Locally Advanced NSCLC (Neoadjuvant/Adjuvant Therapies)

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Background

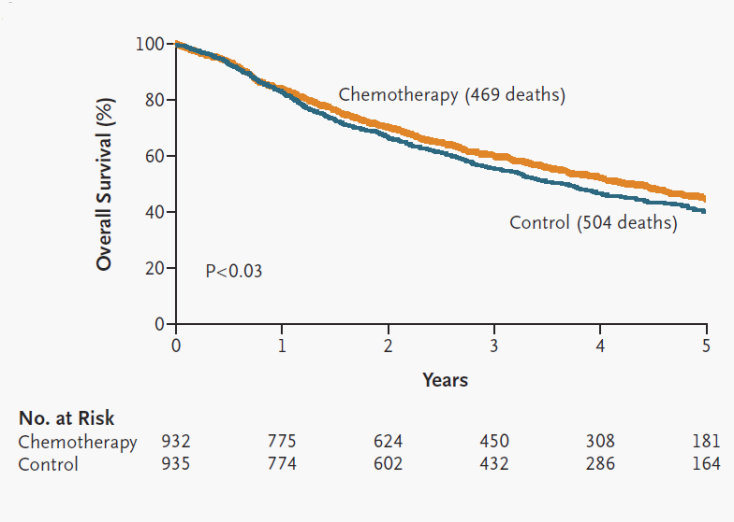
Neo-adjuvant IO

Adjuvant IO

Biomarkers

How do we avoid “over-treatment?”

Adjuvant Chemotherapy



HR 0.86
95%CI (0.76-0.98) p=0.03

Median f/u 56 months

IALT Collaborative Group. *NEJM*. 2004;350:351-60

Adjuvant Chemotherapy Meta-analysis

LACE: 5 trials - 4,584 patients
DFS HR 0.84 (95% CI: 0.78, 0.91); P<.001
OS HR 0.89 [0.82-0.96], p= .005
5% OS benefit at 5 yrs
Grade 3/4 toxicity was 66%, 32% Gr4, 0.9% Grade 5 toxicity

Updated individual patient data of adj chemo trials from 1965+
34 trials - 8,447 patients
OS HR 0.86 [0.81-0.92], p= <.0001
4% absolute OS benefit at 5 yrs

NO Selection (despite years of trying) Became Standard of Care

Pignon JCO 26:3552, 2008; Lancet 375:1267, 2010

Neo-Adjuvant IO

First Step: Neo-Adjuvant Nivolumab

Feasibility N=21: Nivo 3 mg/kg x 2 doses

Did not delay or interfere with surgery

PR (10%)	**2**
SD	18 (85%)
PD	1 (5%)

Major Pathologic Response (MPR)
9/21 pts = 43%

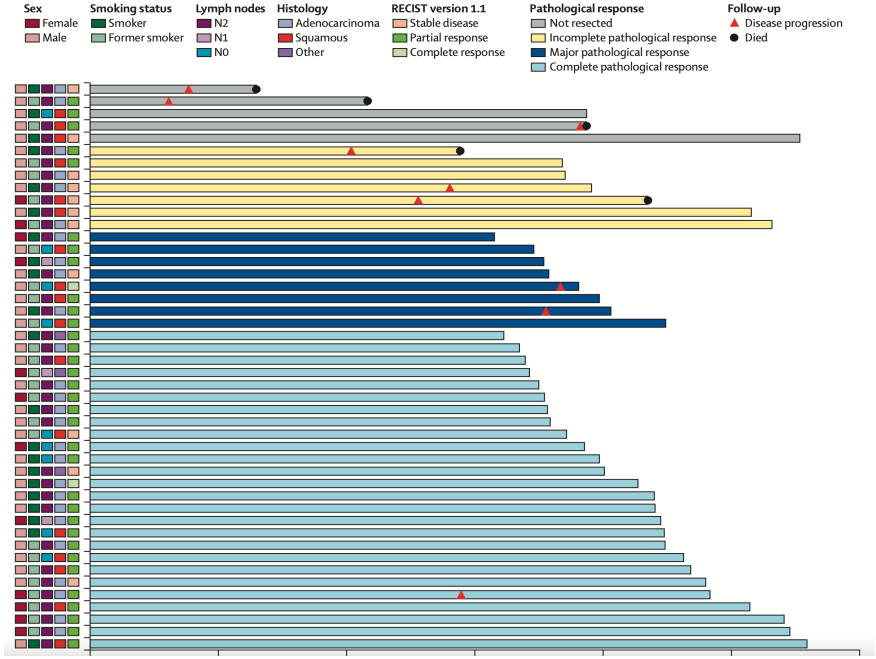
Chaft & Forde, et al.; NEJM 2018

Toxicity

Drug-related Adverse Events N=22	Any Grade N(%)
Fever	1* (5)
Thyroid dysfunction	1 (5)
GI Anorexia/dysgeusia Vomiting/diarrhea LFT abnormality	 2 (9) 1 (5) 1 (5)
Pneumonia	0
Infusion reaction	1 (5)
CNS (delirium)	1 (5)

Subsequent Single Agent IO Neoadjuvant trials MPR ~20%

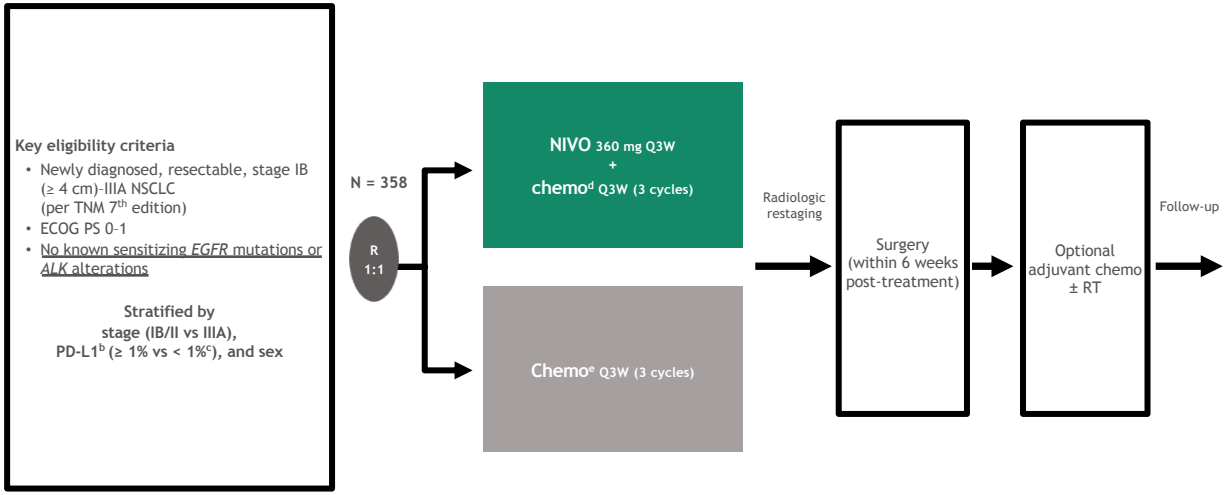
Neoadjuvant Nivolumab + Chemotherapy
The Next Step : NADIM



Screened 51 pts, enrolled 46pts
PFS 77% at 24 mo,
5 no surgery
7 minor response
8 MPR
26 pCR = 56% pCR
74% MPR (inc pCR)

Provencio, *Lancet Oncol* 2020; 21:1413-22

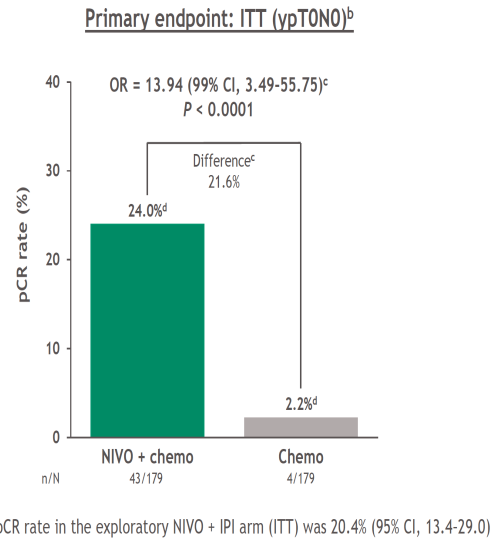
First Phase III: CheckMate816

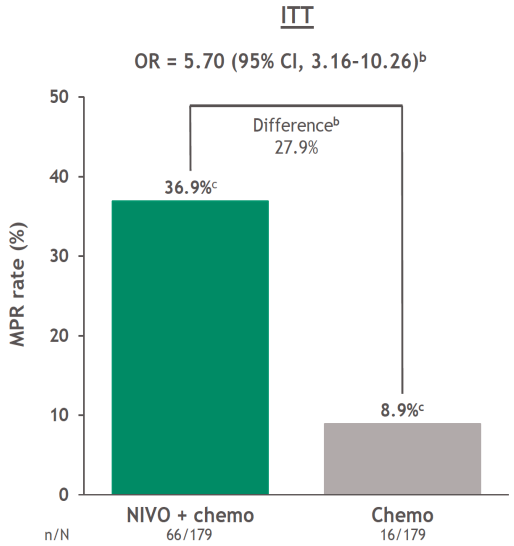


Spicer ASCO 2021 abstr: 8503, Forde NEJM

63% Stage IIIA
50% PD-L1 >1%
No EGFR/ALK
IO + Chemo

CM816 – pCR and MPR in ITT population

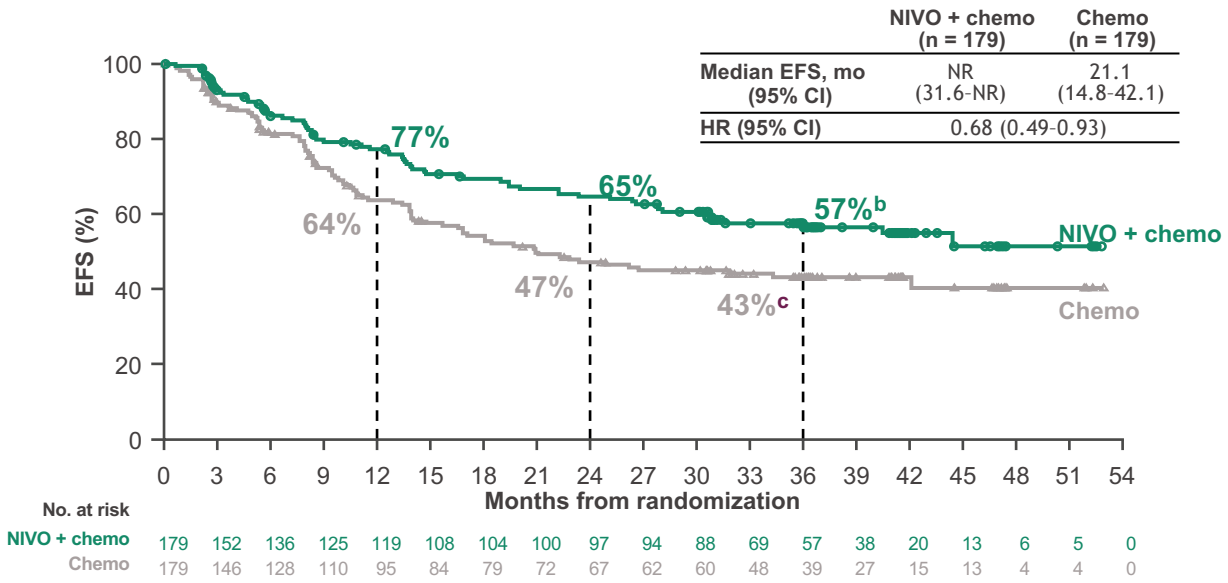




• pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

Forde CM816, AACR2021, NEJM

CM816- EFS with neoadjuvant NIVO + chemo vs chemo: 3-year update[a]

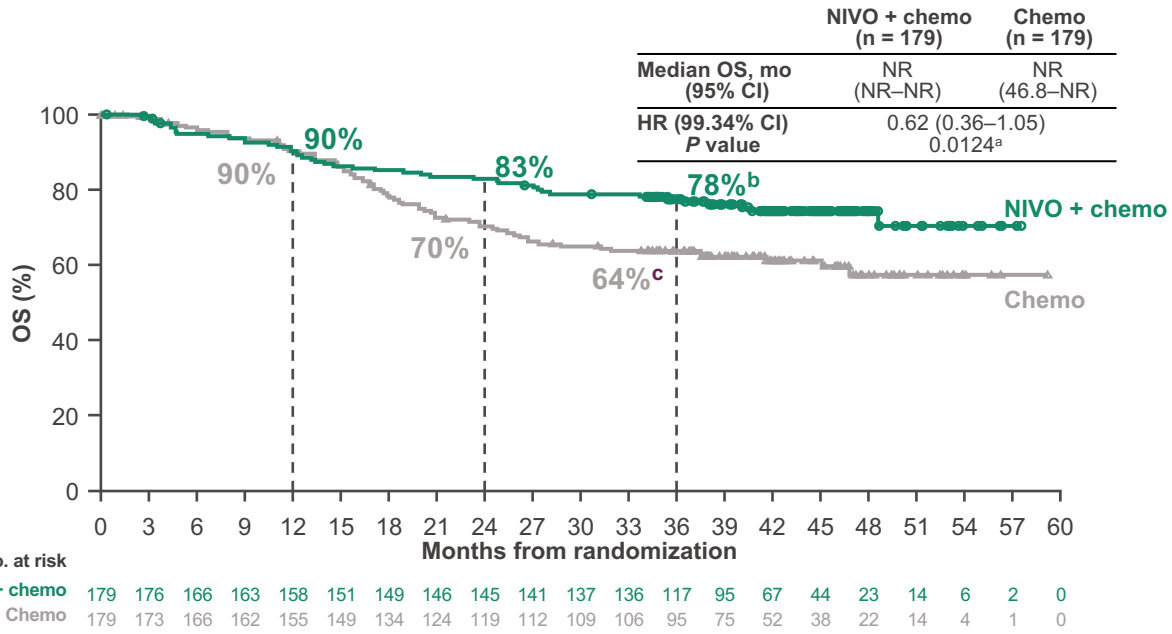


Minimum/median follow-up: 32.9/41.4 months.

[a]Exploratory analysis. Time from randomization to any disease progression precluding surgery, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b,c]95% CIs for 3-year EFS rates: [b]48–64; [c]35–51.

Forde, Spicer, Girard, et al. ELCC2023

CM816: OS with neoadjuvant NIVO + chemo vs chemo: 3-year update



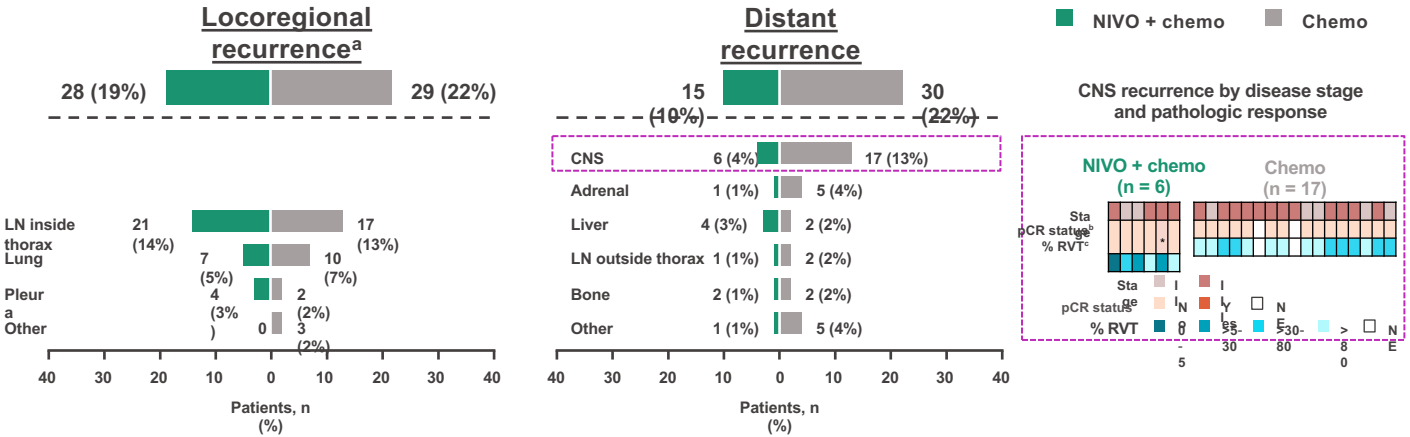
Minimum/median follow-up: 32.9/41.4 months.

[a]Significance boundary for OS was not crossed at this interim analysis. [b,c]95% CIs for 3-year OS rates: [b]71–83; [c]56–70.

Forde, Spicer, Girard, et al. ELCC2023

CM816 Recurrence patterns in patients who underwent surgery

- 42/149 patients (28%) in the NIVO + chemo and 56/135 (42%) in the chemo arms had recurrence post surgery



Minimum/median follow-up: 32.9/41.4 months.

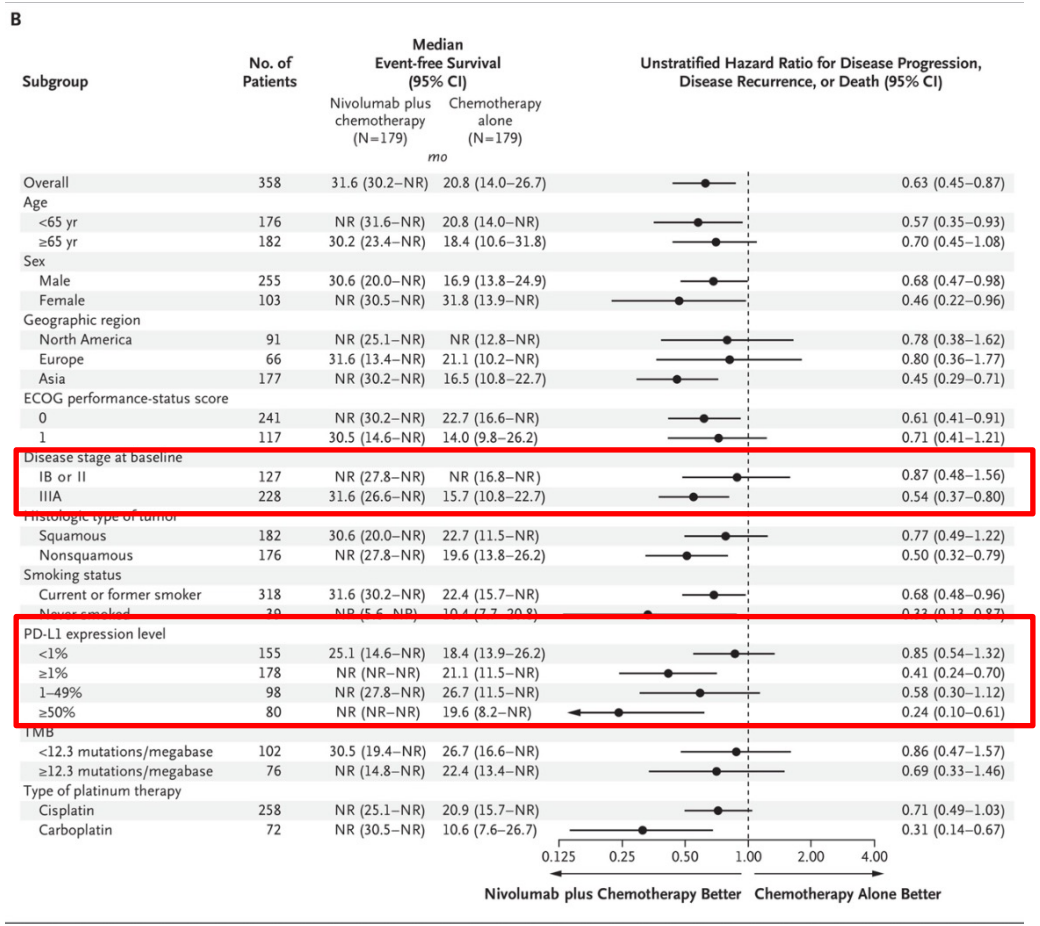
[a]Some patients with locoregional recurrence may have had distant recurrence events. [b]Defined as 0% residual viable tumor cells (RVT) in both primary tumor (lung) and sampled LN (*One patient had an MPR, which was defined as ≤ 10% RVT in both primary tumor and sampled LN). [c]In the primary tumor only.

Forde, Spicer, Girard, et al. ELCC2023

CM816 subsets

Nivo best:
Stage IIIA
Non-Sq
Never-smoke
PD-L1≥50%

Forde NEJM 2022



B

Subgroup	No. of Patients	Median Event-free Survival (95% CI)		Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (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)	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)

CM816 Safety summary[a]

Patients, n (%)	NIVO + chemo (n = 176)		Chemo (n = 176)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All AEs	165 (94)	76 (43)	173 (98)	79 (45)
TRAEs	147 (84)	63 (36)	159 (90)	67 (38)
All AEs leading to discontinuation	18 (10)	10 (6)	20 (11)	7 (4)
TRAEs leading to discontinuation	18 (10)	10 (6)	17 (10)	6 (3)
All SAEs	30 (17)	19 (11)	24 (14)	17 (10)
Treatment-related SAEs	21 (12)	15 (8)	18 (10)	14 (8)
Surgery-related AEs[b,c]	67 (45)	17 (11)	66 (49)	20 (15)
Treatment-related deaths[d]	0		3 (2)[e]	

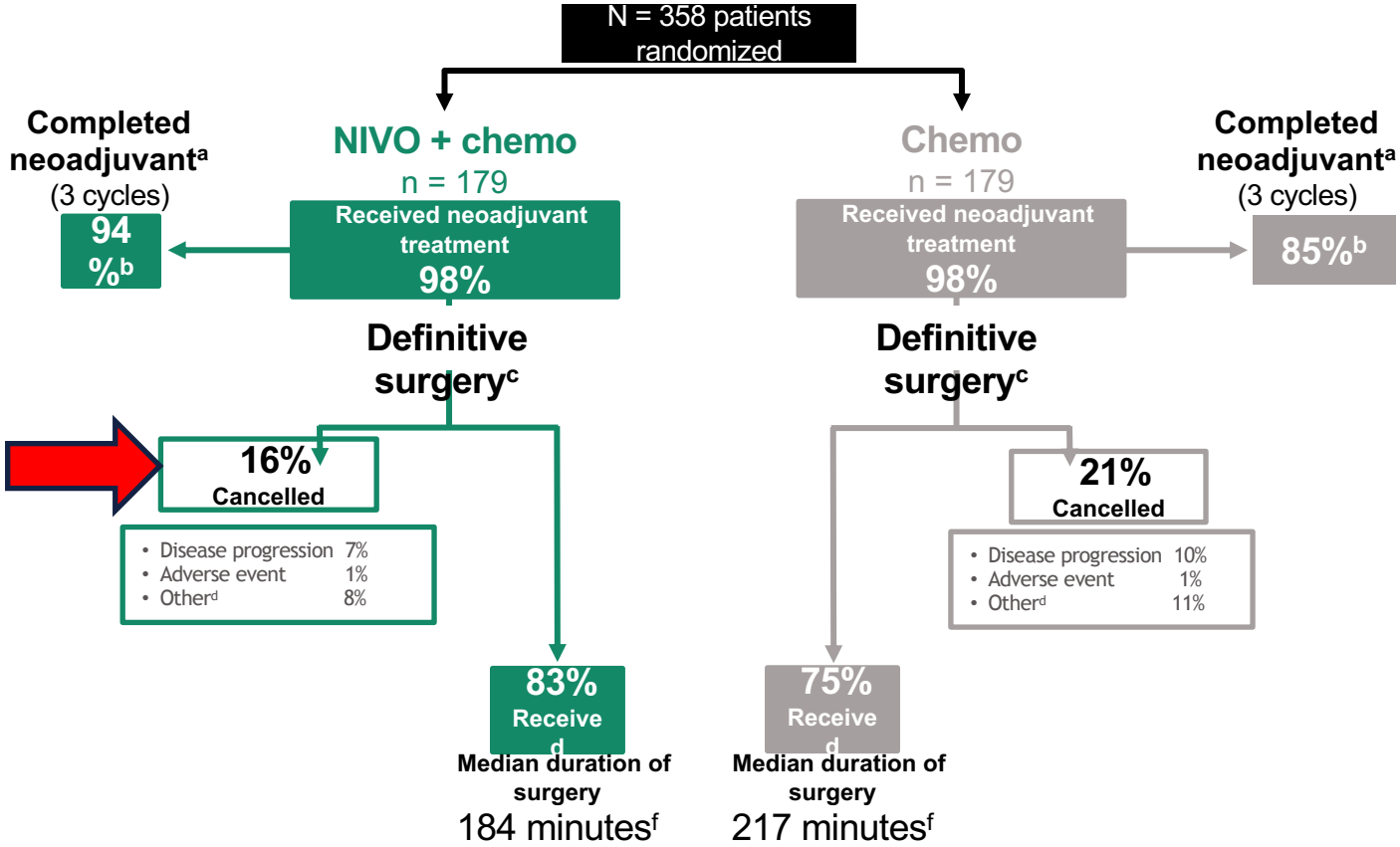
- Grade 5 surgery-related AEs (1 each due to pulmonary embolism and aortic rupture) were reported in 2 patients in the NIVO + chemo arm and were deemed unrelated to treatment

Minimum/median follow-up: 32.9/41.4 months.
Data are presented as n (%). [a]AEs per CTCAE v4.0 and MedDRA v25.0. Includes events reported between the first neoadjuvant dose and 30 days after the last dose of neoadjuvant study treatment. [b]Includes events reported within 90 days after definitive surgery. [c]Denominator is patients who had definitive surgery (n = 149 in the NIVO + chemo arm; n = 135 in the chemo arm). [d]Treatment-related deaths occurring at any time after the first dose of neoadjuvant study treatment. [e]Due to pancytopenia, diarrhea, acute kidney injury (all in 1 patient), enterocolitis (n = 1), and pneumonia (n = 1).

Forde, Spicer, Girard, et al. ELCC2023

CM816: Treatment and surgery summary: all randomized patients

Spicer ASCO 2021



[a]Reasons for patients not completing neoadjuvant treatment: study drug toxicity (6% in the NIVO + chemo and 7% in the chemo arm), disease progression (1% in each arm), and other reasons (7% in the chemo arm only; this included AEs unrelated to study drug, patient request to discontinue treatment, patient withdrew consent, and patient no longer meeting study criteria); [b]Denominator based on patients with neoadjuvant treatment; [c]Definitive surgery not reported: NIVO + chemo, 1%; chemo, 3%; [d]Other reasons included patient refusal, unresectability, and poor lung function; [e]Median (IQR) time from last dose to definitive surgery; [f]Patients (n) with reported duration of surgery: NIVO + chemo, 122; chemo, 121; IQR for median duration of surgery: NIVO + chemo, 130.0-252.0 minutes; chemo, 150.0–283.0 minutes.

Select Phase III Neo-Adjuvant IO Studies

Drug	N	Stages	Description	Primary Endpoint
Nivo + platinum chemo (**ipi/nivo closed**) CM816	350	Stage IB–IIIA, resectable NSCLC	Neo-adjuvant, no adjuvant	MPR / RFS
Atezo + platinum chemo Impower030	374	Stage II–IIIB (T3N2), resectable NSCLC	Neo-adjuvant chemo-ICI, then adjuvant IO	MPR / RFS
Pembro + platinum chemo KN671	786	Stage IIB–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	RFS / OS
Durva + platinum chemo Aegean	300	Stage II–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	MPR

Peri-operative Trials Being Reported

July 7, 2022 — Results from the phase 3 AEGEAN trial showed an improved pathological complete response in patients with resectable non–small cell lung
March 9, 2023 - Durvalumab plus chemotherapy before surgery followed by adjuvant durvalumab produced a statistically significant and clinically meaningful event-free survival (EFS) benefit vs neoadjuvant chemotherapy alone for patients with resectable stage IIA to IIIB non–small cell lung cancer (NSCLC)

March 1, 2023 Merck Announces Phase 3 KEYNOTE-671 Trial Met Primary Endpoint of Event-Free Survival (EFS) in Patients With Resectable Stage II, IIIA or IIIB Non-Small Cell Lung Cancer. Pembrolizumab plus chemotherapy before surgery and continuing as a single agent after surgery showed a statistically significant improvement in EFS versus pre-operative chemotherapy with statistically significant improvements in key secondary endpoints of pathological complete response and major pathological response

April 20, 2023 – ASCOvirtual Plenary **Abstract 425126:** Perioperative toripalimab + platinum-doublet chemotherapy vs chemotherapy in resectable stage II/III non-small cell lung cancer (NSCLC): Interim event-free survival (EFS) analysis of the phase III Neotorch study

AEGEAN: A Phase 3 Trial of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab in Patients with Resectable NSCLC

Study population

- Treatment-naïve
- ECOG PS 0 or 1
- Resectable NSCLC* (stage IIA–IIIB[N2]; AJCC 8th ed)
- Lobectomy, sleeve resection, or bilobectomy as planned surgery*
- Confirmed PD-L1 status†
- No documented *EGFR/ALK* aberrations*

R 1:1

N=802 randomized

Randomization stratified by:

- Disease stage (II vs III)
- PD-L1 expression (≥1% vs <1%)

Durvalumab 1500 mg IV + platinum-based CT‡ Q3W for 4 cycles → **Surgery §** → **Durvalumab 1500 mg IV** Q4W for 12 cycles

Placebo IV + platinum-based CT‡ Q3W for 4 cycles → **Surgery §** → **Placebo IV** Q4W for 12 cycles

Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented *EGFR/ALK* aberrations¶

Primary:

- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

Key secondary:

- MPR by central lab (per IASLC 2020[1])
- DFS using BICR (per RECIST v1.1)
- OS

*The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations. †Ventana SP263 immunohistochemistry assay. ‡Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment). §Post-operative radiotherapy (PORT) was permitted where indicated per local guidance. ¶All efficacy analyses reported in this presentation were performed on the mITT population, which includes all randomized patients who did not have documented *EGFR/ALK* aberrations.

[1]Travis WD, et al. *J Thorac Oncol* 2020;15:709-40.

AEGEAN: Baseline characteristics and planned treatment (mITT)

Baseline characteristics were largely balanced between the study arms

The planned neoadjuvant CT doublet regimen was carboplatin-based for >70% of patients

TNM classification†		D arm (N=366)	PBO arm (N=374)
Primary tumor, %	T1	12.0	11.5
	T2	26.5	28.9
	T3	35.0	34.5
	T4	26.5	25.1
Regional lymph nodes, %	N0	30.1	27.3
	N1	20.5	23.3
	N2	49.5	49.5

Characteristics*		D arm (N=366)	PBO arm (N=374)
Age	Median (range), years	65.0 (30–88)	65.0 (39–85)
	≥75 years, %	12.0	9.6
Sex, %	Male	68.9	74.3
	Female	31.1	25.7
ECOG PS, %	0	68.6	68.2
	1	31.4	31.8
Race‡, %	Asian	39.1	43.9
	White	56.3	51.1
	Other	4.6	5.1
Region, %	Asia	38.8	43.6
	Europe	38.5	37.4
	North America	11.7	11.5
	South America	10.9	7.5
Smoking status, %	Current	26.0	25.4
	Former	60.1	59.6
	Never	13.9	15.0
Disease stage (AJCC 8th ed.), %	II	28.4	29.4
	IIIA	47.3	44.1
	IIIB	24.0	26.2
Histology, %	Squamous	46.2	51.1
	Non-squamous	53.6	47.9
PD-L1 expression, %	TC <1%	33.3	33.4
	TC 1–49%	36.9	38.0
	TC ≥50%	29.8	28.6
Planned neoadjuvant platinum agent, %	Cisplatin	27.3	25.7
	Carboplatin	72.7	74.3

DCO = Nov 10, 2022. *Characteristics with missing/other responses are histology (0.3% in the D arm and 1.1% in PBO arm had 'other' histology) and disease stage (0.3% in D arm had stage IV disease, and 0.3% in the PBO arm had stage III [NOS] disease, as reported per the electronic case report form [eCRF]). †All patients were M0 except one patient in the D arm who was classified as M1 (NOS). ‡Race was self-reported per the eCRF. NOS, not otherwise specified; TC, tumor cells.

AEGEAN: Patient disposition and treatment summary (mITT)

Patients were randomized between January 2, 2019 and April 19, 2022 (minimum follow-up: 6.7 months)

At the first planned interim analysis of EFS (DCO: Nov 10, 2022), median EFS follow-up in censored patients was 11.7 months (range: 0.0–46.1)

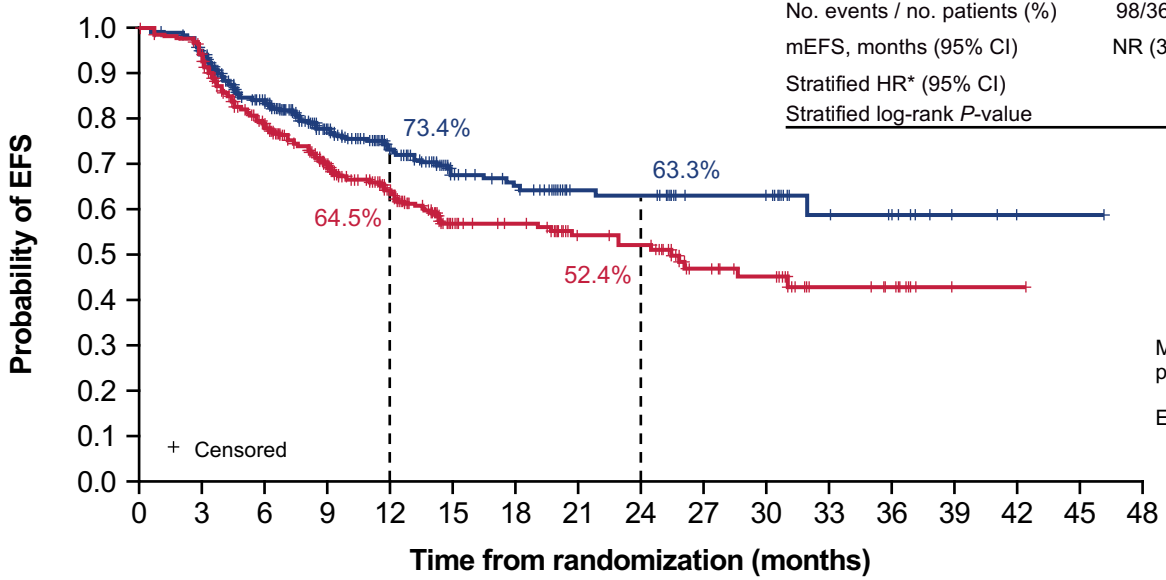
Study phase*		D arm (N=366)	PBO arm (N=374)
Neoadjuvant phase	Randomized, n (%)	366 (100)	374 (100)
	Received Tx, n (%)	366 (100)	371 (99.2)
	Completed 4 cycles of both CT agents, n (%)	310 (84.7)	326 (87.2)
	Completed 4 cycles of D / PBO, n (%)	318 (86.9)	331 (88.5)
Surgery	Underwent surgery†, n (%)	295 (80.6)	302 (80.7)
	Did not undergo surgery†‡, n (%)	71 (19.4)	72 (19.3)
	Completed surgery†, n (%)	284 (77.6)	287 (76.7)
	− R0 resection, n (% of completed surgery)	269 (94.7)	262 (91.3)
	Did not complete surgery†, n (%)	11 (3.0)	15 (4.0)
Adjuvant phase (*ongoing*)	Started D / PBO§, n (%)	241 (65.8)	237 (63.4)
	Completed D / PBO, n (%)	88 (24.0)	79 (21.1)
	Discontinued D / PBO, n (%)	68 (18.6)	70 (18.7)
	Ongoing D / PBO, n (%)	85 (23.2)	88 (23.5)

DCO = Nov 10, 2022. *Except where specified otherwise, percentages were calculated using the full mITT population as the denominator. †As per investigator assessment. Patients who 'underwent' surgery were those for whom curative-intent thoracic surgery was attempted regardless of whether it was completed. Patients who 'completed' surgery were those for whom curative-intent thoracic surgery was completed (assessed at the time of surgery). ‡Includes patients who had surgery outside of the study. §For patients to be eligible for adjuvant D / PBO, surgery must have been completed with R0/R1 margins and no evidence of disease on post-surgical RECIST assessment. DCO, data cutoff.

AEGEAN: EFS using RECIST v1.1 (BICR) (mITT)

First planned interim analysis of EFS

	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	



Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

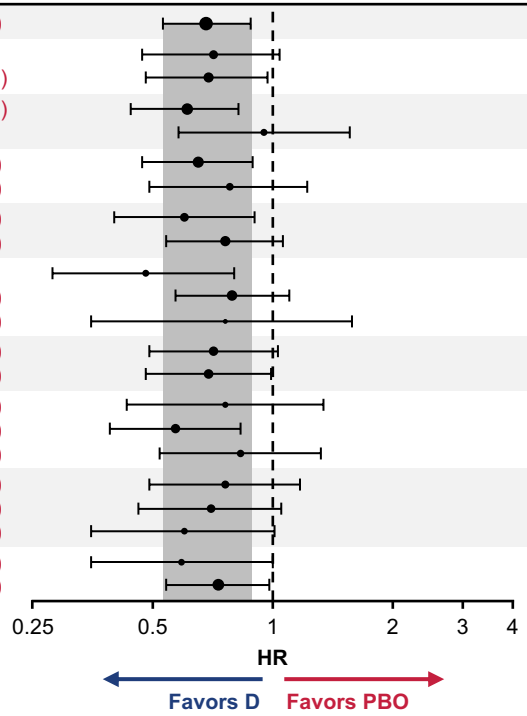
No. at risk:

D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

DCO = Nov 10, 2022. EFS is defined as time from randomization to the earliest of: (A) progressive disease (PD) that precludes surgery; (B) PD discovered and reported by the investigator upon attempting surgery that prevents completion of surgery; (C) local/distant recurrence using BICR per RECIST v1.1; or (D) death from any cause. *HR <1 favors the D arm versus the PBO arm. Median and landmark estimates calculated using the Kaplan–Meier method; HR calculated using a stratified Cox proportional hazards model; and *P*-value calculated using a stratified log rank test. Stratification factors: disease stage (II vs III) and PD-L1 expression status (<1% vs ≥1%). Significance boundary = 0.009899 (based on total 5% alpha), calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary. mEFS, median EFS; NR, not reached.

AEGEAN: EFS using RECIST v1.1 (BICR) by subgroup (mITT)

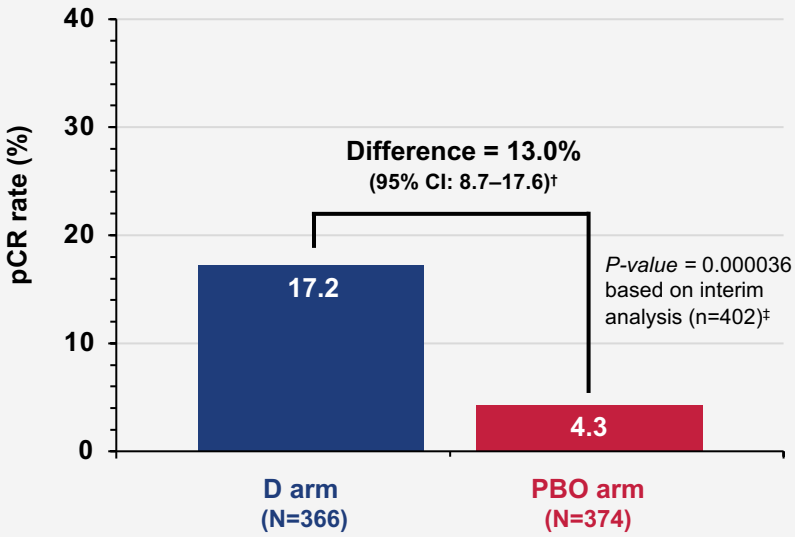
Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	Median EFS, months (95% CI) PBO arm (N=374)	HR (95% CI)
All patients		740	NR (31.9–NR)	25.9 (18.9–NR)	0.68 (0.53–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	NR (18.9–NR)	0.71 (0.47–1.04)
	≥65 years	382	NR (17.9–NR)	24.5 (13.6–31.1)	0.69 (0.48–0.97)
Sex	Male	530	NR (31.9–NR)	22.9 (14.3–31.1)	0.61 (0.44–0.82)
	Female	210	NR (17.5–NR)	NR (13.6–NR)	0.95 (0.58–1.56)
ECOG PS	0	506	NR (31.9–NR)	25.4 (14.3–NR)	0.65 (0.47–0.89)
	1	234	NR (21.8–NR)	25.9 (14.3–NR)	0.78 (0.49–1.22)
Race*	Asian	307	NR (NR–NR)	25.4 (13.9–NR)	0.60 (0.40–0.90)
	Non-Asian	433	31.9 (21.8–NR)	26.2 (14.3–NR)	0.76 (0.54–1.06)
Smoking	Current	190	NR (NR–NR)	14.3 (8.1–NR)	0.48 (0.28–0.80)
	Former	443	NR (31.9–NR)	25.9 (19.5–NR)	0.79 (0.57–1.10)
	Never	107	NR (NR–NR)	24.5 (14.3–NR)	0.76 (0.35–1.58)
Histology	Squamous	360	NR (31.9–NR)	26.2 (13.0–NR)	0.71 (0.49–1.03)
	Non-squamous	375	NR (NR–NR)	25.4 (14.3–NR)	0.69 (0.48–0.99)
Disease stage (AJCC 8th ed.)	Stage II	214	NR (NR–NR)	31.1 (25.4–NR)	0.76 (0.43–1.34)
	Stage IIIA	338	NR (NR–NR)	19.5 (11.7–NR)	0.57 (0.39–0.83)
	Stage IIIB	186	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83 (0.52–1.32)
PD-L1 expression at baseline†	TC <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
	TC 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
	TC ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	31.1 (14.3–NR)	0.59 (0.35–1.00)
	Carboplatin	544	NR (31.9–NR)	25.4 (14.3–NR)	0.73 (0.54–0.98)



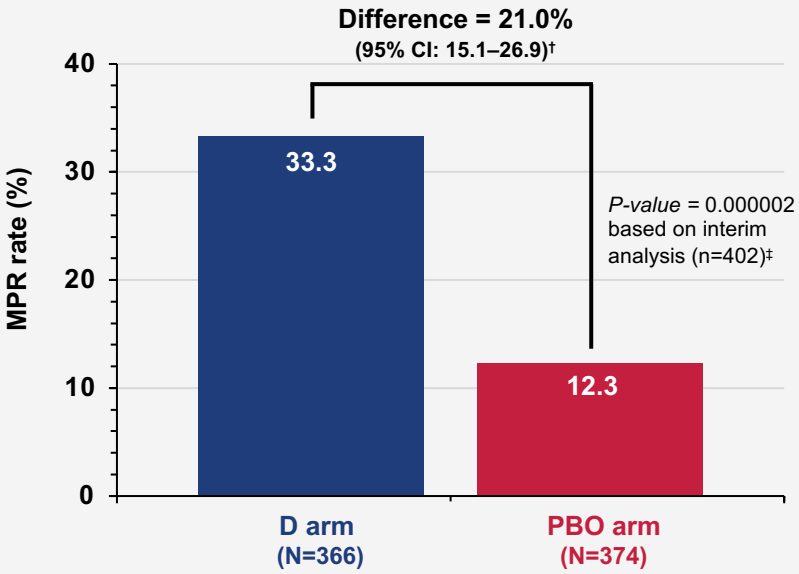
DCO = Nov 10, 2022; median EFS follow-up in censored patients: 11.7 months (range: 0.0–46.1); EFS maturity: 31.9%. Median calculated using the Kaplan–Meier method; HR for all patients (mITT) calculated using a stratified Cox proportional hazards model. HRs for subgroups calculated using unstratified Cox proportional hazards models. The size of circles is proportional to the number of events for each subgroup, and the horizontal bars represent the 95% CIs. *Race was self-reported per the electronic case report form. †Determined using the Ventana SP263 immunohistochemistry assay.

AEGEAN: Pathologic response per IASLC 2020 methodology* (mITT)
Final analysis

pCR (central lab)

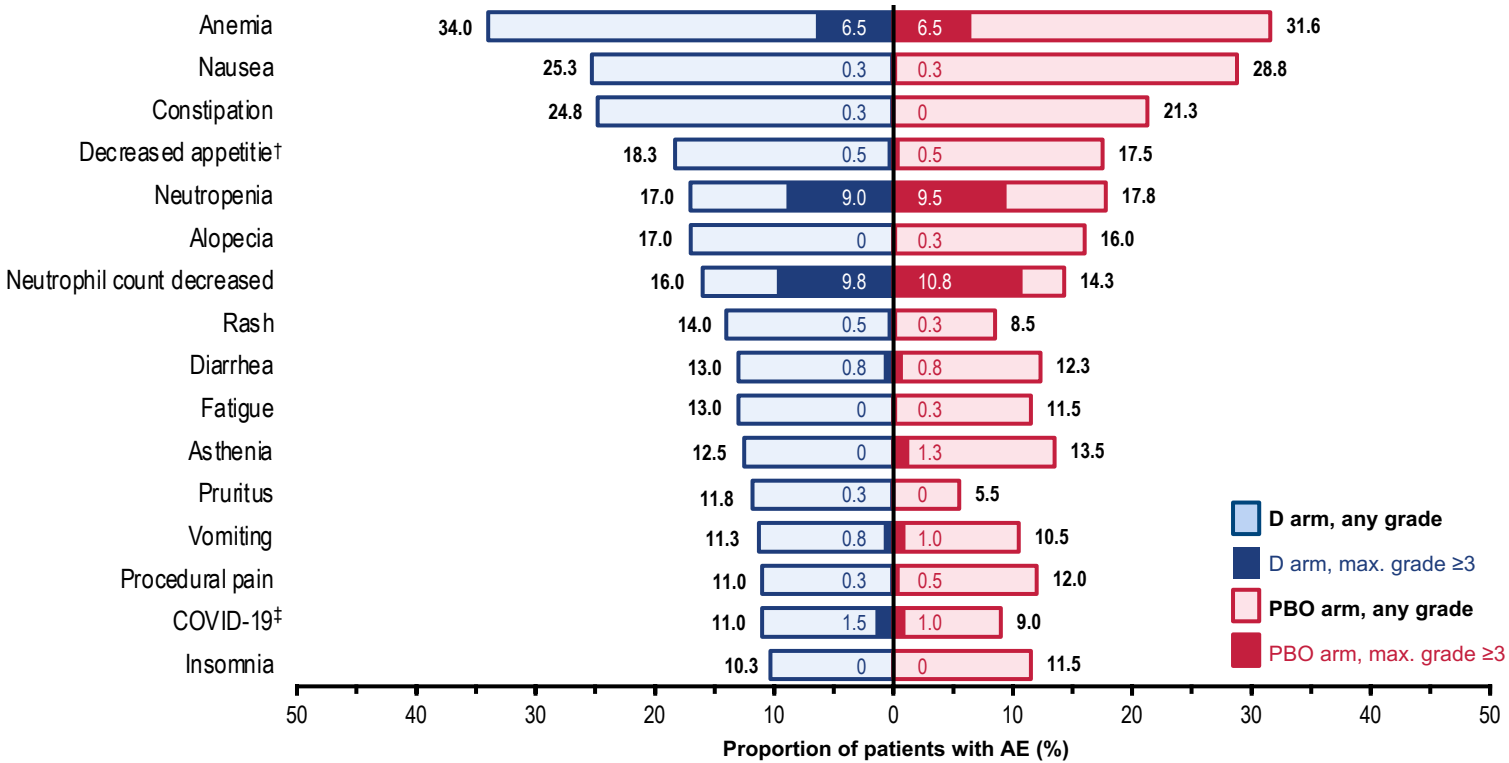


MPR (central lab)



*Using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumor bed (Travis WD, et al. *J Thorac Oncol* 2020;15:709-40). pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled regional lymph nodes. MPR = less than or equal to 10% viable tumor cells in lung primary tumor after complete evaluation of the resected lung cancer specimen. To be eligible for pathologic assessment, patients needed to have received three cycles of neoadjuvant study Tx per protocol. Patients who were not evaluable were classified as non-responders. †CIs calculated by stratified Miettinen and Nurminen method. ‡No formal statistical testing was performed at the pCR final analysis (DCO: Nov 10, 2022; n=740 [data shown]). Statistical significance was achieved at the interim pCR analysis (DCO: Jan 14, 2022; n=402; *P*-value for pCR/MPR calculated using a stratified Cochran-Mantel-Haenszel test with a significance boundary = 0.000082 calculated using a Lan-DeMets alpha spending function with O'Brien Fleming boundary).

AEGEAN: Most frequently reported AEs* (safety analysis set)

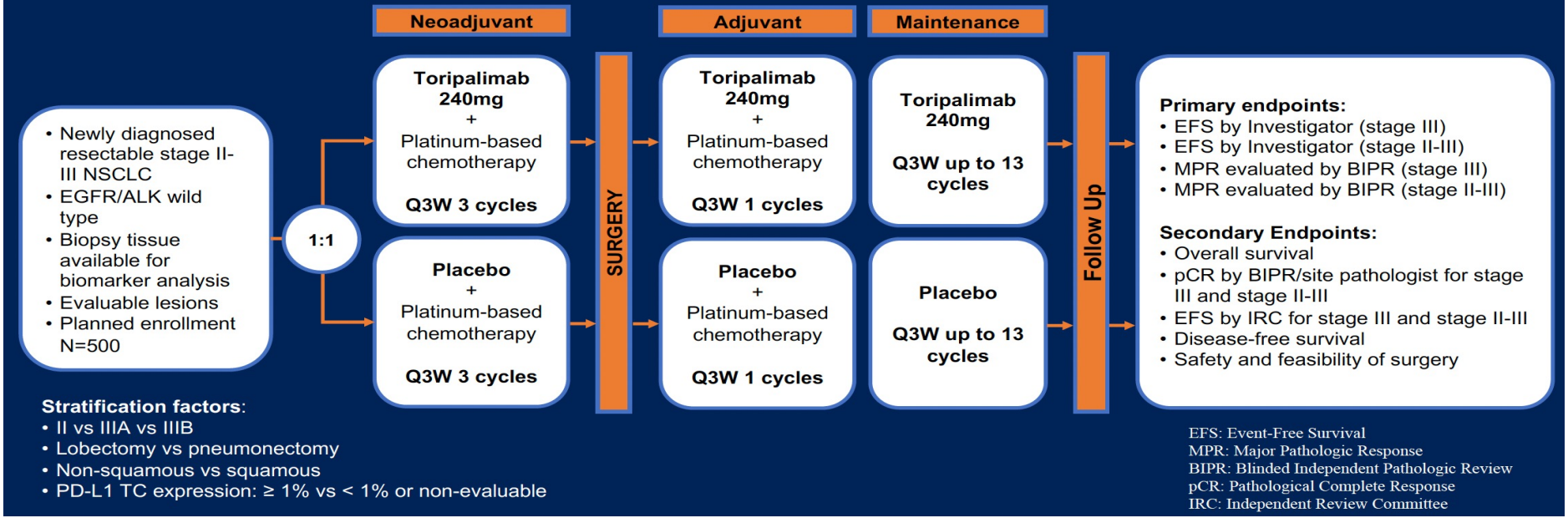


DCO = Nov 10, 2022. *Displayed are AEs reported with a frequency of ≥10% in the D arm during the overall study period; the overall study period spans from the first dose of study Tx (D / PBO / CT) until the earliest of: the last dose of study Tx or surgery + 90 days (taking the latest dose of D / PBO / CT / date of surgery, + 90 days); the DCO date; or the date of the first dose of subsequent anti-cancer Tx. †Two patients (n=1 per arm) had decreased appetite with an outcome of death (grade 5); the fatal event in the D arm was assessed as possibly related to study Tx by the investigator. ‡Six patients had grade 5 COVID-19 events (D arm, n=5; PBO arm, n=1); all COVID-19 deaths were assessed by the investigator as unrelated to study Tx (note: COVID-19 is summarized as a grouped term comprising the 'COVID-19' and 'COVID-19 pneumonia' preferred terms).

Perioperative Toripalimab + Plat-Doublet Chemo vs Chemo in Resectable Stage II/III NSCLC: Interim EFS Analysis of the Phase III Neotorch Study

Neotorch Study Design

- Neotorch is a randomized, double-blind, placebo-controlled, Phase III trial evaluating the efficacy and safety of perioperative toripalimab plus chemotherapy, followed by toripalimab maintenance vs perioperative chemotherapy alone in resectable stage II/III non-small cell lung cancer (NSCLC)



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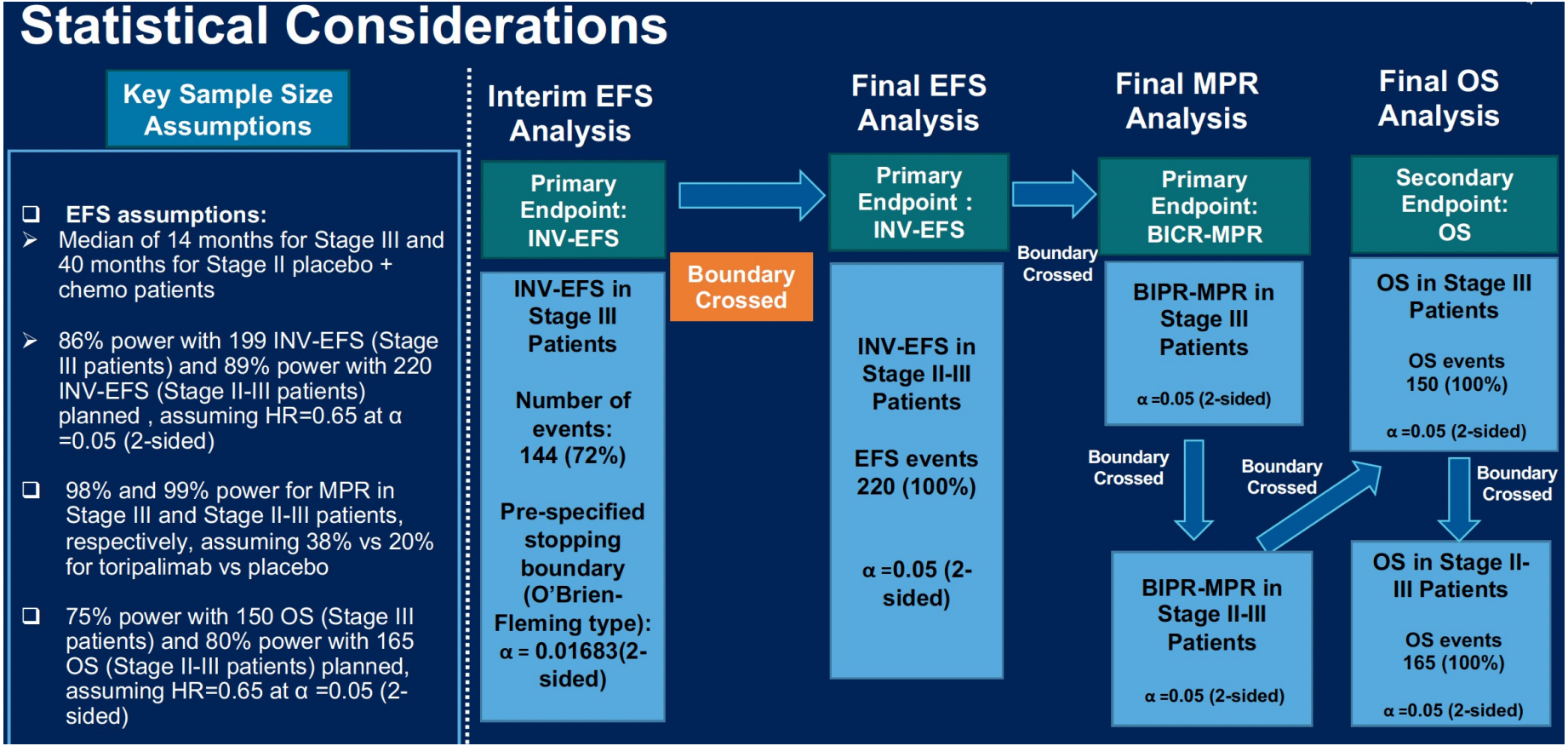
Neotorch



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Neotorch

Baseline characteristics of Stage III Patients

	Toripalimab + chemo n=202	Placebo + chemo n=202	Total n=404
Median age, years (range)	62 (31- 70)	61 (29 - 70)	62 (29 - 70)
Age < 65 years, n (%)	140 (69.3)	138 (68.3)	278 (68.8)
Gender, n (%)			
Male	181 (89.6)	189 (93.6)	370 (91.6)
Smoking status, n (%)			
Non-smoker	28 (13.9)	21 (10.4)	49 (12.1)
Smoker	30 (14.9)	23 (11.4)	53 (13.1)
Former	144 (71.3)	158 (78.2)	302 (74.8)
ECOG, n (%)			
0	70 (34.7)	73 (36.1)	143 (35.4)
1	132 (65.3)	129 (63.9)	261 (64.6)
Histology, n (%)			
Non-squamous	45 (22.3)	45 (22.3)	90 (22.3)
Squamous	157 (77.7)	157 (77.7)	314 (77.7)
PD-L1 expression, n (%)			
TC ≥ 1%	133 (65.8)	132 (65.3)	265 (65.6)
TC < 1% or non-evaluable	69 (34.2)	70 (34.7)	139 (34.4)
Stage, n (%)			
IIIA	136 (67.3)	136 (67.3)	272 (67.3)
IIIB	65 (32.2)	64 (31.7)	129 (31.9)
IIIC	1 (0.5)	0	1 (0.2)
IV	0	2 (1.0)	2 (0.5)

Data cut-off date: Nov. 30, 2022

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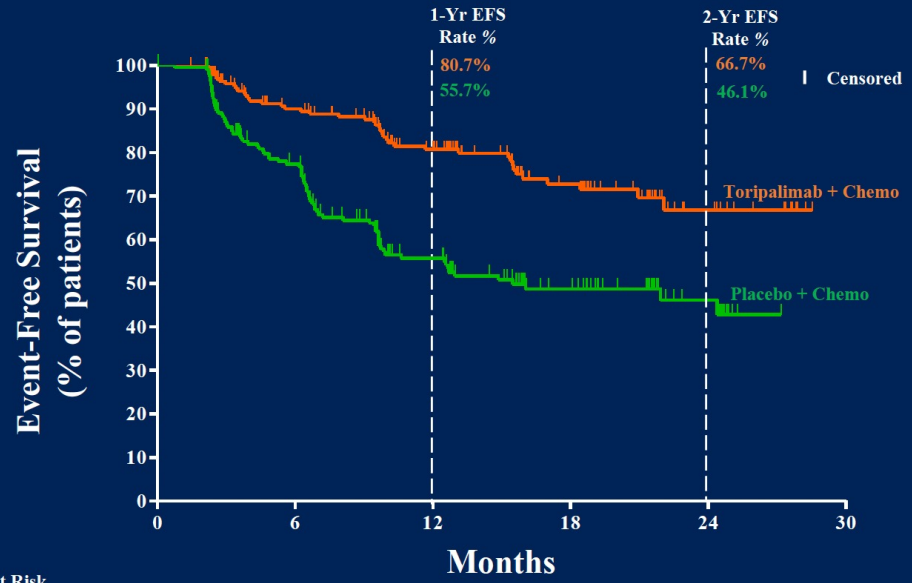
NEOTORCH

Event-Free Survival Analysis by IRC

Intent-to-treat Stage III patients assessed by IRC per RECIST v1.1



No. at Risk

Toripalimab + Chemo	202	150	107	60	17	0
Placebo + Chemo	202	134	74	38	14	0

	No. of Events/ No. of Patients	Median EFS *mo* (95% CI)
Toripalimab + Chemo	43/202	NE (NE, NE)
Placebo + Chemo	87/202	15.5 (9.9, NE)

Median follow-up: 18.25 months

HR 0.40 (95%CI 0.271, 0.572)

nominal P<0.0001

Data cutoff date: Nov. 30, 2022
NE: not evaluable
HR; Hazard ratio
CI: confidence interval

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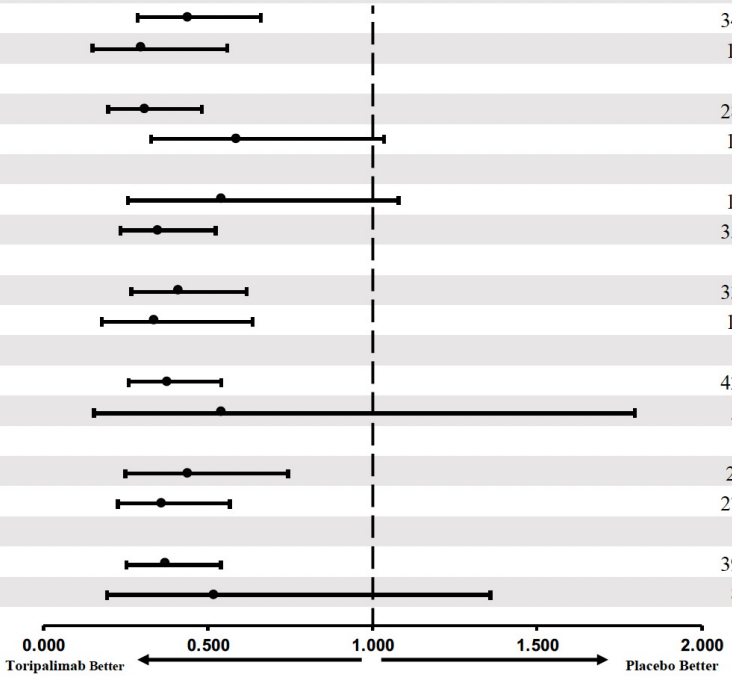
NEOTORCH

INV-EFS Treatment Effects in Key Subgroups

Subgroups	Toripalimab + Chemo Events/Total	Placebo + Chemo Events/Total	Hazard Ratio (95% CI)
Disease Stage			
IIIA	34/136	65/136	0.44 (0.287, 0.661)
IIIB	13/65	31/64	0.30 (0.149, 0.559)
PD-L1 Expression			
TC>=1%	28/133	65/132	0.31 (0.197, 0.481)
TC<1% or Not Evaluable	19/69	32/70	0.59 (0.327, 1.034)
Pathological Type			
Non-squamous Cell Carcinoma	12/45	21/45	0.54 (0.257, 1.079)
Squamous Cell Carcinoma	35/157	76/157	0.35 (0.234, 0.523)
Age			
<65	33/140	66/138	0.41 (0.267, 0.618)
>=65	14/62	31/64	0.34 (0.177, 0.635)
Sex			
Male	42/181	91/189	0.38 (0.259, 0.541)
Female	5/21	6/13	0.54 (0.154, 1.796)
ECOG			
0	20/70	38/73	0.44 (0.249, 0.743)
1	27/132	59/129	0.36 (0.226, 0.566)
Smoking			
Yes (Including Smoker or Former)	39/174	88/181	0.37 (0.252, 0.539)
No	8/28	9/21	0.52 (0.193, 1.358)



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NEOTORCH

Pathological Complete Response + Surgery Performed

	Toripalimab + Chemo (N=202)	Placebo + Chemo (N=202)
pCR assessed by local pathologist		
n (%)	**57 (28.2)**	**2 (1.0)**
95% CI	22.1, 35.0	0.1, 3.5
Stratified analysis		
Difference between arms (95% CI)	27.2 (20.8, 33.5)	
P value	<0.0001	
pCR assessed by BIPR		
n (%)	**50 (24.8)**	**2 (1.0)**
95% CI	19.0, 31.3	0.1, 3.5
Stratified analysis		
Difference between arms (95% CI)	23.7 (17.6, 29.8)	
P value	<0.0001	

pCR: Pathological Complete Response; IRC: Independent Review Committee; P-values are nominal

No surgery performed n(%)	36 (17.8)	54 (26.7)
Patient underwent surgery n(%)	166 (82.2)	148 (73.3)
R0 resection n(%*)	159 (95.8)	137 (92.6)
95% CI	91.5, 98.3	87.1, 96.2
Differences between arms	3.2	
95% CI	-2.0, 8.4	

*percent of R0 resection is based on numbers of patients underwent surgery

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NEOTORCH

Safety Overview

Adverse Event Category N (%)	Toripalimab +Chemotherapy N=202	Placebo + Chemotherapy N=202	Total N=404
Any TEAEs	201(99.5)	199 (98.5)	400 (99.0)
Any TEAEs Grade ≥3	128 (63.4)	109 (54.0)	237 (58.7)
Any SAEs	82 (40.6)	57 (28.2)	139 (34.4)
Any TEAEs leading to death	6 (3.0)	4 (2.0)	10 (2.5)
Any TEAEs leading to interruption of toripalimab/placebo	57 (28.2)	29 (14.4)	86 (21.3)
Any TEAEs leading to discontinuation of toripalimab/placebo	19 (9.4)	15 (7.4)	34 (8.4)
Any Investigator-determined irAEs	85 (42.1)	46 (22.8)	131 (32.4)
Any Investigator-determined Grade ≥3 irAEs	24 (11.9)	6 (3.0)	30 (7.4)
Any infusion-related reactions	7 (3.5)	13 (6.4)	20 (5.0)

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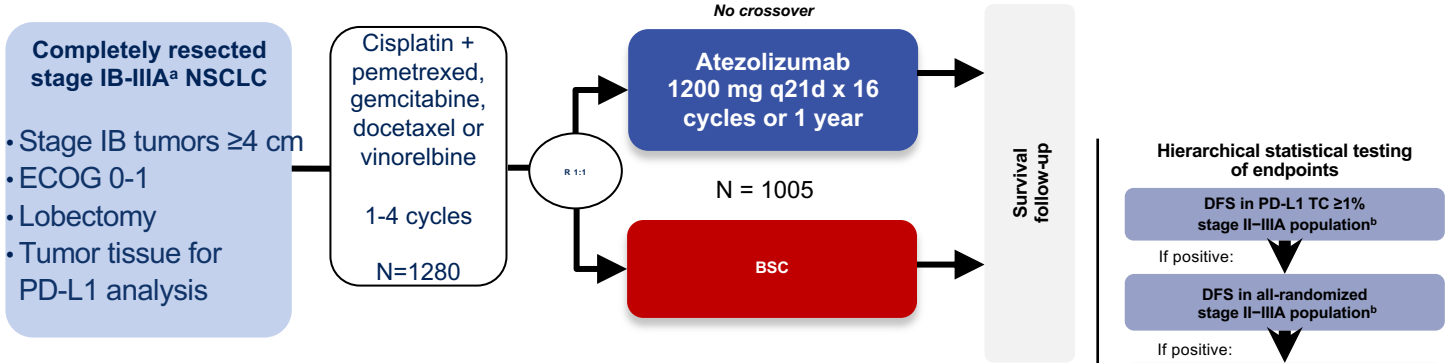
Adjuvant

IMpower010



Stratification factors
- Sex | Stage | Histology | PD-L1 status

Key exploratory endpoints
- OS biomarker analyses

Key secondary endpoints
- OS in ITT | Safety | Exploratory OS biomarker analyses

Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule. ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.
[a] Per UICC/AJCC staging system, 7th edition. [b] Two-sided α=0.05.

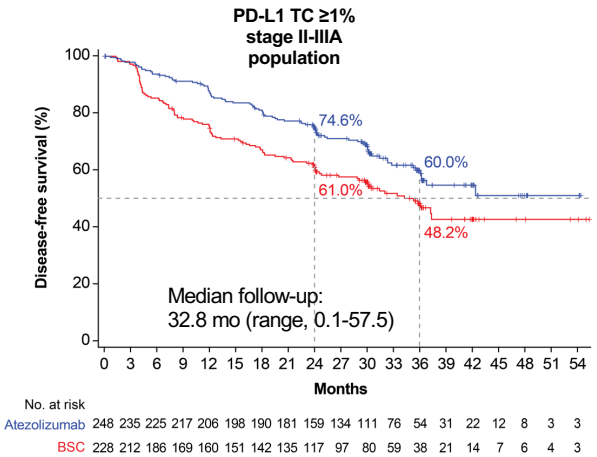
. Wakelee ASCO 2021, abstr 8500:IMpower010 Interim Analysis; Felip Lancet 2021, Felip IASLC WCLC 2022

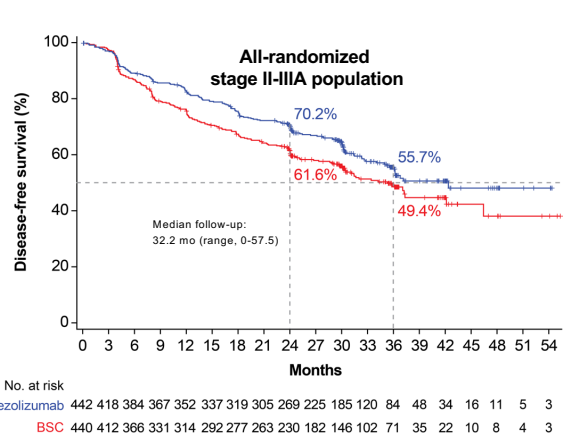
IMpower010 Patient Characteristics

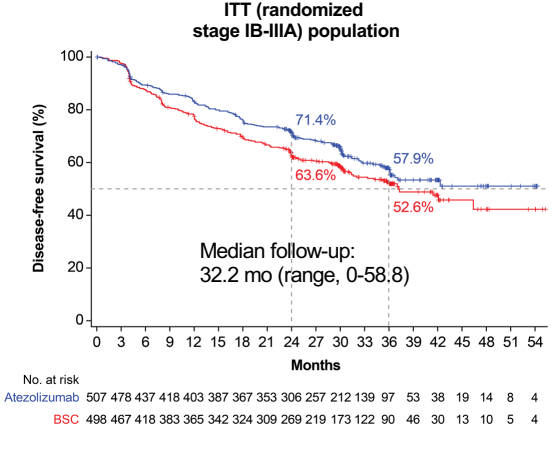
Characteristic	All patients (N=1005)	PD-L1 TC ≥1% (SP263) (stage II-IIIA)		All randomized (stage II-IIIA)		ITT (stage IB-IIIA)	
		Atezolizumab (n=248)	BSC (n=228)	Atezolizumab (n=442)	BSC (n=440)	Atezolizumab (n=507)	BSC (n=498)
Median (range) age, y	**62 (26-84)**	61 (34–82)	62 (26–84)	62 (33–82)	62 (26–84)	62 (33–83)	62 (26–84)
Age ≥65 y, n (%)	**382 (38.0)**	92 (37.1)	97 (42.5)	161 (36.4)	177 (40.2)	184 (36.3)	198 (39.8)
Sex, male, n (%)	**672 (66.9)**	171 (69.0)	147 (64.5)	295 (66.7)	294 (66.8)	337 (66.5)	335 (67.3)
Race, n (%)							
White	**738 (73.4)**	162 (65.3)	166 (72.8)	307 (69.5)	324 (73.6)	362 (71.4)	376 (75.5)
Asian	**242 (24.1)**	78 (31.5)	56 (24.6)	121 (27.4)	106 (24.1)	130 (25.6)	112 (22.5)
Other	**25 (2.5)**	8 (3.2)	6 (2.6)	14 (3.2)	10 (2.3)	15 (3.0)	10 (2.0)
ECOG PS, n (%)							
0	**556 (55.3)**	140 (56.5)	125 (54.8)	239 (54.1)	252 (57.3)	273 (53.8)	283 (56.8)
1	**446 (44.4)**	107 (43.1)	102 (44.7)	201 (45.5)	187 (42.5)	232 (45.8)	214 (43.0)
Histology, non-squamous, n (%)	**659 (65.6)**	152 (61.3)	143 (62.7)	292 (66.1)	296 (67.3)	328 (64.7)	331 (66.5)
Stage, n (%)							
IB	**123 (12.2)**	–	–	–	–	65 (12.8)	58 (11.6)
IIA	**295 (29.4)**	85 (34.3)	76 (33.3)	147 (33.3)	148 (33.6)	147 (29.0)	148 (29.7)
IIB	**174 (17.3)**	46 (18.5)	37 (16.2)	90 (20.4)	84 (19.1)	90 (17.8)	84 (16.9)
IIIA	**413 (41.1)**	117 (47.2)	115 (50.4)	205 (46.4)	208 (47.3)	205 (40.4)	208 (41.8)
Tobacco use history, n (%)							
Never	**222 (22.1)**	51 (20.6)	41 (18.0)	100 (22.6)	96 (21.8)	114 (22.5)	108 (21.7)
Current/previous	**783 (77.9)**	197 (79.4)	187 (82.0)	342 (77.4)	344 (78.2)	393 (77.5)	390 (78.3)
PD-L1 by SP263, TC≥1%, n (%)[a]	**535 (54.6)**	248 (100)	228 (100)	248 (57.8)	228 (53.0)	283 (57.4)	252 (51.9)
EGFR mutation status, n (%)[b]							
Positive	**117 (11.6)**	23 (9.3)	20 (8.8)	49 (11.1)	60 (13.6)	53 (10.5)	64 (12.9)
Negative	**527 (52.4)**	123 (49.6)	125 (54.8)	229 (51.8)	234 (53.2)	261 (51.5)	266 (53.4)
Unknown[c]	**361 (35.9)**	102 (41.1)	83 (36.4)	164 (37.1)	146 (33.2)	193 (38.1)	168 (33.7)
ALK rearrangement status, n (%)[b]							
Positive	**33 (3.3)**	12 (4.8)	11 (4.8)	14 (3.2)	17 (3.9)	15 (3.0)	18 (3.6)
Negative	**574 (57.1)**	133 (53.6)	121 (53.1)	251 (56.8)	256 (58.2)	280 (55.2)	294 (59.0)
Unknown[c]	**398 (39.6)**	103 (41.5)	96 (42.1)	177 (40.0)	167 (38.0)	212 (41.8)	186 (37.3)

Wakelee ASCO 2021 abstr 8500; Felip Lancet 2021

IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA, all-randomized stage II-IIIA and ITT pop (primary endpoint)







	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[b]	0.02[c]	

	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

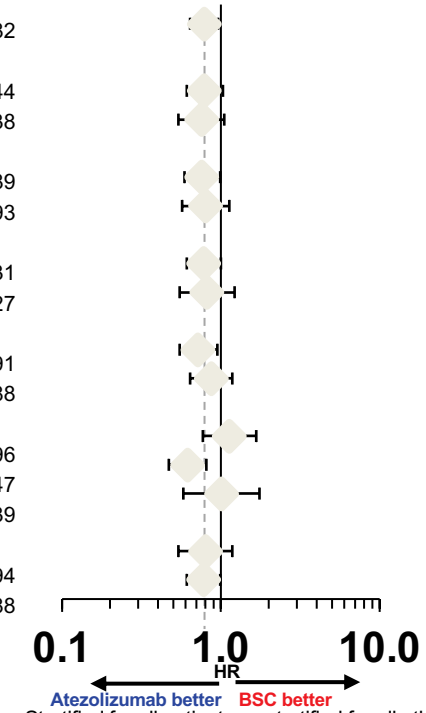
Clinical cutoff: January 21, 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS. [d] The statistical significance boundary for DFS was not crossed.

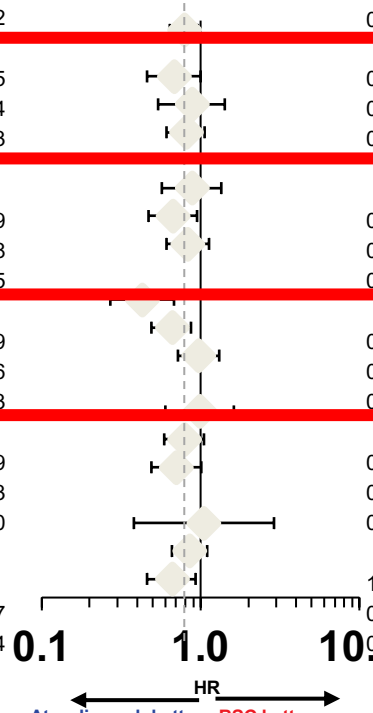
Wakelee ASCO 2021 abstr 8500; Felip Lancet 2021

US FDA approval Oct 15, 2021

IMpower010: DFS in key subgroups of all-rand stage II-IIIA population

Subgroup	N	HR (95% CI)[a]
All patients	882	0.79 (0.64, 0.96)
Age		
<65 y	544	0.79 (0.61, 1.03)
≥65 y	338	0.76 (0.54, 1.05)
Sex		
Male	589	0.76 (0.59, 0.99)
Female	293	0.80 (0.57, 1.13)
Race		
White	631	0.78 (0.61, 1.00)
Asian	227	0.82 (0.55, 1.22)
ECOG PS		
0	491	0.72 (0.55, 0.95)
1	388	0.87 (0.64, 1.18)
Tobacco use history		
Never	196	1.13 (0.77, 1.67)
Previous	547	0.62 (0.47, 0.81)
Current	139	1.01 (0.58, 1.75)
Histology		
Squamous	294	0.80 (0.54, 1.18)
Non-squamous	588	0.78 (0.61, 0.99)
Stage		
IIA	295	0.68 (0.46, 1.00)
IIB	174	0.88 (0.54, 1.42)
IIIA	413	0.81 (0.61, 1.06)
Regional lymph node stage (pN)		
N0	229	0.88 (0.57, 1.35)
N1	348	0.67 (0.47, 0.95)
N2	305	0.83 (0.61, 1.13)
SP263 PD-L1 status		
TC≥50%	229	0.43 (0.27, 0.68)
TC≥1%	476	0.66 (0.49, 0.87)
TC<1%	383	0.97 (0.72, 1.31)
***EGFR* mutation status**		
Yes	109	0.99 (0.60, 1.62)
No	463	0.79 (0.59, 1.05)
Unknown	310	0.70 (0.49, 1.01)
***ALK* rearrangement status**		
Yes	31	1.04 (0.38, 2.90)
No	507	0.85 (0.66, 1.10)
Unknown	344	0.66 (0.46, 0.93)

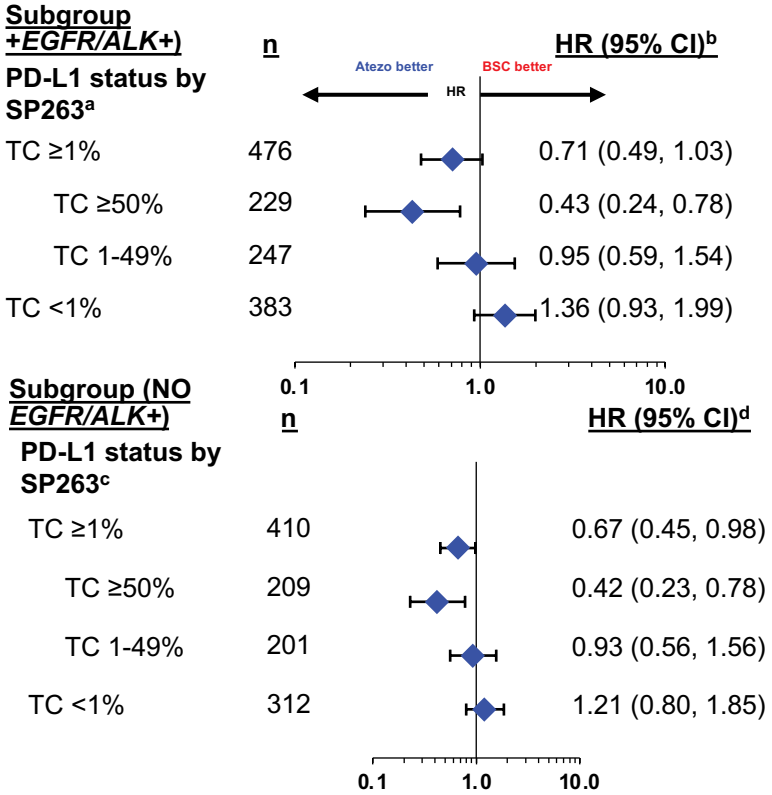


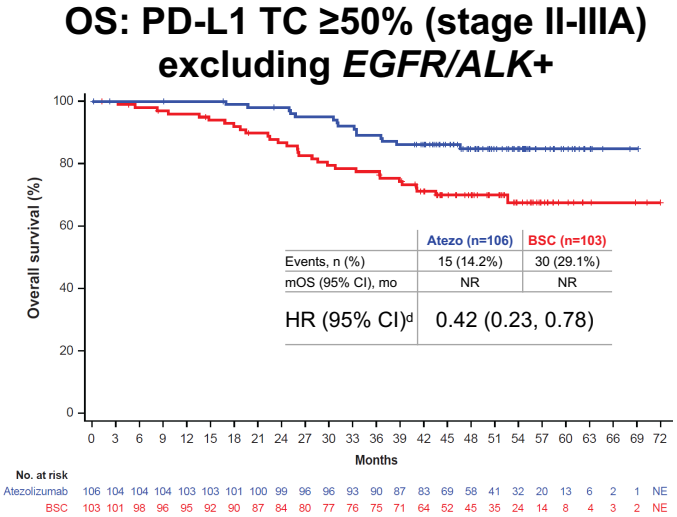


Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

Impower010 OS by Biomarkers (stage II-IIIA)

(data cutoff: 18 Apr ’22, 46 mo follow-up)

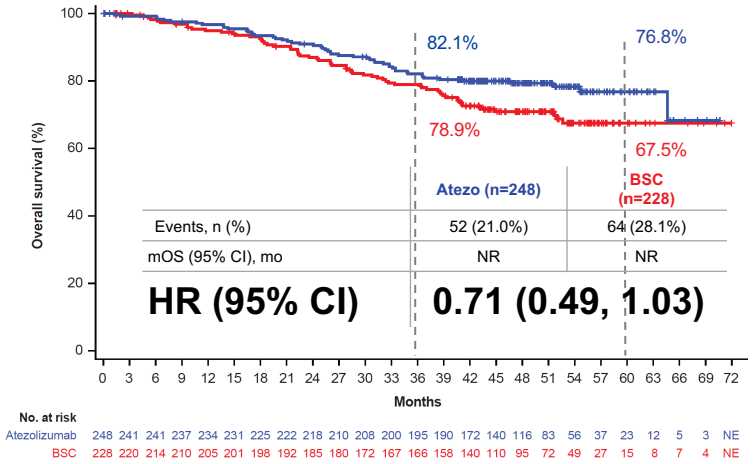




IMpower010: OS IA

(data cut 4/18/22: 46 mo med) f/up)

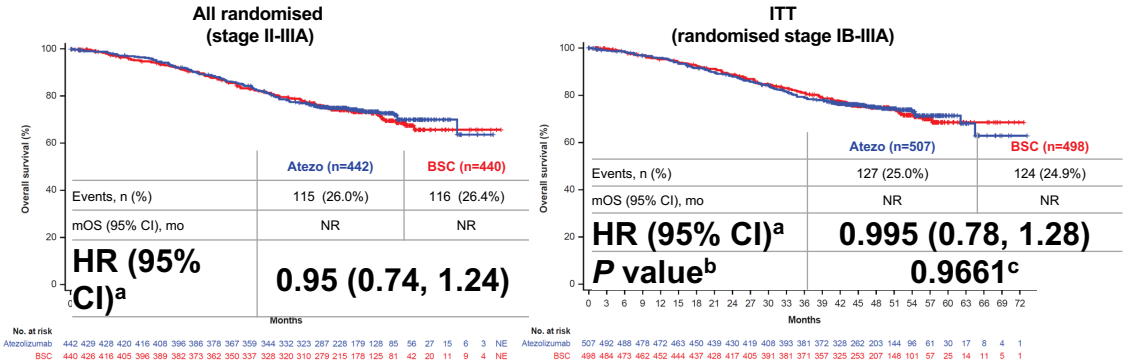
PD-L1 TC ≥1%[a] (stage II-IIIA)



Felip IASLC WCLC 2022 Presidential Plenary

- **At Initial Data Cut 1/21/21**
  - **PD-L1 TC ≥1% stage II-IIIA**
  - **OS HR: 0.77 (95% CI: 0.51, 1.17)**

IMpower010: Results of OS IA (data cut 4/18/22: 46 mo med f/up) Other primary populations



Clinical cutoff: 18 April 2022.[a] Stratified.[b] No formal testing until statistical significance observed for DFS in the ITT population due to the prespecified testing hierarchy.
[c] Descriptive purposes only.

IMpower010: safety summary[a]

n (%)	Atezolizumab (n=495)	BSC (n=495)
Any-cause AE	459 (92.7)	350 (70.7)
Treatment-related AE	335 (67.7)	–
Grade 3-4 AE	108 (21.8)	57 (11.5)
Treatment-related grade 3-4 AE	53 (10.7)	–
Serious AE	87 (17.6)	42 (8.5)
Treatment-related serious AE	37 (7.5)	–
Grade 5 AE	8 (1.6)[b]	3 (0.6)[c]
Treatment-related grade 5 AE	4 (0.8)	–
AE leading to dose interruption of atezolizumab	142 (28.7)	–
AE leading to atezolizumab discontinuation	90 (18.2)	–
Immune-mediated AEs	256 (51.7)	47 (9.5)
Grade 3-4 immune-mediated AEs	39 (7.9)	3 (0.6)
Immune-mediated AEs requiring the use of systemic corticosteroids	60 (12.1)	4 (0.8)

Clinical cutoff: January 21, 2021. AE, adverse event; [a] Data are from the safety population (all randomized patients who received ≥1 atezolizumab dose or for BSC, had ≥1 post-baseline assessment). [b] Interstitial lung disease*; pneumothorax; multiple organ dysfunction syndrome*; cerebrovascular accident; arrhythmia; myocarditis*; acute myeloid leukemia*; acute cardiac failure. [c] Pneumonia; pulmonary embolism; cardiac tamponade and septic shock in the same patient. *, Treatment related per investigator.

IMpower010: immune-mediated AEs[a]

imAEs occuring in ≥1% of patients

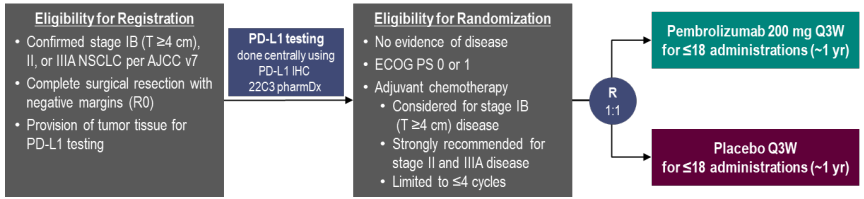
	Atezolizumab (n=495)		BSC (n=495)	
n (%)	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Any immune-mediated AEs	256 (51.7)[b]	39 (7.9%)	47 (9.5)	5 (0.6)
Rash	91 (18.4)	7 (1.4)	11 (2.2)	0
Hepatitis (diagnosis and laboratory abnormalities)	86 (17.4)	20 (4.0)	22 (4.4)	1 (0.2)
Hepatitis (laboratory abnormalities)	81 (16.4)	16 (3.2)	21 (4.2)	1 (0.2)
Hepatitis (diagnosis)	7 (1.4)	4 (0.8)	1 (0.2)	0
Hypothyroidism	86 (17.4)	0	3 (0.6)	0
Hyperthyroidism	32 (6.5)	2 (0.4)	4 (0.8)	0
Pneumonitis	19 (3.8)[c]	4 (0.8)	3 (0.6)	0
Infusion-related reaction	7 (1.4)	1 (0.2)	0	0
Adrenal insufficiency	6 (1.2)	2 (0.4)	0	0

Clinical cutoff: January 21, 2021. [a] Data are from the safety population (all randomized patients who received ≥1 atezolizumab dose or for BSC, had ≥1 post-baseline assessment). [b] Includes 2 (0.4%) Grade 5 events. [c] Includes 1 (0.2%) Grade 5 event.

imAEs occuring in <1% of patients

	Atezolizumab (n=495)		BSC (n=495)	
n (%)	**Any Grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Meningoencephalitis	4 (0.8)	3 (0.6)	0	0
Colitis	4 (0.8)	2 (0.4)	1 (0.2)	0
Diabetes mellitus	4 (0.8)	0	1 (0.2)	0
Myositis (myositis and rhabdomyolysis)	4 (0.8)	0	1 (0.2)	0
Pancreatitis	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Encephalitis	2 (0.4)	2 (0.4)	0	0
Severe cutaneous adverse reaction	2 (0.4)	0	0	0
Autoimmune hemolytic anemia	2 (0.4)	0	0	0
Myocarditis	2 (0.4)[c]	0	0	0
Meningitis	2 (0.4)	1 (0.2)	0	0
Guillain-Barre syndrome	1 (0.2)	1 (0.2)	0	0
Ocular inflammatory toxicity	1 (0.2)	0	1 (0.2)	1 (0.2)
Hypophysitis	1 (0.2)	0	0	0
Nephritis	1 (0.2)	0	0	0
Vasculitis	0	0	1 (0.2)	1 (0.2)

PEARLS/KEYNOTE-091 Study Design



Dual Primary End Points
- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points
- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

Characteristic	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Age, median (range), y	65.0 (31-87)	65.0 (37-85)	64.5 (38-82)	65.0 (37-85)
Male sex	68.0%	68.7%	72.0%	70.3%
Geographic region				
Asia	18.0%	17.9%	17.3%	17.6%
Eastern Europe	19.7%	19.3%	18.5%	18.2%
Western Europe	51.4%	51.3%	53.6%	53.9%
Rest of world	11.0%	11.6%	10.7%	10.3%
ECOG PS 1	35.6%	41.6%	31.0%	38.8%

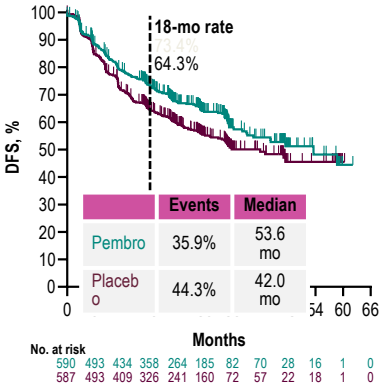
Characteristic	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 590)	Placebo (N = 587)	Pembro (N = 168)	Placebo (N = 165)
Current/former smoker	85.3%	88.8%	91.7%	92.1%
Nonsquamous histology	67.5%	61.8%	61.3%	63.6%
Received adjuvant chemotherapy	85.8%	85.9%	85.1%	85.5%
Pathologic stage[a]				
IB	14.2%	14.5%	12.5%	13.3%
II	55.8%	57.6%	56.5%	56.4%
IIIA	30.0%	27.6%	31.0%	30.3%
EGFR mutation[b]	6.6%	5.8%	3.6%	3.0%
ALK translocation[c]	1.2%	1.2%	1.8%	0.0%

[a]2 (0.3%) participants in the placebo arm had stage IV disease; neither had TPS ≥50%.
[b]*EGFR* mutation status was unknown for 670 (63.5%) in the overall population and 198 (59.5%) in the TPS ≥50% population.
[c]ALK translocation status was unknown for 747 (63.5%) in the ITT and 217 (65.2%) in the TPS ≥50% population.

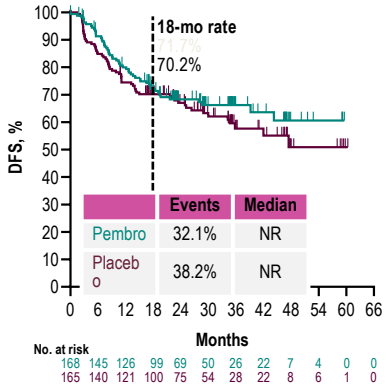
Paz-Ares ESMO plenary 2022, O'Brien ASCO 2022, Lancet Oncol 2023

PEARLS/KN-091:
Results Second Interim Analysis

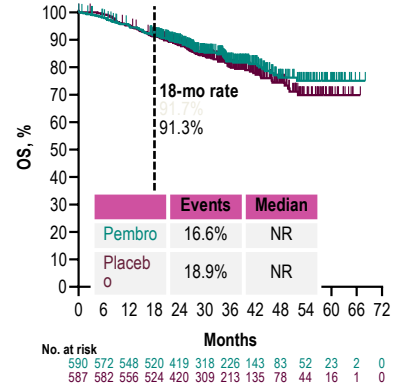
DFS, Overall Population
HR 0.76 (95% CI 0.63-0.91)
***P* = 0.0014**



DFS, PD-L1 TPS ≥50% Population
HR 0.82 (95% CI 0.57-1.18)
***P* = 0.14**



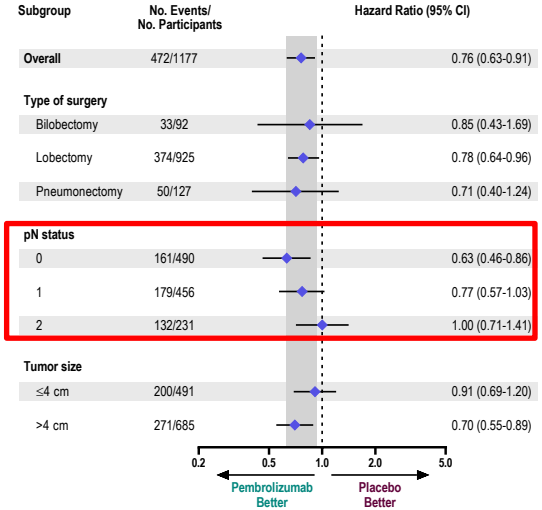
OS, Overall Population
HR 0.87 (95% CI 0.67-1.15)
***P* = 0.170**



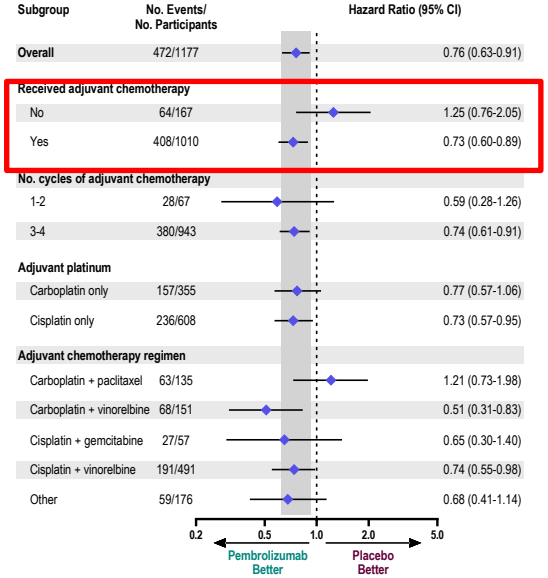
US FDA approval Jan 26, 2023

Impower010 DFS HR: all comer 0.81, PD-L1 ≥50% 0.43

KN-091 Results: DFS in Subgroups

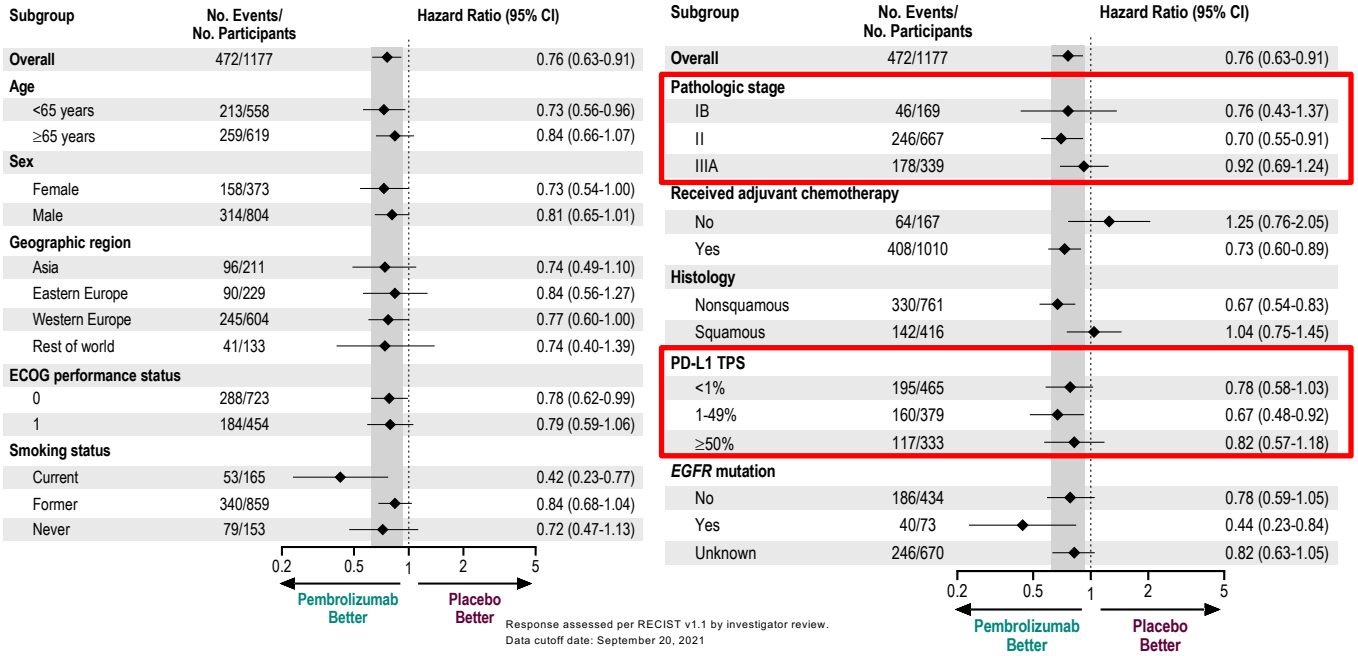


O'Brien ASCO 2022



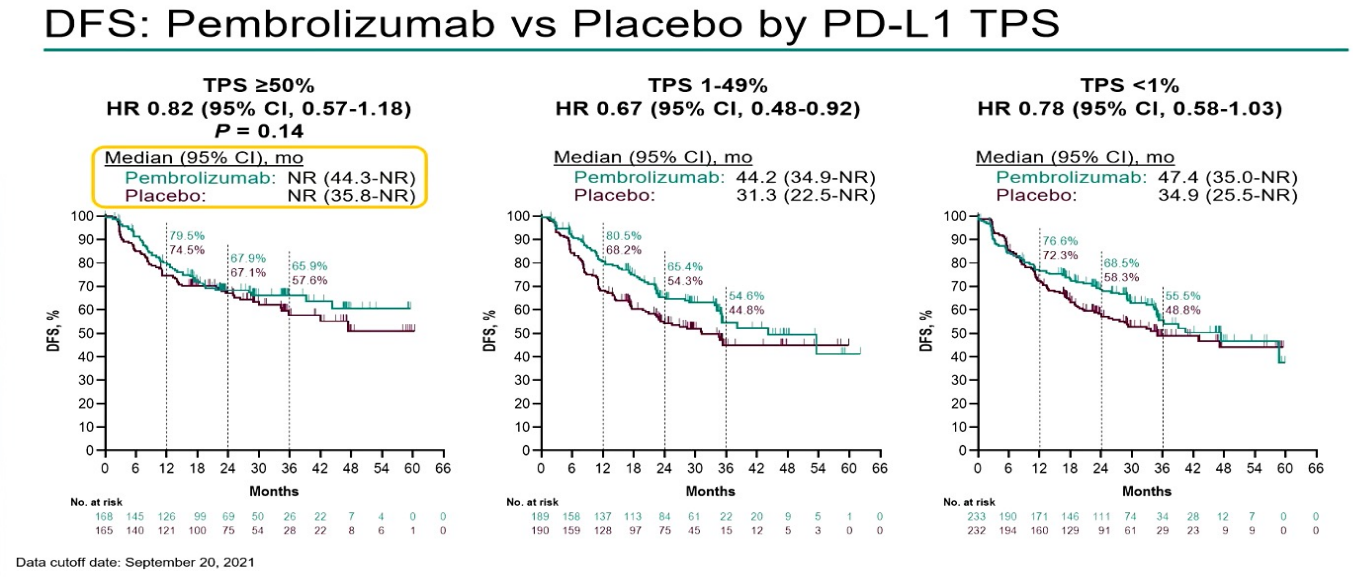
Paz Ares VirtualESMO2022, O'Brien ASCO 2022, Peters ESMO 2022

KN-091 Results: DFS in Subgroups



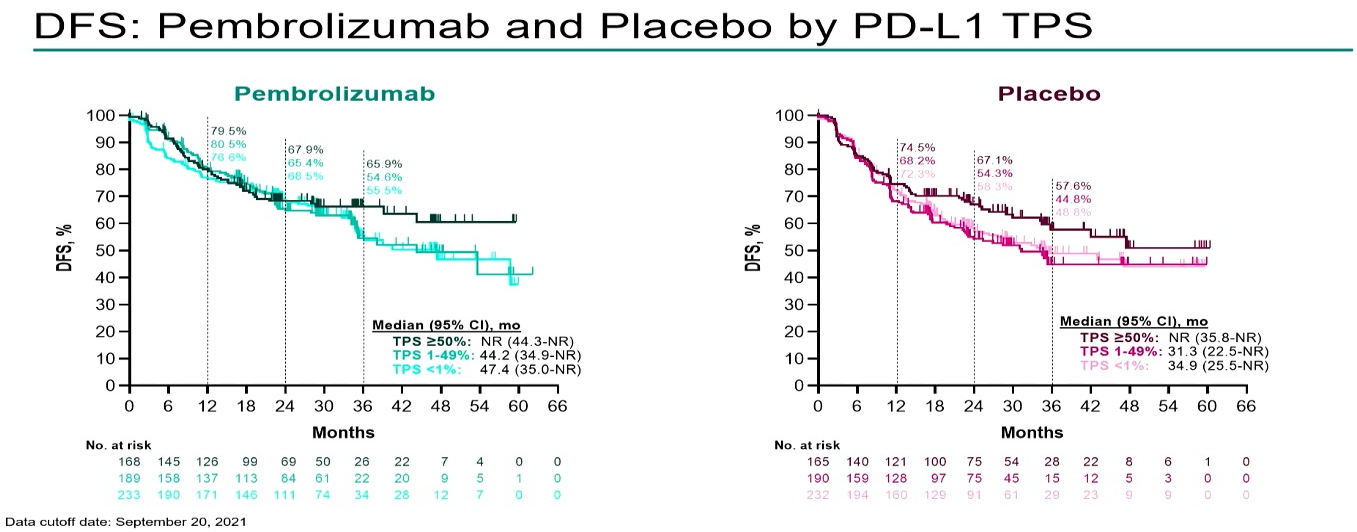
Paz Ares VirtualESMO2022, O'Brien ASCO 2022, Peters ESMO 2022

KN-091 DFS by PD-L1



Paz Ares VirtualESMO2022, O'Brien ASCO 2022, Peters ESMO 2022

KN-091 DFS for Pembro and Placebo by PD-L1

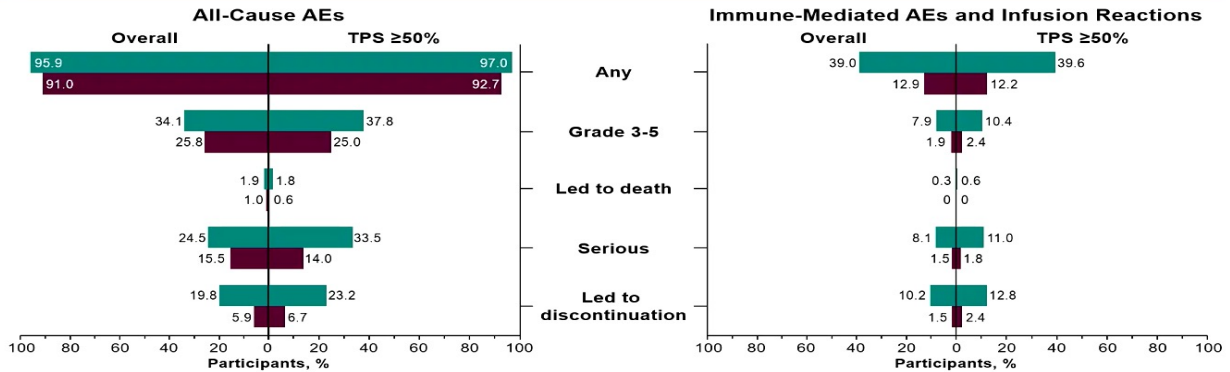


Paz Ares VirtualESMO2022, O'Brien ASCO 2022, Peters ESMO 2022

KN-091 Toxicity

7.3.O - Orléans Auditorium

Summary of Adverse Events and Exposure: Overall and PD-L1 TPS ≥50% Populations



Exposure, median (range)	Overall		PD-L1 TPS ≥50%	
	Pembro (N = 580)	Placebo (N = 581)	Pembro (N = 164)	Placebo (N = 164)
No. of administrations	17 (1-18)	18 (1-19)	17 (1-18)	18 (1-18)

Data cutoff date: September 20, 2021

Paz Ares VirtualESMO2022, O'Brien ASCO 2022, Peters ESMO 2022

Adjuvant PD-1/PD-L1 IO trials

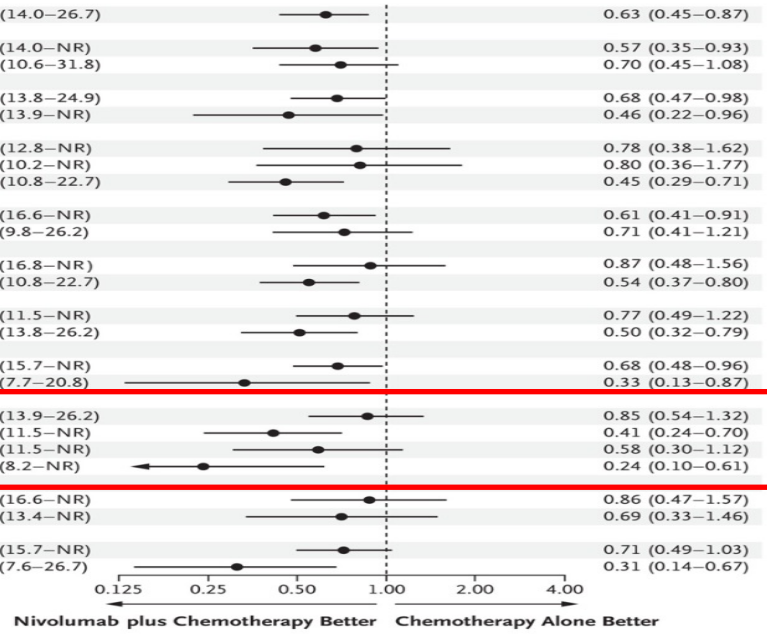
Drug/Trial	Description	Stages entered	Description	Primary endpoint
Nivolumab ANVIL arm of ALCHEMIST	US, NCI (ECOG), Observational control	IB (4cm)-IIIA After Adj Chemo +/- radiation	Phase 3 Allows PD-L1 +/-	OS/DFS
Atezolizumab IMPOWER010	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Durvalumab Mermaid-1	Global, Placebo controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS
Pembrolizumab PEARLS KN-091	ETOP/EORTC, Placebo Controlled	IB (4cm)-IIIA After Adj Chemo	Phase 3 Allows PD-L1 +/-	DFS

Surrogates: PD-L1

CM816 PD-L1

B

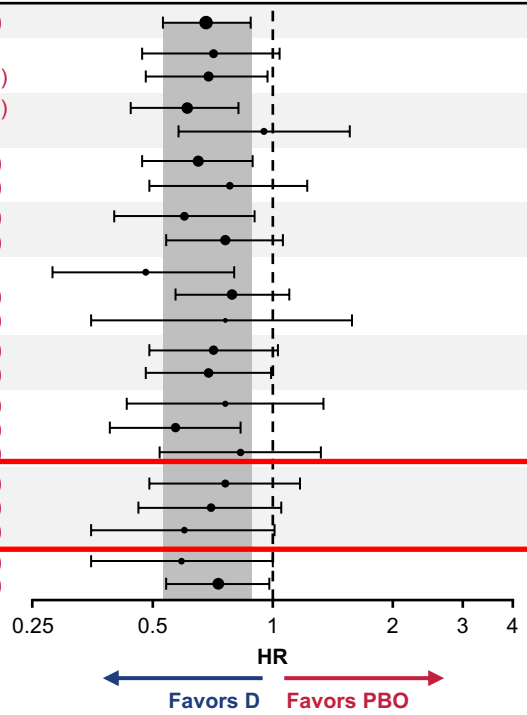
Subgroup	No. of Patients	Median Event-free Survival (95% CI) — Nivolumab plus chemotherapy (N=179)	Median Event-free Survival (95% CI) — Chemotherapy alone (N=179)
		mo	
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)
Age			
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)
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)



Forde NEJM

AEGEAN: EFS using RECIST v1.1 (BICR) by subgroup (mITT)

Subgroup		n	Median EFS, months (95% CI) D arm (N=366)	Median EFS, months (95% CI) PBO arm (N=374)	HR (95% CI)
All patients		740	NR (31.9–NR)	25.9 (18.9–NR)	0.68 (0.53–0.88)
Age at randomization	<65 years	358	NR (NR–NR)	NR (18.9–NR)	0.71 (0.47–1.04)
	≥65 years	382	NR (17.9–NR)	24.5 (13.6–31.1)	0.69 (0.48–0.97)
Sex	Male	530	NR (31.9–NR)	22.9 (14.3–31.1)	0.61 (0.44–0.82)
	Female	210	NR (17.5–NR)	NR (13.6–NR)	0.95 (0.58–1.56)
ECOG PS	0	506	NR (31.9–NR)	25.4 (14.3–NR)	0.65 (0.47–0.89)
	1	234	NR (21.8–NR)	25.9 (14.3–NR)	0.78 (0.49–1.22)
Race*	Asian	307	NR (NR–NR)	25.4 (13.9–NR)	0.60 (0.40–0.90)
	Non-Asian	433	31.9 (21.8–NR)	26.2 (14.3–NR)	0.76 (0.54–1.06)
Smoking	Current	190	NR (NR–NR)	14.3 (8.1–NR)	0.48 (0.28–0.80)
	Former	443	NR (31.9–NR)	25.9 (19.5–NR)	0.79 (0.57–1.10)
	Never	107	NR (NR–NR)	24.5 (14.3–NR)	0.76 (0.35–1.58)
Histology	Squamous	360	NR (31.9–NR)	26.2 (13.0–NR)	0.71 (0.49–1.03)
	Non-squamous	375	NR (NR–NR)	25.4 (14.3–NR)	0.69 (0.48–0.99)
Disease stage (AJCC 8th ed.)	Stage II	214	NR (NR–NR)	31.1 (25.4–NR)	0.76 (0.43–1.34)
	Stage IIIA	338	NR (NR–NR)	19.5 (11.7–NR)	0.57 (0.39–0.83)
	Stage IIIB	186	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83 (0.52–1.32)
PD-L1 expression at baseline†	TC <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
	TC 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
	TC ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)
Planned neoadjuvant platinum agent	Cisplatin	196	NR (NR–NR)	31.1 (14.3–NR)	0.59 (0.35–1.00)
	Carboplatin	544	NR (31.9–NR)	25.4 (14.3–NR)	0.73 (0.54–0.98)

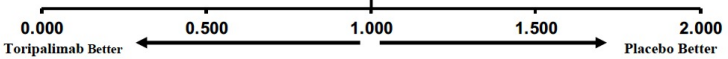


DCO = Nov 10, 2022; median EFS follow-up in censored patients: 11.7 months (range: 0.0–46.1); EFS maturity: 31.9%. Median calculated using the Kaplan–Meier method; HR for all patients (mITT) calculated using a stratified Cox proportional hazards model. HRs for subgroups calculated using unstratified Cox proportional hazards models. The size of circles is proportional to the number of events for each subgroup, and the horizontal bars represent the 95% CIs. *Race was self-reported per the electronic case report form. †Determined using the Ventana SP263 immunohistochemistry assay.

NEOTORCH

INV-EFS Treatment Effects in Key Subgroups

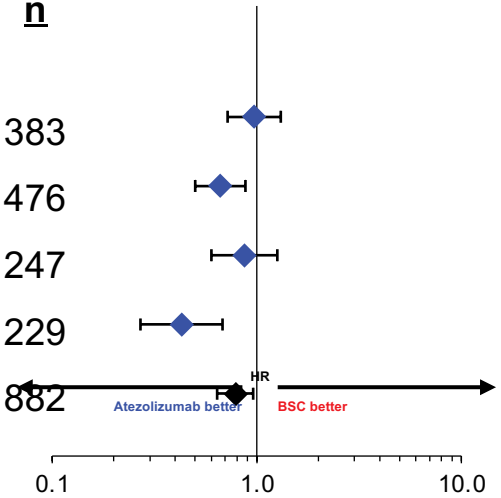
Subgroups	Toripalimab + Chemo Events/Total	Placebo + Chemo Events/Total	Hazard Ratio (95% CI)
Disease Stage			
IIIA	34/136	65/136	0.44 (0.287, 0.661)
IIIB	13/65	31/64	0.30 (0.149, 0.559)
PD-L1 Expression			
TC>=1%	28/133	65/132	0.31 (0.197, 0.481)
TC<1% or Not Evaluable	19/69	32/70	0.59 (0.327, 1.034)
Pathological Type			
Non-squamous Cell Carcinoma	12/45	21/45	0.54 (0.257, 1.079)
Squamous Cell Carcinoma	35/157	76/157	0.35 (0.234, 0.523)
Age			
<65	33/140	66/138	0.41 (0.267, 0.618)
>=65	14/62	31/64	0.34 (0.177, 0.635)
Sex			
Male	42/181	91/189	0.38 (0.259, 0.541)
Female	5/21	6/13	0.54 (0.154, 1.796)
ECOG			
0	20/70	38/73	0.44 (0.249, 0.743)
1	27/132	59/129	0.36 (0.226, 0.566)
Smoking			
Yes (Including Smoker or Former)	39/174	88/181	0.37 (0.252, 0.539)
No	8/28	9/21	0.52 (0.193, 1.358)



Lu, S ASCO Virtual Plenary April 20, 2023

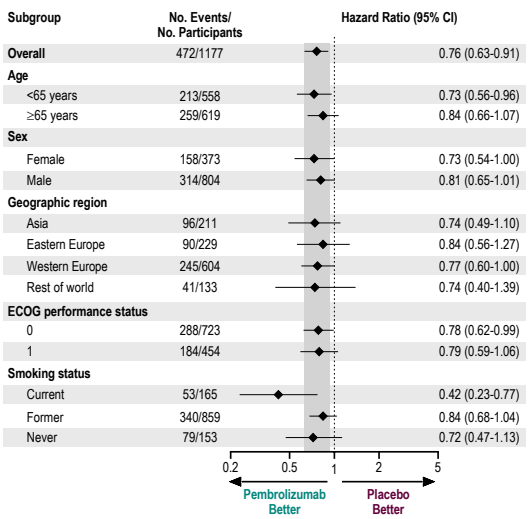
IMpower010 PD-L1

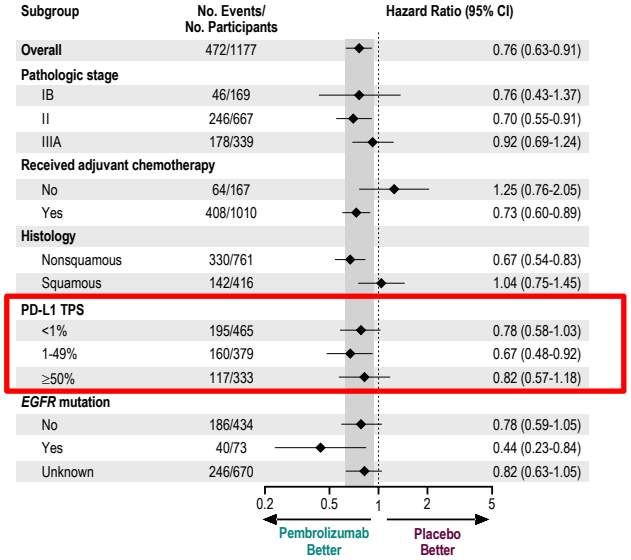
Subgroup *(including EGFR/ALK+)*	n	HR (95% CI)[b,c]
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)



Felip ESMO2021

KN-091 DFS in Key Subgroups, Overall Population





Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

Paz Ares VirtualESMO2022, O'Brien ASCO 2022, Peters ESMO 2022

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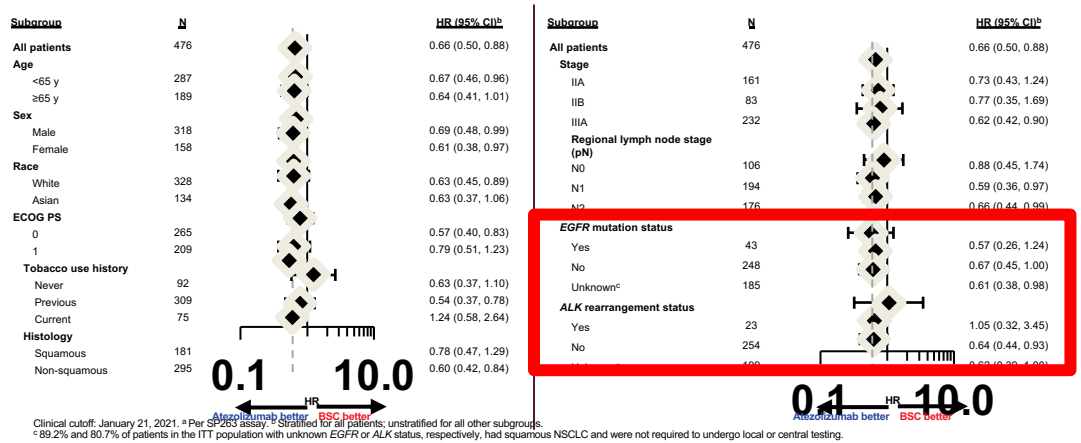
Surrogates: Driver Mutations

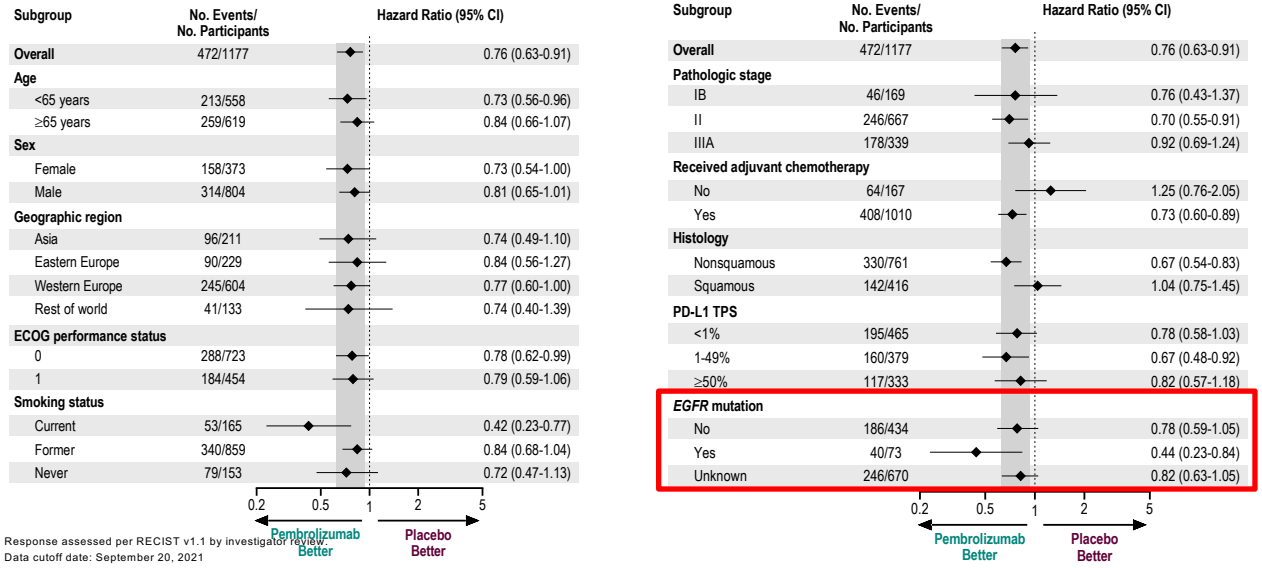
IMpower010: DFS in key subgroups of the PD-L1 TC ≥1% stage II-IIIA population



Clinical cutoff: January 21, 2021. [a] Per SP263 assay. [b] Stratified for all patients; unstratified for all other subgroups.
[c] 89.2% and 80.7% of patients in the ITT population with unknown *EGFR* or *ALK* status, respectively, had squamous NSCLC and were not required to undergo local or central testing.

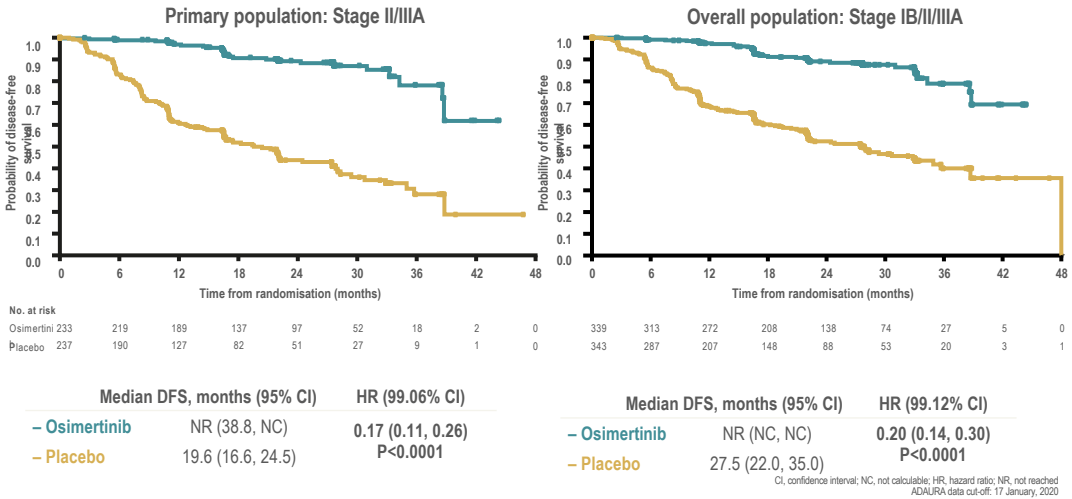
Dr. Heather A. Wakelee ASCO 2021, abstr 8500:IMpower010 Interim Analysis; https://bit.ly/33t6JJ; Felip Lancet 2021

KN-091 DFS in Key Subgroups, Overall Population



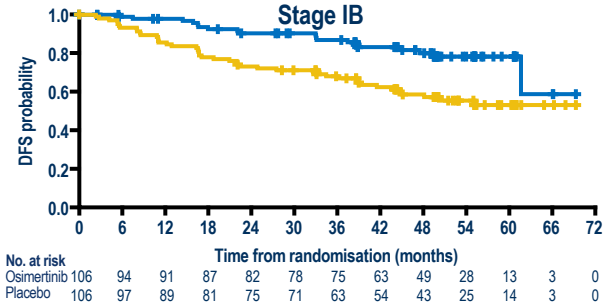
Paz Ares VirtualESMO2022, O'Brien ASCO 2022, Peters ESMO 2022

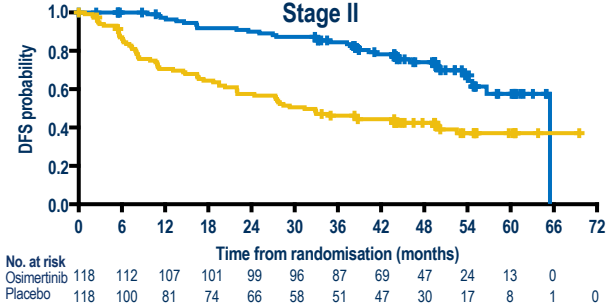
ADAURA: Randomized Phase III of 3 years Adjuvant Osimertinib improves DFS in pts w resected EGFRmut NSCLC



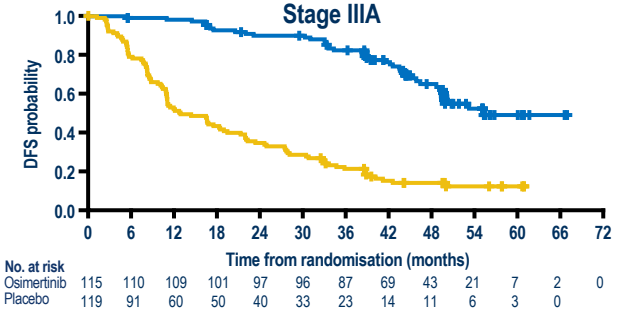
Tsuboi ESMO 2020

ADAURA: UPDATED DFS BY STAGE (AJCC / UICC 7TH EDITION)





	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (70, 87)	74 (64, 82)	65 (54, 74)
– Placebo	59 (48, 68)	42 (33, 51)	14 (8, 22)
Overall HR (95% CI)	0.41 (0.23, 0.69)	0.34 (0.23, 0.52)	0.20 (0.14, 0.29)



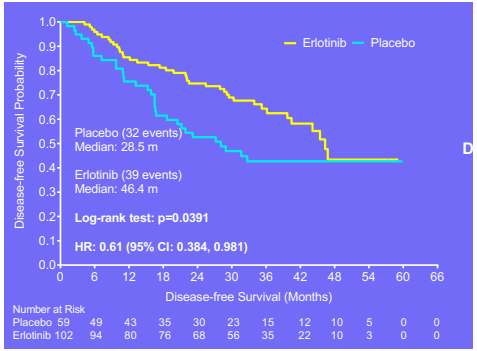
DFS by investigator assessment; Tick marks indicate censored data.

AJCC / UICC, American Joint Committee on Cancer / Union for International Cancer Control; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio
Data cut-off: April 11, 2022.

Masahiro Tsuboi, MD

DFS did NOT = OS in other EGFR TKI Adjuvant trials : BUT ADAURA + OS (per Press release)!!

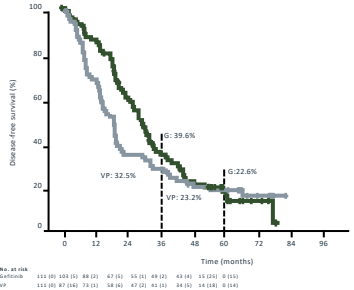
RADIANT DFS/OS – *EGFR* M+

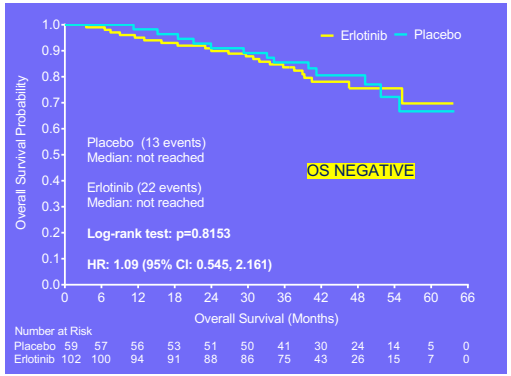


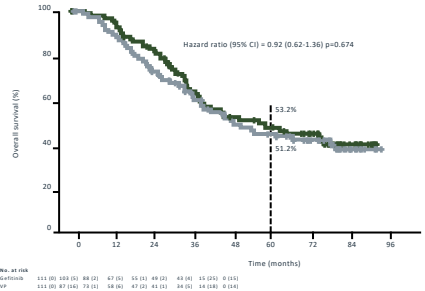
Kelly JCO 2015

CTONG1104/ADJUVANT: DFS/OS

HR (95% CI) = 0.92 (0.62-1.36) p=0.674





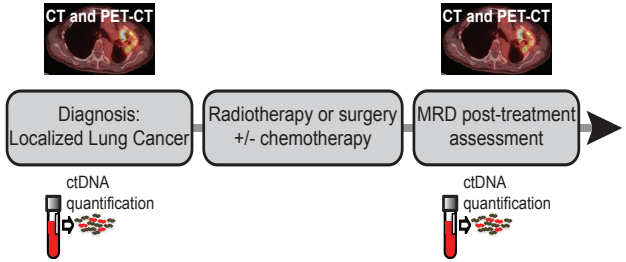


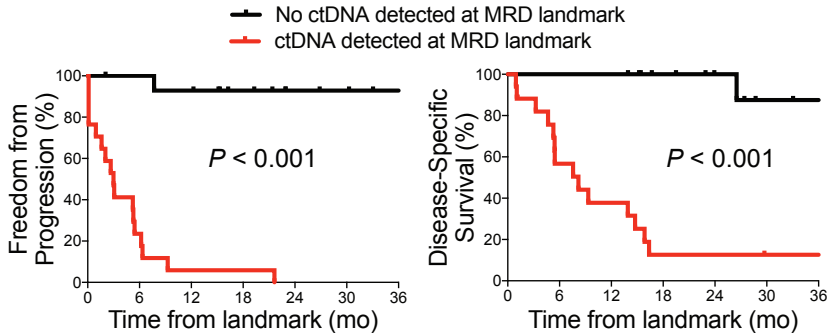
Wu Y-L, et al. ASCO 2020. Abstract 9005

Surrogates: ctDNA

How do we avoid overtreatment

The Promise of MRD



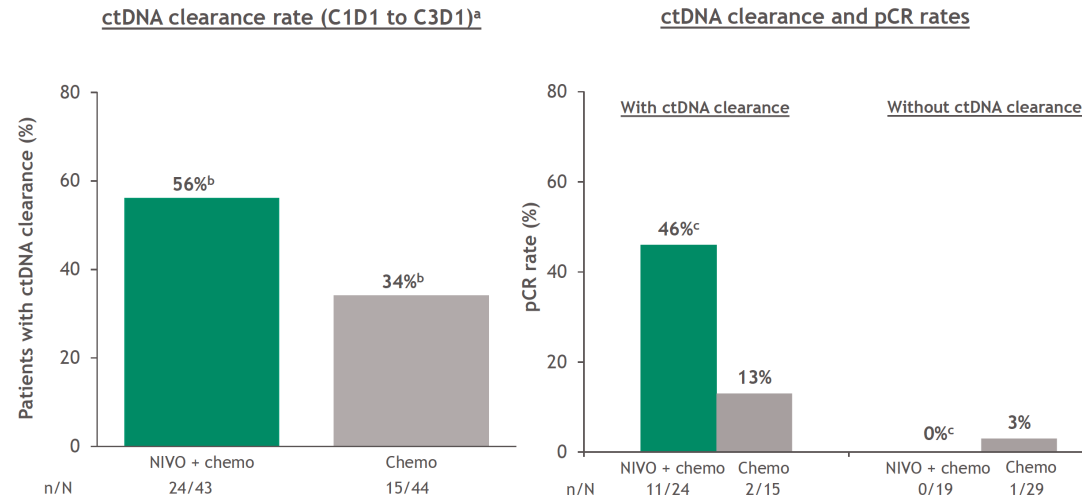


M. Diehn / Stanford

Chaudhuri et al *Cancer Discovery* 2017

CM816 ctDNA data

ctDNA clearance and association with pathological response

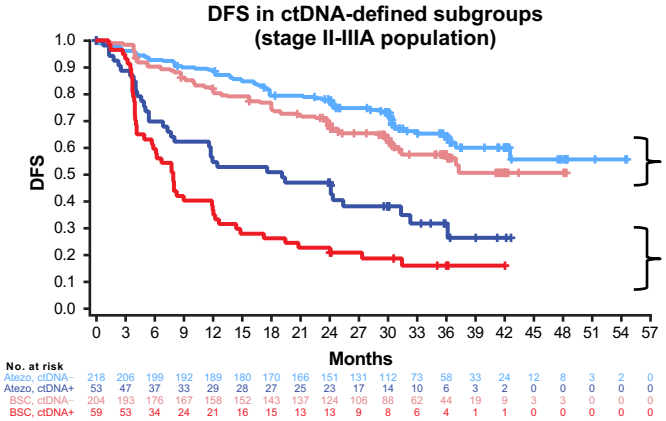


[a]Performed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring); 90 patients were ctDNA evaluable and 87 had detectable ctDNA at C1D1; main reason for sample attrition were lack of tissue for WES and lack of quality control pass for tissue and plasma; [b]ctDNA clearance 95% CI: NIVO + chemo, 40-71; chemo, 20-50; [c]pCR rates 95% CI for NIVO + chemo: with ctDNA clearance, 26-67; without ctDNA clearance, 0-18.

Forde CM816 AACR

IMpower010 ctDNA data

In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

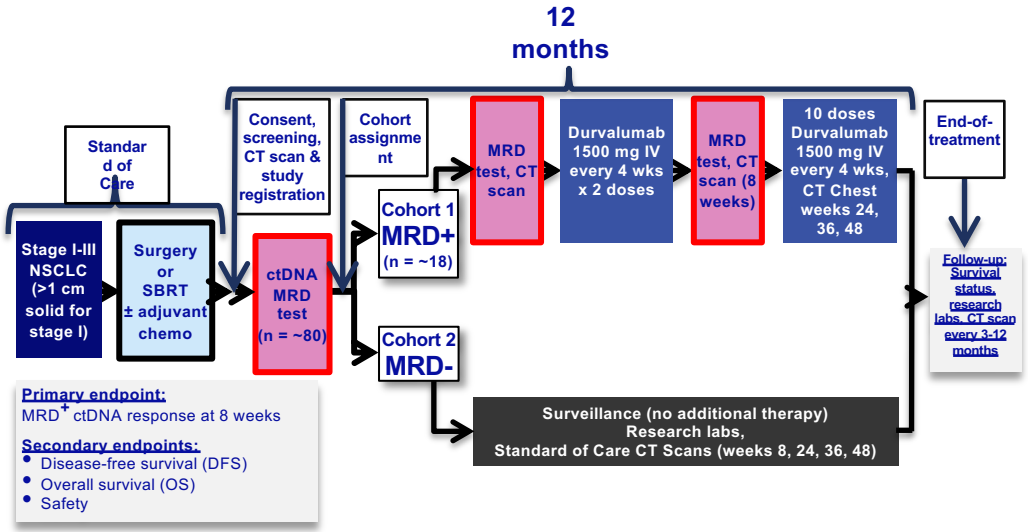


ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

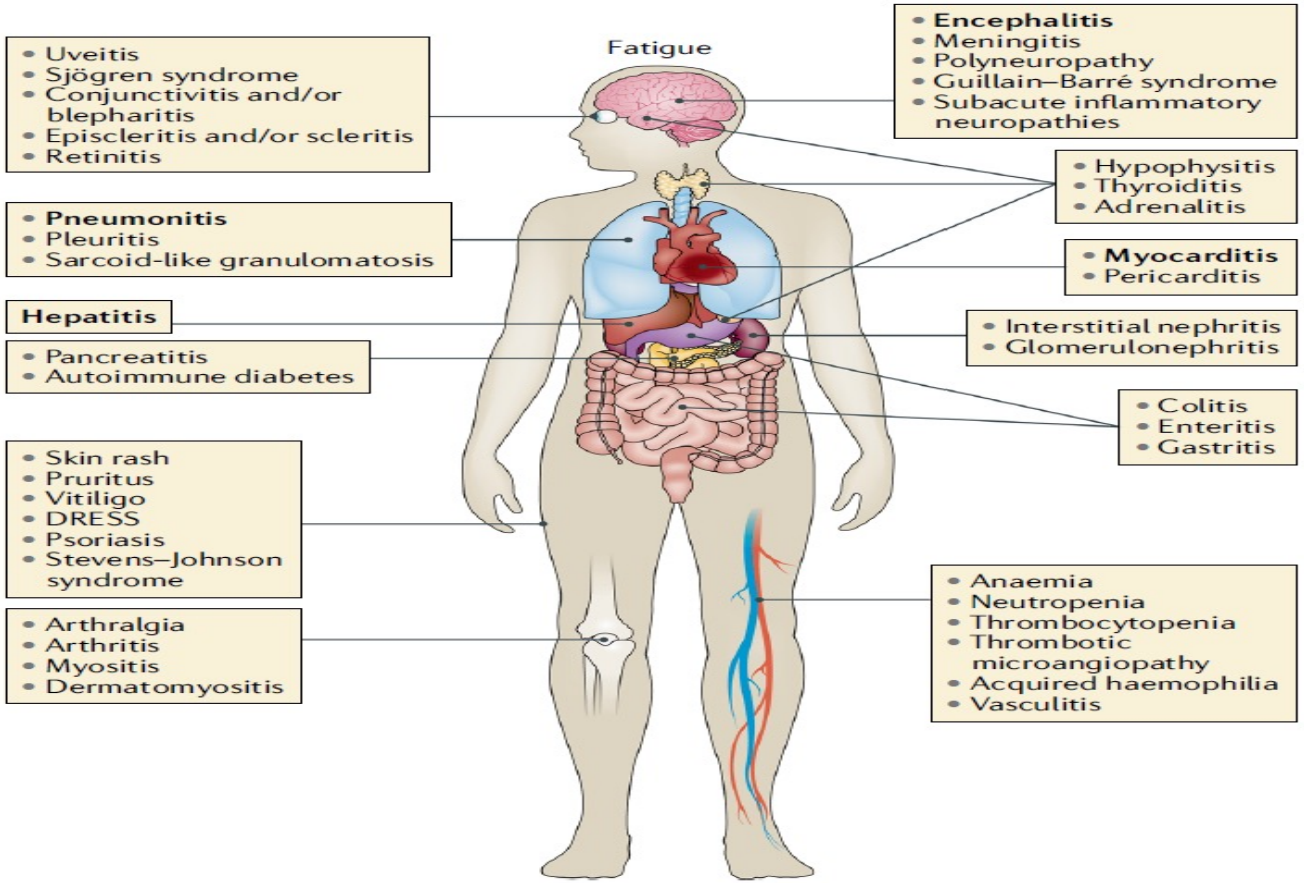
Zhou C et al, ESMO IO 2021

Adjuvant Durvalumab for Early Stage NSCLC with ctDNA MRD after surgery – ongoing trial



PIs: Neal and Diehn

There is ALWAYS a risk for Toxicity:IR AE by site



Martins F, et al. Nat Rev Clin Oncol. 2019 Sep;16(9):563-580. PMID 31092901

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EVOLVING TREATMENTS FOR THE ONCOLOGY PRACTICE

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Neo-adj vs adj – how much does it matter?

Both beneficial, maybe all patients will get Peri-operative (ie both)

How much does the chemotherapy matter?

? Concurrent better, in KN-091 only benefit if given after chemotherapy (not instead of)

Does PD-L1 matter?

YES (except in 1 trial)

How do driver mutations factor in? **Confusing in the IO setting for EGFR**

Do we use stage to determine strategy? **Probably**

Neo-Adjuvant

1)Achieves high pCR

2)Requires treating every patient – toxicity, overtreatment

3)Risks ~10-20% loss of surgery

4)All ongoing neo-adjuvant trials also give adjuvant therapy

*Could neo-adjuvant chemotherapy-IO be given instead of surgery if pCR achieved?

Adjuvant

1) Atezo Improves DFS in pts with PD-L1+ stage II-IIIA NSCLC

2) Pembro Improves DFS but no selection criteria

3) Can potentially be limited to those with ctDNA after resection – not there yet

4)By definition all patients have had surgery

*Can adjuvant IO alone be sufficient to avoid chemotherapy?

Neo-Adj preferred for stage III
Adjuvant may be better for stage I/II

TKI therapy – Osimertinib Profound DFS benefit as Adjuvant in EGFRmut NSCLC

Ongoing neo-adjuvant trial, OS data to be reported, ? Other drivers

Neo-adjuvant IO

– Nivolumab + Chemotherapy a standard

Positive trials with durvalumab, toripalimab, pembrolizumab

Adjuvant IO

– Adjuvant Atezolizumab and Pembolizumb both Positive trials

Many other trials coming soon!

Biomarkers

-PD-L1 useful in most trials, look for driver mutations

How do we avoid "over-treatment?"

-ctDNA and other technology

Use the right treatment to achieve the best possible outcome for every patient

Do not give any more treatment than is necessary to achieve cure