Most Relevant Data on Immunotherapy in Neo-Adjuvant, Adjuvant, and Metastatic NSCLC

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CANCER CENTER of EXCELLENCE
Florida HEALTH

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Neoadjuvant Immunotherapy in NSCLC

CheckMate 816 study design[a]

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG performance status 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
Stage (IB-II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex

N = 358

R 1:1

Primary analysis population

NIVO 360 mg Q3W + chemo[d] Q3W (3 cycles)

Chemo[e] Q3W (3 cycles)

NIVO 3 mg/kg Q2W (3 cycles) + IPI 1 mg/kg (cycle 1 only)[f]

FDA approved 3/2022

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT[g] → Follow-up

Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

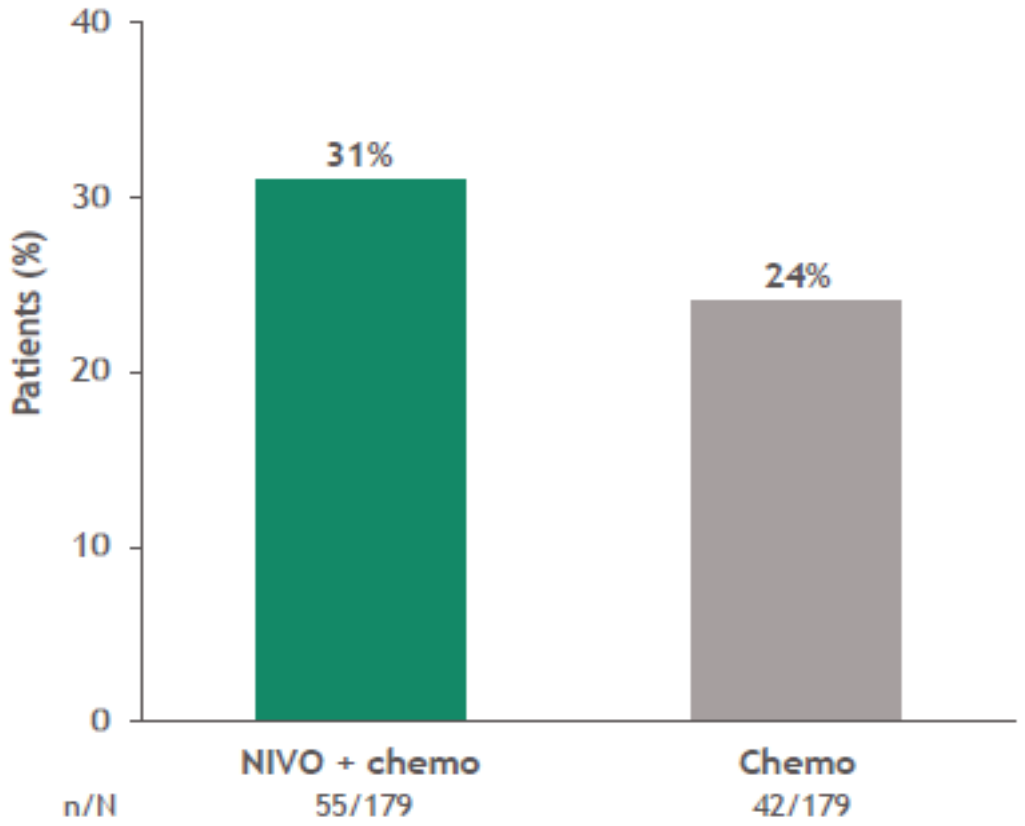
Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

Objective response rate and radiographic down-staging

Objective response rate

Patients, n (%)	NIVO + chemo (n = 179)	Chemo (n = 179)
ORR[a]	96 (54)[b]	67 (37)[b]
Best overall response		
Complete response	1 (1)	3 (2)
Partial response	95 (53)	64 (36)
Stable disease	70 (39)	88 (49)
Progressive disease	8 (4)	11 (6)
Not evaluable	1 (1)	1 (1)
Not reported	4 (2)	12 (7)

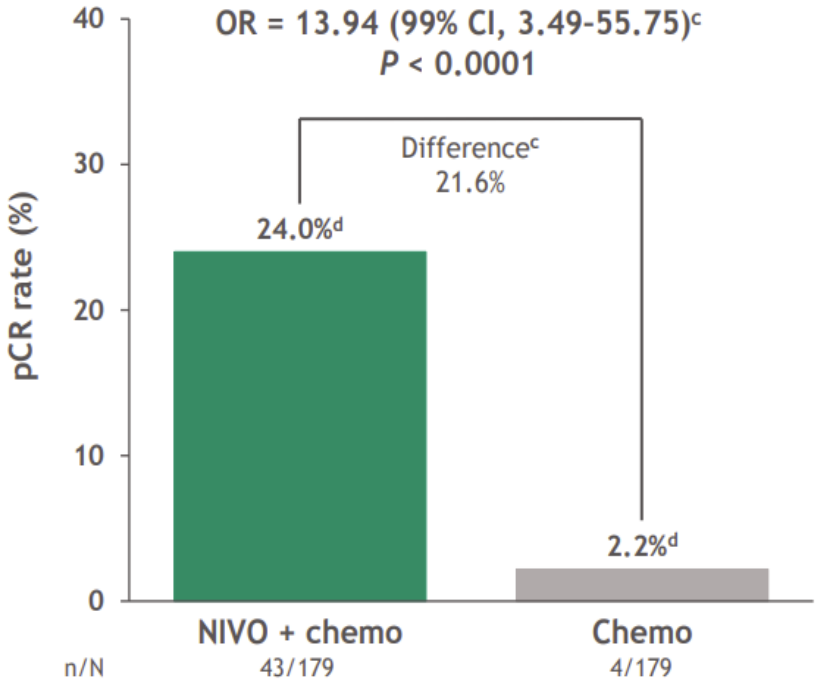
Patients with radiographic down-staging[c]



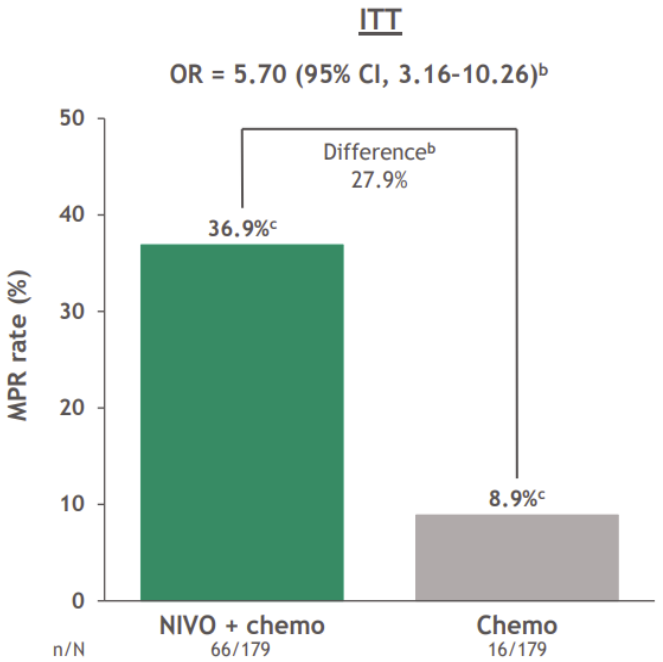
[a]Objective response rate was up to the presurgical scan; [b]ORR rates 95% CI: NIVO + chemo, 46-61; chemo, 30-45; [c]Decrease in stage from baseline to presurgical scan.

Primary endpoint: pCR[a] rate with neoadjuvant NIVO + chemo vs chemo

Primary endpoint: ITT (ypT0N0)[b]

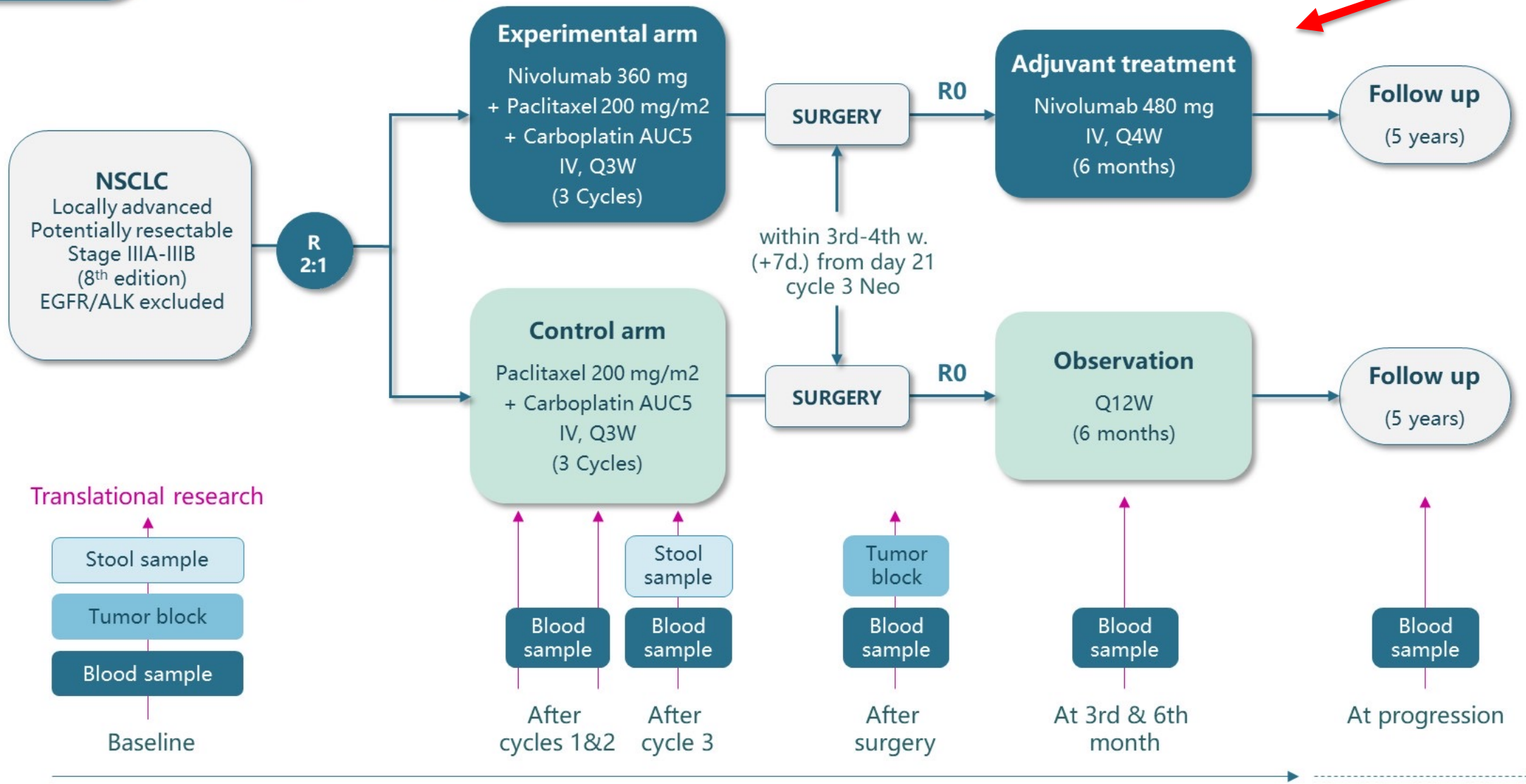


MPR[a] rate with neoadjuvant NIVO + chemo vs chemo



[a]Per BIPR; MPR: ≤ 10% residual viable tumor cells in both the primary tumor (lung) and sampled lymph nodes; [b]Calculated by stratified Cochran-Mantel-Haenszel method; [c]MPR rates 95% CI: NIVO + chemo, 29.8-44.4; chemo, 5.2-14.1.

NADIM II Study design

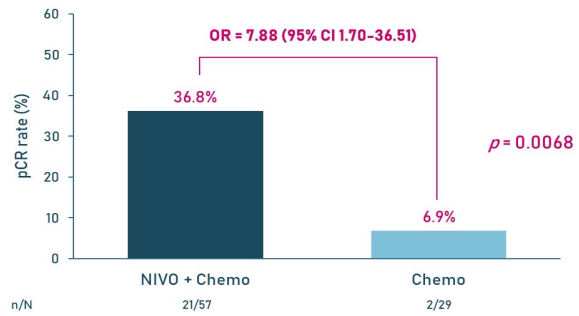


NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

NADIM II Primary endpoint - pCR

pCR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population[b]



Percentage of patients with a complete response

NNT: 3.34 (2.2—6.95)

[a]pCR was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders
Chemo, chemotherapy; ITT, intention-to-treat; Nivo, nivolumab; pCR, pathological complete response; RR, risk ratio

PRESENTED BY: Mariano Provencio MD, PhD.
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Spanish Lung Cancer Group

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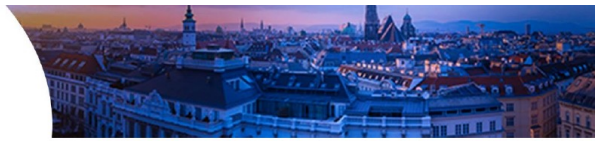
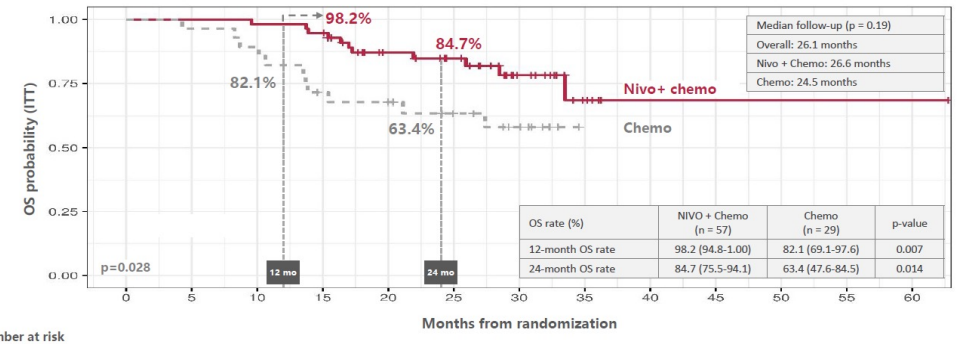


SECONDARY ENDPOINTS – Overall survival



OS rate (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)	p-value
12-month OS rate	98.2 (94.8-1.00)	82.1 (69.1-97.6)	0.007
24-month OS rate	84.7 (75.5-94.1)	63.4 (47.6-84.5)	0.014

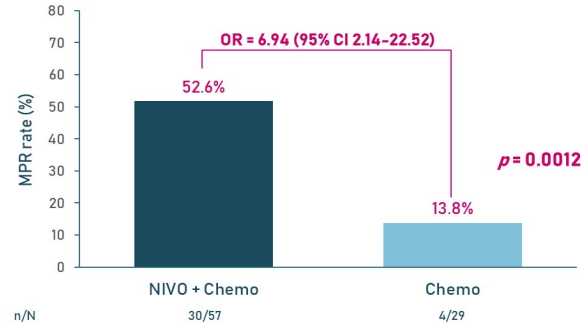
Number at risk

Nivo + chemo	56	56	55	53	37	31	15	5	1	1	1	1	1
Chemo	28	27	25	19	17	13	9	0	0	0	0	0	0

Overall survival was defined as the time from randomization to death. OS was censored on the last date a participant was known to be alive

NADIM II Secondary endpoints - MPR

MPR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population [b]



Percentage of patients with a complete response or a major response

NNT: 2.57 (1.76–4.81)

[a]MPR was defined as ≤10% residual viable tumor cells in both the primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders
Chemo, chemotherapy; ITT, intention-to-treat; MPR, major pathological response; Nivo, nivolumab; RR, risk ratio

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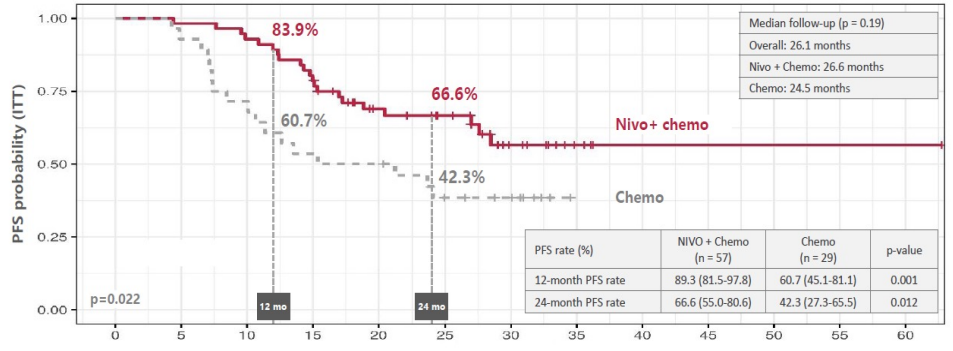
SECONDARY ENDPOINTS – Progression-free survival



PFS rate (%)	NIVO + Chemo (n = 57)	Chemo (n = 29)	p-value
12-month PFS rate	89.3 (81.5-97.8)	60.7 (45.1-81.1)	0.001
24-month PFS rate	66.6 (55.0-80.6)	42.3 (27.3-65.5)	0.012

Number at risk

Nivo + chemo	56	55	52	44	30	24	11	4	1	1	1	1	1
Chemo	28	26	20	15	14	9	7	0	0	0	0	0	0

Progression-free survival was defined as the time from randomization to any of the following events: progression of disease, recurrence disease, or death due to any cause. Progression/recurrence will have determined by RECIST 1.1

ADJUVANT IMMUNOTHERAPY IN NSCLC

IMpower010: Phase III randomised trial of atezolizumab vs BSC in early-stage NSCLC

Completely resected stage IB-IIIA[a] NSCLC

- Stage IB tumors ≥4 cm
- ECOG 0-1
- Lobectomy
- Tumor tissue for PD-L1 analysis

Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

1-4 cycles

N=1280

R 1:1

No crossover

Atezolizumab 1200 mg q21d x 16 cycles or 1 year

N = 1005

BSC

Survival follow-up

Stratification factors

- Sex | Stage | Histology | PD-L1 status

Primary endpoint

- Investigator-assessed DFS tested hierarchically

Key secondary endpoints

- OS in ITT | DFS in PD-L1 TC ≥50% | 3-yr and 5-year DFS

Key exploratory endpoints

- 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.

Hierarchical statistical testing of endpoints

DFS in PD-L1 TC ≥1% stage II–IIIA population[b]

If positive:

DFS in all-randomized stage II–IIIA population[b]

If positive:

DFS in ITT population (stage IB-IIIA)[b]

If positive:

OS in ITT population[b]

Endpoint was met at DFS IA

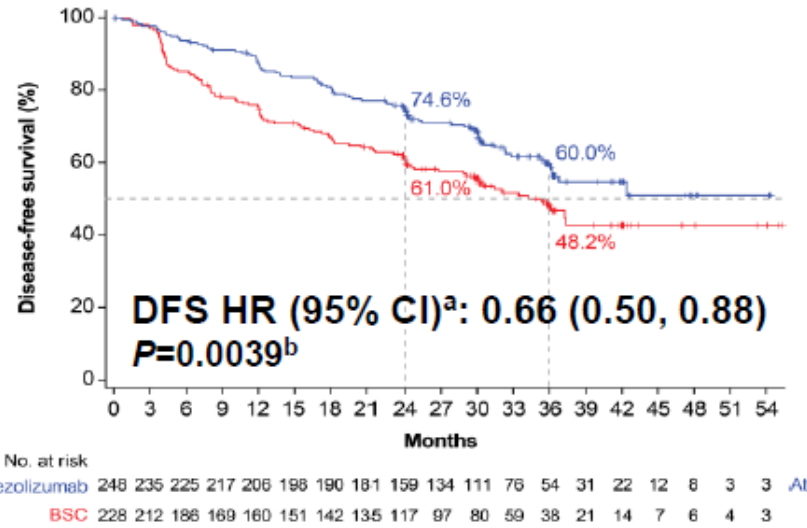
Endpoint was not met at DFS IA and follow up is ongoing

Endpoint was not formally tested

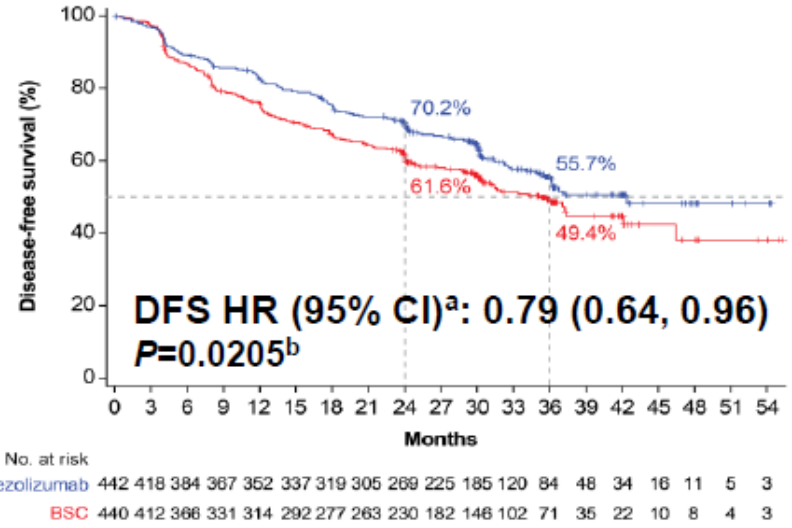
Recap of DFS and OS data from the DFS IA[1,2]

(data cutoff: 21 Jan '21, median follow-up: 32 months)

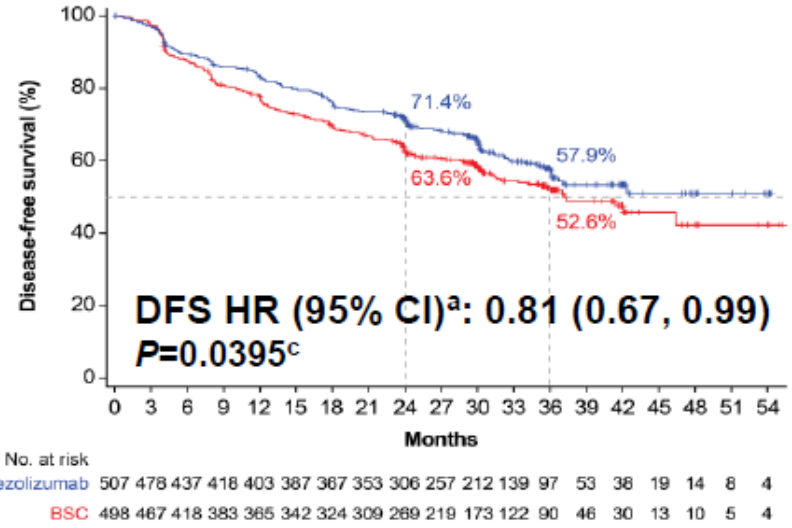
DFS: PD-L1 TC ≥1% stage II-IIIA population



DFS: All-randomised stage II-IIIA population



DFS: ITT (randomised stage IB-IIIA) population



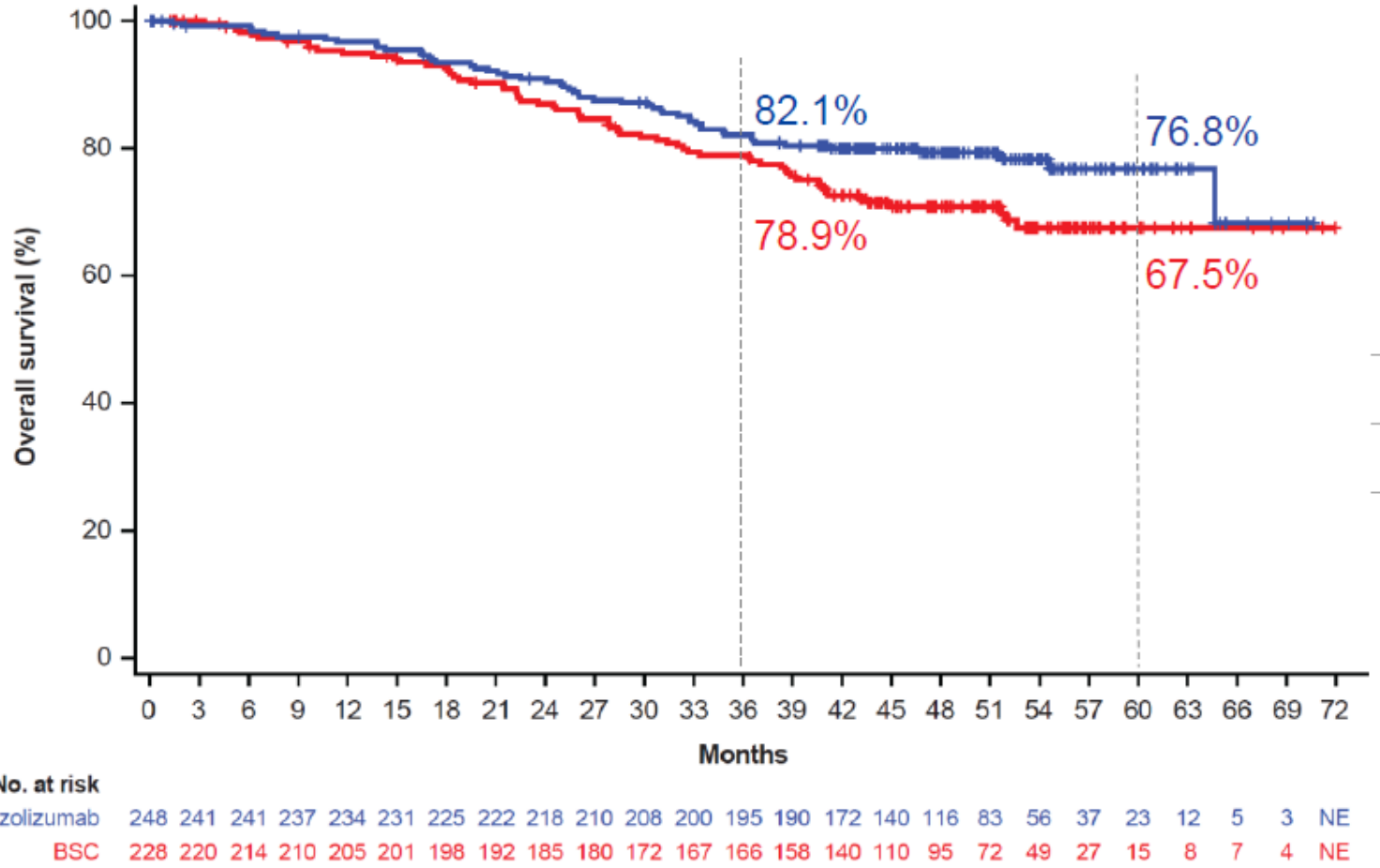
- **OS data** were not mature (event to patient ratio in ITT was 19% in atezolizumab arm, 18% in BSC arm)
  - PD-L1 TC ≥1% stage II-IIIA population: OS HR, 0.77 (95% CI: 0.51, 1.17)[a]
  - All-randomised stage II-IIIA population: OS HR, 0.99 (95% CI: 0.73, 1.33)[a]
  - ITT (randomised stage IB-IIIA) population: OS HR, 1.07 (95% CI: 0.80, 1.42)[a]

Clinical cutoff: 21 Jan 2021. [a] Stratified. [b] Statistical significance boundary for DFS crossed. [c] Statistical significance boundary for DFS not crossed.

1. Felip, E et al Lancet 2021; 938; 1344-1357; 2. Wakelee. HA et al ASCO 2021; abs #8500.

Results of OS IA: PD-L1 TC ≥1%[a] (stage II-IIIA)

(data cutoff: 18 Apr '22, median follow-up: 46 months)



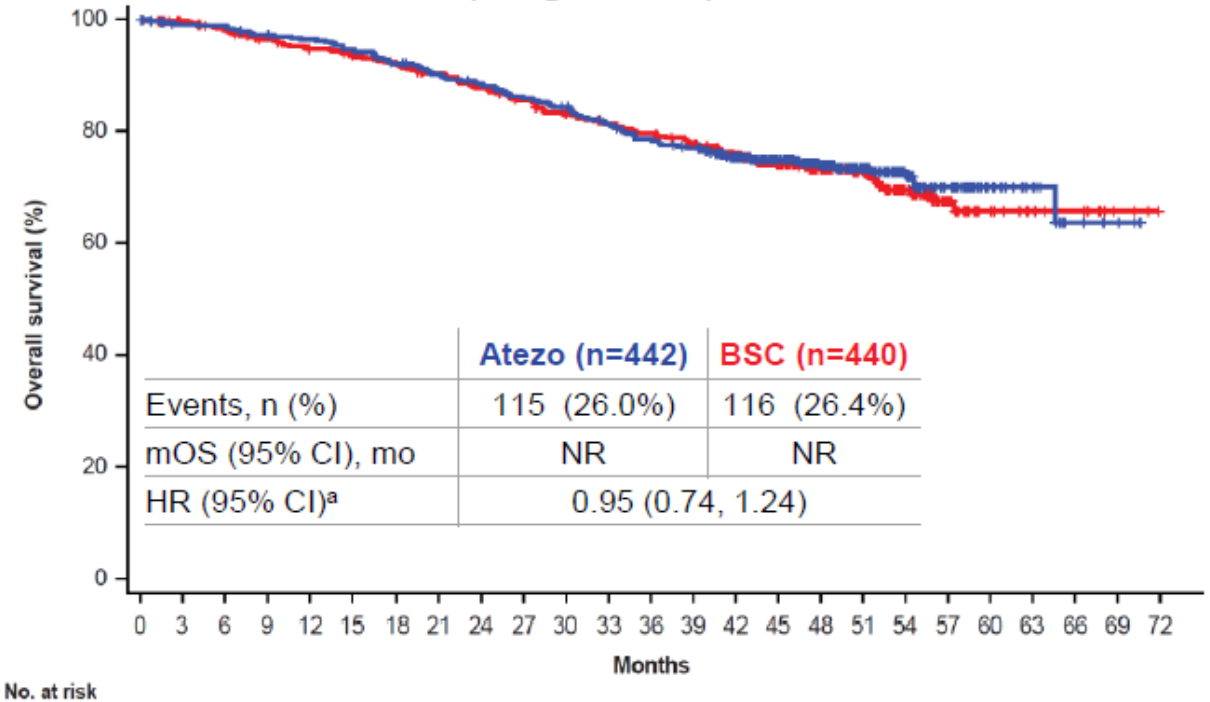
	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[b]	0.71 (0.49, 1.03)	

mOS, median overall survival; NR, not reached. [a]By SP263 assay. [b]Stratified.

Results of OS IA: other primary populations

(data cutoff: 18 Apr '22, median follow-up: 45 months)

All randomised (stage II-IIIA)

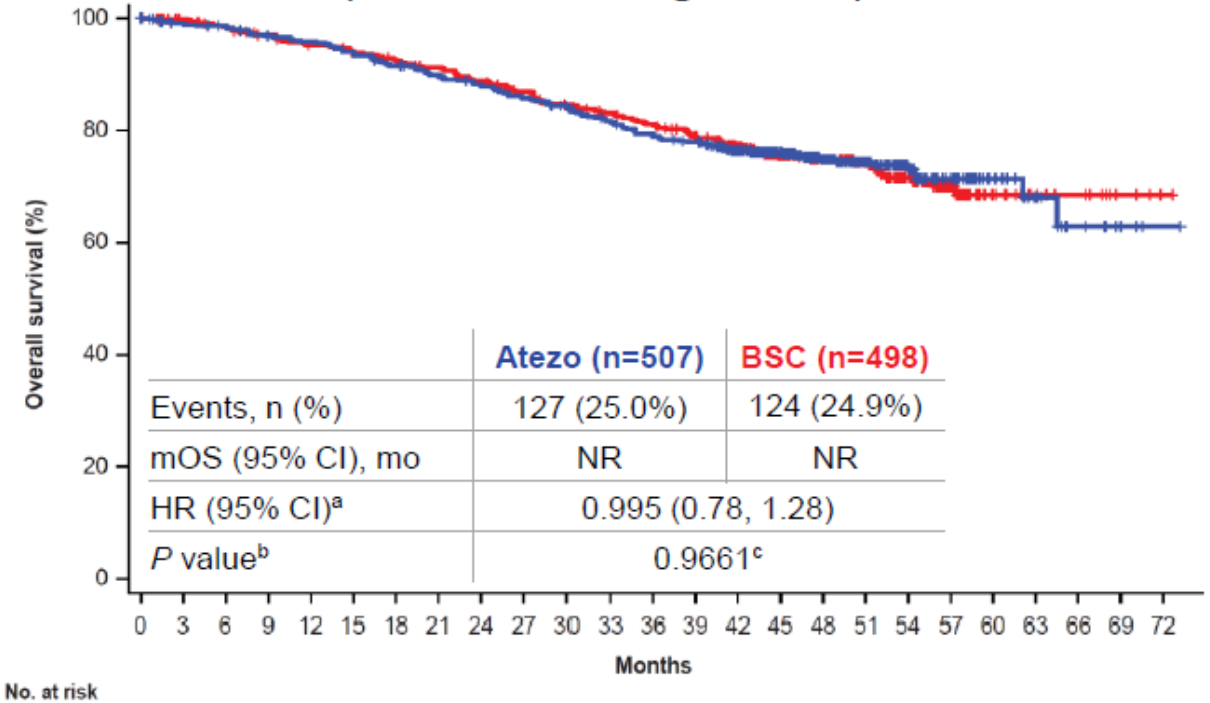


	Atezo (n=442)	BSC (n=440)
Events, n (%)	115 (26.0%)	116 (26.4%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.95 (0.74, 1.24)	

No. at risk

Atezolizumab	442	429	428	420	416	408	396	386	378	367	359	344	332	323	287	228	179	128	85	56	27	15	6	3	NE
BSC	440	426	416	405	396	389	382	373	362	350	337	328	320	310	279	215	178	125	81	42	20	11	9	4	NE

ITT (randomised stage IB-IIIA)



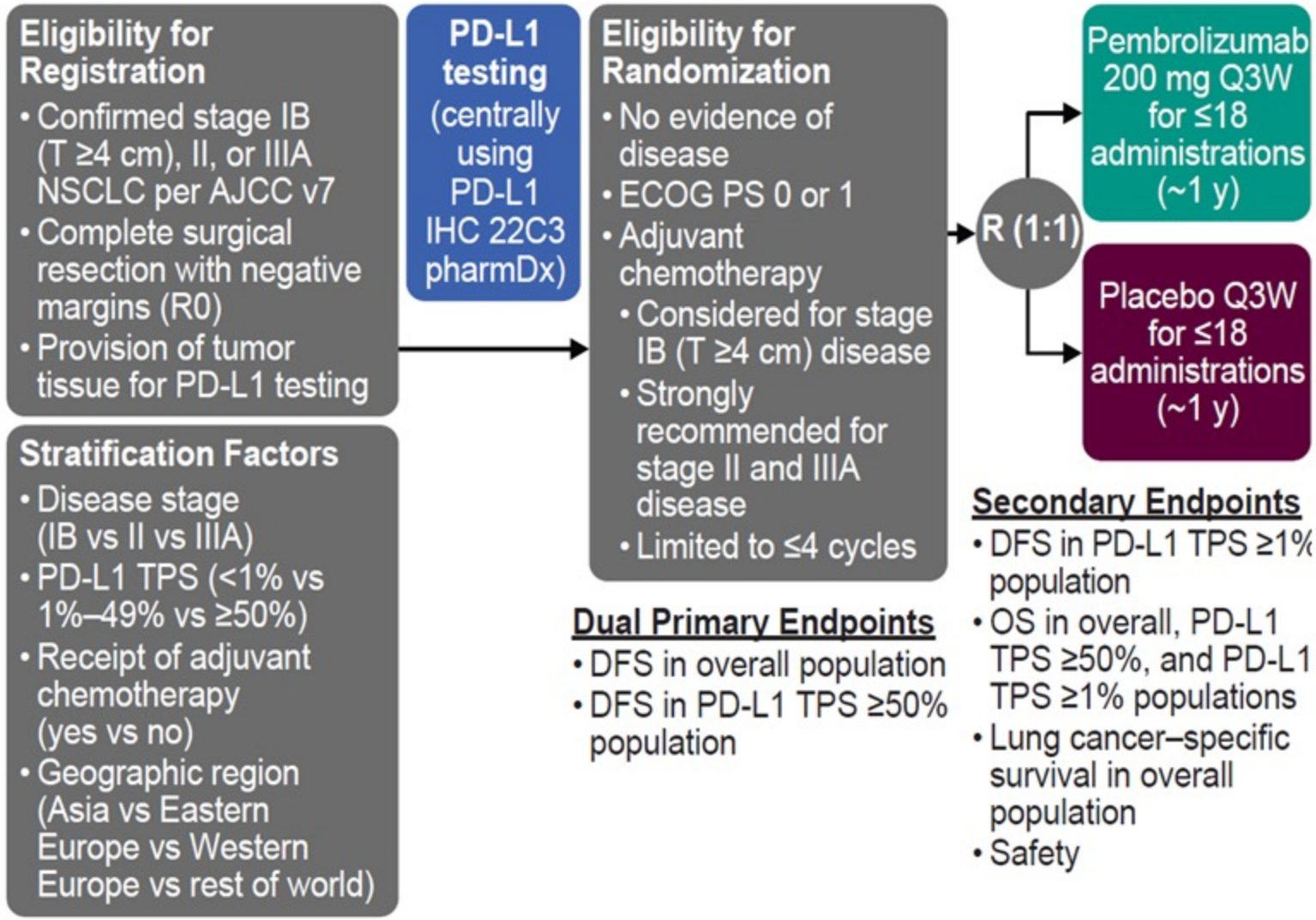
	Atezo (n=507)	BSC (n=498)
Events, n (%)	127 (25.0%)	124 (24.9%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[a]	0.995 (0.78, 1.28)	
P value[b]	0.9661[c]	

No. at risk

Atezolizumab	507	492	488	478	472	463	450	439	430	419	408	393	381	372	328	262	203	144	96	61	30	17	8	4	1
BSC	498	484	473	462	452	444	437	428	417	405	391	381	371	357	325	253	207	148	101	57	25	14	11	5	1

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.

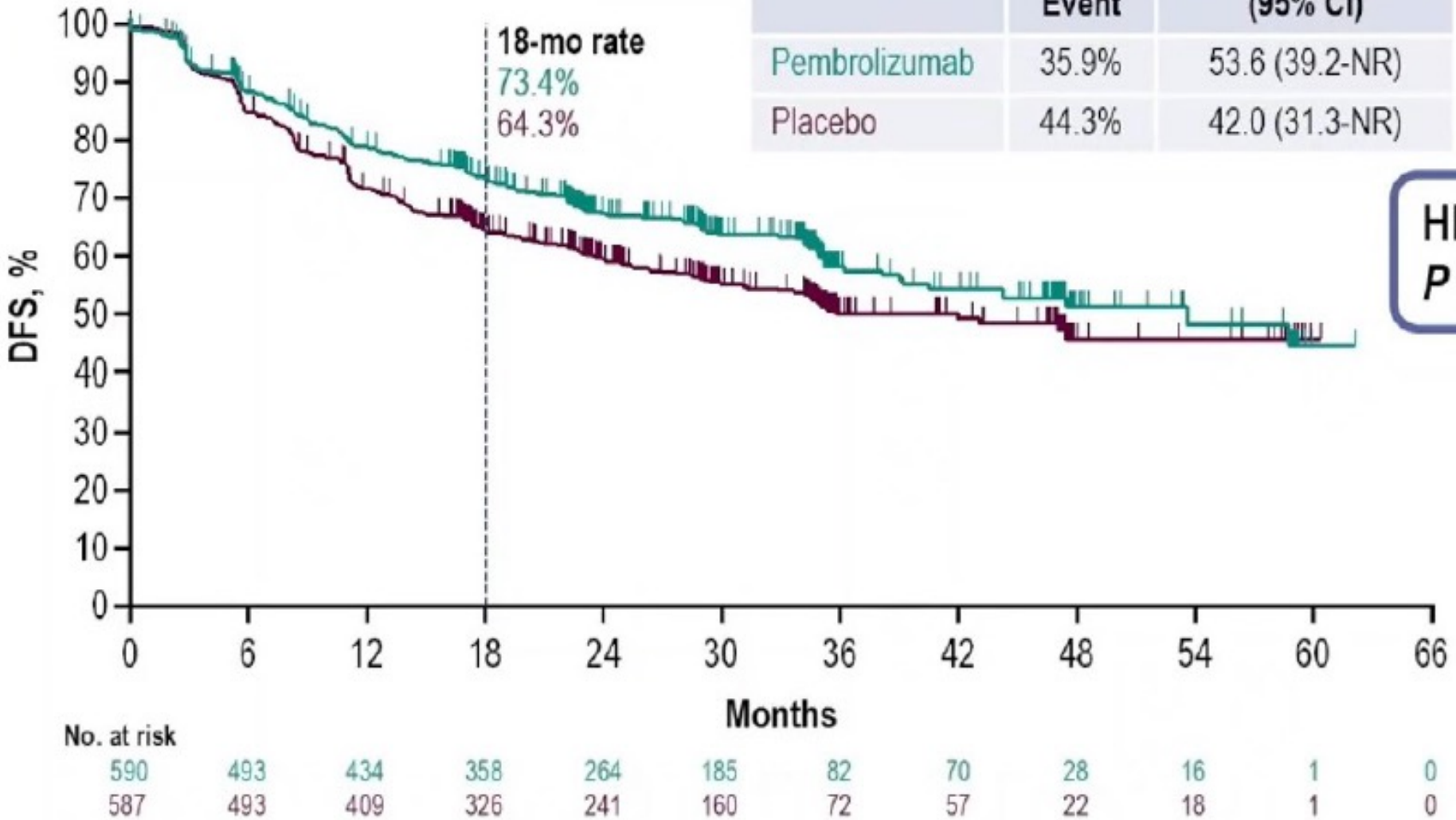
PEARLS/KEYNOTE-091 Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status; Q3W, every 3 weeks.

DFS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	35.9%	53.6 (39.2-NR)
Placebo	44.3%	42.0 (31.3-NR)

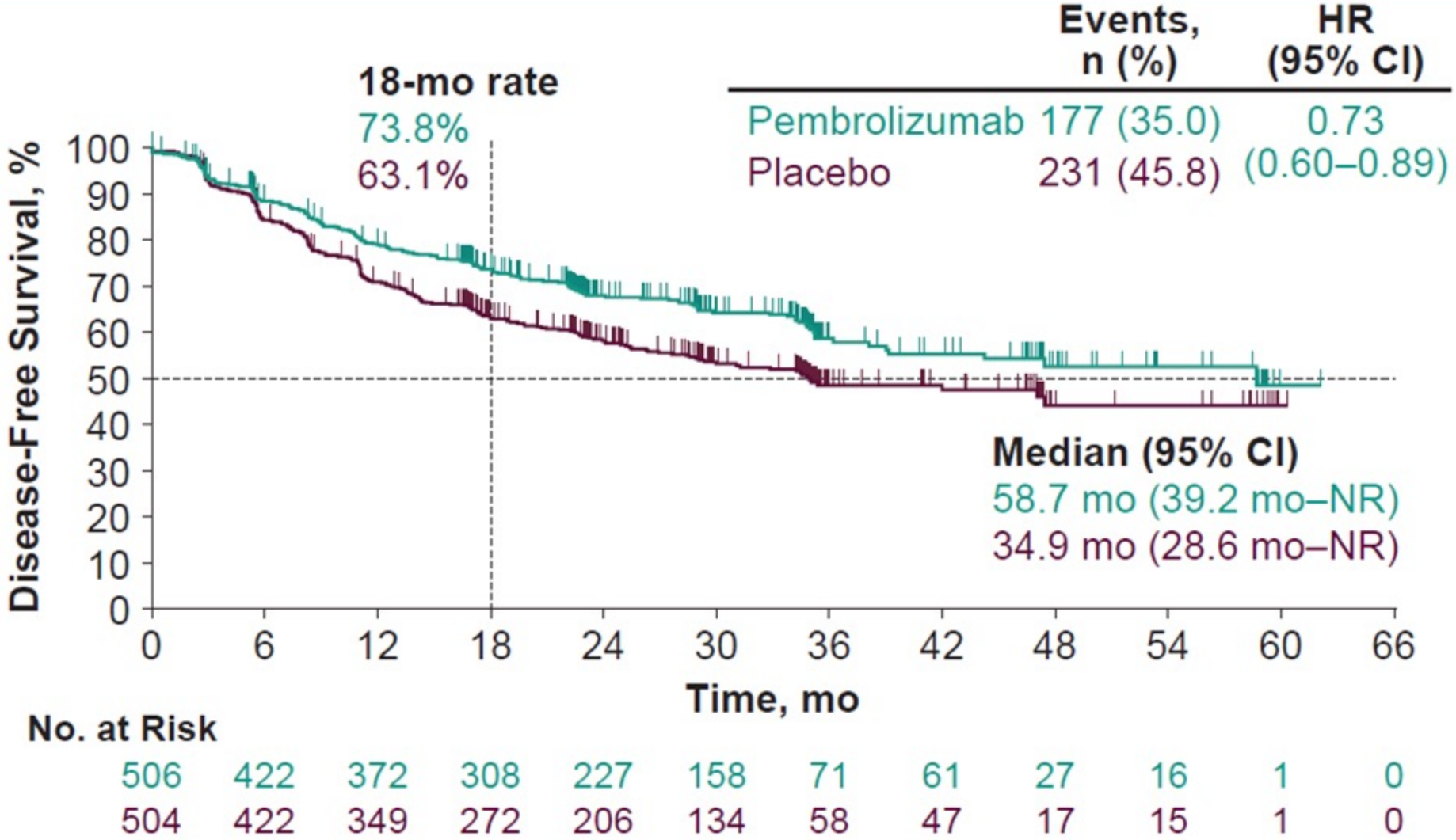


HR 0.76 (95% CI, 0.63-0.91)
P = 0.0014

ESMO VIRTUAL PLENARY

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

Disease-Free Survival in Patients Who Received ≥1 Cycle of Adjuvant Chemotherapy



NR, not reached.

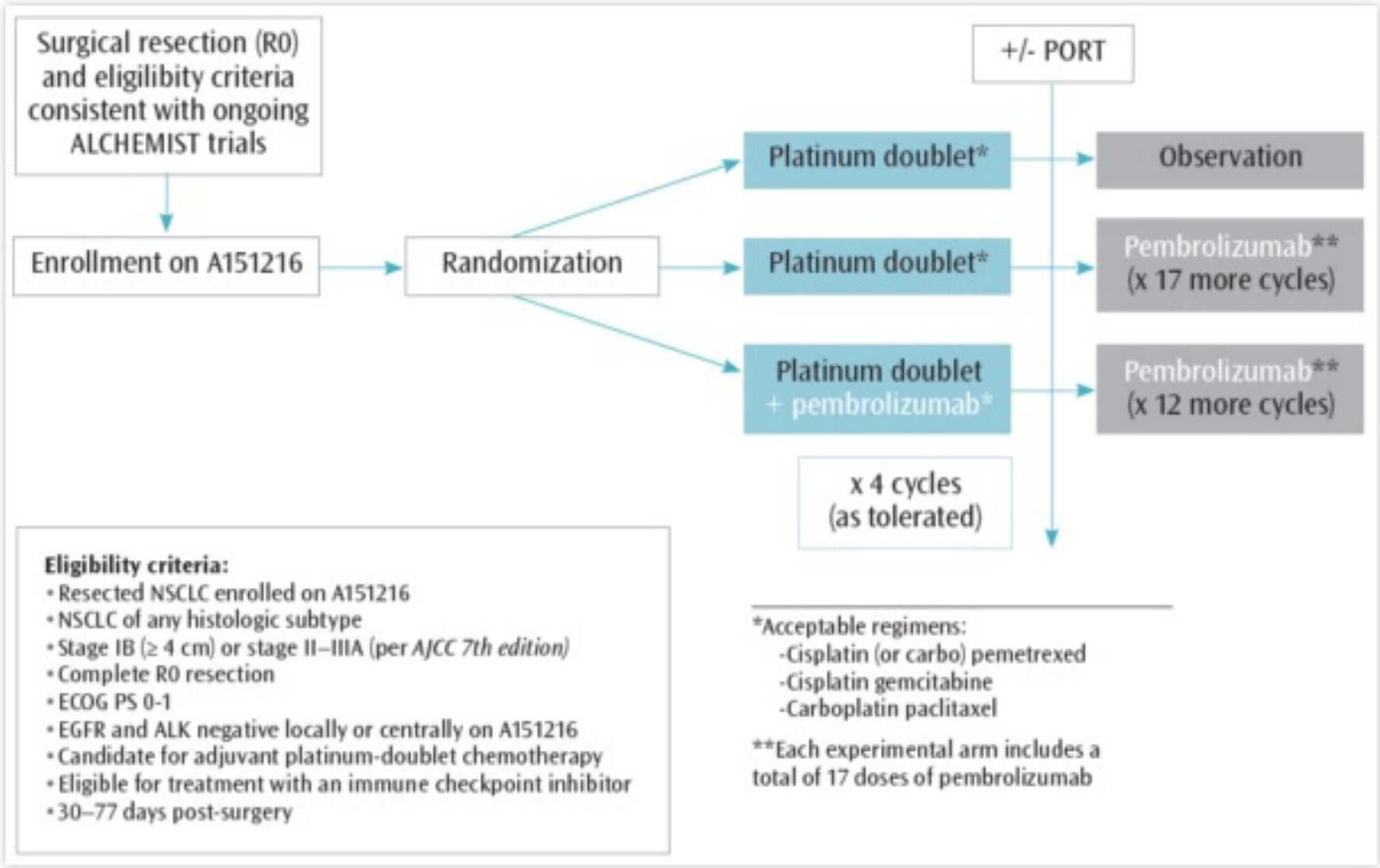
Summary and Conclusions

- Pembrolizumab provided statistically significant, clinically meaningful DFS improvement versus placebo in the overall population
  - Median DFS of 53.6 months with pembrolizumab vs 42.0 months with placebo (HR, 0.76)
  - Generally consistent DFS benefit in participants with PD-L1 TPS <1%, 1-49%, and ≥50%
  - OS data are immature
  - DFS in the PD-L1-defined populations and OS will be tested at future analyses according to the analysis plan
- Pembrolizumab safety profile as expected
- **Data suggest pembrolizumab has the potential to be a new adjuvant treatment option for patients with stage IB (T ≥4 cm) to IIIA NSCLC following complete resection and adjuvant chemotherapy when recommended, regardless of PD-L1 expression**

ESMO VIRTUAL PLENARY

On January 26, 2023, the Food and Drug Administration (FDA) approved pembrolizumab for adjuvant treatment following resection and platinum-based chemotherapy for stage IB (T2a ≥4 cm), II, or IIIA non-small cell lung cancer (NSCLC), regardless PDL1

Figure 1. Schema: ALCHEMIST CHEMO-IO



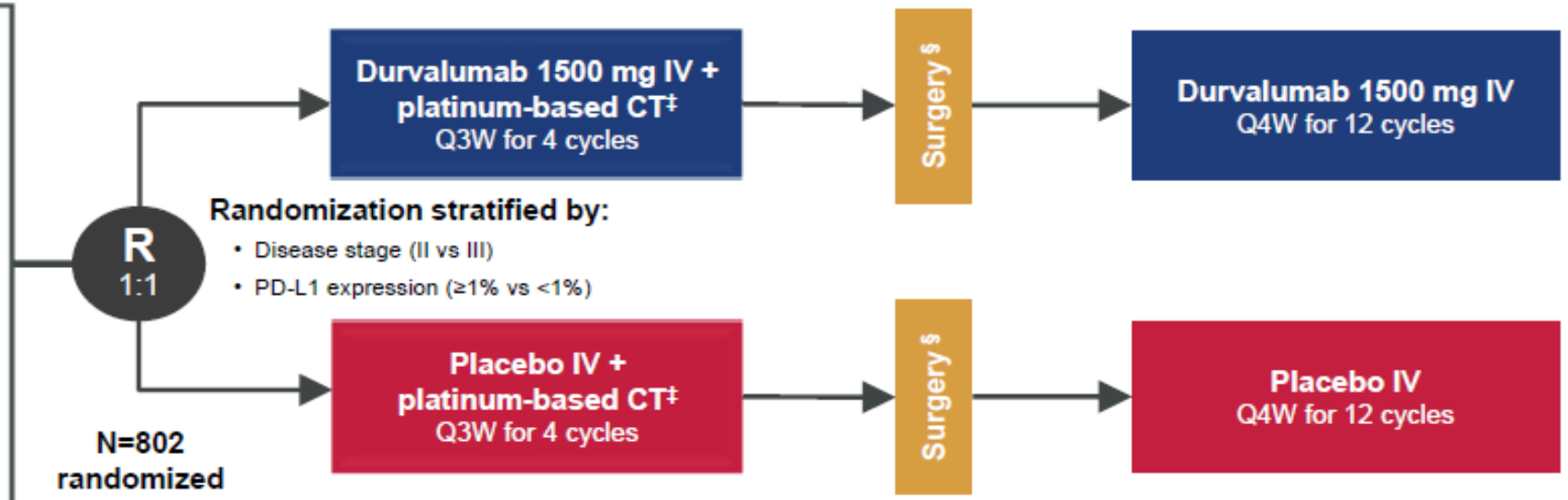
NEOADJUVANT PLUS ADJUVANT (PERIOPERATIVE) IMMUNOTHERAPY IN NSCLC

AEGEAN: a phase 3, global, randomized, double-blind, placebo-controlled study

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

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*



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

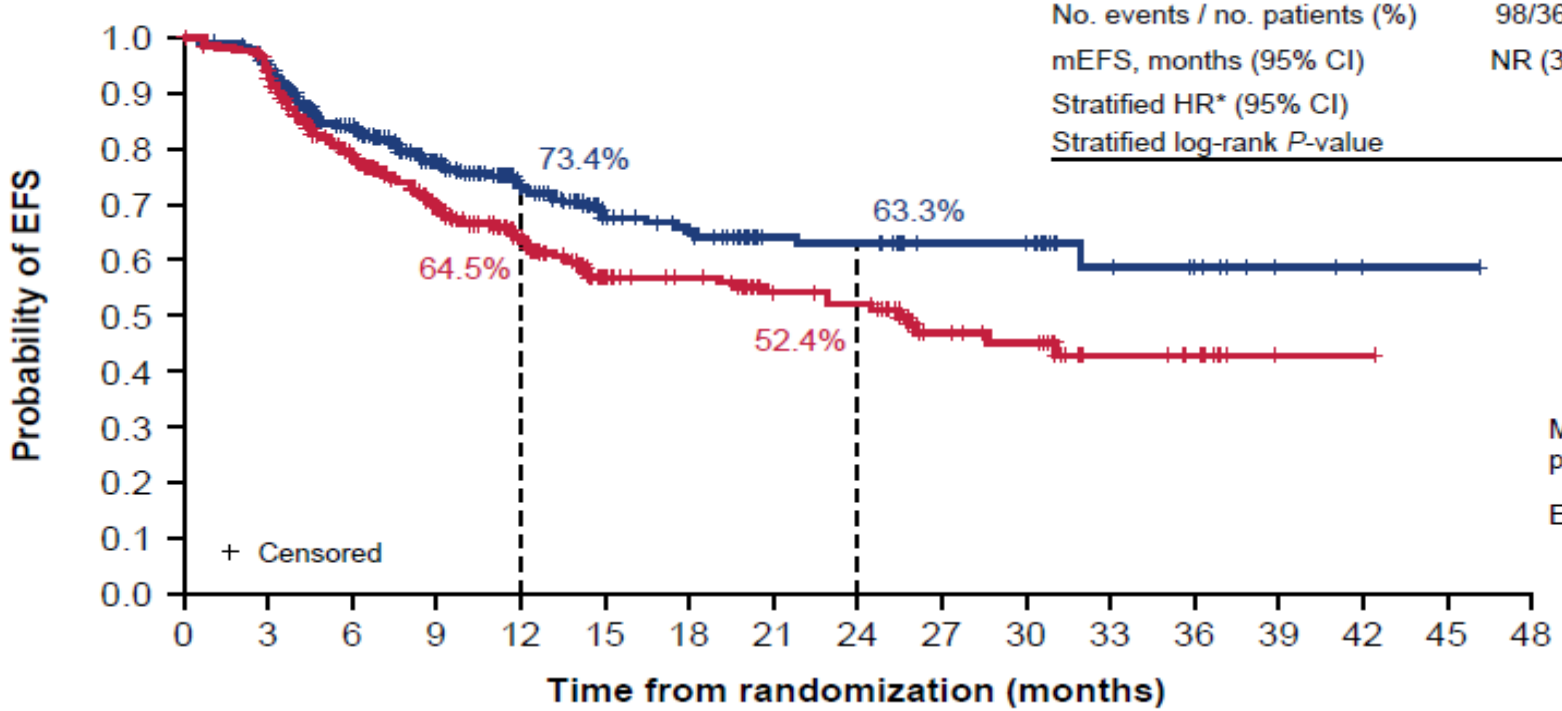
*The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations. †Ventana SP263 immunohistochemistry assay. ‡Choice of CT regimen 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. AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; DFS, disease-free survival; EFS, event-free survival; mITT, modified intent-to-treat; MPR, major pathologic response; pCR, pathologic complete response.

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

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:

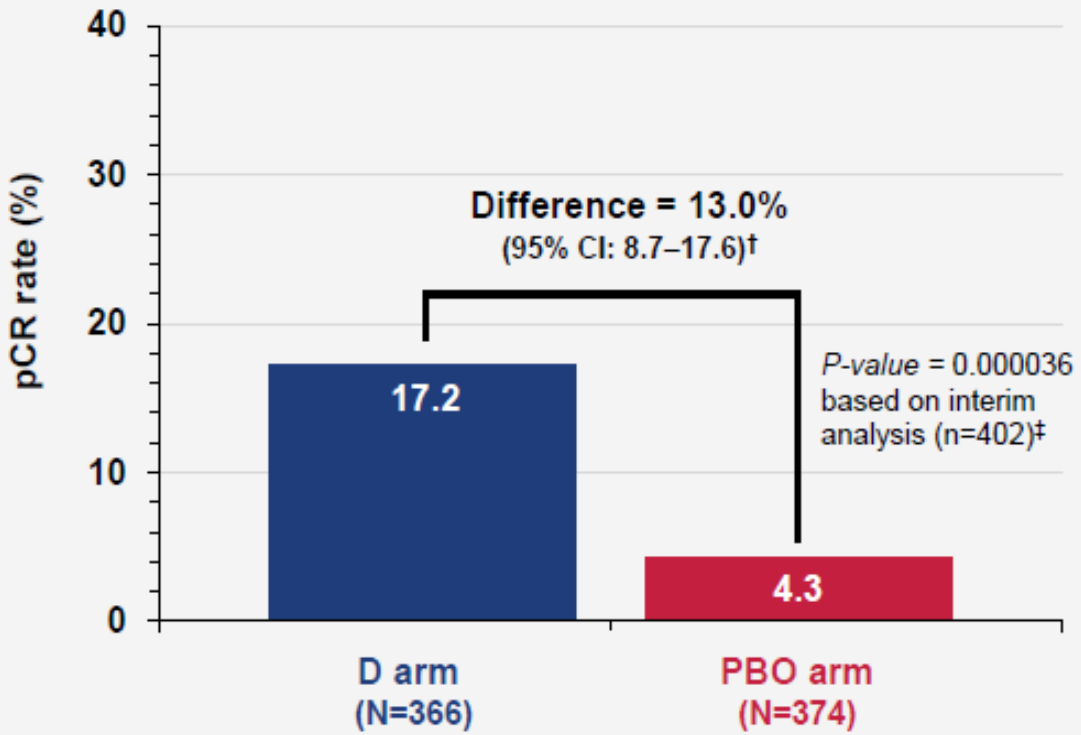
D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

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.

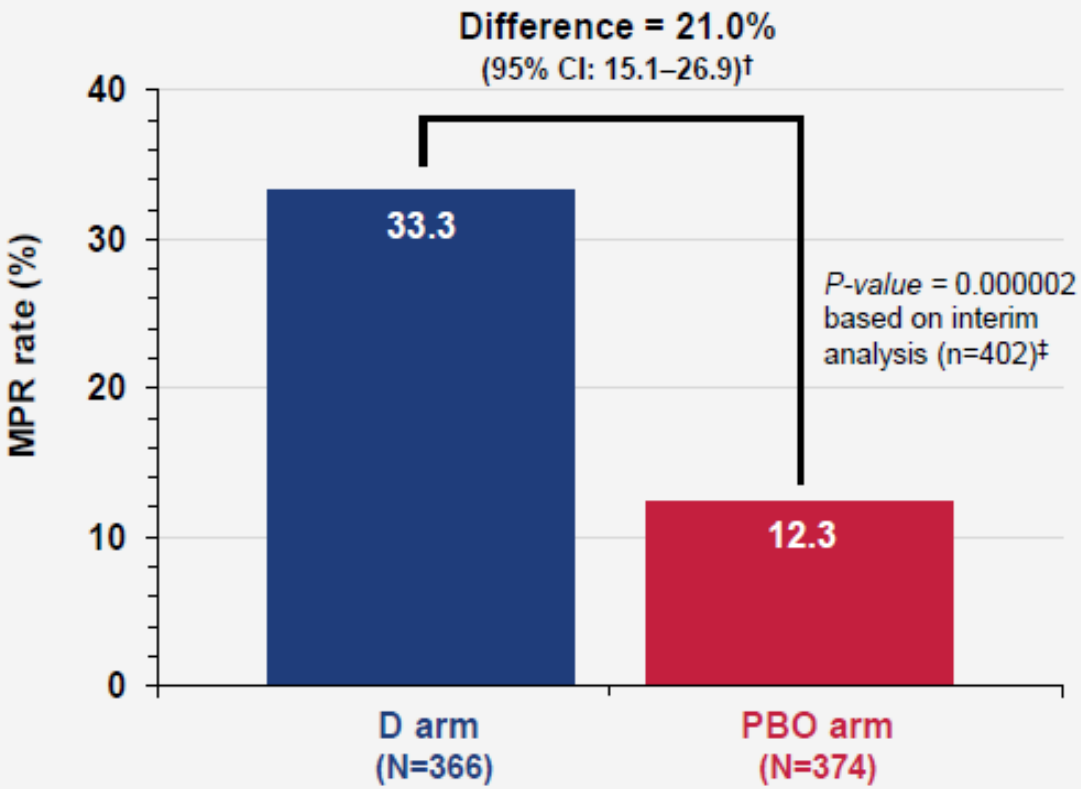
Pathologic response per IASLC 2020 methodology* (mITT)

Final analysis

pCR (central lab)



MPR (central lab)

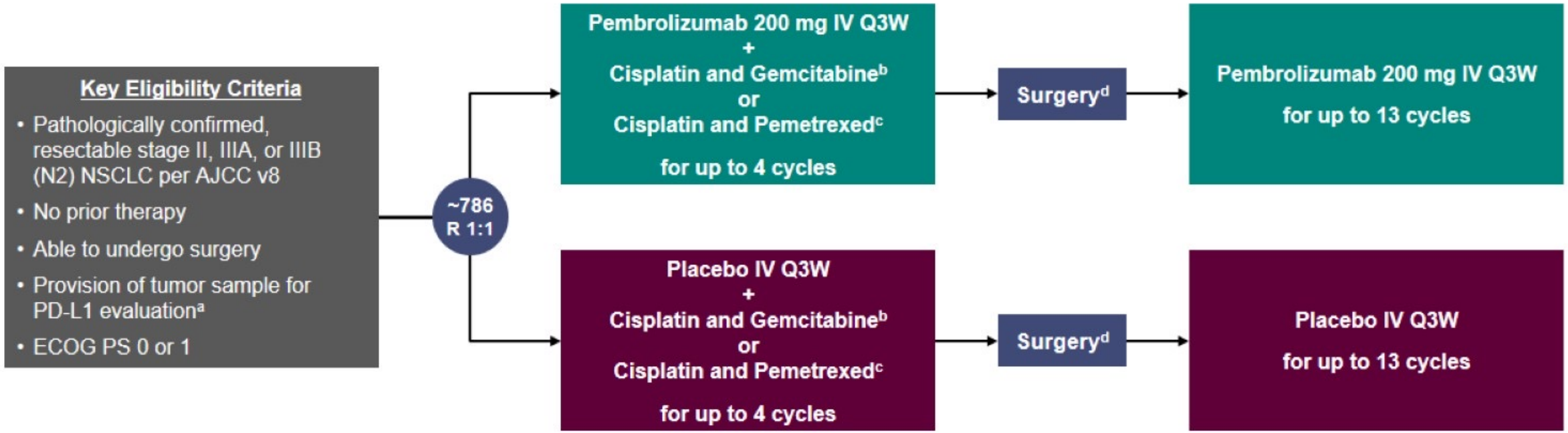


*Using IASLC recommendations for pathologic assessment of response to therapy, including gross assessment and processing of tumor bed (Travis WD, et al. *J Thorac Oncol* 2020;15:709-40). pCR = a lack of any viable tumor cells after complete evaluation of the resected lung cancer specimen and all sampled 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).

Conclusions

- Perioperative durvalumab + neoadjuvant CT significantly improved both pCR and EFS among patients with resectable NSCLC versus neoadjuvant CT alone
  - Difference in pCR rate = 13.0% (95% CI: 8.7–17.6)
  - EFS HR = 0.68 (95% CI: 0.53–0.88); *P* = 0.003902; median follow-up of 11.7 months and 31.9% maturity
  - The AEGEAN study continues for assessment of longer-term EFS, as well as DFS and OS
- Improvements in both pCR and EFS were largely consistent across predefined subgroups
  - EFS benefit was observed regardless of the planned neoadjuvant platinum agent: the HR was 0.59 (95% CI: 0.35–1.00) for cisplatin and 0.73 (95% CI: 0.54–0.98) for carboplatin
- Perioperative durvalumab + neoadjuvant CT was associated with a manageable safety profile that was consistent with the known safety profiles of durvalumab and CT
  - The addition of durvalumab did not impact completion of neoadjuvant CT (4 cycles) or surgery
- AEGEAN is the first phase 3 study to describe the benefit of perioperative immunotherapy + neoadjuvant CT
- Perioperative durvalumab + neoadjuvant CT is a potential new treatment for patients with resectable NSCLC

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



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

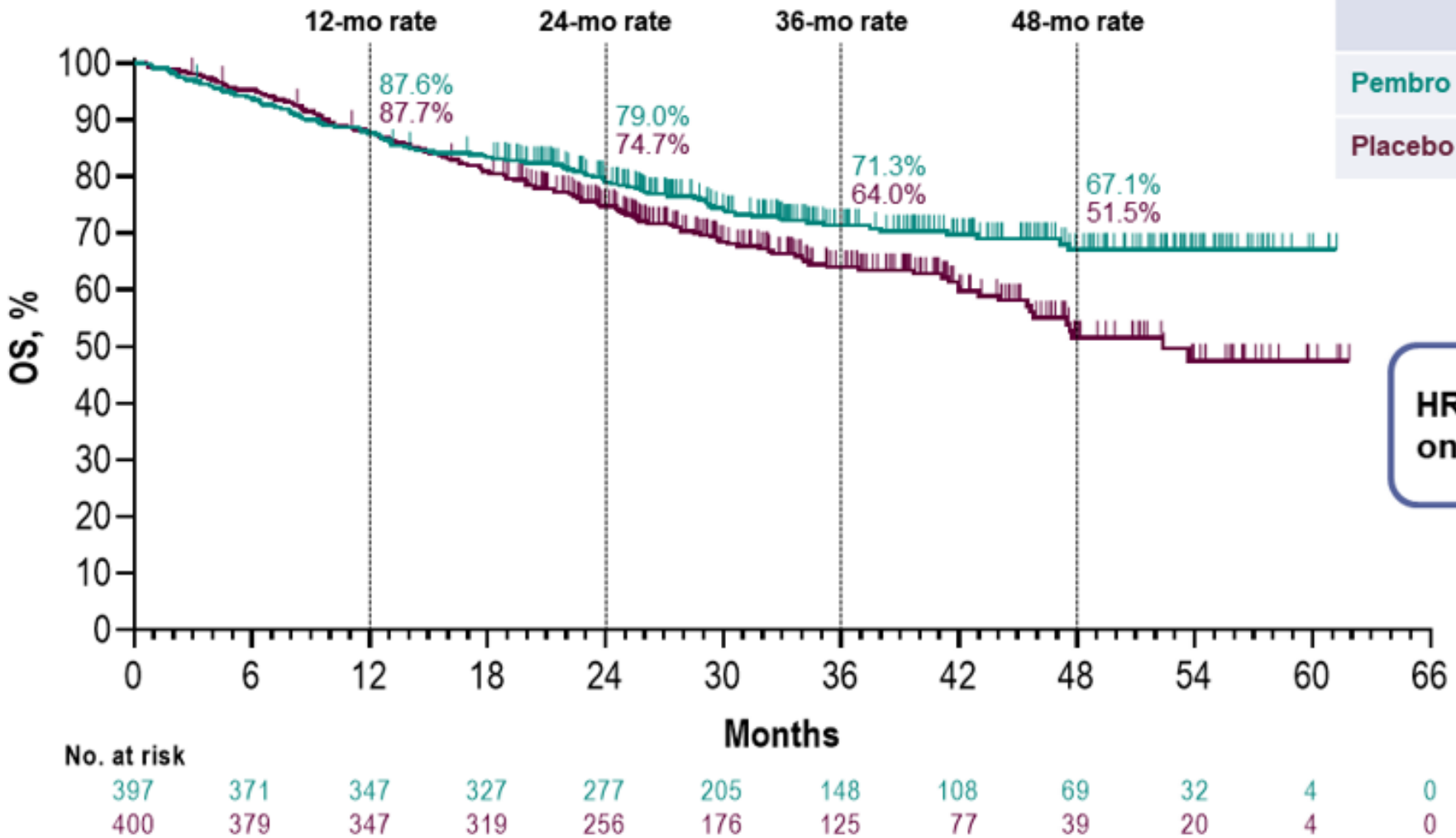
Dual primary end points: EFS per investigator review and OS

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

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

Overall Survival, IA2

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



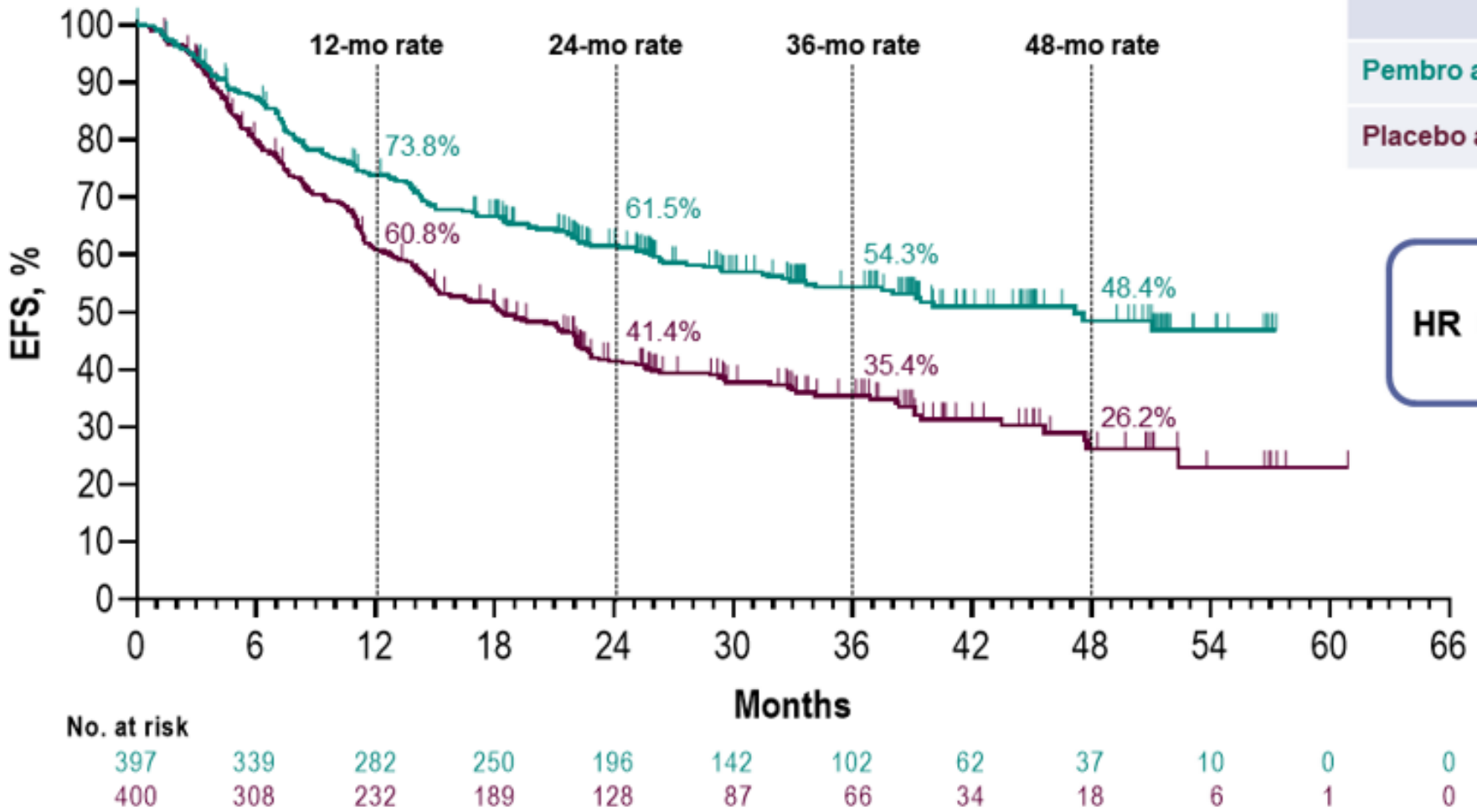
	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

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

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

Event-Free Survival, IA2

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



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

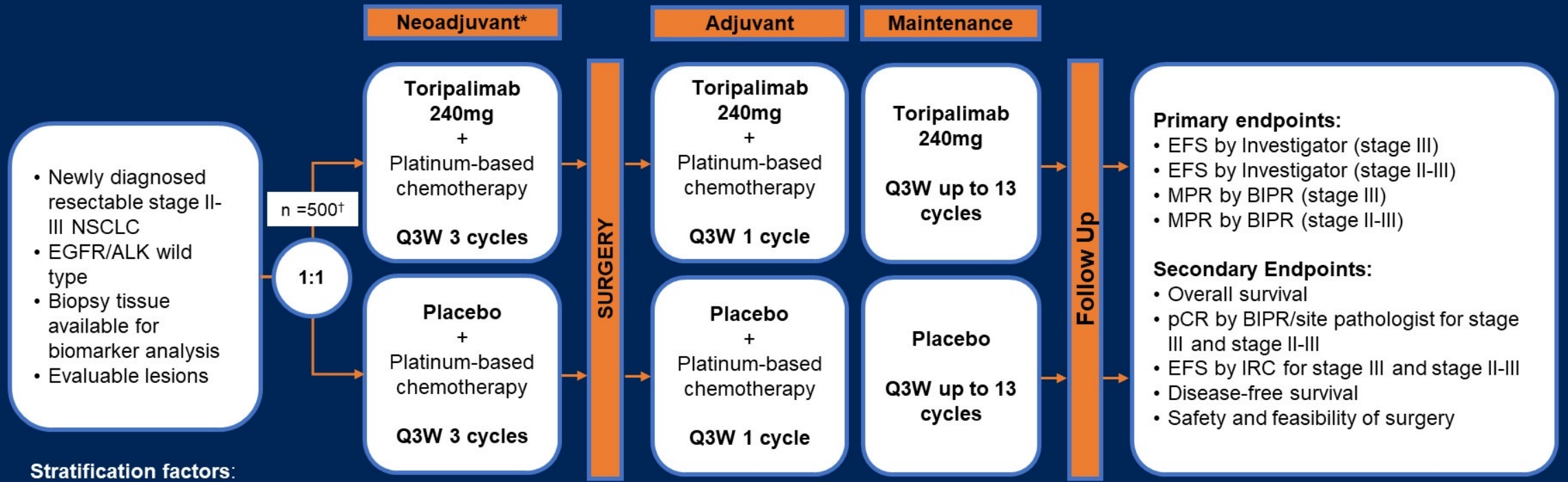
HR 0.59 (95% CI, 0.48-0.72)

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

Summary and Conclusions

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

Neotorch Study Design



Stratification factors:
- II vs IIIA vs IIIB
- Lobectomy vs pneumonectomy
- Non-squamous vs squamous
- PD-L1 TC expression: ≥ 1% vs < 1% or non-evaluable

*3 cycles of neoadjuvant chemotherapy with 4 cycles of peri-operative chemotherapy in total were required with in Neotorch study, meanwhile, surgeons were allowed to determine the most appropriate timing for surgery based on the patient's condition
†About 400 patients with Stage III NSCLC and ~100 patients with Stage II NSCLC patients would be enrolled

EFS: Event-Free Survival
MPR: Major Pathologic Response
BIPR: Blinded Independent Pathologic Review
pCR: Pathological Complete Response
IRC: Independent Review Committee

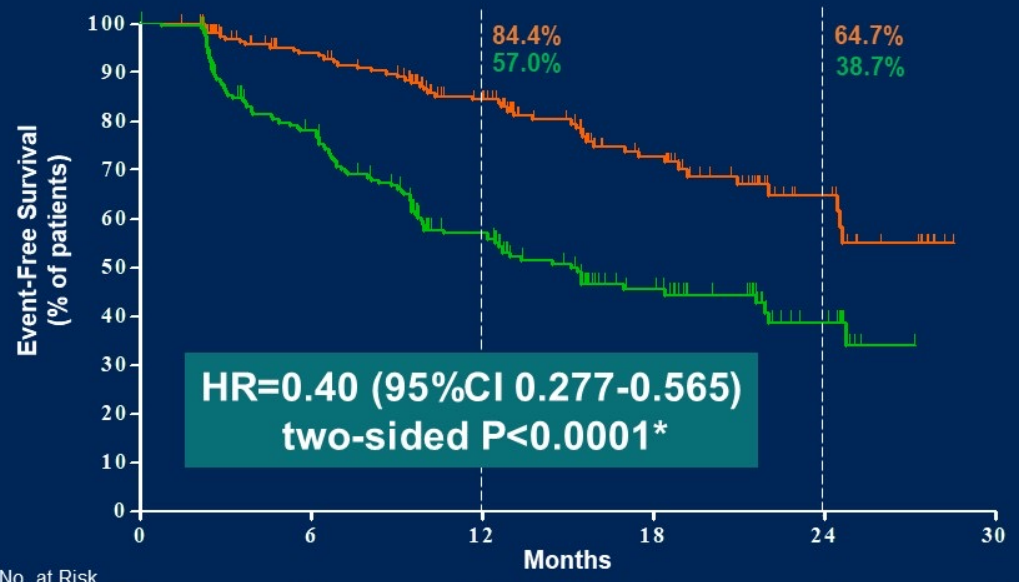
Event-Free Survival Analysis

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

EFS by investigator

	No. of Events/ No. of Patients	Median EFS *mos.* (95% CI)
Toripalimab + chemo	47/202	NE (24.4, NE)
Placebo + chemo	97/202	15.1 (10.6, 21.9)

Median follow-up: 18.25 months



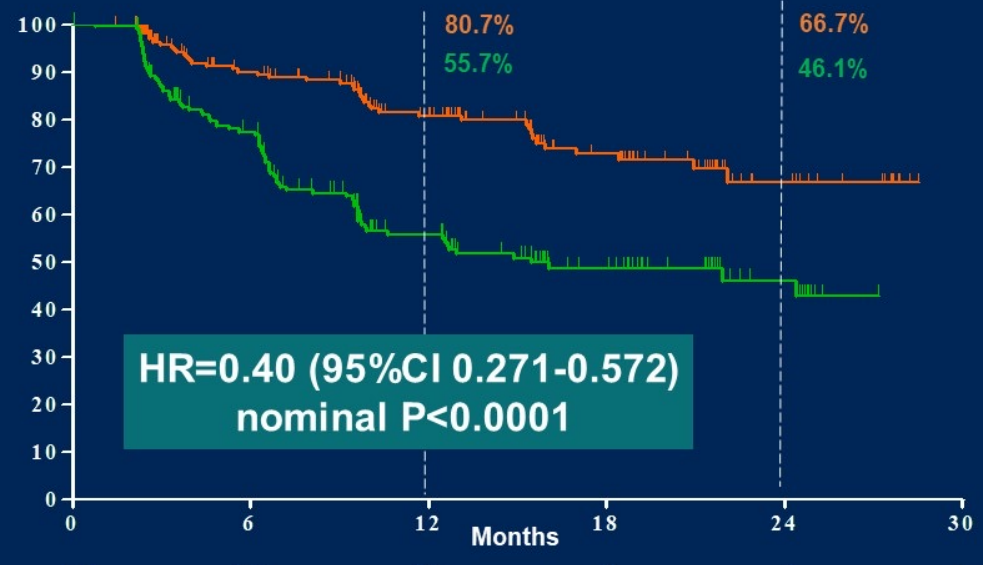
No. at Risk						
Toripalimab + chemo	202	156	116	66	23	0
Placebo + chemo	202	139	86	43	15	0

*2-sided efficacy boundary: 0.01683

EFS by IRC

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

Median follow-up: 18.25 months



	202	150	107	60	17	0
	202	134	74	38	14	0

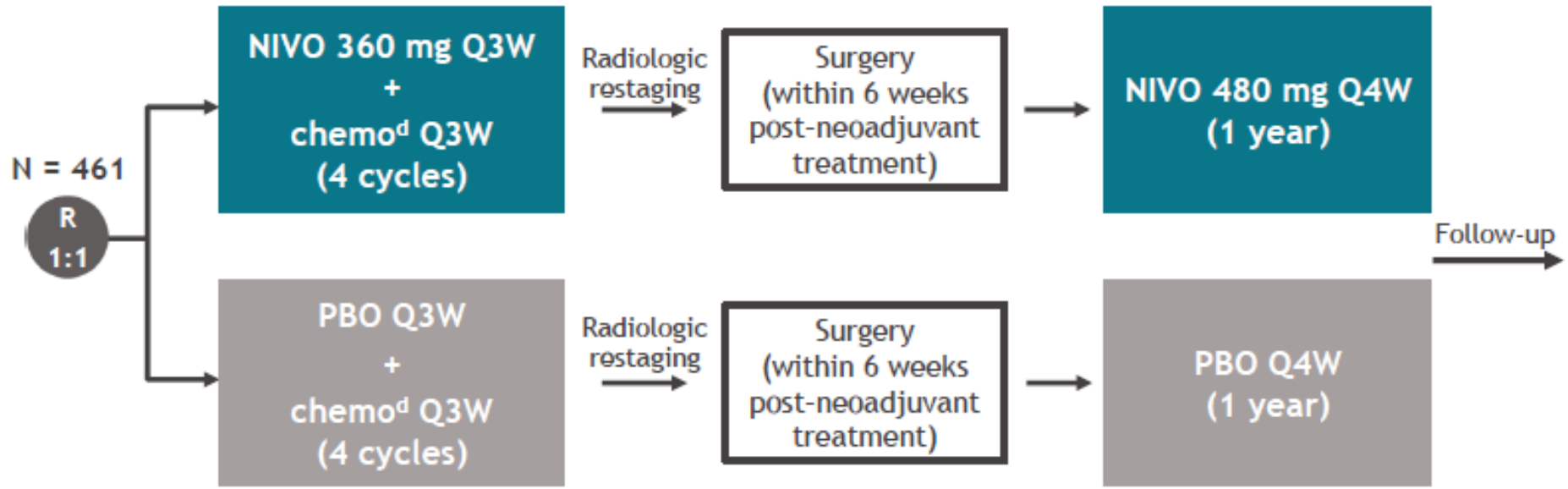
NE: not evaluable
HR; Hazard ratio
CI: confidence interval
Data cutoff date: Nov. 30, 2022

CheckMate 77T[a] study design

Key eligibility criteria

- Resectable, stage IIA (> 4 cm)-IIIB (N2) NSCLC (per AJCC 8th edition)
- No prior systemic anti-cancer treatment
- ECOG PS 0-1
- No *EGFR* mutation/known *ALK* alterations[b]

Stratified by histology (NSQ vs SQ) disease stage (II vs III), and tumor PD-L1[c] (≥ 1% vs < 1% vs not evaluable/indeterminate)



Follow-up, median (range): 25.4 (15.7-44.2) months

Primary endpoint
- EFS by BICR

Secondary endpoints
- pCR[e] by BIPR
- MPR[e] by BIPR
- OS
- Safety

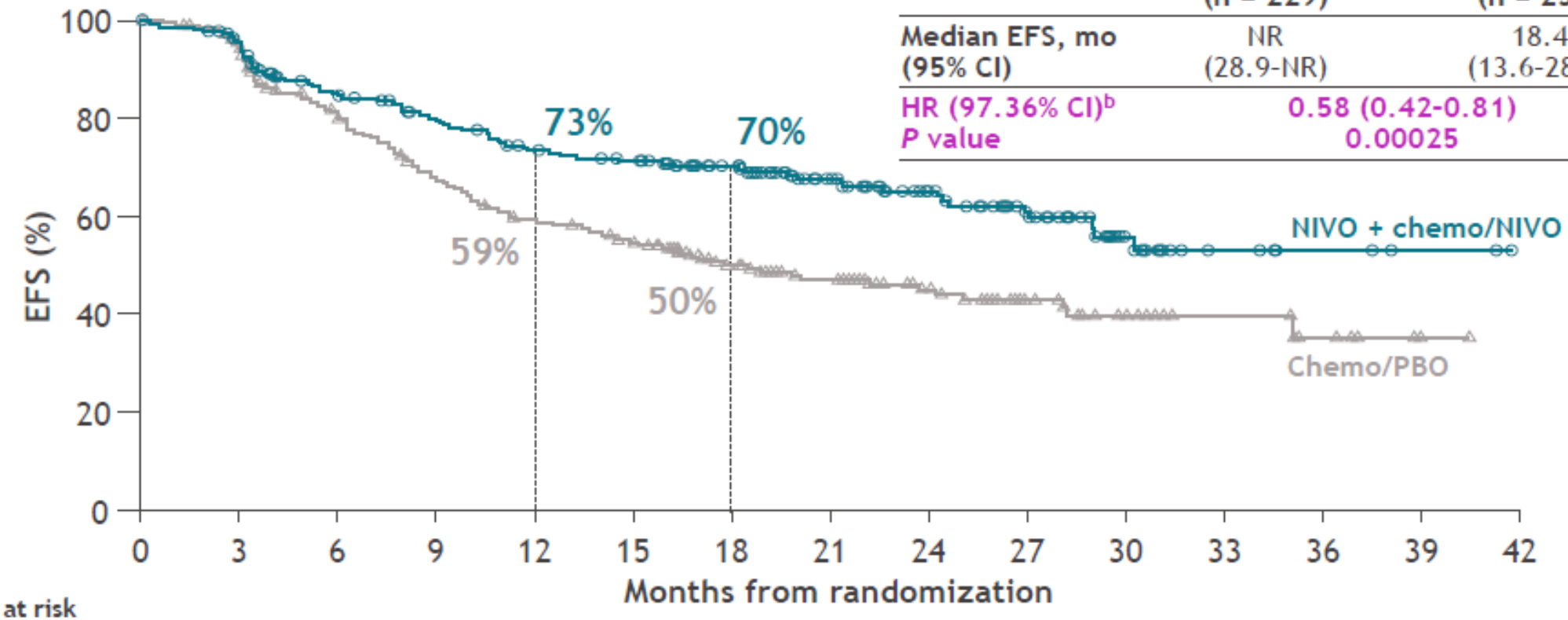
Exploratory analyses
- EFS by pCR/MPR
- EFS by adjuvant treatment

Database lock date: September 6, 2023.

[a]NCT04025879. [b]*EGFR* testing was mandatory in all patients with NSQ histology. *ALK* testing was done in patients with a history of *ALK* alterations. *EGFR*/*ALK* testing done using US FDA/local health authority-approved assays. [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [d]NSQ: cisplatin + pemetrexed, carboplatin + pemetrexed, or carboplatin + paclitaxel; SQ: cisplatin + docetaxel or carboplatin + paclitaxel. [e]Assessed per immune-related pathologic response criteria.[1] BICR, blinded independent central review; BIPR, blinded independent pathological review. 1. Cottrell TR, et al. *Ann Oncol* 2018:29:1853-1860.

Primary endpoint: EFS[a] per BICR with neoadjuvant NIVO + chemo/adjuvant NIVO vs chemo/PBO

	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)
Median EFS, mo (95% CI)	NR (28.9-NR)	18.4 (13.6-28.1)
HR (97.36% CI)[b]	0.58 (0.42-0.81)	
P value	0.00025	



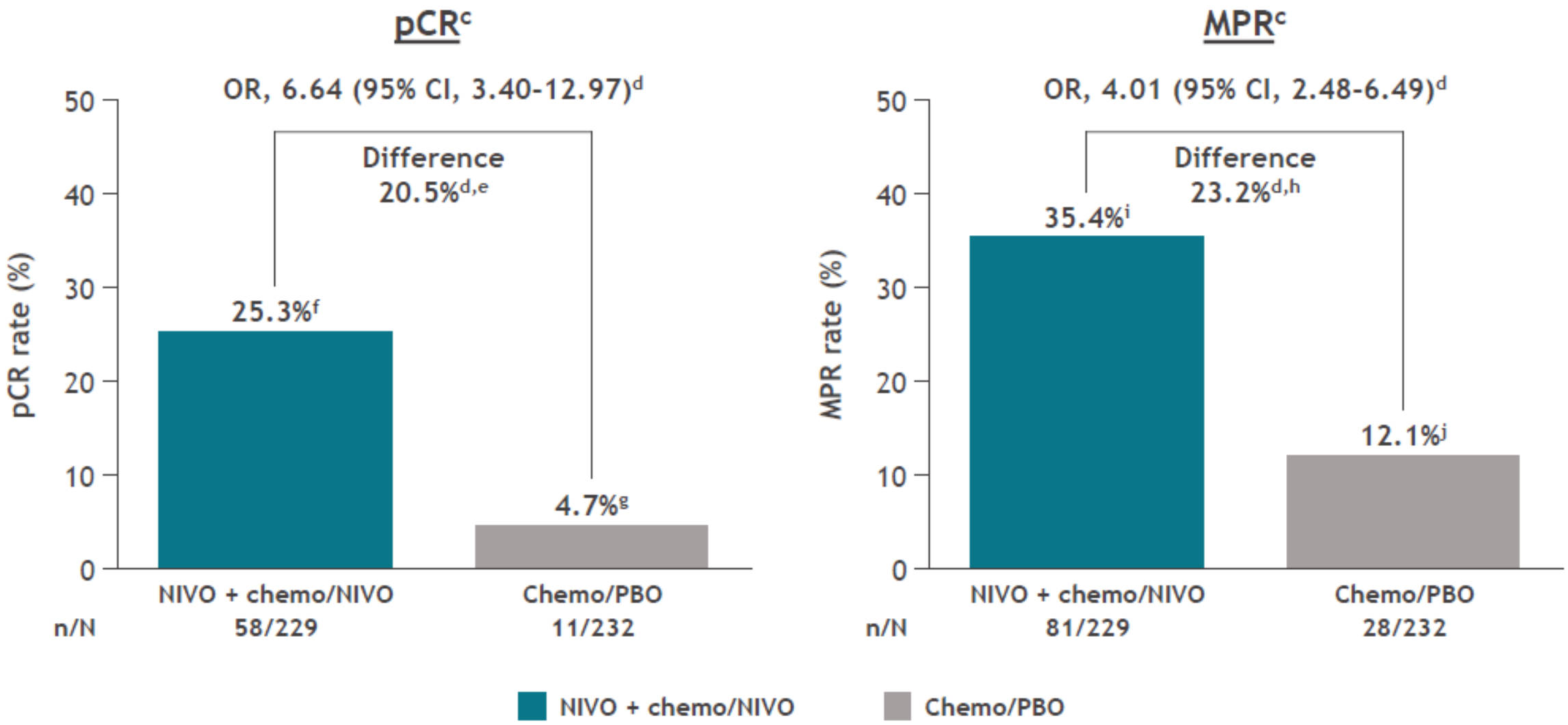
No. at risk															
NIVO + chemo/NIVO	229	208	173	157	141	134	115	89	69	46	20	7	4	2	0
Chemo/PBO	232	204	165	138	118	106	78	59	44	29	19	10	6	1	0

- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

Median follow-up (range): 25.4 months (15.7-44.2).

[a]Time from randomization to any disease progression precluding surgery, abandoned surgery due to unresectability or disease progression, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b]Unstratified HR (95% CI), 0.59 (0.44-0.79).

pCR[a] and MPR[b] per BIPR



[a]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per immune-related pathologic response criteria. [b]≤ 10% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per immune-related pathologic response criteria. [c]Patients who did not undergo surgery or received alternative anti-cancer treatment prior to surgery were classified as non-responders. [d]Calculated using the stratified Cochran-Mantel-Haenszel method. [e-j]95% CI: [e]14.3-26.6; [f]19.8-31.5; [g]2.4-8.3; [h]15.8-30.6; [i]29.2-41.9; [j]8.2-17.0. BIPR, blinded independent pathological review.

Summary

- Neoadjuvant NIVO + chemo followed by surgery and adjuvant NIVO demonstrated statistically significant and clinically meaningful EFS improvement vs chemo/PBO in patients with resectable NSCLC (HR, 0.58; *P* = 0.00025)
  - EFS benefit was seen across most key subgroups
- pCR and MPR rates were also improved: 25.3% vs 4.7% and 35.4% vs 12.1%, respectively
- In an exploratory analysis, perioperative NIVO favored EFS in patients with a pCR following neoadjuvant therapy, with a trend toward improved EFS in patients without a pCR
- Among patients eligible for adjuvant therapy, perioperative NIVO improved EFS vs chemo/PBO, regardless of pCR status
  - Neoadjuvant NIVO + chemo continued to provide benefit over chemo in patients who were unable to receive adjuvant therapy
- Perioperative NIVO-based regimen showed no new safety signals. Surgical feasibility was similar between treatment arms
- **CheckMate 77T is the first phase 3 perioperative study to build on the SOC neoadjuvant NIVO + chemo and supports perioperative NIVO as a potential new treatment option for patients with resectable NSCLC**

Metastatic NSCLC Immunotherapy

First Line Lung Cancer Therapy with no actionable genes

NSQCC:

- Carboplatin/Pemetrexed/Pembrolizumab [Keynote 189]
- Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab [IMPOWER 150]

SQCC:

- Carboplatin/Paclitaxel or nab-paclitaxel/Pembrolizumab [Keynote 407]

NSQCC and SQCC:

- Cemiplimab/Chemotherapy [Empower Lung-3]
- Durvalumab +Tremelimumab/Chemotherapy [Poseidon 3]

IO single Agent (NSQCC OR SQCC)

- Pembrolizumab [Keynote 024 and 042]
- Atezolizumab [IMPOWER 110]
- Cemiplimab [Empower Lung-1]

Immunotherapy combinations:

- Ipilimumab and Nivolumab [Checkmate 227]
- Ipilimumab and Nivolumab plus 2 cycles of chemotherapy [Checkmate 9LA]

EMPOWER

EMPOWER-Lung 3 (Part 2) Study Design (NCT03409614)

Background: Cemiplimab (a high-affinity, fully human anti–PD-1) is approved as first-line monotherapy for advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1 Study[1])

Key eligibility criteria
- Treatment-naive advanced NSCLC (non-squamous and squamous histology; Stage IIIb/c[†], IV)
- Any PD-L1 expression
- No *EGFR*, *ALK*, or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases[‡]

Stratification factors
- PD-L1 expression: <1% vs 1–49% vs ≥50%
- Histology: non-squamous vs squamous

R 2:1

Arm A
Cemiplimab 350 mg Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles[§] → PD or 108 weeks

Arm B
Placebo Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles[§] → PD or 108 weeks

Follow-up

Endpoints
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PRO

N=466

Two interim analyses were prespecified per protocol
Second interim analysis (14 June 2021) presented here

[†]Patient not a candidate for definitive chemoradiation. [‡]Patient must have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). [§]For patients with non-squamous NSCLC, pemetrexed is mandatory as maintenance therapy for those patients initially assigned to receive a pemetrexed-containing regimen. *ALK*, anaplastic lymphoma kinase gene; BOR, best overall response; chemo, chemotherapy; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, every 3 weeks; R, randomised; *ROS1*, c-ros oncogene 1.

1. Sezer A et al. Lancet 2021;397:592–604.

2021 ESMO congress

EMPOWER

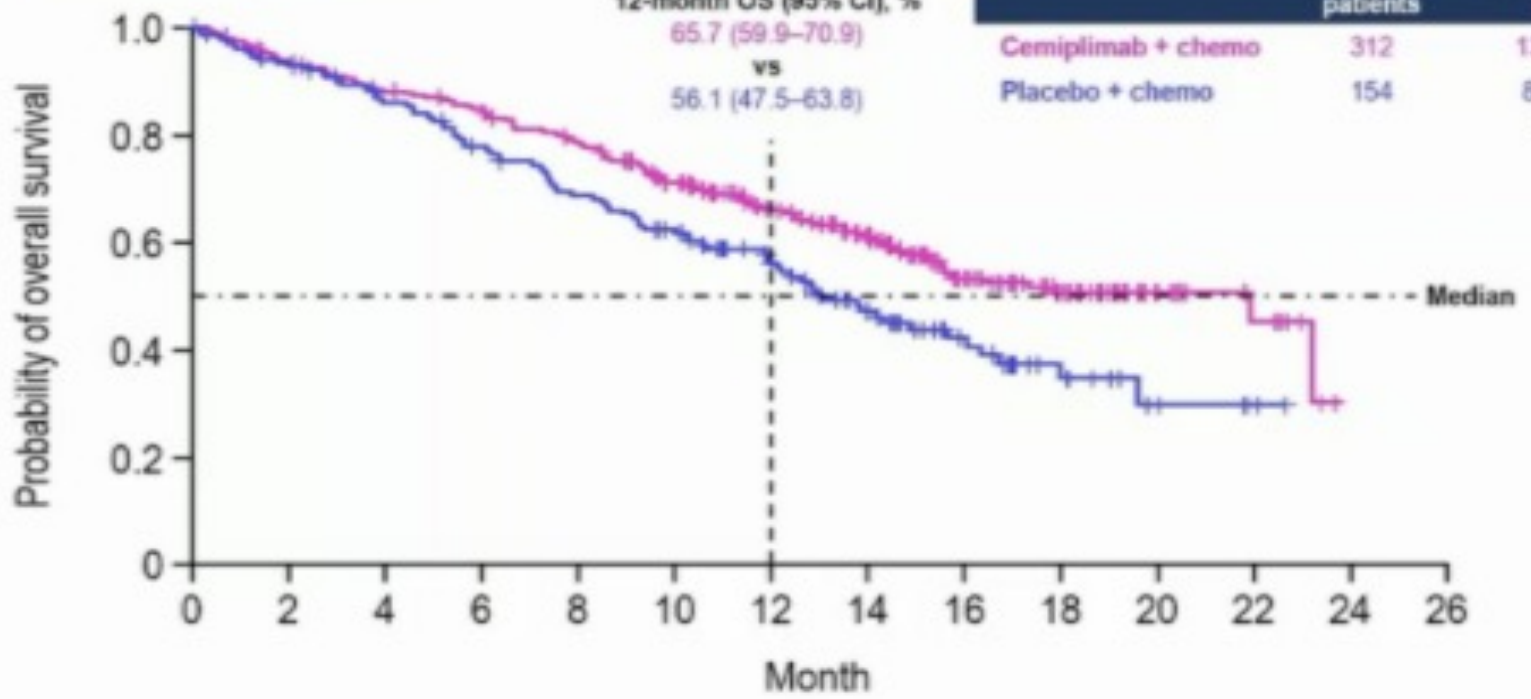
Overall Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	OS, median (95% CI), months
Cemiplimab + chemo	312	132 (42.3)	21.9 (15.5–NE)
Placebo + chemo	154	82 (53.2)	13.0 (11.9–16.1)

HR (95% CI) = 0.71 (0.53–0.93); *P*=0.014

12-month OS (95% CI), %
65.7 (59.9–70.9)
vs
56.1 (47.5–63.8)



No. at risk:

Cemiplimab + chemo	312	289	269	256	233	199	162	131	86	52	18	8	0	0
Placebo + chemo	154	141	126	112	98	85	65	46	26	14	5	2	0	0

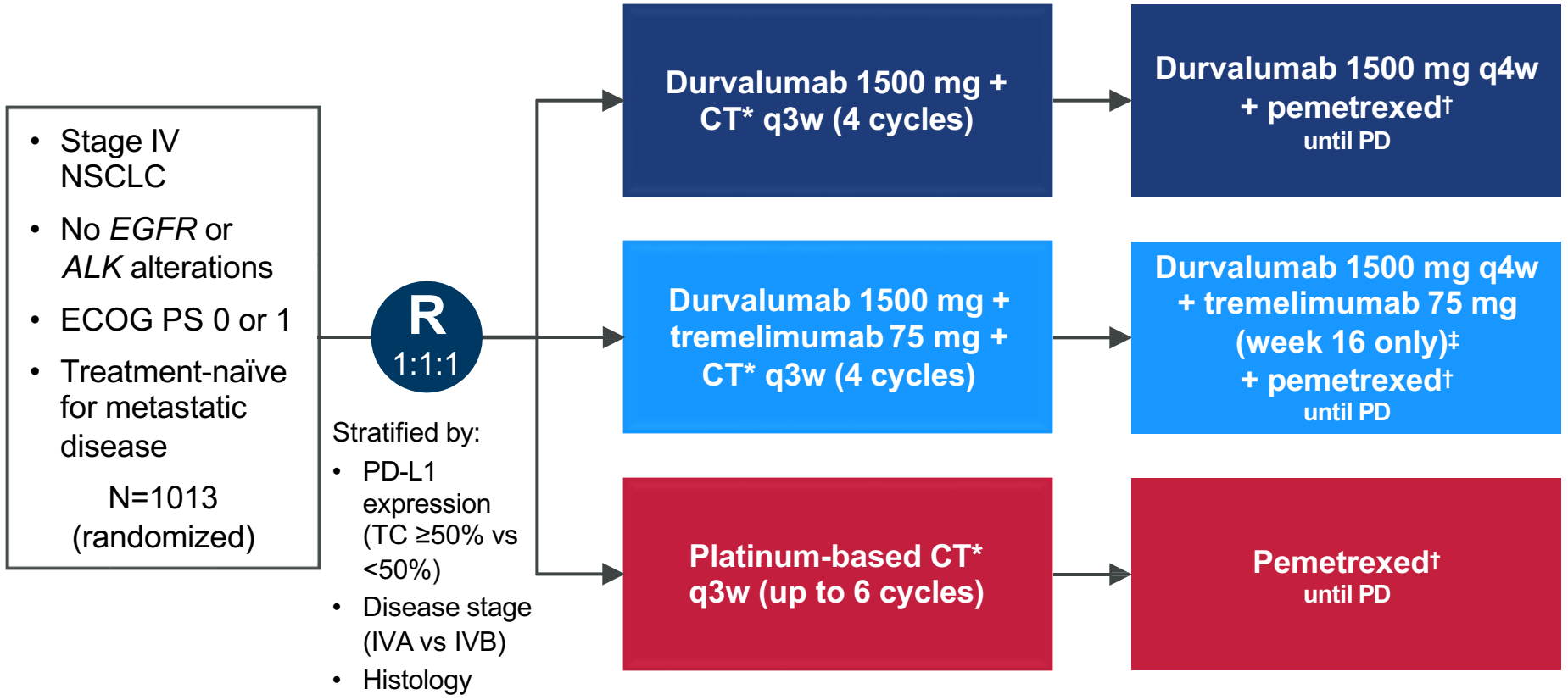
2021 ESMO congress

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Data cut-off date:
14 June 2021

POSEIDON Study Design

Phase 3, global, randomized, open-label, multicenter study



Primary endpoints
- PFS by BICR (D+CT vs CT)
- OS (D+CT vs CT)

Key secondary endpoints
- PFS by BICR (D+T+CT vs CT)
- OS (D+T+CT vs CT)
- OS in patients with bTMB ≥20 mut/Mb (D+T+CT vs CT)

Additional secondary endpoints
- ORR, DoR, and BOR by BICR
- PFS at 12 months
- HRQoL
- Safety and tolerability

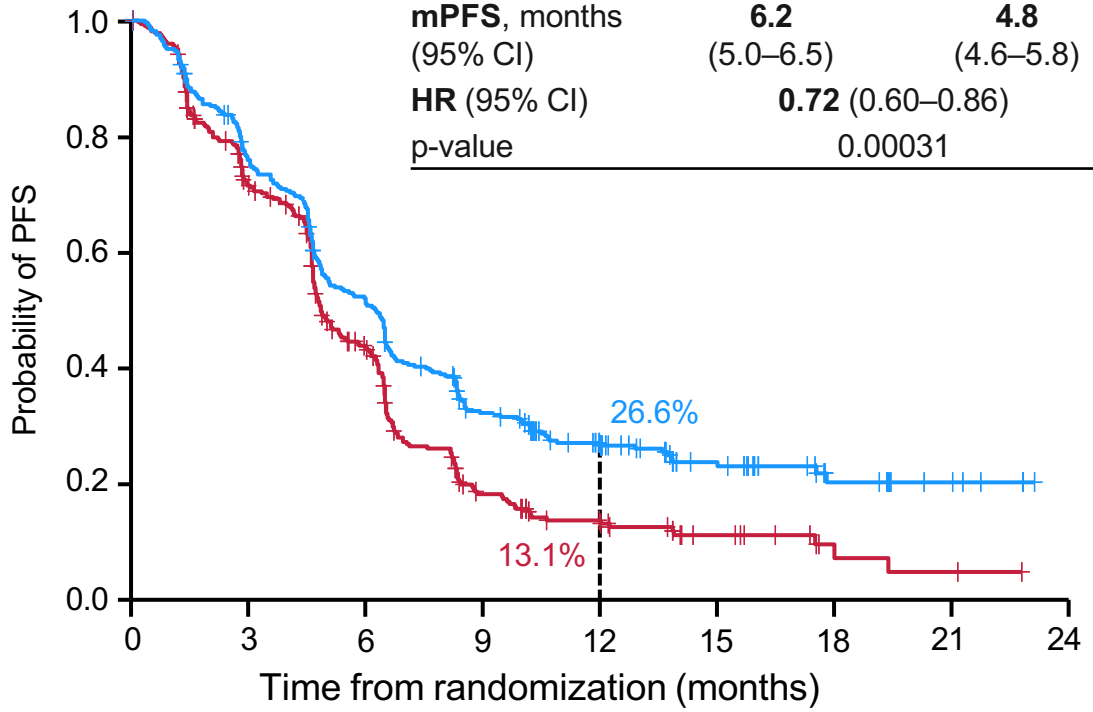
*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology);
†Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

BICR, blinded independent central review; BOR, best objective response; bTMB, blood tumor mutational burden; D, durvalumab; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; Mb, megabase; mut, mutations; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; T, tremelimumab; TC, tumor cell

Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	

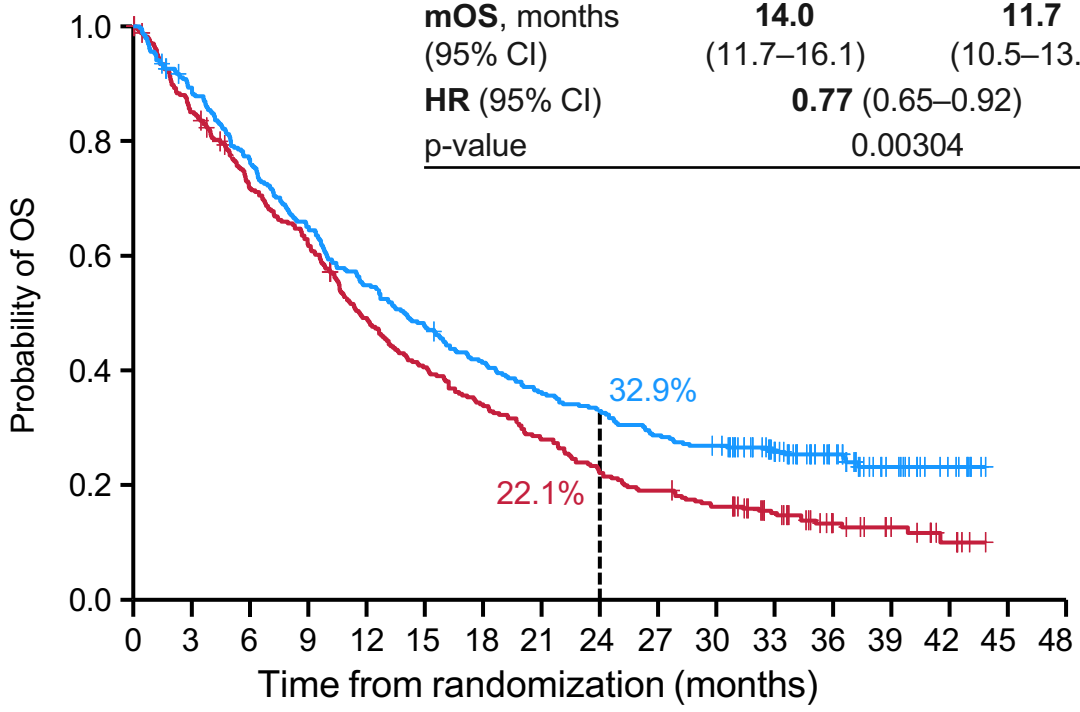


No. at risk									
D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



No. at risk																	
D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021

Conclusions

- In POSEIDON, PFS was significantly improved with first-line durvalumab + CT vs CT in patients with mNSCLC, with a positive trend for OS that did not reach statistical significance
  - PFS HR 0.74 (95% CI 0.62–0.89; p=0.00093)
  - OS HR 0.86 (95% CI 0.72–1.02; p=0.07581)
- First-line durvalumab + tremelimumab + CT demonstrated statistically significant and clinically meaningful improvements in both PFS and OS vs CT in patients with mNSCLC
  - PFS HR 0.72 (95% CI 0.60–0.86; p=0.00031)
  - OS HR 0.77 (95% CI 0.65–0.92; p=0.00304)
  - OS and PFS benefit were more prominent among patients with non-squamous (than squamous) histology
- Overall, the safety profile was similar across all three arms, with no new safety signals identified. Adding tremelimumab to durvalumab + CT did not lead to a meaningful increase in treatment discontinuation
  - TRAE discontinuation rate 15.5% and 14.1% with D+T+CT and D+CT, respectively
- **Durvalumab + tremelimumab + CT represents a potential new first-line treatment option for mNSCLC**

TRAE, treatment-related adverse event

IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

Six-year survival and health-related quality of life outcomes with first-line nivolumab plus ipilimumab in patients with metastatic NSCLC from CheckMate227

Suresh S. Ramalingam,[1] Tudor-Eliade Ciuleanu,[2] Reyes Bernabe Caro,[3] Makoto Nishio,[4] Hideaki Mizutani,[5] Jong-Seok Lee,[6] Clarisse Audigier-Valette,[7] Randeep Sangha,[8] Laszlo Urban,[9] Jacobus A. Burgers,[10] Adam Pluzanski,[11] Ki Hyeong Lee,[12] Bogdan Zurawski,[13] Michael Schenker,[14] Solange Peters,[15] Luis G. Paz-Ares,[16] Hossein Borghaei,[17] Kenneth J. O'Byrne,[18] Julie R. Brahmer,[19] Ravi G. Gupta,[20*] Judith Bushong,[20] Li Li,[20] Yong Yuan,[20] Steven I. Blum,[20] Martin Reck[21]

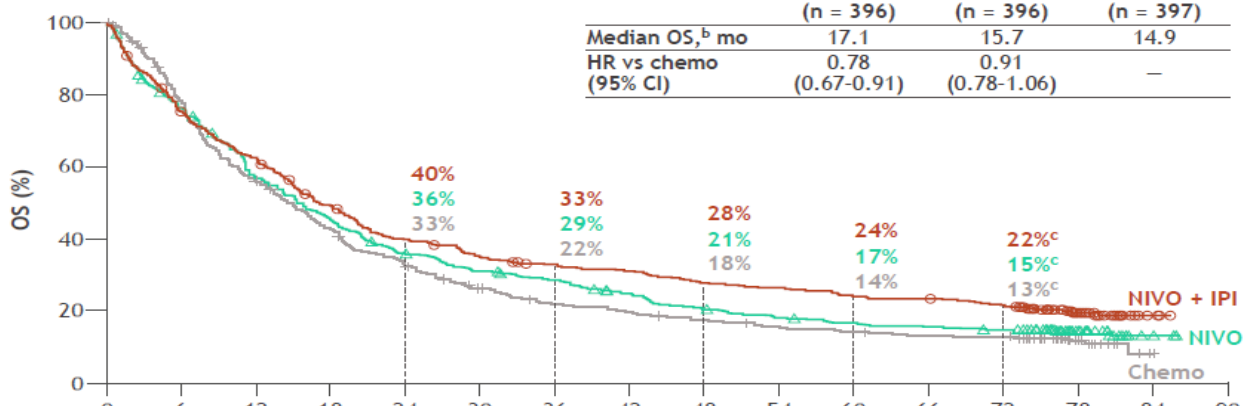
With 6 years' minimum follow-up, patients treated with NIVO + IPI vs chemo continued to derive long-term, durable efficacy benefit in CheckMate 227 Part 1, regardless of tumor PD-L1 expression

– 6-year OS rates: 22% vs 13% (PD-L1 ≥ 1%); 16% vs 5% (PD-L1 < 1%)

– 6-year DOR rates: 27% vs 4% (PD-L1 ≥ 1%); 25% vs NA (PD-L1 < 1%)

OS in patients with tumor PD-L1 ≥ 1%

	NIVO + IPI[a] (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS,[b] mo	17.1	15.7	14.9
HR vs chemo (95% CI)	0.78 (0.67-0.91)	0.91 (0.78-1.06)	–



No. at risk

NIVO + IPI	396	296	246	192	154	134	123	116	104	99	90	88	80	36	4	0
NIVO	396	299	220	176	139	119	108	91	75	66	60	56	52	23	3	0
Chemo	397	306	218	166	126	98	80	72	63	56	50	46	45	16	1	0

- In an exploratory analysis of OS by histology in patients with tumor PD-L1 ≥ 1%, 6-year OS rates with NIVO + IPI vs chemo were 25% vs 16% (NSQ) and 14% vs 5% (SQ)[d]

Minimum/median follow-up for OS: 73.5/78.8 months.
[a]NIVO + IPI vs NIVO OS HR was 0.86 (95% CI, 0.74-1.01). [b]Median OS 95% CIs were 15.0-20.2 (NIVO + IPI), 13.3-18.1 (NIVO), and 12.7-16.7 (chemo). [c]6-year OS rate 95% CIs were 18-26 (NIVO + IPI), 12-19 (NIVO), and 10-17 (chemo). [d]NIVO + IPI vs chemo OS HRs were 0.83 (95% CI, 0.68-1.00; NSQ) and 0.70 (95% CI, 0.53-0.92; SQ).

ORR slightly in favor of combination chemo+IO

	KN 24 (TPS > 50%)	KN 42 (TPS > 50%)	IMPW 10 TC3/IC3 (>50% and >10%)	KN 407 (TPS > 50%)	KN 189 (TPS > 50%)
ORR	45%	39.5%	30.7%	60.3%	61.4%
DOR	Nr (1.8-20.6 m)	20.2 m	Nr (1.8-29.3m)	7.7 m (all patients)	11.2 m (all patients)

Reck M, NEJM 2016, Mok T et al, Lancet 2019, Paz Ares, NEJM 2018, Ghandi, NEJM 2018

Adverse Events more prevalent with Chemo/IO

	KN-42		KN-24		KN-189		KN-407	
	Pembro	CT	Pembro	CT	Pembro + CT	CT	Pembro + CT	CT
All TRAE (%)	62.7%	89.9%	76.6%	90.0%	99.8%	99.0%	98.2%	97.9%
Grade 3-5 TRAE (%)	17.8%	41%	31.2%	53.3%	67.2%	65.0%	69.8%	68.2%
Discontinuation rate (any) (%)	9%	9.4%	13.6%	10.7%	27.7%	14.9%	23.4%	11.8%
Led to death	0.2%	0%	1.3%	2.0%	6.7%	5.9%	8.3%	6.4%

Reck M, NEJM 2016, Mok T et al, Lancet 2019, Paz Ares, NEJM 2018, Ghandi, NEJM 2018

Clinical trials of first-line Chemo-IO and IO regimens included in FDA pooled analysis

Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab** + **Ipilimumab****
CheckMate-9LA	**Nivolumab** + **Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy immunotherapy; IO=immunotherapy.
* Cohort G
** Control arms: Platinum-based doublet chemotherapy
*** Control arm in IMpower150: Bevacizumab plus platinum-based doublet chemotherapy

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Exploratory OS, PFS, and ORR: NSCLC PD-L1 ≥50%

FDA

	Chemo-IO (*N*=455)		IO-alone (*N*=1,298)
OS			
Median, months (95% CI)	25.0 (19.0, NE)		20.9 (18.5, 23.1)
HR (95% CI)		0.82 (0.62, 1.08)	
PFS			
Median, months (95% CI)	9.6 (8.4, 11.1)		7.1 (6.3, 8.3)
HR (95% CI)		0.69 (0.55, 0.87)	
ORR			
% (95% CI)	61 (56, 66)		43 (41, 46)
Odds ratio		1.2 (1.1, 1.3)	

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR-hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.

TIGIT

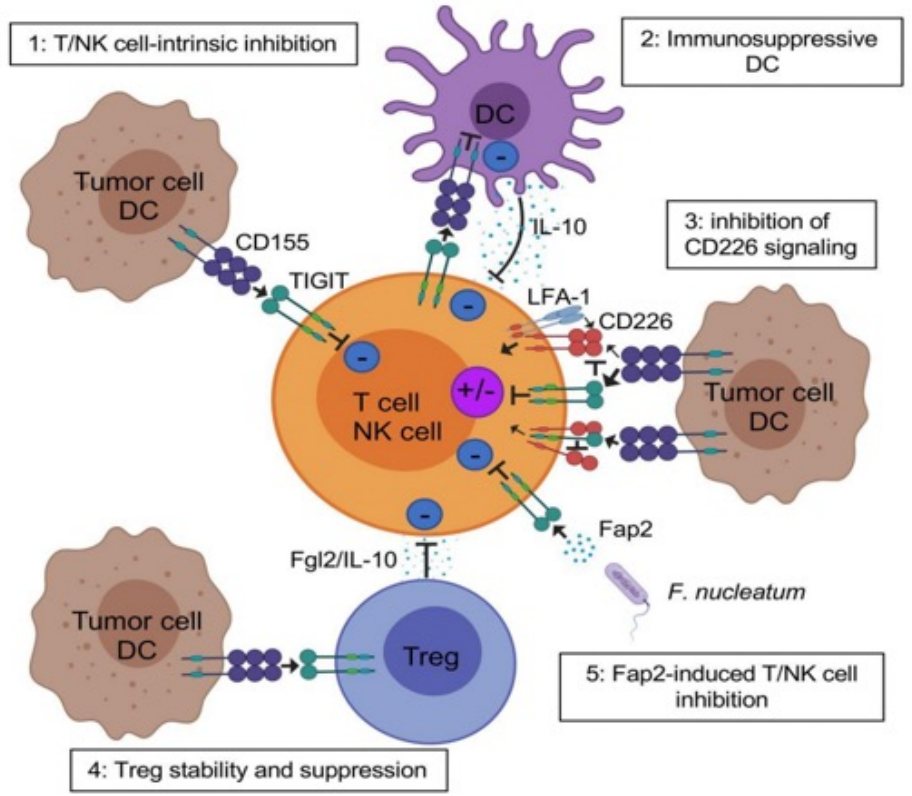
- **TIGIT/CD155**:
- Directly inhibits T cells

- Triggers **IL-10** production, **IL-12** decrease from **APCs** = Indirectly inhibits T cells

- Enhances immunosuppressive **Treg** function

- Interaction with **gut microbiome**: Binds with Fusobacterium nucleatum = Inhibitory signaling

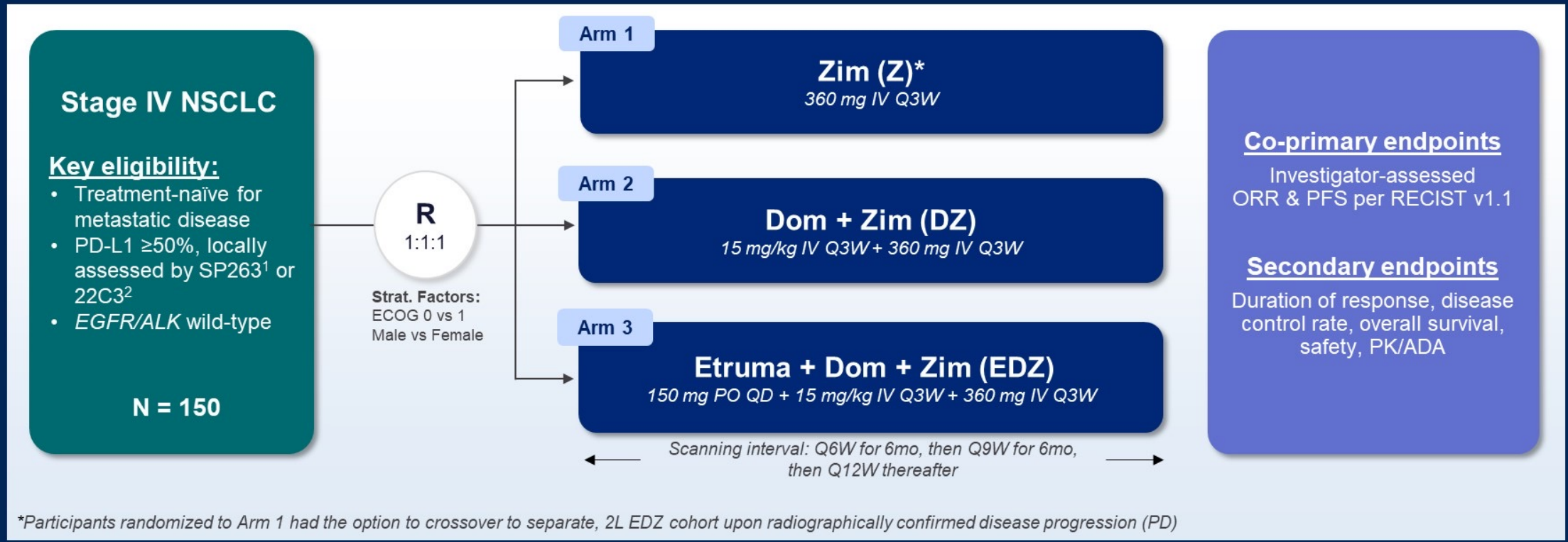
Mechanisms of TIGIT inhibition of T cells in TME



Joe-Marc Chauvin, and Hassane M Zarour J Immunother Cancer 2020;8:e000957

Journal for ImmunoTherapy of Cancer

ARC-7: Randomized, Open-label, Phase 2 Study in First-Line, Metastatic, PD-L1-High NSCLC



*Participants randomized to Arm 1 had the option to crossover to separate, 2L EDZ cohort upon radiographically confirmed disease progression (PD)

ADA: anti-drug antibody, Dom: domvanalimab, Etruma: etrumadenant, ORR: objective response rate, PFS: progression-free survival, PK: pharmacokinetics; R: randomized; Zim: zimberelimab; Q3W: every three weeks
[1]Ventana SP263 assay; [2]PharmDx 22C3 assay

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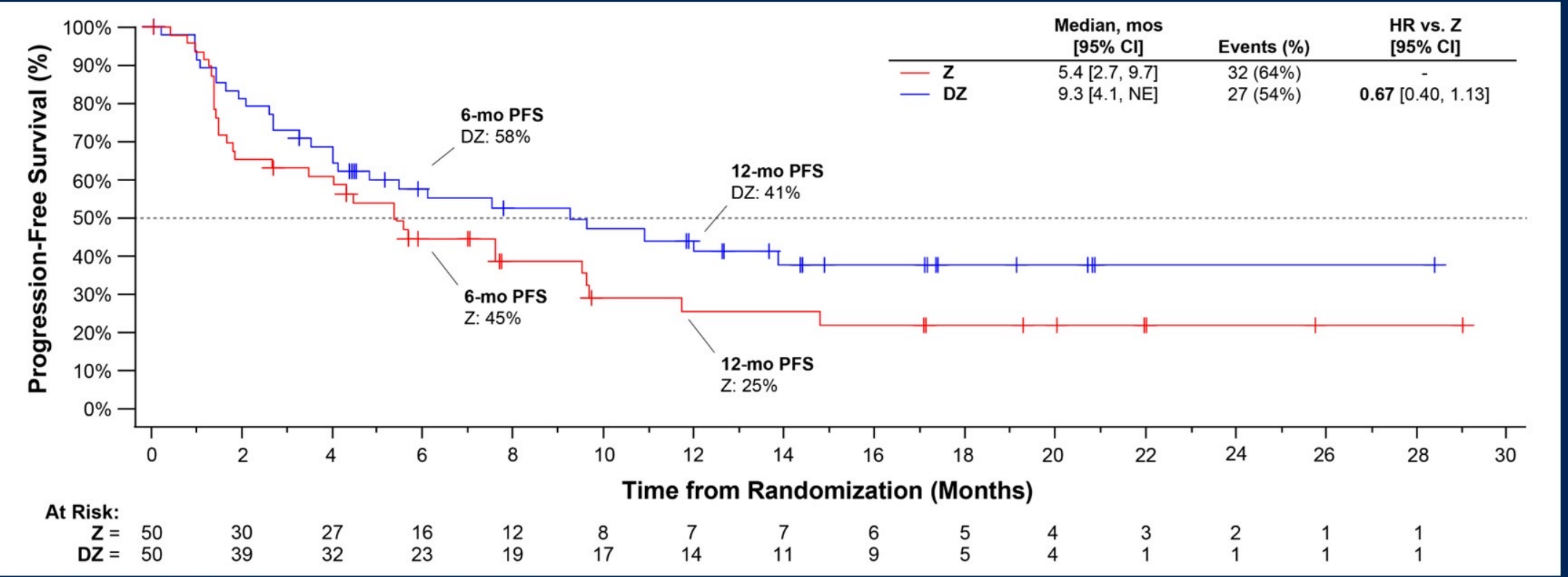
Progression-Free Survival (mITT)

Zim Monotherapy vs. Dom + Zim Doublet



CI: confidence interval; HR: hazard ratio; Mos: months; NE: not evaluable

Addition of dom to zim resulted in 33% reduction in risk of progression or death as compared to zim alone

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Conclusions

- In an updated analysis of ARC-7, with longer median follow-up of 18.5 months, dom-containing arms continued to demonstrate clinically meaningful improvement in ORR and PFS as compared to zim monotherapy. Specifically, TIGIT combinations resulted in:
  - Greater ORR, Δ: +10 to 14%, compared to zim alone
  - Approximately 30% reduction in risk of progression or death compared to zim alone
- Clinical activity and safety of zim performed as expected with agents in the anti-PD-1 class
- Dom + zim combinations with or without etruma were generally well-tolerated with similar, manageable safety profiles across all arms
  - Rates of infusion-related reactions were low across dom-containing arms (4 – 12%), as intended with the Fc-silent design of dom
- The data presented support the ongoing phase 3 studies with domvanalimab: ARC-10 (NCT04736173), STAR-121 (NCT05502237), STAR-221 (NCT05568095) and PACIFIC-8 (NCT05211895)

Current trials in Stage IV NSCLC targeting TIGIT

	VELOCITY-Lung	STAR-121	ARC-7	KEYVIBE-007	KEYVIBE-003	SKYSCRAPER-01	CITYSCAPE
	NCT05633667	NCT05502237	NCT04262856	NCT05226598	NCT04738487	NCT04294810	NCT03563716
Anti-TIGIT	Domvanalimab (DOM)	Domvanalimab (DOM)	Domvanalimab	Vibostolimab*	Vibostolimab*	Tiragolumab	Tiragolumab
Immunotherapy	Zimberelimab (ZIM)	Zimberelimab (ZIM)	Zimberelimab (ZIM)	Pembrolizumab*	Pembrolizumab*	Atezolizumab	Atezolizumab
Additional Tx	Sacituzumab govitecan (SG)/ Etrumadenant (ETRUMA)	Chemotherapy	Etrumadenant (ETRUMA)	Chemotherapy	n/a	n/a	n/a
Control Arm	SOC	Pembrolizumab + CT	Zimberelimab	Pembrolizumab + CT	Pembrolizumab	Placebo + Atezolizumab	Placebo + Atezolizumab
Line of Therapy	1 L	1L	1L	1L	1L	1L	1L
Histology	NSQ	NSQ/SQ	NSQ/SQ	NSQ/SQ	NSQ/SQ	NSQ/SQ	NSQ/SQ
Patient Population	Non-AGA	No EGFR/ALK	PD-L1 >50% No EGFR/ALK	Non-AGA	No EGFR/ALK/ROS1 PD-L1 ≥1%	Non-AGA PD-L1 ≥50%	CT Naïve
Start Date	Not Yet Recruiting	October 2022	May 2020	March 2022	April 2021	March 2020	August 2018
Estimated Completion Date	January 2027	December 2027	February 2024	September 2025	April 2026	February 2025	June 2019
Primary Outcome	ORR	PFS/OS	ORR/PFS	PFS/OS	OS	PFS/OS	ORR: 31.3% PFS: 5.4 months
Trial Type	Phase II	Phase III	Phase II	Phase III	Phase III	Phase III	Phase II

*Coformulation (MK-7684A)