Applications for Community Oncology

Lung Cancer Data Review

April 20, 2023

cornerstone specialty network™

FDA APPROVALS

Nivolumab with platinum-doublet chemotherapy for adult patients with resectable NSCLC in the neoadjuvant setting

Fam-trastuzumab deruxtecan-nxki for adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy

Cemiplimab-rwlc (in combination with platinum-based chemotherapy for adult patients with advanced NSCLC with no EGFR, ALK, or ROS1 aberrations.

Adagrasib, a RAS GTPase family inhibitor, for adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy.

2022 — **2023** — ***More to come***

Capmatinib for adult patients with metastatic NSCLC whose tumors have a mutation leading to mesenchymal-epithelial transition (MET) exon 14 skipping, as detected by an FDA-approved test.

Selpercatinib for adult patients with locally advanced or metastatic NSCLC with a rearranged during transfection (RET) gene fusion, as detected by an FDA-approved test.

Tremelimumab in combination with durvalumab and platinum-based chemotherapy for adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumor aberrations.

Pembrolizumab for adjuvant treatment following resection and platinum-based chemotherapy for stage IB (T2a ≥4 cm), II, or IIIA NSCLC

- **On March 4, 2022**, the Food and Drug Administration approved nivolumab (Opdivo, Bristol-Myers Squibb Company) with platinum-doublet chemotherapy for adult patients with resectable non-small cell lung cancer (NSCLC) in the neoadjuvant setting.
- **On August 10, 2022**, the Food and Drug Administration granted regular approval to capmatinib (Tabrecta, Novartis Pharmaceuticals Corp.) for adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation leading to mesenchymal-epithelial transition (MET) exon 14 skipping, as detected by an FDA-approved test.
- **On August 11, 2022**, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating human epidermal growth factor receptor 2 HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. This is the first drug approved for HER2-mutant NSCLC.
- **On September 21, 2022**, the Food and Drug Administration granted regular approval to selpercatinib (Retevmo, Eli Lilly and Company) for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a rearranged during transfection (RET) gene fusion, as detected by an FDA-approved test.
- **On November 8, 202**2, the Food and Drug Administration approved cemiplimab-rwlc (Libtayo, Regeneron Pharmaceuticals, Inc.) in combination with platinum-based chemotherapy for adult patients with advanced non-small cell lung cancer (NSCLC) with no EGFR, ALK, or ROS1 aberrations.
- **On November 10, 2022**, the Food and Drug Administration approved tremelimumab (Imjudo, AstraZeneca Pharmaceuticals) in combination with durvalumab (Imfinzi, AstraZeneca Pharmaceuticals) and platinum-based chemotherapy for adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.
- **On December 12, 2022**, the Food and Drug Administration (FDA) granted accelerated approval to adagrasib (Krazati, Mirati Therapeutics, Inc.), a RAS GTPase family inhibitor, for adult patients with KRAS G12C¬-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.
- **On January 26, 2023**, the Food and Drug Administration (FDA) approved pembrolizumab (Keytruda, Merck) for adjuvant treatment following resection and platinum-based chemotherapy for stage IB (T2a ≥4 cm), II, or IIIA non-small cell lung cancer (NSCLC).

cornerstone specialty network™

UPCOMING

Positive high-level results from a planned interim analysis of the **AEGEAN** Phase III, placebo- controlled trial showed that treatment with AstraZeneca's Imfinzi (durvalumab) in combination with neoadjuvant chemotherapy before surgery and as adjuvant monotherapy after surgery demonstrated a statistically significant and clinically meaningful improvement in EFS versus neoadjuvant chemotherapy alone followed by surgery for patients with resectable early-stage (IIA-IIIB) NSCLC. (*AACR 2023*)

Merck announces Phase 3 **KEYNOTE-671** trial met primary endpoint of event-free survival (EFS) after treatment with perioperative pembrolizumab + platinum-based chemotherapy in patients with resectable stage II, IIIA OR IIIB non-small cell lung cancer. (*The FDA has set a Prescription Drug User Fee Act date of October 16, 2023)*

Positive high-level results from the **ADAURA** Phase III trial showed AstraZeneca's Tagrisso (osimertinib) demonstrated a statistically significant and clinically meaningful improvement in OS, a key secondary endpoint, compared to placebo in the adjuvant treatment of patients with early-stage (IB, II and IIIA) EGFRm NSCLC after complete tumor resection with curative intent.

Amgen announces encouraging antitumor activity from the **DeLLphi300** clinical trial, a Phase 1 dose exploration and expansion study evaluating the safety and efficacy of investigational tarlatamab, a potential first-in-class half-life extended bispecific T-cell engager (HLE BiTE®) molecule targeting delta-like ligand 3 (DLL3), in small cell lung cancer (SCLC)

cornerstone specialty network™

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung3 • CheckMate-9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreak 100/101 • EXCLAIM • ALTA-1L

cornerstone specialty network™

ADAURA

Does adjuvant osimertinib after complete resection benefit patients with stage IB–IIIA EGFR-mutated NSCLC?

Updated analysis

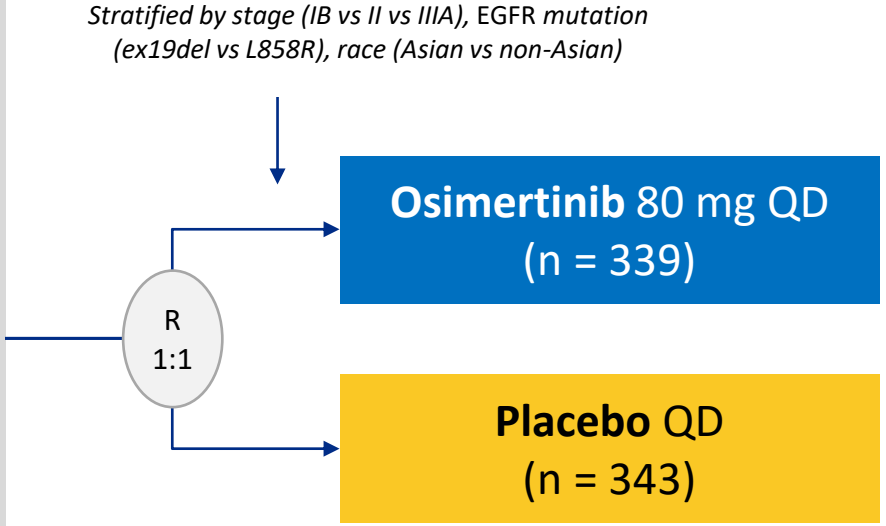
ADAURA

Study Design: Randomized, international double-blinded phase III

- Patients with completely resected stage IB/II/IIIA NSCLC with negative margins
- Confirmed primary nonsquamous NSCLC with *EGFR* ex19del or L858R*
- Aged ≥18 yr (≥20 yr in Japan/Taiwan)
- WHO PS 0/1
- Brain imaging done
- With or without adjuvant CT
- Maximum time between surgery and randomization:
  - 10 wk without adjuvant CT,
  - 26 wk with adjuvant CT

(N = 682)

*Confirmed centrally in tissue.



Planned treatment duration: 3 years

Treatment continues until:
Disease recurrence, treatment completed, or discontinuation criterion met

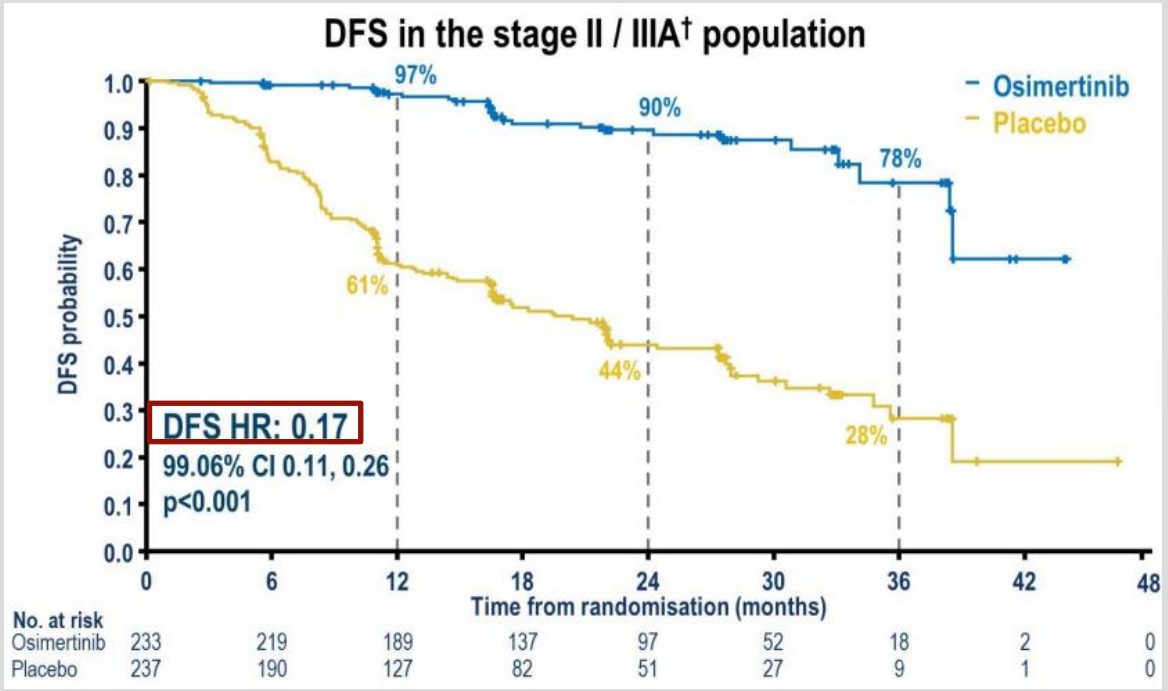
Follow-up:
Until recurrence: Wk 12 and 24, then Q24W to 5 yr, then yearly
After recurrence: Q24W for 5 yr, then yearly.

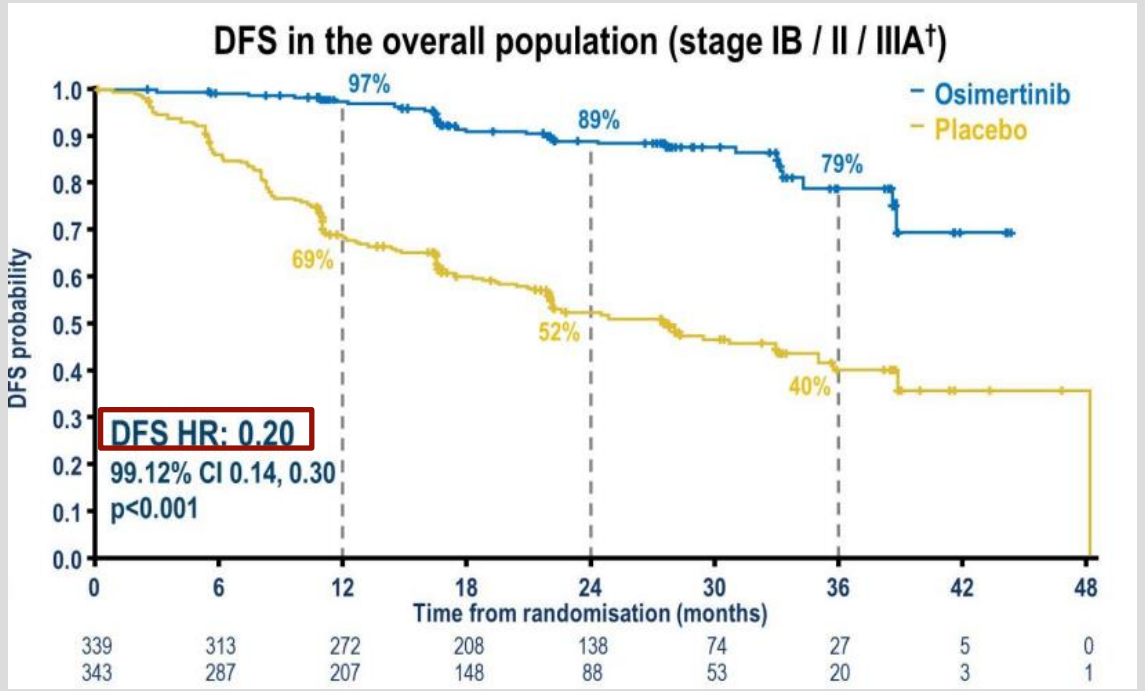
Primary endpoints: investigator-assessed DFS in patients with stage II/ IIIA disease designed to test superiority with assumed DFS HR of 0.70
Key secondary endpoints: DFS in overall population, landmark DFS rates at 2, 3, 4, and 5 years, OS, HRQoL, safety
Exploratory endpoints: patterns of recurrence; time to CNS recurrence (CNS DFS)

Data cutoff: April 11, 2022

ADAURA

Primary Analysis: DFS (previously reported)





Data cutoff: January 17, 2020

J Clin Oncol 2020; 38: 18 suppl. LBA5
ESMO 2022, Abstr LBA47

ADAURA

Baseline Characteristics

Characteristic	Osimertinib (n = 339)	Placebo (n = 343)
Female, %	68	72
Median age, yr (range)	64 (30-86)	62 (31-82)
Smokeing history yes/no,* %	32/68	25/75
Asian/non-Asian, %	64/36	64/36
WHO PS 0/1, %	63/37	64/36
Adenocarcinoma/ other histology, %	96/4	97/3
EGFR ex19del/L858R,† %	55/45	55/45
Adjuvant CT yes/no, %	60/40	60/40

Characteristic, %	Osimertinib (n = 339)	Placebo (n = 343)
AJCC staging at diagnosis (7th edition)		
▪ IA	0	0
▪ IB	32	31
▪ II	33	34
▪ IIIA	35	35
▪ IIIB	0	0
AJCC staging at diagnosis (8th edition)		
▪ IA	1	<1
▪ IB	30	29
▪ II	33	35
▪ IIIA	32	34
▪ IIIB	3	2

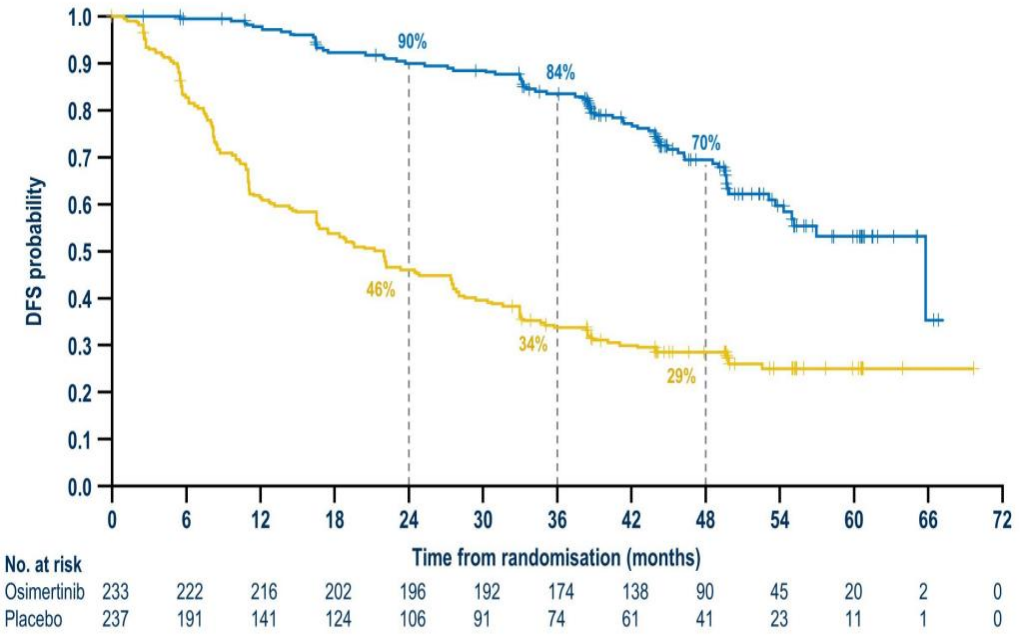
*Former smoker: osimertinib, n = 104; placebo, n = 83; current smoker: osimertinib, n = 4; placebo, n = 3.
†Central test.

ADAURA

Primary Endpoint: Updated DFS

DFS in Stage II/IIIA	Osimertinib (n = 233)	Placebo (n = 237)
Median DFS, mo (95% CI)*	65.8 (54.4-NC)	21.9 (16.6-27.5)
HR (95% CI)	**0.23** (0.18-0.30)	

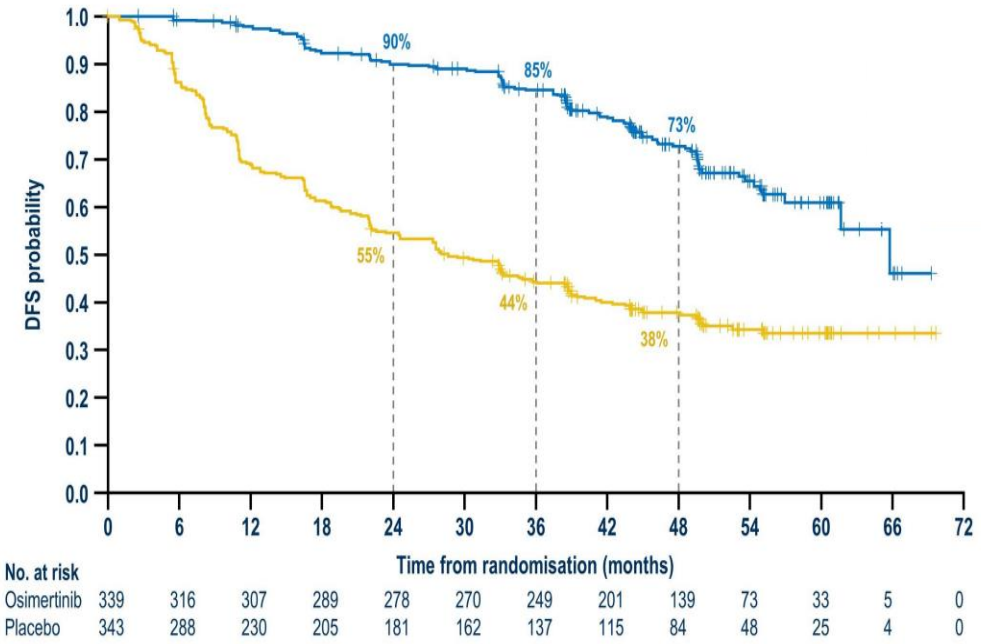
Stage II / IIIA Disease



*Maturity 51%; osimertinib 32%, placebo 70%.

DFS in Stage IB/II/IIIA	Osimertinib (n = 239)	Placebo (n = 343)
Median DFS, mo (95% CI)†	65.8 (61.7-NC)	28.1 (22.1-35.0)
HR (95% CI)	**0.27** (0.21-0.34)	

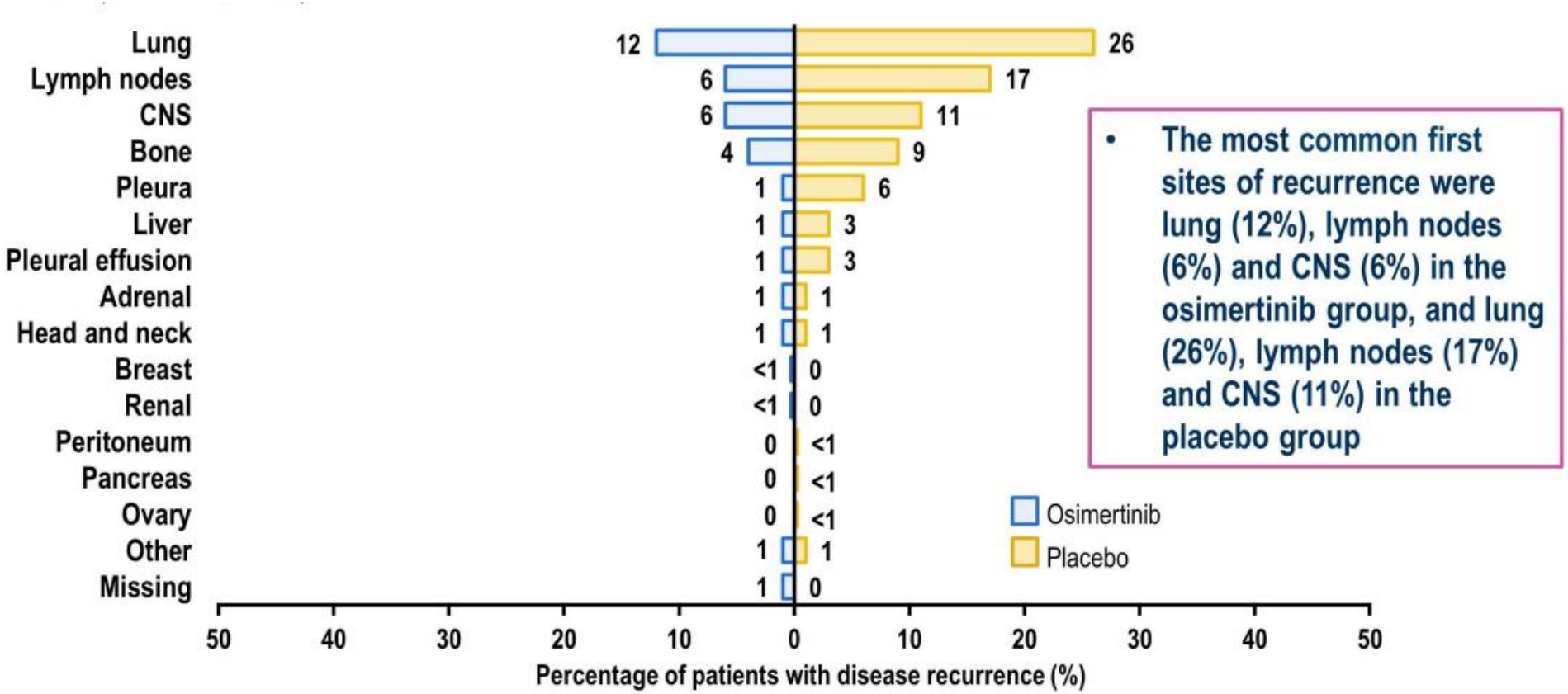
Overall population (Stage IB / II / IIIA Disease)



†Maturity 45%; osimertinib 28%, placebo 62%.

ADAURA

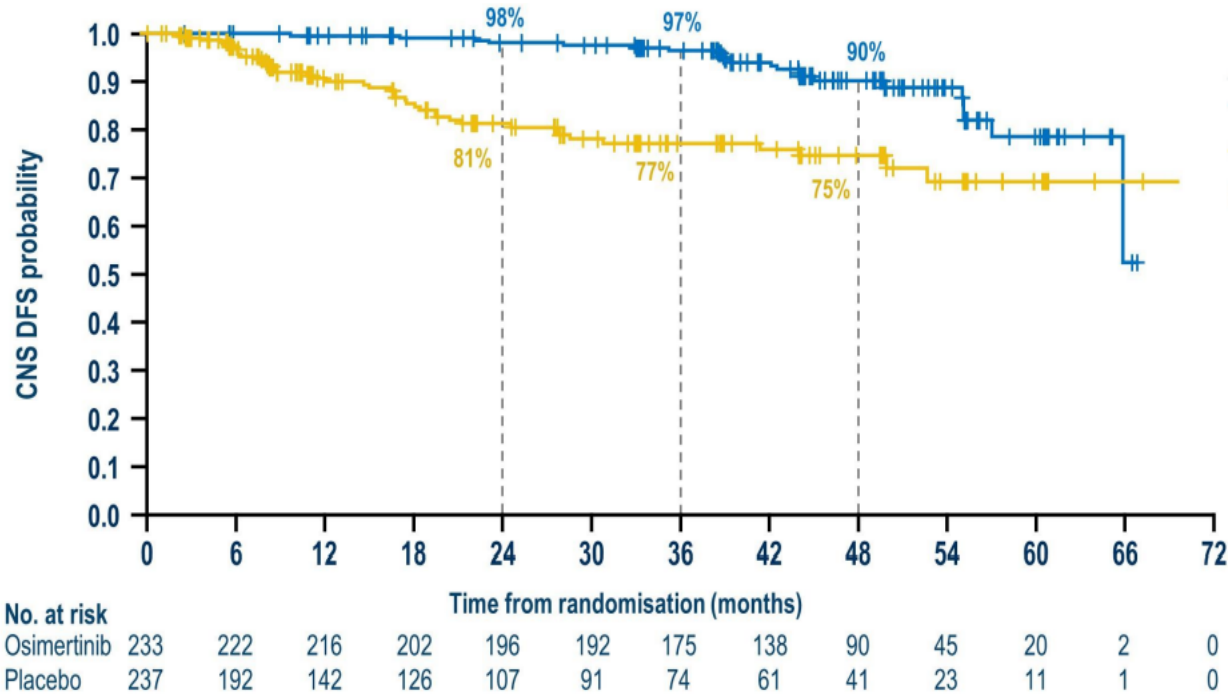
Disease Recurrence



- The most common first sites of recurrence were lung (12%), lymph nodes (6%) and CNS (6%) in the osimertinib group, and lung (26%), lymph nodes (17%) and CNS (11%) in the placebo group

ADAURA

Updated CNS DFS in patients with Stage II / IIIA Disease



Analysis in Stage II/IIIA Disease	Osimertinib (n = 233)	Placebo (n = 237)
CNS DFS events, n	22	41
• On tx at CNS recurrence, n	3	29
Median CNS DFS, mo (95% CI)*	NR (65.8-NC)	NR (NC-NC)
HR (95% CI)	**0.24** (0.14-0.42)	
Probability of CNS recurrence at 36 mo, % (95% CI)	2 (0.9-5.0)	13 (8.5-18.5)

In total, 63 patients had CNS DFS events†

Patients on treatment at time of CNS DFS:

- 14% with osimertinib
- 71% with placebo

*Maturity 13%; Osimertinib 9%, placebo 17%.

†Define as CNS as the first site of disease recurrence, or death without any disease recurrence.

ADAURA

Updated Safety

AE, n (%)	Osimertinib (n = 337)	Placebo (n = 343)
Any-cause AE*	330 (98)	309 (90)
• Grade ≥3 AE	79 (23)	48 (14)
• AE leading to death	1 (<1)	2 (1)
• Serious AE	68 (20)	47 (14)
• AE leading to d/c	43 (13)	9 (3)
• AE leading to dose reduction	42 (12)	3 (1)
• AE leading to dose interrupt	91 (27)	43 (13)
Possibly causally related AE†		
• Any AE	308 (91)	199 (58)
• Grade ≥3 AE	36 (11)	7 (2)
• AE leading to death	0	0
• Serious AE	10 (3)	2 (1)

Completed planned 3-yr duration:

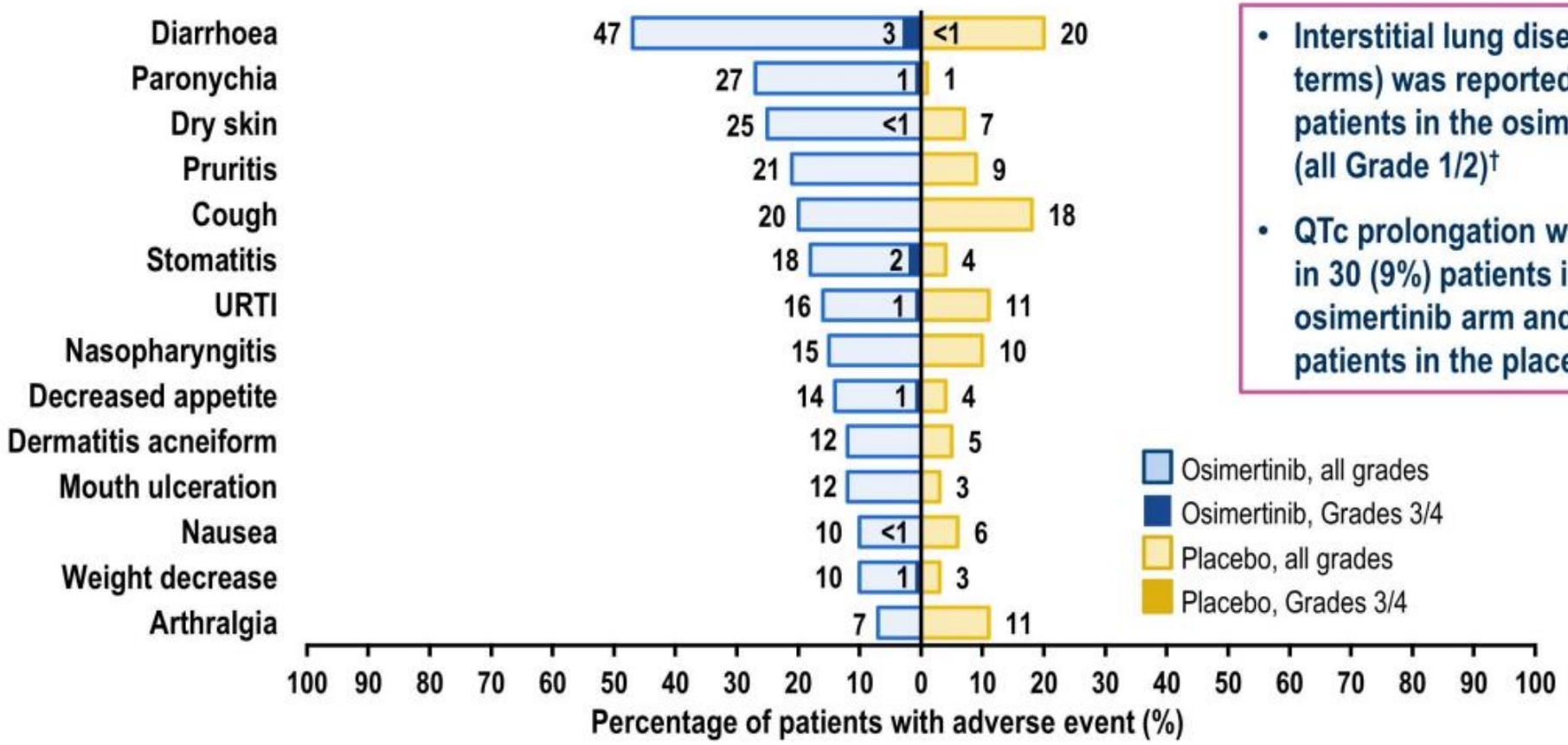
- Osimertinib: 222/337 (66%)
- Placebo: 139/343 (41%)

Median duration of exposure:

- Osimertinib: 35.8 mo (range: 0-38)
- Placebo: 25.1 mo (range: 0-39)

ADAURA

Updated Safety



- Interstitial lung disease (grouped terms) was reported in 11 (3%)* patients in the osimertinib arm (all Grade 1/2)†
- QTc prolongation was reported in 30 (9%) patients in the osimertinib arm and 8 (2%) patients in the placebo arm‡

SUMMAY

ADAURA

- With 2 additional years of follow-up, adjuvant osimertinib significantly prolonged DFS vs placebo following complete resection of stage IB/II/IIIA EGFR+ NSCLC
  - 77% reduction in risk of recurrence or death with osimertinib in stage II/IIIA disease (primary endpoint; HR: 0.23; 95% CI: 0.18-0.30)
  - Median DFS: 65.8 mo with osimertinib vs 21.9 mo with placebo
  - 73% reduction in the risk of recurrence or death with osimertinib in overall population (HR: 0.27), including stage IB, II, and IIIA disease
  - DFS prolonged with osimertinib across subgroups, regardless of receipt of prior adjuvant CT
  - Clinically meaningful improvement in CNS DFS in stage II-IIIA (HR: 0.24; 95% CI: 0.14-0.42)
- No new safety signals observed with osimertinib

ESMO 2022, Abstr LBA47

ADAURA

Osimertinib should be standard of care in the adjuvant setting for patients with stage IB/II/IIIA EGFR-mutated NSCLC following complete resection

Key Studies

Neo/Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung3 • CheckMate -9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreak 100/101 • EXCLAIM • ALTA-1L

cornerstone specialty network™

CLINICAL QUESTION

CheckMate-816

Does nivolumab in combination with platinum-doublet chemotherapy benefit patients with early stage NSCLC ?

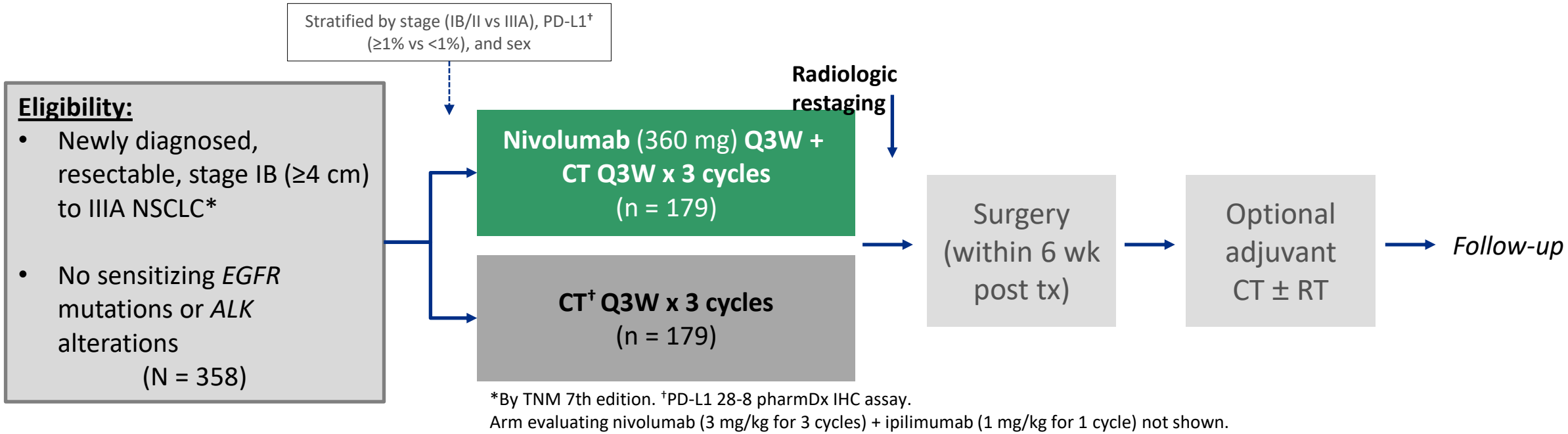
*On **March 4 2022**, the Food and Drug Administration approved nivolumab (Opdivo, Bristol-Myers Squibb Company) with platinum-doublet chemotherapy for adult patients with resectable non-small cell lung cancer (NSCLC) in the neoadjuvant setting. This represents the first FDA approval for neoadjuvant therapy for early-stage NSCLC.*

cornerstone specialty network™

KEY DATA

CheckMate-816

Study Design: Randomized, open-label phase III trial neoadjuvant nivolumab + platinum chemotherapy for resectable Stage IB-IIIA NSCLC



*By TNM 7th edition. †PD-L1 28-8 pharmDx IHC assay.
Arm evaluating nivolumab (3 mg/kg for 3 cycles) + ipilimumab (1 mg/kg for 1 cycle) not shown.

Primary endpoints: pCR (by BIPR), EFS (by BICR)
Key secondary endpoints: OS, MPR (by BIPR), time to death or distant metastasis
Key exploratory endpoints: ORR (by BICR), surgery feasibility, peri/postoperative surgery-related AEs

†Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin, pemetrexed + cisplatin, or paclitaxel + carboplatin

Data cutoff: October 20, 2021; median follow up: 29.5 months

CheckMate-816

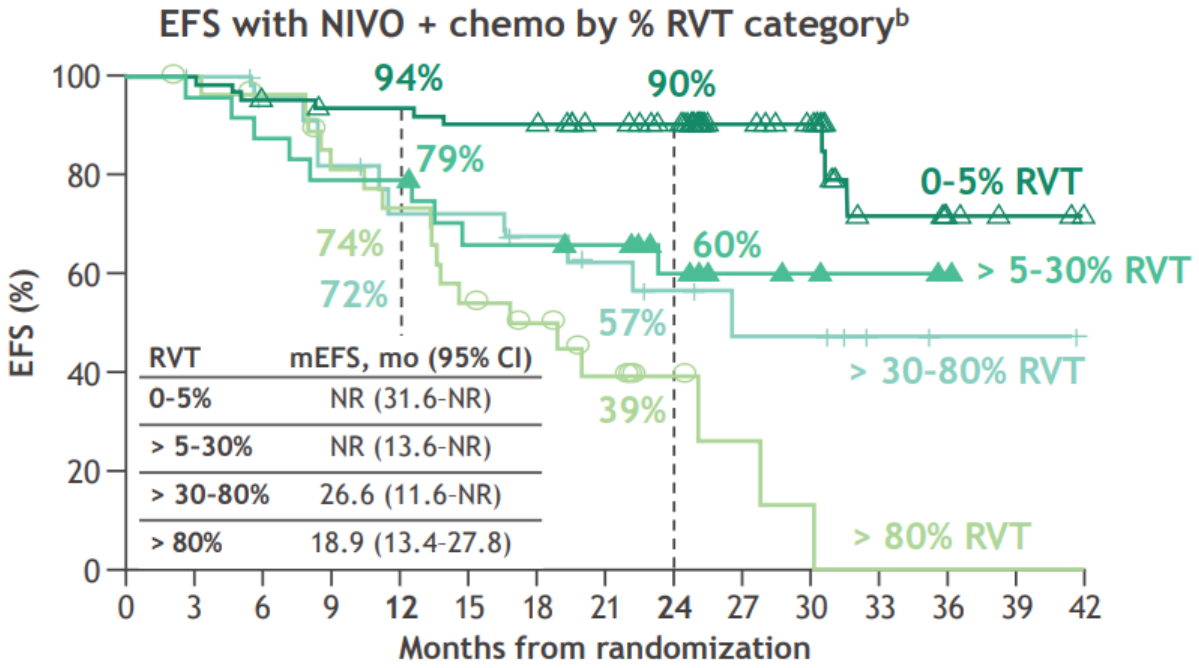
Primary Endpoints

Neoadjuvant nivo plus platinum-doublet chemotherapy results in significant improvements compared with chemotherapy alone

- Statistically significant improvement in EFS over chemotherapy alone with a **37**% reduction in the risk of progression, recurrence or death (HR 0.63; 95% CI: 0.45 to 0.87; P=0.0052)

- pCR rate **24**% vs 2.2%

- Depth of pathological response (low % residual viable tumor [RVT]) was associated with improved EFS outcomes with neoadjuvant NIVO + chemo



Key Secondary Endpoint

- Overall survival (OS): **HR=0.57** (95% CI: 0.38–0.87); OS data were immature at the pre-specified interim analysis, and did not cross the boundary for statistical significance

[b]ASCO 2022 LBA8511; AACR 2022 CT012,; NEJM 386(21):1973

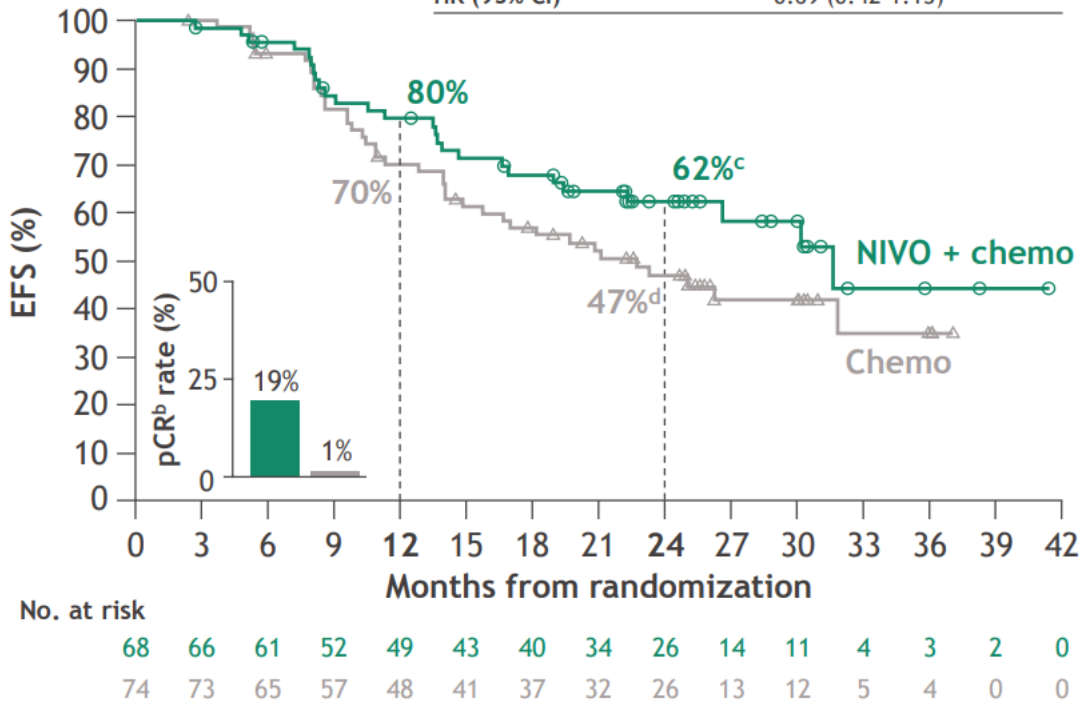
KEY DATA

CheckMate-816

EFS in patients with or without pathologic evidence of LN involvement

With LN involvement

	NIVO + chemo (n = 68)	Chemo (n = 74)
Median EFS, mo (95% CI)	31.6 (22.2-NR)	22.7 (14.8-NR)
HR (95% CI)	0.69 (0.42-1.13)	

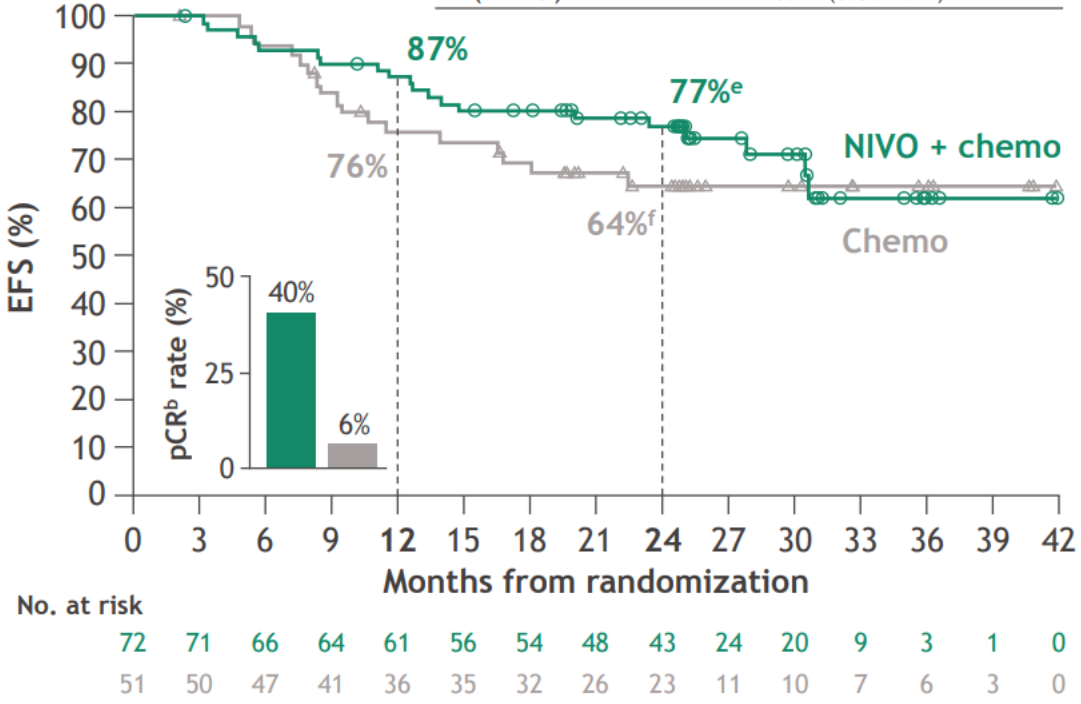


No. at risk

68	66	61	52	49	43	40	34	26	14	11	4	3	2	0
74	73	65	57	48	41	37	32	26	13	12	5	4	0	0

Without LN involvement

	NIVO + chemo (n = 72)	Chemo (n = 51)
Median EFS, mo (95% CI)	NR (30.7-NR)	NR (22.4-NR)
HR (95% CI)	0.74 (0.39-1.41)	



No. at risk

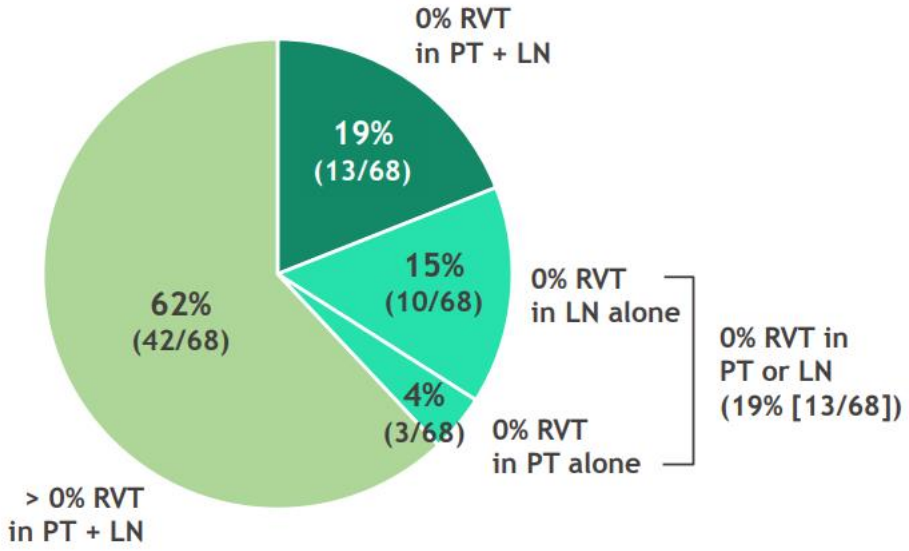
72	71	66	64	61	56	54	48	43	24	20	9	3	1	0
51	50	47	41	36	35	32	26	23	11	10	7	6	3	0

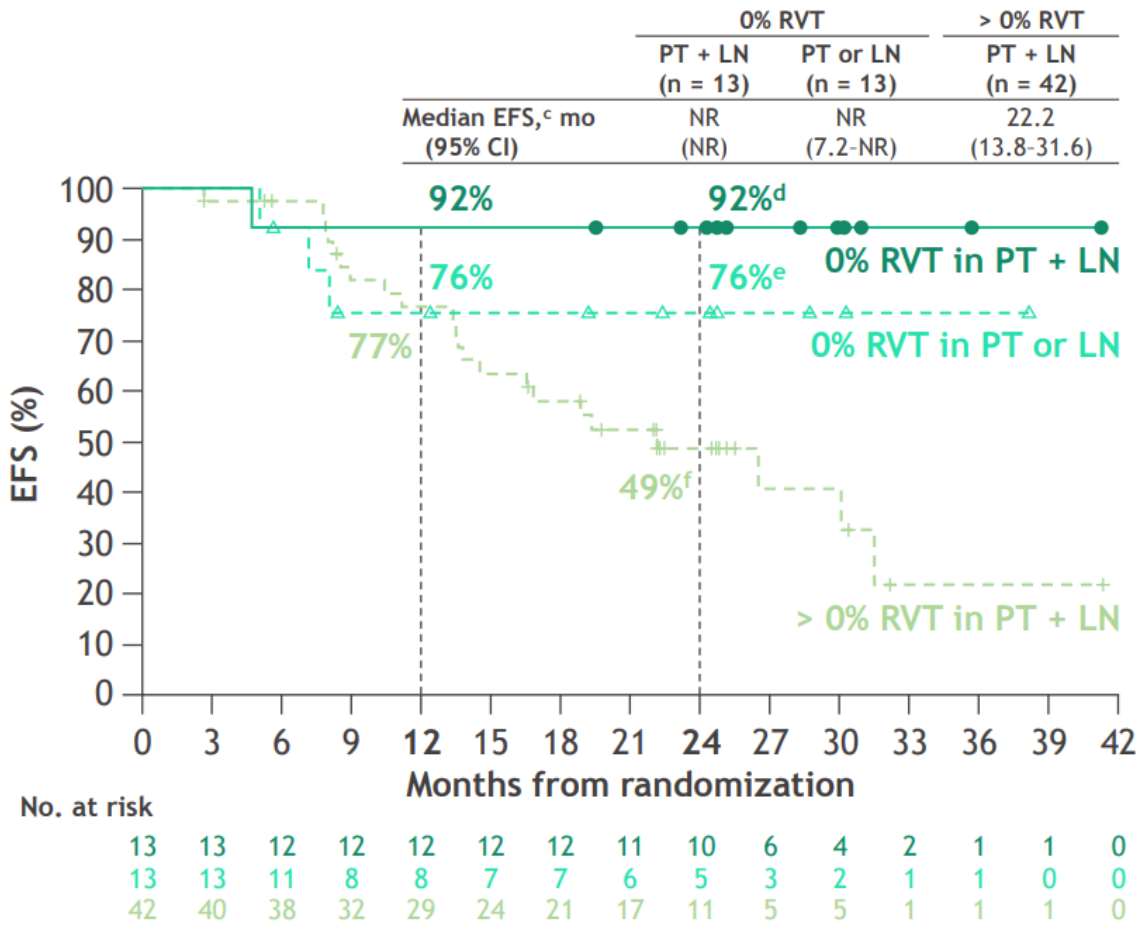
ESMO 2022. Abstr LBA50.

CheckMate-816

EFS by %RVT in patients with LN involvement[a]: Nivo + CT

% RVT: primary tumor (PT) and lymph node (LN)[b]





Minimum / median follow-up: 21 months / 29.5 months.

[a]LN involvement refers to pathologic evidence of LN disease at resection that had or had not fully regressed after neoadjuvant treatment (0% or > 0% RVT in the resected LN).
[b]Patients in the chemo arm with 0% RVT in both PT + LN, 1% (1/74); PT alone, 1% (1/74); LN alone, 4% (3/74); either PT or LN, 5% (4/74); > 0% RVT in PT + LN, 93% (69/74).
[c]HRs were not computed because of the low number of events in the 0% RVT subgroups. 95% CI: d57–99, e42–91,f32–64

SUMMARY

CheckMate-816

- Post hoc analysis revealed that patients with resectable NSCLC had improved EFS and pCR with neoadjuvant nivo + CT compared to CT alone regardless of pathologic evidence of LN involvement
- Greatest EFS achieved in patients treated with neoadjuvant nivolumab + CT with 0% RVT in both primary tumor and LN (vs those with 0% RVT in either LN or primary tumor, or those with >0% RVT)
- The % regression (area of immune-mediated tumor clearance) and % RVT for nivo + CT were inversely correlated and was predictive of EFS at 2 yr regardless of LN involvement
- Overall survival (OS): HR=0.57 (95% CI: 0.38–0.87); OS data were immature at the pre-specified interim analysis, and did not cross the boundary for statistical significance
  - 24 mo OS rate, 83% with nivo + chemo vs 71% with chemo alone

CheckMate-816

Neoadjuvant nivolumab in combination with platinum-doublet chemotherapy benefits patients with early stage NSCLC regardless of LN involvement and should be considered as a standard of care

Improves the chance of successful, less extensive surgical treatment and reduces the risk of recurrence

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung3 • CheckMate -9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreak 100/101 • EXCLAIM • ALTA-1L

cornerstone specialty network™

NADIM II

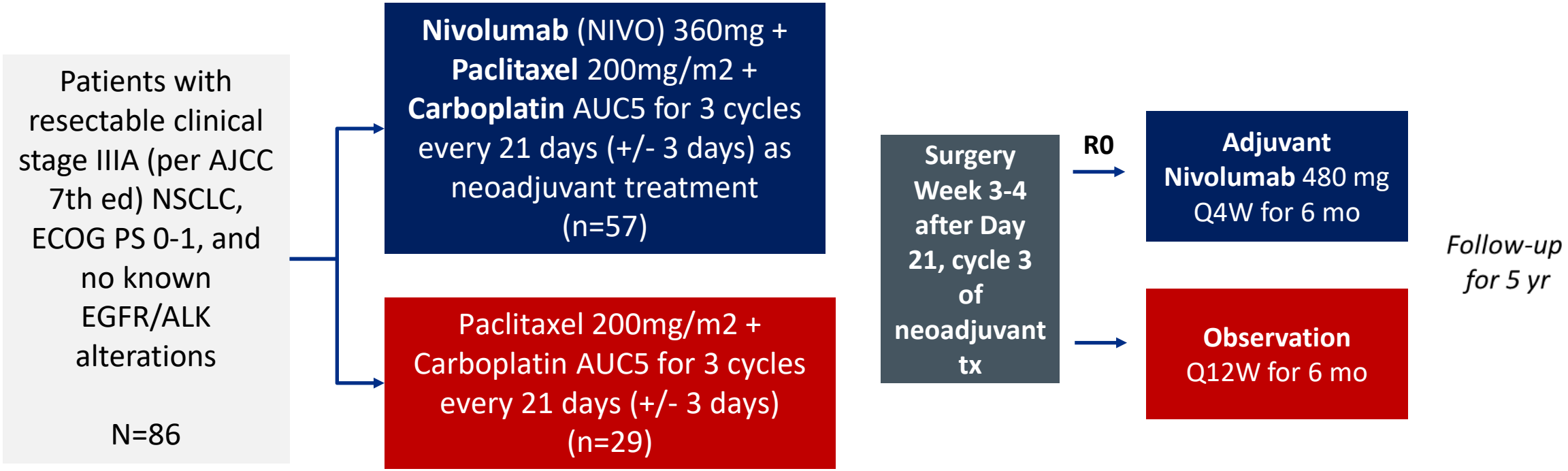
Does neoadjuvant nivolumab plus chemotherapy provide benefit for patients with resectable stage IIIA-B NSCLC ?

Interim analysis: PFS and OS results

KEY DATA

NADIM II

Study Design: open-label, randomized, two-arm, phase II, multi-center clinical trial



Primary endpoint: pCR in ITT population
Secondary endpoints: PFS, OS, MPR, delayed/cancelled surgery, safety, and biomarker analysis

Median follow-up time: 21.9 months
Data cutoff: March 2021

KEY DATA

NADIM II

Baseline Characteristics

Characteristic, n (%)	Nivo + CT (n = 57)	CT (n = 29)
Median age, yr (range)	63 (58-70)	62 (57-66)
Female	21 (36.8)	13 (44.8)
History of tobacco use		
• Never	5 (8.7)	0
• Former	23 (40.4)	10 (34.5)
• Current	29 (50.9)	19 (65.5)
ECOG PS		
• 0	31 (54.4)	16 (55.2)
• 1	26 (45.6)	13 (44.8)
Histology		
• Adenocarcinoma	25 (43.9)	11 (37.9)
• Adenosquamous	1 (1.8)	0
• Squamous	21 (36.8)	14 (48.3)
• Large cell carcinoma	2 (3.5)	1 (3.5)
• NOS/undifferentiated	7 (12.3)	2 (6.9)
• Other	1 (1.8)	1 (3.5)

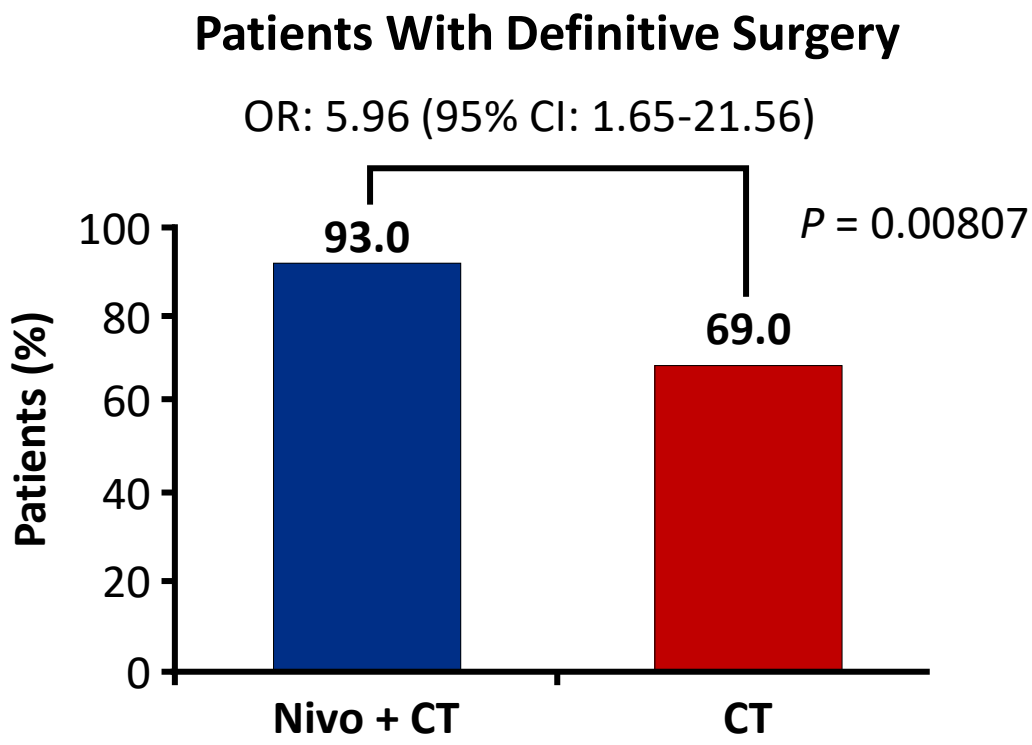
Characteristic, n (%)	Nivo + CT (n = 57)	CT (n = 29)
TNM classification (AJCC 8th ed)		
• T1N2M0	12 (21.1)	4 (13.8)
• T2N2M0	16 (28.1)	7 (24.1)
• T3N1M0	2 (3.5)	1 (3.5)
• T3N2M0	13 (22.8)	5 (19.3)
• T4N0M0	6 (10.5)	9 (31.0)
• T4N1M0	8 (14.0)	3 (10.3)
Median tumor size, mm (range)	43 (29-54)	52 (39-75)
Nodal stage		
• N0	6 (10.5)	9 (31.0)
• N1	10 (17.5)	4 (13.8)
• N2	41 (71.9)	16 (55.2)
N2 multiple station	21 (36.8)	10 (34.5)

NADIM II

Surgery Summary

Type of Surgery, n (%)[1]	Nivo + CT (n = 53)	CT (n = 20)	Total (n = 73)
Pneumonectomy	6 (11.3)	2 (10.0)	8 (11.0)
Lobectomy	40 (75.5)	17 (85.0)	57 (78.1)
Bilobectomy	4 (7.5)	1 (5.0)	5 (6.8)
Segmentectomy	2 (3.8)	0 (0.0)	2 (2.7)
Right lower lobectomy + segmentectomy	1 (1.9)	0 (0.0)	1 (1.4)

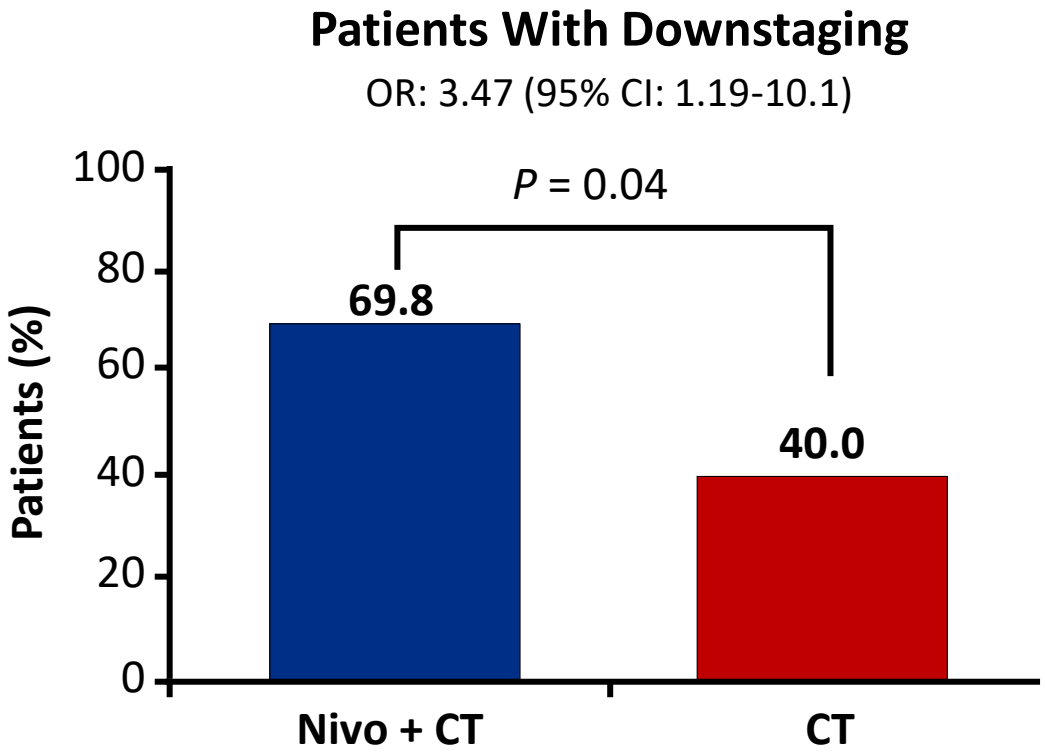
Resection Degree, n (%)[1]	Nivo + CT (n = 57)	CT (n = 29)
RO	49 (92.5)	13 (65.0)
Odds ratio: 6.60 (95% CI: 1.67-26.02); P = 0.007		



NADIM II

Downstaging (Secondary Endpoint)

Downstaging, n (%)	Nivo + CT (n = 53)	CT (n = 20)	Total (n = 73)
Yes	37 (69.8)	8 (40.0)	45 (61.6)
No	16 (30.2)	12 (60.0)	28 (38.4)

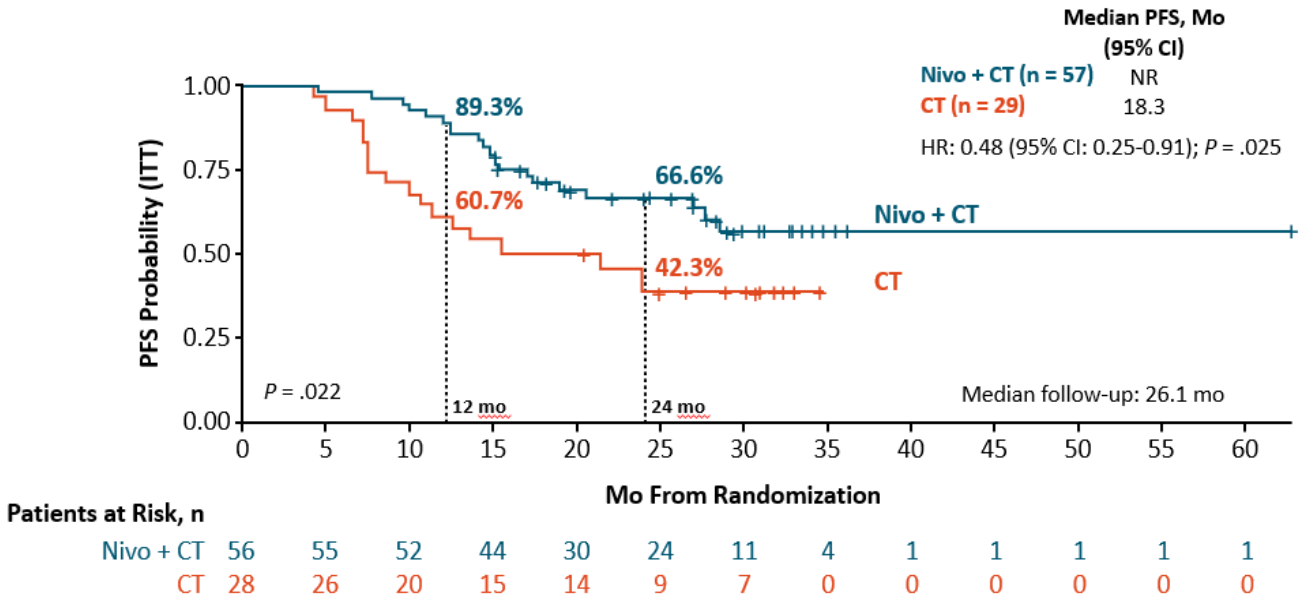


KEY DATA

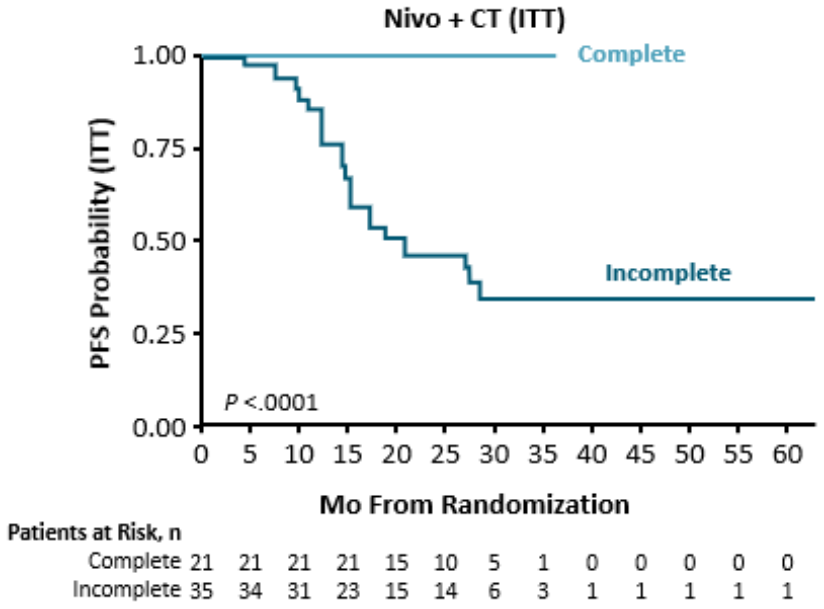
NADIM II

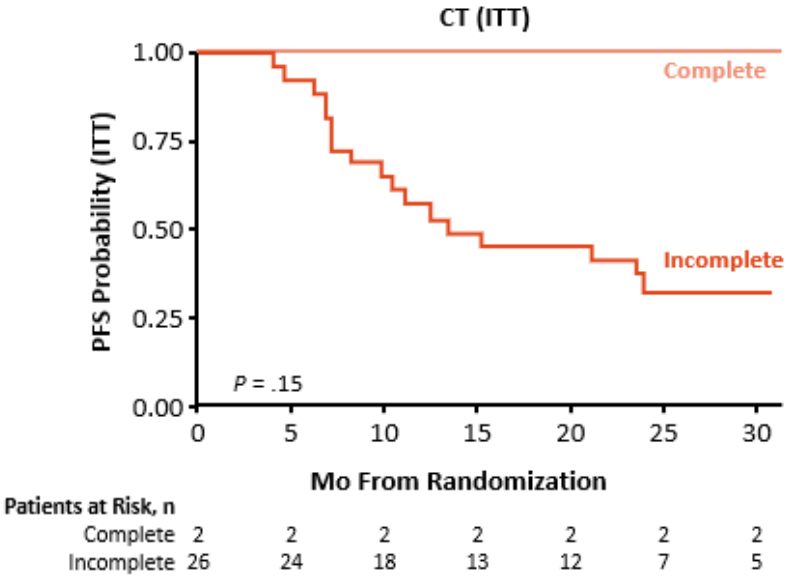
Secondary Endpoints: PFS

- PFS at 24 months was **66.6%** for patients treated with nivolumab plus chemotherapy versus **42.3%** for patients treated with chemotherapy
- **HR 0.48**
- Median PFS not reached in nivo + CT arm



PFS by pCR Status



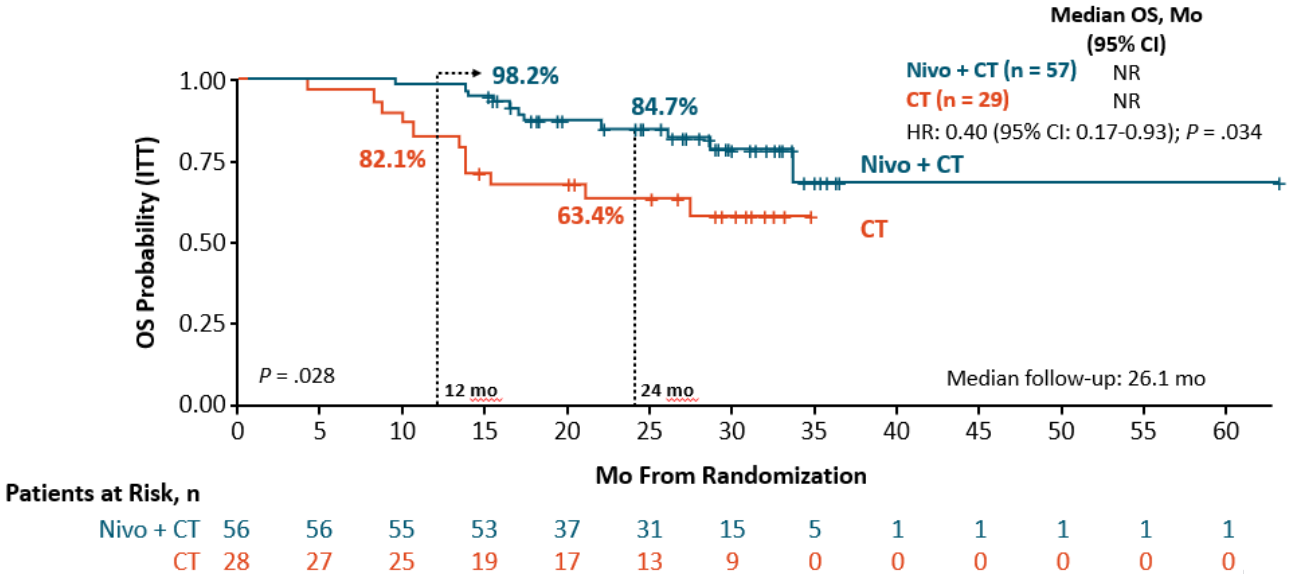


KEY DATA

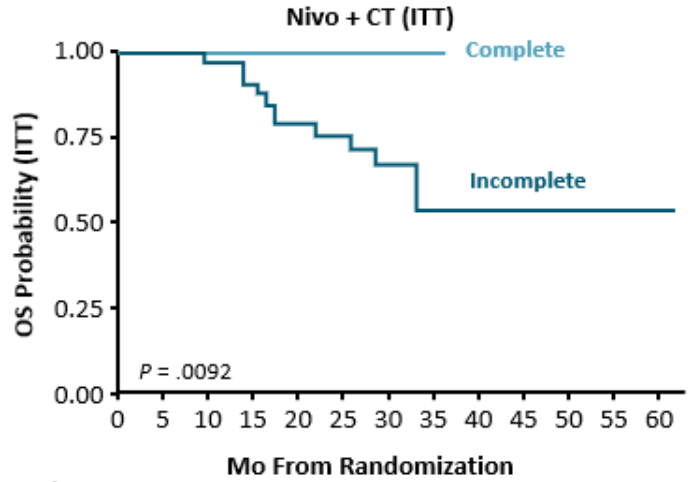
NADIM II

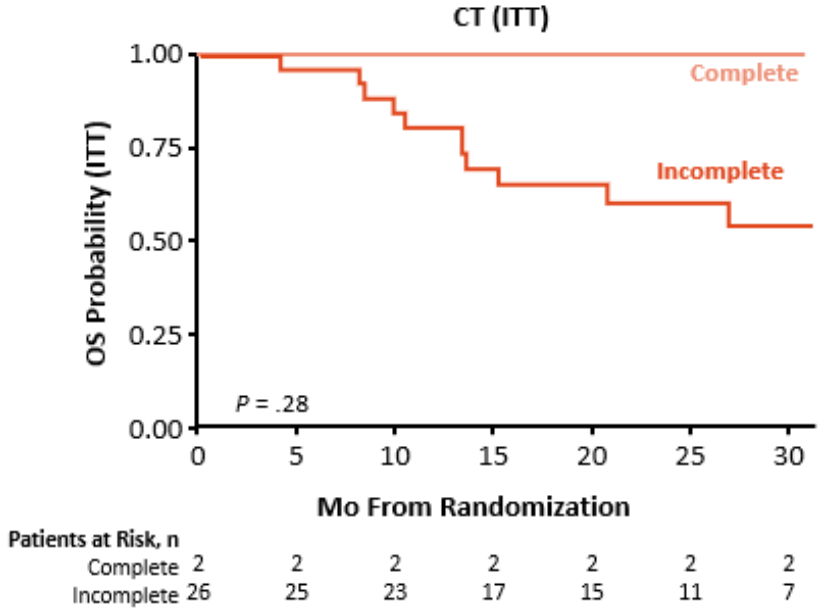
Secondary Endpoints: OS

- OS at 24 months was **84.7%** for patients treated with nivolumab plus chemotherapy versus **63.4%** for patients treated with chemotherapy
- **HR 0.40**
- Median OS not reached in either arm



OS by pCR Status





SUMMARY

NADIM II

- The first trial to show improved OS with a neoadjuvant immunotherapy-based combination for patients with resectable stage IIIA–B NSCLC
- PFS and OS improved and sustained with nivo + CT compared to chemo alone
  - PFS rate: 12 mo, 89.3% vs 60.7%; 24 mo, 66.6% vs 42.3%
  - OS rate: 12 mo, 98.2% vs 82.1%; 24 mo, 84.7% vs 63.4%

NADIM II supports the results of CheckMate-816

NADIM II

Neoadjuvant nivolumab in combination with chemotherapy benefits patients with early stage NSCLC and should be considered as a standard of care

Improves the chance of successful surgical treatment and reduces the risk of recurrence

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung3 • CheckMate -9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreak 100/101 • EXCLAIM • ALTA-1L

CLINICAL QUESTION

KEYNOTE-091

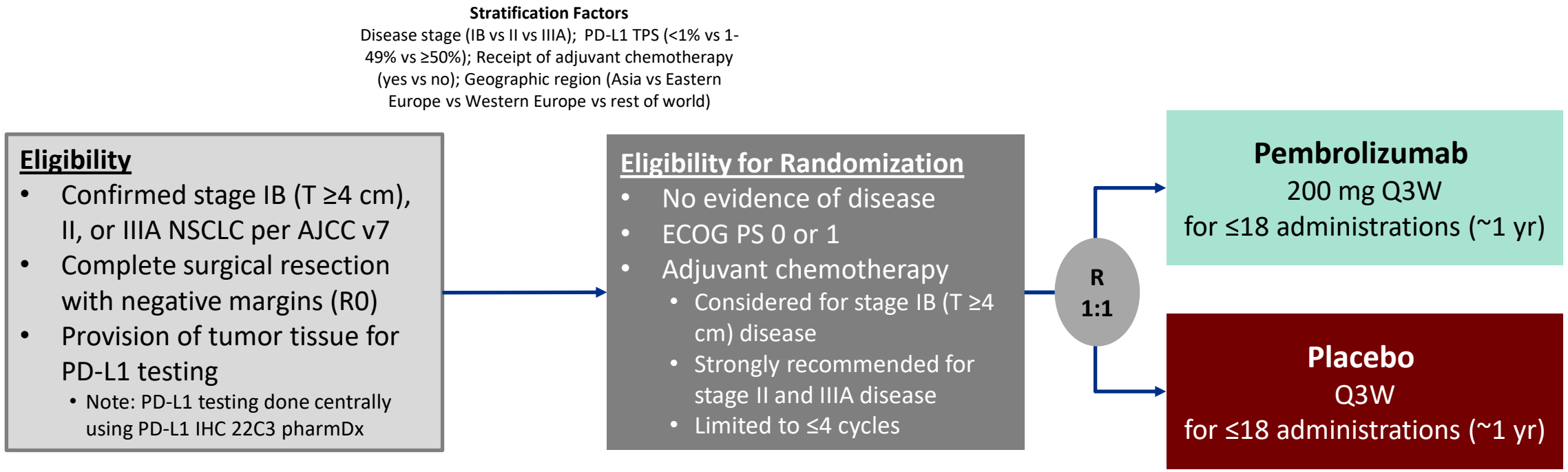
Does pembrolizumab provide benefit for patients with early stage NSCLC (stage IB to IIIA) after resection and adjuvant chemotherapy?

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

cornerstone specialty network™

KEYNOTE-091

Study Design: Randomized, triple-blind Phase 3 study



Primary endpoints: DFS in the overall population and DFS in the PD-L1 TPS ≥50% population
Secondary endpoints: 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, and safety

Data cutoff date: September 20, 2021

KEYNOTE-091 also known as EORTC-1416-LCG/ETOP-8-15 – PEARLS

KEY DATA

KEYNOTE-091

Overall Population, Baseline Characteristics

(%)	Pembrolizumab (n=590)	Placebo (n=587)
Age (Y) , Median (range)	65 (31-87)	65 (37-85)
Male	401 (68.0%)	403 (68.7%)
Geographic Region		
• Asia	106 (18.0%)	105 (17.9%)
• Eastern Europe	116 (19.7%)	113 (19.3%)
• Western Europe	303 (51.4%)	301 (51.3%)
• Rest of World	65 (11.0%)	68 (11.6%)
ECOG PS1	210 (35.6%)	244 (41.6%)
Current/former smoker	503 (85.3%)	521 (88.8%)
EGFR Mutation[a]	39 (6.6%)	34 (5.8%)
ALK translocation[b]	7 (1.2%)	7 (1.2%)

	Pembrolizumab (n=590)	Placebo (n=587)
Nonsquamous histology	398 (67.5%)	363 (61.8%)
Pathologic stage[c]		
• IB	84 (14.2%)	85 (14.5%)
• II	329 (55.8%)	338 (57.6%)
• IIIA	177 (30.0%)	162 (27.6%)
Received adjuvant chemo		
• Yes	506 (85.8%)	504 (85.9%)
• No	84 (14.2%)	83 (14.1%)
PD-L1 TPS		
• <1%	233 (39.5%)	232 (39.5%)
• 1 – 49%	189 (32.0%)	190 (32.4%)
• ≥50%	168 (28.5%)	165 (28.1%)

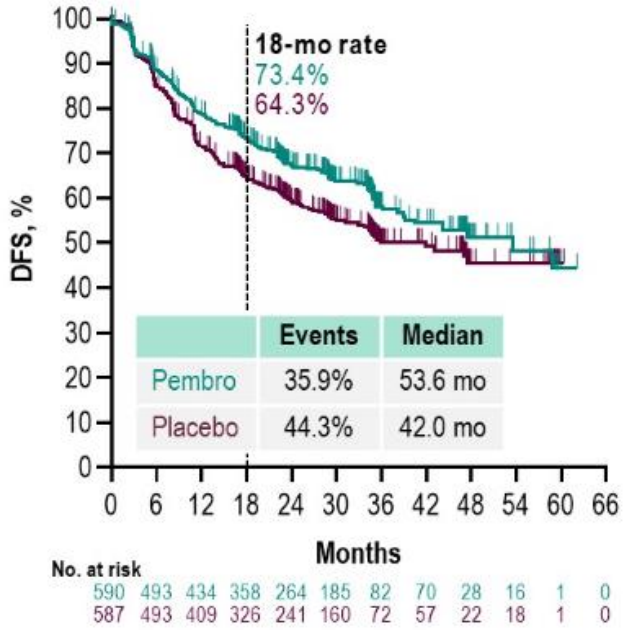
[a] EGFR status unknown for 333 (56.4%) in pembro arm and 337 (57.4%) in placebo arm.
[b] ALK status unknown for 357 (60.5%) in pembro arm and 390 (66.4%) in placebo arm.
[c] 2 (0.3%) participants in the placebo group had stage IV disease.

ESMO Virtual Plenary 2022: Abstr VP3-2022
ASCO 2022 Abstr 8512

KEYNOTE-091

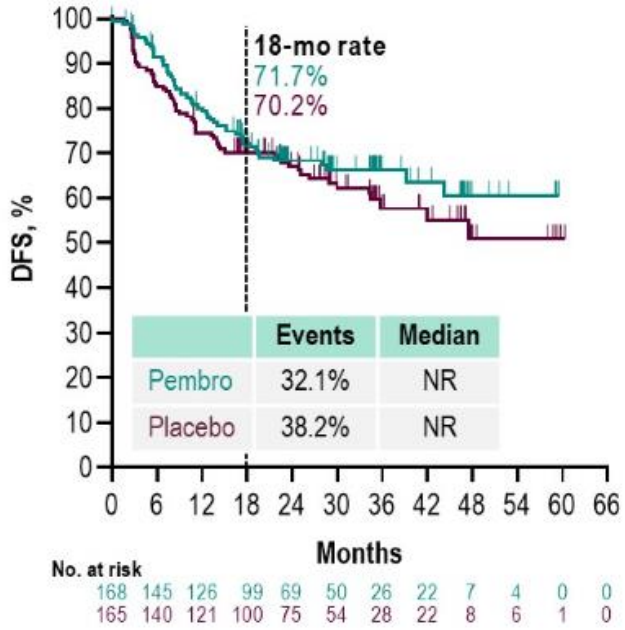
Primary Results from the Protocol-Specified Second Interim Analysis (IA2)

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



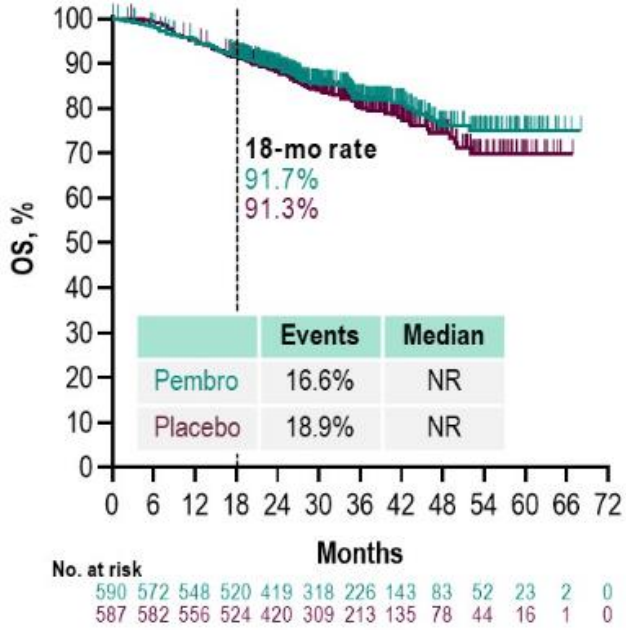
	Events	Median
Pembro	35.9%	53.6 mo
Placebo	44.3%	42.0 mo

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



	Events	Median
Pembro	32.1%	NR
Placebo	38.2%	NR

OS, Overall Population
HR 0.87 (95% CI 0.67-1.15)
***P* = 0.17**

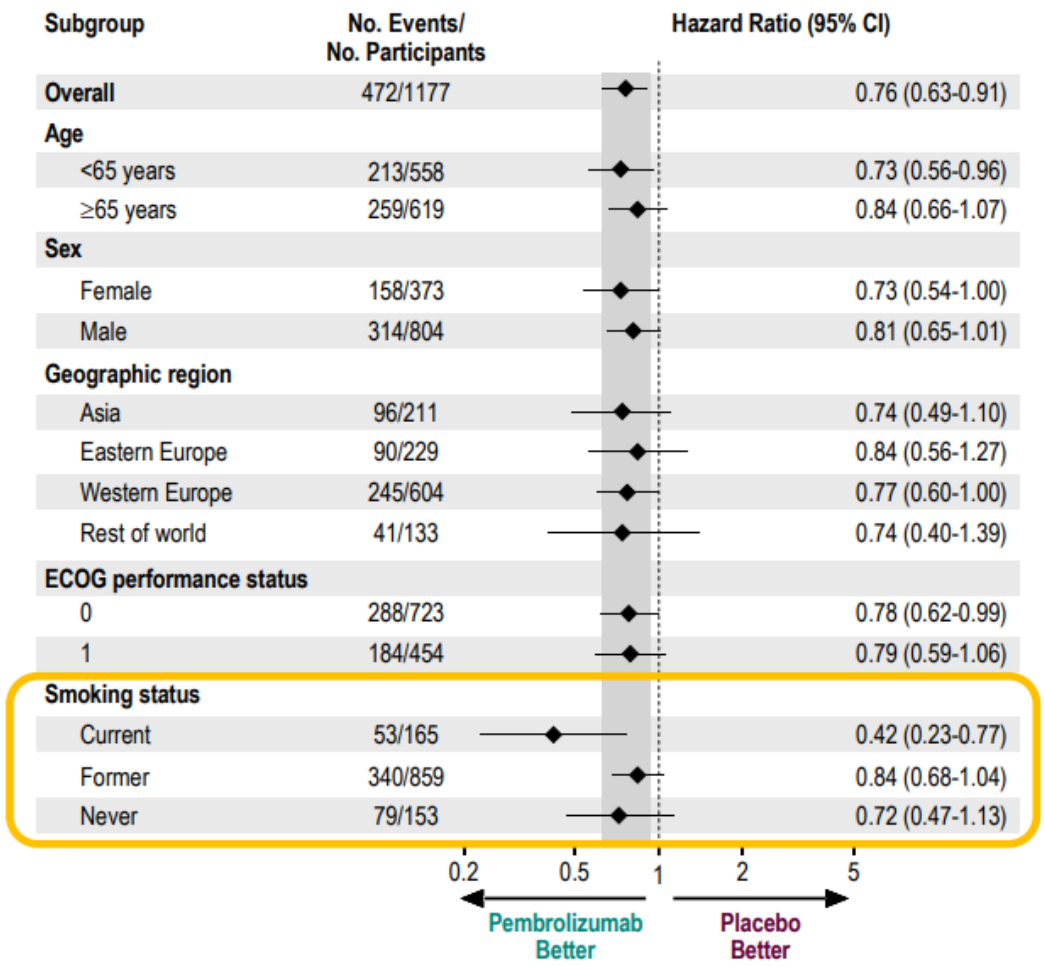


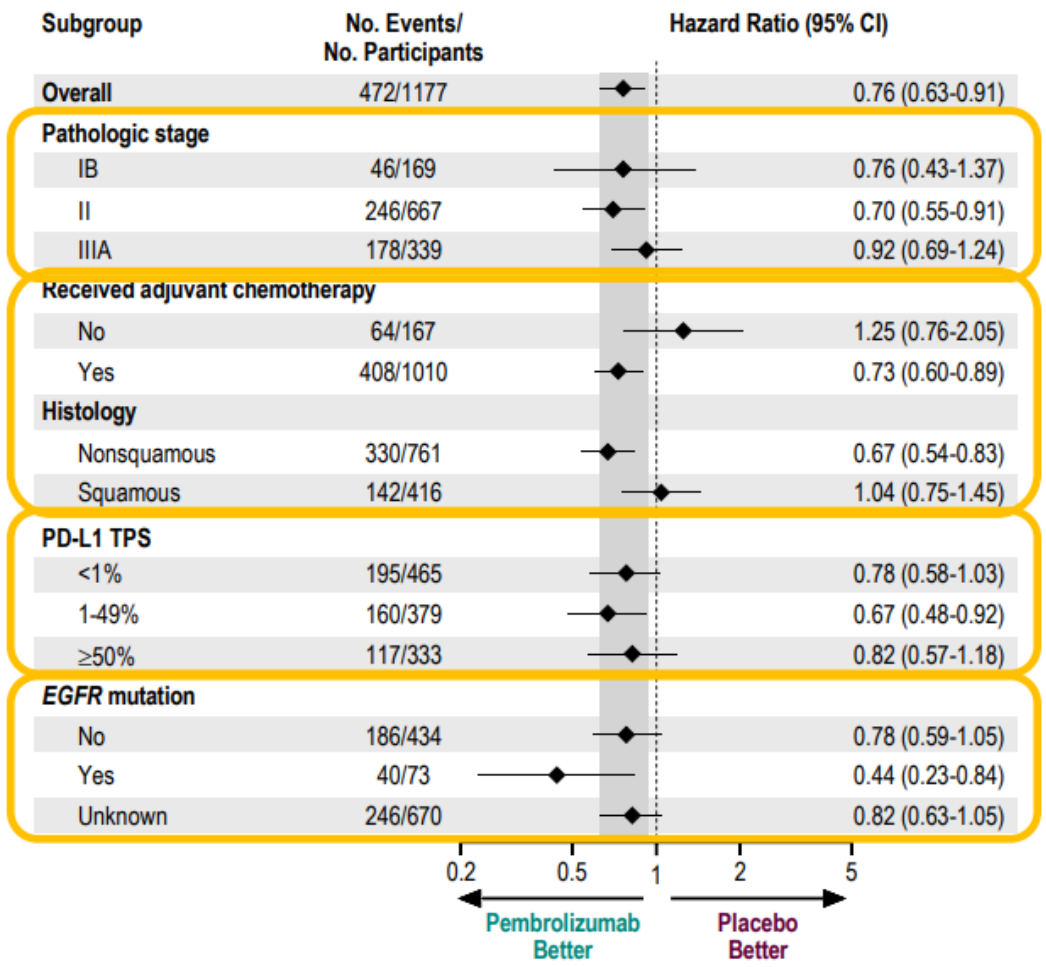
	Events	Median
Pembro	16.6%	NR
Placebo	18.9%	NR

ESMO Virtual Plenary 2022: Abstr VP3-2022
ASCO 2022 Abstr 8512

KEYNOTE-091

Overall Population, DFS in Key Subgroups





Response assessed per RECIST v1.1 by investigator review.

ESMO Virtual Plenary 2022: Abstr VP3-2022
ASCO 2022 Abstr 8512

KEYNOTE-091

Impact of the Type of Surgical Resection, Baseline Disease Burden, and Use of Adjuvant Chemotherapy on DFS at IA2

	Pembro (N = 590)	Placebo (N = 587)
Type of surgery, n (%)		
Bilobectomy	47 (8.0)	45 (7.7)
Lobectomy	461 (78.1)	464 (79.0)
Pneumonectomy	65 (11.0)	62 (10.6)
Other	17 (2.9)	16 (2.7)
pN status, n (%)		
0	233 (39.5)	257 (43.8)
1	233 (39.5)	223 (38.0)
2	124 (21.0)	107 (18.2)
Tumor size, n (%)		
≤4 cm	252 (42.7)	239 (40.7)
>4 cm	337 (57.1)	348 (59.3)
Missing	1 (0.2)	0

	Pembro (N = 590)	Placebo (N = 587)
Received adjuvant chemotherapy		
No, n (%)	84 (14.2)	83 (14.1)
Reason for not receiving, n		
Participant refused	36	30
Physician decision[a]	46	47
Unknown	2	6
Disease stage in those who did not receive, n		
IB	24	30
II	48	43
IIIA	12	10
Yes, n (%)	506 (85.8)	504 (85.9)
1-2 cycles	35 (5.9)	32 (5.5)
3-4 cycles	471 (79.8)	472 (80.4)

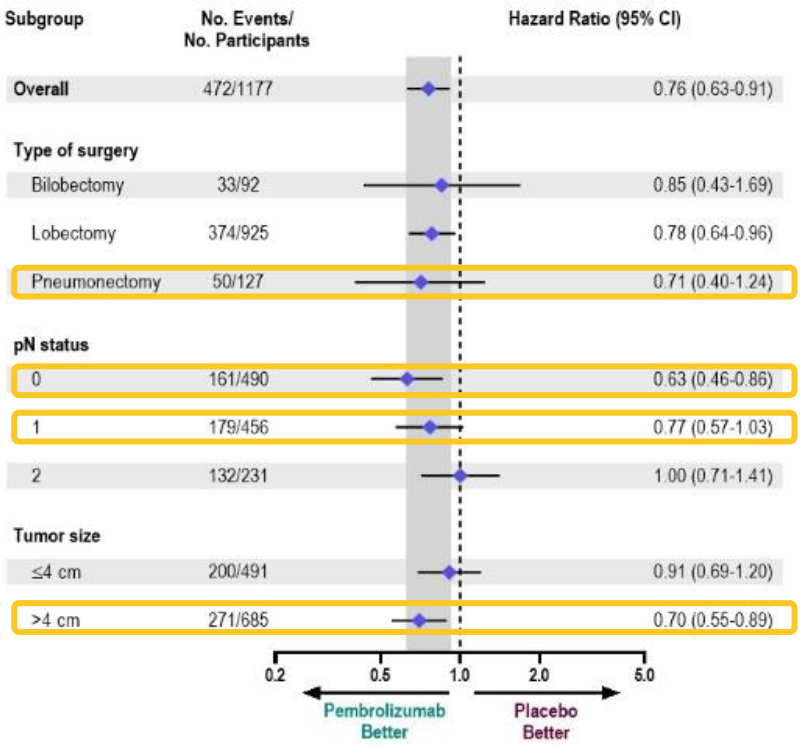
	Pembro (N = 590)	Placebo (N = 587)
Type of adjuvant platinum, n (%)		
Carboplatin-based only	184 (31.2)	171 (29.1)
Cisplatin-based only	301 (51.0)	307 (52.3)
Carboplatin- and cisplatin-based	21 (3.6)	26 (4.4)
Adjuvant regimen, n (%)		
Carboplatin + paclitaxel	60 (10.2)	75 (12.8)
Carboplatin + vinorelbine	81 (13.7)	70 (11.9)
Cisplatin + gemcitabine	27 (4.6)	30 (5.1)
Cisplatin + vinorelbine	241 (40.8)	250 (42.6)
Other	97 (16.4)	79 (13.5)

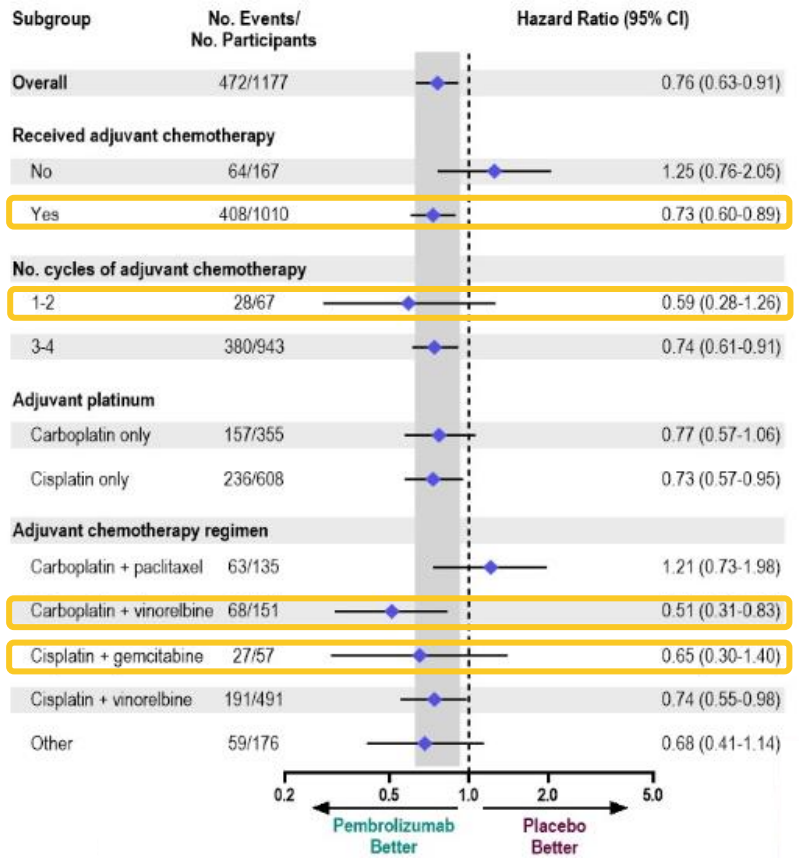
[a] Based on unfavorable benefit/risk profile for the individual participant

ESMO Virtual Plenary 2022: Abstr VP3-2022
ASCO 2022 Abstr 8512

KEYNOTE-091

DFS in Subgroups: based on surgical resection, disease burden, and use of adjuvant chemotherapy





ESMO Virtual Plenary 2022: Abstr VP3-2022
ASCO 2022 Abstr 8512

KEYNOTE-091

Adverse Events

	Pembrolizumab (n=580)	Placebo (n=581)
Any	556 (95.9%)	529 (91.0%)
Grade 3 – 5	198 (34.1%)	150 (25.8%)
Led to death	11 (1.9%)	6 (1.0%)
• Treatment related	4 (0.7%)*	0 (0%)
Serious	142 (24.5%)	90 (15.5%)
Treatment discontinuation	115 (19.8%)	34 (5.9%)
Treatment Interruption	221 (38.1%)	145 (25.0%)

* 1 participant each with myocarditis + cardiogenic shock, myocarditis + septic shock, pneumonia, and sudden death.

ESMO Virtual Plenary 2022: Abstr VP3-2022
ASCO 2022 Abstr 8512

SUMMARY

KEYNOTE-091

- Adjuvant treatment with pembrolizumab significantly improved DFS in the overall population of patients with early-stage NSCLC following surgical resection

- Pembrolizumab improved DFS regardless of type of surgery, lymph node involvement, tumor size, and type and extent of adjuvant chemotherapy in patients with completely resected stage IB (T ≥4 cm) to IIIA NSCLC.
  - 27% reduction in the risk of disease recurrence or death after adjuvant chemotherapy with pembrolizumab compared to placebo
  - For patients who received adjuvant chemotherapy, median DFS was 58.7 months in the pembrolizumab arm (95% CI: 39.2, not reached) and 34.9 months in the placebo arm (95% CI: 28.6, not reached) (hazard ratio=0.73; 95% CI: 0.60, 0.89])

- OS data immature at time of interim analysis

- The safety profile of pembrolizumab was consistent with prior experience across indications and lines of therapy

ESMO Virtual Plenary 2022: Abstr VP3-2022
ASCO 2022 Abstr 8512

KEYNOTE-091

Pembrolizumab demonstrated benefit in the adjuvant setting following resection and platinum-based chemotherapy for patients with early-stage NSCLC regardless of PD-L1 status and should be considered a standard of care

QUESTION

Is neoadjuvant chemoimmunotherapy superior to adjuvant immunotherapy for all stages of early-stage non-small cell lung cancer?

	CheckMate-816 (Nivolumab)	NADIM II (Nivolumab)
Indication/FDA approval	Nivolumab with platinum-doublet chemotherapy for adult patients with resectable NSCLC in the **neoadjuvant** setting	
Treatment Arms	**Nivolumab + chemo** vs chemo (R 1:1) No known EGFR/ALK alterations Optional adjuvant CT ± RT post surgery	**Nivolumab + chemo** vs chemo (R 2:1) No known EGFR/ALK alterations If RO resection: Adjuvant Nivo post surgery)
N	358	86
Median EFS, overall population **HR (95% CI)**	31.6 vs 20.8 months HR 0.63 (97.38% CI: 0.43 - 0.91; p=0.0052)	---
Median EFS by PD-L1 expression **<1%** **≥1%** **1-49%** **≥50%**	 25.1 vs 18.4; HR 0.85 (0.54-1.32) (n=155) NR vs 21.2; HR 0.41 (0.24-0.70) (n=178) NR vs 26.7; HR 0.58 (0.30-1.12) (n=98) NR vs 19.6; HR 0.24 (0.10-0.61) (n=80)	PDL1 expression (≥1%) significantly identified patients with improved PFS HR: 0.26 (95%CI: 0.08-0.77; P = 0.015)
pCR; Odds ratio And by PD-L1 expression **<1%** **≥1%** **1-49%** **≥50%**	24% vs 2.2%; 13.94 (99% CI: 3.49 –55.75;P<0.001) 16.7% vs 2.6% 32.6% vs 2.2% 23.5% vs 0% 44.7% vs 4.8%	36.8% vs 6.9% ; P = 0.0068 ---
Overall Survival HR (95% CI)	Not reached vs Not reached HR 0.57 (99.67% CI, 0.30 – 1.07; P=0.008)	OS at 24 months: 84.7% vs 63.4% HR 0.40 (0.17 – 0.93; P=0.034)
Reference	N Engl J Med. 2022 May 26;386(21):1973-1985.	2022 World Conference on Lung Cancer. Abstract PL03.12

	PEARLS/KEYNOTE-091 (Pembrolizumab)	IMpower010 (Atezolizumab)
Indication/FDA approval	For **adjuvant** treatment following resection and platinum-based chemotherapy in patients with **stage IB (T2a ≥4 cm), II, or IIIA** NSCLC	For **adjuvant** treatment following resection and platinum-based chemotherapy in patients with **Stage II to IIIA** NSCLC whose tumors have **PD-L1 expression on ≥ 1%** of tumor cells, as determined by an FDA-approved test
Treatment Arms	**Pembrolizumab** vs placebo (R 1:1)	**Atezolizumab** vs best supportive care (R 1:1)
N	1,177	1,280
Median DFS, overall population **HR (95% CI)**	53.6 vs 42.0 months HR 0.76 (95% CI: 0.63 – 0.91; P=0.0014)	Not reached vs 35.3 months HR 0.66 (95% CI: 0.50 – 0.88; P=0.004)
Median DFS by PD-L1 expression **<1%** **≥1%** **1-49%** **≥50%**	 HR 0.78 (0.58 – 1.03) (n=465) --- HR 0.67 (0.48 – 0.92) (n=337) NR vs NR; HR 0.82 (0.57 – 1.18.; P=0.14) (n=333)	 --- NR vs 35.3; HR 0.66 (n=476) 32.8 vs 31.4; HR 0.87 (n=247) NR vs 35.7; HR 0. 43 (0.27 – 0.68) (n=229)
Median OS by PD-L1 expression **≥1%** **1-49%** **≥50%**	Overall survival results were not mature with only 42% of pre-specified OS events in the overall population	 HR 0.71 (0.49 – 1.03) HR 0.95 (0.59 – 1.54) HR 0.43 (0.24 – 0.78)
Overall Survival HR (95% CI)	Not reached vs Not reached HR 0.87 (0.67 – 1.15.; P=0.17)	Not reached vs Not reached HR 0.71 (0.49 – 1.03)
Reference	ESMO Virtual Plenary 2022: Abstr VP3-2022; ASCO 2022 Abstr 8512 The Lancet 2022, vol 23 (10): 1274-1286	WCLC2022 Absrt PL03.09 (Plenary 3: Presidential Symposium) The Lancet 2021, vol 398 (10308): 1344-1357

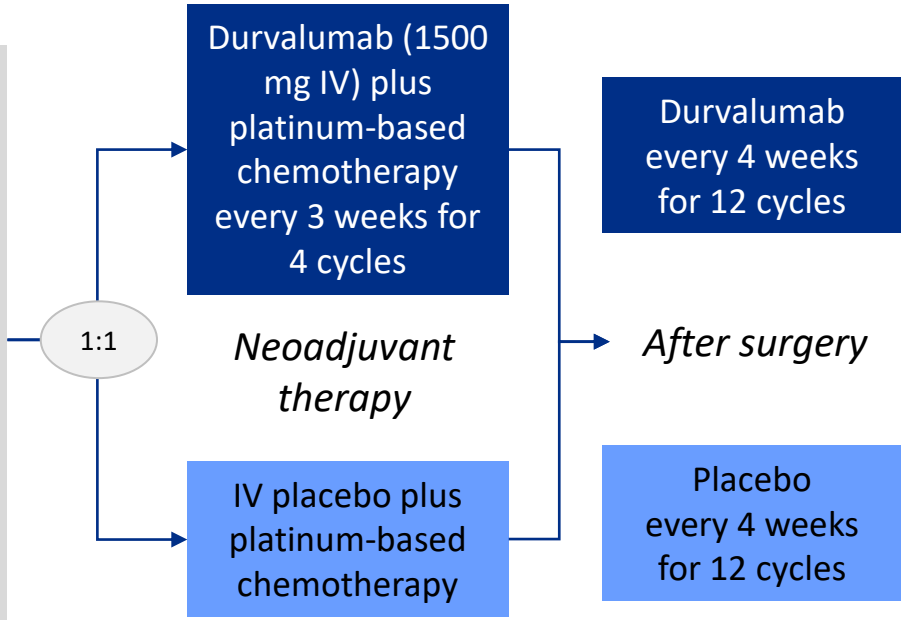
NEW AND NOTEWORTHY

AEGEAN: 2023 AACR Annual Meeting

*Positive high-level results from a planned interim analysis of the **AEGEAN** Phase III, placebo- controlled trial showed that treatment with AstraZeneca's Imfinzi (durvalumab) in combination with neoadjuvant chemotherapy before surgery and as adjuvant monotherapy after surgery demonstrated a statistically significant and clinically meaningful improvement in EFS versus neoadjuvant chemotherapy alone followed by surgery for patients with resectable early-stage (IIA-IIIB) NSCLC.*

- Patients with treatment-naïve, resectable stage IIA to IIIB NSCLC
- ECOG PS 0 or 1
- Confirmed PD-L1 status
- No documented EGFR or ALK aberrations

N=802



Minimum follow-up was 6.7 months; Median follow-up 11.7 months

- Median EFS was not reached (NR; 95% CI, 31.9-NR) with durvalumab vs 25.9 months (95% CI, 18.9-NR) with placebo (stratified HR, 0.68; 95% CI, 0.53-0.88; *P* = 0.003902)
- 12- and 24-month EFS rates with durvalumab were 73.4% and 63.3%, respectively, vs 64.5% and 52.4% with placebo
- pCR rate with durvalumab (n = 366) was 17.2% vs 4.3% with placebo (n = 374), reflecting an absolute difference of 12.9% (95% CI, 8.7%-17.6%; *P* = 0.000036)
- Major pathologic response (MPR) rates with durvalumab and placebo were 33.3% and 12.3%, respectively, reflecting an absolute difference of 21.0% (95% CI, 15.1%-26.9%; *P* = 0.000002)

cornerstone specialty network™

Heymach JV, Harpole D, Mitsudomi T, et al. AEGEAN: a phase 3 trial of neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in patients with resectable NSCLC. Presented at: 2023 AACR Annual Meeting; April 14-19, 2023; Orlando, FL. Abstract CT005.

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung 1 • CheckMate-9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreak 100/101 • EXCLAIM • ALTA-1L

cornerstone specialty network™

EMPOWER-Lung 1 Clinical Trial

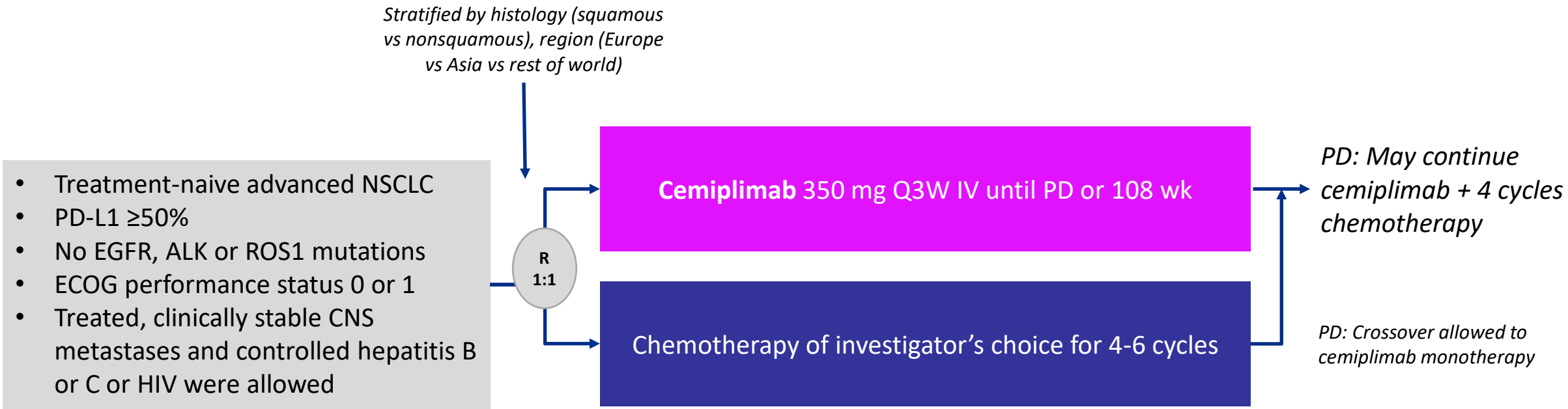
Does cemiplimab provide benefit for patients with advanced NSCLC with PD-L1 ≥50%?

3-year survival data

KEY DATA

EMPOWER-Lung 1 Clinical Trial

Study Design: Phase 3 study



*radiological stability not required

Primary endpoints: OS, PFS
Secondary endpoints: ORR, DoR, HRQoL, safety

ITT (N=712†)
- Median time from randomization to data cutoff: 37.1 months (range: 24.0– 56.5)

(†Two additional patients added after data cutoff for the Sezer et al. Lancet 2021 manuscript.)

PD-L1 ≥50% population (N=565†)
- PD-L1 testing by 22C3 assay performed per instructions for use

Data cutoff: 4 March 2022

ESMO 2022 LBA54.
Nature Medicine | VOL 28 | November 2022 | 2374–2380

KEY DATA

EMPOWER-Lung 1 Clinical Trial

Baseline Characteristics

	ITT		PD-L1 ≥50%	
Characteristic, n (%)	**Cemiplimab (n=357)***	**CT (n =355)**	Cemiplimab (n=284)*	CT (n=281)
Median age, yr (range)	63.0 (58.0 : 69.0)	64.0 (57.0 : 69.0)	63 (58.0 : 69.0)	64.0 (58.0 : 70.0)
• ≥65 yr, n (%)	157 (44.0)	164 (46.2)	127 (44.7)	133 (47.3)
Male	313 (87.7)	294 (82.8)	249 (87.7)	231 (82.2)
ECOG PS 0	96 (26.9)	97 (27.3)	77 (27.1)	76 (27.0)
• 1	261 (73.1)	258 (72.7)	207 (72.9)	205 (73.0)
Region of enrollment				
• Europe	276 (77.3)	279 (78.6)	216 (76.1)	217 (77.2)
• Asia	39 (10.9)	38 (10.7)	31 (10.9)	29 (10.3)
• Rest of the world	42 (11.8)	38 (10.7)	37 (13.0)	35 (12.5)
Histology				
• Squamous	160 (44.8)	153 (43.1)	123 (43.3)	122 (43.4)
• Nonsquamous	197 (55.2)	202 (56.9)	161 (56.7)	159 (56.6)
Stage at screening				
• III	63 (17.6)	52 (14.7)	45 (15.8)	42 (15.0)
• IV	294 (82.4)	303 (85.4)	239 (84.2)	239 (85.1)

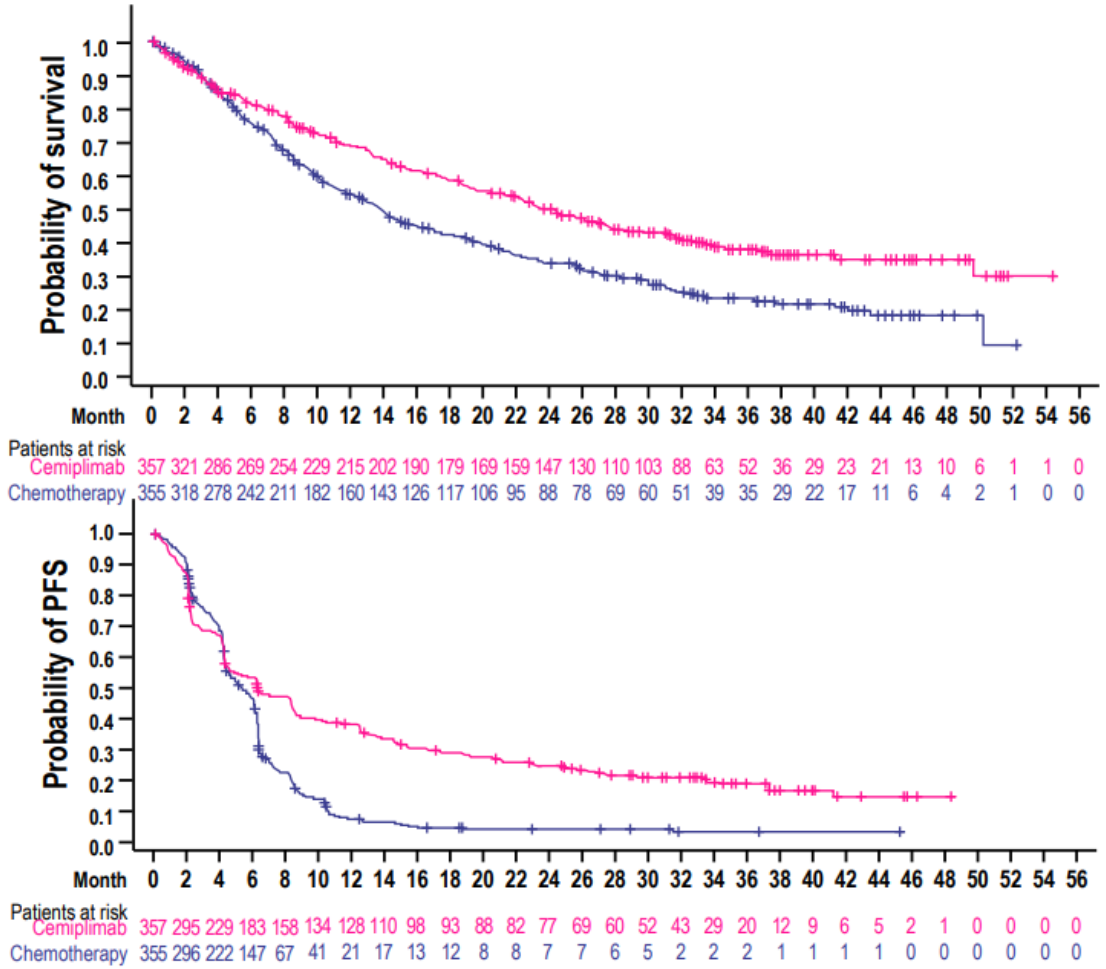
*Two additional patients added after data cutoff for the Sezer et al. Lancet 2021 manuscript ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PD-L1, programmed cell death-ligand 1

ESMO 2022 LBA54.

KEY DATA

EMPOWER-Lung 1 Clinical Trial

3 year follow up: ITT OS and PFS



ITT: 3-year outcomes		
	Patients, n	Median OS, months
Cemiplimab	357	23.4 (95% CI, 19.4, 27.4)
Chemotherapy	355	13.7 (95% CI, 11.2, 16.2)
		HR, 0.63 (95% CI, 0.52–0.77); *P*=0.0001

ITT: 3-year outcomes		
	Patients, n	Median PFS, months
Cemiplimab	357	6.3 (95% CI, 4.6, 8.3)
Chemotherapy	355	5.3 (95% CI, 4.3, 6.0)
		HR, 0.56 (95% CI, 0.47, 0.67); *P*=0.0001

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression free survival

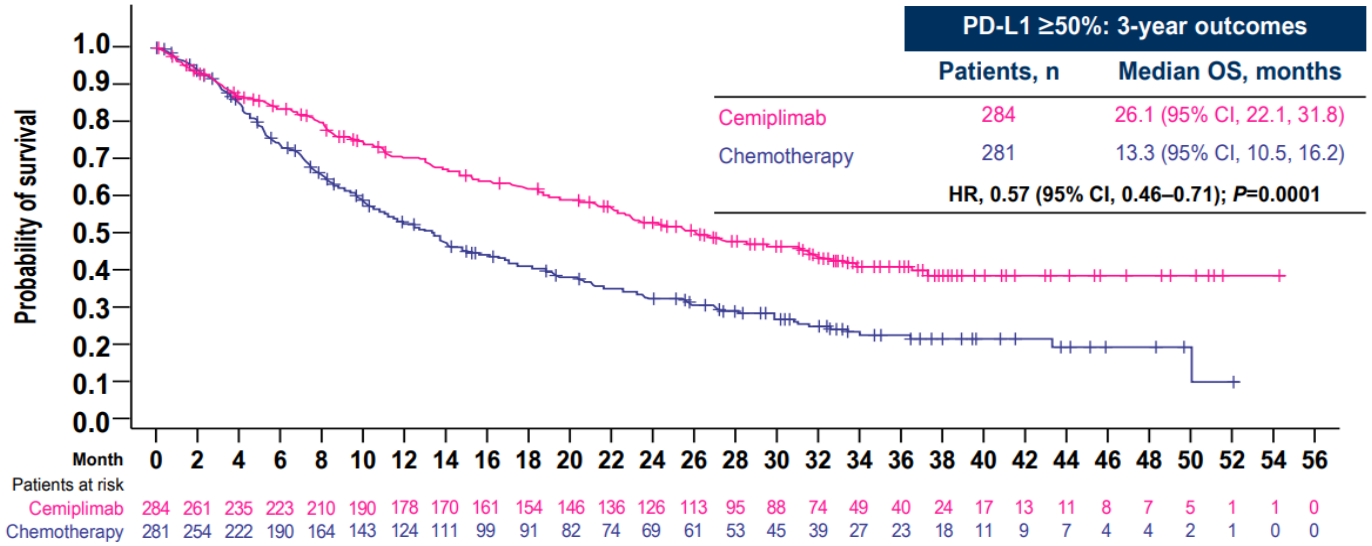
Data cutoff date: 4 March 2022

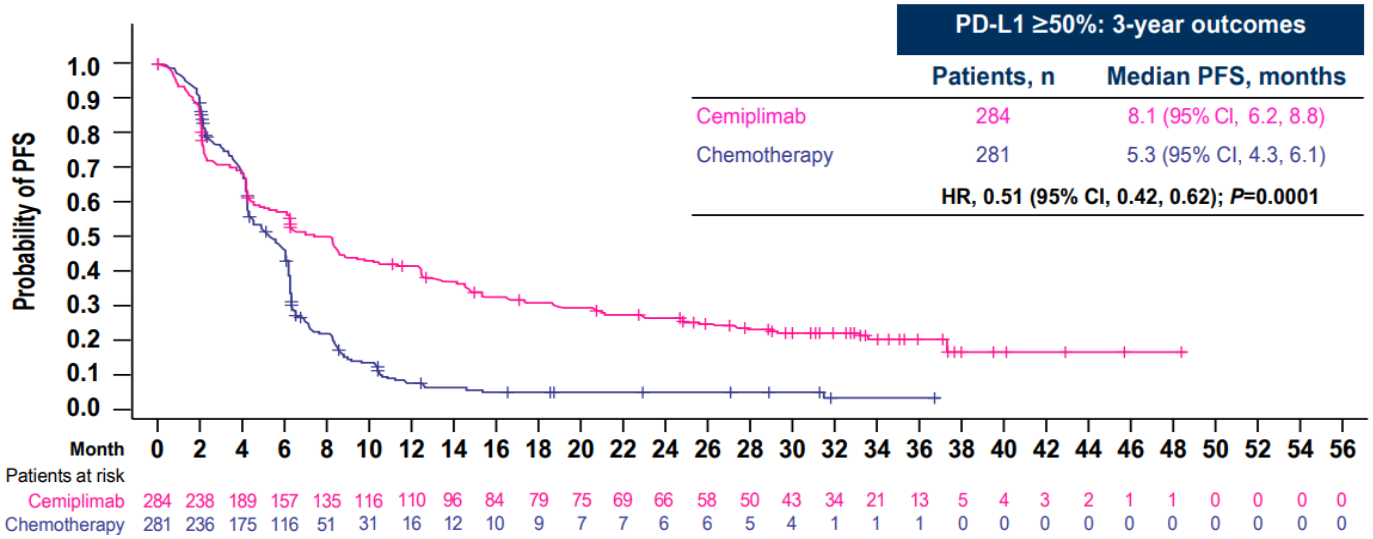
ESMO 2022 LBA54.

KEY DATA

EMPOWER-Lung 1 Clinical Trial

3 year follow up: PD-L1 ≥50% OS and PFS





ESMO 2022 LBA54.

KEY DATA

EMPOWER-Lung 1 Clinical Trial

Efficacy

	ITT		PD-L1 ≥50%	
	Cemiplimab (n=357)	Chemotherapy (n=355)	Cemiplimab (n=284)	Chemotherapy (n=281)
Objective Response Rate (ORR: CR+PR)	**151 (42.3)**	**76 (21.4)**	**132 (46.5)**	**59 (21.0)**
95 CI for ORR (n%)	(37.1, 41.8)	(17.3, 26.0)	(40.6, 52.5)	(16.4, 26.2)
Odds ratios (range), two-sided p-value	2.691 (1.936, 3.740) p <0.0001		3.264 (2.255, 4.724) p <0.0001	
Best Overall Tumor Response, n (%)				
Complete Response (CR)	29 (8.1)	7 (2.0)	23 (8.1)	6 (2.1)
Partial Response (PR)	122 (34.2)	69 (19.4)	109 (38.4)	53 (18.9)
Stable Disease (SD)	90 (25.2)	175 (49.3)	65 (22.9)	142 (50.5)
Non-CR/Non-PD	2 (0.6)	4 (1.1)	2 (0.7)	2 (0.7)
Progressive Disease (PD)	76 (21.3)	56 (15.8)	60 (21.1)	45 (16.0)
Not Evaluable (NE)	38 (10.6)	44 (12.4)	25 (8.8)	33 (11.7)
Median DOR, months (95% CI)	23.6 (18.6, 33.0)	5.9 (4.3, 6.3)	23.6 (16.8, 33.0)	5.9 (4.3, 6.5)

CI, confidence interval; ITT, intention-to-treat; PD-L1, programmed cell death-ligand 1; ORR, objective response rate; DOR, duration of response

ESMO 2022 LBA54.

NE: not evaluable

KEY DATA

EMPOWER-Lung 1 Clinical Trial

Safety

	Cemiplimab (n=356)		Chemotherapy (n=343)	
Median duration of exposure (range), weeks	36 (0.3–136.0)		18 (0.6–141.1)	
Treatment-emergent AEs, regardless of attribution, n (%)	**Any grade**	**Grade 3–5**	**Any grade**	**Grade 3–5**
Overall	330 (92.7)	163 (45.8)	329 (95.9)	177 (51.6)
Led to discontinuation	32 (9.0)	20 (5.6)	17 (5.0)	10 (2.9)
Led to death	36 (10.1)	36 (10.1)	33 (9.6)	33 (9.6)
Treatment-related AEs, n (%)				
Overall	223 (62.6)	65 (18.3)	310 (90.4)	137 (39.9)
Led to discontinuation	26 (7.3)	15 (4.2)	15 (4.4)	10 (2.9)
Led to death	10 (2.8)	10 (2.8)	7 (2.0)	7 (2.0)
Sponsor-identified immune-related AEs, n (%)				
Overall	80 (22.5)	17 (4.8)	8 (2.3)	1 (0.3)
Led to discontinuation	16 (4.5)	9 (2.5)	0	0
Led to death	2 (0.6)	2 (0.6)	0	0

*Although each pair of neutropenia and decreased neutrophil count; and thrombocytopenia and decreased platelet count might reflect the same condition, they were listed as distinct events for the safety report of the study
AEs, adverse events; PD-L1, programmed death-ligand 1

Treatment-emergent AEs in ≥10% of pts in either arm, n (%)	Cemiplimab (n=356)		Chemotherapy (n=343)	
	Any grade	**Grade 3–5**	**Any grade**	**Grade 3–5**
Anaemia	70 (19.7)	15 (4.2)	180 (52.5)	60 (17.5)
Nausea	28 (7.9)	0	99 (28.9)	4 (1.2)
Alopecia	4 (1.1)	0	86 (25.1)	2 (0.6)
Decreased appetite	51 (14.3)	2 (0.6)	67 (19.5)	1 (0.3)
Fatigue	49 (13.8)	7 (2.0)	64 (18.7)	5 (1.5)
Neutropenia*	10 (2.8)	3 (0.8)	64 (18.7)	35 (10.2)
Constipation	29 (8.1)	0	56 (16.3)	0
Thrombocytopenia*	7 (2.0)	1 (0.3)	56 (16.3)	28 (8.2)
Vomiting	17 (4.8)	0	50 (14.6)	4 (1.2)
Decreased neutrophil count*	2 (0.6)	1 (0.3)	43 (12.5)	19 (5.5)
Back pain	43 (12.1)	0	22 (6.4)	2 (0.6)
Pneumonia	41 (11.5)	19 (5.3)	41 (12.0)	21 (6.1)
Arthralgia	42 (11.8)	0	37 (10.8)	1 (0.3)
Decreased platelet count*	6 (1.7)	0	40 (11.7)	13 (3.8)
Peripheral neuropathy	3 (0.8)	1 (0.3)	39 (11.4)	2 (0.6)
Dyspnoea	40 (11.2)	10 (2.8)	28 (8.2)	8 (2.3)
Cough	36 (10.1)	0	31 (9.0)	1 (0.3)
Pruritus	36 (10.1)	0	12 (3.5)	0

ESMO 2022 LBA54.

NE: not evaluable

KEY DATA

EMPOWER-Lung 1 Clinical Trial

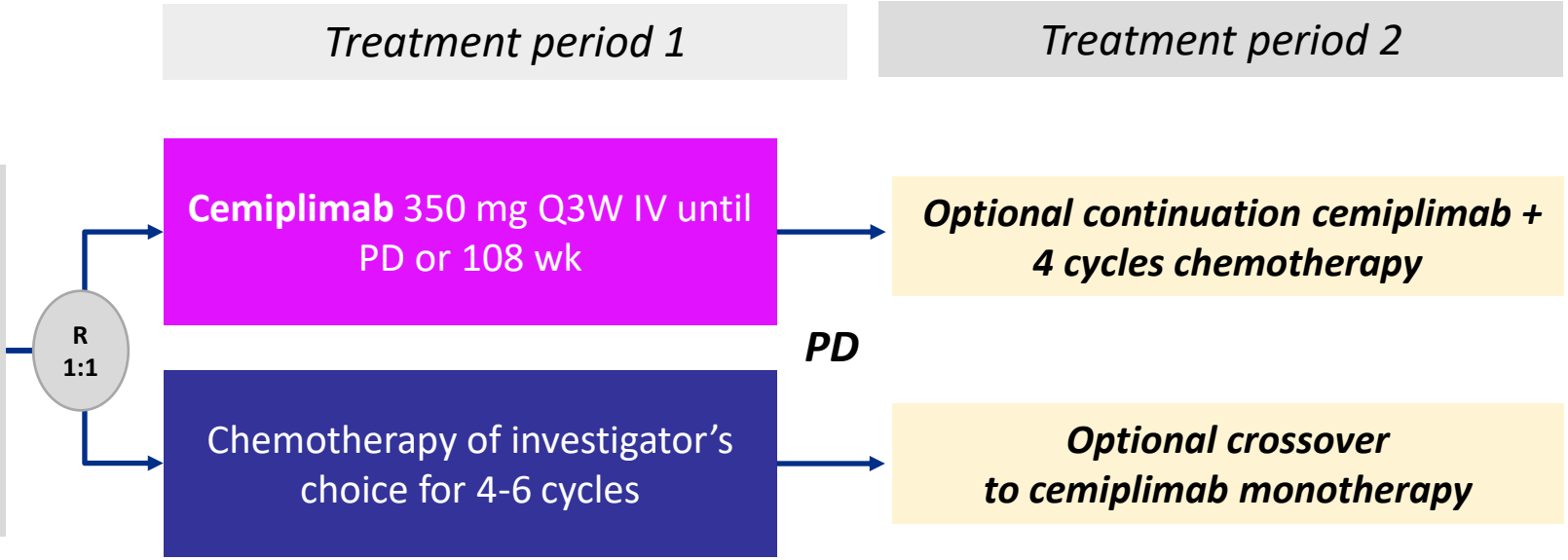
Study Design: Phase 3 study
Continued Cemiplimab Beyond Progression with Addition of Chemotherapy

- Treatment-naive advanced NSCLC
- PD-L1 ≥50%
- No EGFR, ALK or ROS1 mutations
- ECOG performance status 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

*radiological stability not required

Stratified by histology (squamous vs nonsquamous), region (Europe vs Asia vs rest of world)

Primary endpoints: OS, PFS
Secondary endpoints: ORR, DoR, HRQoL, safety



Post progressive disease analysis: N = 64
Patients with at least: one dose of chemotherapy + one scan following progressive disease on cemiplimab
Response to cemiplimab + chemotherapy was assessed by BICR against a new baseline, defined as the last scan prior to the initial dose of chemotherapy

ESMO 2022 LBA54.

KEY DATA

EMPOWER-Lung 1 Clinical Trial

Baseline Characteristics

n (%), unless stated otherwise	ITT Cemiplimab (n=357)	Beyond Progression Cemiplimab (N=64)
Age		
Median (Q1 : Q3)	63.0 (58.0 : 69.0)	62.5 (57.5 : 69.0)
≥65, n (%)	157 (44.0)	28 (43.8)
Sex		
Male	313 (87.7)	55 (85.9)
Female	44 (12.3)	9 (14.1)
Region of enrolment		
Europe	276 (77.3)	51 (79.7)
Asia	39 (10.9)	7 (10.9)
Rest of the world	42 (11.8)	6 (9.4)
ECOG performance status score		
0	96 (26.9)	20 (31.3)
1	261 (73.1)	44 (68.8)
Histology/Cytology, n (%)		
Squamous	160 (44.8)	37 (57.8)
Non-squamous	197 (55.2)	27 (42.2)
Cancer stage at screening n (%)		
Stage III	63 (17.6)	12 (18.7)
Stage IV	294 (82.4)	52 (81.3)

ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; Data cutoff date: Left column – March 4, 2022; Right column – March 1, 2020

ESMO 2022 LBA54.

KEY DATA

EMPOWER-Lung 1 Clinical Trial

Efficacy: Continued Cemiplimab Beyond Progression with Addition of Chemotherapy

	Cemiplimab Beyond Progression N=64	
	Period 1	Period 2
Objective Response Rate (ORR: CR+PR), n (%)	19 (29.7)	20 (31.3)
95% CI for ORR (range %)	(18.9, 42.4)	(20.2, 44.1)
Best Overall Tumor Response, n (%)		
Complete Response (CR)	0	3 (4.7)
Partial Response (PR)	19 (29.7)	17 (26.6)
Stable Disease (SD)	28 (43.8)	35 (54.7)
Non-CR/Non-PD	0	0
Progressive Disease (PD)	13 (20.3)	9 (14.1)
Not Evaluable (NE)	4 (6.3)	0

CI, confidence interval

Data cutoff date: March 1, 2020 – Left Column; Oct 1, 2021 – Right column

	Cemiplimab Beyond Progression N=64	
PFS	Period 1	Period 2
Median (95% CI, months)	6.2 (4.2, 8.2)	6.6 (6.1, 9.3)
Estimated Event-Free Probability, % (95% CI)		
6 months	50.7 (37.0, 62.9)	66.2 (53.0, 76.5)
12 months	24.1 (13.3, 36.6)	31.2 (19.5, 43.7)
18 months	0 (NE, NE)	15.7 (7.2, 27.2)
24 months	0 (NE, NE)	8.4 (2.0, 20.7)

CI, confidence interval; PFS, progression free survival; NE, non-evaluable

	Cemiplimab Beyond Progression N=64	
OS	Period 1+2 Randomization to Death	Period 2 Day 1 of Continued Treatment to Death
Median (95% CI, months)	27.4 (23.0, 31.8)*	15.1 (11.3, 18.7)
Estimated Survival Probability, % (95% CI)		
6 months	100 (NE, NE)	91.9 (81.6, 96.5)
12 months	91.8 (81.4, 96.5)	56.8 (43.0, 68.5)
24 months	60.5 (46.6, 71.8)	26.2 (14.3, 39.8)
36 months	32.3 (20.1, 45.1)	NE (NE, NE)

*Includes the 15.1 months of survival beyond progression. CI, confidence interval; OS, overall survival; NE, non-evaluable

ESMO 2022 LBA54.

KEY DATA

EMPOWER-Lung 1 Clinical Trial

Safety: Continued Cemiplimab Beyond Progression with Addition of Chemotherapy

n (%), unless stated	Cemiplimab + Chemotherapy beyond progression (N=64)	
Median duration of cemiplimab exposure in Period 2 (range), weeks	**27.1 (6.0–109.1)**	
AEs in Period 2, regardless of attribution	**Any grade**	**Grade 3–5**
Overall	59 (92.2)	23 (35.9)
Led to discontinuation	3 (4.7)	3 (4.7)
Led to death	3 (4.7)	3 (4.7)

AEs, adverse events; pts, patients

AEs in Period 2, in ≥10% of pts in either arm, n (%)	Cemiplimab + Chemotherapy beyond progression (N=64)	
	Any grade	**Grade 3–5**
Anaemia	22 (34.4)	6 (9.4)
Diarrhoea	17 (26.6)	2 (3.1)
Nausea	15 (23.4)	0
Alopecia	15 (23.4)	0
Neutropenia	9 (14.1)	2 (3.1)
Asthenia	8 (12.5)	1 (1.6)
Vomiting	7 (10.9)	1 (1.6)
Decreased appetite	7 (10.9)	0
Hypoalbuminaemia	7 (10.9)	0

ESMO 2022 LBA54.

SUMMARY

EMPOWER-Lung 1 Clinical Trial

- At 3-year follow-up, there was a further and significant improvement in the observed OS and PFS benefit of cemiplimab monotherapy versus chemotherapy in patients with advanced NSCLC with PD-L1 ≥50%
  - The improvement in OS was achieved despite a crossover rate of 75%
  - At 3-year follow-up, the HRs of cemiplimab versus chemotherapy improved (compared to at 1-year follow-up) for both PFS and OS

- Continued cemiplimab beyond progression with the addition of chemotherapy provided meaningful and durable ORR and OS benefits

- Durable ORR and OS benefits compare favorably to historical data of patients receiving chemotherapy alone as 2L therapy (after immune-checkpoint inhibitor monotherapy)

ESMO 2022 LBA54.

EMPOWER-Lung 1 Clinical Trial

First-line cemiplimab improved outcomes for patients with advanced or metastatic NSCLC with PD-L1 ≥ 50% (and no EGFR, ALK, or ROS1 alterations) and is a beneficial chemotherapy treatment-free option for this subset of patients

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung 1 • CheckMate-9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreak 100/101 • EXCLAIM • ALTA-1L

CLINICAL QUESTION

CheckMate-9LA Clinical Trial

Does first-line combination immunotherapy provide benefit for patients with advanced NSCLC?

Updated analysis

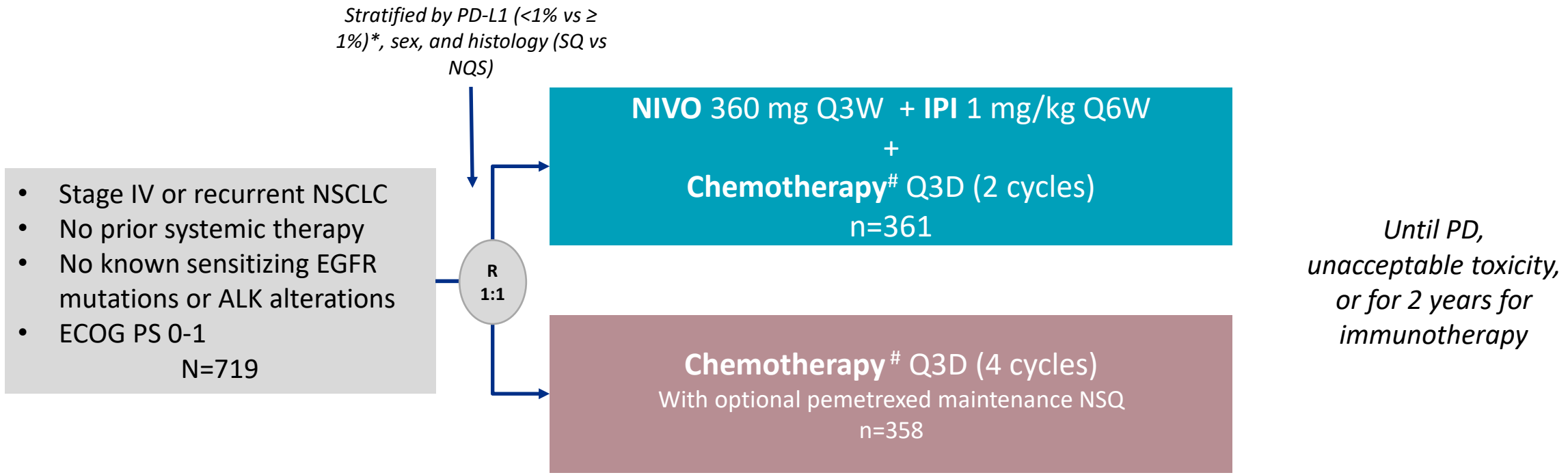
A 3-year update of CheckMate -9LA evaluating nivolumab/ipilimumab plus chemotherapy vs chemotherapy alone

cornerstone specialty network™

KEY DATA

CheckMate-9LA Clinical Trial

Study Design: 3-year update NIVO + IPI + Chemo vs Chemo in 1L advanced NSCLC



*determined by the PD-L1 IHC 28-8 pharmDx assay (Dako)
#NSQ: pemetrexed + cisplatin or carboplatin; SQ paclitaxel + Carboplatin

Primary endpoints: OS
Secondary endpoints: PFS by BICR, ORR by BICR, efficacy by tumor PD-L1 expression
Exploratory endpoints: Efficacy by oncogenic drivermutation status (KRAS, TP53, STK11, KEAP1)

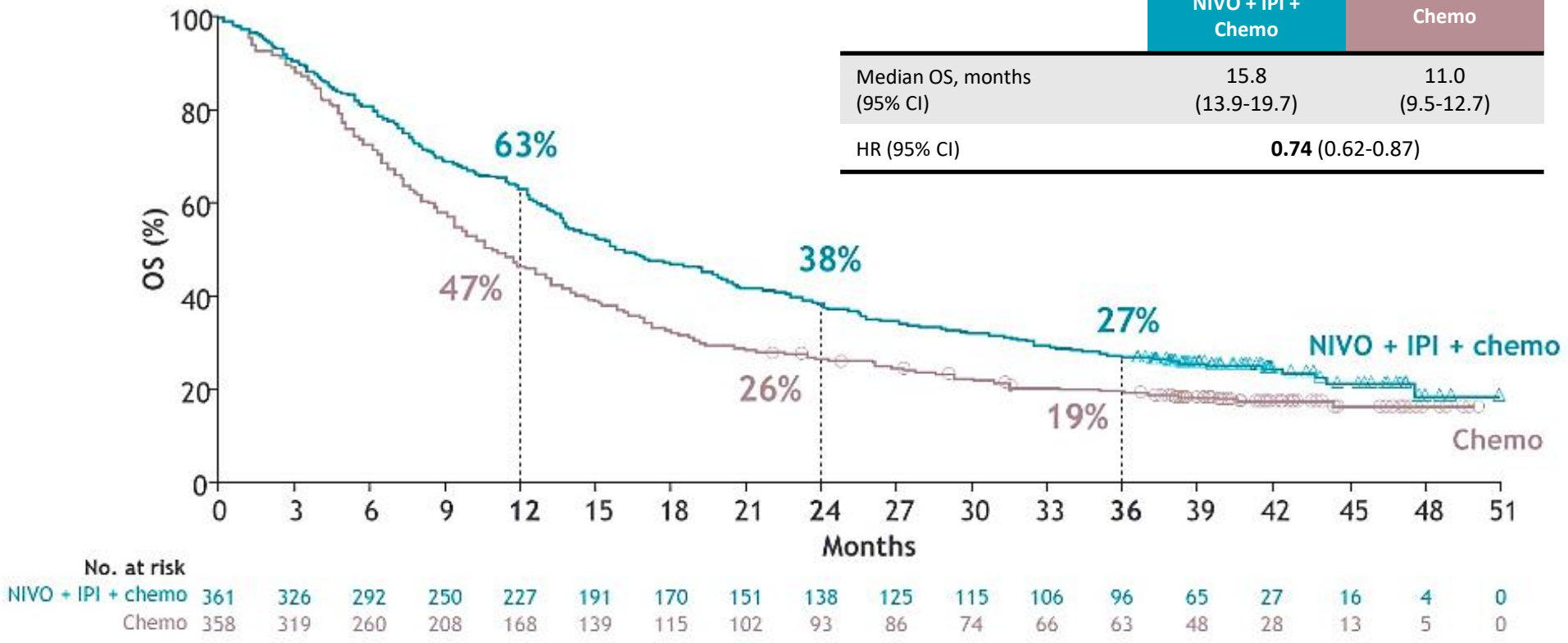
Data cutoff: 15 February 2022
Minimum/median follow-up for OS: 36.1 / 42.6 months

KEY DATA

CheckMate-9LA Clinical Trial

3-year update: OS in all randomized patients

	NIVO + IPI + Chemo	Chemo
Median OS, months (95% CI)	15.8 (13.9-19.7)	11.0 (9.5-12.7)
HR (95% CI)	**0.74** (0.62-0.87)	



ASCO 2022 Abstract #: 9026

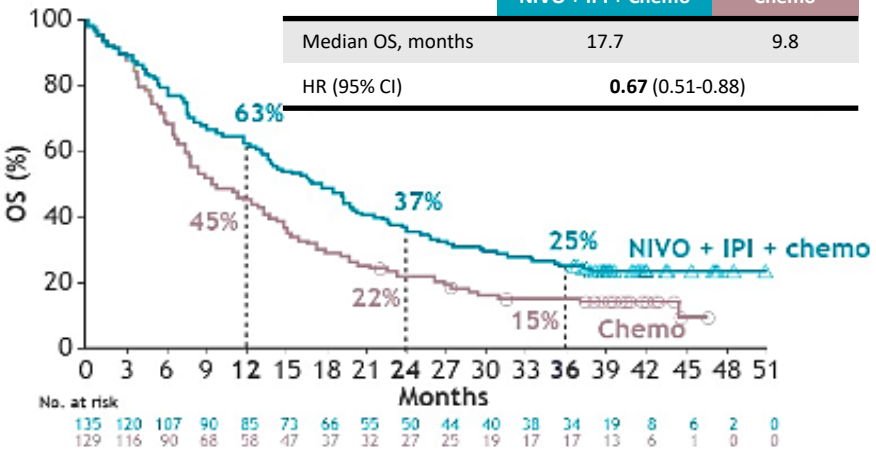
KEY DATA

CheckMate-9LA Clinical Trial

OS by PD-L1 expression

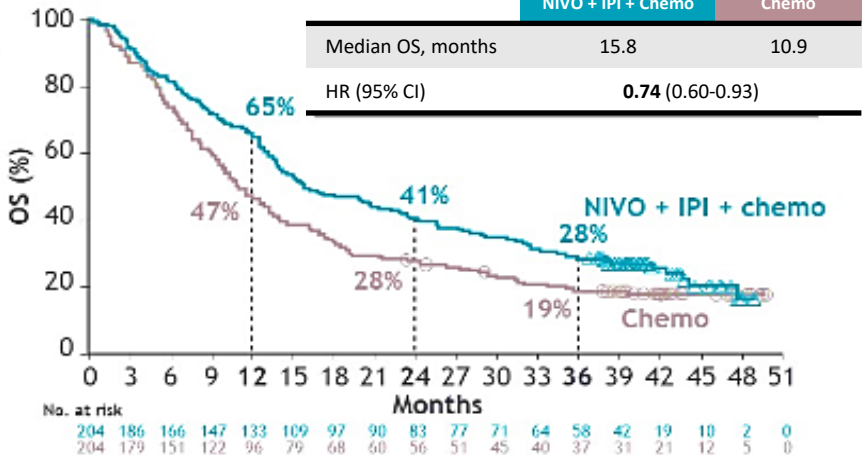
PD-L1 < 1%

	NIVO + IPI + Chemo	Chemo
Median OS, months	17.7	9.8
HR (95% CI)	**0.67** (0.51-0.88)	



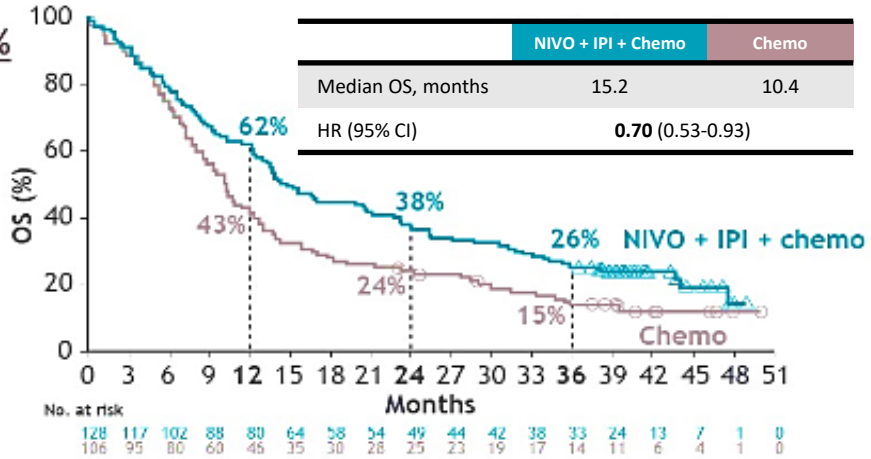
PD-L1 ≥ 1%

	NIVO + IPI + Chemo	Chemo
Median OS, months	15.8	10.9
HR (95% CI)	**0.74** (0.60-0.93)	



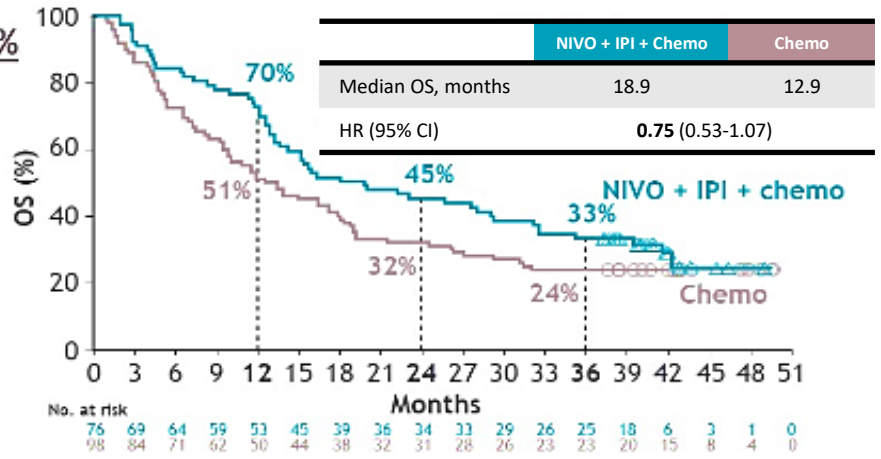
PD-L1 1-49%

	NIVO + IPI + Chemo	Chemo
Median OS, months	15.2	10.4
HR (95% CI)	**0.70** (0.53-0.93)	



PD-L1 ≥ 50%

	NIVO + IPI + Chemo	Chemo
Median OS, months	18.9	12.9
HR (95% CI)	**0.75** (0.53-1.07)	



Database lock: February 15, 2022; minimum follow-up: 36.1 months.

[a]95% CI, 13.7-20.3 (NIVO + IPI + chemo) and 7.7-13.5 (chemo); [b]95% CI, 13.8-22.2 (NIVO + IPI + chemo) and 9.5-13.2 (chemo); [c]95% CI, 12.6-21.2 (NIVO + IPI + chemo) and 8.7-12.4 (chemo); [d]95% CI, 13.1-29.1 (NIVO + IPI + chemo) and 9.4-17.6 (chemo).

ASCO 2022 Abstract #: 9026

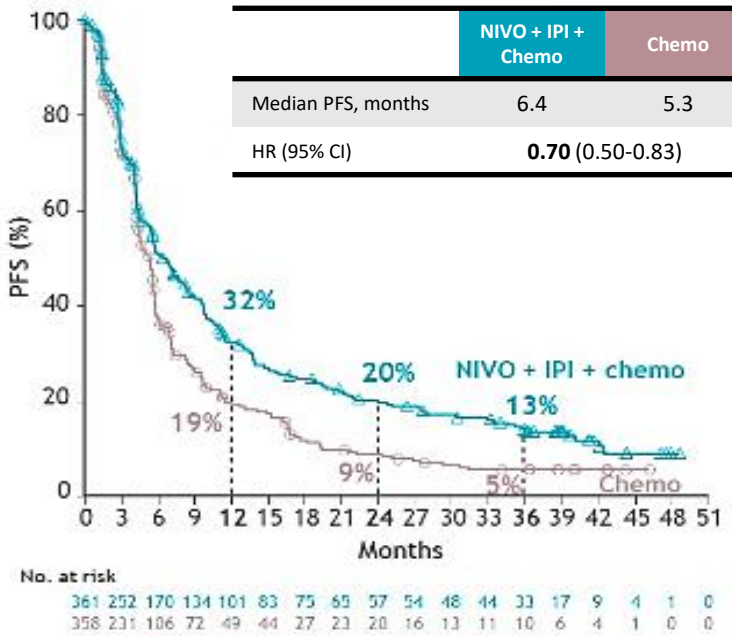
KEY DATA

CheckMate-9LA Clinical Trial

PFS, ORR, and DoR

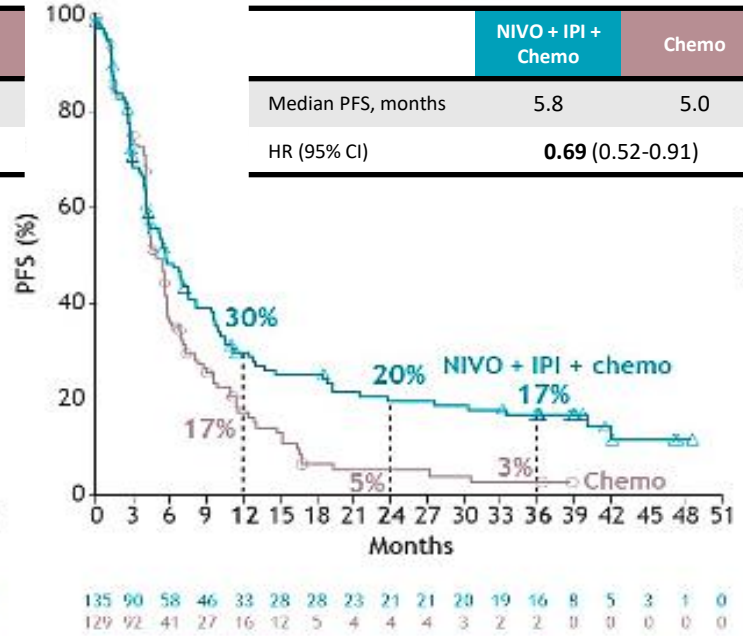
All randomized

	NIVO + IPI + Chemo	Chemo
Median PFS, months	6.4	5.3
HR (95% CI)	**0.70** (0.50-0.83)	



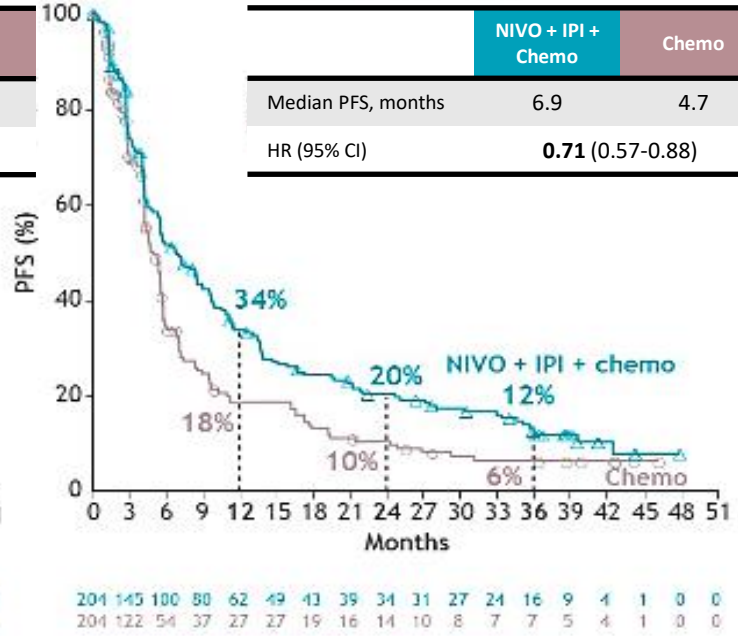
PD-L1 < 1%

	NIVO + IPI + Chemo	Chemo
Median PFS, months	5.8	5.0
HR (95% CI)	**0.69** (0.52-0.91)	



PD-L1 ≥ 1%

	NIVO + IPI + Chemo	Chemo
Median PFS, months	6.9	4.7
HR (95% CI)	**0.71** (0.57-0.88)	



All randomized	NIVO + IPI + Chemo	Chemo
ORR, % (95% CI)	38 (33-43)	25 (21-30)
DOR median, months (95% CI)	12.4 (8.7-20.1)	5.6 (4.4-7.2)
3-year DOR rate, % (95% CI)	23 (15-31)	14 (8-23)

PD-L1 <1%	NIVO + IPI + Chemo	Chemo
ORR, % (95% CI)	32 (24-40)	20 (14-28)
DOR median, months (95% CI)	17.5 (6.9-38.9)	4.3 (2.8-7.1)
3-year DOR rate, % (95% CI)	37 (22-53)	0

PD-L1 ≥≥%	NIVO + IPI + Chemo	Chemo
ORR, % (95% CI)	42 (35-49)	28 (22-34)
DOR median, months (95% CI)	11.3 (8.5-20.3)	5.6 (4.4-9.6)
3-year DOR rate, % (95% CI)	18 (10-28)	17 (8-28)

ASCO 2022 Abstract #: 9026

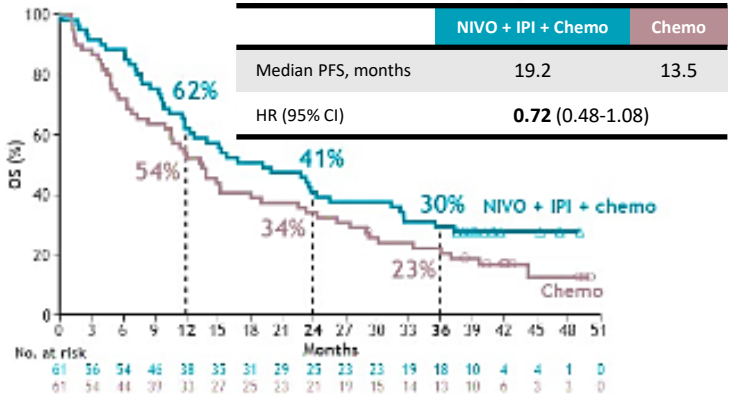
KEY DATA

CheckMate-9LA Clinical Trial

Exploratory endpoint: OS by oncogenic mutation

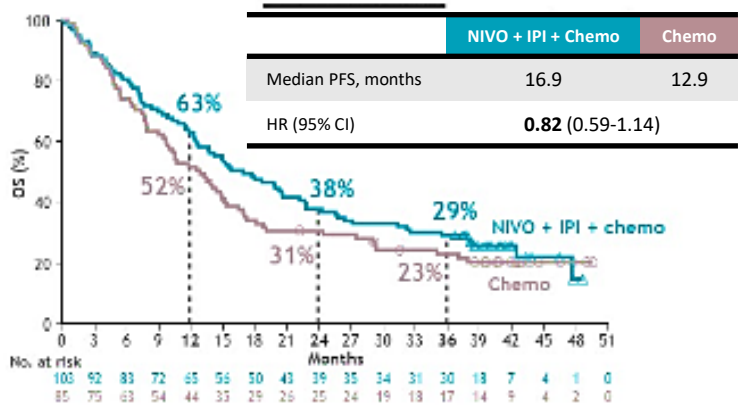
KRAS-mut

	NIVO + IPI + Chemo	Chemo
Median PFS, months	19.2	13.5
HR (95% CI)	**0.72** (0.48-1.08)	



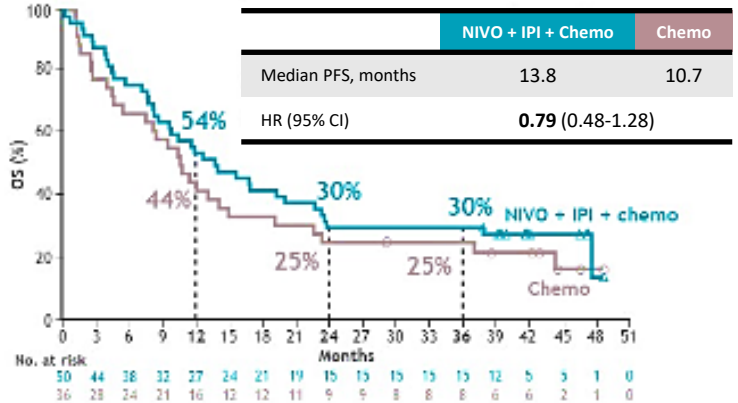
TP53-mut

	NIVO + IPI + Chemo	Chemo
Median PFS, months	16.9	12.9
HR (95% CI)	**0.82** (0.59-1.14)	



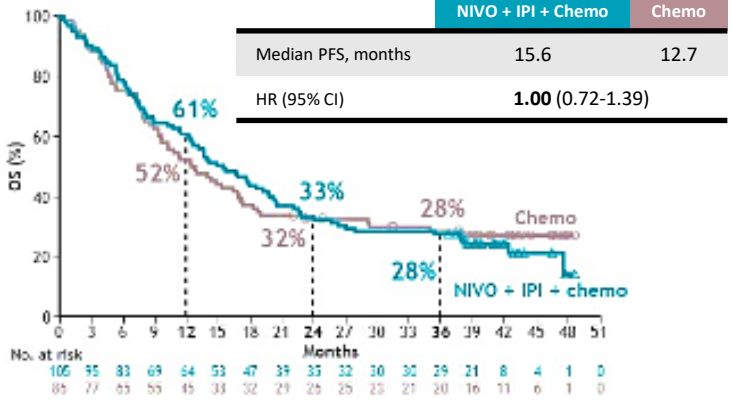
STK11-mut

	NIVO + IPI + Chemo	Chemo
Median PFS, months	13.8	10.7
HR (95% CI)	**0.79** (0.48-1.28)	



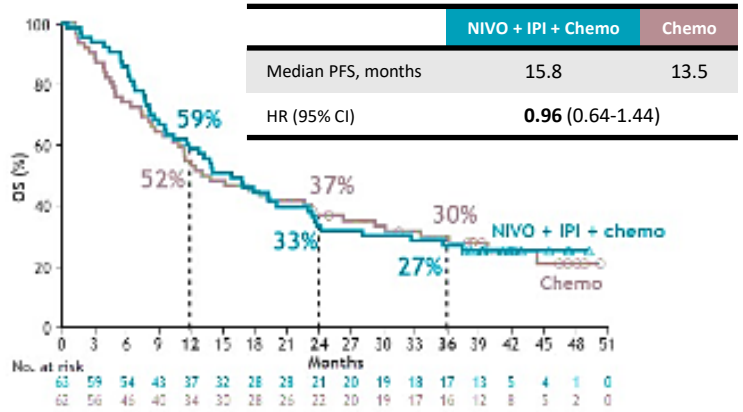
KRAS-wt

	NIVO + IPI + Chemo	Chemo
Median PFS, months	15.6	12.7
HR (95% CI)	**1.00** (0.72-1.39)	



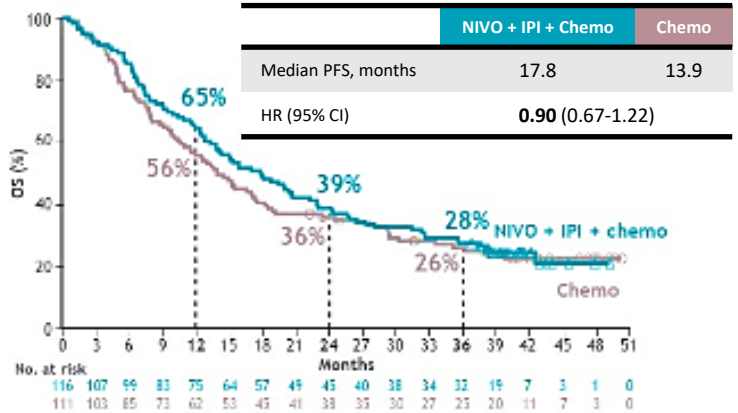
TP53-wt

	NIVO + IPI + Chemo	Chemo
Median PFS, months	15.8	13.5
HR (95% CI)	**0.96** (0.64-1.44)	



STK11-wt

	NIVO + IPI + Chemo	Chemo
Median PFS, months	17.8	13.9
HR (95% CI)	**0.90** (0.67-1.22)	



- Similar trend of OS benefit was seen with NIVO + IPI + chemo vs chemo in *KRAS G12C*-mut (n = 50) and *KEAP1*-mut (n = 32) subgroups

CheckMate-227 Clinical Trials

Does first-line combination immunotherapy provide benefit for patients with advanced NSCLC?

Updated analysis

A 5-year update of CheckMate -227 evaluating nivolumab/ipilimumab vs chemotherapy

cornerstone specialty network™

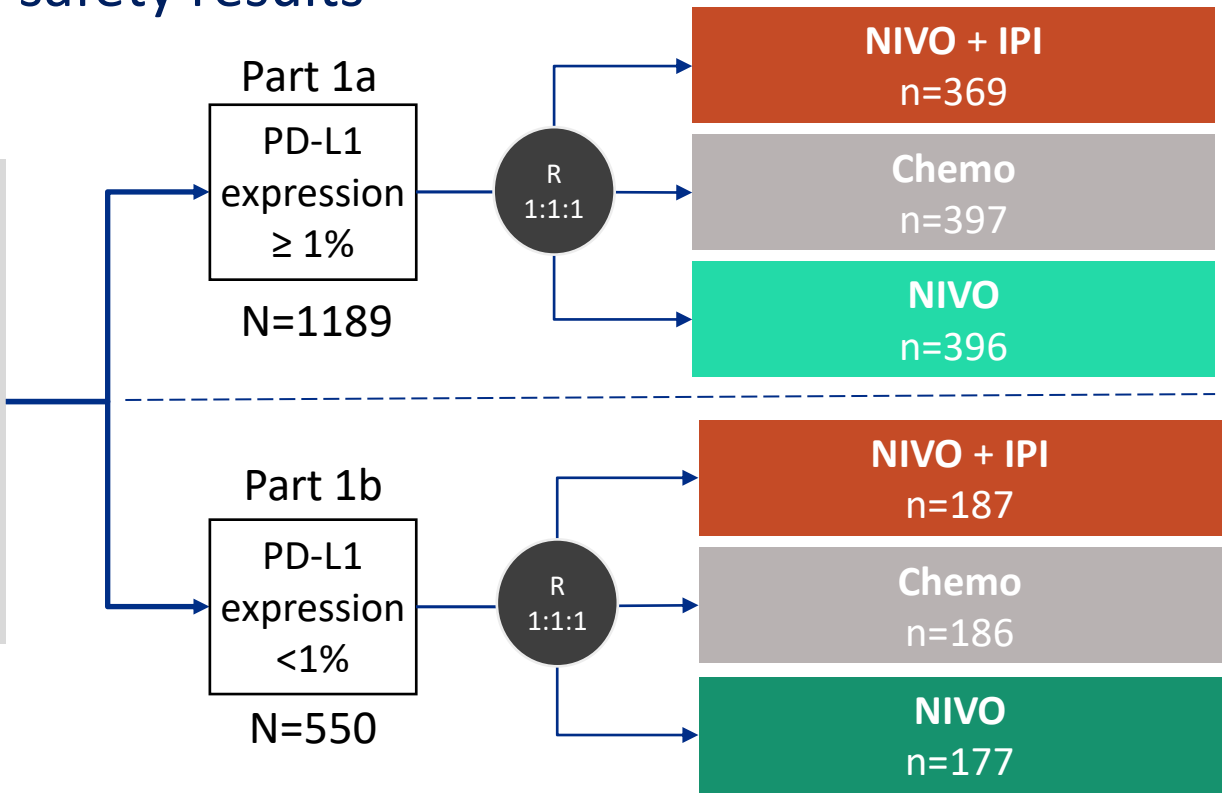
KEY DATA

CheckMate-227 Clinical Trial

Study Design: NIVO + IPI versus chemotherapy as a 1L treatment for advanced NSCLC
Updated 5-year efficacy and safety results

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No known sensitizing EGFR mutations or known ALK alterations
- No untreated CNS metastases
- ECOG PS 0-1

Stratified by SQ vs NSQ



Until PD, unacceptable toxicity, or for 2 years for immunotherapy

Independent Primary endpoints: NIVO + IPI vs Chemo

- PFS in high TMB (≥ 10 mut /Mb) population
- OS in PD-L1 ≥1% population

Database lock: February 18, 2021; minimum / median follow-up for OS: 49.4 months / 54.8 months.

Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy. [a]NCT02477826; [b]NSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [c]Both endpoints were met; results were previously reported. 1. Hellmann MD, et al. *N Engl J Med* 2018;378:2093-2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381:2020-2031.

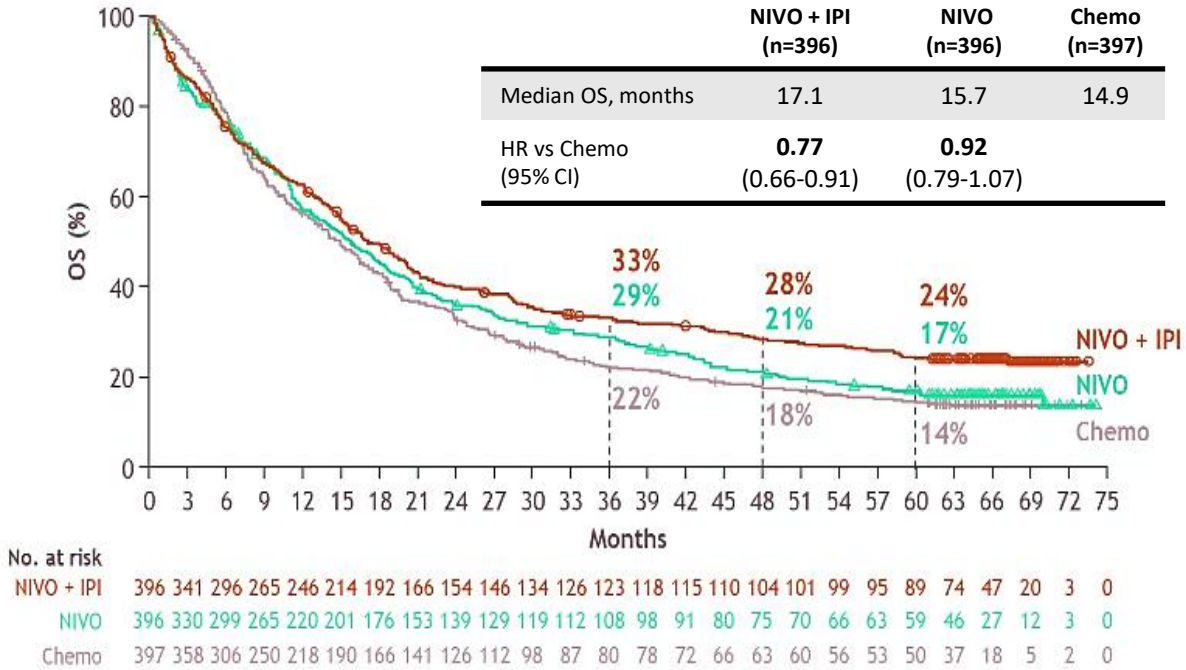
KEY DATA

CheckMate-227 Clinical Trial

5 Year Update: Overall Survival

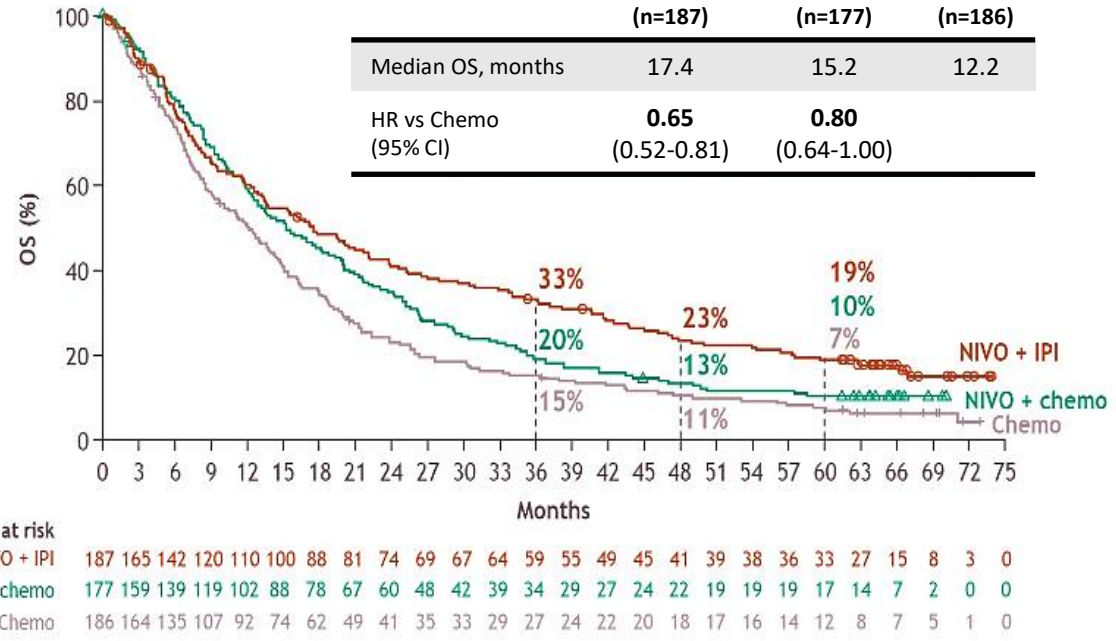
PD-L1 ≥1%

	NIVO + IPI (n=396)	NIVO (n=396)	Chemo (n=397)
Median OS, months	17.1	15.7	14.9
HR vs Chemo (95% CI)	**0.77** (0.66-0.91)	**0.92** (0.79-1.07)	



PD-L1 <1%

	NIVO + IPI (n=187)	NIVO (n=177)	Chemo (n=186)
Median OS, months	17.4	15.2	12.2
HR vs Chemo (95% CI)	**0.65** (0.52-0.81)	**0.80** (0.64-1.00)	



ASCO 2022 Abstract #: 9025

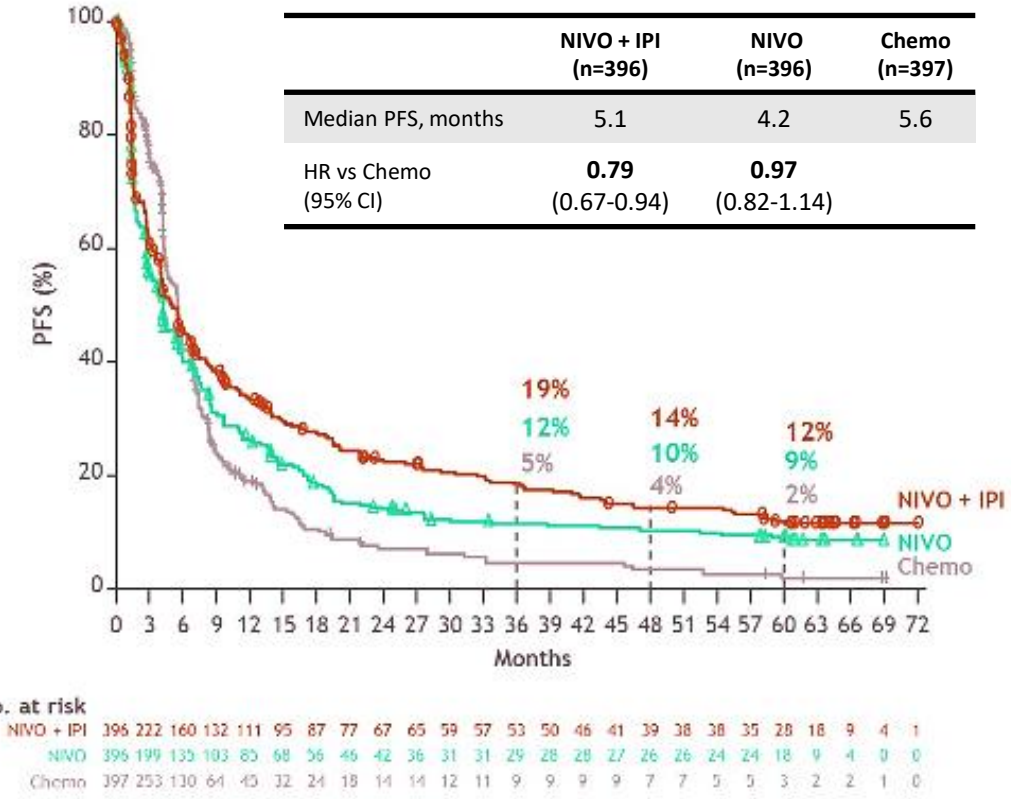
KEY DATA

CheckMate-227 Clinical Trial

5 Year Update: Progression Free Survival

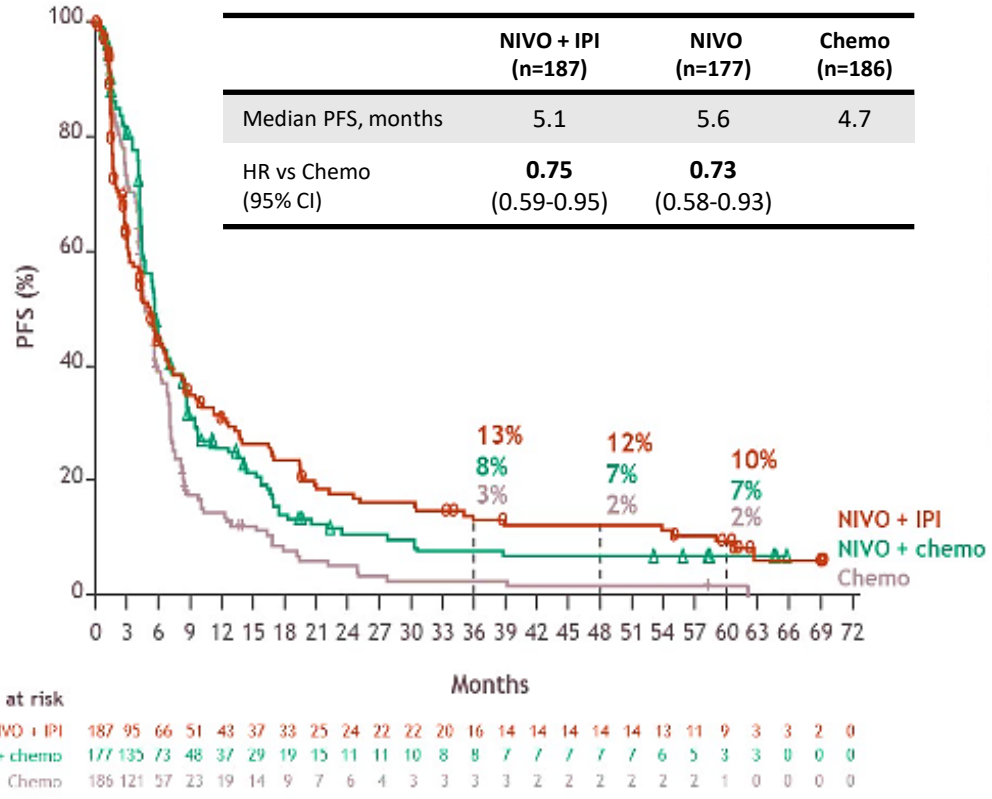
PD-L1 ≥1%

	NIVO + IPI (n=396)	NIVO (n=396)	Chemo (n=397)
Median PFS, months	5.1	4.2	5.6
HR vs Chemo (95% CI)	**0.79** (0.67-0.94)	**0.97** (0.82-1.14)	



PD-L1 <1%

	NIVO + IPI (n=187)	NIVO (n=177)	Chemo (n=186)
Median PFS, months	5.1	5.6	4.7
HR vs Chemo (95% CI)	**0.75** (0.59-0.95)	**0.73** (0.58-0.93)	



ASCO 2022 Abstract #: 9025

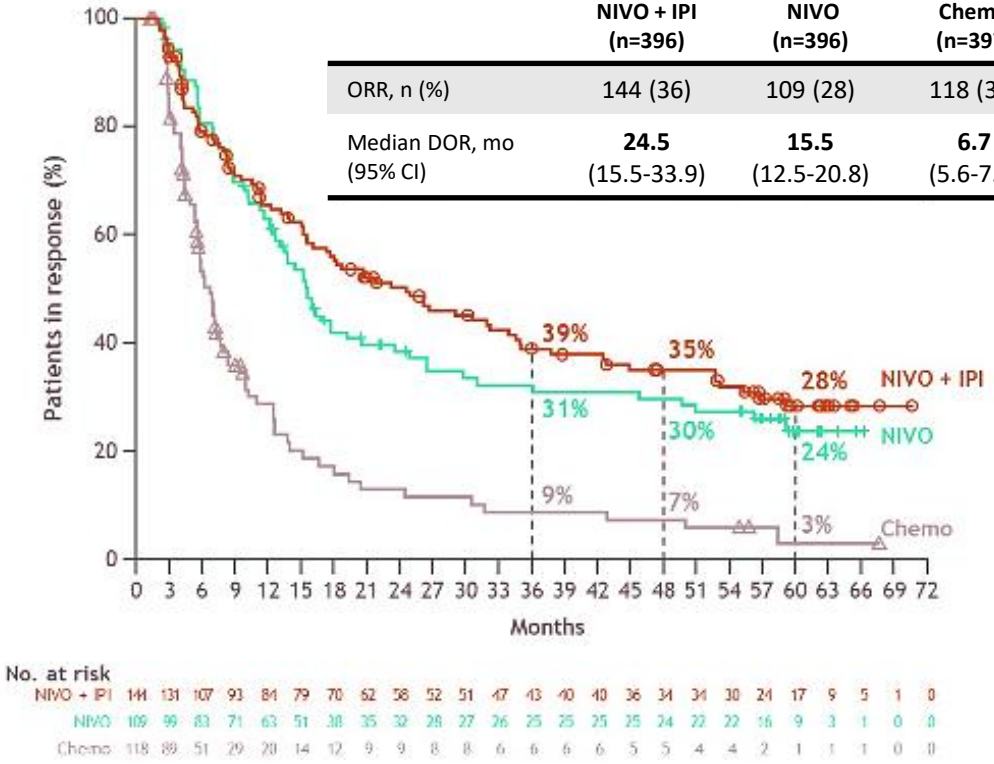
KEY DATA

CheckMate-227 Clinical Trial

5 Year Update: Duration Of Response

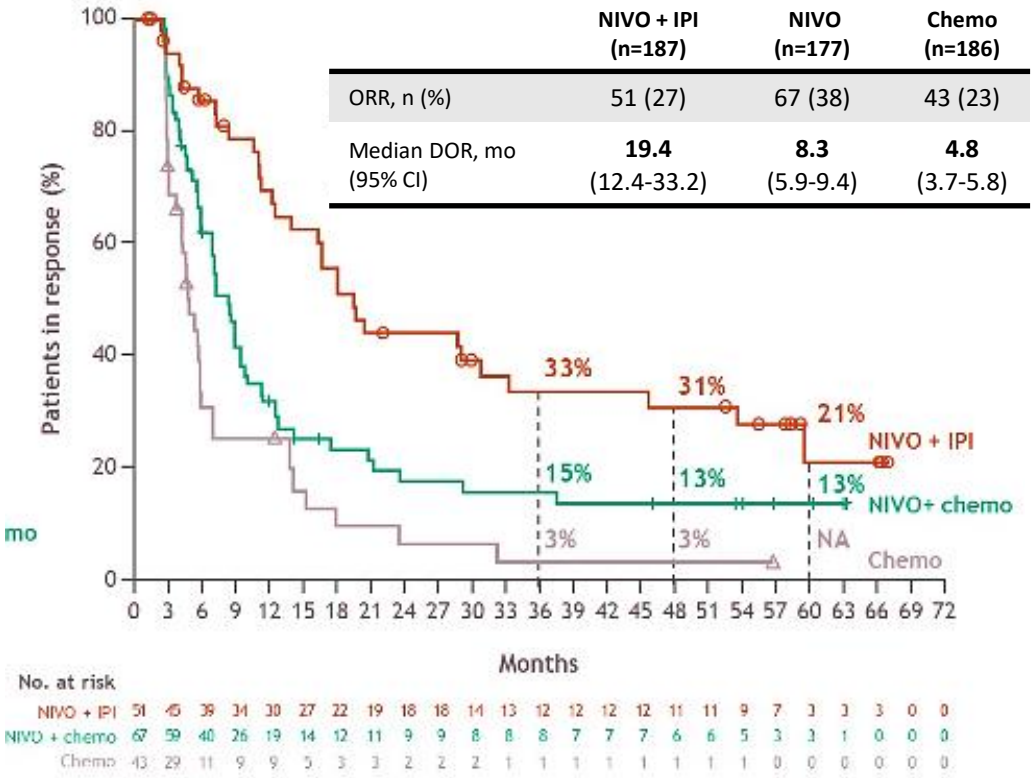
PD-L1 ≥1%

	NIVO + IPI (n=396)	NIVO (n=396)	Chemo (n=397)
ORR, n (%)	144 (36)	109 (28)	118 (30)
Median DOR, mo (95% CI)	**24.5** (15.5-33.9)	**15.5** (12.5-20.8)	**6.7** (5.6-7.6)



PD-L1 <1%

	NIVO + IPI (n=187)	NIVO (n=177)	Chemo (n=186)
ORR, n (%)	51 (27)	67 (38)	43 (23)
Median DOR, mo (95% CI)	**19.4** (12.4-33.2)	**8.3** (5.9-9.4)	**4.8** (3.7-5.8)



ASCO 2022 Abstract #: 9025

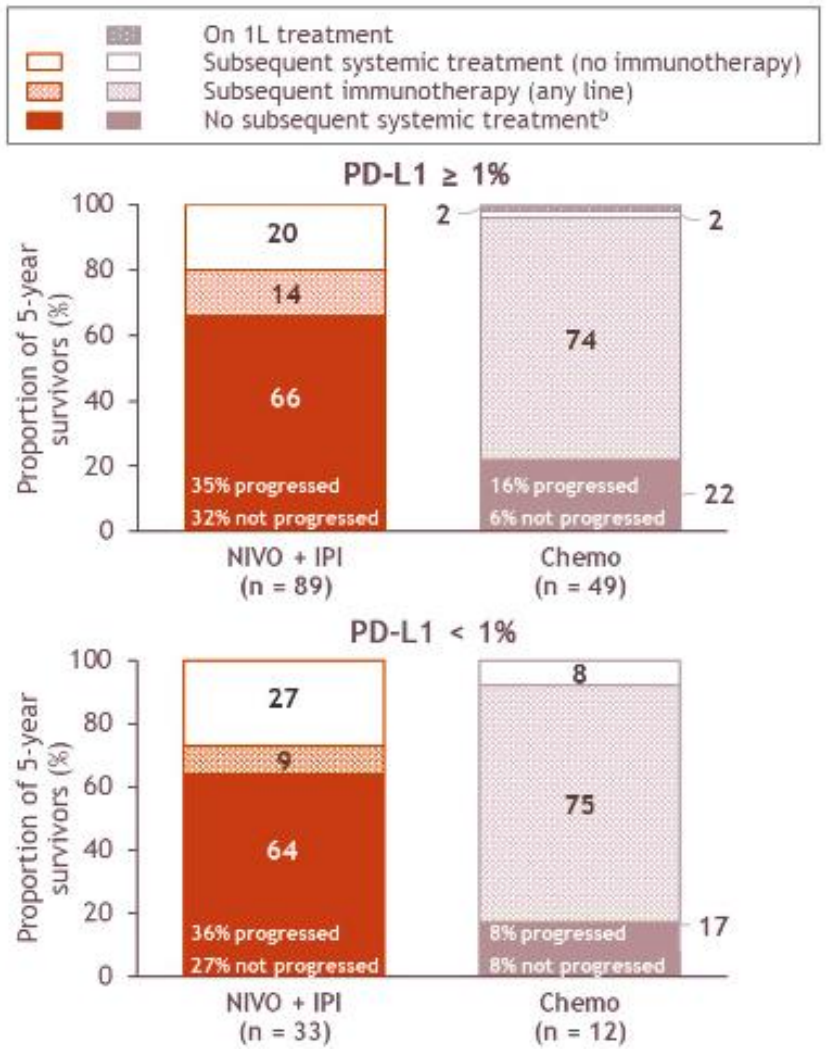
KEY DATA

CheckMate-227 Clinical Trial

5-year survivors

Patients alive at 5-year	PD-L1 ≥ 1%		PD-L1 < 1%	
	NIVO + IPI n=89	Chemo n=50	NIVO + IPI n=33	Chemo n=12
Median PFS, mo (95% CI)	59.1 (35.8-NA)	9.5 (7.0-22.1)	60.7 (19.4-NA)	24.9 (4.0-61.9)
5-year PFS, % (95% CI)	49 (37-60)	14 (4-28)	51 (30-68)	30 (5-62)
ORR, n (%) (95% CI)	71 (80) (69.9-87.6)	27 (54) (39.3-68.2)	27 (82) (64.5-93.0)	6 (50) (21.1-78.9)
Median DOR, mo (95% CI)	NR (52.6-NA)	12.4 (5.6-24.4)	59.4 (18.0-NA)	15.2 (2.7-NA)
5-year DOR, % (95% CI)	54 (40-66)	17 (4-36)	41 (14-66)	NA

- In 5-year survivors treated with NIVO + IPI vs chemo:
  - 66% vs 20% (PD-L1 ≥1%) and 64% vs 17% (PD-L1 <1%) remained treatment-free ≥ 3 years after discontinuation of study treatment



SUMMARY

CheckMate -9LA and CheckMate -227 Clinical Trials

CheckMate -9LA: At 3 years: OS, PFS and DOR benefits were maintained across key subgroups with high unmet need, including those with PD-L1 expression <1%. Updated results continue to support NIVO + IPI + 2 cycles of chemotherapy as an efficacious 1L treatment option for patients with advanced NSCLC.

CheckMate -227: At 5 years: OS, PFS and DOR benefits were maintained. Updated results continue to support NIVO + IPI as an efficacious 1L treatment option regardless of PD-L1 expression for patients with advanced NSCLC.

The longest follow-up of any Phase 3 trial for an immunotherapy combination in non-small cell lung cancer

CheckMate -9LA and CheckMate -227 Clinical Trials

Nivolumab (Opdivo®) plus ipilimumab (Yervoy®)-based combinations continue to demonstrate long-term survival benefits in the 1L setting for patients with advanced NSCLC

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Actionable NSCLC
• CheckMate-816 • NADIM II • ADAURA • KEYNOTE-091	• EMPOWER-Lung 1 • CheckMate -9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreak 100/101 • EXCLAIM • ALTA-1L

POSEIDON Clinical Trial

Does front-line durvalumab with tremelimumab and chemotherapy provide benefit for patients with metastatic NSCLC?

Updated analysis

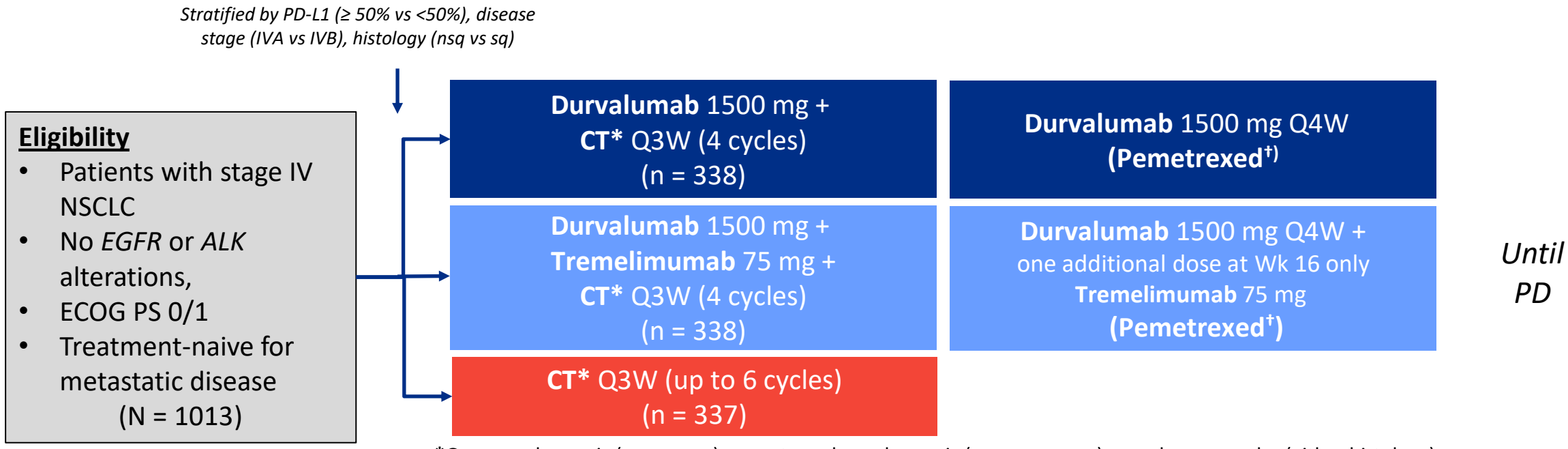
***On November 10, 2022**, the Food and Drug Administration approved tremelimumab (Imjudo, AstraZeneca Pharmaceuticals) in combination with durvalumab (Imfinzi, AstraZeneca Pharmaceuticals) and platinum-based chemotherapy for adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.*

cornerstone specialty network™

KEY DATA

POSEIDON Clinical Trial

Study Design: Open-label, multicenter, randomized phase III trial



*Gem + carbo or cis (squamous), pemetrexed + carbo or cis (nonsquamous), or nab-pac + carbo (either histology).
†Maintenance pemetrexed only given to patients with nonsquamous NSCLC who received first-line pemetrexed.

Primary endpoints: PFS by BICR, OS (D + CT vs CT); positivity for either triggered analysis of key secondary endpoints

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

Other secondary endpoints: ORR, DoR, BOR by BICR; 12-mo PFS; HRQoL; safety/tolerability

ESMO 2022. Abstr LBA59

KEY DATA

POSEIDON Clinical Trial

Baseline Characteristics

Characteristic	Durvalumab + CT (n = 338)	Durvalumab + Tremelimumab + CT (n = 338)	CT (n = 337)
Median age, yr (range)	64.5 (32-87)	63.0 (27-87)	64.0 (32-84)
Male, %	74.9	79.6	73.6
White/Asian/other, %	53.8/36.4/9.8	60.7/29.3/10.1	53.1/38.0/8.9
E Europe/Asia/N Am/W Europe/other, %	30.5/35.5/13.6/7.7/12.7	36.1/28.4/13.0/8.6/13.9	28.2/36.8/11.9/8.3/14.8
ECOG PS 0/1, %	32.3/67.8	32.5/67.5	35.3/64.4
Squamous/non-squamous histology, %	37.9/61.8	36.7/63.3	36.2/63.5
AJCC disease stage IVA/IVB, %	50.3/49.4	50.6/48.8	49.3/50.4
Current or former/never smoker, %	75.1/24.9	82.5/17.5	76.3/23.4
PD-L1 expression ≥ 50%/≥ 1%, %	27.8/66.3	29.9/63.0	28.8/61.4
CNS metastases, %	8.3	9.8	13.4
Liver metastases, %	18.3	20.4	23.7

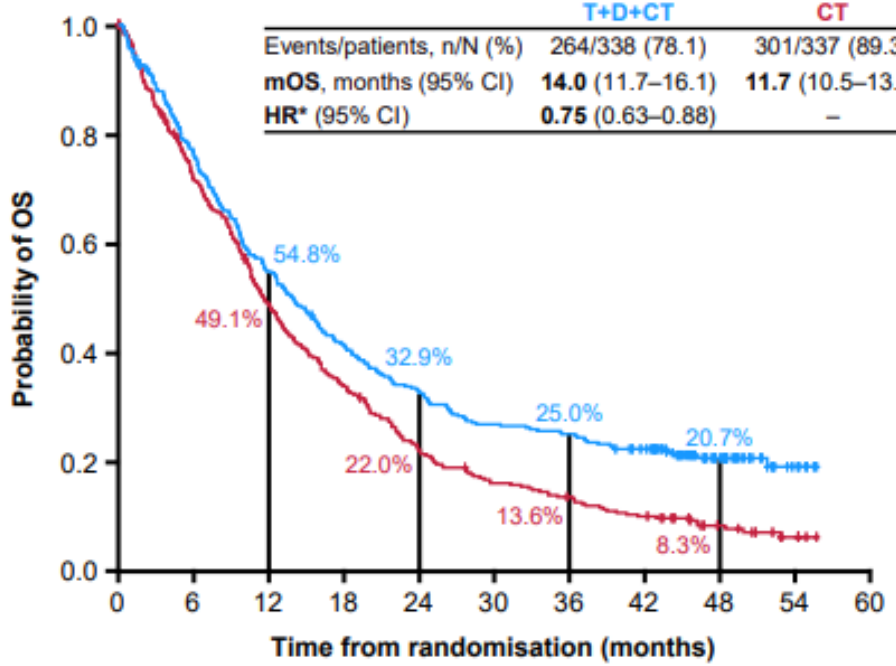
ESMO 2022. Abstr LBA59

POSEIDON Clinical Trial

Updated overall survival

T+D+CT vs CT

	T+D+CT	CT
Events/patients, n/N (%)	264/338 (78.1)	301/337 (89.3)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR* (95% CI)	**0.75** (0.63–0.88)	–

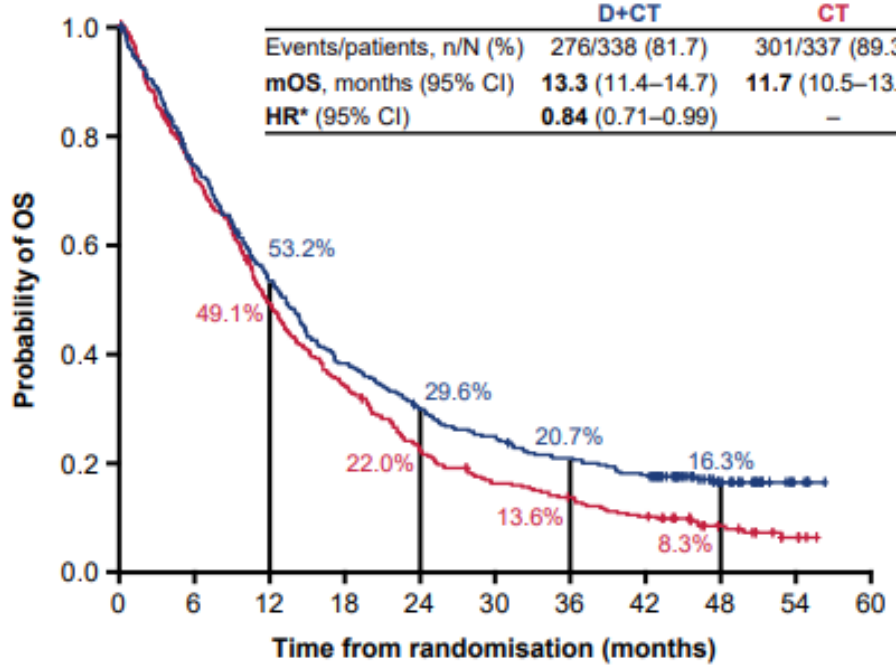


No. at risk

T+D+CT	338	256	183	137	109	89	83	70	32	6	0
CT	337	236	160	111	71	51	42	31	14	5	0

D+CT vs CT

	D+CT	CT
Events/patients, n/N (%)	276/338 (81.7)	301/337 (89.3)
mOS, months (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR* (95% CI)	**0.84** (0.71–0.99)	–



No. at risk

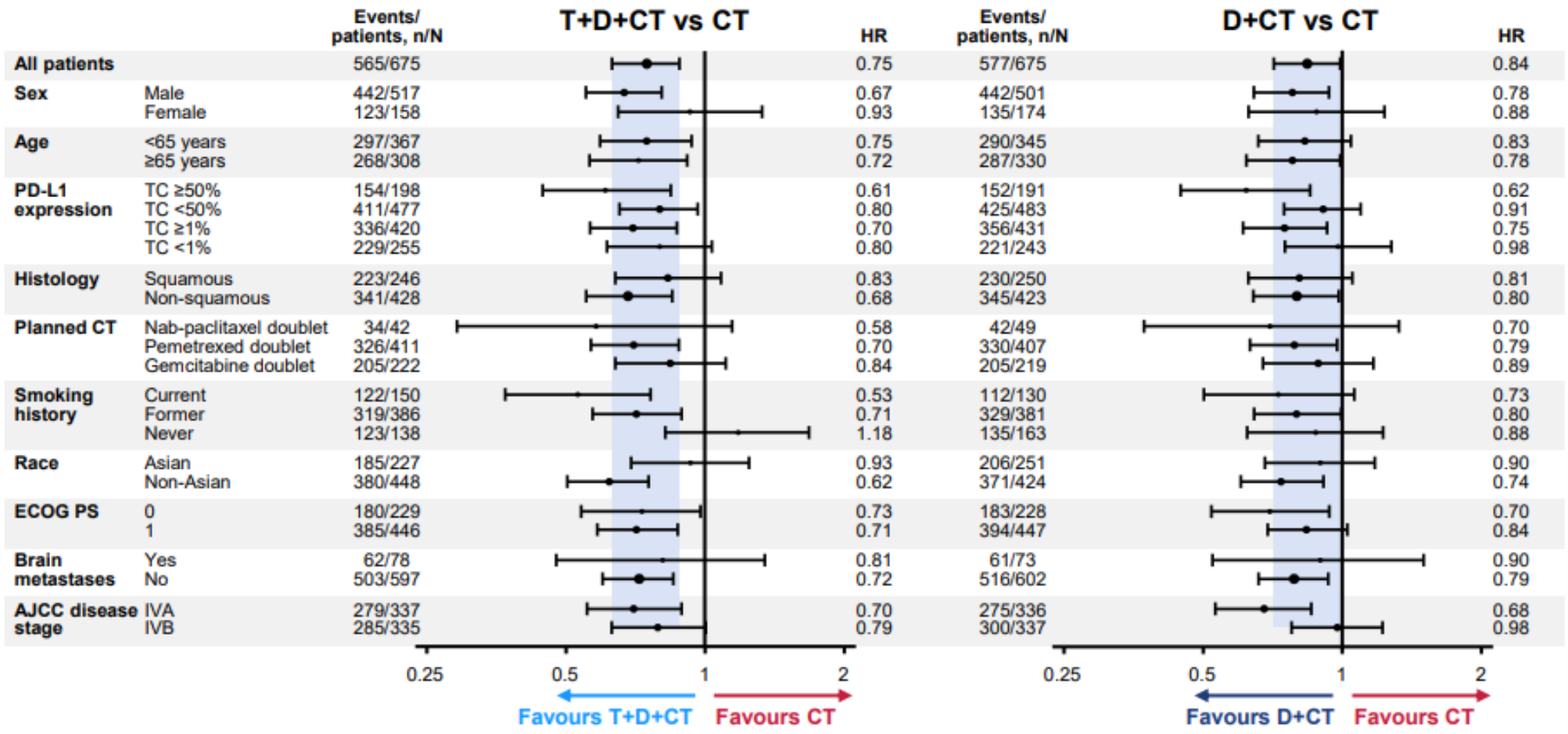
D+CT	338	247	176	126	97	81	67	57	26	5	0
CT	337	236	160	111	71	51	42	31	14	5	0

Median follow-up in censored patients at DCO: 46.5 months (range 0.0–56.5)

*HR <1 favours D(±T)+CT vs CT (stratified analysis); DCO, 11 Mar 2022

POSEIDON Clinical Trial

Updated OS by Subgroup



HR <1 favours D(±T)+CT vs CT (all patients analysis stratified, subgroup analysis unstratified); size of circle is proportional to the number of events across both treatment groups; DCO, 11 Mar 2022

ESMO 2022. Abstr LBA59

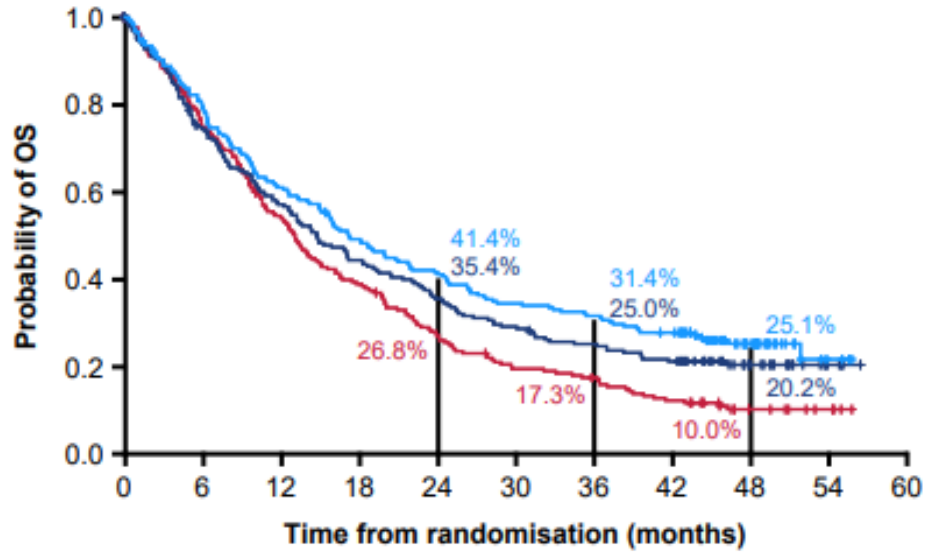
KEY DATA

POSEIDON Clinical Trial

Updated OS by histology

NSQ

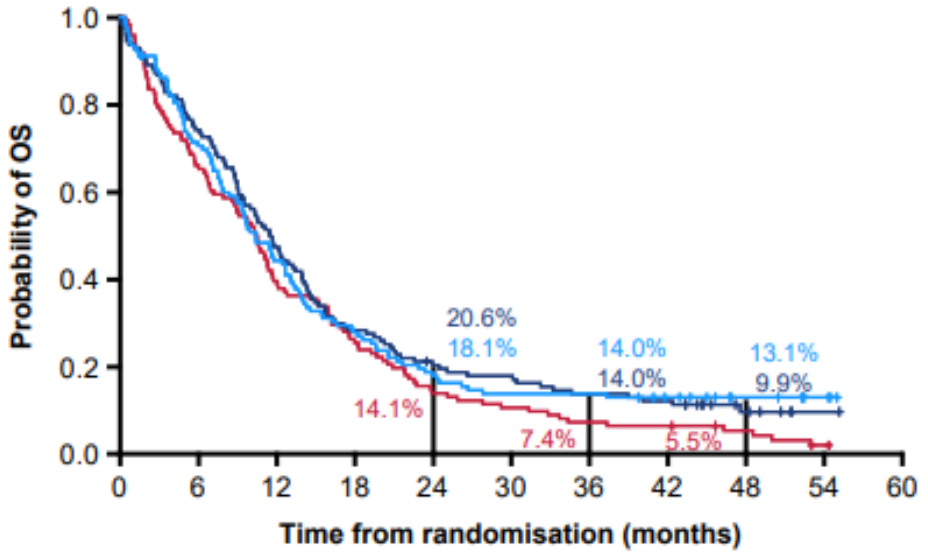
	T+D+CT	D+CT	CT
Events/patients, n/N	158/214	162/209	183/214
mOS, months (95% CI)	**17.2** (14.9–21.8)	**14.8** (11.8–18.3)	**13.1** (10.6–15.1)
HR* (95% CI)	**0.68** (0.55–0.85)	**0.80** (0.64–0.98)	–



No. at risk											
T+D+CT	214	169	129	103	87	72	66	57	25	3	0
D+CT	209	152	116	90	72	59	50	42	20	4	0
CT	214	155	111	79	54	38	33	23	9	4	0

SQ

	T+D+CT	D+CT	CT
Events/patients, n/N	106/124	113/128	117/122
mOS, months (95% CI)	**10.4** (8.4–12.7)	**11.5** (9.4–14.0)	**10.5** (8.0–11.7)
HR* (95% CI)	**0.83** (0.64–1.08)	**0.81** (0.63–1.06)	–



No. at risk											
T+D+CT	124	87	54	34	22	17	17	13	7	3	0
D+CT	128	95	60	36	25	22	17	15	6	1	0
CT	122	80	48	32	17	13	9	8	5	1	0

*HR <1 favours D(±T)+CT vs CT (unstratified analysis); DCO, 11 Mar 2022

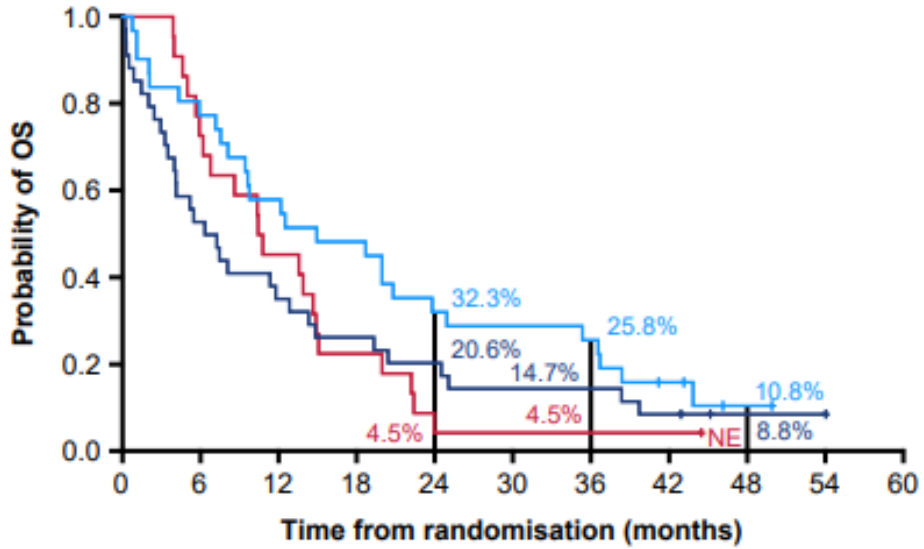
ESMO 2022. Abstr LBA59

POSEIDON Clinical Trial

Updated OS by *STK11* mutation status

*STK11*m

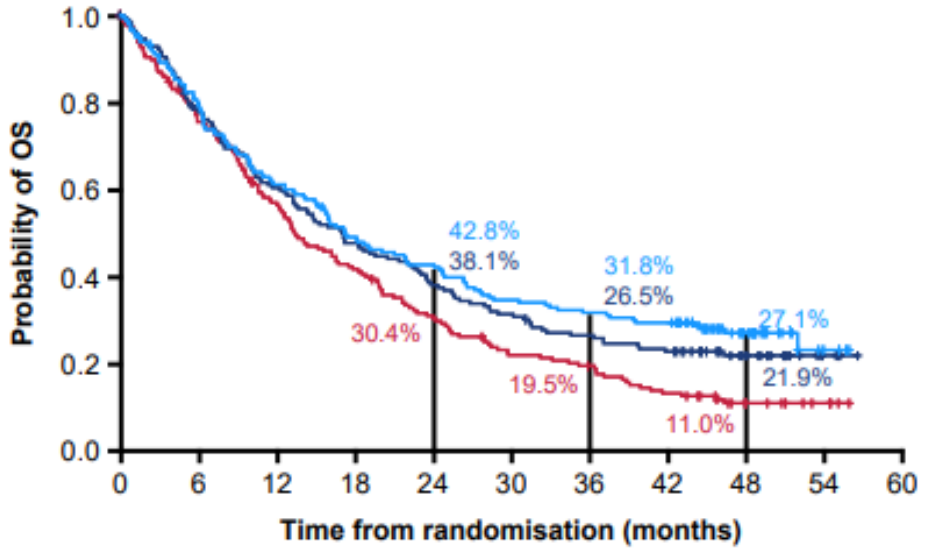
	T+D+CT	D+CT	CT
Events/patients, n/N	27/31	31/34	21/22
mOS, months (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.62** (0.34–1.12)	**1.06** (0.61–1.89)	–



No. at risk											
T+D+CT	31	24	18	15	10	9	8	4	1	0	0
D+CT	34	18	12	9	7	5	5	3	1	0	0
CT	22	16	10	5	1	1	1	1	0	0	0

*STK11*wt

	T+D+CT	D+CT	CT
Events/patients, n/N	127/177	129/169	151/179
mOS, months (95% CI)	**17.2** (14.9–22.1)	**17.1** (13.3–22.3)	**13.4** (11.5–17.5)
HR* (95% CI)	**0.70** (0.55–0.89)	**0.77** (0.61–0.98)	–



No. at risk											
T+D+CT	177	140	107	85	74	60	55	51	23	3	0
D+CT	169	130	100	79	63	52	43	37	19	4	0
CT	179	131	97	71	51	36	31	21	9	4	0

STK11 mutations were present in 31 patients in the triplet combination group and 22 in the chemotherapy alone group
*HR <1 favours D(±T)+CT vs CT (unstratified analysis); DCO, 11 Mar 2022

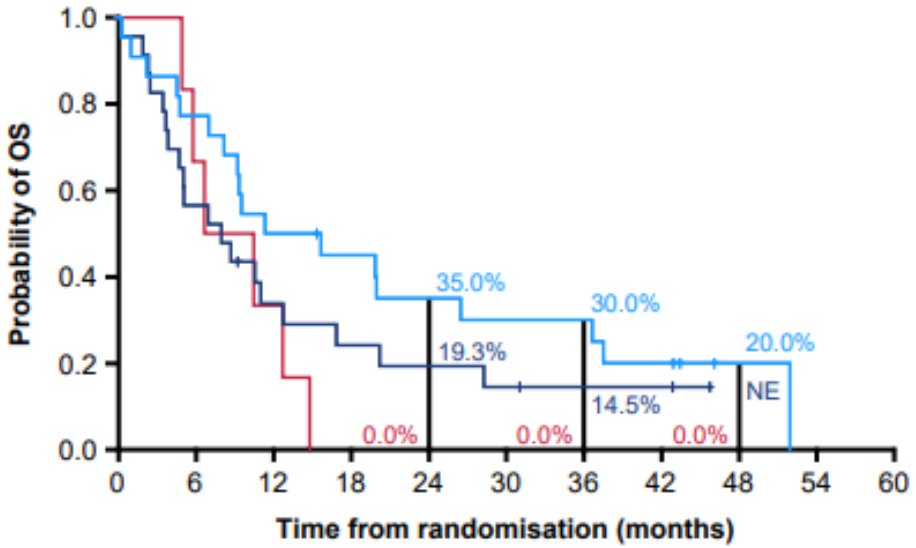
ESMO 2022. Abstr LBA59

POSEIDON Clinical Trial

Updated OS by *KEAP1* mutation status

*KEAP1*m

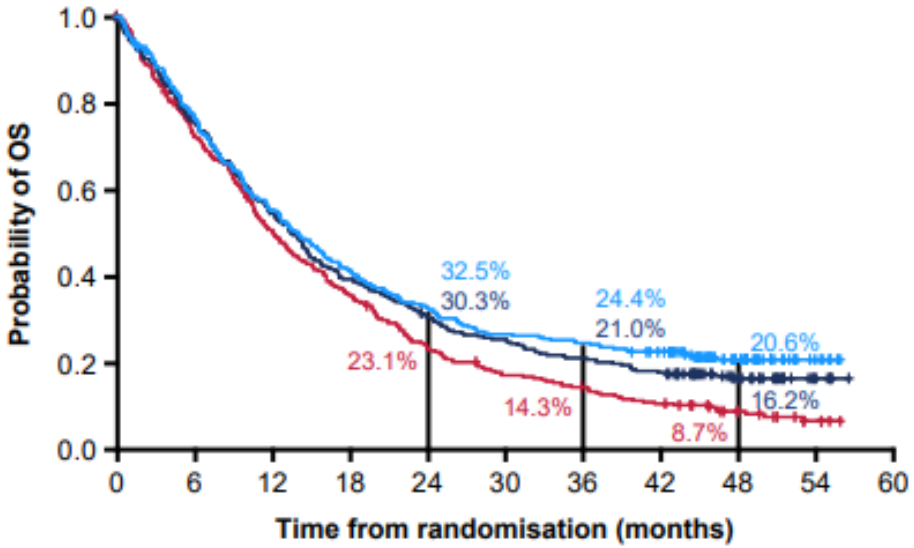
	T+D+CT	D+CT	CT
Events/patients, n/N	18/22	19/23	6/6
mOS, months (95% CI)	**13.7** (7.2–26.5)	**8.1** (4.0–12.9)	**8.7** (5.1–NE)
HR* (95% CI)	**0.43** (0.16–1.25)	**0.77** (0.31–2.15)	–



No. at risk											
T+D+CT	22	17	11	9	7	6	6	4	1	0	0
D+CT	23	13	7	5	4	3	2	2	0	0	0
CT	6	4	2	0	0	0	0	0	0	0	0

*KEAP1*wt

	T+D+CT	D+CT	CT
Events/patients, n/N	236/303	253/307	278/312
mOS, months (95% CI)	**14.0** (11.8–16.1)	**13.5** (11.7–14.9)	**12.2** (10.6–13.9)
HR* (95% CI)	**0.75** (0.63–0.89)	**0.81** (0.69–0.97)	–



No. at risk											
T+D+CT	303	230	165	123	97	79	73	63	30	6	0
D+CT	307	230	165	119	91	76	63	53	26	5	0
CT	312	221	153	108	69	50	41	30	14	5	0

KEAP1 mutations were present in 22 patients in the triplet combination group and 6 patients in the chemotherapy alone group

*HR <1 favours D(±T)+CT vs CT (unstratified analysis); DCO, 11 Mar 2022

ESMO 2022. Abstr LBA59

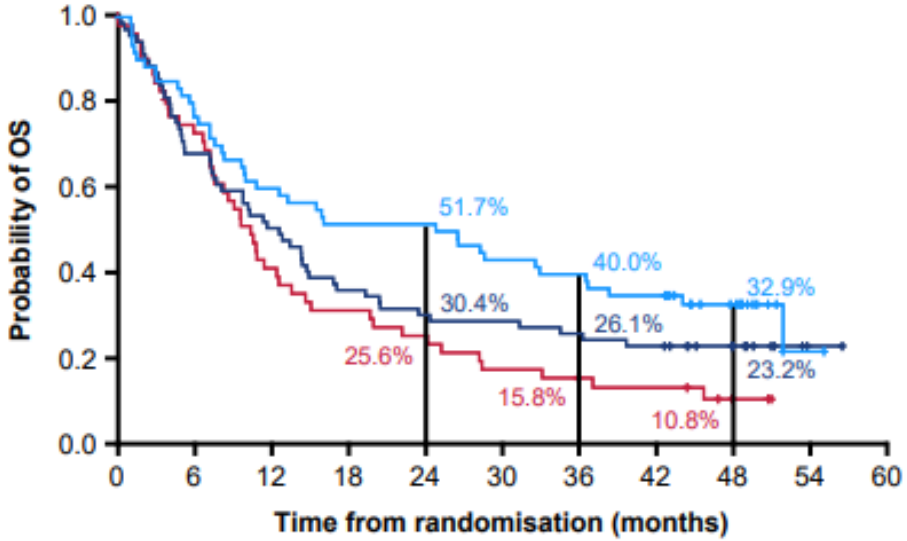
KEY DATA

POSEIDON Clinical Trial

Updated OS by *KRAS* mutation status

*KRAS*m

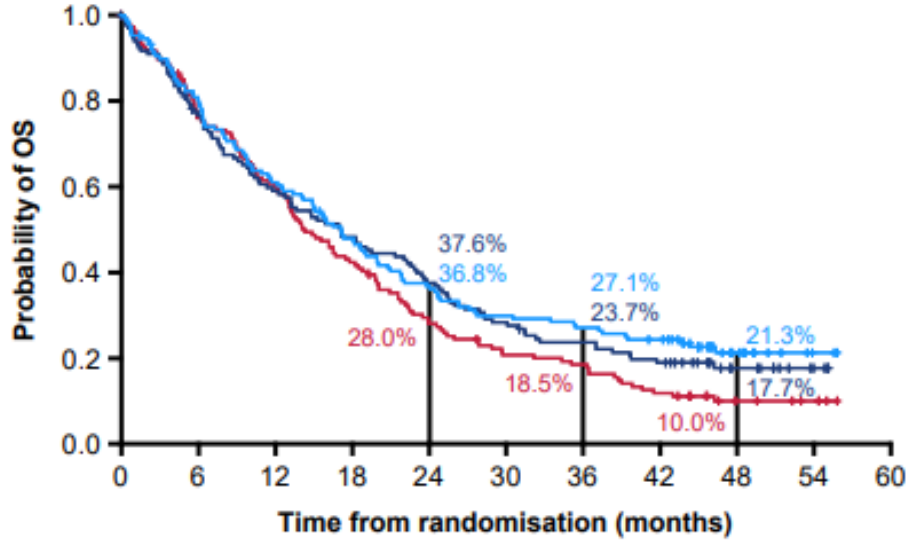
	T+D+CT	D+CT	CT
Events/patients, n/N	41/60	53/69	45/53
mOS, months (95% CI)	**25.7** (9.9–36.7)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.55** (0.36–0.85)	**0.78** (0.52–1.16)	–



No. at risk											
T+D+CT	60	46	36	31	31	26	24	21	12	1	0
D+CT	69	47	35	25	21	20	18	16	9	1	0
CT	53	37	21	16	13	9	7	6	2	0	0

*KRAS*wt

	T+D+CT	D+CT	CT
Events/patients, n/N	113/148	107/134	127/148
mOS, months (95% CI)	**17.1** (13.4–20.1)	**17.1** (12.3–22.6)	**14.4** (12.6–18.3)
HR* (95% CI)	**0.78** (0.60–1.00)	**0.83** (0.64–1.08)	–



No. at risk											
T+D+CT	148	118	89	69	53	43	39	34	12	2	0
D+CT	134	101	77	63	49	37	30	24	11	3	0
CT	148	110	86	60	39	28	25	16	7	4	0

KRAS mutations were present in 60 patients in the triplet combination group and 53 patients in the chemotherapy alone group

*HR <1 favours D(±T)+CT vs CT (unstratified analysis); DCO, 11 Mar 2022

ESMO 2022. Abstr LBA59

POSEIDON Clinical Trial

Updated safety

	D+T+CT (n=330)	D+CT (n=334)	CT (n=333)
All-cause AEs, n (%)			
• SAEs	146 (44.2)	135 (40.4)	117 (35.1)
• AEs leading to death	41 (12.4)	35 (10.5)	30 (9.0)
Treatment-related AEs, n (%)			
• SAEs	91 (27.6)	69 (19.5)	59 (17.7)
• AEs leading to death	11 (3.3)	7 (2.1)	8 (2.4)

ESMO 2022. Abstr LBA59

SUMMARY

POSEIDON Clinical Trial

Durvalumab plus tremelimumab and chemotherapy:

- Median overall survival of 14 months vs 11.7 months with chemotherapy alone
  - OS HR vs CT 0.75 (95% CI 0.63–0.88)
  - The rate of overall survival at 36 months was 25% vs 13.6%
- OS benefit with triplet vs CT appeared more pronounced in patients with NSQ (than SQ) histology
  - NSQ OS HR 0.68; 95% CI 0.55–0.85
- Improved overall survival benefit observed compared with chemotherapy alone in lung cancers associated with mutations that are considered more difficult to treat: STK11, KEAP1, and KRAS

Durvalumab plus chemotherapy

- Median overall survival of 13.3 months vs 11.7 months with chemotherapy alone
  - OS HR vs CT 0.84 (95% CI 0.71–0.99)
  - The rate of overall survival at 36 months was 20.7% vs 13.6%

- There were no new safety signals observed in the long-term follow-up of SAEs

ESMO 2022. Abstr LBA59

POSEIDON Clinical Trial

Durvalumab plus tremelimumab and chemotherapy is a first-line treatment option for metastatic NSCLC

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung 1 • CheckMate-9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreaK100/101 • EXCLAIM • ALTA-1L

cornerstone specialty network™

CLINICAL QUESTION

KRYSTAL-1 Clinical Trial

Does adagrasib provide clinical benefit for patients with *KRAS G12C*-mutated non-small cell lung cancer (NSCLC) after progression on 1L treatment?

*On **December 12, 2022**, the FDA granted accelerated approval to adagrasib (Krazati, Mirati Therapeutics, Inc.), a RAS GTPase family inhibitor, for adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.*

cornerstone specialty network™

KEY DATA

KRYSTAL-1 Clinical Trial

Study Design: Multi-cohort, open-label non-randomized Phase 1/2 trial

- **Phase 2 cohort**: Adults with unresectable/metastatic NSCLC harboring KRASG12C mutation
- Previously treated with PD-1/PD-L1 inhibitor in combination or sequence with platinum-based CT
- Treated, stable CNS mets permitted
- ECOG PS 0/1

(N = 116)

- **Phase 1b cohort**: active, untreated CNS mets (N=25)

Adagrasib
600-mg capsules BID
in fasted state

Until PD, unacceptable toxicity, consent withdrawal, or death; therapy could continue beyond PD if deriving clinical benefit per investigator

Phase 2 cohort
Primary efficacy endpoint: objective response per BICR
Secondary efficacy endpoints: DCR, DoR, PFS, OS, 1-yr survival rate

Phase 1b cohort
- Safety
- Intracranial and systemic activity via BICR
- Adagrasib concentration in CSF (measured when feasible)

Spira. ASCO 2022. Abstr 9002
Sabira. ASCO 2022 LBA9009

KEY DATA

KRYSTAL-1 Clinical Trial

Baseline Characteristics

Characteristic	Patients (N = 116)
Median age, yr (range)	64 (25-89)
Female, n (%)	65 (56.0)
Race, n (%)	
• White	97 (83.6)
• Black	9 (7.8)
• Asian	5 (4.3)
• American Indian or Alaskan Native	1 (0.9)
• Other	4 (3.4)
ECOG PS 1, n (%)	97 (83.6)
History of smoking, n (%)	
• Never	5 (4.3)
• Current	11 (9.5)
• Former	100 (86.2)

Characteristic, n (%)	Patients (N = 116)
No. prior lines of systemic tx	
• 1	50 (43.1)
• 2	40 (34.5)
• 3	12 (10.3)
• ≥4	14 (12.1)
Prior platinum-based tx and/or checkpoint inhibitor tx	
• Platinum-based tx only	2 (1.7)
• Both	114 (98.3)
Baseline metastases	
• Bone	46 (39.7)
• CNS	24 (20.7)
• Adrenal	22 (19.0)
• Liver	19 (16.4)

Spira. ASCO 2022. Abstr 9002
Sabira. ASCO 2022 LBA9009

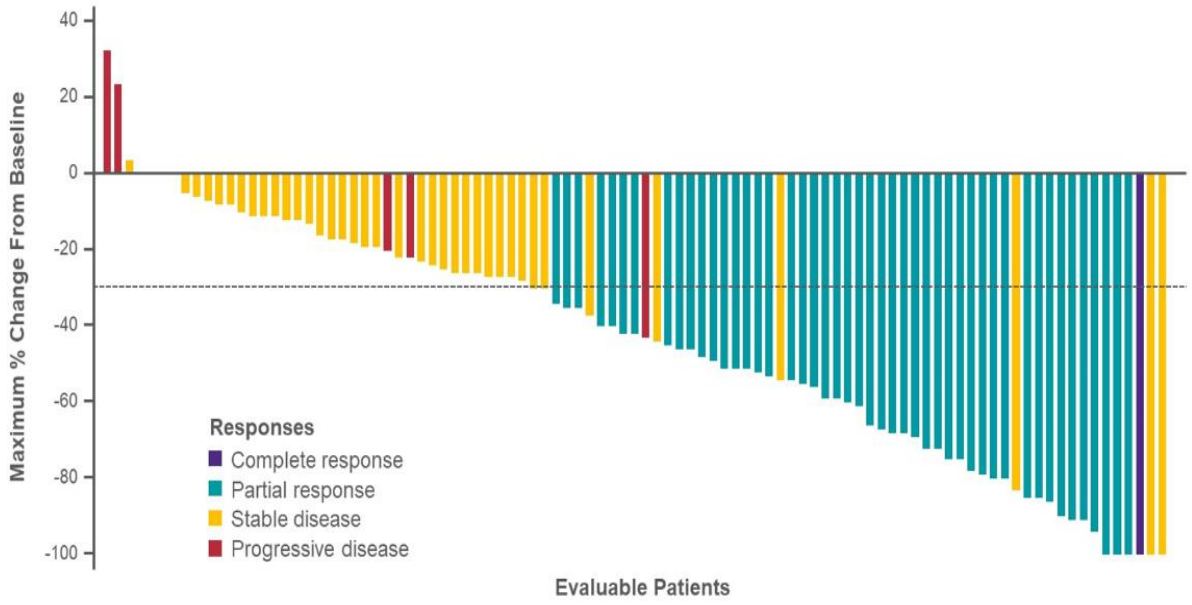
KEY DATA

KRYSTAL-1 Clinical Trial

Primary Endpoint: ORR per BICR

Outcome, n (%)	Patients With Measurable Disease at Baseline (n = 112)
Objective response rate	48 (42.9)
Best overall response	
• CR	1 (0.9)
• PR	47 (42.0)
• SD ≥6 wk	41 (36.6)
• PD	6 (5.4)
• Not evaluable	17 (5.2)
Disease Control Rate	89 (79.5)

Best tumor change from baseline



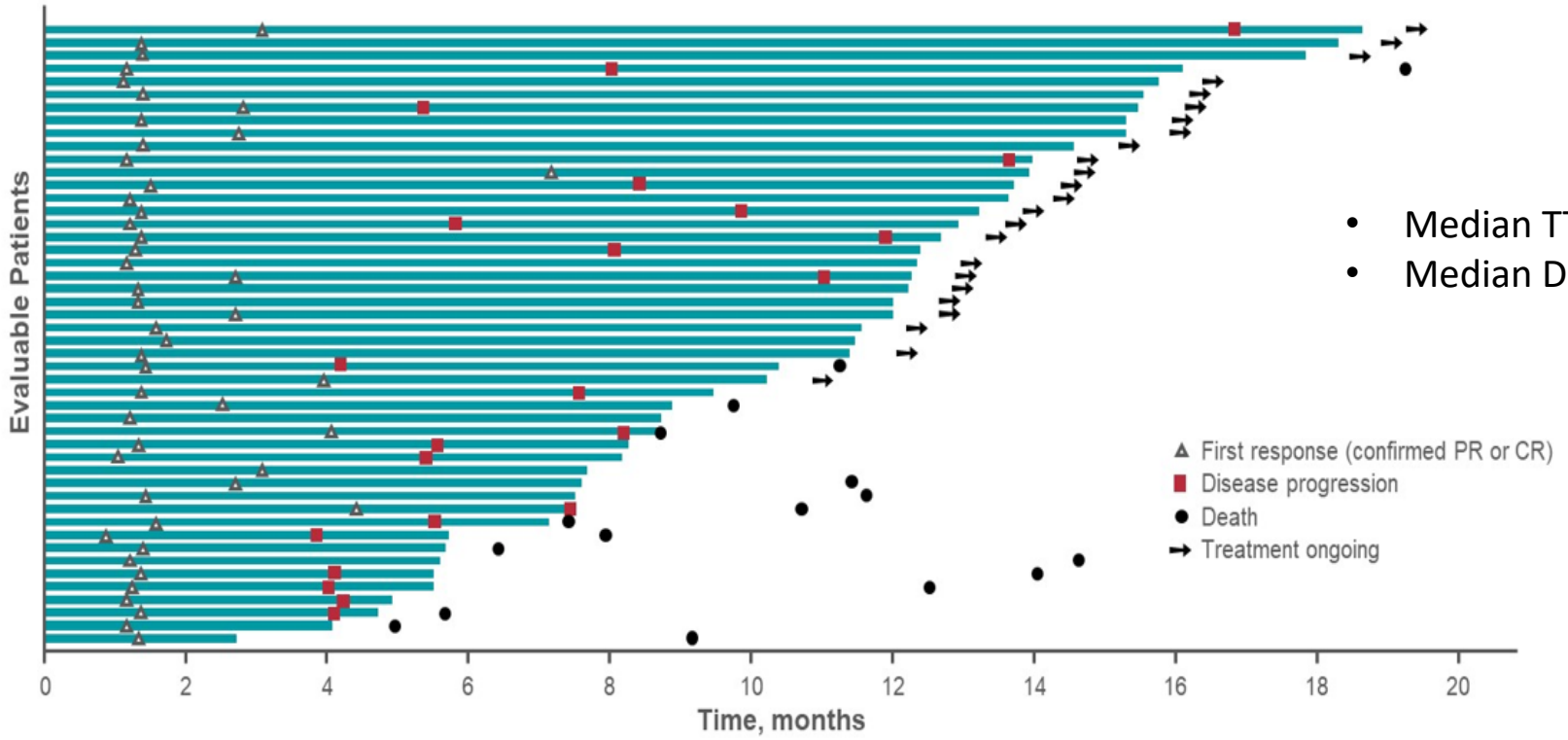
- Tumor shrinkage noted in 89 patients (79.5%)

Spira. ASCO 2022. Abstr 9002
Sabira. ASCO 2022 LBA9009

KEY DATA

KRYSTAL-1 Clinical Trial

Duration of Response



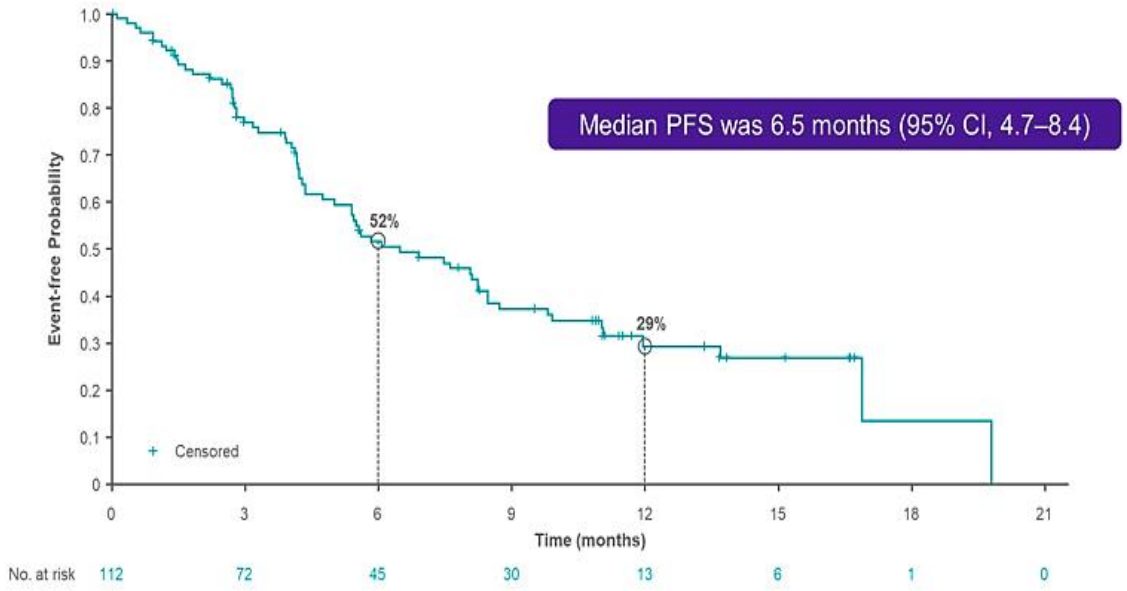
- Median TTR: 1.4 mo (range: 0.9-7.2)
- Median DoR: 8.5 mo (95% CI: 6.2-13.8)

Spira. ASCO 2022. Abstr 9002
Sabira. ASCO 2022 LBA9009

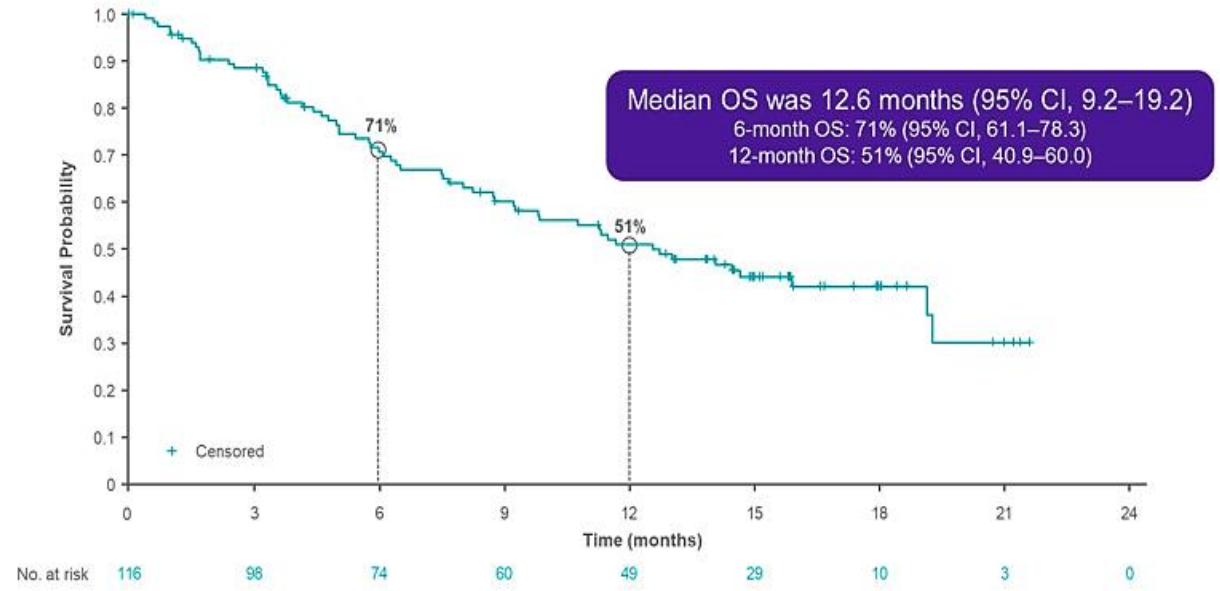
KEY DATA

KRYSTAL-1 Clinical Trial

Progression-Free Survival



Overall Survival



Spira. ASCO 2022. Abstr 9002
Sabira. ASCO 2022 LBA9009

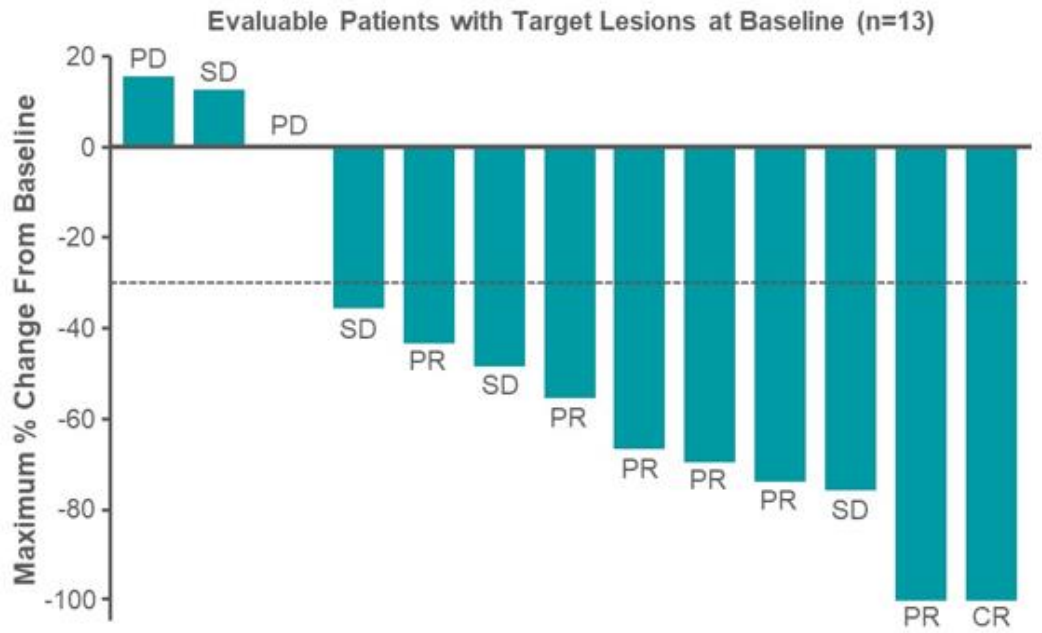
KEY DATA

KRYSTAL-1 Clinical Trial

Intracranial Response in Pts with treated, stable CNS mets

Best Overall Response	Overall (n=33)	Pts with non-target lesions only (n=19)	Pts with target lesions (n=13)
IC ORR, n (%)	**11 (33)**	**4 (21)**	**7 (54)**
• CR	5 (15)	4 (21)	1 (8)
• PR	6 (18)	-	6 (46)
• SD	17 (52)	13 (68)	4 (31)
IC DCR, n (%)	**28 (85)**	**17 (89)**	**11 (85)**

Median IC DOR was 11.2 months (95% CI 3.0 – NE)
Median IC PFS was 5.4 months (95% CI 3.3 – 11.6)



Data not shown for those with only nontarget lesions at baseline (n = 19) or not evaluable because postbaseline scan was too early (n = 1).

Most radiographically evaluable patients (81.8%) received radiation therapy prior to adagrasib

Spira. ASCO 2022. Abstr 9002
Sabira. ASCO 2022 LBA9009

KEY DATA

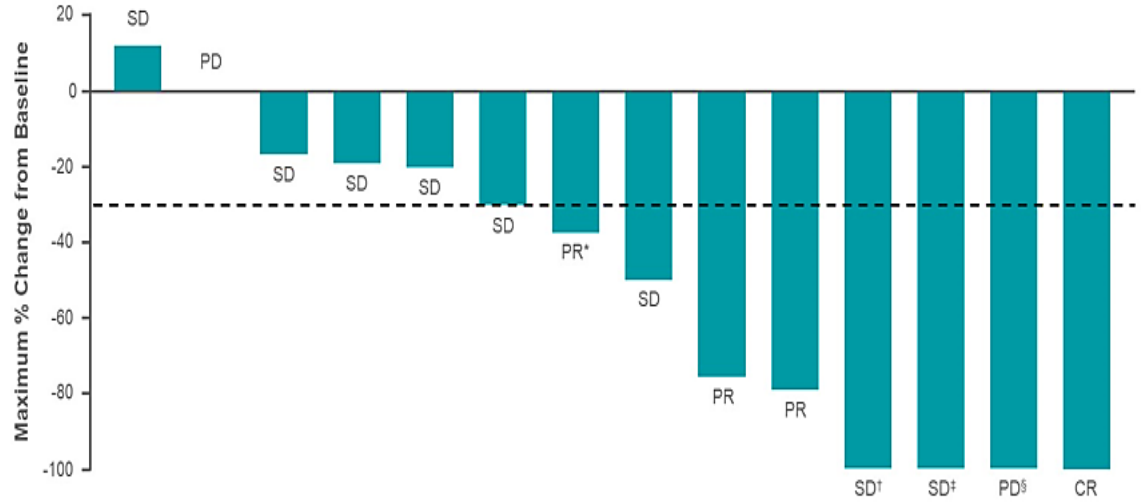
KRYSTAL-1 Clinical Trial

Phase 1b: active, untreated CNS metastases Cohort

Intracranial Response in Pts with active, untreated CNS mets

Best Overall Response	Overall (n=19)	Pts with non-target lesions only (n=4)	Pts with target lesions (n=15)
IC ORR, n (%)	**6 (32)**	**2 (50)**	**4 (27)**
• CR	3 (16)	2 (50)	1 (7)
• PR	3 (16)	0	3 (20)
• SD	10 (53)	2 (50)	8 (53)
• PD	2 (11)	0	2 (13)
• Not evaluable	1 (5)	0	1 (7)
IC DCR, n (%)	**16 (84)**	**4 (100)**	**12 (80)**

Intracranial best tumor change from baseline



Spira. ASCO 2022. Abstr 9002
Sabira. ASCO 2022 LBA9009

KEY DATA

KRYSTAL-1 Clinical Trial

Safety

TRAEs, n (%)	Patients (N = 116)		
	Any Gr	Gr 3	Gr 4
Any	113 (97.4)	47 (40.5)	3 (2.6)
Most common TRAEs (≥20%)			
• Diarrhea	73 (62.9)	1 (0.9)	0
• Nausea	72 (62.1)	5 (4.3)	0
• Vomiting	55 (47.4)	1 (0.9)	0
• Fatigue	47 (40.5)	5 (4.3)	0
• ALT increase	32 (27.6)	4 (3.4)	1 (0.9)
• Blood creatinine increase	30 (25.9)	1 (0.9)	0
• AST increase	29 (25.0)	4 (3.4)	0
• Decreased appetite	28 (24.1)	4 (3.4)	0

- There were 2 grade 5 TRAEs:
  - one cardiac failure
  - one pulmonary hemorrhage

Dose Modifications, n (%)	Patients (N = 116)
Reduction	60 (51.7)
Interruption	71 (61.2)
Discontinuation	8 (6.9)

- Most common TRAEs leading to dose modifications: GI-related events, hepatic events (increased ALT, AST), fatigue
- Among patients experiencing GI-related AEs, 94.8% occurred within first 3 cycles, and incidence decreased markedly thereafter

Spira. ASCO 2022. Abstr 9002
Sabira. ASCO 2022 LBA9009

SUMMARY

KRYSTAL-1 Clinical Trial

- Adagrasib monotherapy demonstrates promising efficacy in pretreated patients with NSCLC harboring a KRASG12C mutation
  - 43% ORR and the disease control rate was 80%
  - Median PFS was 6.5 months (95% CI, 4.7-8.4)
  - Median OS was 12.6 months (95% CI, 9.2-19.2)
  - Intracranial ORR was 33.3% (95% CI, 18.0-51.8)

- *A phase 3 study, KRYSTAL-12 (NCT04685135), is underway that will compare the effectiveness of adagrasib vs docetaxel. The primary completion date is set for August 2023.*
- *A phase 3 study, KRYSTAL-7 (NCT04613596) is underway for adagrasib in combination pembrolizumab in patients KRAS G12C mutation*

Spira. ASCO 2022. Abstr 9002
Sabira. ASCO 2022 LBA9009

KRYSTAL-1 Clinical Trial

Adagrasib provides clinical benefit in patients pretreated for KRAS G12C mutated NSCLC and provides an additional option for patients with and without brain metastases

More to come…

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung 1 • CheckMate-9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreaK100/101 • EXCLAIM • ALTA-1L

KEY DATA

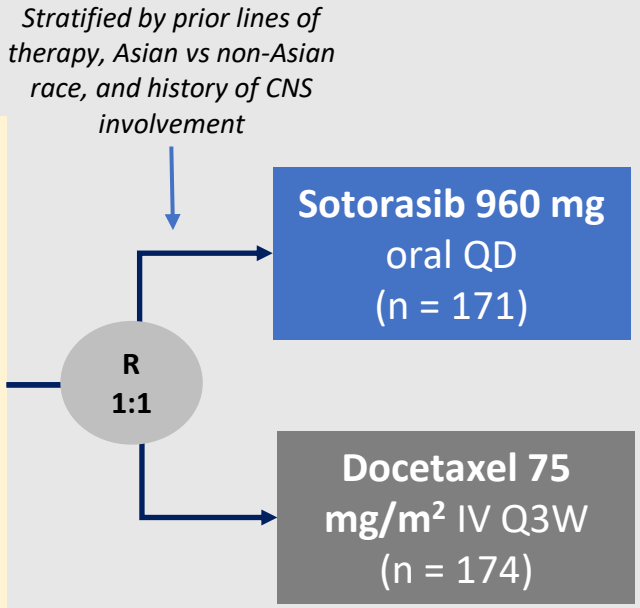
CodeBreaK200 Clinical Trial

Previously presented as part of the CSN ESMO Symposium 2022

On May 28, 2021, the Food and Drug Administration granted accelerated approval to sotorasib (Lumakras™), a RAS GTPase family inhibitor based on CodeBreaK 100, for adult patients with KRAS G12C -mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

- Patients with locally advanced/unresectable or metastatic *KRAS* G12C-mutated NSCLC
- ≥1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor
- no active brain metastases
- ECOG PS 0/1

(N = 345)



Primary endpoint: PFS by BICR

Secondary endpoints: OS†, ORR, DOR, TTR, DCR, safety/tolerability, PRO

- Modest but significant PFS improvement with sotorasib vs docetaxel in previously treated patients with *KRAS* G12C-mutated advanced NSCLC
  - Median PFS: 5.6 vs 4.5 mo (HR: 0.66; *P* = 0.002)
  - 12-mo PFS rate: 24.8% vs 10.1%
  - Benefit similar across most subgroups
- ORR (28.1% vs 13.2%, P < 0.001); but no difference in OS (not powered)
- Acceptable safety profile; fewer grade ≥3 TRAEs with sotorasib vs docetaxel
- Patient-reported outcomes more favorable for sotorasib vs docetaxel

ESMO 2022. Abstr LBA10.

CLINICAL QUESTION

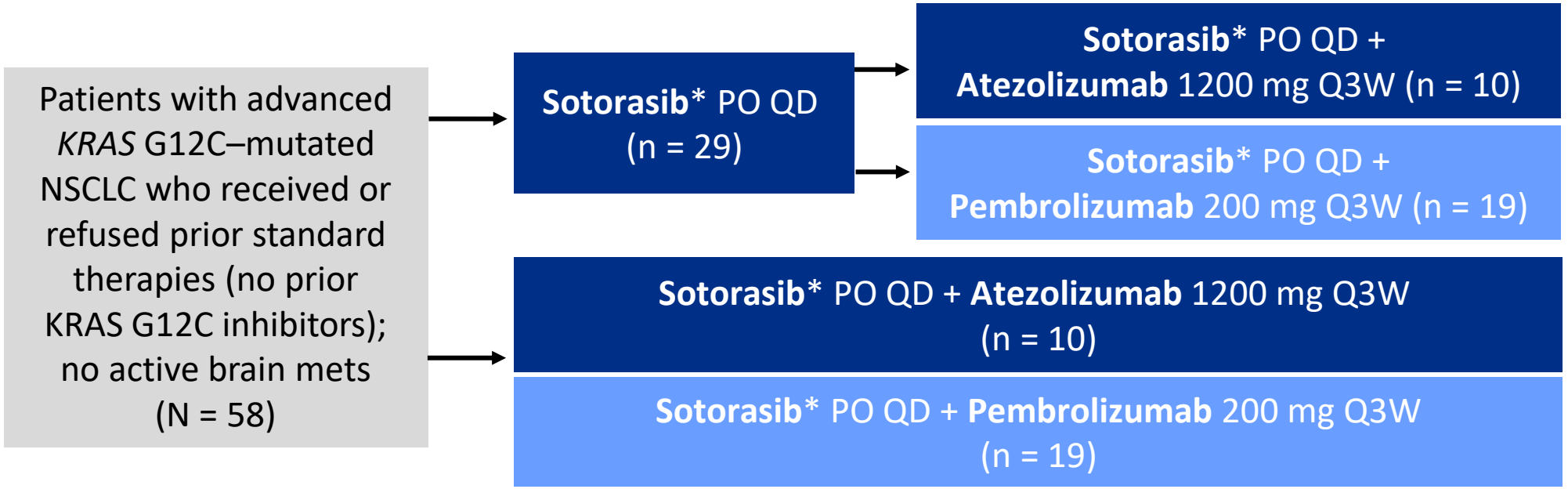
CodeBreaK100/101 Clinical Trial

Does sotorasib in combination with IO therapy provide benefit for patients with *KRAS*-mutated non-small cell lung cancer (NSCLC) as a lead in therapy?

KEY DATA

CodeBreaK100/101 Clinical Trial

Study Design: Multicenter, open-label phase Ib studies of sotorasib as monotherapy or in combination with other anticancer therapies in advanced solid tumors with KRAS G12C mutations



***Sotorasib dose exploration:** 120 mg, 240 mg, 360 mg, 720 mg, 960 mg

Primary endpoint: safety
Key secondary endpoints: ORR, DCR, DoR, PK

Median follow-up: 12.8 mo (range: 1.6-29.9)

WCLC 2022. Abstr OA03.06.

KEY DATA

CodeBreaK100/101 Clinical Trial

Baseline Characteristics

	Total (N = 58)
Median age, yr (range)	66 (29-86)
Smoking history, n (%)	54 (93)
Median prior lines of therapy, n (range)	1 (0-7)
Treated as first-line therapy, n (%)	12 (21)
Prior anti–PD-1/PD-L1, n (%)	39 (67)
▪ Prior anti–PD-1/PD-L1 as last prior line	25 (43)
ECOG PS, n (%)	
▪ 0	11 (19)
▪ 1	47 (81)

	Total (N = 58)
Brain metastasis, n (%)	18 (31)
Liver metastasis, n (%)	15 (26)
PD-L1 expression, n (%)	
▪ <1%	10 (17)
▪ 1% to 49%	16 (28)
▪ ≥50%	21 (36)
▪ Unknown	11 (19)

WCLC 2022. Abstr OA03.06.

CodeBreaK100/101 Clinical Trial

Safety by Dose of Sotorasib + Concurrent Pembro

TRAE, n (%)	Sotorasib 120 mg (n = 5)		Sotorasib 360 mg (n = 8)		Sotorasib 720 mg (n = 2)		Sotorasib 960 mg (n = 4)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
All TRAEs	5 (100)	4 (80)	7 (88)	6 (75)	2 (100)	2 (100)	3 (75)	3 (75)
Hepatotoxicity	2 (40)	2 (40)	3 (38)	2 (25)	2 (100)	2 (100)	3 (75)	3 (75)
• ALT increased	2 (40)	1 (20)	3 (38)	1 (13)	2 (100)	2 (100)	3 (75)	3 (75)
• AST increased	2 (40)	2 (40)	3 (38)	0	2 (100)	2 (100)	3 (75)	1 (25)

- Concurrent therapy resulted in higher rate of TRAEs than with either monotherapy, no grade 5 TRAEs
- Trend toward fewer liver enzyme elevations, but sample size was small
- Based on safety data for concurrent dosing, lead-in with sotorasib was considered

WCLC 2022. Abstr OA03.06.

KEY DATA

CodeBreaK100/101 Clinical Trial

Safety Summary With Lead-in vs Concurrent Sotorasib + ICI

Event	Sotorasib + Atezolizumab		Sotorasib + Pembrolizumab	
	Lead-in (n = 10)	Concurrent (n = 10)	Lead-in (n = 19)	Concurrent (n = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
• Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
• Grade 4	0	1 (10)	0	1 (5)
TRAE leading to sotorasib and/or ICI discontinuation, n (%)	1 (10)	5 (50)	6 (32)	10 (53)
Median duration of sotorasib, mo (min, max)	6.5 (1, 18)	4.4 (1, 14)	2.8 (1, 15)	4.9 (2, 30)
Median duration of combination, mo (min, max)	1.5 (0, 18)	2.5 (1, 14)	0.7 (1, 15)	2.3 (1, 9)
Median onset of grade ≥3 hepatotoxicity, days (range)	50 (28-93)	67 (36-147)	73 (45-127)	51 (29-190)

- No treatment-related deaths reported
- Sotorasib lead-in had reduced incidence of grade 3/4 TRAEs and TRAE-related discontinuation
- 88% of patients had first occurrence of grade 3/4 hepatotoxicity outside of DLT window; 97% of events resolved with corticosteroids, treatment modification, and/or discontinuation

WCLC 2022. Abstr OA03.06.

KEY DATA

CodeBreaK100/101 Clinical Trial

TRAEs With Sotorasib Lead-in + Pembrolizumab

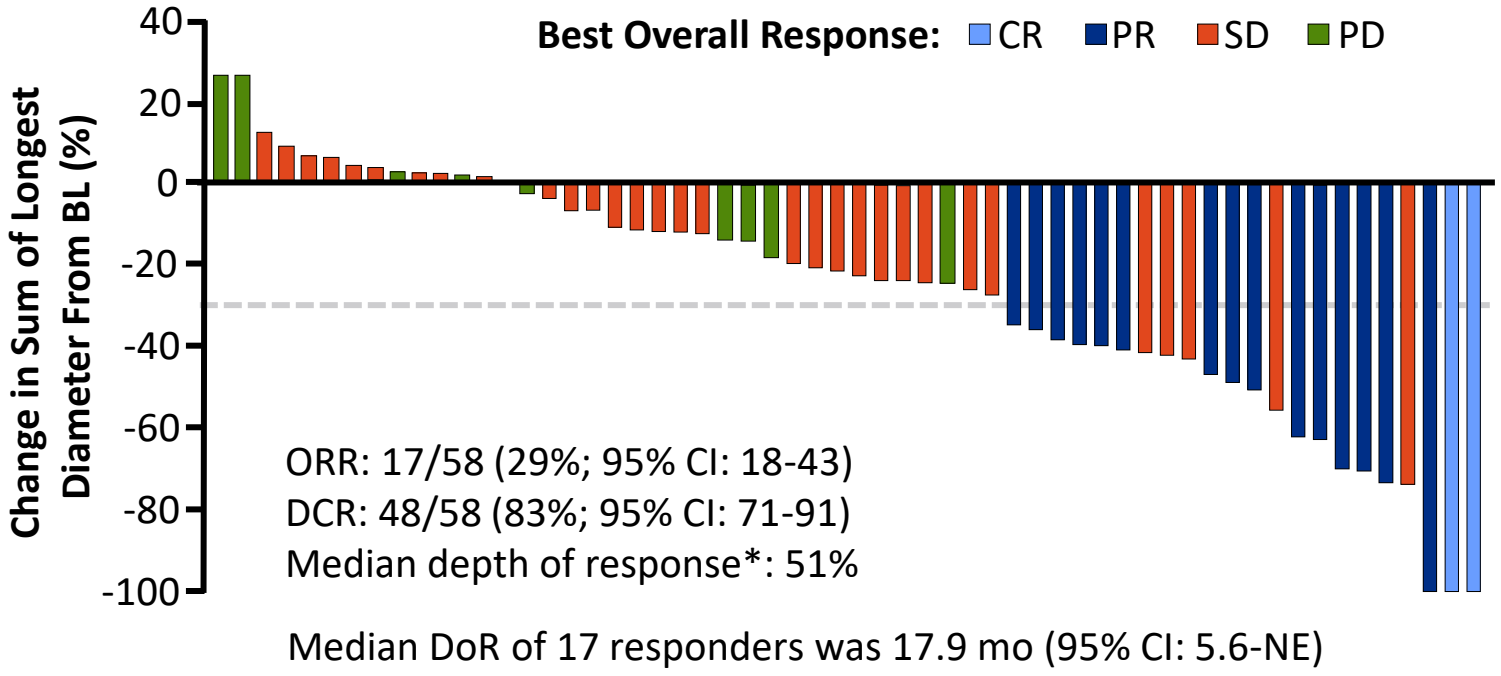
TRAE, n (%)	Sotorasib 120 mg (n = 3)		Sotorasib 240 mg (n = 5)		Sotorasib 360 mg (n = 11)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
All TRAEs	3 (100)	3 (100)	3 (60)	1 (20)	9 (82)	6 (55)
• ALT increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	3 (27)
• AST increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	2 (18)
• ALP increased	2 (67)	0	0	0	3 (27)	2 (18)
• Diarrhea	1 (33)	0	1 (20)	0	6 (55)	1 (9)
• Arthralgia	1 (33)	0	0	0	2 (18)	0
• Nausea	0	0	0	0	4 (36)	0
• Fatigue	0	0	0	0	4 (36)	0
• Hypokalemia	0	0	0	0	3 (27)	2 (18)
• Decreased appetite	0	0	0	0	3 (27)	0
• Headache	0	0	0	0	2 (18)	0
• Hepatotoxicity	2 (67)	2 (67)	2 (40)	1 (20)	6 (55)	5 (45)

WCLC 2022. Abstr OA03.06.

CodeBreaK100/101 Clinical Trial

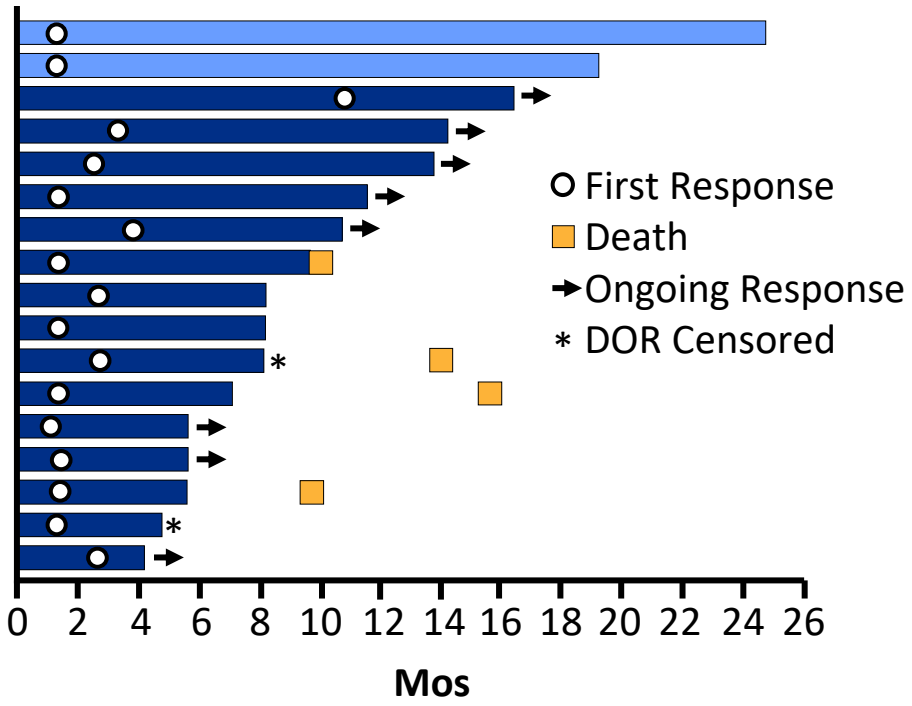
TRAEs With Sotorasib Lead-in + Pembrolizumab

Response



Median DoR of 17 responders was 17.9 mo (95% CI: 5.6-NE)

Duration of Response

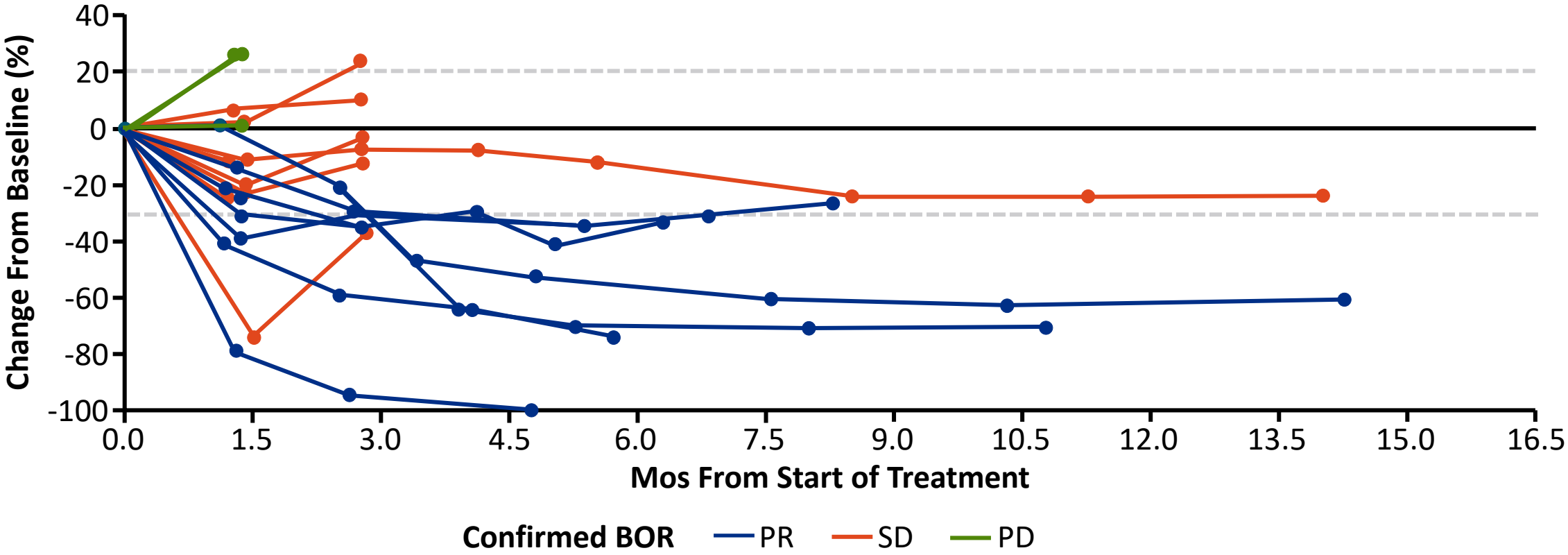


WCLC 2022. Abstr OA03.06.

KEY DATA

CodeBreaK100/101 Clinical Trial

Change in Tumor Burden in Sotorasib Lead-in + Pembrolizumab Cohort

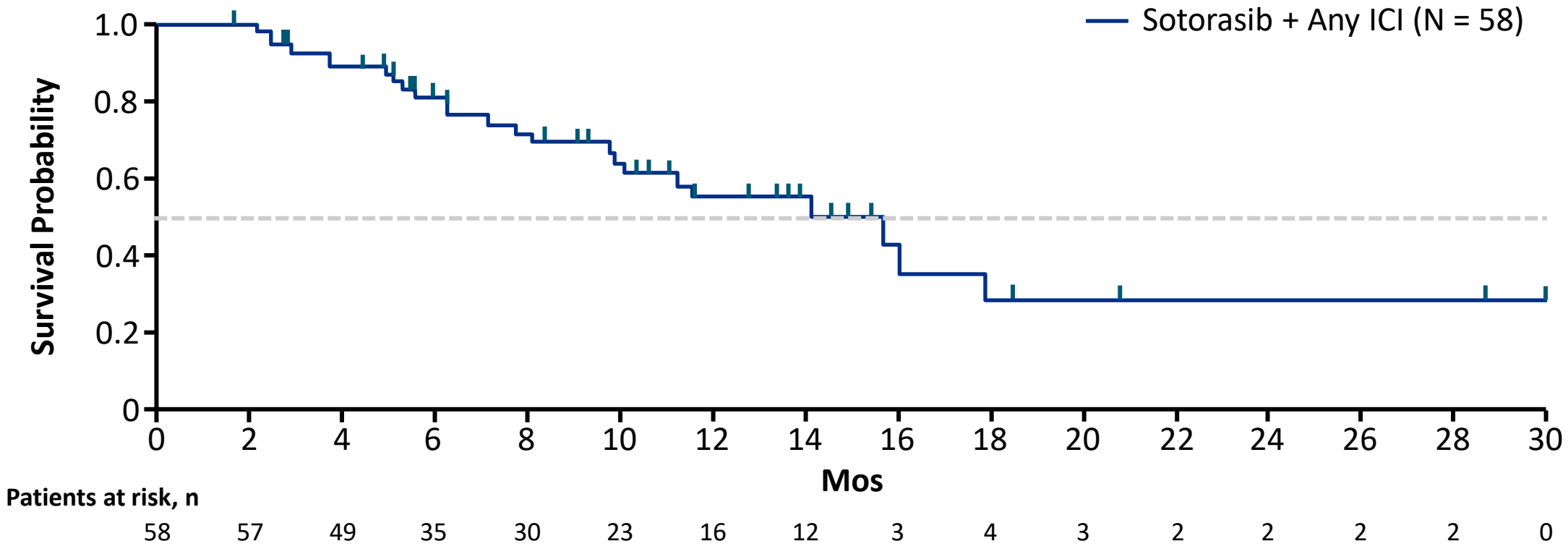


WCLC 2022. Abstr OA03.06.

KEY DATA

CodeBreaK100/101 Clinical Trial

Overall Survival across all cohorts



WCLC 2022. Abstr OA03.06.

SUMMARY

CodeBreaK100/101 Clinical Trial

- Sotorasib plus atezolizumab or pembrolizumab showed promising efficacy but resulted in high incidence of grade ≥3 TRAEs
  - Hepatotoxicity most common grade ≥3 TRAE; median onset of 50-73 d that resolved with corticosteroids and/or treatment modifications/discontinuation
  - Other grade ≥3 TRAEs were uncommon and included diarrhea and hypokalemia

- Sotorasib lead-in reduced incidence of grade ≥3 TRAEs and TRAEs leading to discontinuation vs concurrent administration

- ORR with combination of sotorasib + atezolizumab or pembrolizumab was 29% and DCR 83% across all cohorts; median DoR: 17.9 mo (95% CI: 5.6-NE)

WCLC 2022. Abstr OA03.06.

CodeBreaK100/101 Clinical Trial

Sotorasib in combination with IO therapy reveals promising benefit and relatively low rates of toxicity with a lead-in dosing strategy

More to come…

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung 1 • CheckMate-9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreak100/101 • EXCLAIM • ALTA-1L

CLINICAL QUESTION

EXCLAIM Clinical Trial

Does mobocertinib provide benefit for patients with *EGFR exon 20 insertion-positive metastatic* non-small cell lung cancer (NSCLC) after progression on platinum-based chemotherapy?

On September 15, 2021, the Food and Drug Administration granted accelerated approval to mobocertinib (Exkivity, Takeda Pharmaceuticals, Inc.) for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

cornerstone specialty network™

KEY DATA

EXCLAIM Clinical Trial

Study Design: 3-part, non-randomized, open-label, phase 1/2 clinical trial

Part 1

Phase 1 dose escalation:

3 + 3 design

- Advanced NSCLC
- ECOG PS<2

Part 2

Phase 2 expansion:

Mobocertinib 160 mg QD

Primary endpoint:

- ORR by RECIST v1.1

Secondary endpoints:

- Safety, tolerability, PK, efficacy

Cohort 1: prior platinum n=22

Refractory EGFR ex 20 ins; no active measurable CNS metastases

Cohort 2: refractory HER2 exon 20 insertions or point mut; no active measurable CNS metastases

Cohort 3: refractory EGFR or HER2 exon 20 insertions or pointt mut; with measurable CNS metastases

Cohort 4: treatment naïve or refractory; other EFGR muts: +/- T790M, uncommon EGFR

Cohort 5: refractory HER2 exon 20 insertions with prior response to EGFR TKI

Cohort 6: Treatment naïve EGFR exon 20 insertions

Cohort 7: Refractory other tumor types (non-NSCLC) with EGFR/HER2 mutations

Part 3: EXCLAIM

Extension cohort: n=96 (prior platinum; n=86)

Previously treated patients with EGFR exon 20 insertions

Conducted between June 2016 and November 2020 (data cutoff date)

JAMA Oncol. 2022 September 15; 8(9): 1359.
ESMO 2022 Abstr 988P

KEY DATA

EXCLAIM Clinical Trial

Baseline Characteristics

Characteristic, n (%)	No (%) PPP cohort (n=114)	EXCLAIM cohort (n=96)
Age, median (range), y	60 (27-84)	59 (27-80)
Sex, Female	75 (66)	62 (65)
Race		
• Asian	68 (60)	66 (69)
• Black or African American	3 (3)	2 (2)
• White	42 (37)	28 (29)
• Not reported	1(1)	0
Ethnicity		
• Hispanic or Latino	113 (99)	95 (99)
Histology Type		
• Adenocarcinoma	112 (98)	95 (99)
• Squamous	1 (1)	1 (1)
• Large cell	1 (1)	0
Baseline brain metastases	40 (35)	33 (34)

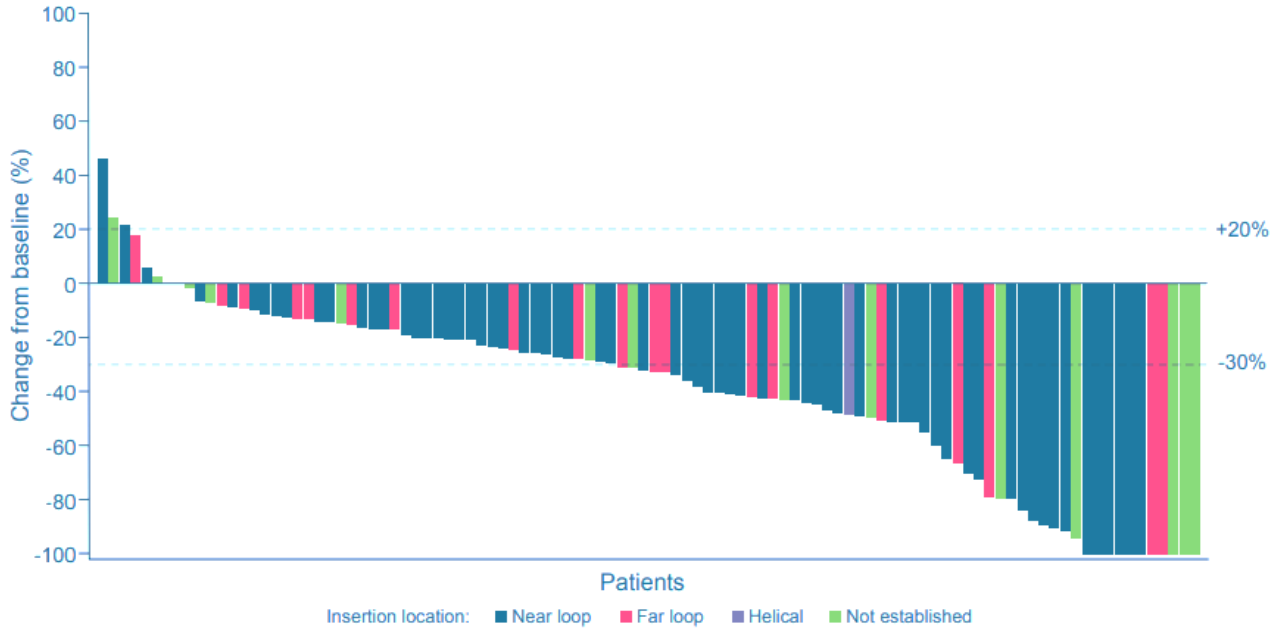
Characteristic, n (%)	No (%) PPP cohort (n=114)	EXCLAIM cohort (n=96)
ECOG status		
• 0	29 (25)	28 (29)
• 1	85 (75)	68 (71)
Smoking history		
• Never	81 (71)	70 (73)
• Former	31 (27)	24 (25)
• Current	2 (2)	2 (2)
# of prior therapies		
• 1	47 (41)	49 (51)
• 2	36 (32)	30 (31)
• 3	31 (27)	27 (18)
Platinum-based chemo	114 (100)	86 (90)
Immunotherapy	49 (43)	33 (34)
EGFR TKI	29 (25)	30 (31)

JAMA Oncol. 2022 September 15; 8(9): 1359.
ESMO 2022 Abstr 988P

KEY DATA

EXCLAIM Clinical Trial

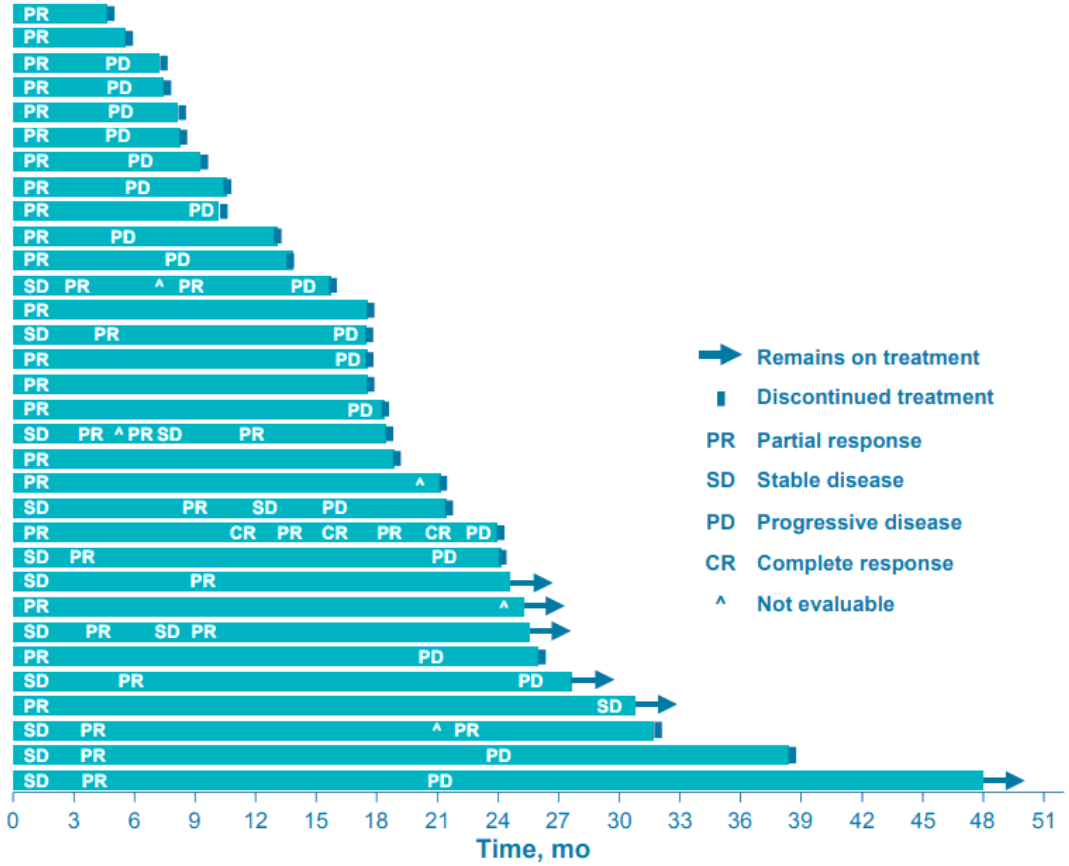
Best percentage change in target lesions



Data cutoff date: November 1, 2021

[a] Includes patients with measurable disease who have at least 1 post-baseline assessment.

Objective response by time on treatment



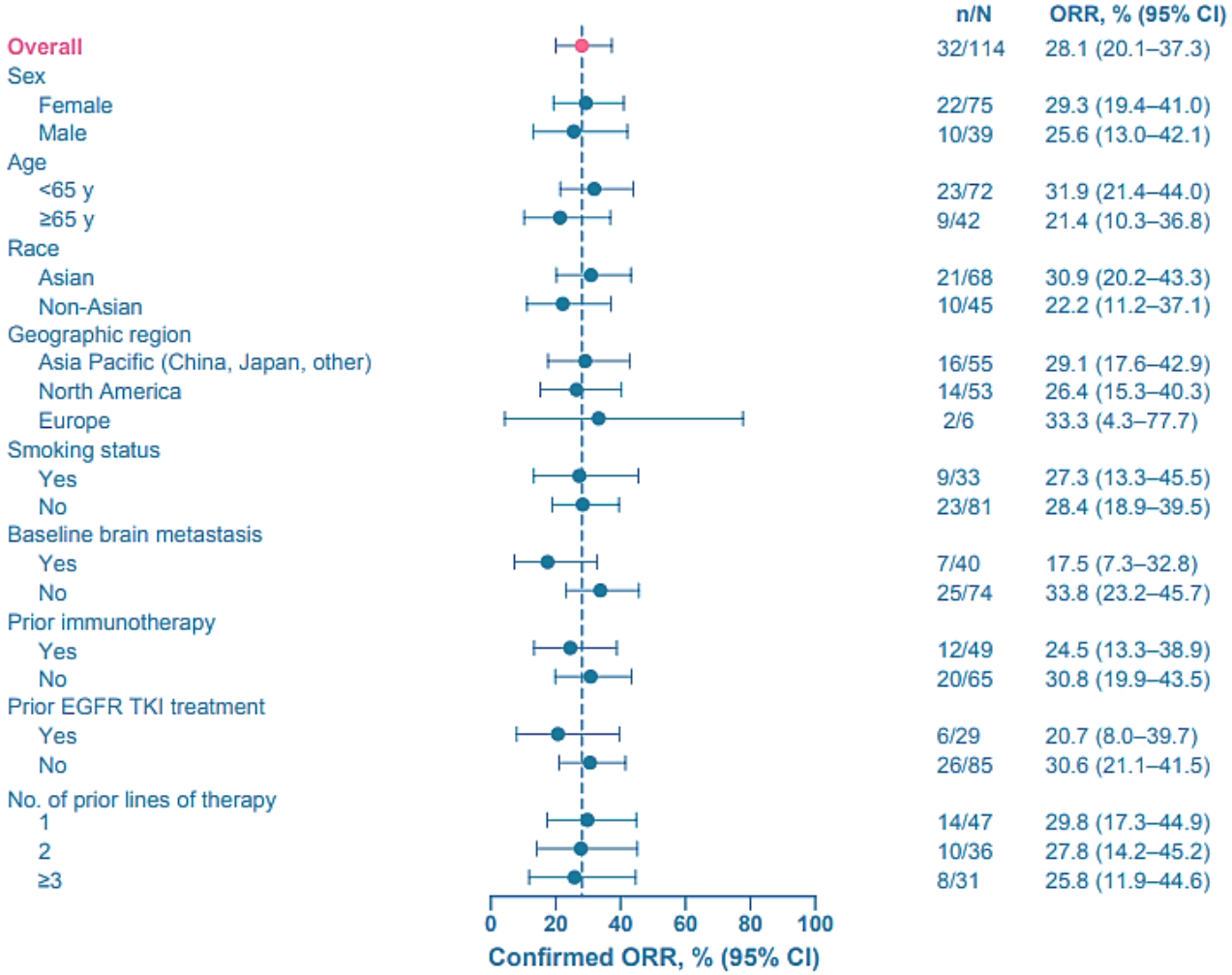
Data cutoff date: November 1, 2021

JAMA Oncol. 2022 September 15; 8(9): 1359.
ESMO 2022 Abstr 988P

KEY DATA

EXCLAIM Clinical Trial

Efficacy by subgroups

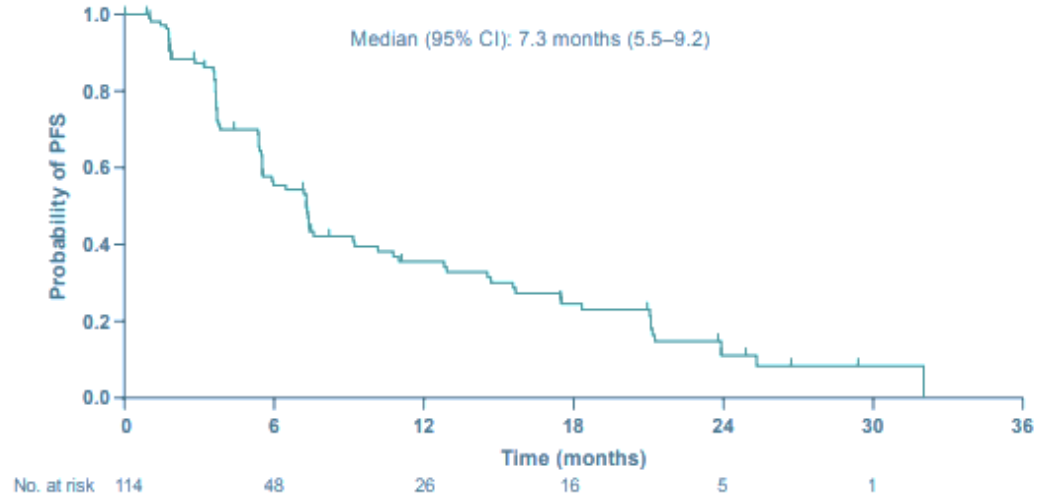


JAMA Oncol. 2022 September 15; 8(9): 1359.
ESMO 2022 Abstr 988P

KEY DATA

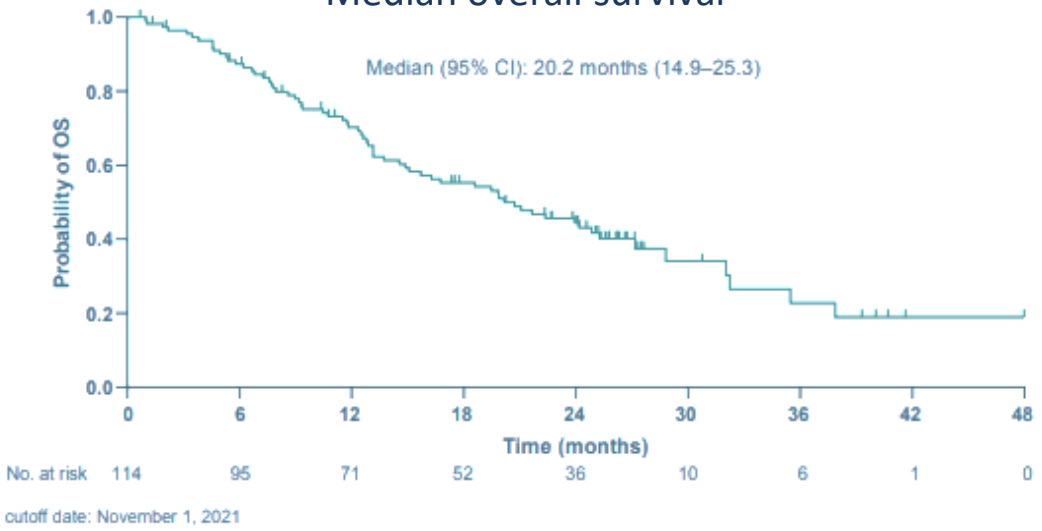
EXCLAIM Clinical Trial

Median progression-free survival



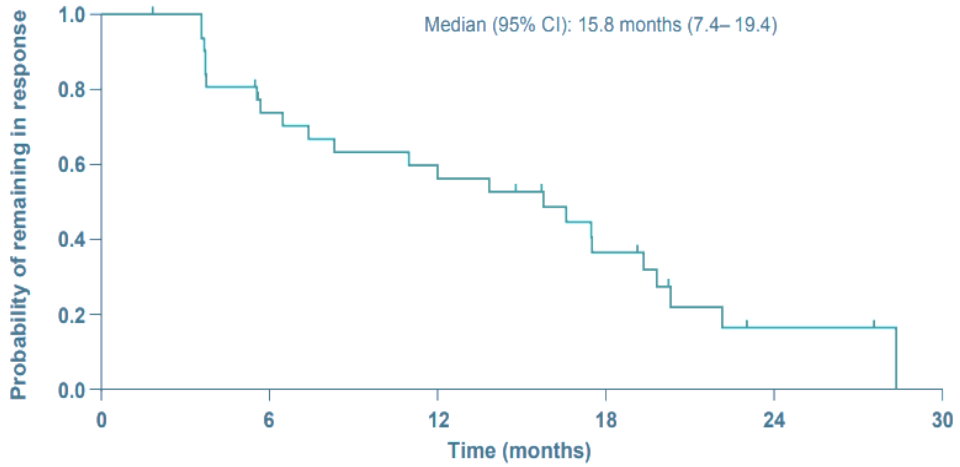
B

Median overall survival



Data cutoff date: November 1, 2021

Median duration of response



Data cutoff date: November 1, 2021

JAMA Oncol. 2022 September 15; 8(9): 1359.
ESMO 2022 Abstr 988P

KEY DATA

EXCLAIM Clinical Trial

Safety

Adverse events, n (%)	No (%) PPP cohort (n=114)		EXCLAIM cohort (n=96)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	114 (100)	79 (69)	96 (100)	63 (66)
Any treatment-related	113 (99)	54 (47)	95 (99)	40 (42)
Serious	56 (49)	52 (46)	45 (47)	42 (44)
Leading to dose reduction	29 (25)	---	21 (22)	---
Leading to treatment discontinuation	19 (17)	---	10 (10)	---

JAMA Oncol. 2022 September 15; 8(9): 1359.
ESMO 2022 Abstr 988P

SUMMARY

EXCLAIM Clinical Trial

- Treatment with mobocertinib provided clinical benefit to patients that were platinum pretreated with exon 20 insertion-positive mNSCLC (cohort 1 and the EXCLAIM study)
  - Confirmed ORR was 28% per IRC and 35% per investigators in the PPP cohort
  - DCR was 78% ; median DoR was 15.8 months; median PFS was 7.3 months; median OS was 20.2 months

- The safety profile was manageable and consistent with the known profile for EGFR TKIs

The EXCLAIM-2 Clinical Study is an investigational study testing the safety and effectiveness of an investigational medication versus platinum-based chemotherapy for patients with non-small cell lung cancer (NSCLC) with tumors that are positive for an EGFR exon 20 insertion mutation who have not yet been treated

JAMA Oncol. 2022 September 15; 8(9): 1359.
ESMO 2022 Abstr 988P

EXCLAIM Clinical Trial

Mobocertinib provides benefit and an additional treatment option for patients with NSCLC EGFR exon 20 insertions

Testing of patients is critical

More to come…

Key Studies

(Neo)Adjuvant NSCLC	Metastatic NSCLC and Actionable NSCLC	Targeted Therapy in NSCLC
• ADAURA • CheckMate-816 • NADIM II • KEYNOTE-091	• EMPOWER-Lung 1 • CheckMate-9LA • CheckMate-227 • POSEIDON	• KRYSTAL-1 • CodeBreaK100/101 • EXCLAIM • ALTA-1L

ALTA-1L Clinical Trial

Does brigatinib provide benefit for patients with ALK inhibitor-naïve advanced ALK-positive non-small cell lung cancer (NSCLC)?

Final analysis

On May 22, 2020, the Food and Drug Administration approved brigatinib (ALUNBRIG, Takeda) for adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.

cornerstone specialty network™

KEY DATA

ALTA-1L Clinical Trial

Study Design: randomized, open-label, phase 3, multicenter, international study

Stratified by the presence or absence of baseline brain metastases and completion of at least one full cycle of chemotherapy for locally advanced or metastatic disease (yes or no)

- Patients aged 18 years or older with locally advanced or metastatic NSCLC who had not received ALK-targeted therapy
- Asymptomatic or stable central nervous system (CNS) metastases were permitted

Brigatinib 180 mg once daily (with 7- d lead-in at 90 mg once daily)

Crizotinib 250 mg twice daily

Until PD, intolerable toxicity, or another discontinuation criterion

Patients in the crizotinib arm could cross over to brigatinib after BIRC-assessed progression (after 10-d washout from crizotinib)

Primary Endpoint: PFS by BIRC

Secondary Endpoints: BIRC-assessed confirmed objective response rate (ORR), confirmed intracranial ORR, intracranial PFS, overall survival (OS), duration of response, safety, and change from baseline in GHS/QoL (per EORTC QLQ-C30)

Exploratory end points included BIRC-assessed PFS and confirmed ORR on brigatinib in patients who crossed over after BIRC-confirmed disease progression on crizotinib, and relationship between PFS and AUC. Investigator assessments of PFS were also analyzed.

Journal of Thoracic Oncology Vol. 16 No. 12: 2091–2108

KEY DATA

ALTA-1L Clinical Trial

Baseline Characteristics

Characteristic, n (%)	Brigatinib	Crizotinib	Total
Age, median, range	58 (27-86)	60 (28-89)	59 (27-89)
Sex, female	69 (50)	81 (59)	150 (55)
Race			
• Non-Asian	78 (57)	89 (64)	167 (61)
• Asian	59 (43)	49 (36)	108 (39)
ECOG PS			
• 0 or 1	131 (96)	132 (96)	263 (96)
• 2	6 (4)	6 (4)	12 (4)
History of tobacco use			
• Never	84 (61)	75 (54)	159 (58)
• Former	49 (36)	56 (41)	105 (38)
• Current	4 (3)	7 (5)	11 (4)
Stage of disease at trial entry			
• IIIB	8 (6)	12 (9)	20 (7)
• IV	129 (94)	126 (91)	255 (93)

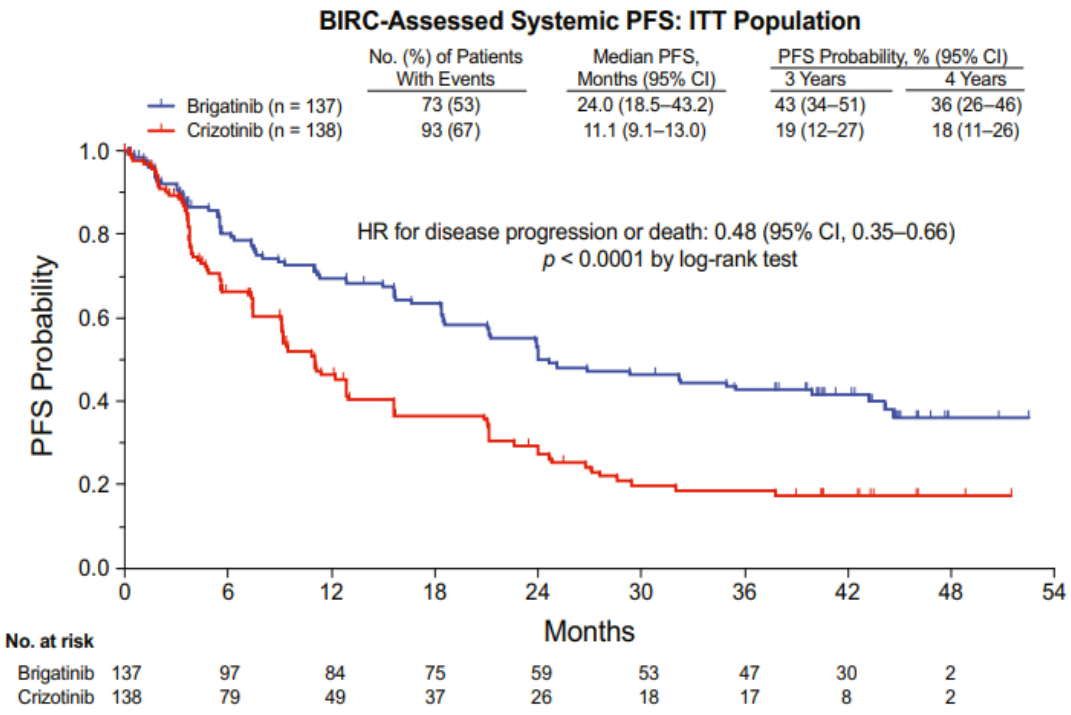
Characteristic, n (%)	Brigatinib	Crizotinib	Total
Histologic type			
• Adenocarcinoma	126 (92)	137 (99)	263 (96)
• Adenosquamous carcinoma	3 (2)	1 (1)	4 (1)
• Squamous cell carcinoma	4 (3)	0	4 (1)
• Large cell carcinoma	2 (1)	0	2 (1)
• Other	2(1)	0	2 (1)
ALK status	123 (90)	112 (81)	235 (85)
Brain Mets	40 (29)	41 (30)	81 (29)
Prior RT to brain	18 (13)	19 (14)	37 (13)
Prior chemotherapy	36 (26)	37 (27)	73 (27)

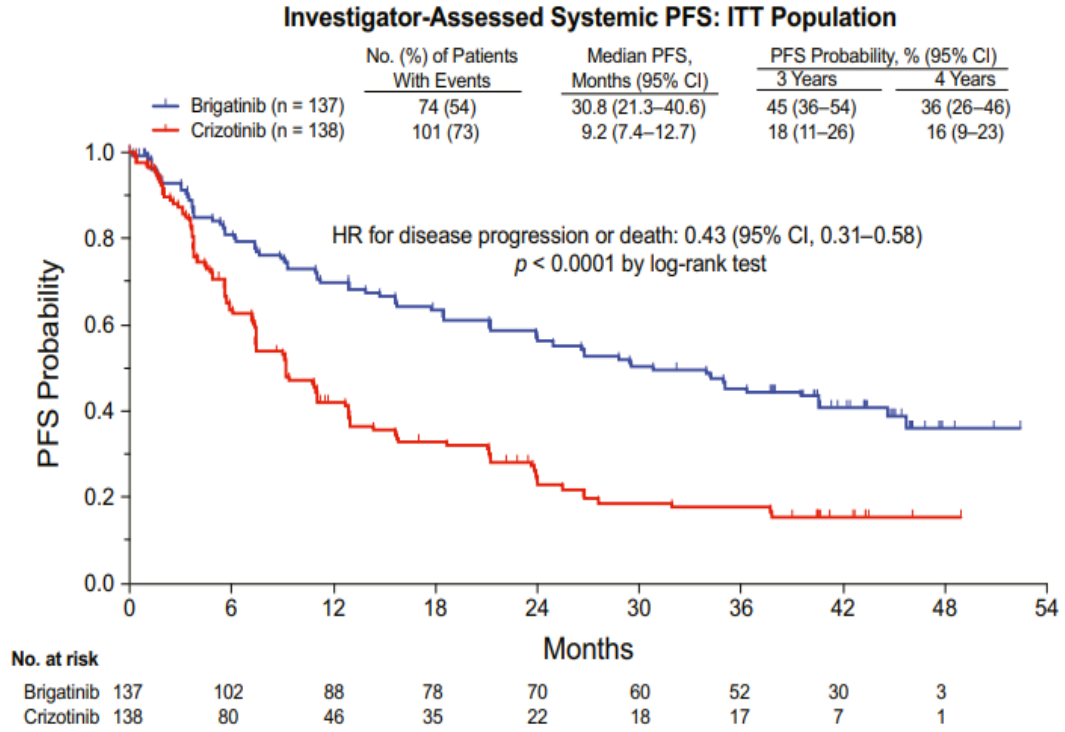
N Engl J Med 2018; 379:2027-2039
Journal of Thoracic Oncology Vol. 16 No. 12: 2091–2108

KEY DATA

ALTA-1L Clinical Trial

Primary Endpoint: PFS





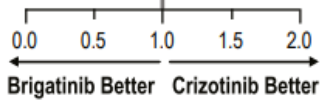
Journal of Thoracic Oncology Vol. 16 No. 12: 2091–2108

KEY DATA

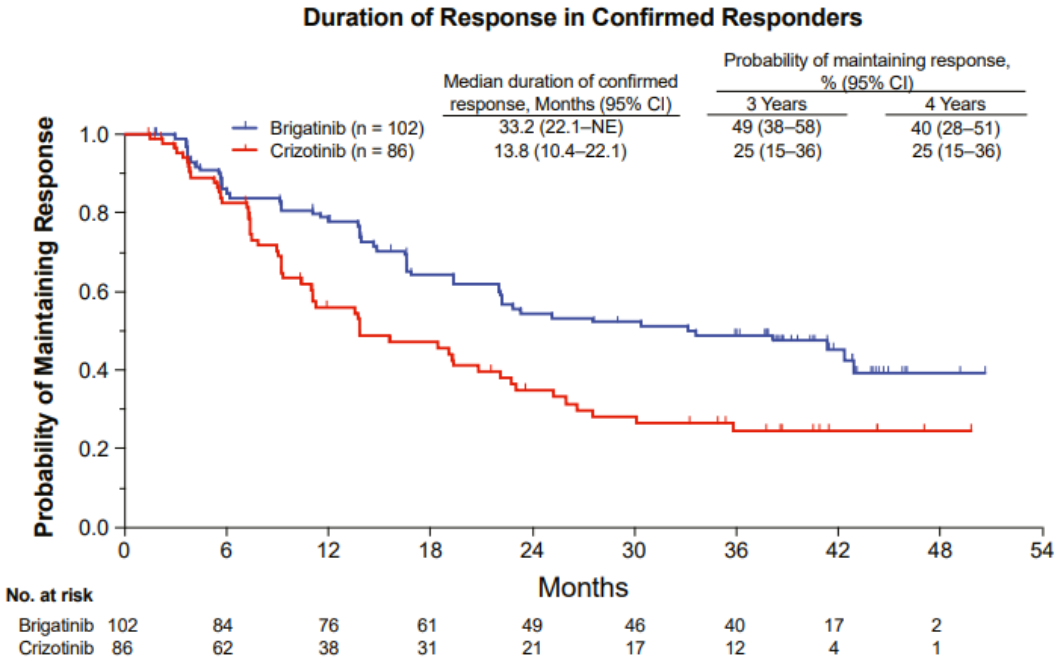
ALTA-1L Clinical Trial

PFS by subgroup

Subgroup		No. of Patients Brigatinib/Crizotinib	HR for Disease Progression or Death (95% CI)
Overall		137/138	0.48 (0.35—0.66)
Age	18 to 64 years	93/95	0.42 (0.29—0.63)
	≥65 years	44/43	0.58 (0.33—1.01)
Sex	Female	69/81	0.47 (0.30—0.73)
	Male	68/57	0.48 (0.30—0.75)
Race	Non-Asian	78/89	0.56 (0.38—0.84)
	Asian	59/49	0.35 (0.20—0.59)
Smoking status[a]	Never smoker	84/75	0.43 (0.28—0.65)
	Former smoker	50/56	0.48 (0.29—0.80)
ECOG perfomance status[b]	0	54/53	0.25 (0.13—0.48)
	1	76/78	0.54 (0.37—0.79)
Brain metastases at baseline[c]	Yes	40/41	0.25 (0.14—0.46)
	No	97/97	0.62 (0.43—0.91)
Prior chemotherapy[d]	Yes	36/37	0.45 (0.24—0.83)
	No	101/101	0.50 (0.35—0.73)



Duration of Response



Journal of Thoracic Oncology Vol. 16 No. 12: 2091–2108

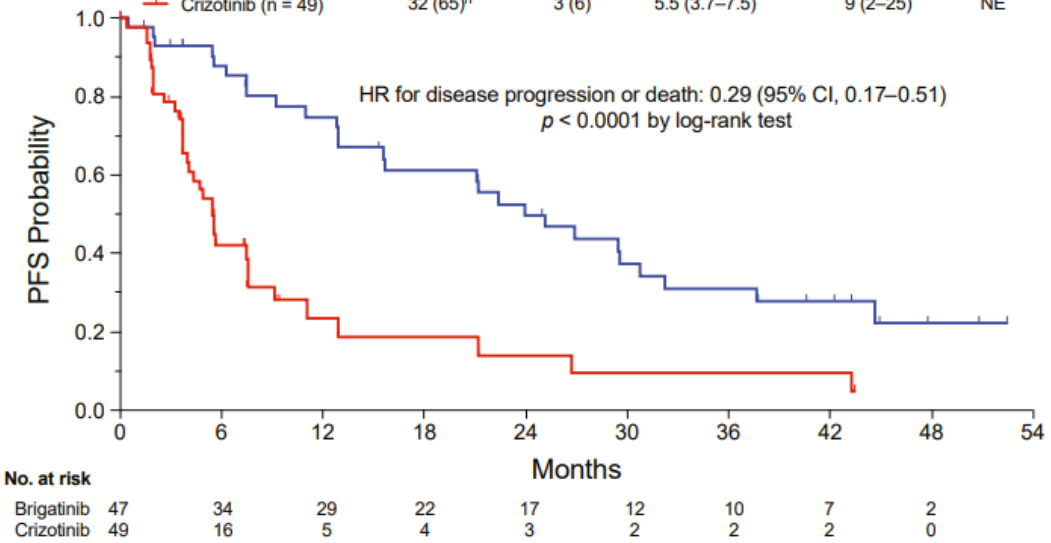
KEY DATA

ALTA-1L Clinical Trial

Intracranial PFS

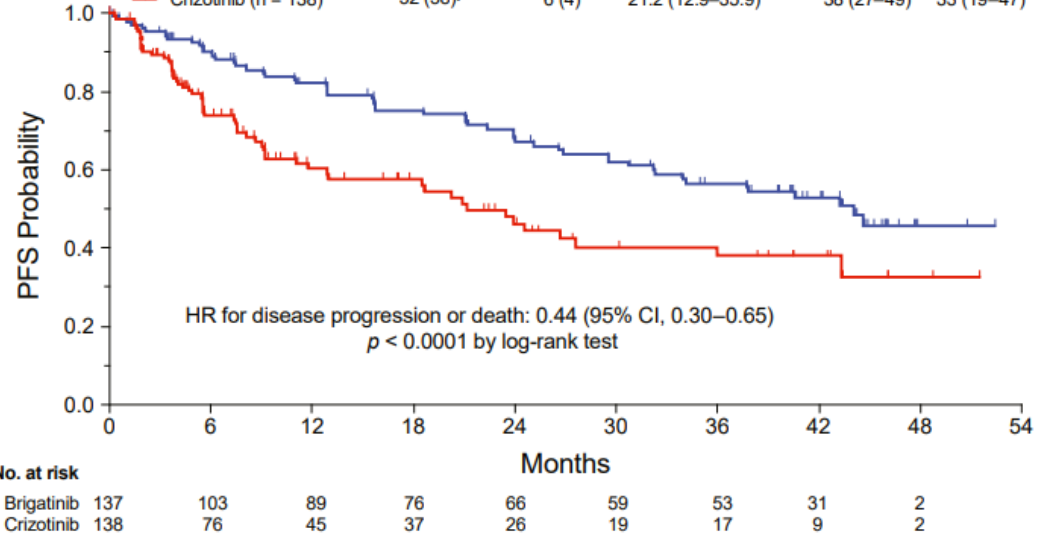
BIRC[e]-Assessed Intracranial PFS: Patients With Brain Metastases at Baseline[f]

	No. (%) of Patients With Events		Median Intracranial PFS, Months (95% CI)	Intracranial PFS Probability, % (95% CI)	
	Intracranial Progression	Death		3 Years	4 Years
Brigatinib (n = 47)	27 (57)[g]	0	24.0 (12.9–30.8)	31 (17–47)	22 (9–39)
Crizotinib (n = 49)	32 (65)[h]	3 (6)	5.5 (3.7–7.5)	9 (2–25)	NE



BIRC[e]-Assessed Intracranial PFS: ITT Population

	No. (%) of Patients With Events		Median Intracranial PFS, Months (95% CI)	Intracranial PFS Probability, % (95% CI)	
	Intracranial Progression	Death		3 Years	4 Years
Brigatinib (n = 137)	41 (30)[i]	11 (8)	44.1 (32.2–NE)	56 (47–66)	46 (34–57)
Crizotinib (n = 138)	52 (38)[i]	6 (4)	21.2 (12.9–35.9)	38 (27–49)	33 (19–47)

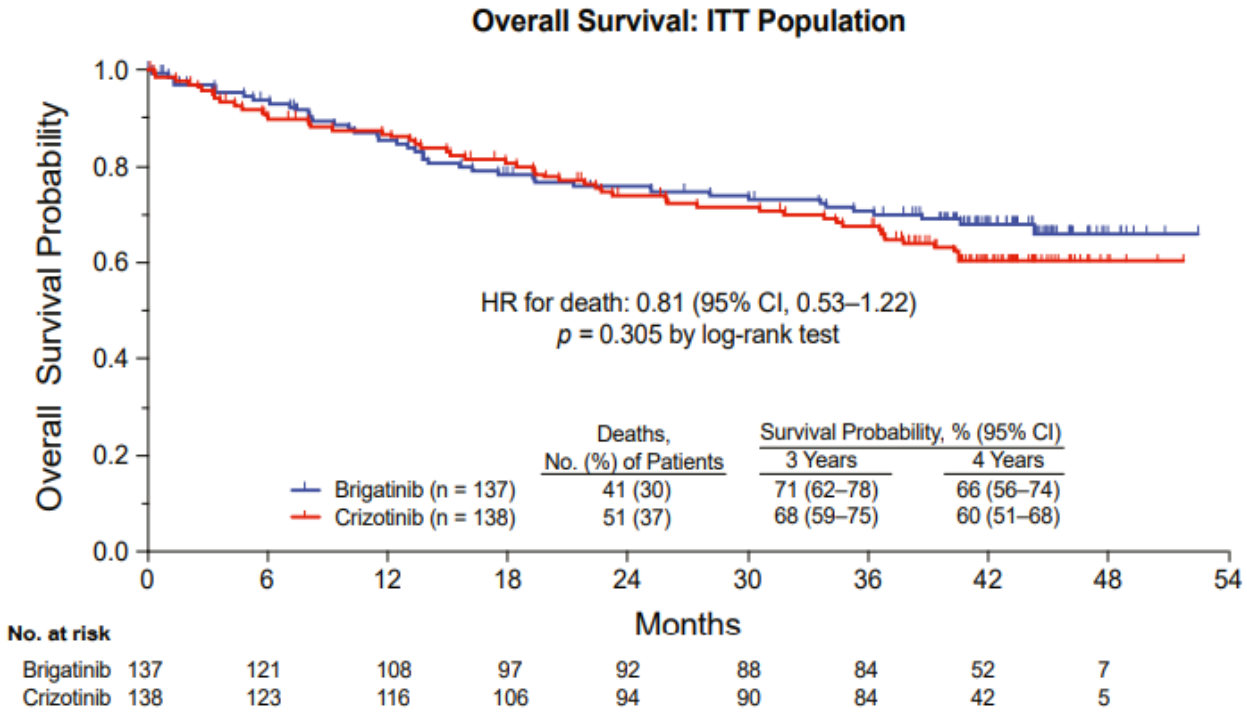


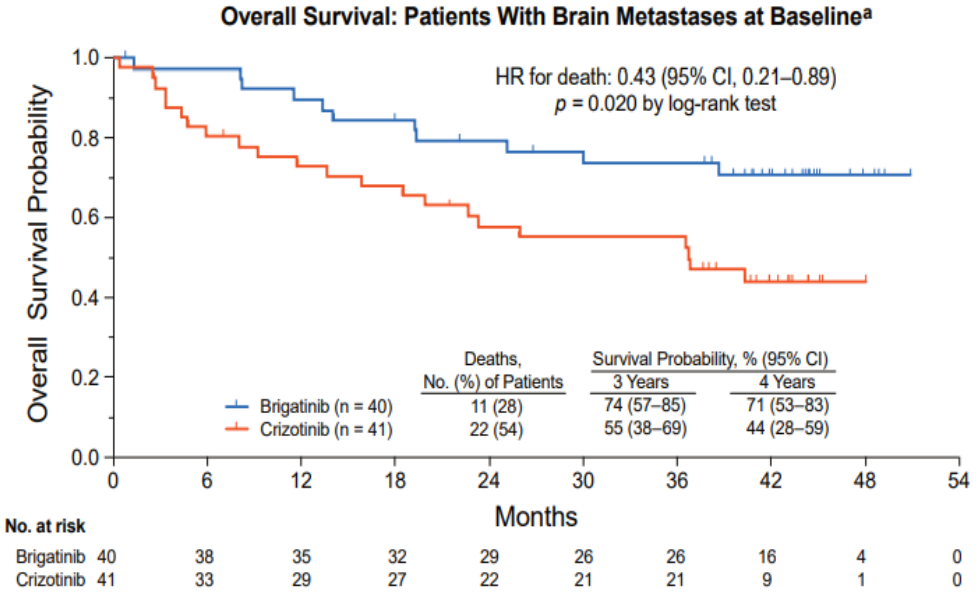
Journal of Thoracic Oncology Vol. 16 No. 12: 2091–2108

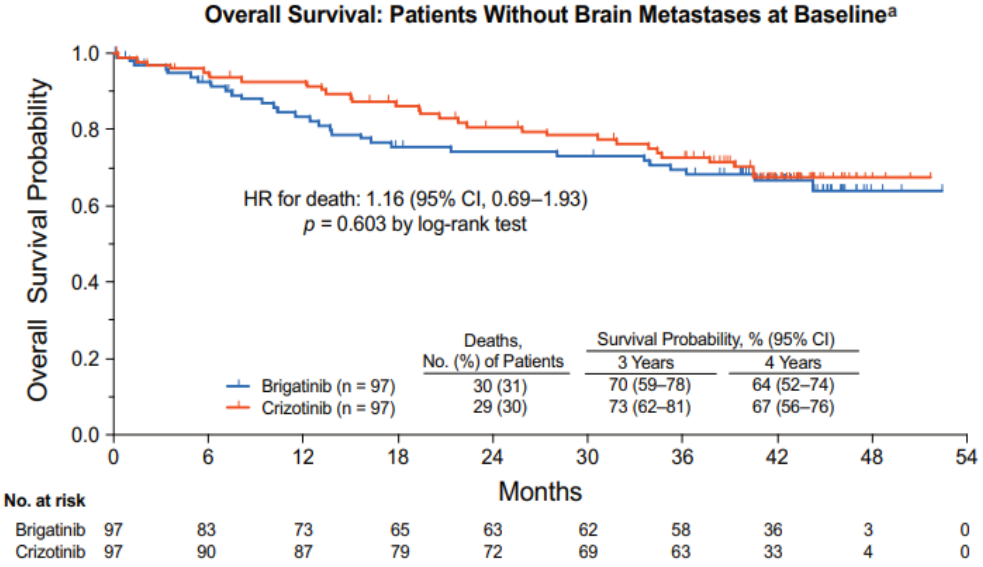
KEY DATA

ALTA-1L Clinical Trial

Overall Survival







Journal of Thoracic Oncology Vol. 16 No. 12: 2091–2108

KEY DATA

ALTA-1L Clinical Trial

Safety

Patients with 1 event, n (%)	Brigatinib (n = 136)	Crizotinib (n = 137)
Any-grade adverse	136 (100)	137 (100)
Grade 3-4 adverse event	95 (70)	77 (56)
Adverse events leading to death (grade 5)	11 (8)	11 (8)
Treatment-related	0	0
Adverse event leading to treatment discontinuation	18 (13)	12 (9)
Adverse event leading to dose reduction	60 (44)	34 (25)
Adverse event leading to dose interruption	98 (72)	65 (47)

Journal of Thoracic Oncology Vol. 16 No. 12: 2091–2108

SUMMARY

ALTA-1L Clinical Trial

- In the final analysis, with longer follow-up, brigatinib continued to exhibit superior efficacy and tolerability versus crizotinib in patients with or without brain metastases

- Brigatinib showed consistent superiority in progression-free survival (PFS) versus crizotinib

Journal of Thoracic Oncology Vol. 16 No. 12: 2091–2108

ALTA-1L Clinical Trial

Brigatinib provides clinical benefit and an alternative option for patients with ALK inhibitor-naïve advanced ALK-positive NSCLC