Perioperative Immunotherapy in NSCLC

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Disclosures

I have no disclosures related to this presentation

Resectable NSCLC

- Stage I, II, or III
- In older studies → only 25-30% of NSCLCs are suitable for potentially curative resection
- Still after resection, patients will still be at risk to have recurrence and death.
  - 25% in Stage IB
  - 35-50% in stage II

Ann Oncol. 2010;21 Suppl 7:vii196-vii198
J Thorac Oncol. 2015 Jul;10(7):990-1003

Adjuvant Therapy

- Platinum-based adjuvant chemotherapy
  - SOC for resectable stage II–IIIA disease
  - OS benefit is estimated to be around 5%
  - Considered in high-risk stage IB

J Natl Compr Canc Netw. 2022;20(8):953-961.

Perioperative immunotherapy

- Immune checkpoint inhibitors changed treatment for advanced NSCLC.

- Predictive markers: PD-L1 , EGFR and ALK

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Why do we need neoadjuvant treatment

- ❑ Decrease tumor size
- ❑ Improve the likelihood of complete resection
- ❑ Eliminate any micrometastases.
- ❑ Allows for pathologic evaluation of the tumor response after immunotherapy.

J Natl Compr Canc Netw. 2022;20(8):953-961.

Neoadjuvant mono-immunotherapy

CheckMate 159

- Design:
  - One of the first pilot studies to evaluate neoadjuvant immunotherapy's safety and feasibility in NSCLC.
  - Phase II trial evaluated 21 patients with stage I–IIIA.
  - Patients received 2 doses of preoperative nivolumab .
- Outcomes:
  - Tumor major pathologic response (MPR): defined as tumor viability <= 10% in the surgical specimen
- Result:
  - MPR→ 45% of patients; 10% had a pathologic complete response
  - Compared to old studies → MPR rate with neoadjuvant chemotherapy has ranged from 16% to 21%.

N Engl J Med 2018; 378:1976-1986
Lancet Oncol 2014;15:e42–50.

LCMC3 study

- Design:
  - Phase II trial included 181 patients with stage IB-IIIB
  - Patients received 2 doses of neoadjuvant atezolizumab prior to surgery
- Outcome:
  - Primary outcome MPR (MPR; ≤10% viable malignant cells)
- Results:
  - MPR rate was 20%
  - pCR rate was 7%.

Nat Med. 2022;28(10):2155-2161.
Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 8503

NEOSTAR

- Design:
  - Randomized phase II study, enrolled 44 patients with “operable” NSCLC
  - Neoadjuvant nivolumab or nivolumab + ipilimumab for 3 cycles followed by surgery
- Outcome:
  - Primary endpoint was MPR
- Results:
  - Ipi/nivo: 50% MPR , pCR 38%
  - Nivo: 24% MPR , cPR 10%

Nat Med. 2021;27(3):504-514.

Other trials

- ChiCTR-OIC-17013726
  - Sintilimab (anti-PD-1) for 2 cycles prior to surgery for stage IA-IIIB
  - MPR 40.5%, pCR 16.2%
  - 2 year follow up:
    - 2-yr DFS rate was 73.3%.
    - 2-yr OS for overall population 87.5%

- NCT02259621
  - Ipilimumab and nivolumab for 3 cycles … Terminated due to toxicity

J Thorac Oncol. 2020;15(5):816–26
Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2
8522.

Conclusion

- Neoadjuvant immunotherapy as monotherapy has some efficacy in inducing tumor response and does not interfere with surgical outcomes.
- However, it is not clear if the pathologic response rates will lead to survival benefit
- But to date, response rates seem to be lower than those seen with combination immunotherapy and chemotherapy in unselected patients, which may limit its application.

Neoadjuvant Chemo-Immunotherapy

Atezolizumab and chemotherapy

- Design:
  - Phase II trial involved 30 patients with stage IB-IIIA NSCLC.
  - Patients treated with 2 cycles of neoadjuvant atezolizumab, nab-paclitaxel, and carboplatin → if no progression, then another 2 cycles followed by surgery.
- Outcomes:
  - Primary outcome: MPR (defined as the presence of 10% or less residual viable tumor at the time of surgery)

Lancet Oncol 2020;21:786–795.

Results

	Patients (n=30)
Age	67 (62–74)
Sex	
Male	15 (50%)
Female	15 (50%)
Histology	
Adenocarcinoma	17 (57%)
Squamous cell carcinoma	12 (40%)
Large cell neuroendocrine	1 (3%)
Stage at presentation*	
IIA	4 (13%)
IIB	3 (10%)
IIIA	23 (77%)
PD-L1 expression†	
≥50%	8 (27%)
≥1%	16 (55%)
<1%	12 (40%)
Unknown	2 (7%)

97% patients were taken into the operating theatre, and 87% underwent successful R0 resection.

Lancet Oncol 2020;21:786–795.

Primary outcome (MPR)

	Major pathological response	Pathological complete response
Intention-to-treat population	17/30 (57%; 95% CI 37–75)	10/30 (33%; 95% CI 17–53)
Cancer type*		
Adenocarcinoma	8/15 (53%)	5/15 (33%)
Squamous cell carcinoma	8/10 (80%)	5/10 (50%)
p value	0·17	0·41

Data are n/N (%) unless otherwise indicated. One patient had large cell neuroendocrine carcinoma and is not included in this table. *Only includes patients who underwent successful R0 surgical resection.

***Table 3:* Pathological response rates**

Lancet Oncol 2020;21:786–795.

	Patients (n=29)*
Had successful surgical resection with curative intent	26/29 (87%)†
Type of surgery	
Video-assisted thoracoscopic surgery	12/26 (46%)
Thoracotomy	14/26 (54%)
Surgical resection	
Lobectomy	19/26 (73%)
Bilobectomy	4/26 (15%)
Pneumonectomy	3/26 (12%)
Margins	
Negative	26/26 (100%)
Positive	0
Downstaging of nodal status in patients with N2 at baseline*	
N2 to N0	11/19 (58%)
N2 to N1	2/19 (11%)
N2 to N2	5/19 (26%)
Surgical complications	
Intraoperative platelet or blood transfusion	2/29 (7%)
30-day mortality	1/29 (3%)‡
30–90-day mortality	0
Length of hospital stay, days	4 (3–6)
Readmission within 30 days	1/29 (3%)§
Postoperative arrhythmia	3/29 (10%)
Urinary tract infection or urinary retention	2/29 (7%)

Lancet Oncol 2020;21:786–795.

Conclusion

“Atezolizumab plus carboplatin and nab-paclitaxel could be a potential neoadjuvant regimen for resectable non-small-cell lung cancer, with a high proportion of patients achieving a major pathological response, and manageable treatment-related toxic effects, which did not compromise surgical resection.”

CheckMate 816

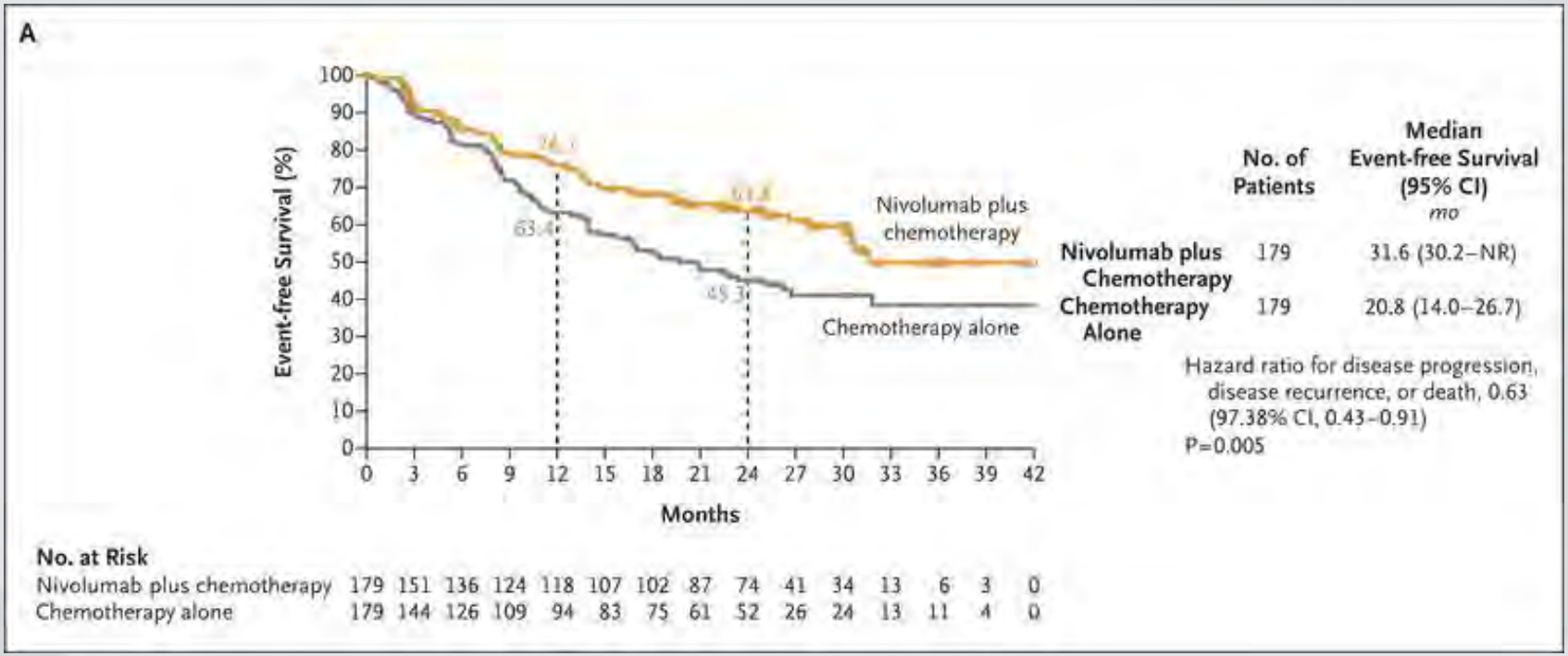
- Design:
  - Phase III study involved 358 patients with stage IB-IIIA NSCLC without EGFR/ALK mutations
  - Patients received 3 cycles of neoadjuvant nivolumab + platinum-based chemotherapy or chemotherapy alone.
- Outcomes:
  - Event free survival (EFS)
  - Pathological complete response (0% viable tumor in resected lung and lymph nodes)

N Engl J Med 2022; 386:1973-1985

Characteristic	Nivolumab plus Chemotherapy (N=179)	Chemotherapy Alone (N=179)
Age		
Median (range) — yr	64 (41–82)	65 (34–84)
Distribution — no. (%)		
<65 yr	93 (52.0)	83 (46.4)
≥65 yr	86 (48.0)	96 (53.6)
Sex — no. (%)		
Male	128 (71.5)	127 (70.9)
Female	51 (28.5)	52 (29.1)
Geographic region — no. (%)		
North America	41 (22.9)	50 (27.9)
Europe	41 (22.9)	25 (14.0)
Asia	85 (47.5)	92 (51.4)
Rest of the world*	12 (6.7)	12 (6.7)
ECOG performance-status score — no. (%)†		
0	124 (69.3)	117 (65.4)
1	55 (30.7)	62 (34.6)
Disease stage — no. (%)‡		
IB or II	65 (36.3)	62 (34.6)
IIIA	113 (63.1)	115 (64.2)
Histologic type of tumor — no. (%)		
Squamous	87 (48.6)	95 (53.1)
Nonsquamous	92 (51.4)	84 (46.9)
Smoking status — no. (%)§		
Never smoked	19 (10.6)	20 (11.2)
Current or former smoker	160 (89.4)	158 (88.3)
PD-L1 expression level — no. (%)¶		
Could not be evaluated	12 (6.7)	13 (7.3)
<1%	78 (43.6)	77 (43.0)
≥1%	89 (49.7)	89 (49.7)
1–49%	51 (28.5)	47 (26.3)
≥50%	38 (21.2)	42 (23.5)
Tumor mutational burden — no. (%)‖		
Could not be evaluated or was not reported	91 (50.8)	89 (49.7)
<12.3 mutations per megabase	49 (27.4)	53 (29.6)
≥12.3 mutations per megabase	39 (21.8)	37 (20.7)
Type of platinum therapy — no. (%)		
Cisplatin	124 (69.3)	134 (74.9)

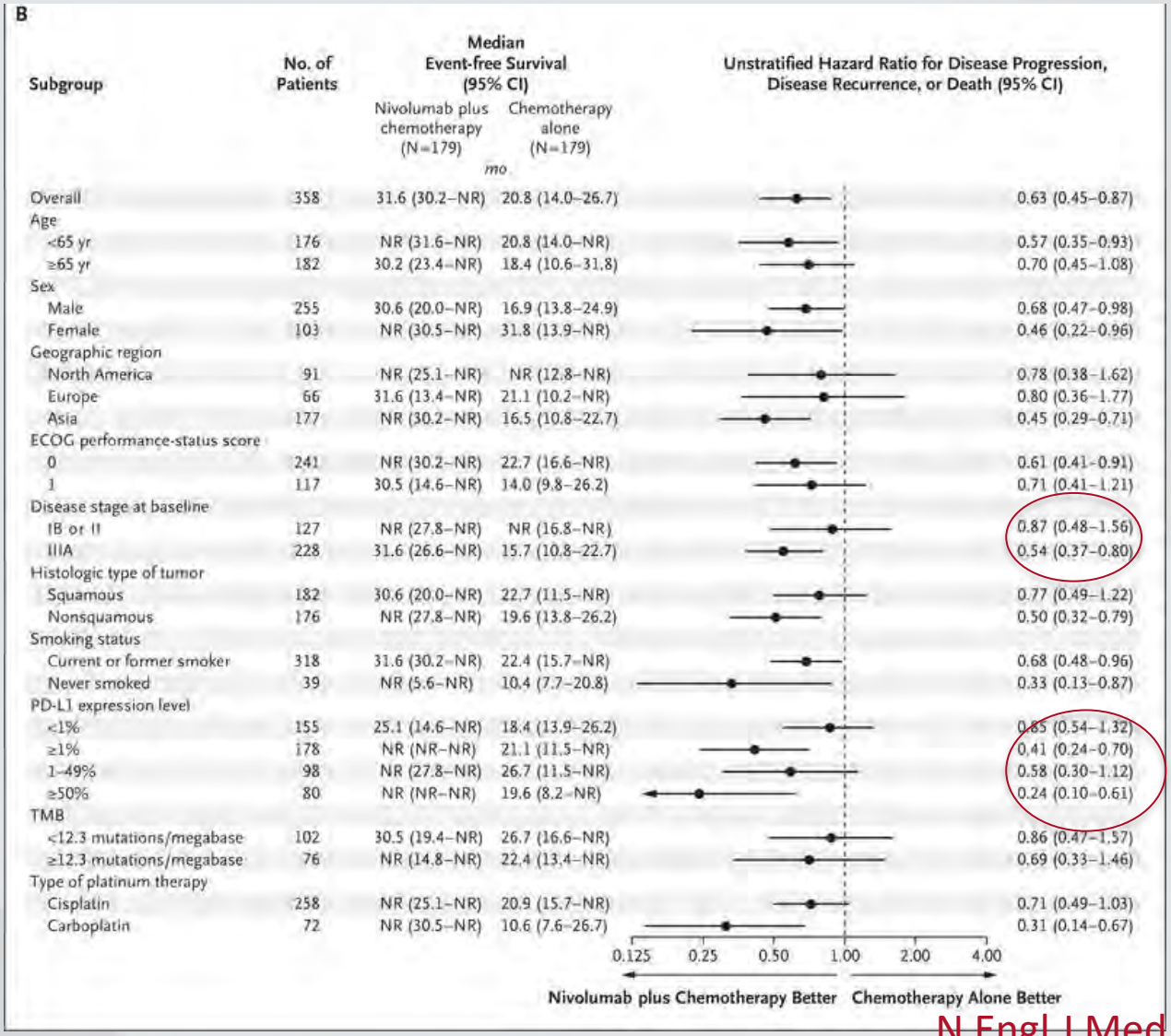
N Engl J Med 2022; 386:1973-1985

EFS



N Engl J Med 2022; 386:1973-1985

EFS



B

Subgroup	No. of Patients	Median Event-free Survival (95% CI)	
		Nivolumab plus chemotherapy (N=179)	Chemotherapy alone (N=179)
		mo	
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)
Age			
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)
Sex			
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)
Geographic region			
North America	91	NR (25.1–NR)	NR (12.8–NR)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)
ECOG performance-status score			
0	241	NR (30.2–NR)	22.7 (16.6–NR)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)
Disease stage at baseline			
IB or II	127	NR (27.8–NR)	NR (16.8–NR)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)
Histologic type of tumor			
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)
Smoking status			
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)
PD-L1 expression level			
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)
TMB			
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)
Type of platinum therapy			
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)

Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)

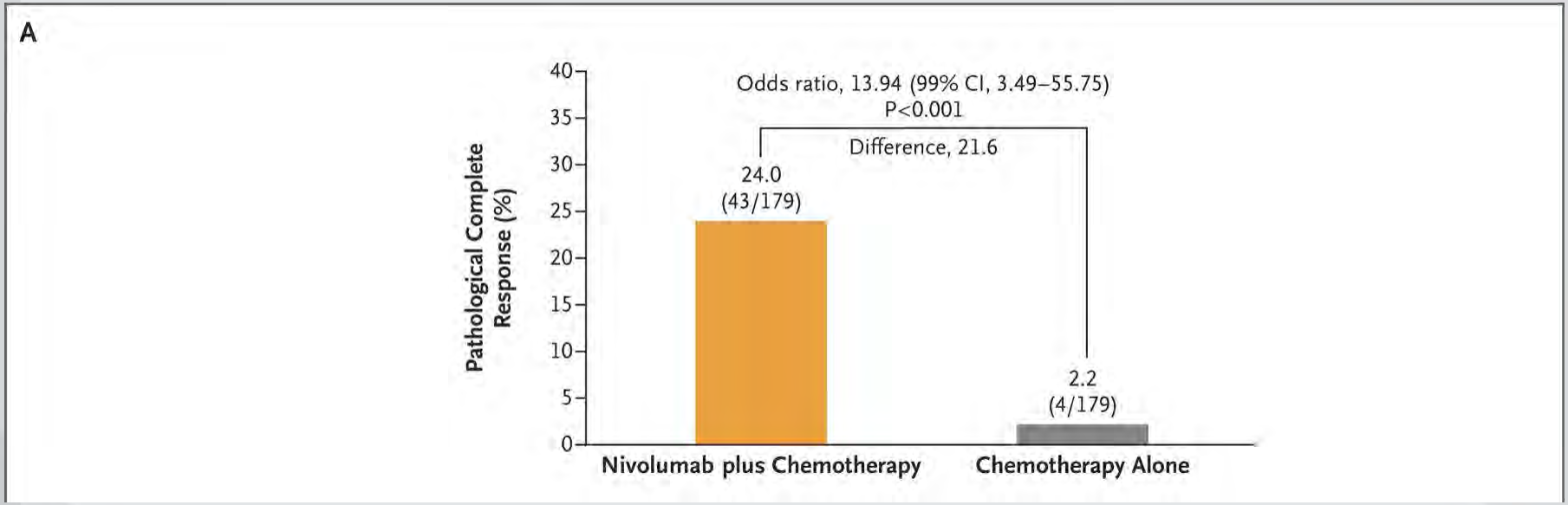
0.63 (0.45–0.87)
0.57 (0.35–0.93)
0.70 (0.45–1.08)
0.68 (0.47–0.98)
0.46 (0.22–0.96)
0.78 (0.38–1.62)
0.80 (0.36–1.77)
0.45 (0.29–0.71)
0.61 (0.41–0.91)
0.71 (0.41–1.21)
0.87 (0.48–1.56)
0.54 (0.37–0.80)
0.77 (0.49–1.22)
0.50 (0.32–0.79)
0.68 (0.48–0.96)
0.33 (0.13–0.87)
0.85 (0.54–1.32)
0.41 (0.24–0.70)
0.58 (0.30–1.12)
0.24 (0.10–0.61)
0.86 (0.47–1.57)
0.69 (0.33–1.46)
0.71 (0.49–1.03)
0.31 (0.14–0.67)

0.125 0.25 0.50 1.00 2.00 4.00

Nivolumab plus Chemotherapy Better | Chemotherapy Alone Better

N Engl J Med 2022; 386:1973-

pCR



N Engl J Med 2022; 386:1973-1985

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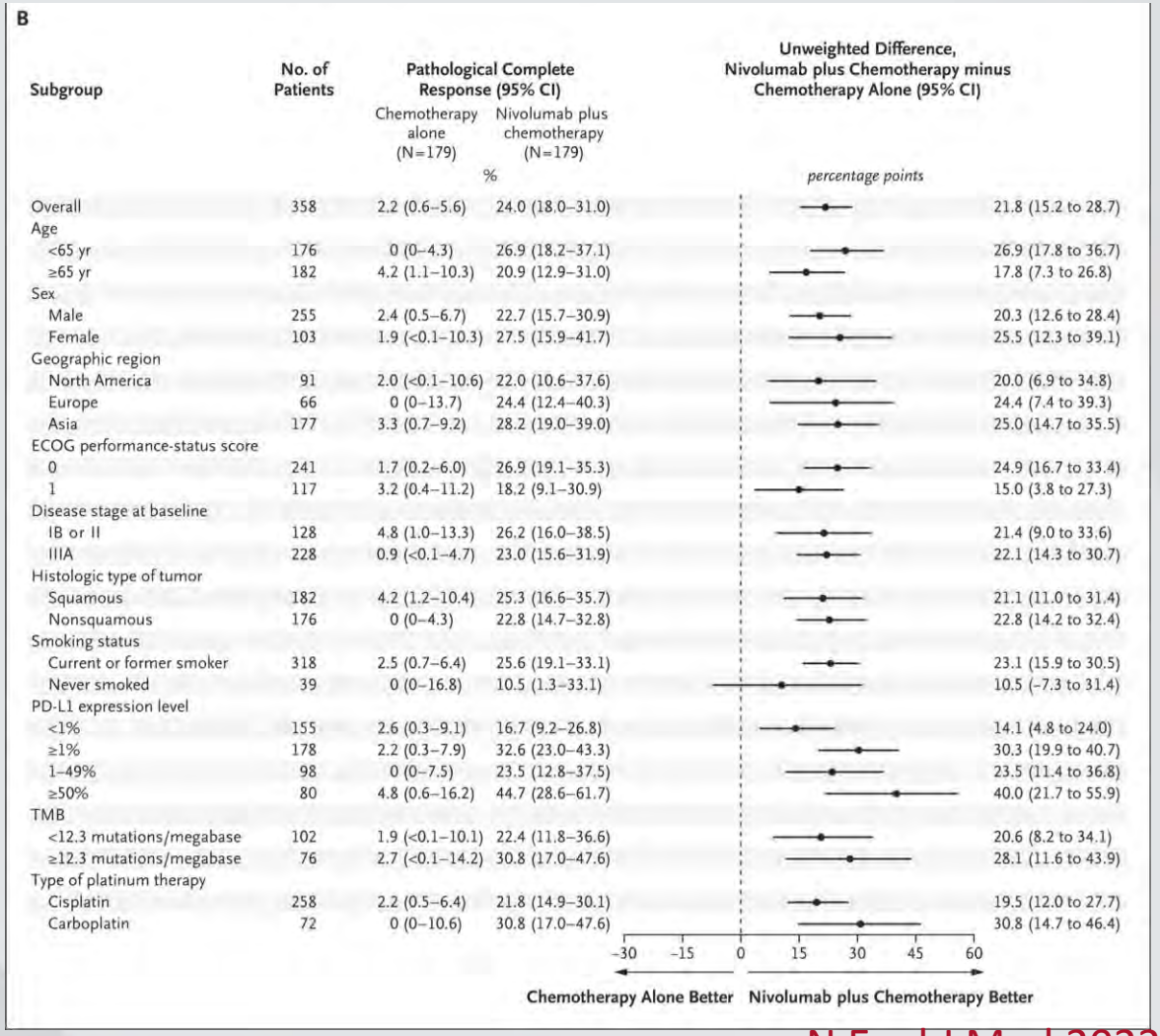
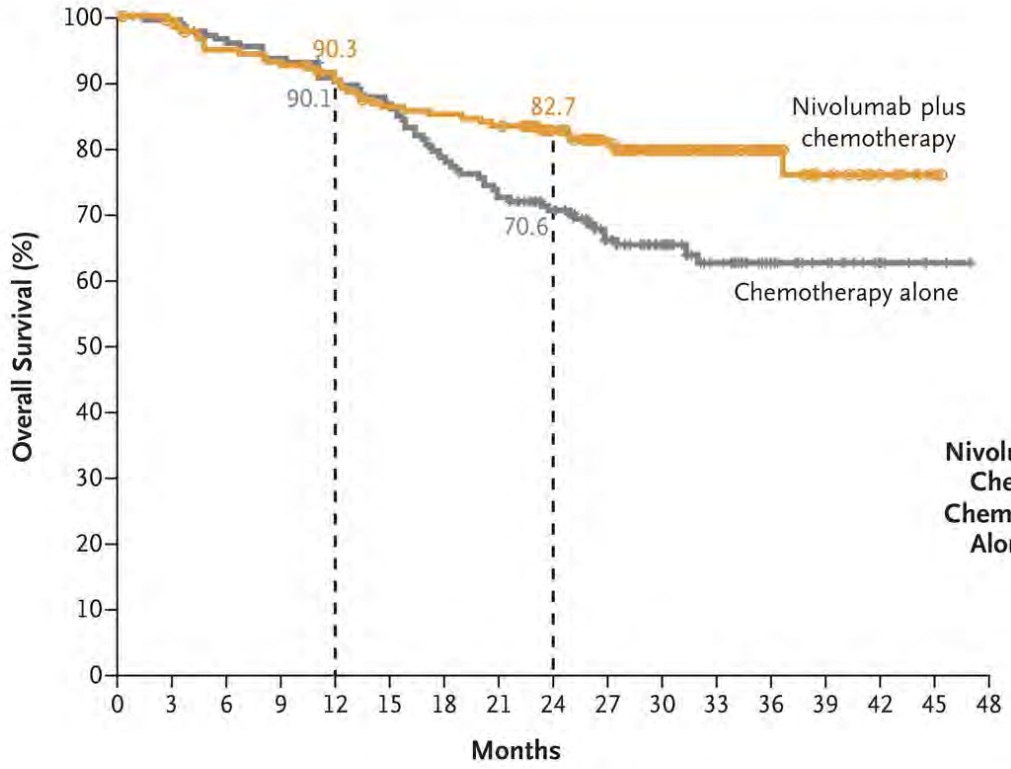


B

Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Unweighted Difference, Nivolumab plus Chemotherapy minus Chemotherapy Alone (95% CI)
		Chemotherapy alone (N=179)	Nivolumab plus chemotherapy (N=179)	
		%		*percentage points*
Overall	358	2.2 (0.6–5.6)	24.0 (18.0–31.0)	21.8 (15.2 to 28.7)
Age				
<65 yr	176	0 (0–4.3)	26.9 (18.2–37.1)	26.9 (17.8 to 36.7)
≥65 yr	182	4.2 (1.1–10.3)	20.9 (12.9–31.0)	17.8 (7.3 to 26.8)
Sex				
Male	255	2.4 (0.5–6.7)	22.7 (15.7–30.9)	20.3 (12.6 to 28.4)
Female	103	1.9 (<0.1–10.3)	27.5 (15.9–41.7)	25.5 (12.3 to 39.1)
Geographic region				
North America	91	2.0 (<0.1–10.6)	22.0 (10.6–37.6)	20.0 (6.9 to 34.8)
Europe	66	0 (0–13.7)	24.4 (12.4–40.3)	24.4 (7.4 to 39.3)
Asia	177	3.3 (0.7–9.2)	28.2 (19.0–39.0)	25.0 (14.7 to 35.5)
ECOG performance-status score				
0	241	1.7 (0.2–6.0)	26.9 (19.1–35.3)	24.9 (16.7 to 33.4)
1	117	3.2 (0.4–11.2)	18.2 (9.1–30.9)	15.0 (3.8 to 27.3)
Disease stage at baseline				
IB or II	128	4.8 (1.0–13.3)	26.2 (16.0–38.5)	21.4 (9.0 to 33.6)
IIIA	228	0.9 (<0.1–4.7)	23.0 (15.6–31.9)	22.1 (14.3 to 30.7)
Histologic type of tumor				
Squamous	182	4.2 (1.2–10.4)	25.3 (16.6–35.7)	21.1 (11.0 to 31.4)
Nonsquamous	176	0 (0–4.3)	22.8 (14.7–32.8)	22.8 (14.2 to 32.4)
Smoking status				
Current or former smoker	318	2.5 (0.7–6.4)	25.6 (19.1–33.1)	23.1 (15.9 to 30.5)
Never smoked	39	0 (0–16.8)	10.5 (1.3–33.1)	10.5 (–7.3 to 31.4)
PD-L1 expression level				
<1%	155	2.6 (0.3–9.1)	16.7 (9.2–26.8)	14.1 (4.8 to 24.0)
≥1%	178	2.2 (0.3–7.9)	32.6 (23.0–43.3)	30.3 (19.9 to 40.7)
1–49%	98	0 (0–7.5)	23.5 (12.8–37.5)	23.5 (11.4 to 36.8)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)	40.0 (21.7 to 55.9)
TMB				
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)	20.6 (8.2 to 34.1)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)	28.1 (11.6 to 43.9)
Type of platinum therapy				
Cisplatin	258	2.2 (0.5–6.4)	21.8 (14.9–30.1)	19.5 (12.0 to 27.7)
Carboplatin	72	0 (0–10.6)	30.8 (17.0–47.6)	30.8 (14.7 to 46.4)

N Engl J Med 2022; 386:1973-1985

OS



	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008

No. at Risk

Nivolumab plus chemotherapy	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemotherapy alone	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

N Engl J Med 2022; 386:1973-1985

Table S16. Adverse Events Leading to Surgery Delay and/or Cancellation.

	Nivolumab plus Chemotherapy (N = 176)		Chemotherapy (N = 176)	
Event	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
All adverse events leading to surgery delay	6 (3.4)	2 (1.1)	9 (5.1)	4 (2.3)
Bronchitis	1 (0.6)	0	0	0
Pneumonia	1 (0.6)	1 (0.6)	0	0
Herpes zoster	0	0	1 (0.6)	0
Increased lipase	1 (0.6)	0	0	0
Lung diffusion test	0	0	1 (0.6)	0
Decreased neutrophil count	0	0	1 (0.6)	0
Decreased white blood cell count	0	0	1 (0.6)	0
Pneumonitis	1 (0.6)	0	0	0
Pulmonary embolism	0	0	2 (1.1)	1 (0.6)
Maculopapular rash	1 (0.6)	0	0	0
Embolism	1 (0.6)	1 (0.6)	0	0
Deep vein thrombosis	0	0	1 (0.6)	0
Ventricular thrombosis	0	0	1 (0.6)	1 (0.6)
Myocardial infarction	0	0	1 (0.6)	1 (0.6)
Stress cardiomyopathy	0	0	1 (0.6)	1 (0.6)
Colitis	0	0	1 (0.6)	1 (0.6)
Ataxia	0	0	1 (0.6)	0
All adverse events leading to surgery cancellation	2 (1.1)	0	1 (0.6)	0
Ischemic stroke	1 (0.6)	0	0	0
Tuberculosis	1 (0.6)	0	0	0
Increased blood creatinine	0	0	1 (0.6)	0

As per Common Terminology Criteria for Adverse Events Version 4.0; Medical Dictionary for Regulatory Activities Version: 23.0.

N Engl J Med 2022; 386:1973-1985

Table 2. Adverse Events.*

Event	Nivolumab plus Chemotherapy (N=176)		Chemotherapy Alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse events of any cause — no. (%)†				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related adverse events — no. (%)†				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death‡	0	—	3 (1.7)	—
Surgery-related adverse events — no./total no. (%)§	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)

* Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 24.0, and were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

† Included are events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose.

‡ Treatment-related deaths in the chemotherapy-alone group were due to pancytopenia, diarrhea, acute kidney injury (all in one patient), enterocolitis, and pneumonia.

§ The denominators are based on patients who underwent definitive surgery. Included are events reported up to 90 days after definitive surgery. Grade 5 surgery-related adverse events (defined as events that led to death ≤24 hours after the onset of an adverse event) were reported in two patients in the nivolumab-plus-chemotherapy group and were deemed by the investigator to be unrelated to the trial drugs (one each due to pulmonary embolism and aortic rupture).

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PERIOPERATIVE SYSTEMIC THERAPY

Neoadjuvant Systemic Therapy

- All patients should be evaluated for preoperative therapy, with strong consideration for nivolumab + chemotherapy for those patients with tumors ≥4 cm or node positive and no contraindications to immune checkpoint inhibitors.* Otherwise refer to the Neoadjuvant Systemic Therapy for Patients Not Candidates for Immune Checkpoint Inhibitors.
- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]).
  Principles of Molecular and Biomarker Analysis (NSCL-H)
- After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction systemic therapy as an alternative.

Neoadjuvant Systemic Therapy in Patients Candidates for Immune Checkpoint Inhibitors

- Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[1]
  - Platinum-doublet chemotherapy options include:
    - Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
    - Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)
    - Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)
    - Cisplatin 75 mg/m² day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
  - Chemotherapy Regimens for Patients Not Candidates for Cisplatin-Based Therapy
    - Carboplatin AUC 5 or AUC 6 day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)
    - Carboplatin AUC 5 or AUC 6 day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)

Neoadjuvant Systemic Therapy for Patients Not Candidates for Immune Checkpoint Inhibitors

Preferred (nonsquamous)

- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[2]

Preferred (squamous)

- Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[3]
- Cisplatin 75 mg/m² day 1, docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[4]

Other Recommended

- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5]
- Cisplatin 100 mg/m² day 1, vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[6,7]
- Cisplatin 75–80 mg/m² day 1, vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[6]

Useful in Certain Circumstances

- Chemotherapy Regimens for Patients Not Candidates for Cisplatin-Based Therapy
  - Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[8]
  - Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[9] (squamous histology)
  - Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[10] (nonsquamous histology)

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

Adjuvant Systemic Therapy

Adjuvant Immunotherapy

University of Nebraska Medical Center℠

IMPOWER 010

- Design:
  - phase 3 study , enrolled more than 1000 patients with completely resected stage IB-IIIA
  - Patients were assigned (after receiving adjuvant chemotherapy) to either receiving adjuvant atezolizumab or observation

- Outcomes:
  - DFS (tested hierarchically)
    - Stage II–IIIA population (PD-L1 1% or more)
    - All patients in the stage II–IIIA population
    - Intention-to-treat population (stage IB–IIIA)

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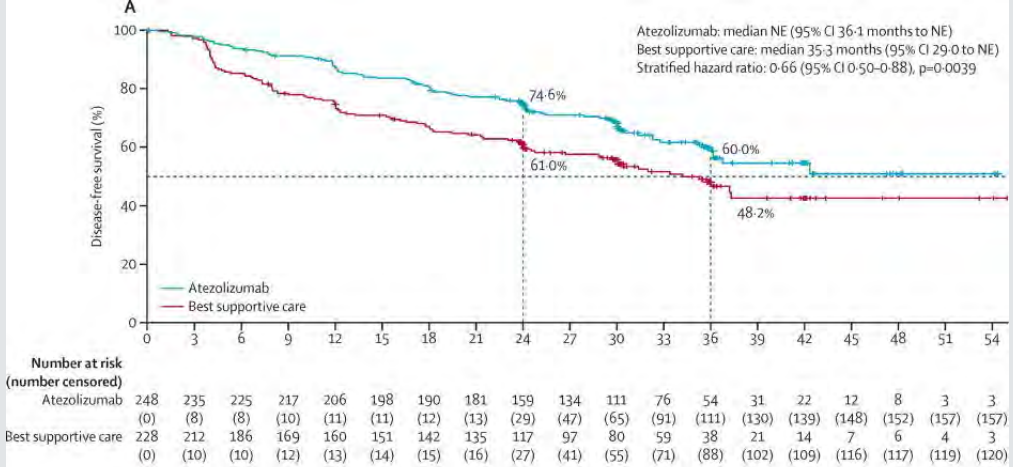
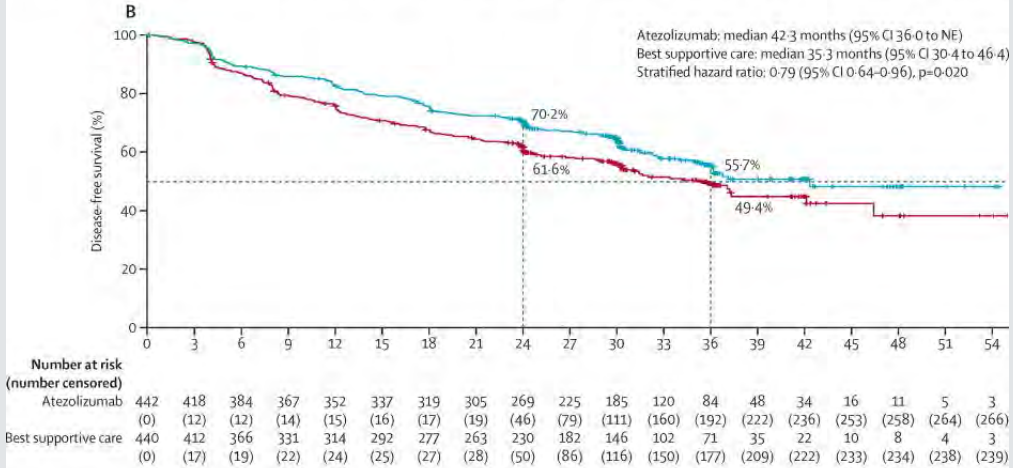
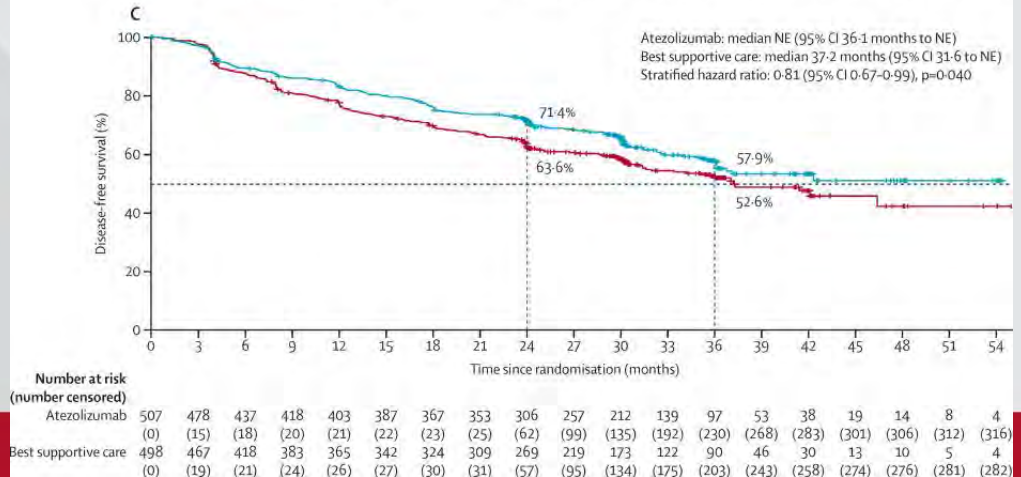
Ann Oncol. 2023;S0923-7534(23)00764-0.

	PD-L1 TC ≥1% stage II–IIIA group (SP263)		All stage II–IIIA group		Intention-to-treat group (stage IB–IIIA)	
	Atezolizumab (n=248)	Best supportive care (n=228)	Atezolizumab (n=442)	Best supportive care (n=440)	Atezolizumab (n=507)	Best supportive care (n=498)
Age, years	61 (56-67)	62 (56-68)	62 (56-67)	62 (55-68)	62 (57-67)	62 (56-68)
Age group						
<65 years	156 (63%)	131 (57%)	281 (64%)	263 (60%)	323 (64%)	300 (60%)
≥65 years	92 (37%)	97 (43%)	161 (36%)	177 (40%)	184 (36%)	198 (40%)
Sex						
Male	171 (69%)	147 (64%)	295 (67%)	294 (67%)	337 (66%)	335 (67%)
Female	77 (31%)	81 (36%)	147 (33%)	146 (33%)	170 (34%)	164 (33%)
Race						
White	162 (65%)	166 (73%)	307 (69%)	324 (74%)	362 (71%)	376 (76%)
Asian	78 (31%)	56 (25%)	121 (27%)	106 (24%)	130 (26%)	112 (23%)
Black or African American	2 (<1%)	0	4 (1%)	1 (<1%)	5 (1%)	1 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Multiple	0	1 (<1%)	0	1 (<1%)	0	1 (<1%)
Unknown	5 (2%)	4 (2%)	9 (2%)	7 (2%)	9 (2%)	7 (1%)
ECOG performance status*						
0	140 (56%)	125 (55%)	239 (54%)	252 (57%)	273 (54%)	283 (57%)
1	107 (43%)	102 (45%)	201 (45%)	187 (43%)	232 (46%)	214 (43%)
2	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
Histology						
Squamous	96 (39%)	85 (37%)	150 (34%)	144 (33%)	179 (35%)	167 (34%)
Non-squamous	152 (61%)	143 (63%)	292 (66%)	296 (67%)	328 (65%)	331 (67%)
Tobacco use history						
Never	51 (21%)	41 (18%)	100 (23%)	96 (22%)	114 (23%)	108 (22%)
Previous	163 (66%)	146 (64%)	277 (63%)	270 (61%)	317 (63%)	304 (61%)
Current	34 (14%)	41 (18%)	65 (15%)	74 (17%)	76 (15%)	86 (17%)
Stage						
IB	..	..	..	..	65 (13%)	58 (12%)
IIA	85 (34%)	76 (33%)	147 (33%)	148 (34%)	147 (29%)	148 (30%)
IIB	46 (19%)	37 (16%)	90 (20%)	84 (19%)	90 (18%)	84 (17%)
IIIA	117 (47%)	115 (50%)	205 (46%)	208 (47%)	205 (40%)	208 (42%)
Type of surgery						
Lobectomy	186 (75%)	173 (76%)	335 (76%)	340 (77%)	394 (78%)	391 (79%)
Sleeve lobectomy	3 (1%)	3 (1%)	4 (1%)	4 (<1%)	4 (<1%)	4 (<1%)
Bilobectomy	15 (6%)	9 (4%)	30 (7%)	17 (4%)	31 (6%)	19 (4%)
Pneumonectomy	43 (17%)	42 (18%)	72 (16%)	78 (18%)	77 (15%)	83 (17%)
Other	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
EGFR mutation status†						
Yes	23 (9%)	20 (9%)	49 (11%)	60 (14%)	53 (10%)	64 (13%)
No	123 (50%)	125 (55%)	229 (52%)	234 (53%)	261 (52%)	266 (53%)
Unknown	102 (41%)	83 (36%)	164 (37%)	146 (33%)	193 (38%)	168 (34%)
ALK rearrangement status†						
Yes	12 (5%)	11 (5%)	14 (3%)	17 (4%)	15 (3%)	18 (4%)
No	133 (54%)	121 (53%)	251 (57%)	256 (58%)	280 (55%)	294 (59%)
Unknown	103 (42%)	96 (42%)	177 (40%)	167 (38%)	212 (42%)	186 (37%)
PD-L1 status by SP263‡						
<1%	..	..	181 (41%)	202 (46%)	210 (41%)	234 (47%)
≥1%	248 (100%)	228 (100%)	248 (56%)	228 (52%)	283 (56%)	252 (51%)
PD-L1 status by SP142§						
TC0/1 and IC0/1	77 (31%)	66 (29%)	198 (45%)	198 (45%)	231 (46%)	231 (46%)
TC0/1 and IC2/3	66 (27%)	61 (27%)	127 (29%)	132 (30%)	146 (29%)	145 (29%)
TC2/3 and any IC	105 (42%)	101 (44%)	117 (26%)	110 (25%)	130 (26%)	122 (25%)

Lancet. 2021;398(10308):1344-1357





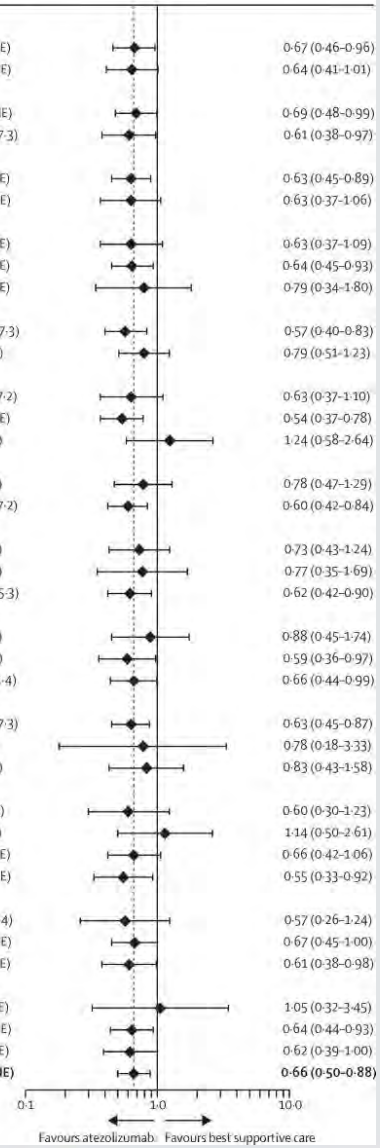


- Stage II-IIIA PD-L1 positive population: DFS not reached vs 35.3 m (HR 0·66; 95% CI 0·50–0·88; p=0·0039)
- All patients in the stage II–IIIA population → 42.3 m vs 35.3 m (HR 0·79; 0·64–0·96; p=0·020).
- ITT population → not reached vs 37.2 m (HR 0·81 (0·67–0·99; p=0·040).

Lancet. 2021;398(10308):1344-1357.

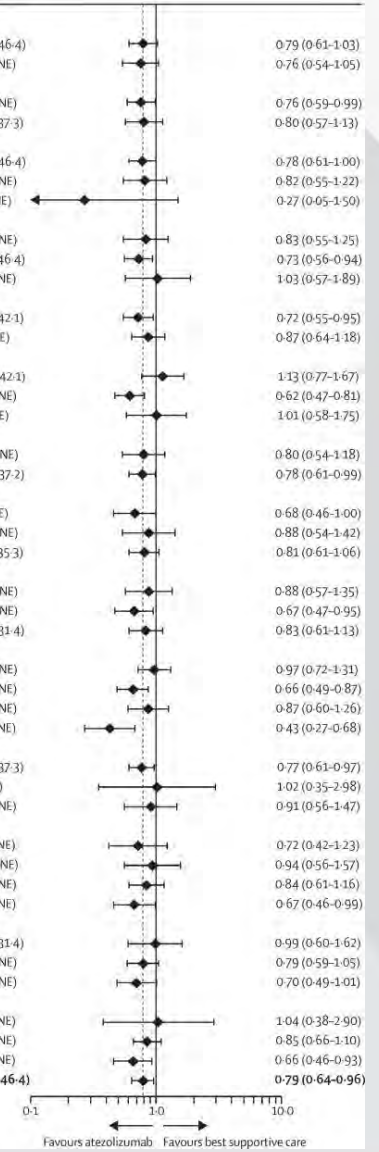
A

	Atezolizumab group		Best supportive care group		Hazard ratio (95% CI)
	Events/patients, n/N	Median DFS (95% CI), months	Events/patients, n/N	Median DFS (95% CI), months	
Age					
<65 years	156/287	NE (36·0–NE)	131/287	34·2 (29·7–NE)	0·67 (0·46–0·96)
≥65 years	92/189	42·3 (32·3–NE)	97/189	36·0 (23·0–NE)	0·64 (0·41–1·01)
Sex					
Male	171/318	NE (36·7–NE)	147/318	36·0 (29·0–NE)	0·69 (0·48–0·99)
Female	77/158	NE (31·3–NE)	81/158	30·1 (23·9–37·3)	0·61 (0·38–0·97)
Race					
White	162/328	NE (36·1–NE)	166/328	35·3 (29·7–NE)	0·63 (0·45–0·89)
Asian	78/134	42·3 (30·5–NE)	56/134	31·4 (18·0–NE)	0·63 (0·37–1·06)
Region					
Asia-Pacific	75/129	42·3 (30·5–NE)	54/129	31·4 (18·3–NE)	0·63 (0·37–1·09)
Europe and the Middle East	145/289	NE (36·1–NE)	144/289	35·3 (29·7–NE)	0·64 (0·45–0·93)
North America	28/57	NE (24·1–NE)	29/57	35·7 (23·9–NE)	0·79 (0·34–1·80)
ECOG performance status					
0	140/265	NE (35·5–NE)	125/265	30·4 (24·0–37·3)	0·57 (0·40–0·83)
1	107/209	36·7 (36·0–NE)	102/209	NE (28·8–NE)	0·79 (0·51–1·23)
Tobacco use history					
Never	51/92	31·3 (29·4–36·1)	41/92	20·5 (12·2–37·2)	0·63 (0·37–1·10)
Previous	163/309	NE (42·3–NE)	146/309	35·3 (26·7–NE)	0·54 (0·37–0·78)
Current	34/75	36·7 (27·9–NE)	41/75	NE (34·2–NE)	1·24 (0·58–2·64)
Histology					
Squamous	96/181	NE (36·1–NE)	85/181	NE (32·0–NE)	0·78 (0·47–1·29)
Non-squamous	152/295	42·3 (35·5–NE)	143/295	30·1 (23·0–37·2)	0·60 (0·42–0·84)
Stage					
IIA	85/161	NE (36·1–NE)	76/161	NE (29·7–NE)	0·73 (0·43–1·24)
IIB	46/83	NE (35·3–NE)	37/83	NE (32·0–NE)	0·77 (0·35–1·69)
IIIA	117/232	42·3 (30·5–NE)	115/232	26·7 (18·0–35·3)	0·62 (0·42–0·90)
Regional lymph node stage (pN)					
N0	60/106	36·7 (35·5–NE)	46/106	NE (32·0–NE)	0·88 (0·45–1·74)
N1	100/194	NE (NE–NE)	94/194	NE (30·4–NE)	0·59 (0·36–0·97)
N2	88/176	32·3 (24·2–NE)	88/176	21·3 (15·7–31·4)	0·66 (0·44–0·99)
Type of surgery					
Lobectomy	186/359	NE (36·0–NE)	173/359	33·4 (26·7–37·3)	0·63 (0·45–0·87)
Bilobectomy	15/24	36·7 (36·1–NE)	9/24	NE (6·2–NE)	0·78 (0·18–3·33)
Pneumonectomy	43/85	36·1 (30·1–NE)	42/85	NE (19·4–NE)	0·83 (0·43–1·58)
Chemotherapy regimen					
Cisplatin plus docetaxel	34/71	36·1 (31·3–NE)	37/71	18·0 (8·3–NE)	0·60 (0·30–1·23)
Cisplatin plus gemcitabine	47/75	36·1 (30·1–NE)	28/75	NE (35·3–NE)	1·14 (0·50–2·61)
Cisplatin plus pemetrexed	84/169	NE (32·8–NE)	85/169	31·4 (24·5–NE)	0·66 (0·42–1·06)
Cisplatin plus vinorelbine	83/161	NE (NE–NE)	78/161	34·2 (23·9–NE)	0·55 (0·33–0·92)
***EGFR* mutation status**					
Yes	23/43	29·7 (18·0–NE)	20/43	16·6 (6·7–31·4)	0·57 (0·26–1·24)
No	123/248	NE (35·5–NE)	125/248	36·0 (26·7–NE)	0·67 (0·45–1·00)
Unknown	102/185	NE (36·1–NE)	83/185	35·3 (23·9–NE)	0·61 (0·38–0·98)
***ALK* rearrangement status**					
Yes	12/23	30·5 (17·1–NE)	11/23	37·2 (21·3–NE)	1·05 (0·32–3·45)
No	133/254	42·3 (35·5–NE)	121/254	30·4 (23·9–NE)	0·64 (0·44–0·93)
Unknown	103/199	NE (36·7–NE)	96/199	37·3 (30·1–NE)	0·62 (0·39–1·00)
All patients	**248/476**	**NE (36·1–NE)**	**228/476**	**35·3 (29·0–NE)**	**0·66 (0·50–0·88)**



B

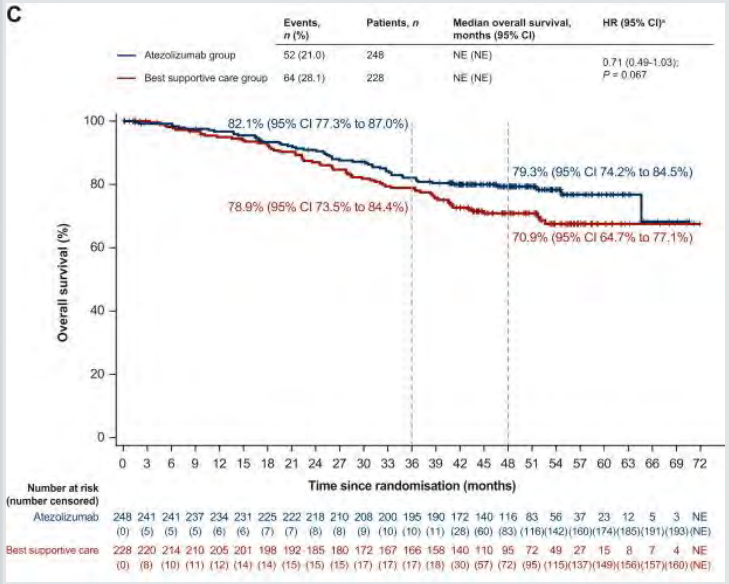
	Atezolizumab group		Best supportive care group		Hazard ratio (95% CI)
	Events/patients, n/N	Median DFS (95% CI), months	Events/patients, n/N	Median DFS (95% CI), months	
Age					
<65 years	281/544	NE (35·5–NE)	263/544	35·7 (30·4–46·4)	0·79 (0·61–1·03)
≥65 years	161/338	42·3 (31·3–NE)	177/338	31·0 (24·7–NE)	0·76 (0·54–1·05)
Sex					
Male	295/589	NE (36·7–NE)	294/589	36·0 (31·0–NE)	0·76 (0·59–0·99)
Female	147/293	34·9 (30·2–NE)	146/293	30·4 (25·1–37·3)	0·80 (0·57–1·13)
Race					
White	307/631	37·1 (35·3–NE)	324/631	35·7 (30·4–46·4)	0·78 (0·61–1·00)
Asian	121/227	42·3 (30·2–NE)	106/227	31·6 (23·9–NE)	0·82 (0·55–1·22)
Unknown	9/16	NE (NE–NE)	7/16	28·6 (4·5–NE)	0·27 (0·05–1·50)
Region					
Asia-Pacific	116/219	42·3 (30·2–NE)	103/219	31·6 (24·0–NE)	0·83 (0·55–1·25)
Europe and the Middle East	270/560	NE (35·3–NE)	290/560	35·3 (30·1–46·4)	0·73 (0·56–0·94)
North America	55/101	35·5 (24·1–NE)	46/101	35·7 (23·9–NE)	1·03 (0·57–1·89)
ECOG performance status					
0	239/491	NE (35·5–NE)	252/491	35·3 (29·7–42·1)	0·72 (0·55–0·95)
1	201/388	36·1 (31·4–NE)	187/388	NE (28·6–NE)	0·87 (0·64–1·18)
Tobacco use history					
Never	100/196	30·1 (24·0–32·8)	96/196	30·4 (24·0–42·1)	1·13 (0·77–1·67)
Previous	277/547	NE (42·3–NE)	270/547	32·0 (29·7–NE)	0·62 (0·47–0·81)
Current	65/139	NE (30·1–NE)	74/139	NE (34·2–NE)	1·01 (0·58–1·75)
Histology					
Squamous	150/294	NE (36·1–NE)	144/294	46·4 (33·4–NE)	0·80 (0·54–1·18)
Non-squamous	292/588	37·1 (31·4–NE)	296/588	30·4 (24·5–37·2)	0·78 (0·61–0·99)
Stage					
IIA	147/295	NE (36·7–NE)	148/295	NE (31·0–NE)	0·68 (0·46–1·00)
IIB	90/174	37·1 (32·3–NE)	84/174	46·4 (32·0–NE)	0·88 (0·54–1·42)
IIIA	205/413	32·3 (25·4–NE)	208/413	29·7 (23·7–35·3)	0·81 (0·61–1·06)
Regional lymph node stage (pN)					
N0	118/229	NE (35·5–NE)	111/229	46·4 (37·0–NE)	0·88 (0·57–1·35)
N1	170/348	NE (37·1–NE)	178/348	36·0 (30·4–NE)	0·67 (0·47–0·95)
N2	154/305	30·2 (24·0–42·3)	151/305	24·1 (18·0–31·4)	0·83 (0·61–1·13)
PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2–NE)	202/383	37·0 (28·6–NE)	0·97 (0·72–1·31)
TC ≥1%	248/476	NE (36·1–NE)	228/476	35·3 (29·0–NE)	0·66 (0·49–0·87)
TC 1–49%	133/247	32·8 (29·4–NE)	114/247	31·4 (24·0–NE)	0·87 (0·60–1·26)
TC ≥50%	115/229	NE (42·3–NE)	114/229	35·7 (29·7–NE)	0·43 (0·27–0·68)
Type of surgery					
Lobectomy	335/675	42·3 (34·0–NE)	340/675	32·0 (29·7–37·3)	0·77 (0·61–0·97)
Bilobectomy	30/47	36·7 (36·1–NE)	17/47	NE (6·2–NE)	1·02 (0·35–2·98)
Pneumonectomy	72/150	36·1 (30·1–NE)	78/150	42·1 (23·4–NE)	0·91 (0·56–1·47)
Chemotherapy regimen					
Cisplatin plus docetaxel	59/124	36·1 (31·3–NE)	65/124	37·3 (12·0–NE)	0·72 (0·42–1·23)
Cisplatin plus gemcitabine	77/138	36·1 (30·1–NE)	61/138	46·4 (23·8–NE)	0·94 (0·56–1·57)
Cisplatin plus pemetrexed	172/349	42·3 (32·8–NE)	177/349	31·4 (26·7–NE)	0·84 (0·61–1·16)
Cisplatin plus vinorelbine	134/271	NE (36·0–NE)	137/271	37·0 (30·1–NE)	0·67 (0·46–0·99)
***EGFR* mutation status**					
Yes	49/109	24·1 (16·1–36·1)	60/109	24·0 (12·2–31·4)	0·99 (0·60–1·62)
No	229/463	NE (32·8–NE)	234/463	36·0 (30·1–NE)	0·79 (0·59–1·05)
Unknown	164/310	NE (36·1–NE)	146/310	42·1 (30·4–NE)	0·70 (0·49–1·01)
***ALK* rearrangement status**					
Yes	14/31	30·5 (17·1–NE)	17/31	37·2 (19·5–NE)	1·04 (0·38–2·90)
No	251/507	36·1 (30·2–NE)	256/507	31·4 (24·7–NE)	0·85 (0·66–1·10)
Unknown	177/344	NE (36·1–NE)	167/344	37·3 (31·0–NE)	0·66 (0·46–0·93)
All patients	**442/882**	**42·3 (36·0–NE)**	**440/882**	**35·3 (30·4–46·4)**	**0·79 (0·64–0·96)**

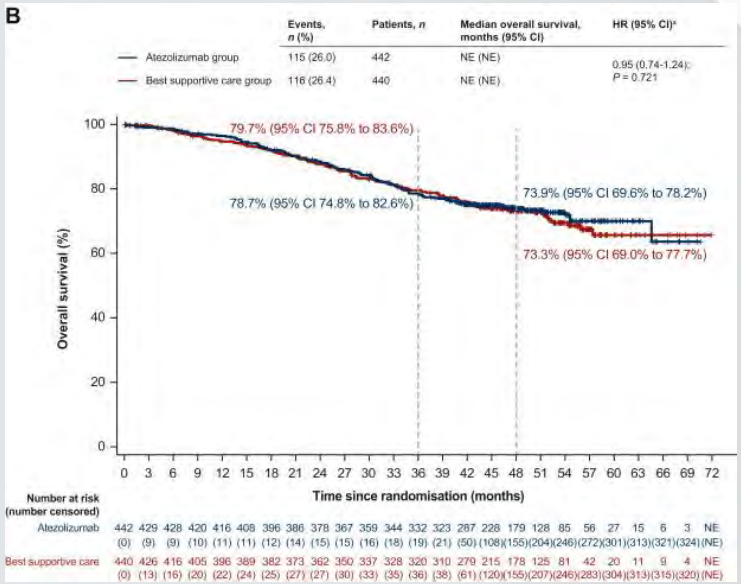


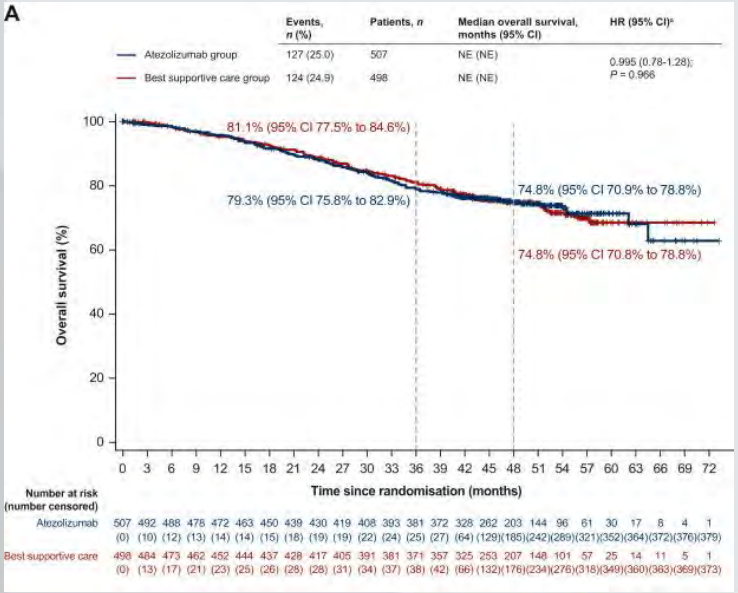
Conclusion

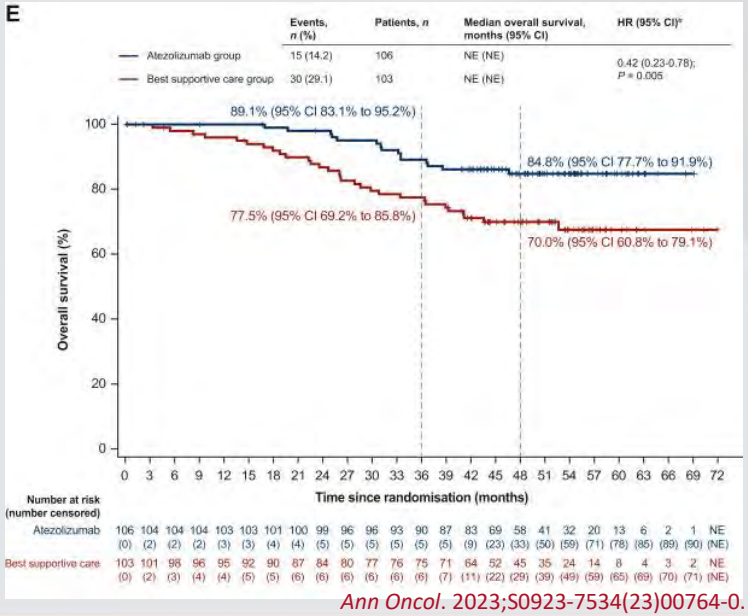
IMpower010 showed a disease-free survival benefit with atezolizumab versus best supportive care after adjuvant chemotherapy in patients with resected stage II-IIIA NSCLC, with pronounced benefit in the subgroup whose tumours expressed PD-L1 on 1% or more of tumour cells, and no new safety signals. Atezolizumab after adjuvant chemotherapy offers a promising treatment option for patients with resected early-stage NSCLC.

Update 2023









Ann Oncol. 2023;S0923-7534(23)00764-0.

Conclusion

Although OS remains immature for the ITT population, these data indicate a positive trend favouring atezolizumab in PD-L1 subgroup analyses, primarily driven by the PD-L1 TC ≥50% stage II-IIIA subgroup. No new safety signals were observed after 13 months' additional follow-up.

KEYNOTE 091

- Design:
  - Phase III , enrolled more than 1000 patients with completely resected stage IB-IIIA NSCLC of any histology or PD-L1 expression level
  - Patients randomized to either pembrolizumab or placebo for up to 18 cycles.

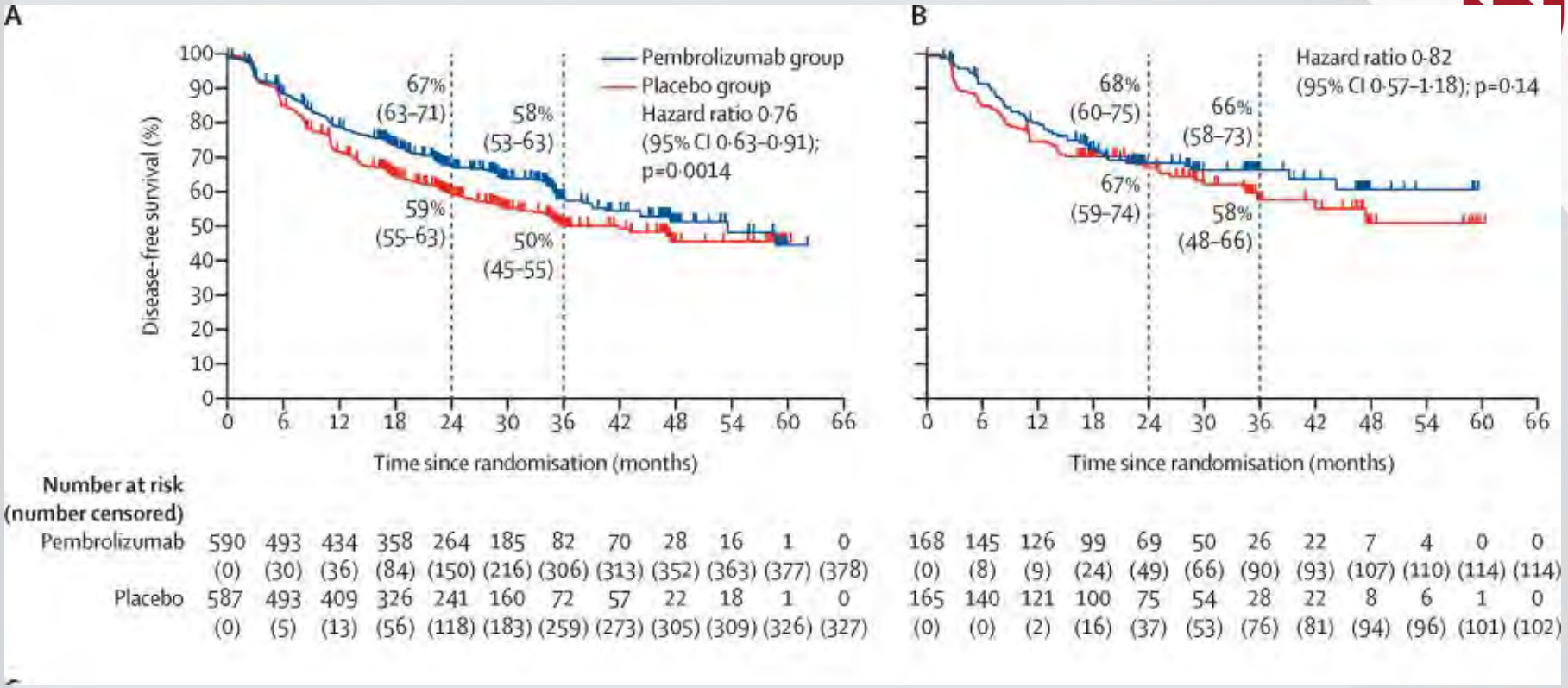
- Outcomes:
  - DFS in the overall population
  - DFS PD-L1 >= 50%

Lancet Oncol. 2022;23(10):1274-1286.

Results

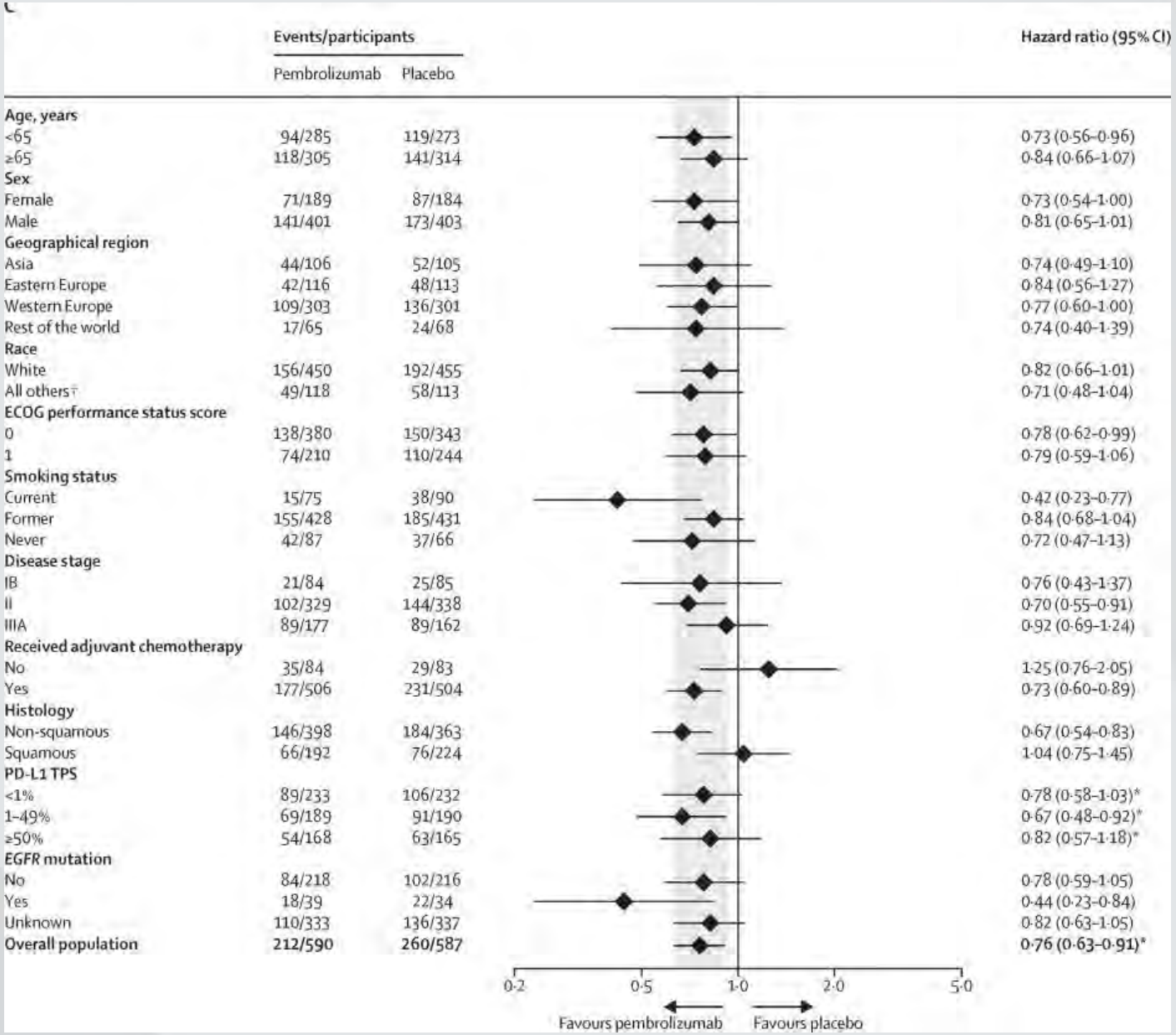
	Overall intention-to-treat population		PD-L1 TPS of ≥50% population	
	Pembrolizumab group (n=590)	Placebo group (n=587)	Pembrolizumab group (n=168)	Placebo group (n=165)
Age, years	65·0 (59·0–70·0)	65·0 (59·0–70·0)	64·5 (60·0–69·5)	65·0 (58·0–71·0)
<65	285 (48%)	273 (47%)	84 (50%)	82 (50%)
≥65	305 (52%)	314 (53%)	84 (50%)	83 (50%)
Sex				
Female	189 (32%)	184 (31%)	47 (28%)	49 (30%)
Male	401 (68%)	403 (69%)	121 (72%)	116 (70%)
Race				
American Indian or Alaskan Native	1 (<1%)	0	1 (1%)	0
Asian	107 (18%)	107 (18%)	29 (17%)	29 (18%)
Black or African American	0	3 (1%)	0	0
Multiple	4 (1%)	1 (<1%)	0	1 (1%)
Other	6 (1%)	2 (<1%)	3 (2%)	1 (1%)
White	450 (76%)	455 (78%)	128 (76%)	127 (77%)
Missing	22 (4%)	19 (3%)	7 (4%)	7 (4%)
Geographical region				
Asia	106 (18%)	105 (18%)	29 (17%)	29 (18%)
Eastern Europe	116 (20%)	113 (19%)	31 (18%)	30 (18%)
Western Europe	303 (51%)	301 (51%)	90 (54%)	89 (54%)
Rest of the world	65 (11%)	68 (12%)	18 (11%)	17 (10%)
ECOG performance status				
0	380 (64%)	343 (58%)	116 (69%)	101 (61%)
1	210 (36%)	244 (42%)	52 (31%)	64 (39%)
Smoking status				
Current	75 (13%)	90 (15%)	24 (14%)	29 (18%)
Former	428 (73%)	431 (73%)	130 (77%)	123 (75%)
Never	87 (15%)	66 (11%)	14 (8%)	13 (8%)
Histology				
Non-squamous	398 (67%)	363 (62%)	103 (61%)	105 (64%)
Squamous	192 (33%)	224 (38%)	65 (39%)	60 (36%)
Disease stage				
IB	84 (14%)	85 (14%)	21 (13%)	22 (13%)
II	329 (56%)	338 (58%)	95 (57%)	93 (56%)
IIIA	177 (30%)	162 (28%)	52 (31%)	50 (30%)
IV	0	2 (<1%)*	0	0
Regional lymph node stage (pN)				
N0	233 (39%)	257 (44%)	47 (28%)	59 (36%)
N1	233 (39%)	223 (38%)	84 (50%)	72 (44%)
N2	124 (21%)	107 (18%)	37 (22%)	34 (21%)
Received adjuvant chemotherapy				
No	84 (14%)	83 (14%)	25 (15%)	24 (15%)
Yes†	506 (86%)	504 (86%)	143 (85%)	141 (85%)
1–2 cycles	35 (6%)	32 (5%)	8 (5%)	8 (5%)
3–4 cycles	471 (80%)	472 (80%)	135 (80%)	133 (81%)
PD-L1 TPS				
<1%	233 (39%)	232 (40%)	0	0
1–49%	189 (32%)	190 (32%)	0	0
≥50%	168 (28%)	165 (28%)	168 (100%)	165 (100%)

(Table 1 continues on next page)



In the overall population→ DFS was 53·6 months (95% CI 39·2 to not reached) in the pembrolizumab group vs 42·0 months (31·3 to not reached) in the placebo group (HR 0·76 [95% CI 0·63–0·91], p=0·0014).

In the PD-L1 TPS of 50% or greater→ DFS was not reached in either the pembrolizumab group (95% CI 44·3 to not reached) or the placebo group (95% CI 35·8 to not reached; HR 0·82 [95% CI 0·57–1·18]; p=0·14).


Events/participants
Pembrolizumab
Placebo
Hazard ratio (95% CI)
Age, years
<65 94/285 119/273 0·73 (0·56–0·96)
≥65 118/305 141/314 0·84 (0·66–1·07)
Sex
Female 71/189 87/184 0·73 (0·54–1·00)
Male 141/401 173/403 0·81 (0·65–1·01)
Geographical region
Asia 44/106 52/105 0·74 (0·49–1·10)
Eastern Europe 42/116 48/113 0·84 (0·56–1·27)
Western Europe 109/303 136/301 0·77 (0·60–1·00)
Rest of the world 17/65 24/68 0·74 (0·40–1·39)
Race
White 156/450 192/455 0·82 (0·66–1·01)
All others† 49/118 58/113 0·71 (0·48–1·04)
ECOG performance status score
0 138/380 150/343 0·78 (0·62–0·99)
1 74/210 110/244 0·79 (0·59–1·06)
Smoking status
Current 15/75 38/90 0·42 (0·23–0·77)
Former 155/428 185/431 0·84 (0·68–1·04)
Never 42/87 37/66 0·72 (0·47–1·13)
Disease stage
IB 21/84 25/85 0·76 (0·43–1·37)
II 102/329 144/338 0·70 (0·55–0·91)
IIIA 89/177 89/162 0·92 (0·69–1·24)
Received adjuvant chemotherapy
No 35/84 29/83 1·25 (0·76–2·05)
Yes 177/506 231/504 0·73 (0·60–0·89)
Histology
Non-squamous 146/398 184/363 0·67 (0·54–0·83)
Squamous 66/192 76/224 1·04 (0·75–1·45)
PD-L1 TPS
<1% 89/233 106/232 0·78 (0·58–1·03)*
1–49% 69/189 91/190 0·67 (0·48–0·92)*
≥50% 54/168 63/165 0·82 (0·57–1·18)*
EGFR mutation
No 84/218 102/216 0·78 (0·59–1·05)
Yes 18/39 22/34 0·44 (0·23–0·84)
Unknown 110/333 136/337 0·82 (0·63–1·05)
Overall population 212/590 260/587 0·76 (0·63–0·91)*
0·2
0·5
1·0
2·0
5·0
Favours pembrolizumab
Favours placebo

Conclusion

Pembrolizumab significantly improved disease-free survival compared with placebo and was not associated with new safety signals in completely resected, PD-L1-unselected, stage IB–IIIA NSCLC. Pembrolizumab is potentially a new treatment option for stage IB–IIIA NSCLC after complete resection and, when recommended, adjuvant chemotherapy, regardless of PD-L1 expression.

PERIOPERATIVE SYSTEMIC THERAPY

Adjuvant Systemic Therapy

- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]). Principles of Molecular and Biomarker Analysis (NSCL-H).

Preferred (nonsquamous)

- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[2]

Preferred (squamous)

- Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[3]
- Cisplatin 75 mg/m² day 1, docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[4]

Other Recommended

- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5]
- Cisplatin 100 mg/m² day 1, vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[6,7]
- Cisplatin 75–80 mg/m² day 1, vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[6]

Useful in Certain Circumstances

- Chemotherapy Regimens for Patients Not Candidates for Cisplatin-Based Therapy
  - Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[8]
  - Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[9]
  - Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[10] (nonsquamous histology)

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

Systemic Therapy Following Previous Adjuvant Systemic Therapy

- Osimertinib 80 mg daily[11]
  - Osimertinib for patients with completely resected stage IB–IIIA or stage IIIB (T3, N2) NSCLC and positive for *EGFR* (exon 19 deletion, exon 21 L858R) mutations who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[12]
  - Atezolizumab for patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC with PD-L1 ≥1% and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors.*
- Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks for up to 1 year[13]
  - Pembrolizumab for patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors.*

Perioperative chemo-immunotherapy

NADIM II

- Design:
  - Phase 2, enrolled stage IIIA-IIIB NSCLC.
  - Patients received neoadjuvant nivolumab plus platinum-based chemotherapy or chemotherapy alone, followed by surgery.
  - Patients in the experimental group who had R0 resections received adjuvant treatment with nivolumab for 6 months.

- Outcomes:
  - The primary end point was pCR
  - Secondary end points included PFS and OS at 24 months

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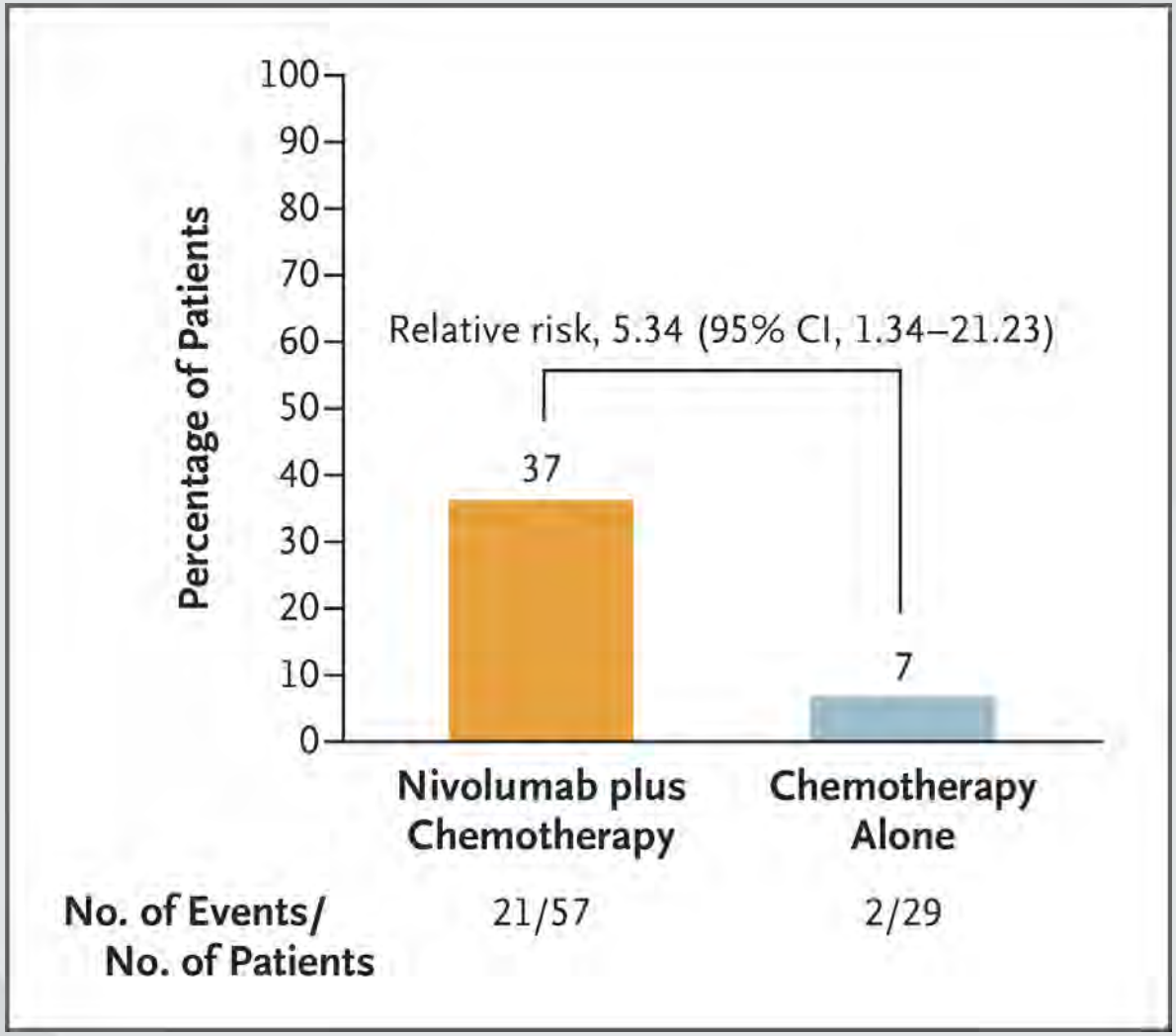
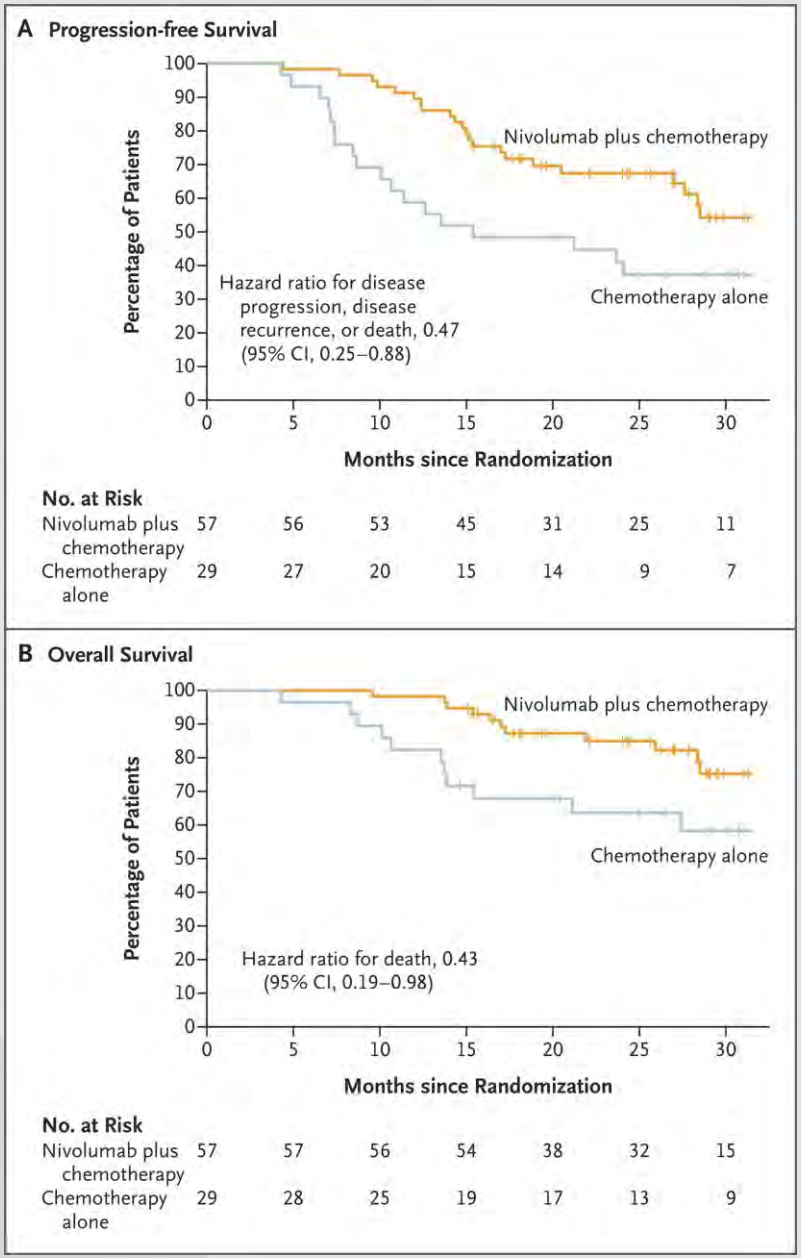
Results

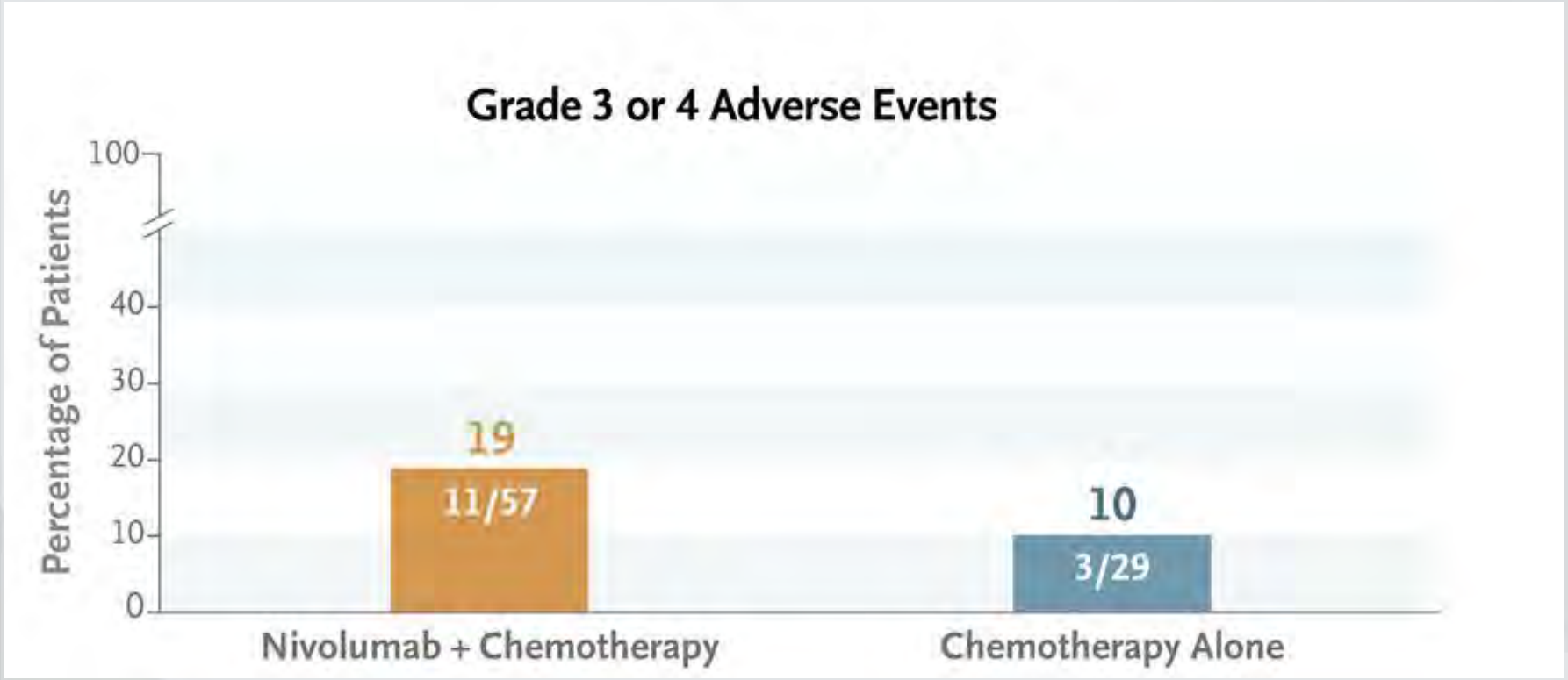
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Nivolumab plus Chemotherapy (N=57)	Chemotherapy Alone (N=29)
Median age (IQR) — yr	65 (58–70)	63 (57–66)
Body-mass index — no. (%)†		
≤25	15 (26)	10 (34)
>25	42 (74)	19 (66)
Female sex — no. (%)	21 (37)	13 (45)
History of tobacco use — no. (%)		
Never smoked	5 (9)	0
Former smoker	22 (39)	8 (28)
Current smoker	30 (53)	21 (72)
ECOG performance-status score — no. (%)‡		
0	31 (54)	16 (55)
1	26 (46)	13 (45)
Histologic type — no. (%)		
Adenocarcinoma	25 (44)	11 (38)
Adenosquamous carcinoma	1 (2)	0
Squamous-cell carcinoma	21 (37)	14 (48)
Large-cell carcinoma	2 (4)	1 (3)
Not otherwise specified or undifferentiated	7 (12)	2 (7)
Other	1 (2)	1 (3)
TNM classification — no. (%)§		
T1N2M0	12 (21)	4 (14)
T2N2M0	16 (28)	7 (24)
T3N1M0	2 (4)	1 (3)
T3N2M0	13 (23)	5 (17)
T4N0M0	6 (11)	9 (31)
T4N1M0	8 (14)	3 (10)
Median tumor size (range) — mm	50 (15–155)	52 (15–166)
Node stage — no. (%)		
N0	6 (11)	9 (31)
N1	10 (18)	4 (14)
N2	41 (72)	16 (55)
N2, multiple stations	22 (39)	11 (38)


Percentage of Patients
100
90
80
70
60
50
40
30
20
10
0
Relative risk, 5.34 (95% CI, 1.34–21.23)
37
7
Nivolumab plus Chemotherapy
Chemotherapy Alone
No. of Events/ No. of Patients
21/57
2/29



- PFS at 2 years: 67.2% vs 40.9% (HR, 0.47; 95% CI, 0.25 to 0.88).
- OS at 2 years: 85.0% vs 63.6% (hazard ratio for death, 0.43; 95% CI, 0.19 to 0.98).


Grade 3 or 4 Adverse Events
Percentage of Patients
100
40
30
20
10
0
19
11/57
10
3/29
Nivolumab + Chemotherapy
Chemotherapy Alone

Conclusion

In patients with resectable stage IIIA or IIIB NSCLC, perioperative treatment with nivolumab plus chemotherapy resulted in a higher percentage of patients with a pathological complete response and longer survival than chemotherapy alone.

KEYNOTE-671

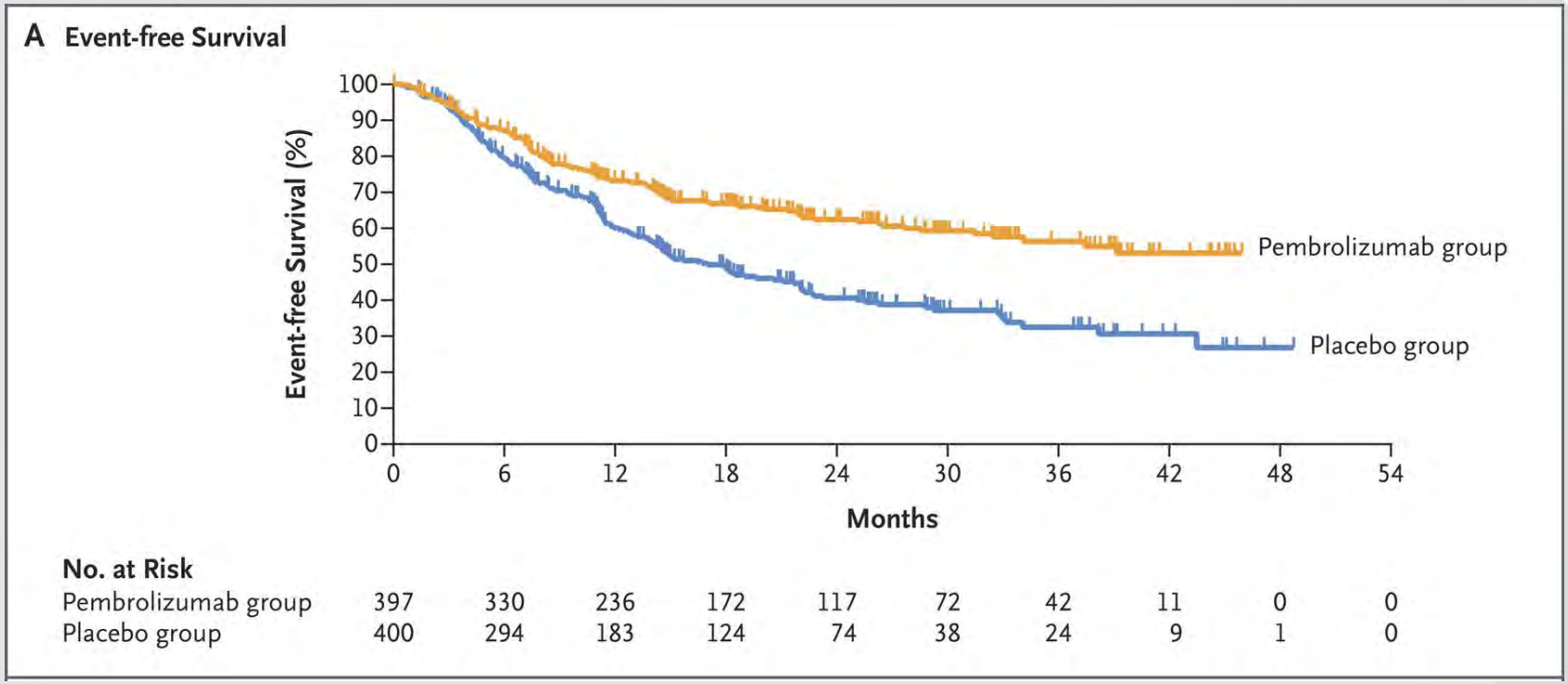
- Design:
  - Phase 3 trial , enrolled stage II-IIIB NSCLC
  - Patients received neoadjuvant pembrolizumab + chemo vs placebo + chemo for 4 cycles→ followed by surgery → either adjuvant pembrolizumab or placebo for up to 13 cycles
- Outcomes:
  - EFS and OS

N Engl J Med 2023; 389:491-503

Table 1. Demographic and Disease Characteristics of the Participants at Baseline (Intention-to-Treat Population).*

Characteristic	Pembrolizumab Group (N=397)	Placebo Group (N=400)
Age		
Median (range) — yr	63 (26–83)	64 (35–81)
≥65 yr — no. (%)	176 (44.3)	186 (46.5)
Male sex — no. (%)	279 (70.3)	284 (71.0)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	1 (0.3)	0
Asian	124 (31.2)	125 (31.2)
Black	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 — no. (%)		
East Asia	123 (31.0)	121 (30.2)
Other	274 (69.0)	279 (69.8)
ECOG performance-status score — no. (%)‡		
0	253 (63.7)	246 (61.5)
1	144 (36.3)	154 (38.5)
Smoking status — no. (%)		
Current smoker	96 (24.2)	103 (25.8)
Former smoker	247 (62.2)	250 (62.5)
Never smoked	54 (13.6)	47 (11.8)
Pathological stage at baseline — no. (%)		
II	118 (29.7)	121 (30.2)
III	279 (70.3)	279 (69.8)
IIIA	217 (54.7)	225 (56.2)
IIIB	62 (15.6)	54 (13.5)
Tumor stage — no. (%)		
T1	55 (13.9)	61 (15.2)
T2	106 (26.7)	126 (31.5)
T3	121 (30.5)	109 (27.2)
T4	115 (29.0)	104 (26.0)
Node stage — no. (%)		
N0	148 (37.3)	142 (35.5)
N1	81 (20.4)	71 (17.8)
N2	168 (42.3)	187 (46.8)
Histologic features — no. (%)		
Nonsquamous	226 (56.9)	227 (56.8)
Squamous	171 (43.1)	173 (43.2)
PD-L1 tumor proportion score — no. (%)		
≥50%	132 (33.2)	134 (33.5)
<50%	265 (66.8)	266 (66.5)
1–49%	127 (32.0)	115 (28.8)
<1%	138 (34.8)	151 (37.8)
EGFR mutation status — no. (%)		
No	111 (28.0)	127 (31.8)
Yes	14 (3.5)	19 (4.8)
Unknown	272 (68.5)	254 (63.5)
ALK translocation status — no. (%)		
No	104 (26.2)	133 (33.2)
Yes	12 (3.0)	9 (2.2)
Unknown	281 (70.8)	258 (64.5)

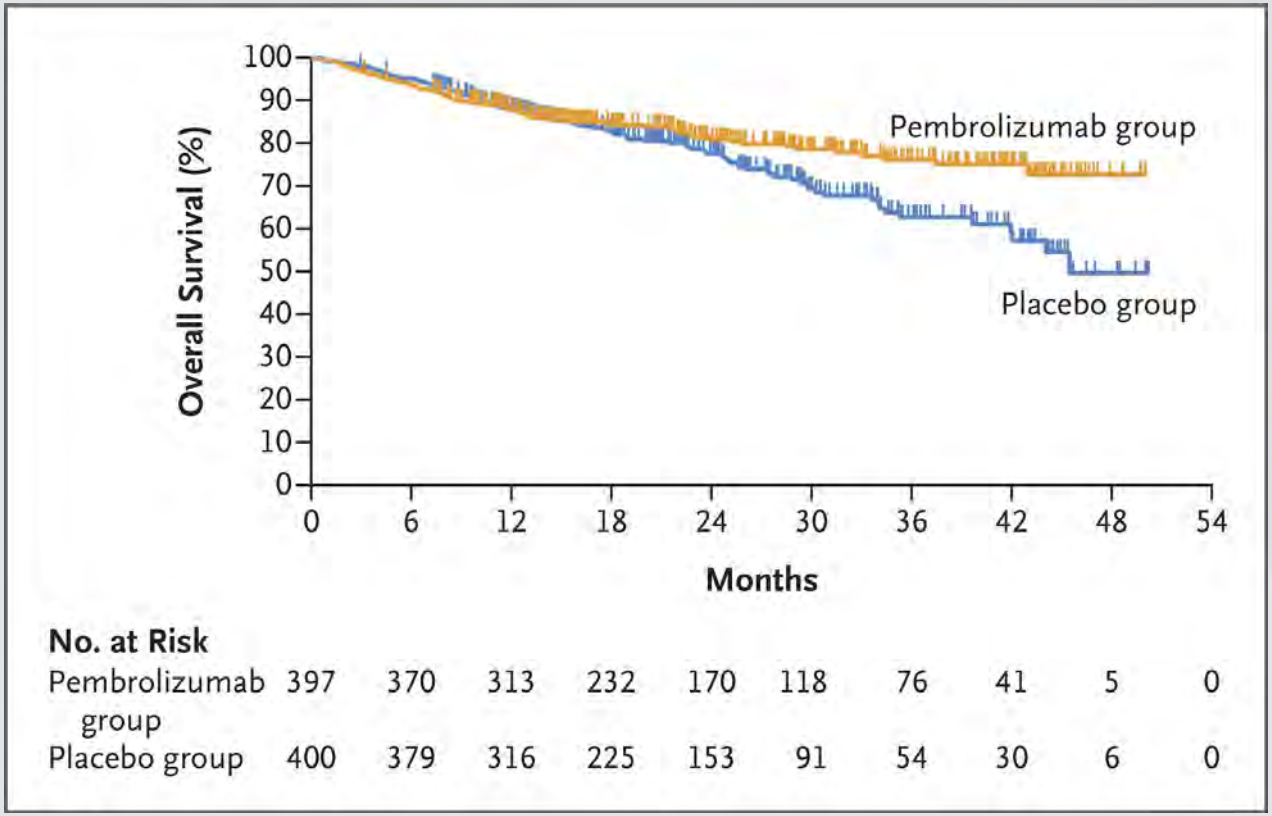
* The intention-to-treat population included all the participants who had undergone randomization. Percentages may not total 100 because of rounding. PD-L1 denotes programmed death ligand 1.
† Race and ethnic group were reported by the participant.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.



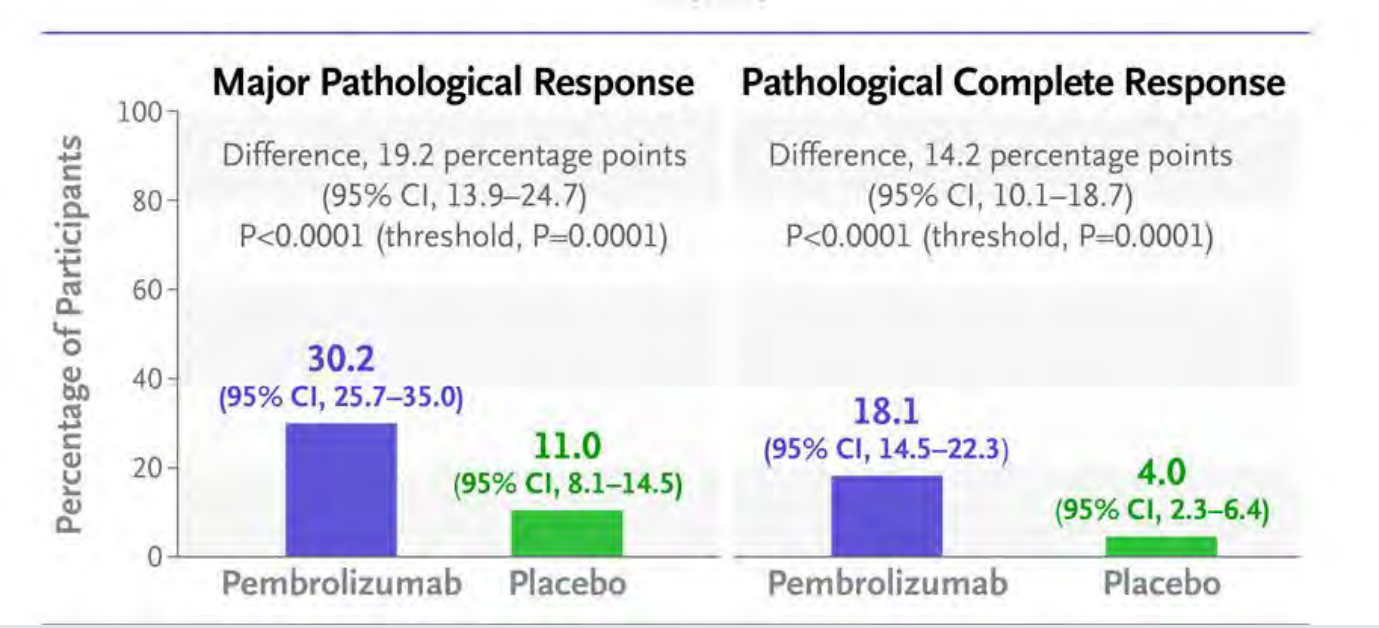
EFS at 2 years : 62.4% vs 40.6% (HR, 0.58; 95% confidence interval [CI], 0.46 to 0.72; P<0.001).

B Subgroup Analysis of Event-free Survival

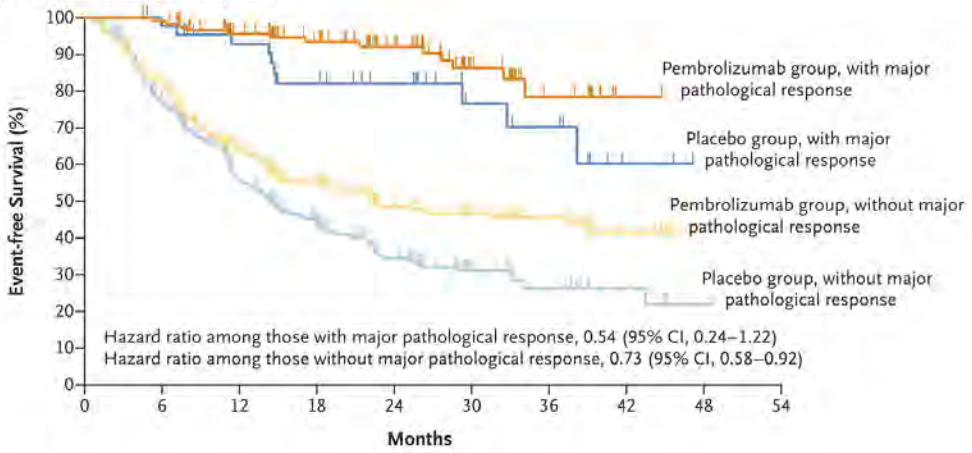
Subgroup	Pembrolizumab Group	Placebo Group	Hazard Ratio for Event or Death (95% CI)
	no. of events/no. of participants		
All patients	139/397	205/400	0.58 (0.46–0.72)
Age			
<65 yr	74/221	113/214	0.53 (0.39–0.71)
≥65 yr	65/176	92/186	0.64 (0.46–0.88)
Sex			
Female	31/118	55/116	0.44 (0.28–0.68)
Male	108/279	150/284	0.63 (0.49–0.80)
Race			
White	85/250	123/239	0.54 (0.41–0.72)
Other	46/134	70/145	0.62 (0.42–0.89)
Geographic region			
East Asia	43/123	57/121	0.66 (0.45–0.99)
Other	96/274	148/279	0.54 (0.41–0.69)
Smoking status			
Current smoker	37/96	57/103	0.52 (0.34–0.78)
Former smoker	84/247	128/250	0.57 (0.43–0.75)
Never smoked	18/54	20/47	0.68 (0.36–1.30)
Pathological stage			
II	34/118	48/121	0.65 (0.42–1.01)
III	105/279	157/279	0.54 (0.42–0.70)
Histologic features			
Nonsquamous	73/226	107/227	0.58 (0.43–0.78)
Squamous	66/171	98/173	0.57 (0.41–0.77)
PD-L1 TPS (50% cutoff)			
<50%	107/265	142/266	0.64 (0.49–0.82)
≥50%	32/132	63/134	0.42 (0.28–0.65)
PD-L1 TPS (1% cutoff)			
<1%	63/138	80/151	0.77 (0.55–1.07)
≥1%	76/259	125/249	0.47 (0.36–0.63)
PD-L1 TPS			
<1%	63/138	80/151	0.77 (0.55–1.07)
1–49%	44/127	62/115	0.51 (0.34–0.75)
≥50%	32/132	63/134	0.42 (0.28–0.65)
EGFR mutation			
No	31/111	64/127	0.48 (0.31–0.74)
Yes	1/14	10/19	0.09 (0.01–0.74)
Unknown	107/272	131/254	0.64 (0.49–0.83)
ALK translocation			
No	29/104	76/133	0.41 (0.26–0.62)
Unknown	106/281	128/258	0.63 (0.49–0.82)



OS at 2 years → 80.9% vs 77.6% (P=0.02, which did not meet the significance criterion).


Major Pathological Response
Difference, 19.2 percentage points
(95% CI, 13.9–24.7)
P<0.0001 (threshold, P=0.0001)
Pathological Complete Response
Difference, 14.2 percentage points
(95% CI, 10.1–18.7)
P<0.0001 (threshold, P=0.0001)
Percentage of Participants
100
80
60
40
20
0
30.2
(95% CI, 25.7–35.0)
11.0
(95% CI, 8.1–14.5)
18.1
(95% CI, 14.5–22.3)
4.0
(95% CI, 2.3–6.4)
Pembrolizumab
Placebo
Pembrolizumab
Placebo

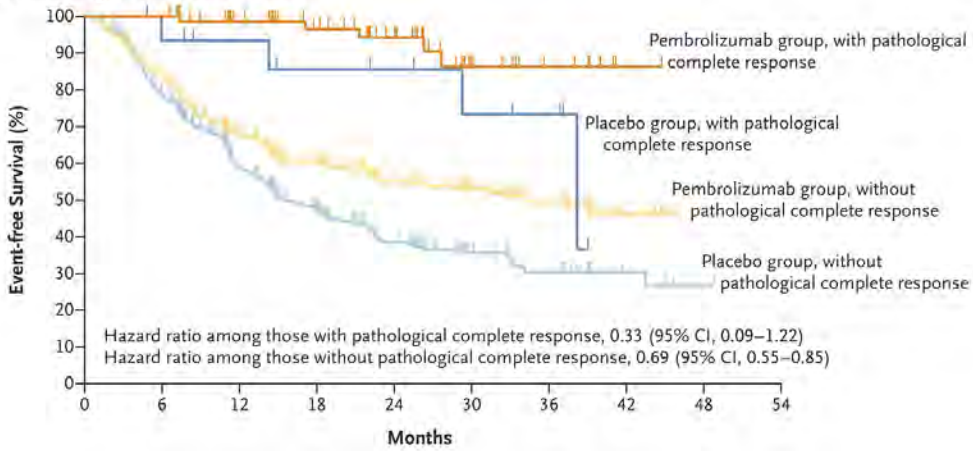
A Event-free Survival According to Major Pathological Response



No. at Risk

With major pathological response										
Pembrolizumab group	120	117	99	79	60	30	15	1	0	0
Placebo group	44	42	36	28	22	12	10	2	0	0
Without major pathological response										
Pembrolizumab group	277	213	137	93	57	42	27	10	0	0
Placebo group	356	252	147	96	52	26	14	7	1	0

B Event-free Survival According to Pathological Complete Response



No. at Risk

With pathological complete response										
Pembrolizumab group	72	72	59	46	33	15	8	1	0	0
Placebo group	16	14	12	10	9	5	4	0	0	0
Without pathological complete response										
Pembrolizumab group	325	258	177	126	84	57	34	10	0	0
Placebo group	384	280	171	114	65	33	20	9	1	0

Table 2. Treatment-Related Adverse Events across Treatment Phases (As-Treated Population).*

Event	Pembrolizumab Group (N=396)	Placebo Group (N=399)
	number of participants (percent)	
Any treatment-related adverse event	383 (96.7)	379 (95.0)
Grade 3–5 treatment-related adverse event	178 (44.9)	149 (37.3)
Serious treatment-related adverse event	70 (17.7)	57 (14.3)
Treatment-related adverse event that led to death	4 (1.0)†	3 (0.8)‡
Treatment-related adverse event that led to discontinuation of all trial treatment	50 (12.6)	21 (5.3)

Conclusion

Among patients with resectable, early-stage NSCLC, neoadjuvant pembrolizumab plus chemotherapy followed by resection and adjuvant pembrolizumab significantly improved event-free survival, major pathological response, and pathological complete response as compared with neoadjuvant chemotherapy alone followed by surgery. Overall survival did not differ significantly between the groups in this analysis.

Summary

- Utilization of chemo-immunotherapy has resulted in better PFS, promising data in OS with acceptable safety profile.
- Currently, we are using this approach in some stage III cases.
- Chance to expand practice in the future when OS data are mature.

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