Role of adjuvant and neoadjuvant Immunotherapy in resectable NSCLC

Dr. Pratibha Jha

Outline of presentation

Introduction

Basics of immunotherapy

Current management protocols of resectable NSCLC

Immunotherapy as neoadjuvant therapy

Immunotherapy as adjuvant therapy

Take home message

Introduction

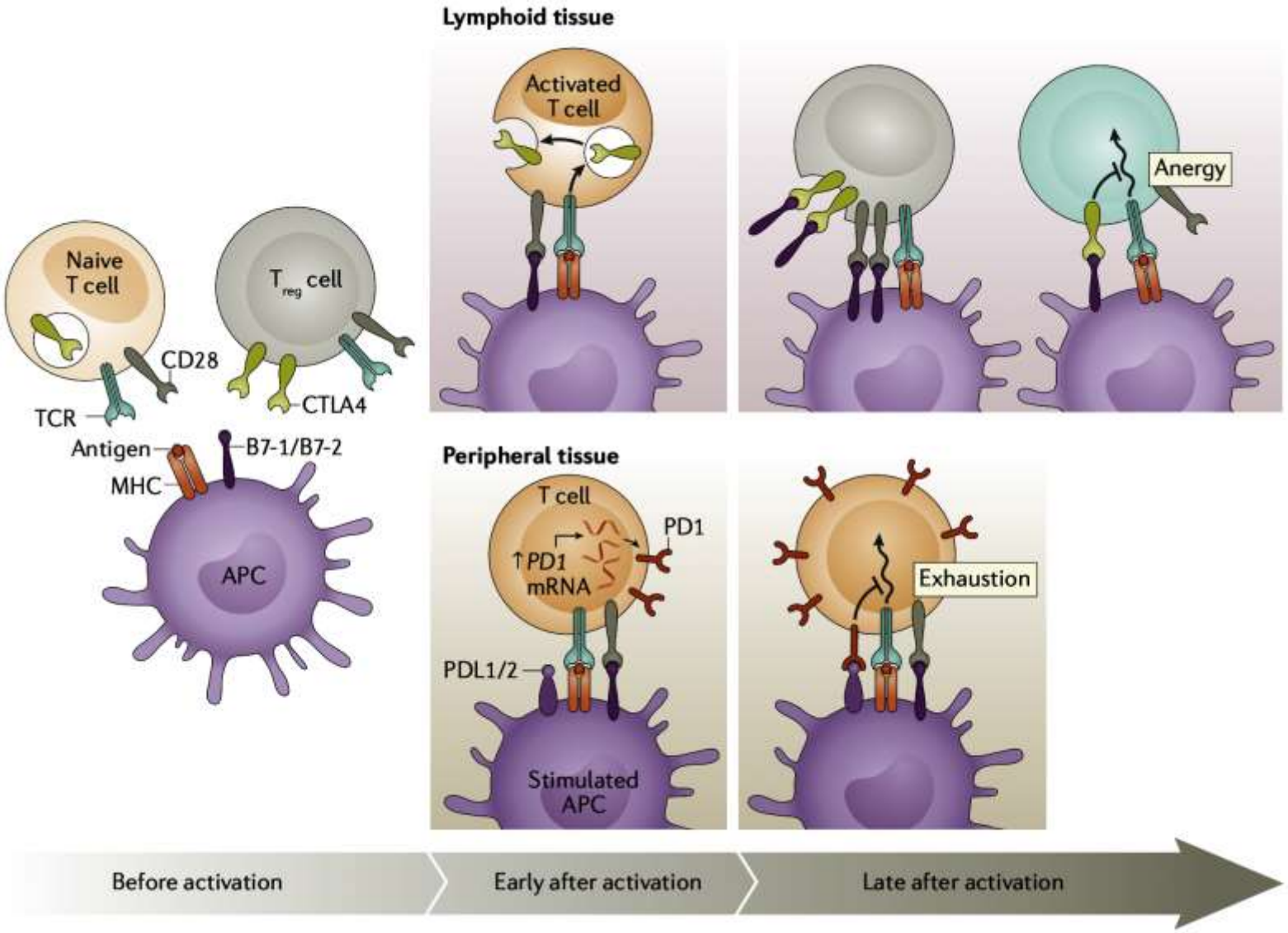
- Immunotherapy has revolutionized the management of advanced metastatic NSCLC with significantly improved progression free survival and overall survival.
- Around 20-25% of new diagnosed patients with NSCLC have resectable disease. Despite surgery and adjuvant therapy, about 20–30% of patients with stage I, 50% with stage II, and 60% with stage IIIA die within 5 years.
- Neoadjuvant chemotherapy improves the 5 year survival by only 5%
- This inspired trial of immunotherapy (IO) in the adjuvant and neoadjuvant setting to improve overall survival

Basics of Immunotherapy

Mechanism of T cell activation

- T cell activation requires recognition of neoantigens on APC's, activation by co-stimulatory molecules and cytokine stimulation.
- T-cells also express inhibitory pathways called immune checkpoints that negatively regulate the T-cell activation which is essential to maintain self-tolerance.
- Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) and Programmed Cell Death Protein 1 (PD-1) are examples of immune checkpoints on the T cells
- The ligands of CTLA-4 are CD80/86, present on the surface APC's and the ligands of PD-1 are PD Ligand Protein 1 and 2 (PDL-1 and PDL-2), present on the surface of both APCs and tumour cells.

Mechanism of T-cell activation

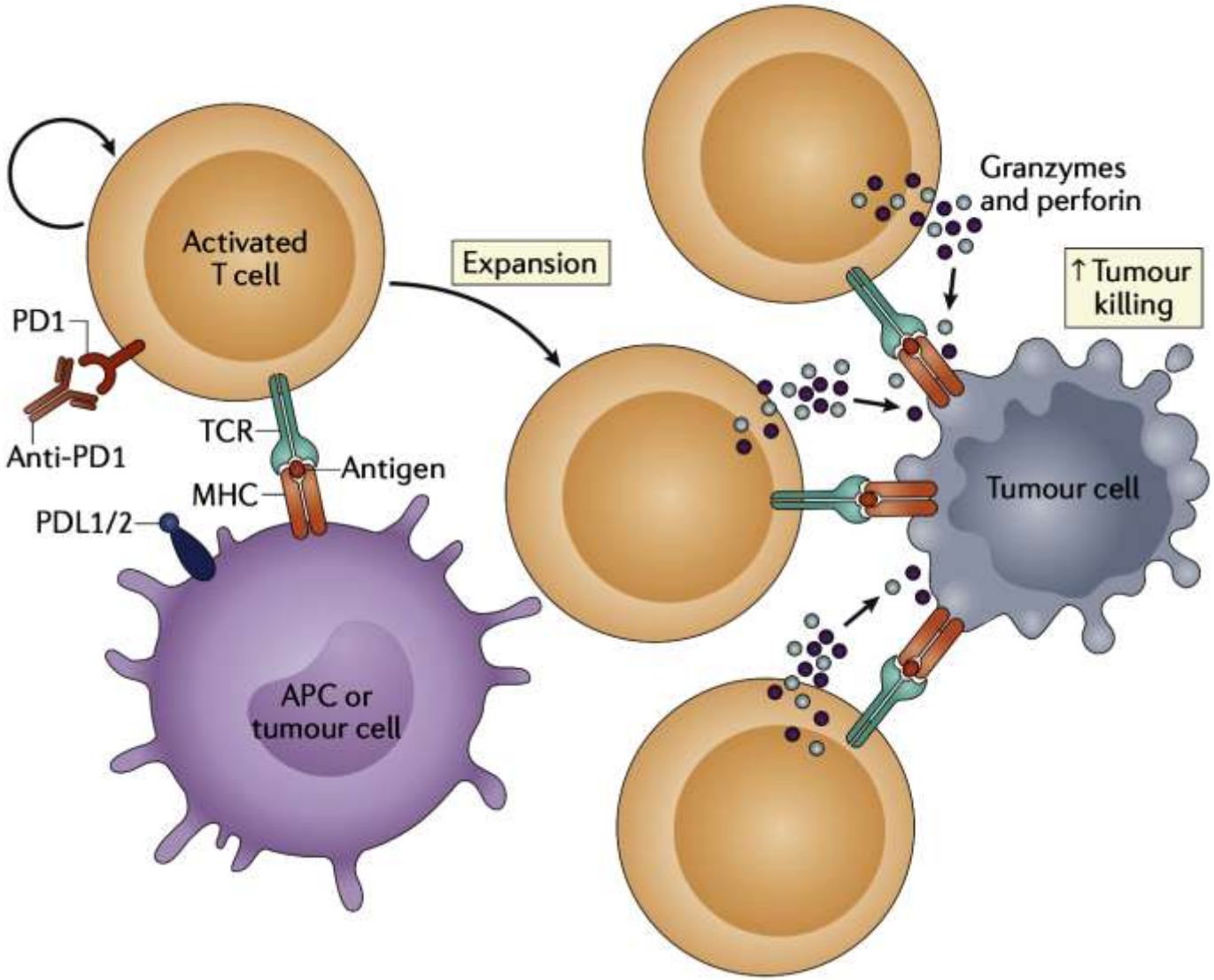


Waldman AD,et al. Nat Rev Immunol.2020;20:651–668

Mechanism of immunotherapy

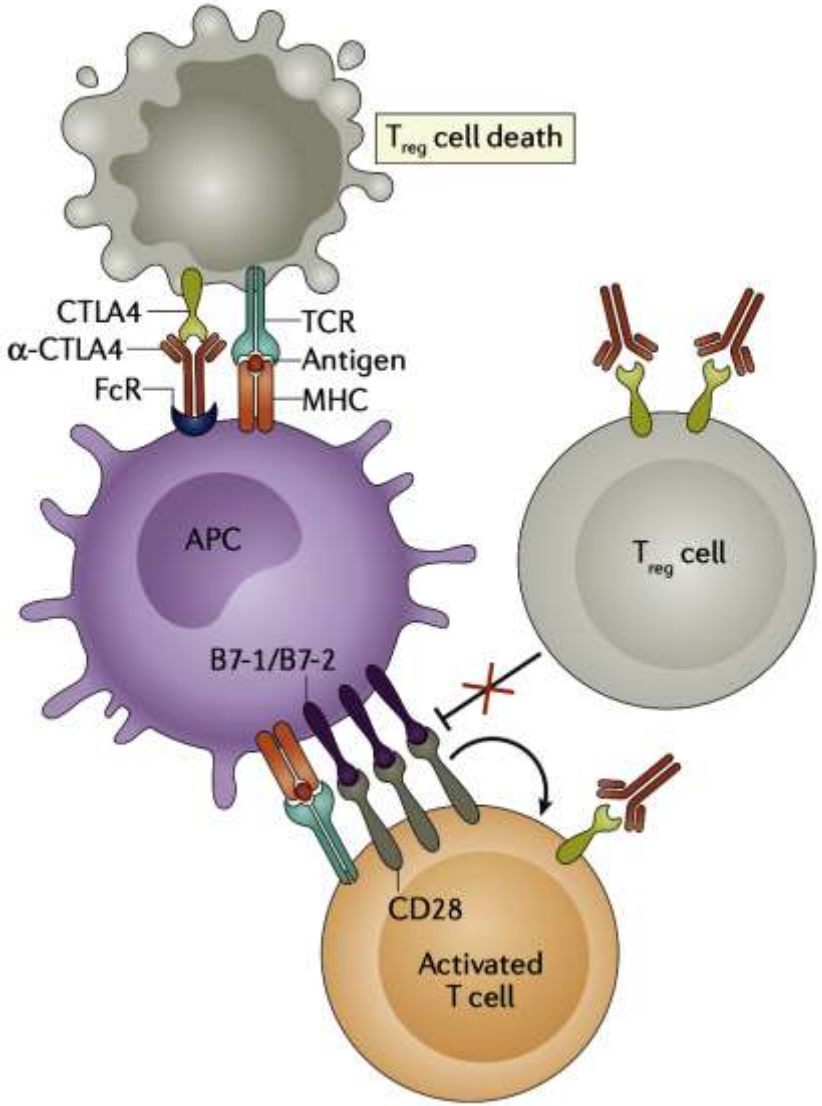
- Tumor-induced suppression of T-cell activation, mediated by activating above immune checkpoints represents one of the major mechanisms by which tumors avoid recognition and rejection by the immune system.
- Immunotherapy utilizes body's own defence system to kill cancer cells
- Antibodies interacting either with CTLA- 4, PD-1 or PD-L1 have revolutionized the field of cancer treatment.
    - PD-1 inhibitors: Nivolumab, pembrolizumab, cemiplimab.
    - PD-L1 inhibitors : Atezolizumab, durvalumab, Avelumab
    - CTLA-4 inhibitors : Ipilimumab, Tremelimumab

Effect of PD-1 /PD-L1 antibodies



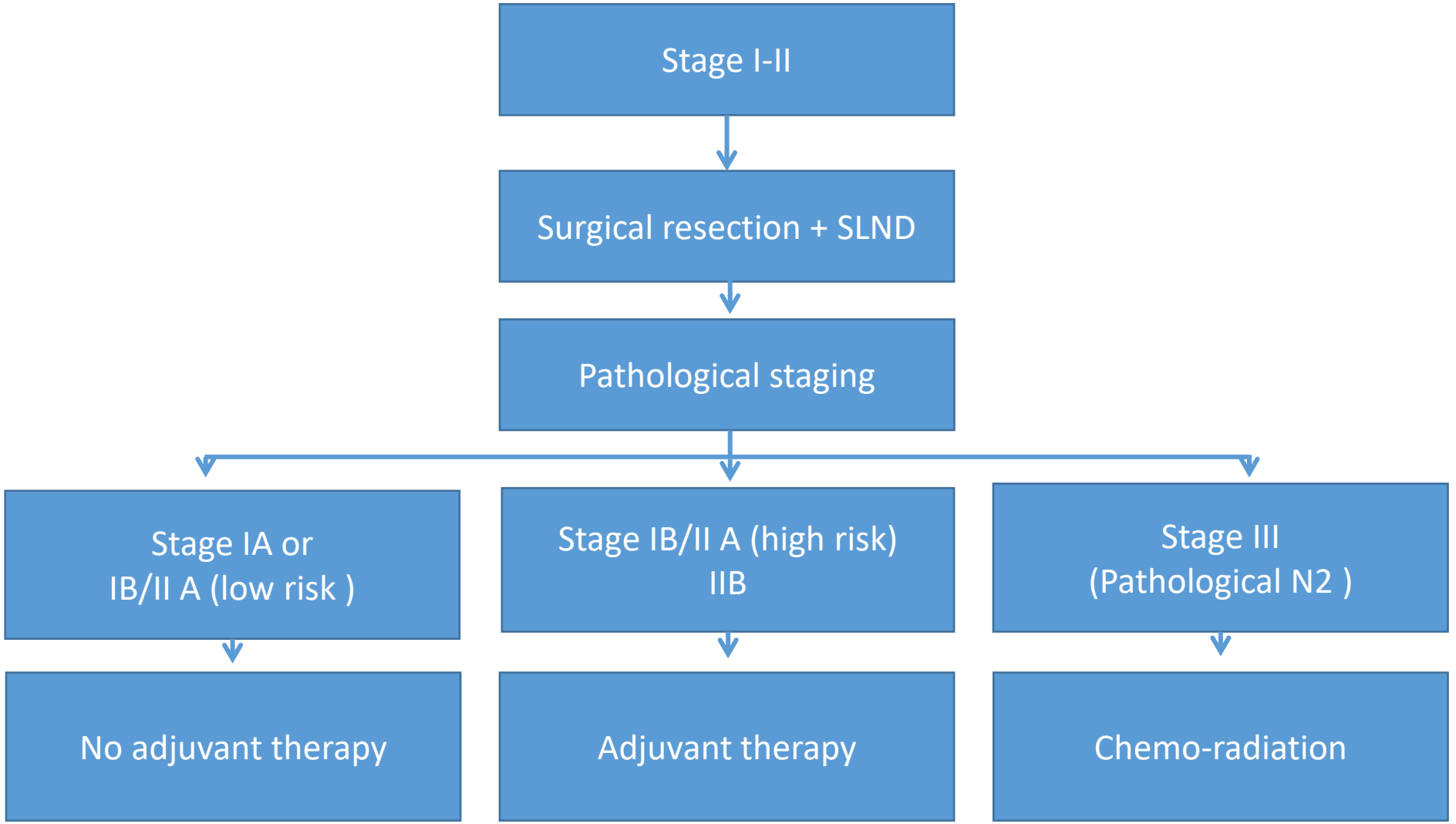
Waldman AD,et al. Nat Rev Immunol.2020;20:651–668

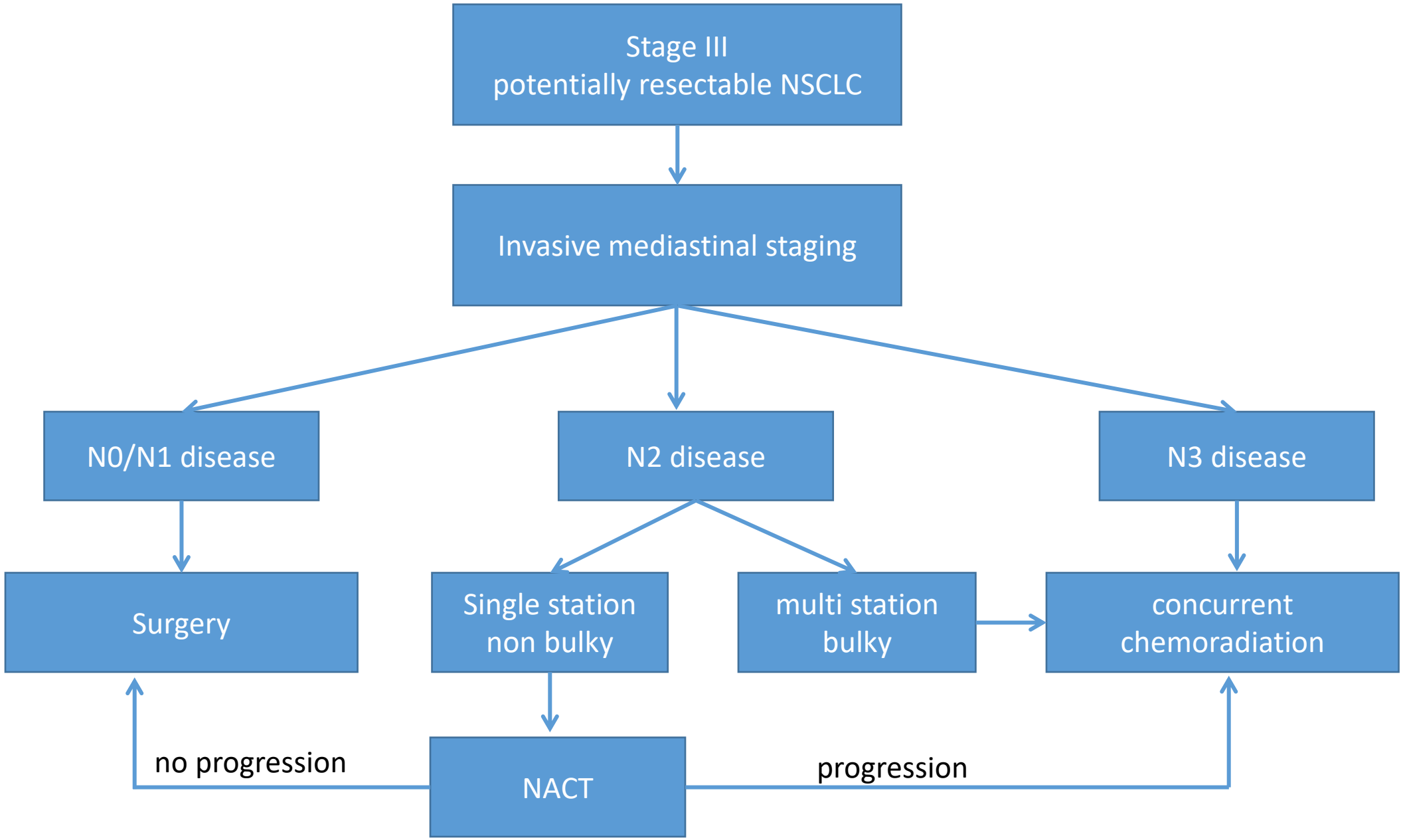
Effect of CTLA-4 antibodies



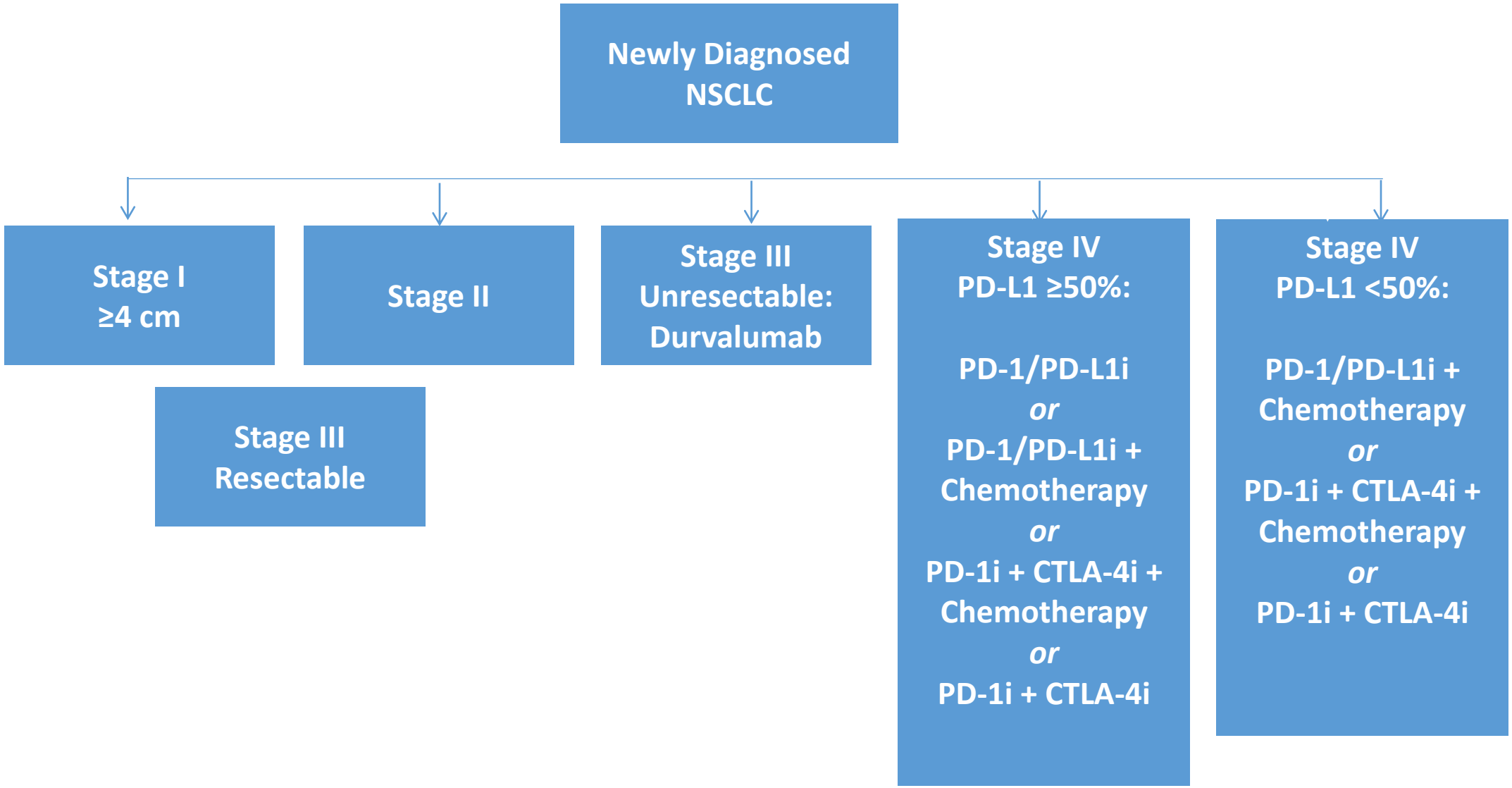
Waldman AD,et al. Nat Rev Immunol.2020;20:651–668

Management algorithm for resectable NSCLC




Stage III
potentially resectable NSCLC
Invasive mediastinal staging
N0/N1 disease
N2 disease
N3 disease
Surgery
Single station
non bulky
multi station
bulky
concurrent
chemoradiation
no progression
NACT
progression

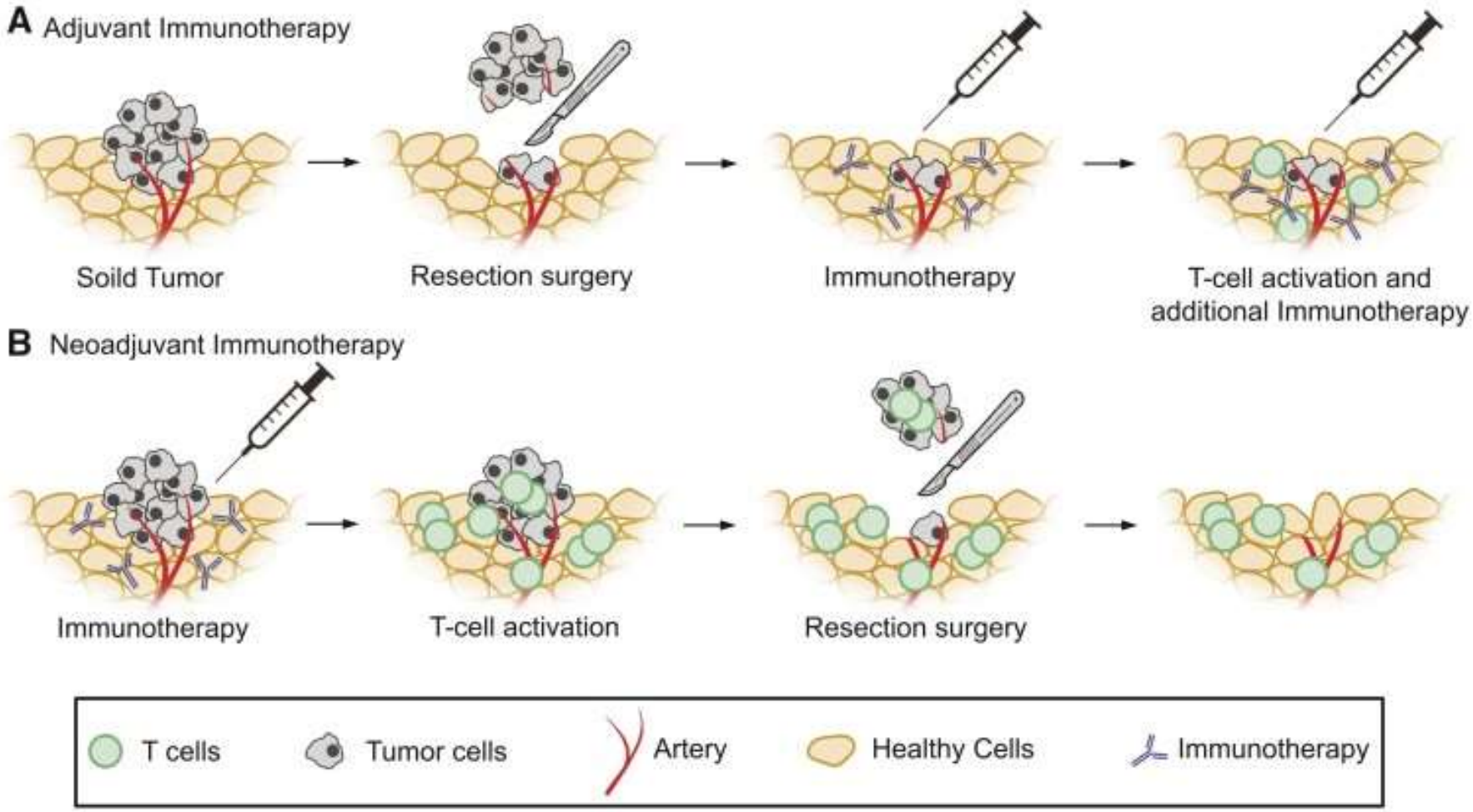
Immunotherapy in NSCLC



Role of IO as neo-adjuvant therapy

Immunotherapy as neo-adjuvant therapy

- Neoadjuvant therapy is defined as any therapy delivered prior to definitive local therapy intended to increase the cure rate.
- It can downstage tumour, improve the resection rate and more promptly treat subclinical micro-metastases
- Rationale : IO may be superior as neoadjuvant therapy compared to adjuvant therapy as the presence of the full tumour mass at the initiation of immunotherapy allows the induction of a stronger adaptive antitumour response and early development of immune memory that might provide long-term protection.



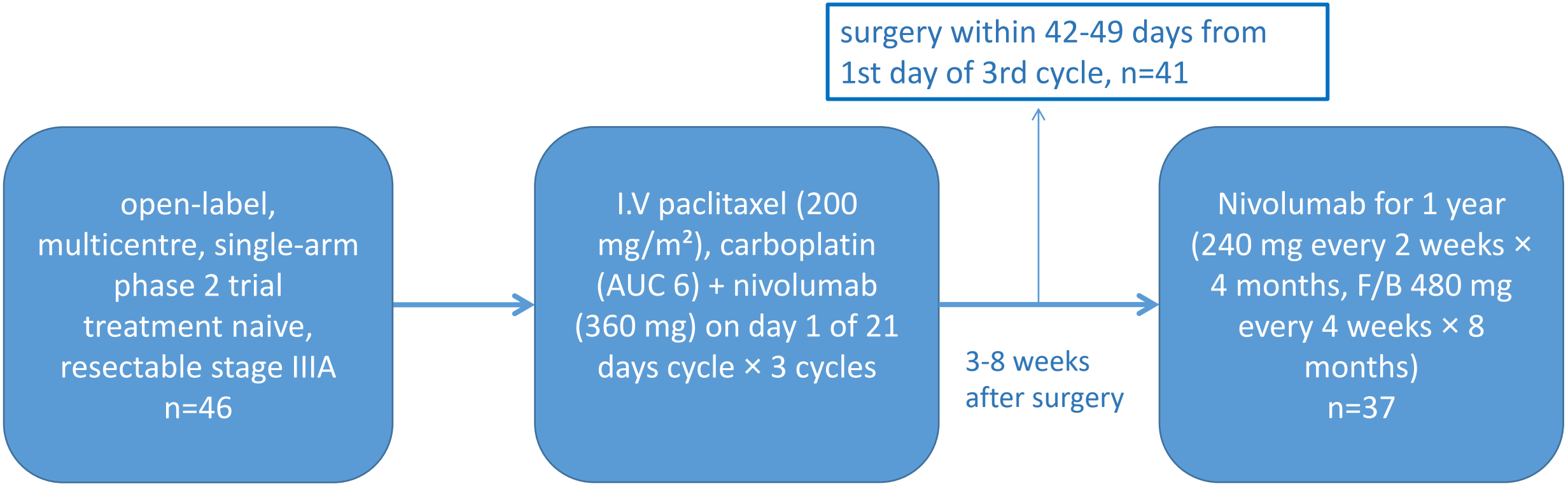
Krishnamoorthy M, et al. J Natl Cancer Inst. 2021 Jul; 113(7): 823–832

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

Mariano Provencio, Ernest Nadal, Amelia Insa, María Rosario García-Campelo, Joaquín Casal-Rubio, Manuel Dómine, Margarita Majem, Delvys Rodríguez-Abreu, Alex Martínez-Martí, Javier De Castro Carpeño, Manuel Cobo, Guillermo López Vivanco, Edel Del Barco, Reyes Bernabé Caro, Nuria Viñolas, Isidoro Barneto Aranda, Santiago Viteri, Eva Pereira, Ana Royuela, Marta Casarrubios, Clara Salas Antón, Edwin R Parra, Ignacio Wistuba, Virginia Calvo, Raquel Laza-Briviesca, Atocha Romero, Bartomeu Massuti, Alberto Cruz-Bermúdez

Lancet Oncol 2020. S1470-2045(20)30453-8

Study design

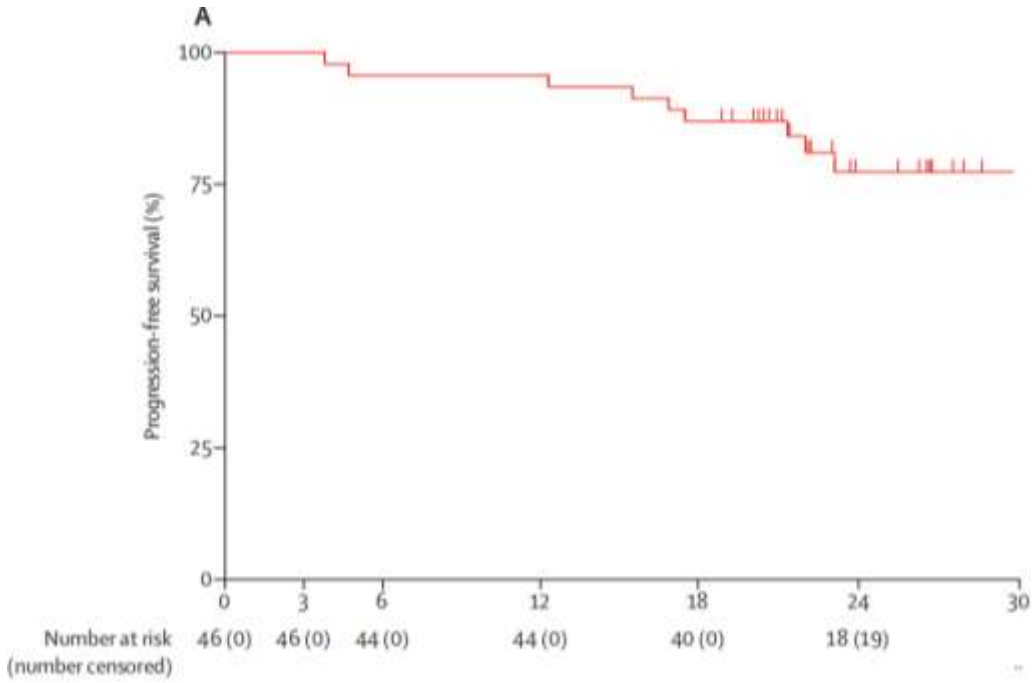


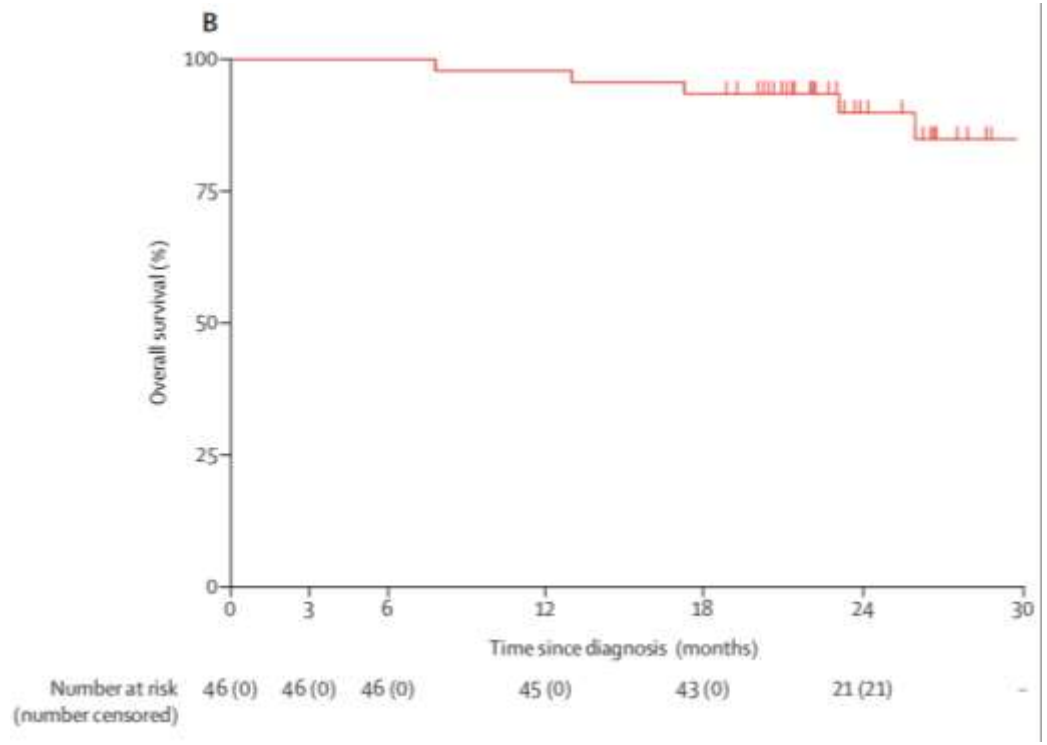
Primary endpoint was progression-free survival at 24 months
Secondary endpoints were overall survival at 3 years

Baseline demographics

- ECOG 0-1
- Included 77% of patients with N2 disease
- EGFR/ALK + patients were excluded

	Patients (n=46)
Age, years	63 (58–70)
Sex	
Male	34 (74%)
Female	12 (26%)
ECOG performance status	
0	25 (54%)
1	21 (46%)
Smoking status	
Former smoker (≥1 year)	25 (54%)
Current smoker	21 (46%)
Pack-years	49 (39–61)
Histology	
Adenocarcinoma	26 (57%)
Squamous cell carcinoma	16 (35%)
Not specified or undifferentiated	4 (9%)
Comorbidities	
Yes	43 (93%)
No	3 (7%)
Dyslipidaemia	16 (35%)
Hypertension	15 (33%)
Diabetes	9 (20%)
Chronic obstructive pulmonary disease	9 (20%)
Heart disease	7 (15%)
Hypercholesterolaemia	4 (9%)
Depressive disorder or anxiety	4 (9%)
Nephropathy	2 (4%)
Asthma	1 (2%)
Vasculopathy	1 (2%)
Tumour lesion size, mm	35 (23–60)
Nodal stage	
N0	9 (20%)
N1	3 (7%)
N2	34 (74%)
Single	9 (20%)
Multiple	25 (54%)
Tumour, Node, Metastasis staging classification	
T1N2M0	15 (33%)
T2N1M0	1 (2%)
T2N2M0	6 (13%)
T3N1M0	1 (2%)
T3N2M0	13 (28%)
T4N0M0	9 (20%)
T4N1M0	1 (2%)





PFS was 95·7% (95% CI 83·7–98·9) at 12 months , 87·0% (73·3–93·9) at 18 months, and **77·1% (59·9–87·7) at 24 months**

OS was 97·8% (95% CI 85·5–99·7) at 12 months, 93·5% (81·1–97·8) at 18 months, and **89·9% (74·5–96·2) at 24 months**

Adverse events

- 43/46 (93%) patients had TRAE's and 14 (30%) had ≥ grade 3
-
- None of the adverse events were associated with surgery delays or deaths

- The most common grade 3 TRAE's were increased lipase (three [7%]) and febrile neutropenia (three [7%]).

	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	43 (93%)	14 (30%)	2 (4%)
Asthenia or fatigue	23 (50%)	1 (2%)	0
Alopecia	16 (35%)	1 (2%)	0
Nausea	15 (33%)	0	0
Neurotoxicity	13 (28%)	2 (4%)	0
Arthralgia	12 (26%)	0	0
Diarrhoea	11 (24%)	0	0
Skin disorders (rash)	10 (22%)	1 (2%)	0
Myalgia	9 (20%)	0	0
Vomiting	8 (17%)	0	0
Decreased appetite or anorexia	8 (17%)	1 (2%)	0
Constipation	8 (17%)	0	0
Paraesthesia	8 (17%)	0	0
Pruritus	7 (15%)	0	0
Anaemia	7 (15%)	0	0
Increased aminotransferases	4 (9%)	1 (2%)	0
Neutropenia	2 (4%)	1 (2%)	1 (2%)
Increased serum amylase	1 (2%)	2 (4%)	0
Increased creatinine	1 (2%)	2 (4%)	0
Increased lipase	0	2 (4%)	1 (2%)
Febrile neutropenia	0	3 (7%)	0
Pemphigoid of the hand	0	1 (2%)	0

Data are n (%). Toxicity was monitored continuously for 100 days after the last dose of neoadjuvant nivolumab. No grade 5 treatment-related adverse events were observed.

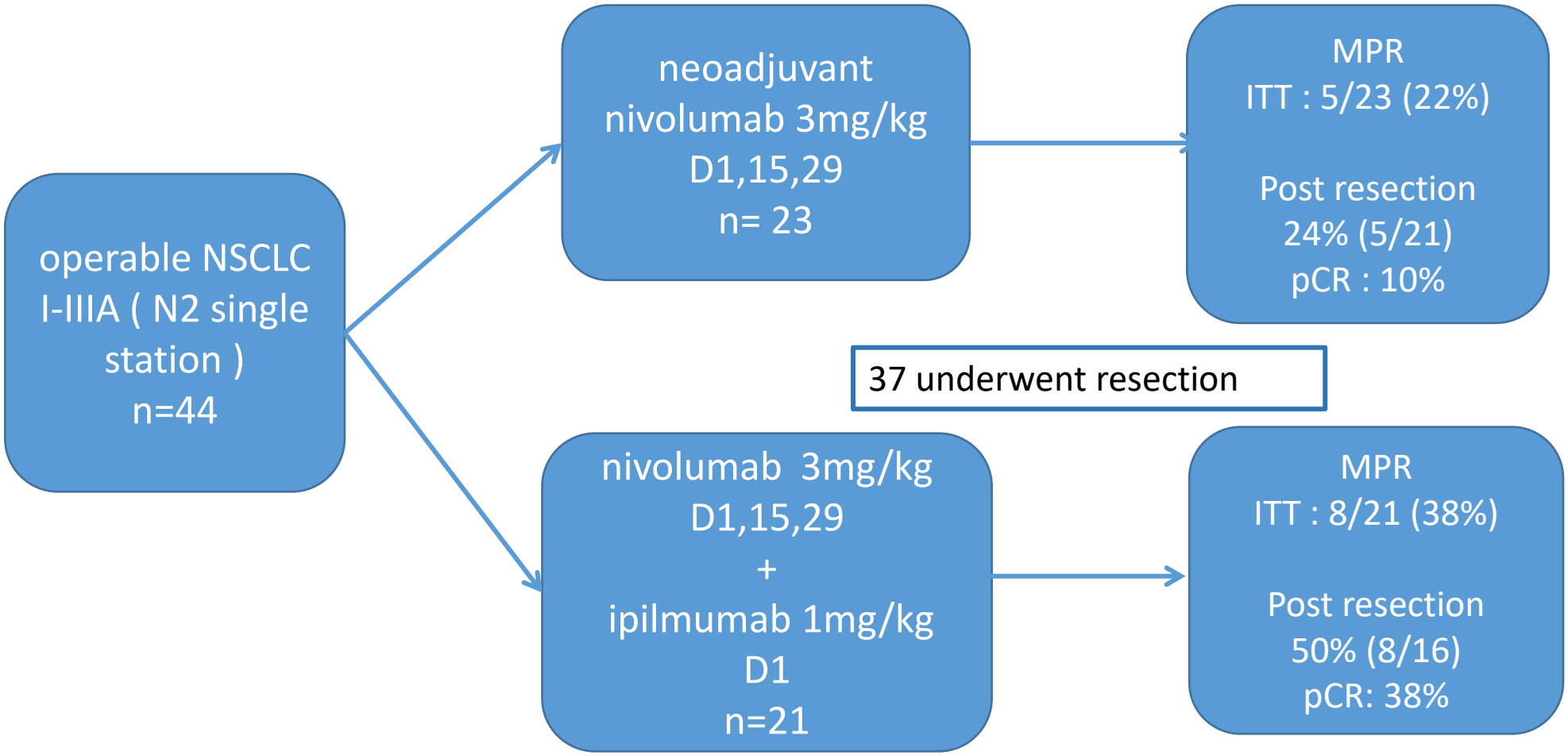
Table 2: **Treatment-related adverse events during neoadjuvant treatment in the modified intention-to-treat population (n=46)**

ARTICLES
https://doi.org/10.1038/s41591-020-01224-2
nature medicine

Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial

Cascone T, et al. Nat Med. 2021 Mar;27(3):504-514

Study design



☑ Met primary endpoint

- 39 (89%) patients underwent resection. None deferred due to TRAEs
- Compared to historical results of NACT (MPR -7-27%, pCR -4%), dual therapy had better MPR and pCR (however wide CI's). Hence, larger studies needed.
- 3 patients could not complete treatment , 1 in nivolumab group (grade III hypoxia due to large non-malignant effusion), 2 in dual group (grade III colitis and grade II pneumonitis)

nature medicine

ARTICLES

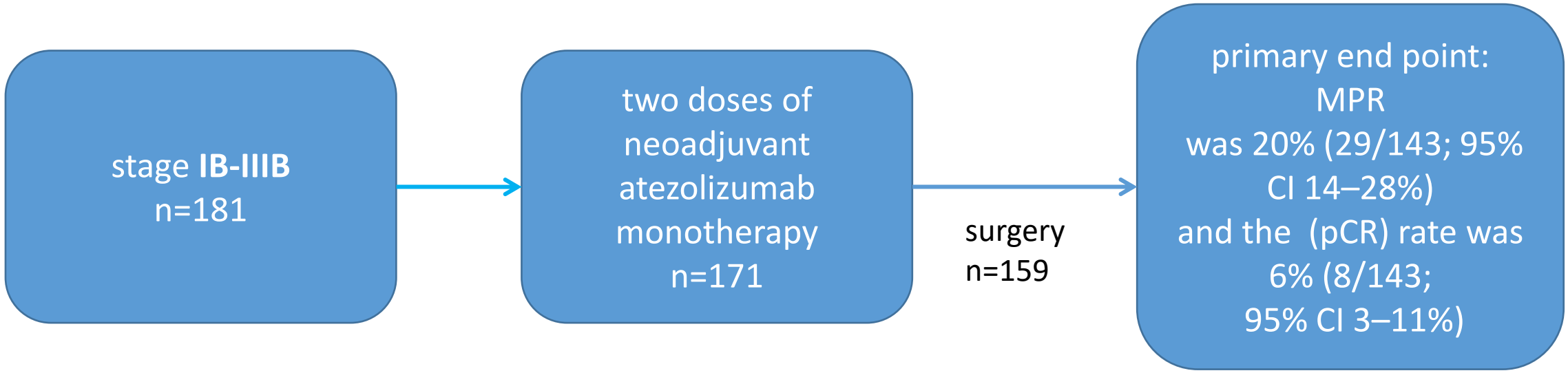
https://doi.org/10.1038/s41591-022-01962-5

Check for updates

OPEN

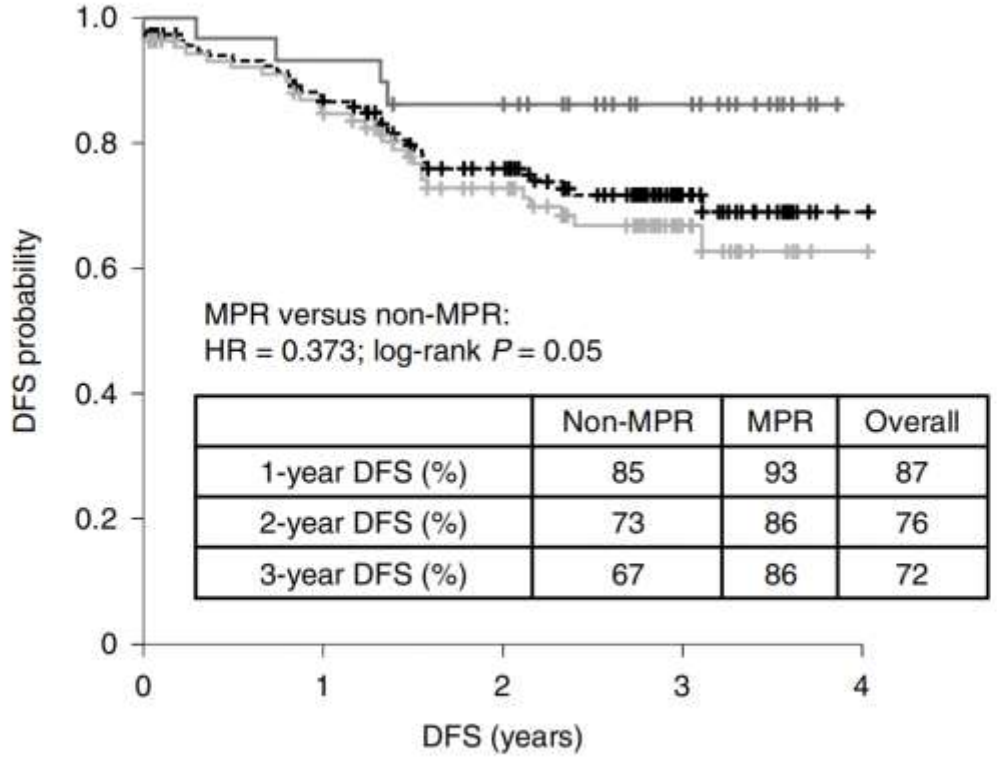
Neoadjuvant atezolizumab for resectable non-small cell lung cancer: an open-label, single-arm phase II trial

Study design



Surgery was accomplished in 159 patients, at a median time of 22 days after completion of ATZ, and the R0 resection rate was 92%.

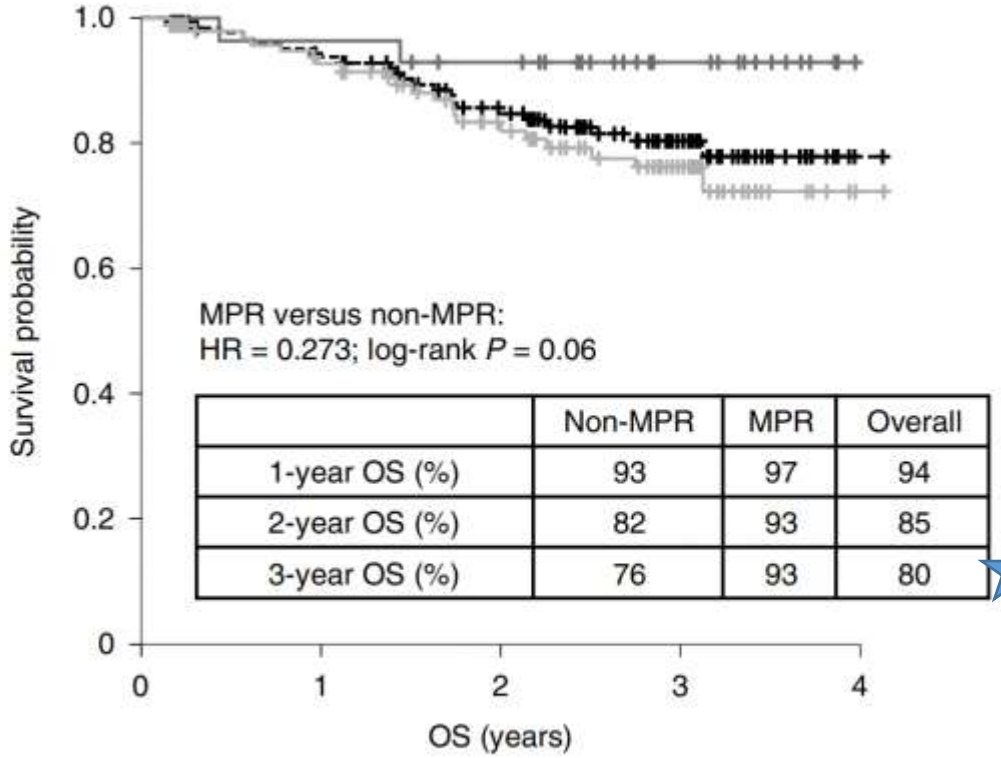
b



	Non-MPR	MPR	Overall
1-year DFS (%)	85	93	87
2-year DFS (%)	73	86	76
3-year DFS (%)	67	86	72

Overall	137	106	78	32	1
Non-MPR	108	79	54	19	1
MPR	29	27	24	13	0

c



	Non-MPR	MPR	Overall
1-year OS (%)	93	97	94
2-year OS (%)	82	93	85
3-year OS (%)	76	93	80

Overall	137	115	88	48	1
Non-MPR	108	87	63	35	1
MPR	29	28	25	13	0

Supplemental Table 4. Safety during the neoadjuvant phase.

	Patients (*N*=181)		
	Any grade, *n* (%)	**Grade 3–4, *n* (%)**	**Grade 5, *n* (%)**
Any AE[a]	175 (97)	65 (36)	3 (2)[c]
Fatigue	71 (39)	2(1)	0
Procedural pain	53 (29)	9 (5)	0
Dyspnea	38 (21)	5 (3)	0
Nausea	37 (20)	0	0
Constipation	36 (20)	0	0
Decreased appetite	29 (16)	0	0
Cough	29 (16)	0	0
Pyrexia	29 (16)	2 (1)	0
Headache	26 (14)	0	0
Diarrhea	24 (13)	5 (3)	0
Pruritus	19 (10)	0	0
Anemia	19 (10)	2 (1)	0
Treatment-related AE[a]	110 (61)	19 (10)[b]	1 (<1%)[c]
Fatigue	36 (20)	1 (<1)	0
Immune-mediated AE	75 (41)	17 (9)	1 (<1)[c]
Treatment-related	61 (34)	15 (8)	1 (<1)[c]
AE leading to treatment discontinuation	9 (5)	2 (1)	0

AE, adverse event.
[a]Preferred terms reported in ≥10% of patients are presented. [b]The following treatment-related grade ≥3 AEs were reported in >1 patient: pneumonitis (*n*=4), pneumonia (*n*=3), colitis (*n*=2), empyema (*n*=2), and respiratory failure (*n*=2). [c]Three deaths were reported within 90 days of neoadjuvant atezolizumab: sudden death not otherwise specified, death due to disease progression, and pneumonitis. Only pneumonitis was considered related to study treatment.

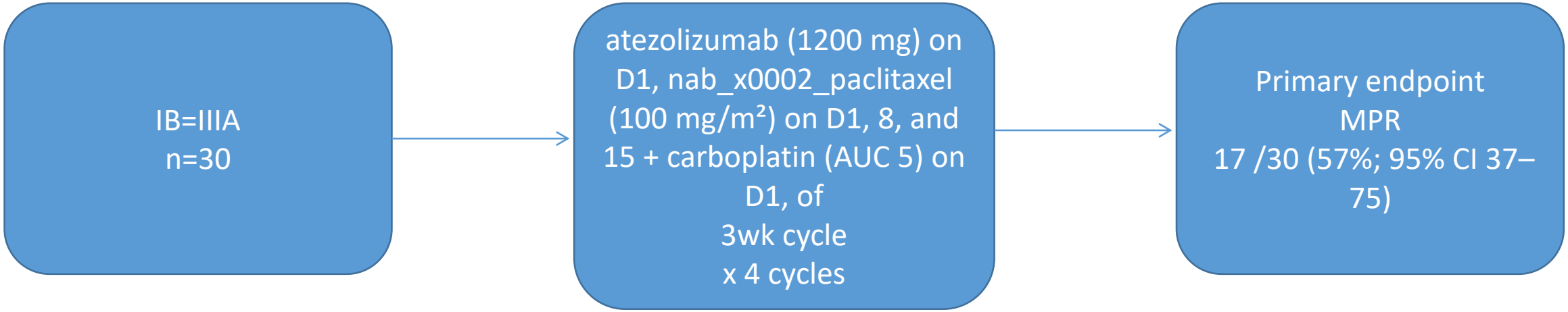
Immune-related AEs were reported in 75 (41%) patients, most commonly increases in AST (9%, n=16), ALT (8%, n=15), maculopapular rash (8%, n=15),

Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial

Catherine A Shu, Justin F Gainor, Mark M Awad, Codruta Chiuzan, Claud M Grigg, Aliyah Pabani, Robert F Garofano, Mark B Stoopler, Simon K Cheng, Abby White, Michael Lanuti, Frank D'Ovidio, Matthew Bacchetta, Joshua R Sonett, Anjali Saqi, Naiyer A Rizvi

Lancet Oncol 2020.S1470-2045(20)30146-7

Study design



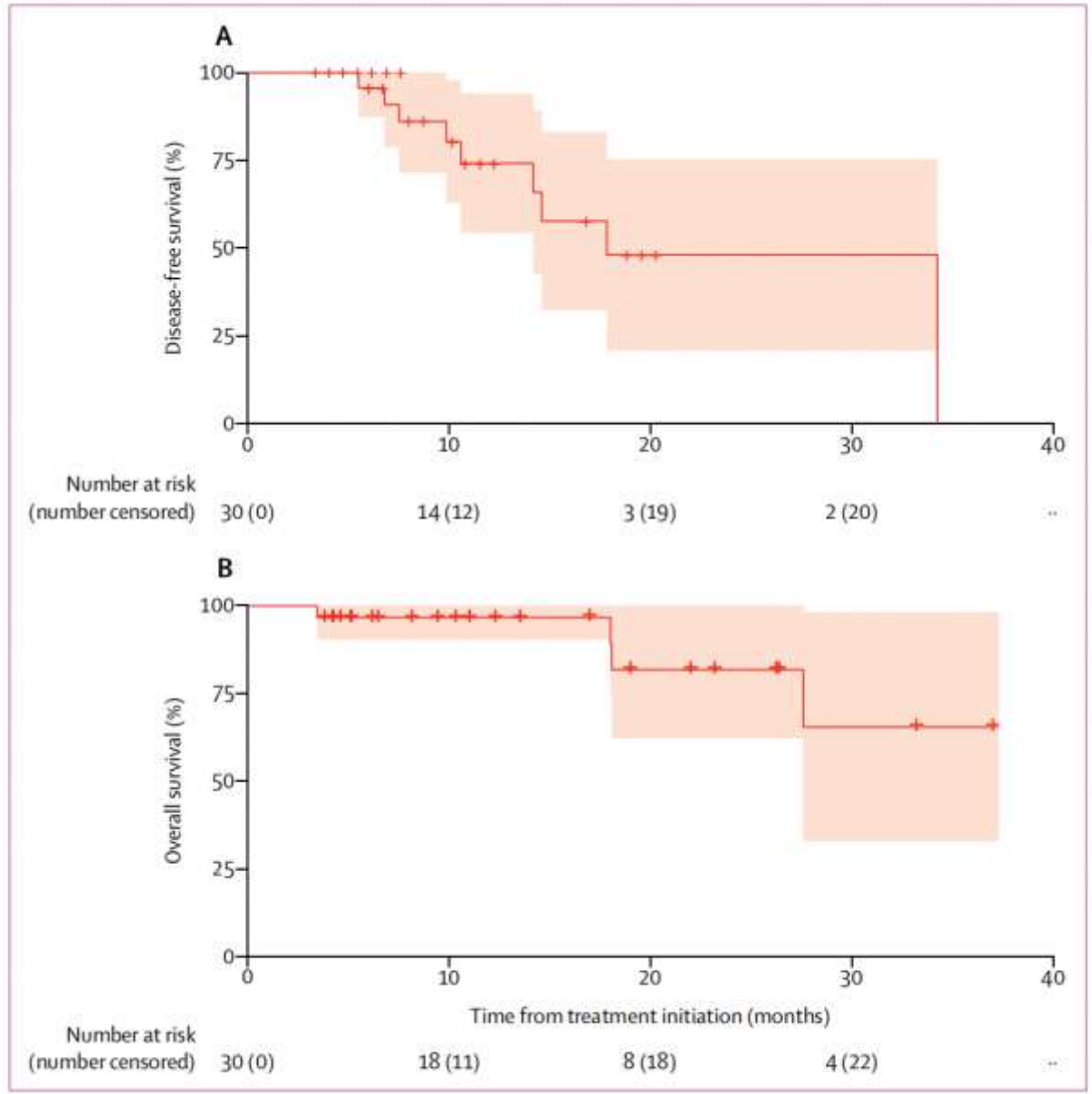


***Figure 2*: Kaplan-Meier survival curves**
(A) Disease-free survival. (B) Overall survival. Shaded areas represent 95% CIs.

Adverse events

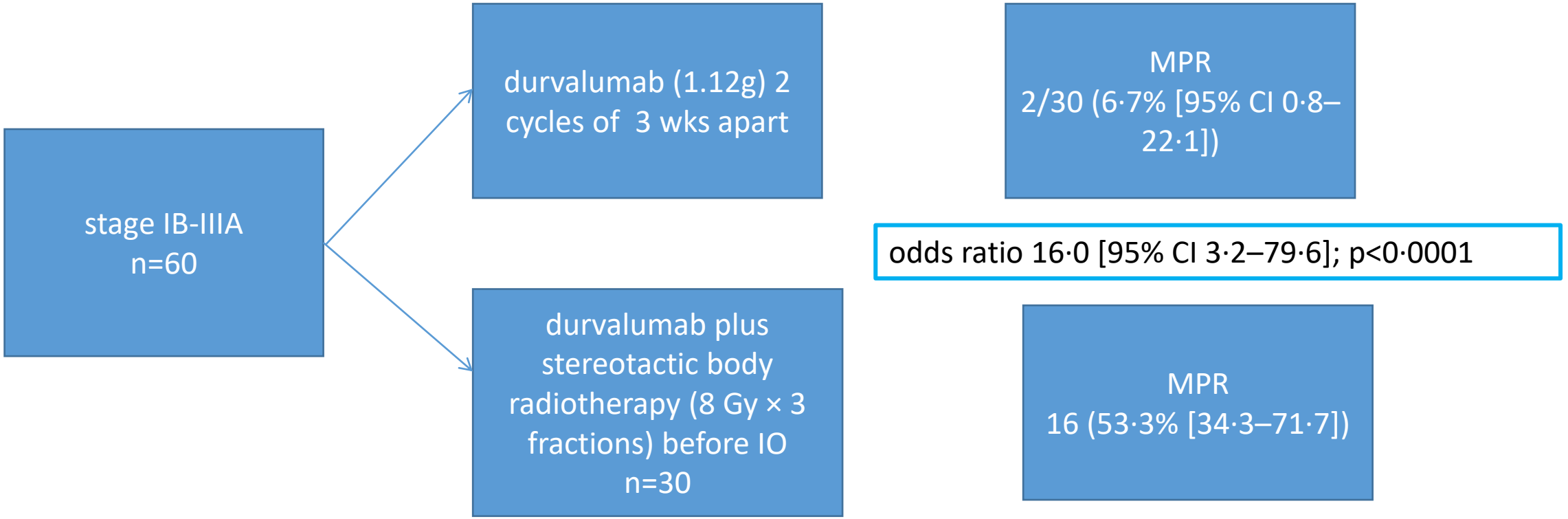
	Grade 1–2	Grade 3	Grade 4
Alanine aminotransferase increased*	4 (13%)	2 (7%)	0
Alopecia	14 (47%)	0	0
Anaemia	20 (67%)	1 (3%)	0
Anorexia	3 (10%)	0	0
Arthralgia or myalgia*	5 (17%)	0	0
Aspartate aminotransferase increased*	3 (10%)	2 (7%)	0
Constipation	7 (27%)	0	0
Diarrhoea*	8 (30%)	1 (3%)	0
Dysgeusia	7 (27%)	0	0
Dyspnoea	3 (10%)	0	0
Epistaxis	3 (10%)	0	0
Fatigue	16 (53%)	1 (3%)	0
Febrile neutropenia	0	1 (3%)	0
Fever	3 (10%)	0	0
Hyperglycaemia*	0	0	1 (3%)
Hyponatraemia	1 (3%)	1 (3%)	0
Hypomagnesaemia	3 (10%)	0	0
Hypophosphataemia	3 (10%)	0	0
Hypothyroidism*	3 (10%)	0	0
Mucositis oral	4 (13%)	0	0
Nausea	13 (43%)	0	0
Peripheral sensory neuropathy	5 (17%)	0	0
Neutropenia	11 (37%)	12 (40%)	3 (10%)
Paresthesia	3 (10%)	0	0
Rash	5 (17%)	0	0
Thrombocytopenia	17 (57%)	1 (3%)	1 (3%)
Vomiting	5 (17%)	0	0
Weight loss	1 (3%)	1 (3%)	0

Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial

Nasser K Altorki, Timothy E McGraw, Alain C Borczuk, Ashish Saxena, Jeffrey L Port, Brendon M Stiles, Benjamin E Lee, Nicholas J Sanfilippo, Ronald J Scheff, Bradley B Pua, James F Gruden, Paul J Christos, Cathy Spinelli, Joyce Gakuria, Manik Uppal, Bhavneet Binder, Olivier Elemento, Karla V Ballman, Silvia C Formenti

Lancet Oncol 2021; 22: 824–35

Study design



	Durvalumab monotherapy group (n=30)*				Durvalumab plus SBRT group (n=30)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Fatigue	8 (27%)	1 (3%)	0	0	14 (47%)	1 (3%)	0	0
Diarrhoea	6 (20%)	0	0	0	3 (10%)	0	0	0
Hyperlipasaemia	5 (17%)	0	0	0	3 (10%)	3 (10%)	0	0
Cough	0	0	0	0	7 (23%)	0	0	0
Constipation	4 (13%)	0	0	0	0	0	0	0
Back pain	3 (10%)	0	0	0	0	0	0	0
Hyponatraemia	0	3 (10%)	0	0	0	0	0	0
Nausea	3 (10%)	0	0	0	5 (17%)	0	0	0
Arthralgia	0	0	0	0	3 (10%)	0	0	0
Adrenal insufficiency	0	1 (3%)	0	0	0	0	0	0
Hyperuricaemia	0	1 (3%)	0	0	0	0	0	0
Myalgia	0	0	0	0	5 (17%)	0	0	0
Neutrophil count decreased	0	1 (3%)	0	0	0	0	0	0
Platelet count decreased	0	0	0	0	0	0	1 (3%)	0
Stroke	0	0	0	1 (3%)	0	0	0	0
Thromboembolic event	0	1 (3%)	0	0	0	1 (3%)	0	0
Anorexia	0	0	0	0	3 (10%)	0	0	0
Cardiopulmonary event	0	0	0	0	0	0	0	1 (3%)
Hepatitis	0	0	0	0	0	1 (3%)	0	0
Hyperglycaemia	0	0	0	0	0	2 (7%)	0	0

Data are n (%). Grade 1–2 adverse events were with an incidence of 10% or more in each treatment group and all grade 3–5 adverse events are listed in descending order of frequency. SBRT=stereotactic body radiotherapy. *Some patients had more than one adverse event.

***Table 4*: Adverse events during neoadjuvant treatment**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2022 VOL. 386 NO. 21

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

n engl j med 386;21

Study design

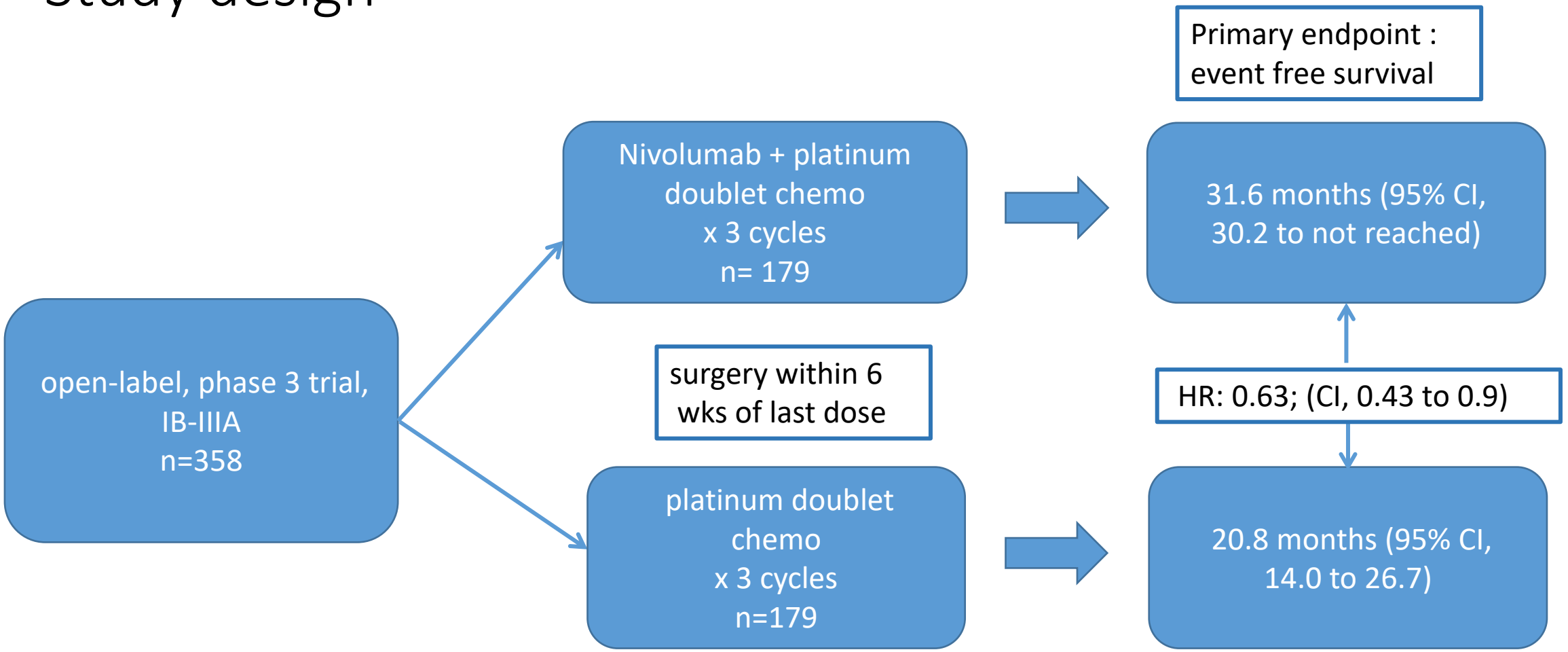
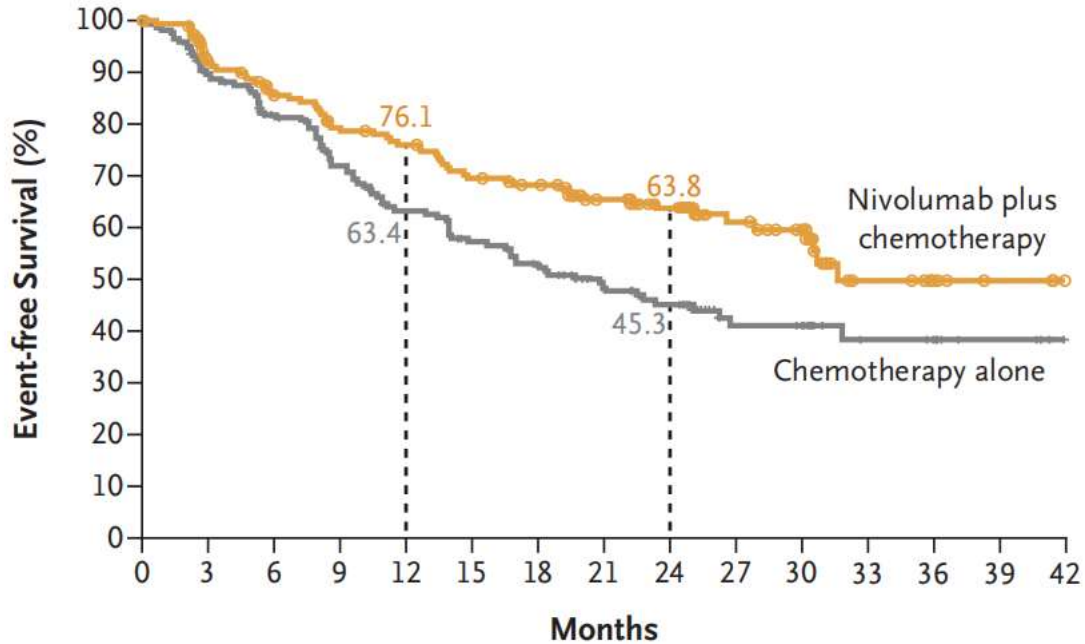


Table 1. Characteristics of the Patients at Baseline.

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)

Table S5. Surgical Outcomes Summary.

	Nivolumab plus Chemotherapy (N = 179)	Chemotherapy (N = 179)
Patients with definitive surgery* — no. (%)	149 (83.2)	135 (75.4)
Time from last neoadjuvant dose to definitive surgery — wk		
Median (IQR)	5.3 (4.6–6.0)	5.0 (4.6–5.9)
Patients with cancelled definitive surgery — no. (%)	28 (15.6)	37 (20.7)
Disease progression	12 (6.7)	17 (9.5)
Adverse event	2 (1.1)	1 (0.6)
Other†	14 (7.8)	19 (10.6)
Patients with delayed surgery‡,§ — no. (%)	31 (20.8)	24 (17.8)
Administrative reason	17 (11.4)	8 (5.9)
Adverse event	6 (4.0)	9 (6.7)
Other	8 (5.4)	7 (5.2)
Length of delay in surgery — wk		
Median (IQR)	2.0 (0.6–3.0)	2.4 (1.0–3.7)
Of patients with delayed surgery, proportion no. (%) with delay of¶		
≤2 wk	17 (54.8)	11 (45.8)
>2 and ≤4 wk	8 (25.8)	8 (33.3)
>4 and ≤6 wk	3 (9.7)	2 (8.3)
>6 wk	3 (9.7)	3 (12.5)
Duration of surgery‖ — min		
Median (IQR)	185.0 (133.0–260.0)	213.5 (150.0–283.0)
Surgical approach§ — no. (%)		
Thoracotomy	88 (59.1)	85 (63.0)
Minimally invasive**	44 (29.5)	29 (21.5)
Minimally invasive to thoracotomy	17 (11.4)	21 (15.6)
Type of surgery§,†† — no. (%)		
Lobectomy	115 (77.2)	82 (60.7)
Sleeve lobectomy	2 (1.3)	10 (7.4)
Bilobectomy	3 (2.0)	4 (3.0)
Pneumonectomy	25 (16.8)	34 (25.2)
Other	24 (16.1)	21 (15.6)
Completeness of resection§ — no. (%)		
R0 (no residual tumor)	124 (83.2)	105 (77.8)
R1 (microscopic residual tumor)	16 (10.7)	21 (15.6)
R2 (macroscopic residual tumor)	5 (3.4)	4 (3.0)
Rx (unknown)	4 (2.7)	5 (3.7)
Sampled lymph nodes — median (IQR)	19 (12–25)	18.5 (10–26)
Median length of hospital stay — days (IQR)	10.0 (7.0–14.0)	10.0 (7.0–15.0)
Median length of hospital stay by surgery type — days (IQR)		
Lobectomy	10.0 (7.0–15.0)	9.0 (6.0–14.0)
Pneumonectomy	10.0 (8.0–13.0)	11.0 (9.0–16.0)
Other‡‡	8.5 (4.0–13.0)	9.0 (7.0–14.0)

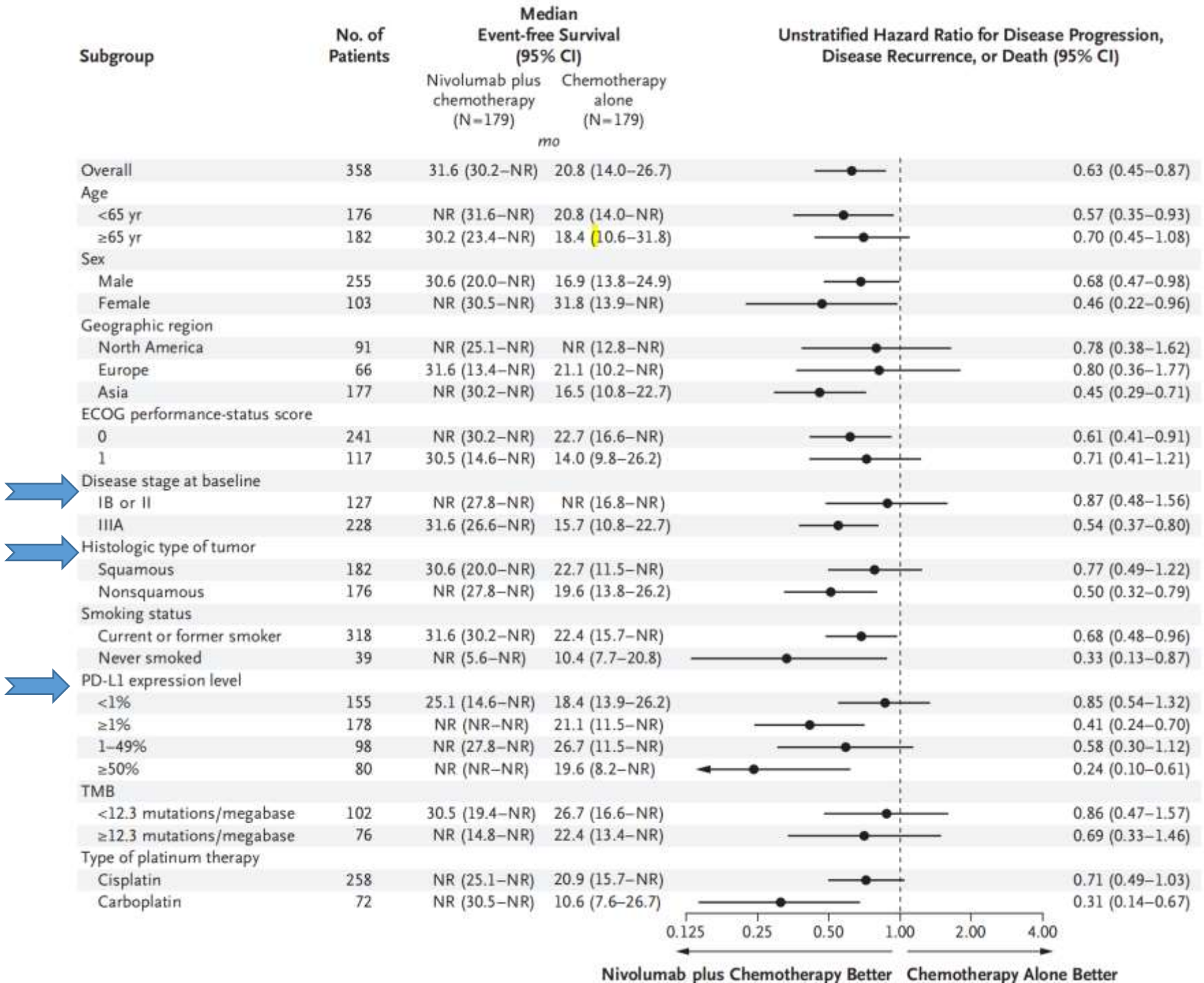


	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

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


Subgroup
No. of Patients
Median Event-free Survival (95% CI)
Nivolumab plus chemotherapy (N=179)
Chemotherapy alone (N=179)
mo
Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
Overall 358 31.6 (30.2–NR) 20.8 (14.0–26.7) 0.63 (0.45–0.87)
Age
<65 yr 176 NR (31.6–NR) 20.8 (14.0–NR) 0.57 (0.35–0.93)
≥65 yr 182 30.2 (23.4–NR) 18.4 (10.6–31.8) 0.70 (0.45–1.08)
Sex
Male 255 30.6 (20.0–NR) 16.9 (13.8–24.9) 0.68 (0.47–0.98)
Female 103 NR (30.5–NR) 31.8 (13.9–NR) 0.46 (0.22–0.96)
Geographic region
North America 91 NR (25.1–NR) NR (12.8–NR) 0.78 (0.38–1.62)
Europe 66 31.6 (13.4–NR) 21.1 (10.2–NR) 0.80 (0.36–1.77)
Asia 177 NR (30.2–NR) 16.5 (10.8–22.7) 0.45 (0.29–0.71)
ECOG performance-status score
0 241 NR (30.2–NR) 22.7 (16.6–NR) 0.61 (0.41–0.91)
1 117 30.5 (14.6–NR) 14.0 (9.8–26.2) 0.71 (0.41–1.21)
Disease stage at baseline
IB or II 127 NR (27.8–NR) NR (16.8–NR) 0.87 (0.48–1.56)
IIIA 228 31.6 (26.6–NR) 15.7 (10.8–22.7) 0.54 (0.37–0.80)
Histologic type of tumor
Squamous 182 30.6 (20.0–NR) 22.7 (11.5–NR) 0.77 (0.49–1.22)
Nonsquamous 176 NR (27.8–NR) 19.6 (13.8–26.2) 0.50 (0.32–0.79)
Smoking status
Current or former smoker 318 31.6 (30.2–NR) 22.4 (15.7–NR) 0.68 (0.48–0.96)
Never smoked 39 NR (5.6–NR) 10.4 (7.7–20.8) 0.33 (0.13–0.87)
PD-L1 expression level
<1% 155 25.1 (14.6–NR) 18.4 (13.9–26.2) 0.85 (0.54–1.32)
≥1% 178 NR (NR–NR) 21.1 (11.5–NR) 0.41 (0.24–0.70)
1–49% 98 NR (27.8–NR) 26.7 (11.5–NR) 0.58 (0.30–1.12)
≥50% 80 NR (NR–NR) 19.6 (8.2–NR) 0.24 (0.10–0.61)
TMB
<12.3 mutations/megabase 102 30.5 (19.4–NR) 26.7 (16.6–NR) 0.86 (0.47–1.57)
≥12.3 mutations/megabase 76 NR (14.8–NR) 22.4 (13.4–NR) 0.69 (0.33–1.46)
Type of platinum therapy
Cisplatin 258 NR (25.1–NR) 20.9 (15.7–NR) 0.71 (0.49–1.03)
Carboplatin 72 NR (30.5–NR) 10.6 (7.6–26.7) 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

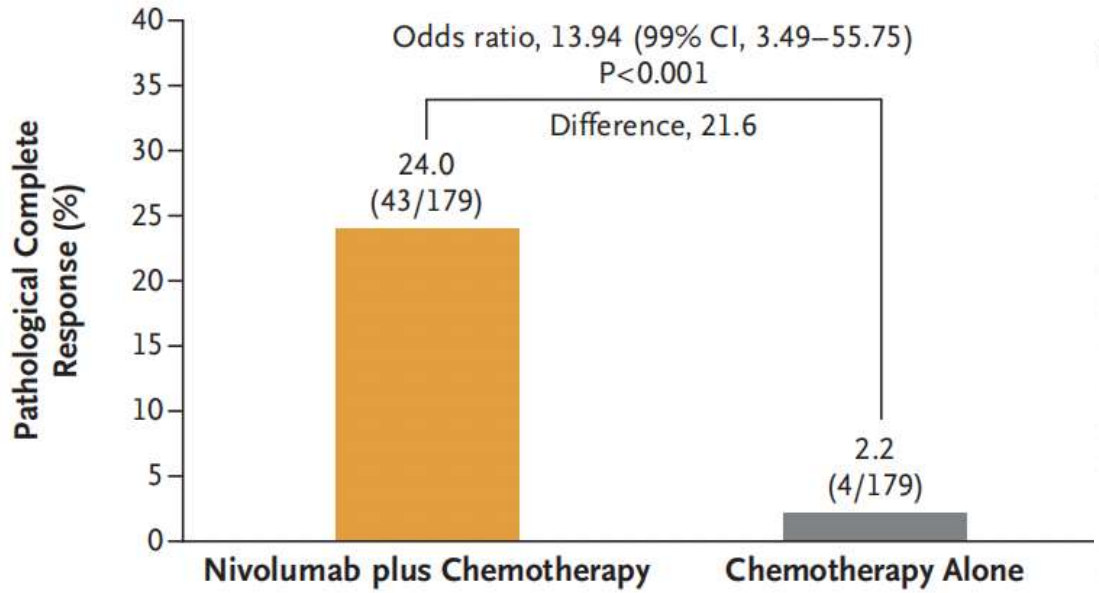
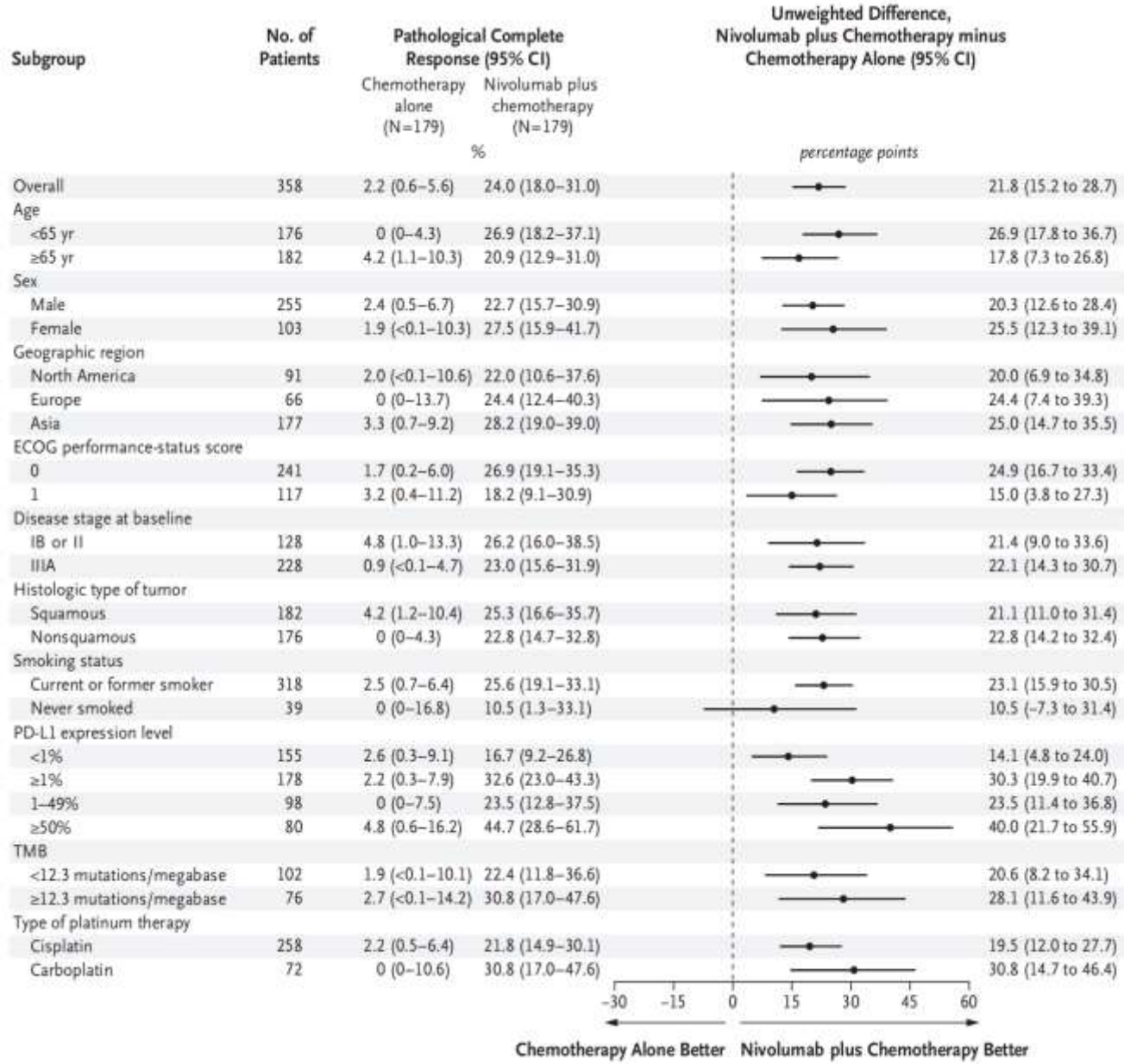
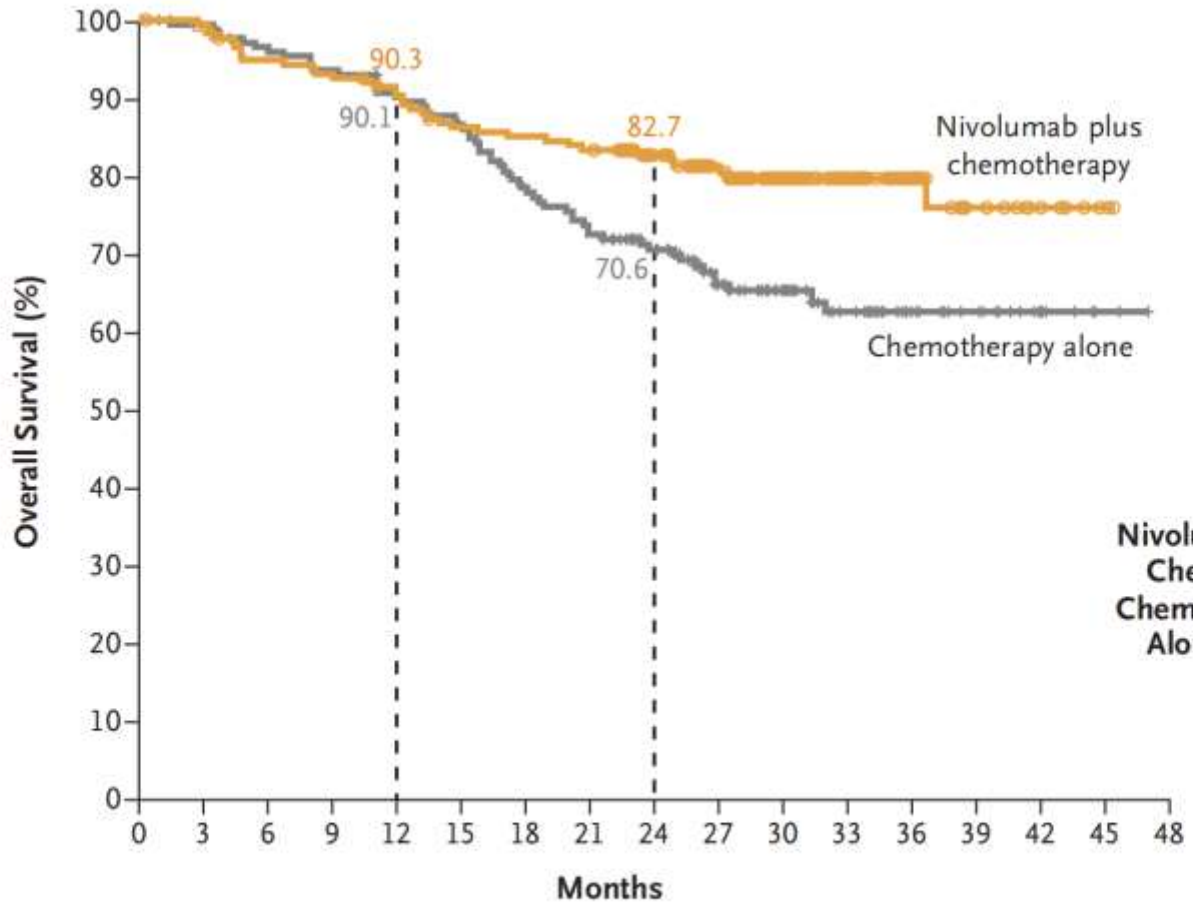


Table S8. Pathological Response in Patients Who Underwent Resection.*

	Nivolumab plus Chemotherapy (N = 141)	Chemotherapy (N = 126)
	number of patients (percent) (95% CI)	
pCR†	43 (30.5) (23.0–38.8)	4 (3.2) (0.9–7.9)
MPR‡	66 (46.8) (38.4–55.4)	16 (12.7) (7.4–19.8)





	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

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)

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

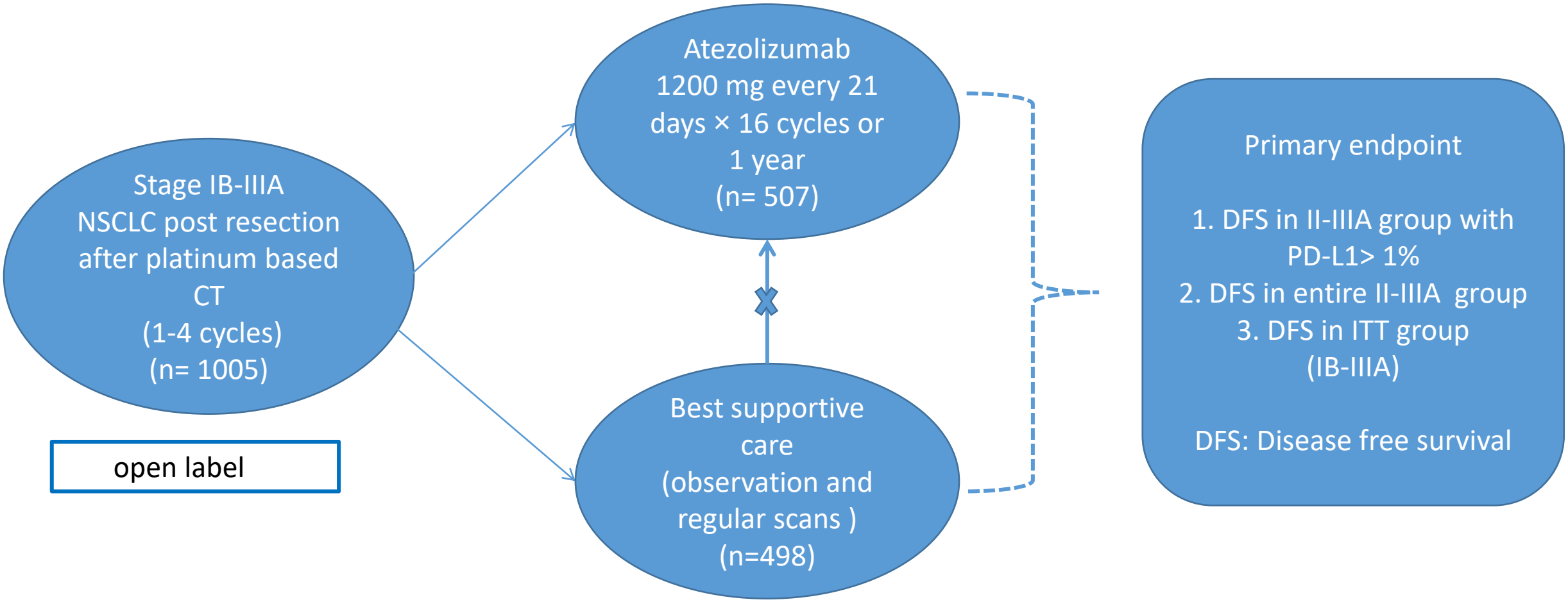
Role of IO as adjuvant therapy

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

*Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators**

Lancet 2021; 398: 1344–57

Study design



open label

Inclusion criteria : R0 resection, ECOG 0-1, surgery before 28-84 days of enrolment

EGFR /ALK positive cases were allowed

Baseline demographics

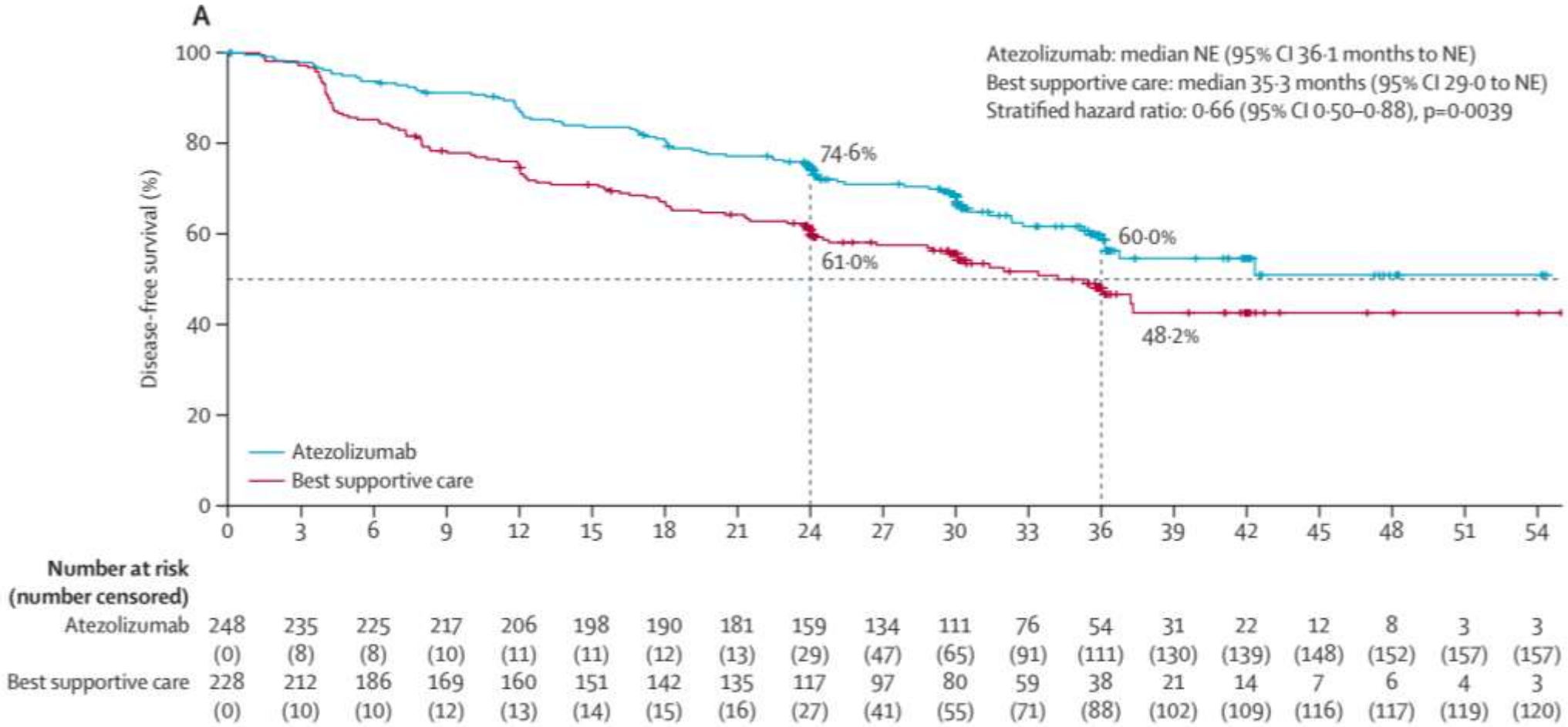
	PD-L1 TC ≥1% stage II–IIIA group (SP263)		All stage II–IIIA group		Intention-to-treat group (stage IB–IIIA)	
	Atezolizumab (n=248)	Best supportive care (n=228)	Atezolizumab (n=442)	Best supportive care (n=440)	Atezolizumab (n=507)	Best supportive care (n=498)
Age, years	61 (56–67)	62 (56–68)	62 (56–67)	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%)

	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)
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%)

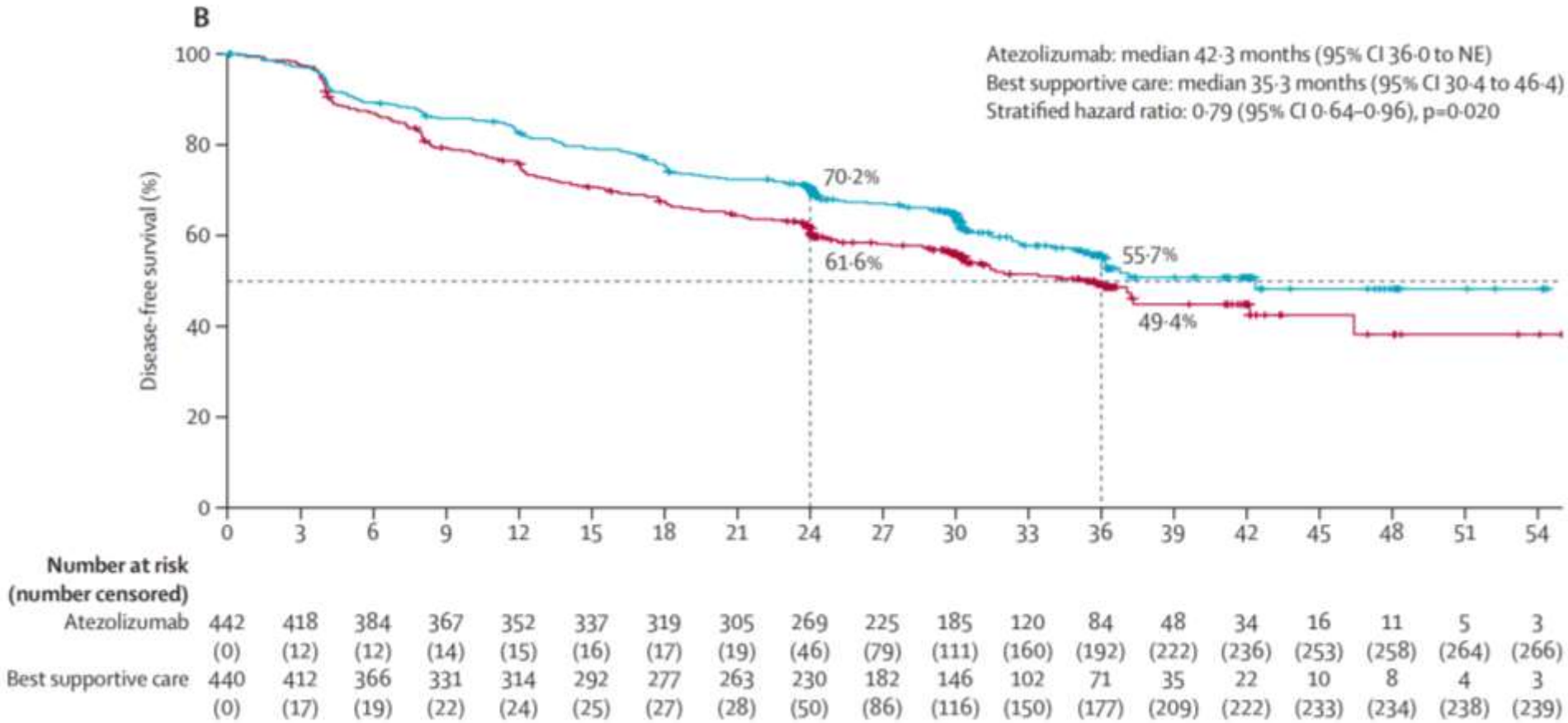
Results

- At a median follow-up of 32·2 months, atezolizumab improved DFS vs BSC in patients in the stage II–IIIA (PD-L1 > 1%) (HR 0·66; 95% CI 0·50–0·88) and in all patients in stage II–IIIA group (0·79; 0·64–0·96; p=0·020).
- In the ITT population, HR for DFS was 0·81 (0·67–0·99; p=0·040).
- The 3-year DFS rates were 60% in the atezolizumab group and 48% in the BSC care group
- For the secondary endpoint of DFS in patients stage II–IIIA group with PD-L1 on 50% or more, HR was 0·43 (95% CI 0·27–0·68)
- Atezolizumab-related grade 3 and 4 adverse events occurred in 53 (11%) of 495 patients and grade 5 events in four patients (1%).

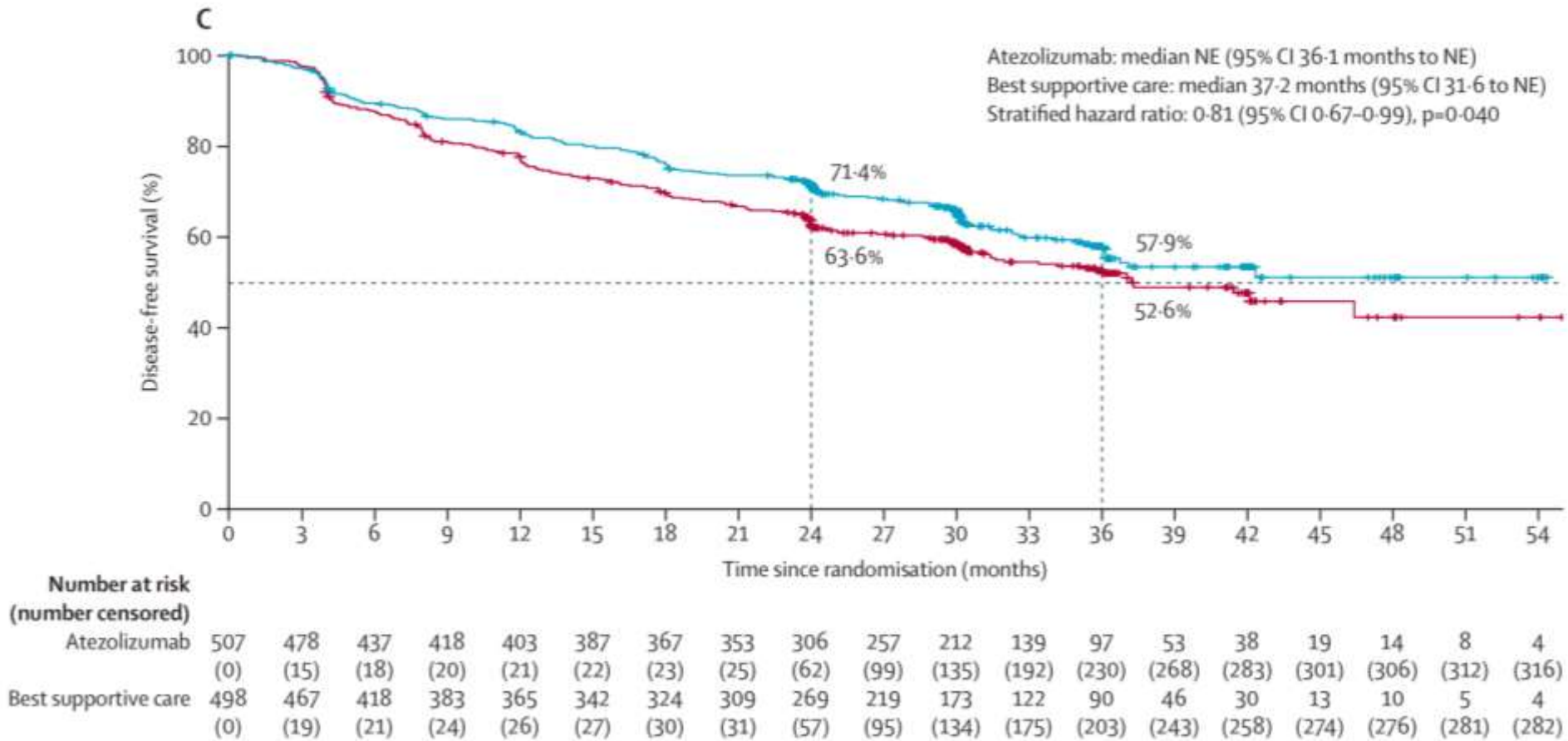
Results



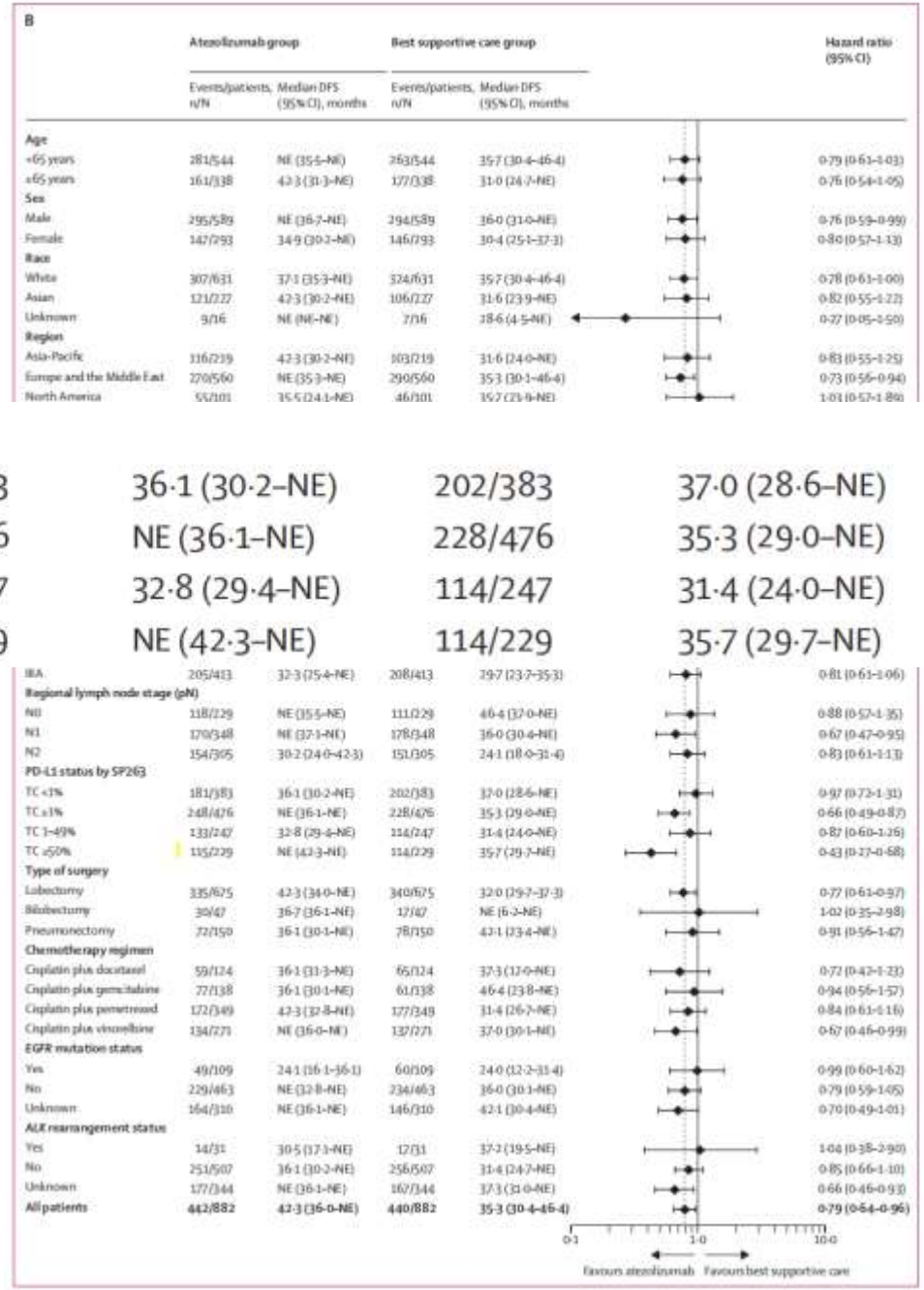
Disease free survival in stage II-IIIA with PD-L1 >1%



Disease free survival in all stage II-IIIA patients

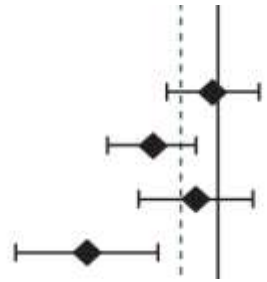


Disease free survival in ITT population



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)



Adverse events

	Atezolizumab group (n=495)			Best supportive care group (n=495)		
	All grades	Grade 3–4	Grade 5	All grades	Grade 3–4	Grade 5
Any cause	459 (93%)	108 (22%)	8 (2%)†	350 (71%)	57 (12%)	3 (1%)‡
Cough	66 (13%)	0	0	46 (9%)	0	0
Pyrexia	65 (13%)	4 (1%)	0	11 (2%)	1 (<1%)	0
Hypothyroidism	55 (11%)	0	0	3 (1%)	0	0
Alanine aminotransferase increased	53 (11%)	8 (2%)	0	16 (3%)	1 (<1%)	0
Aspartate aminotransferase increased	53 (11%)	7 (1%)	0	16 (3%)	0	0
Arthralgia	52 (11%)	2 (<1%)	0	26 (5%)	0	0
Pruritus	51 (10%)	0	0	3 (1%)	0	0
Nasopharyngitis	33 (7%)	0	0	50 (10%)	0	0

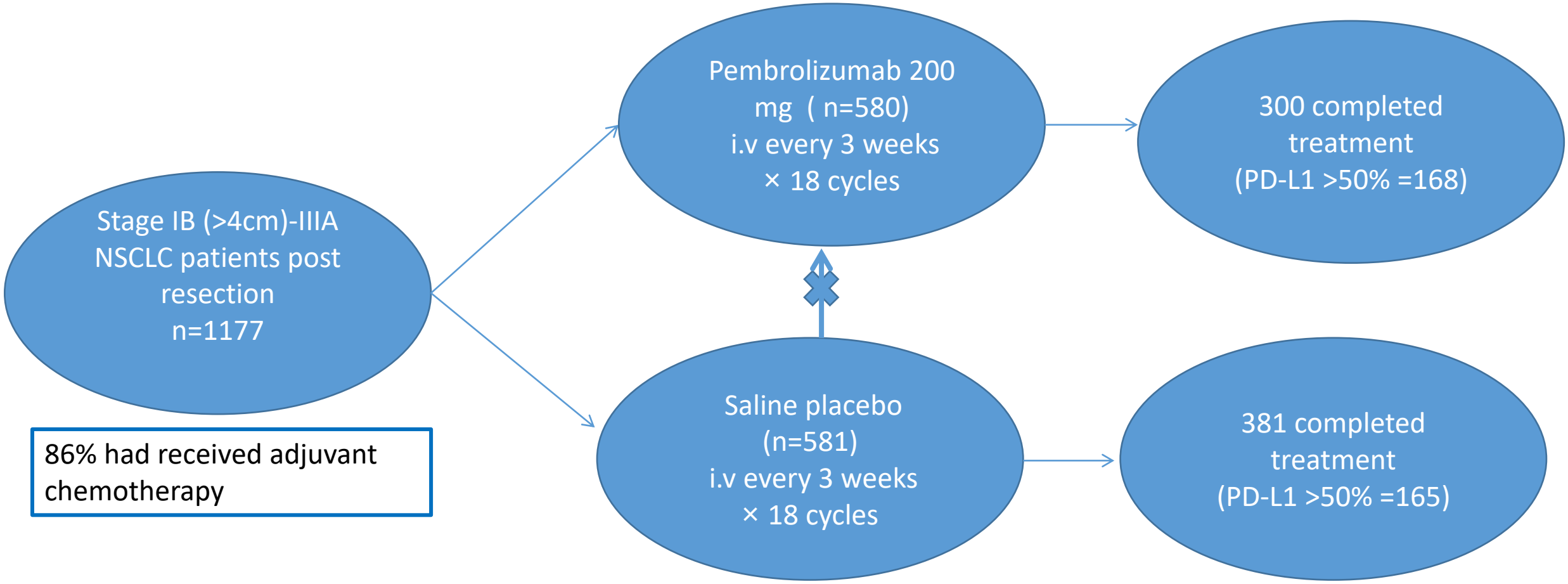
	Atezolizumab group (n=495)	Best supportive care group (n=495)
Adverse event		
Any grade	459 (93%)	350 (71%)
Grade 3–4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
Immune-mediated adverse events		
Any grade	256 (52%)	47 (9%)
Grade 3–4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial

Mary O'Brien, Luis Paz-Ares*, Sandrine Marreaud, Urania Dafni, Kersti Oselin, Libor Havel, Emilio Esteban, Dolores Isla, Alex Martinez-Marti, Martin Faehling, Masahiro Tsuboi, Jong-Seok Lee, Kazuhiko Nakagawa, Jing Yang, Ayman Samkari, Steven M Keller, Murielle Mauer, Nitish Jha, Rolf Stahel, Benjamin Besse†, Solange Peters†, on behalf of the EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators‡*

Lancet Oncol 2022; 23: 1274–86

Study design



86% had received adjuvant chemotherapy

Inclusion criteria : R0 resection, no N2 disease, known PD-L1 status , no previous radiotherapy
No evidence of disease within 3 months of surgery(CT chest + abdomen + brain)
EGFR/ALK testing not mandatory

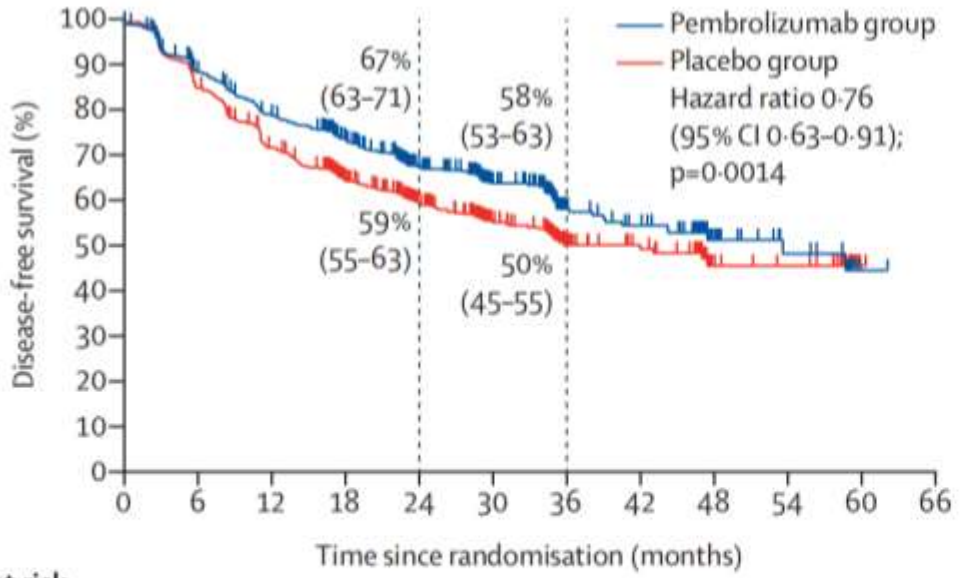
Baseline characteristics

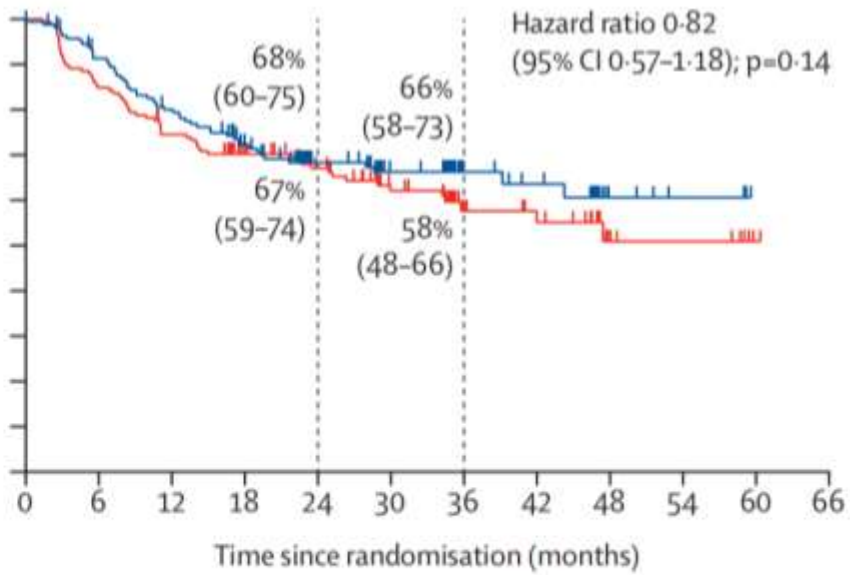
	Overall intention-to-treat population		PD-L1 TPS of ≥50% population	
	Pembrolizumab group (n=590)	Placebo group (n=587)	Pembrolizumab group (n=168)	Placebo group (n=165)
Age, years	65·0 (59·0–70·0)	65·0 (59·0–70·0)	64·5 (60·0–69·5)	65·0 (58·0–71·0)
<65	285 (48%)	273 (47%)	84 (50%)	82 (50%)
≥65	305 (52%)	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)

Results

Primary endpoint : Disease-free survival in the overall population and in the population with PD-L1 tumour proportion score (TPS) of 50% or greater



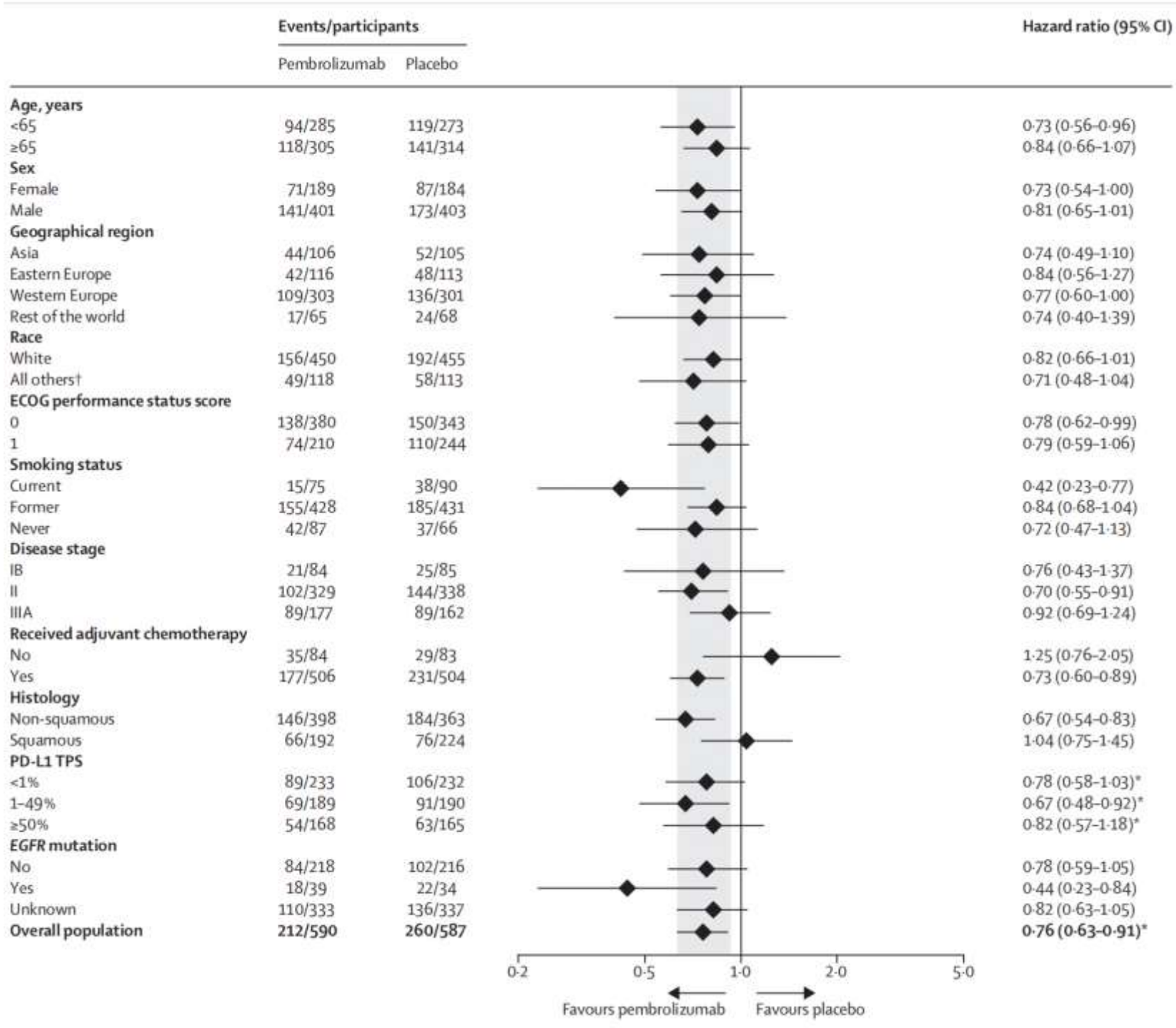


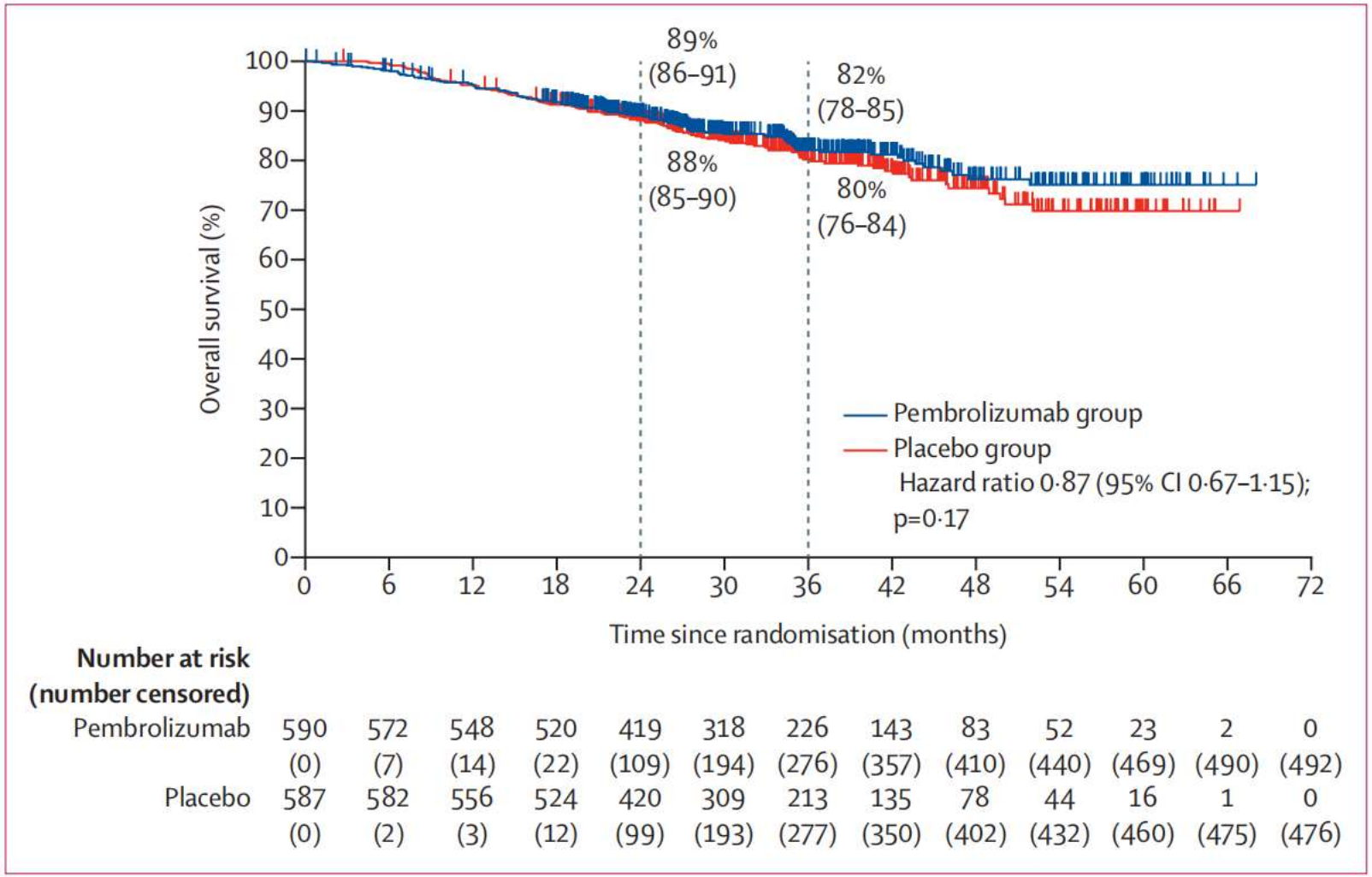
Number at risk (number censored)												
Pembrolizumab	590	493	434	358	264	185	82	70	28	16	1	0
	(0)	(30)	(36)	(84)	(150)	(216)	(306)	(313)	(352)	(363)	(377)	(378)
Placebo	587	493	409	326	241	160	72	57	22	18	1	0
	(0)	(5)	(13)	(56)	(118)	(183)	(259)	(273)	(305)	(309)	(326)	(327)

168	145	126	99	69	50	26	22	7	4	0	0
(0)	(8)	(9)	(24)	(49)	(66)	(90)	(93)	(107)	(110)	(114)	(114)
165	140	121	100	75	54	28	22	8	6	1	0
(0)	(0)	(2)	(16)	(37)	(53)	(76)	(81)	(94)	(96)	(101)	(102)

overall ITT

PD-L1 ≥ 50%


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



Number at risk (number censored)													
Pembrolizumab	590	572	548	520	419	318	226	143	83	52	23	2	0
	(0)	(7)	(14)	(22)	(109)	(194)	(276)	(357)	(410)	(440)	(469)	(490)	(492)
Placebo	587	582	556	524	420	309	213	135	78	44	16	1	0
	(0)	(2)	(3)	(12)	(99)	(193)	(277)	(350)	(402)	(432)	(460)	(475)	(476)

Figure 3: **Kaplan-Meier estimate of overall survival in the intention-to-treat population**

Adverse events

	Pembrolizumab group (n=580)				Placebo group (n=581)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	358 (62%)	166 (29%)	21 (4%)	11 (2%)	379 (65%)	130 (22%)	14 (2%)	6 (1%)
Increased bodyweight	127 (22%)	6 (1%)	0	0	159 (27%)	9 (2%)	0	0
Pruritus	124 (21%)	1 (<1%)	0	0	72 (12%)	2 (<1%)	0	0
Hypothyroidism	119 (21%)	1 (<1%)	0	0	27 (5%)	0	0	0
Arthralgia	104 (18%)	4 (1%)	0	0	74 (13%)	1 (<1%)	0	0
Diarrhoea	99 (17%)	7 (1%)	0	0	81 (14%)	2 (<1%)	0	0
Fatigue	95 (16%)	1 (<1%)	0	0	86 (15%)	3 (1%)	0	0
Cough	86 (15%)	1 (<1%)	0	0	98 (17%)	0	0	0
Hypertension	32 (6%)	35 (6%)	0	0	42 (7%)	32 (6%)	0	0
Dyspnoea	58 (10%)	8 (1%)	0	0	65 (11%)	7 (1%)	0	0
Hyperthyroidism	61 (11%)	1 (<1%)	0	0	17 (3%)	0	0	0
Upper respiratory tract infection	53 (9%)	0	0	0	55 (9%)	0	0	0
Nausea	51 (9%)	1 (<1%)	0	0	37 (6%)	0	0	0
Nasopharyngitis	50 (9%)	0	0	0	32 (6%)	0	0	0
Rash	47 (8%)	2 (<1%)	0	0	29 (5%)	0	0	0
Increased alanine aminotransferase	42 (7%)	4 (1%)	0	0	31 (5%)	3 (1%)	0	0
Back pain	44 (8%)	1 (<1%)	0	0	46 (8%)	0	0	0
Headache	43 (7%)	2 (<1%)	0	0	45 (8%)	1 (<1%)	0	0
Asthenia	41 (7%)	3 (1%)	0	0	29 (5%)	3 (1%)	0	0
Maculopapular rash	40 (7%)	3 (1%)	0	0	20 (3%)	0	0	0
Increased aspartate aminotransferase	39 (7%)	2 (<1%)	0	0	28 (5%)	4 (1%)	0	0
Decreased appetite	40 (7%)	1 (<1%)	0	0	26 (4%)	1 (<1%)	0	0
Decreased bodyweight	39 (7%)	0	0	0	25 (4%)	0	0	0
Increased blood creatinine	38 (7%)	0	0	0	32 (6%)	0	0	0
Myalgia	35 (6%)	2 (<1%)	0	0	15 (3%)	0	0	0
Productive cough	37 (6%)	0	0	0	15 (3%)	0	0	0
Constipation	35 (6%)	0	0	0	41 (7%)	0	0	0
Influenza-like illness	34 (6%)	0	0	0	32 (6%)	0	0	0
Pneumonitis	27 (5%)	5 (1%)	2 (<1%)	0	12 (2%)	4 (1%)	0	0
Pyrexia	31 (5%)	1 (<1%)	0	0	33 (6%)	1 (<1%)	0	0
Dry skin	31 (5%)	0	0	0	21 (4%)	0	0	0
Pain in extremity	18 (3%)	0	0	0	30 (5%)	1 (<1%)	0	0
Paraesthesia	18 (3%)	0	0	0	32 (6%)	0	0	0

Data are n (%).

Table 2: **Adverse events of any cause and grade that occurred in ≥5% of participants in either treatment group in the safety population**

	Pembrolizumab group (n=580)				Placebo group (n=581)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	180 (31%)	38 (7%)	6 (1%)	2 (<1%)	64 (11%)	11 (2%)	0	0
Hypothyroidism	119 (21%)	1 (<1%)	0	0	27 (5%)	0	0	0
Hyperthyroidism	61 (11%)	1 (<1%)	0	0	17 (3%)	0	0	0
Pneumonitis	32 (6%)	6 (1%)	2 (<1%)	0	13 (2%)	4 (1%)	0	0
Severe skin reactions	5 (1%)	11 (2%)	0	0	2 (<1%)	2 (<1%)	0	0
Colitis	10 (2%)	4 (1%)	0	0	4 (1%)	1 (<1%)	0	0
Adrenal insufficiency	6 (1%)	4 (1%)	0	0	0	0	0	0
Hepatitis	1 (<1%)	5 (1%)	4 (1%)	0	2 (<1%)	2 (<1%)	0	0
Hypophysitis	4 (1%)	3 (1%)	0	0	0	0	0	0
Thyroiditis	6 (1%)	0	0	0	1 (<1%)	0	0	0
Infusion reactions	5 (1%)	0	0	0	4 (1%)	0	0	0
Myocarditis	1 (<1%)	2 (<1%)	0	2 (<1%)	0	1 (<1%)	0	0
Nephritis	4 (1%)	0	0	0	0	0	0	0
Pancreatitis	2 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Myositis	1 (<1%)	0	0	0	0	0	0	0
Sarcoidosis	0	1 (<1%)	0	0	0	0	0	0
Type 1 diabetes	0	1 (<1%)	0	0	0	0	0	0
Vasculitis	0	1 (<1%)	0	0	0	0	0	0

Data are n (%). Potentially immune-mediated adverse events and infusion reactions were based on a list of terms prepared by the sponsor and were considered regardless of attribution to trial treatment by the investigator. In addition to the specific preferred terms listed, related terms were included.

***Table 3*: Potentially immune-mediated adverse events and infusion reactions of any incidence in the safety population**

KEYNOTE-091

- Adjuvant chemotherapy not mandatory
- Triple blind , placebo controlled
- Stage III (only 30%)
- Similar benefit across all subgroups of PD-L1 (even PD-L1 <1%)

IMPOWER-010

- Adjuvant chemotherapy mandatory
- Open label, no placebo arm
- Higher proportion of stage III and non smokers
- No improvement in stage IB and PD-L1 <1 % population

Take Home message

- Patients with stage IB-IIIA NSCLC without EGFR/ALK mutation benefit from neoadjuvant chemo-immunotherapy with improved event free survival
- Patients with stage IB-IIIA post resection and adjuvant chemotherapy can benefit from adjuvant immunotherapy given for 16-18 cycles with acceptable safety profile.
- However more data from ongoing trials are needed