): acute coronary syndrome, pneumonia, and pulmonary hemorrhage (no new treatment-related deaths vs IA1). [d] AE leading to death: pneumonitis (recorded in the database as immune-mediated lung disease; no new immune-mediated deaths vs IA1). Data cutoff date for IA2: July 10, 2023.

Treatment-Related AEs With Incidence ≥10% Across Treatment Phases, IA2



Treatment-related AEs were AEs considered by the investigator to be related to chemotherapy, pembrolizumab, and placebo. Data cutoff date for IA2: July 10, 2023.

Immune-Mediated AEs and Infusion Reactions Across Treatment Phases, IA2



Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator. Data cutoff date for IA2: July 10, 2023.

Summary and Conclusions

- A statistically significant, clinically important OS improvement was seen for neoadjuvant pembrolizumab plus chemotherapy followed by surgery and adjuvant pembrolizumab versus neoadjuvant chemotherapy and surgery alone
  - With median follow-up of 3 years, the HR for death was 0.72 (95% CI, 0.56-0.93)
  - Median OS was not reached in the pembrolizumab arm vs 52.4 months in the placebo arm
  - OS benefit was generally consistent across the majority of subgroups analyzed
- EFS benefit observed at IA1 was maintained at IA2
  - At IA2, median EFS was almost 2.5 years longer in the pembrolizumab arm compared with the placebo arm
- AE profile was consistent with IA1 with no new safety signals and no new treatment-related deaths
  - Any increases in incidence of individual treatment-related AE rates were mostly by 1-2 participants each
  - Most immune-mediated AEs were due to hypothyroidism
- **The significant OS improvement in the absence of new safety signals establishes the perioperative pembrolizumab regimen as a new standard of care for resectable stage II, IIIA, or IIIB (N2) NSCLC**
  - **On October 16, 2023, the US FDA granted pembrolizumab approval for the treatment of resectable (tumors ≥4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery**

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Gracias!

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