Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

Journal Club 19.12.2022

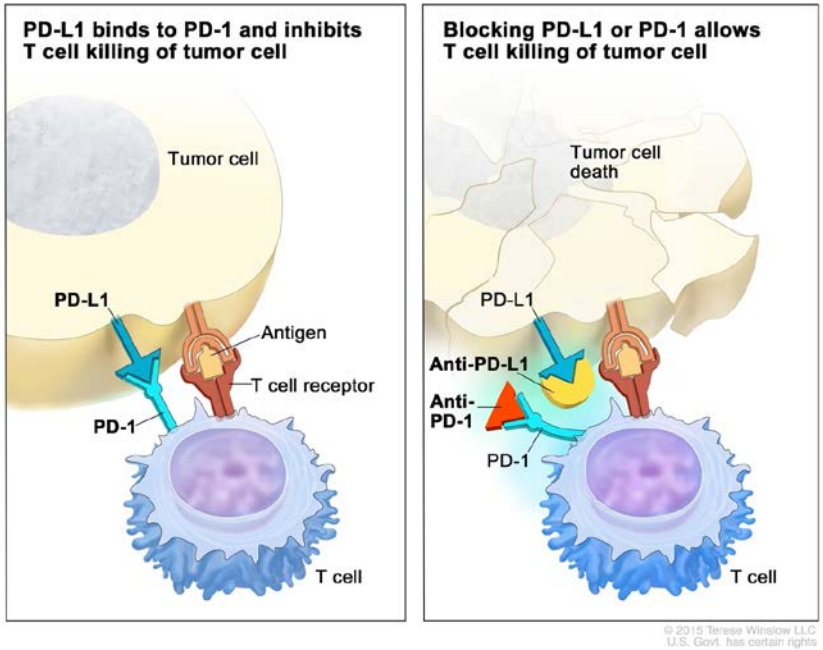
Martin Korpan

Structure of my presentation

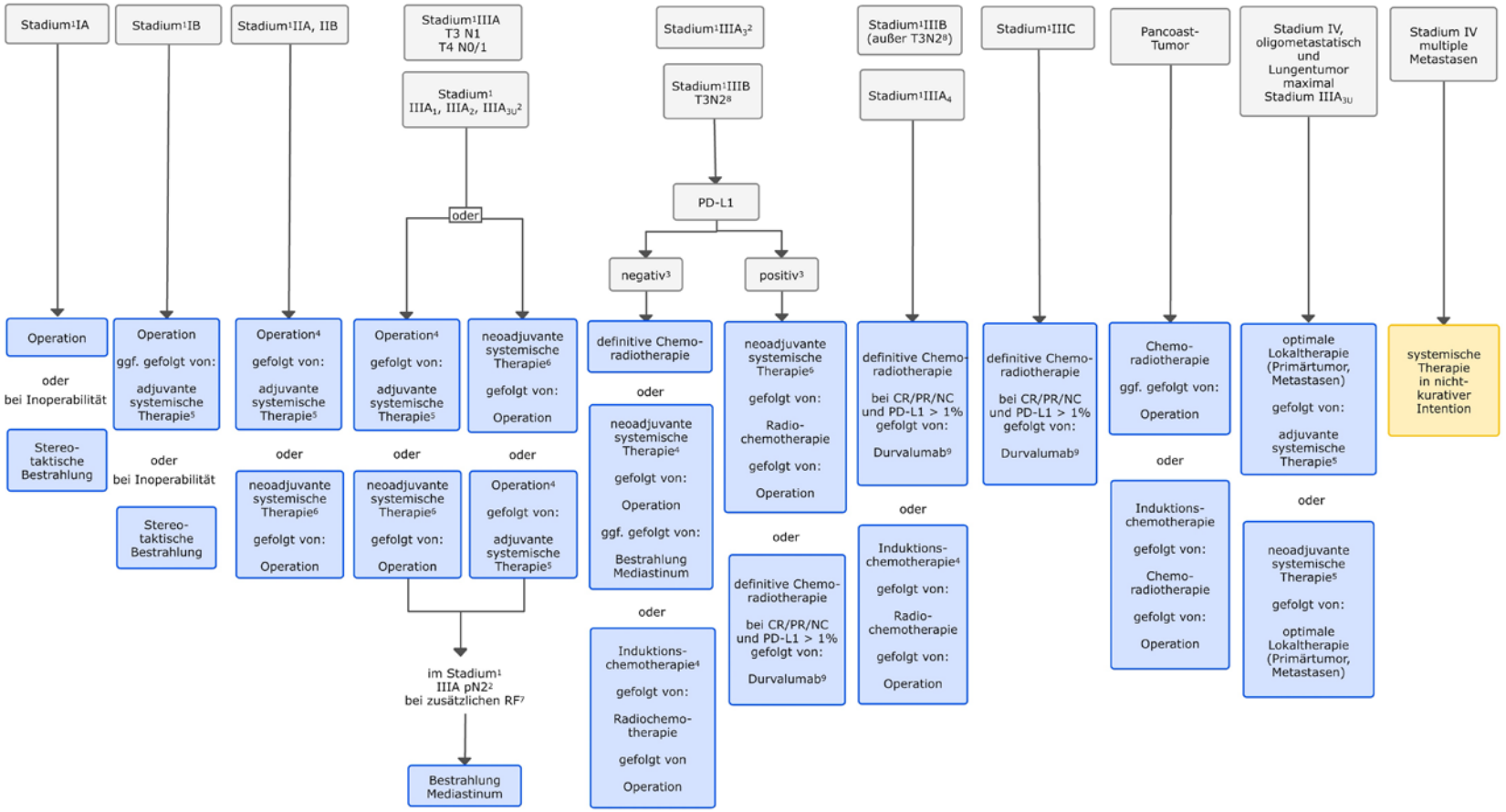
- Background Nivolumab
- Treatment possibilities in NSCLC
- Authors
- Background of the clinical trial
- Methods
- Results
- Discussion

Background Nivolumab

- Checkpoint-Inhibitor
- Use in Cancer:
  - Hodgkin lymphoma
  - Progressive mCRC (MSI) after FOLFIRINOX treatment
  - Malignant pleural mesothelioma with ipilimumab
  - Melanoma (with ipilimumab)
  - NSCLC with Ipilimumab
    - no EGFR or ALK mutation



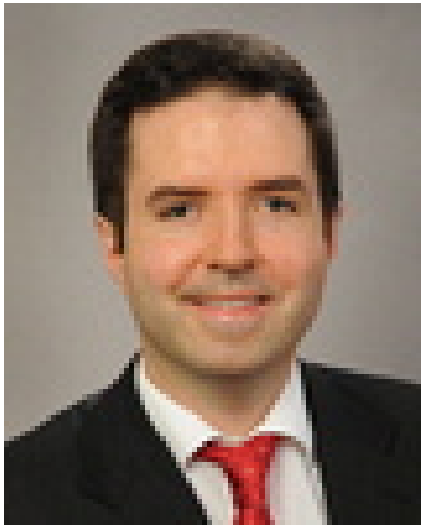
Treatment possibilities in NSCLC



Authors of the “Checkmate 816“ trial

First author: Patrick M. Forde

- John Hopkins University, Baltimore, USA
- Beaumont hospital
- Main research focus: immunotherapy in lung cancer
- H-index: 43



Last author: Nicolas Girard

- University of Versailles, France
- Hôpital Saint Cloud, Paris
- Main research focus: Thymic Cancer and immunotherapy
- H-index: 61

Background of the clinical trial

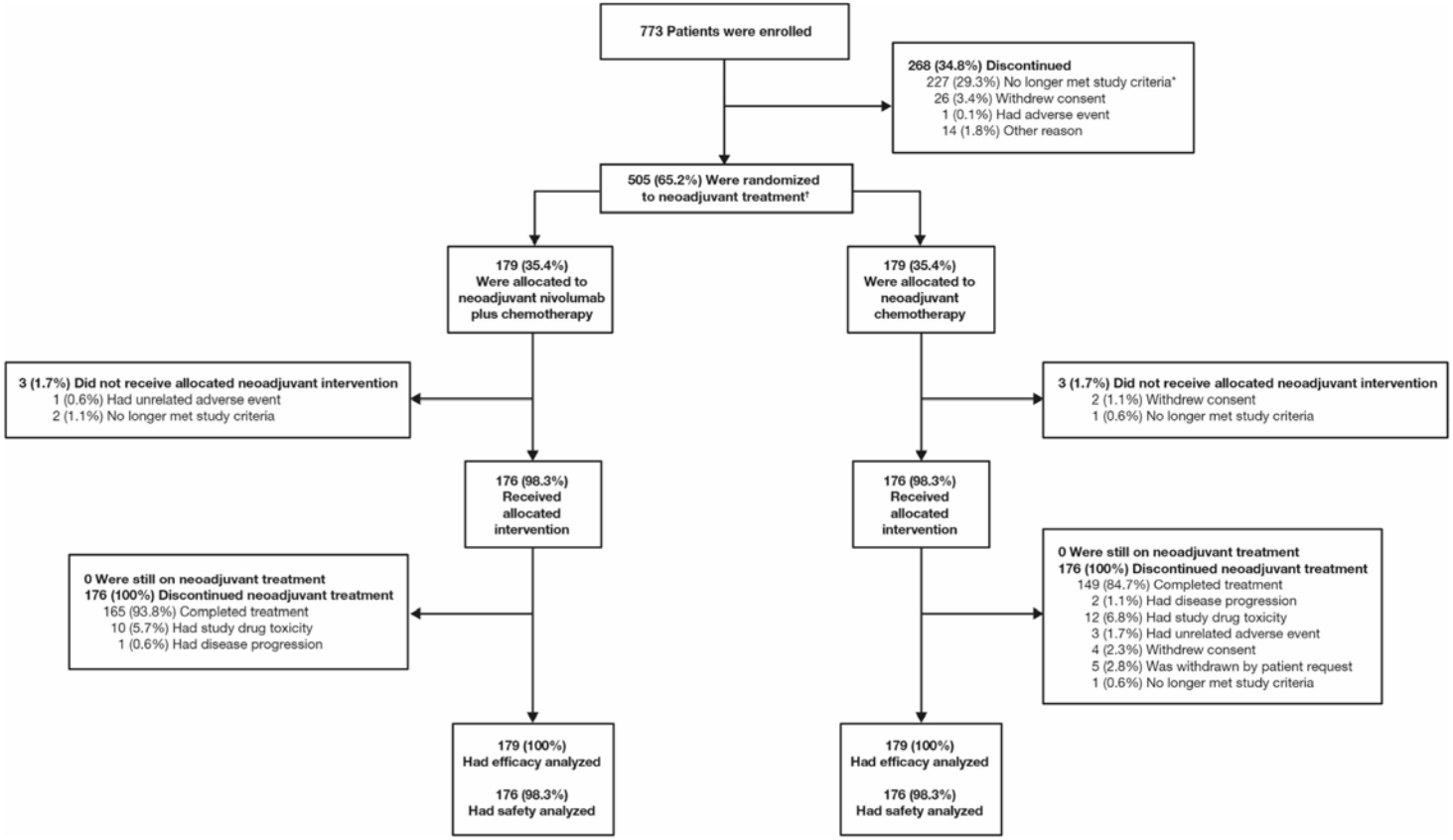
- 20 – 25 % of patients diagnosed with NSCLC have resectable disease
- 30 – 50 % of operated patients have recurrence
- Benefit of Nivolumab in patients with metastatic NSCLC
- Promising phase 2 trials for neoadjuvant nivolumab
- Checkmate 816 → phase 3 trial comparing nivo + chemo vs. Chemo alone

Inclusion vs. Exclusion Criteria

- Stage IB (≥4 cm) to IIIA NSCLC
- ECOG 0 – 1
- No previous anti-cancer therapy
- Mediastinal lymph node samples for assessment
- Adequate pulmonary function for lung resection

- EGFR or ALK mutation
- unresectability
- Stage IV
- Immunosuppressive medication
- Systemic corticosteroids

Figure S2. CONSORT Flow Chart of Patient Disposition.



* Screen failure.

† Includes 113 enrolled patients randomized to an exploratory neoadjuvant nivolumab plus ipilimumab arm for which enrollment was closed early and the arm discontinued, and 34 patients randomized to chemotherapy in the initial protocol (i.e. prior to the addition of the nivolumab plus chemotherapy arm) who were not included in the primary analysis population.

Treatment

- 360 mg Nivolumab + either Cisplatin- or Carboplatin-based vs. Cisplatin- or Carboplatin-based chemotherapy alone
- 3 cycles q21
- surgery was planned to occur within 6 weeks after the completion of neoadjuvant treatment
- Consecutive adjuvant CTx, RTx or both was possible

1.	2.	3.	4.	5.
Cisplatin	Cisplatin	Carboplatin	Cisplatin	Cisplatin
Paclitaxel	Pemetrexed	Paclitaxel	Vinorelbine	Docetaxel

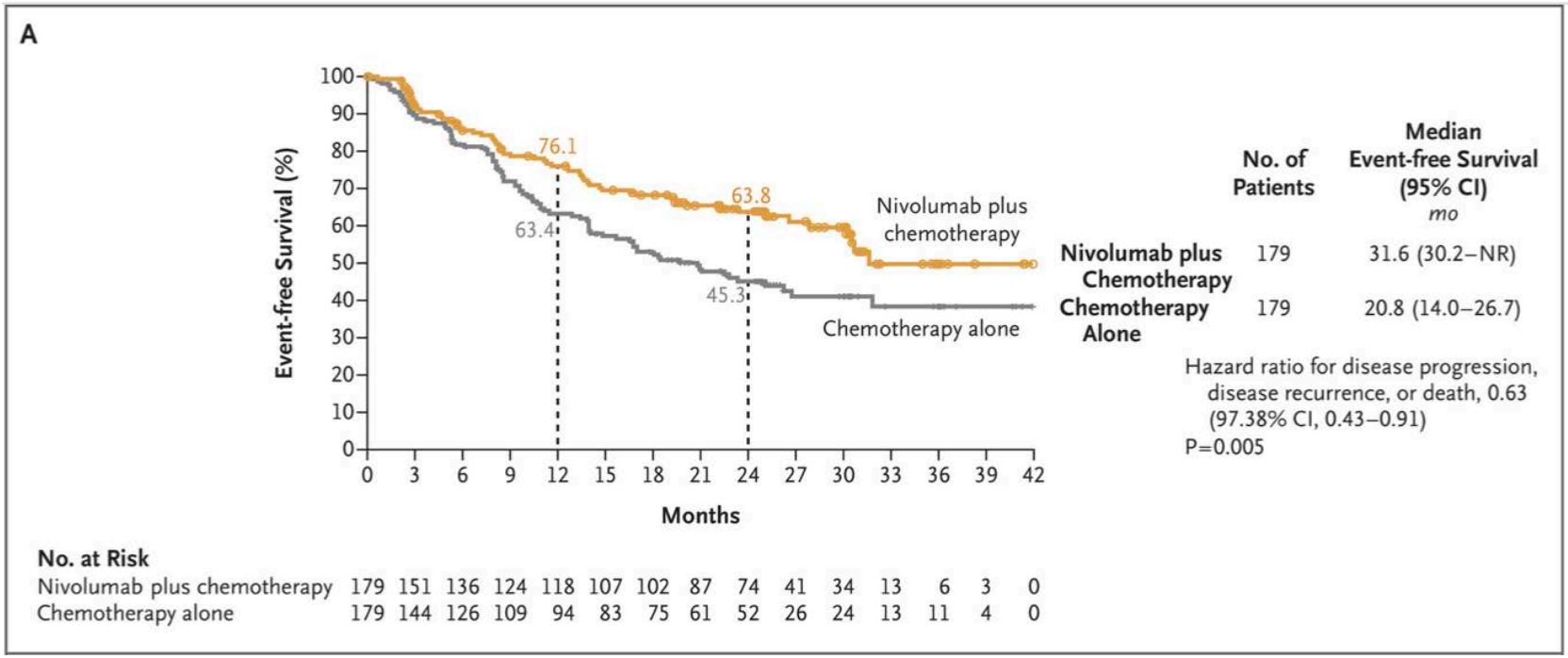
Endpoints

- Two primary endpoints:
  - *Event-Free-Survival*
    - Time from randomization to any progression precluding surgery / after surgery / in the absence of surgery / or death from any cause
    - Data on patients with subsequent therapy was censored at the last tumor assessment before therapy
  - *Complete Response*
    - R0 (0% residual tumor cells in primary tumor and sampled lymph nodes)

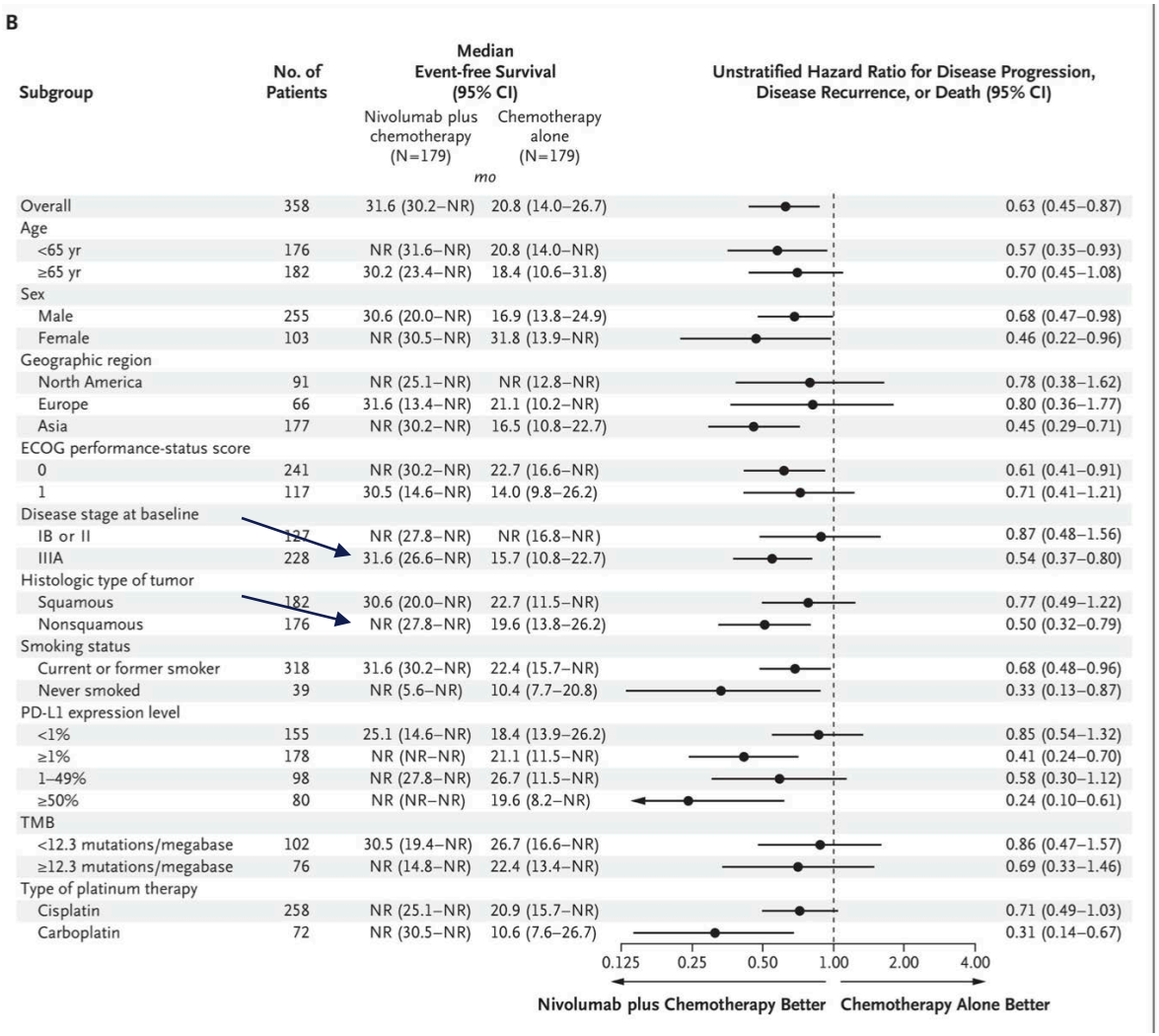
Table 1. Characteristics of the Patients at Baseline.

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)
Carboplatin	39 (21.8)	33 (18.4)

Results: EFS


A
Event-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42
Months
76.1
63.8
63.4
45.3
Nivolumab plus chemotherapy
Chemotherapy alone
No. at Risk
Nivolumab plus chemotherapy 179 151 136 124 118 107 102 87 74 41 34 13 6 3 0
Chemotherapy alone 179 144 126 109 94 83 75 61 52 26 24 13 11 4 0
No. of Patients
Median Event-free Survival (95% CI) mo
Nivolumab plus Chemotherapy 179 31.6 (30.2–NR)
Chemotherapy Alone 179 20.8 (14.0–26.7)
Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

Results: EFS comparison



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)

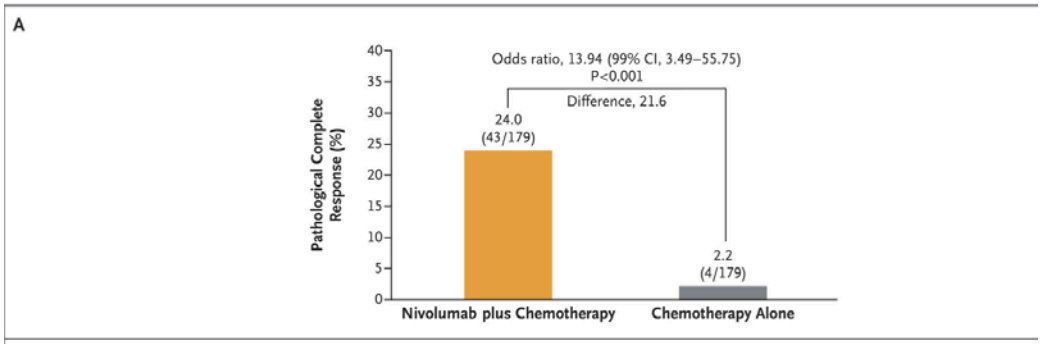
Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)

Unstratified Hazard Ratio (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

Results: pathological complete response



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)

Treatment Summary

Table S2. Treatment Summary.

	Nivolumab plus Chemotherapy (N = 179)	Chemotherapy (N = 179)
Patients receiving neoadjuvant treatment — no. (%)	176 (98.3)	176 (98.3)
Reason off neoadjuvant treatment — no. (%)*		
Completed (3 cycles)	165 (93.8)	149 (84.7)
Study drug toxicity	10 (5.7)	12 (6.8)
Disease progression	1 (0.6)	2 (1.1)
Other†	0	13 (7.4)
Patients receiving adjuvant treatment — no. (%)*	35 (19.9)	56 (31.8)
Chemotherapy (≤4 cycles) alone	21 (11.9)	39 (22.2)
Radiotherapy alone	9 (5.1)	12 (6.8)
Chemotherapy and radiotherapy	5 (2.8)	5 (2.8)

* Denominator based on patients receiving neoadjuvant treatment.

† Reasons were adverse event unrelated to study drug in 3 patients, patient request to discontinue study treatment in 5 patients, and patient no longer met study criteria in 1 patient.

Side effects

	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)			
Treatment-related adverse events*				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Nausea	58 (33.0)	1 (0.6)	73 (41.5)	1 (0.6)
Anemia	42 (23.9)	5 (2.8)	40 (22.7)	6 (3.4)
Constipation	37 (21.0)	0	36 (20.5)	2 (1.1)
Decreased appetite	29 (16.5)	2 (1.1)	38 (21.6)	4 (2.3)
Neutropenia	28 (15.9)	15 (8.5)	29 (16.5)	21 (11.9)
Decreased neutrophil count	26 (14.8)	13 (7.4)	37 (21.0)	19 (10.8)
Surgery-related adverse events†,‡				
All	62 (41.6)	17 (11.4)	63 (46.7)	20 (14.8)
Anemia	18 (12.1)	3 (2.0)	17 (12.6)	3 (2.2)
Pain	11 (7.4)	1 (0.7)	21 (15.6)	0
Wound complication	11 (7.4)	1 (0.7)	8 (5.9)	0
Procedural pain	9 (6.0)	0	6 (4.4)	0
Pneumonia	8 (5.4)	3 (2.0)	8 (5.9)	4 (3.0)

* Included events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose as per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

† Includes events reported up to 90 days after definitive surgery. CTCAE Version 4.0; MedDRA Version 23.0.

‡ Denominator based on patients with definitive surgery (N=149 in the nivolumab plus chemotherapy group, N=135 in the chemotherapy group).

Immune-mediated side effects

Table S14. Immune-Mediated Adverse Events.

	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)			
Rash	15 (8.5)	3 (1.7)	1 (0.6)	0
Hypersensitivity	2 (1.1)	0	0	0
Pneumonitis	2 (1.1)	0	1 (0.6)	1 (0.6)
Endocrine				
Adrenal insufficiency	2 (1.1)	2 (1.1)	0	0
Hypophysitis	1 (0.6)	1 (0.6)	0	0
Hypothyroidism/thyroiditis	4 (2.3)	0	0	0
Hyperthyroidism	7 (4.0)	0	0	0
Diabetes mellitus	2 (1.1)	0	0	0

Defined as specific events considered as potential immune-mediated events by the investigator, regardless of causality, that occurred within 100 days of the last dose as per Common Terminology Criteria for Adverse Events Version 4.0; Medical Dictionary for Regulatory Activities Version: 23.0, with no clear alternate etiology based on investigator assessment, or with an immune-mediated component, that were treated with immune-modulating medication. Endocrine adverse events were considered immune mediated regardless of immune-modulating medication use since endocrine drug reactions are often managed without immune-modulating medication.

Limitations

- Not transparently presented, what patients received which chemo-regimen
- choice of exact chemo therapy was at the discretion of each investigator
- Sponsor decision to discontinue the nivolumab + ipilimumab arm (due to two phase 2 studies conducted by the sponsor)
- P value for overall survival did not cross the boundary for statistical significance

Conclusion

- Significantly longer event-free survival than chemo alone
- Higher percentage of patients with a pathological complete response
- Greater benefit in patients
  - with stage IIIa disease
  - With higher PD-L1 expression
- FDA approval for resectable NSCLC ≥ 4cm or node positive

Questions?

References

- https://www.nejm.org/doi/10.1056/NEJMoa2202170
- https://www.cancer.gov/about-cancer/treatment/drugs/nivolumab (14.12.2022)
- Liang Y, Wakelee HA. Adjuvant chemotherapy of completely resected early stage non-small cell lung cancer (NSCLC). Transl Lung Cancer Res 2013;2:403-410.
- NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-1571.
- Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med 2020;383:1711-1723.
- Reck M, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update. ESMO Open 2021;6:100273-100273.

References

- Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497-1508.
- Paz-Ares LG, Ramalingam SS, Ciuleanu TE, et al. First-line nivolumab plus ipilimumab in advanced NSCLC: 4-year outcomes from the randomized, open-label, phase 3 CheckMate 227 part 1 trial. J Thorac Oncol 2022;17:289-308.