Lung cancer update
ASCO 2024

Christian Rolfo, MD, PhD, MBA, Dr.hc.
Professor of Medicine
Director Division Medical Oncology
Associate Director for Early Phase Clinical Trials

The James

THE OHIO STATE UNIVERSITY
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Disclosures

- Advisory Board: AstraZeneca, Daiichi Sankyo, Regeneron and Novocure; Bristol-Myers Squibb (BMS), Novartis, Invitae, Guardant Health,COR2ED, Bayer, Boehringer Ingelheim, Abbvie, Invitae, Janssen, EMD Serono
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- Scientific advisory board member of Imagene
- Leadership roles: in International Society of Liquid Biopsy, The European School of Oncology, International Association for Study of Lung Cancer, and Oncology Latin American Association.
- Editor role: Editor in chief of CROH and Honorary editor at Journal of Liquid Biopsy Elsevier. Editorial board Lung Cancer and ILCN (IASLC).

Agenda

- **Early (resectable) NSCLC**

  Adjuvant/Neoadjuvant IO ± CT; TKIs ± CT

- **Locally advanced inoperable NSCLC EGFRmut**

  CT/RT -> osimertinib

- **Metastatic NSCLC non-oncogene-addicted**

  1ª linea: ivonescimab

  2ª linea: Dato-DXd

- **Advanced NSCLC oncogene-addicted**

  EGFRmut: osimertinib + CT o amivantamab

  EGFRex20ins: amivantamab, nuovi TKIs, combo

  ALK/ROS1/MET: lorlatinib e nuovi TKIs

  HER2mut: Trastuzumab DXt e nuovi TKIs

  KRAS G12Cmut: nuovi TKIs e combo

- **SCLC**

  LS: CT-RT -> durvalumab

NSCLC

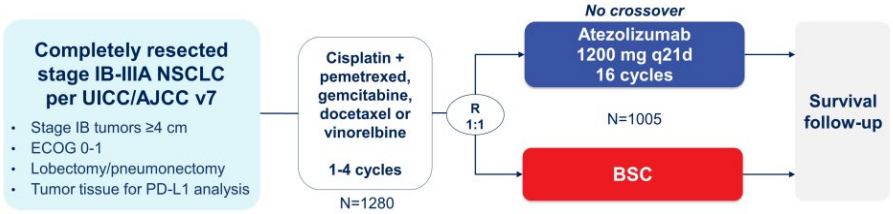
Adjuvant

Phase III adjuvant IO clinical trials

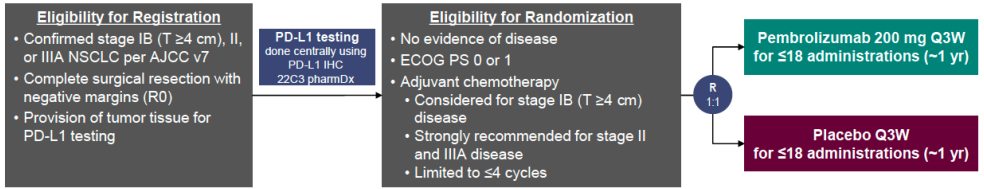
ClinicalTrials.gov ID	Drug	Setting	N	Endpoint
NCT02595944 ANVIL	Nivolumab	Adjuvant, Stage IB–IIIA, resected NSCLC	714	OS
NCT02486718 IMpower010	Atezolizumab	Adjuvant, Stage IB–IIIA, resected NSCLC	1127	DFS
NCT02504372 PEARLS	Pembrolizumab	Adjuvant, Stage IB–IIIA resected NSCLC	1380	DFS
NCT02273375 BR31	Durvalumab	Adjuvant, Stage IB–IIIA, completely resected, PD-L1-positive NSCLC	1100	DFS

Three major randomized phase 3 trials evaluated single agent IO

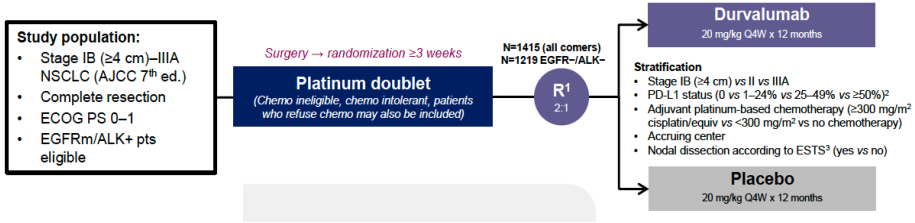
IMpower010



PEARLS/KEYNOTE-091



CCTG BR.31



Same primary endpoint (DFS) ..but

Impower 010 (Atezolizumab/ BSC)

Randomization 1:1

Hierarchical statistical testing

- DFS in PDL1 ≥ 1%, stage II-IIIA
- *Secondary endpoint: DFS in PDL1 ≥ 50%* stage II- IIIA

KEYNOTE 091 (Pembrolizumab/Placebo)

Randomization 1:1

Dual Primary endpoints

- DFS in overall population
- DFS in PDL1 ≥ 50%

CCTG BR.31(Durvalumab/ Placebo)

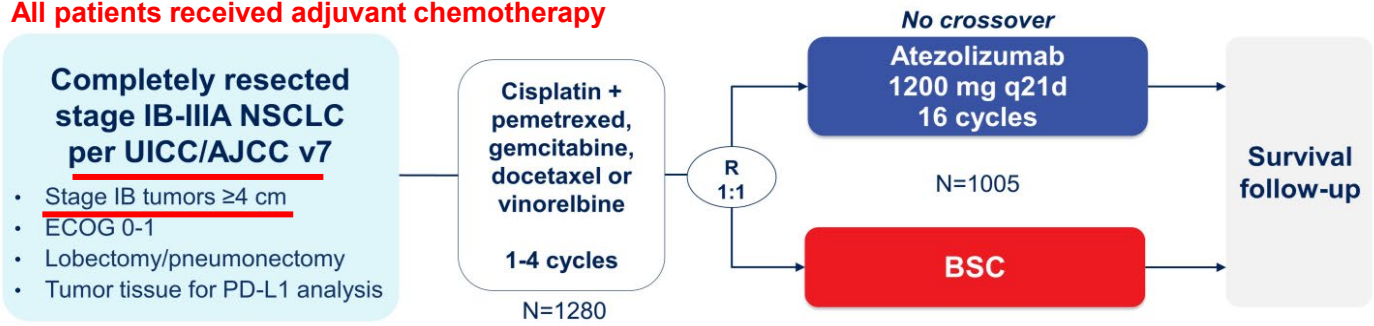
Randomization 2:1

Hierarchical procedure

- DFS in PDL1 ≥ 25%, EGFR/ALK-

IMpower 010: trial design

All patients received adjuvant chemotherapy



Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

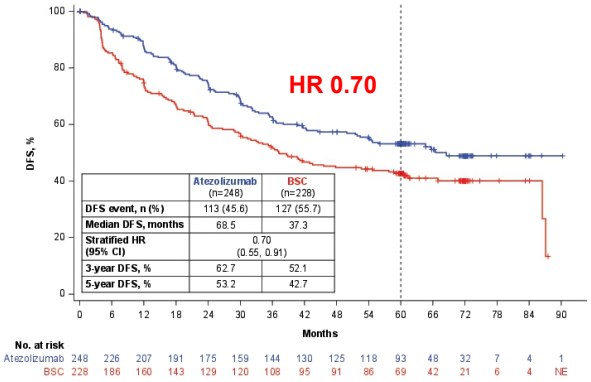
Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  2. All-randomized stage II-IIIA population
  3. ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

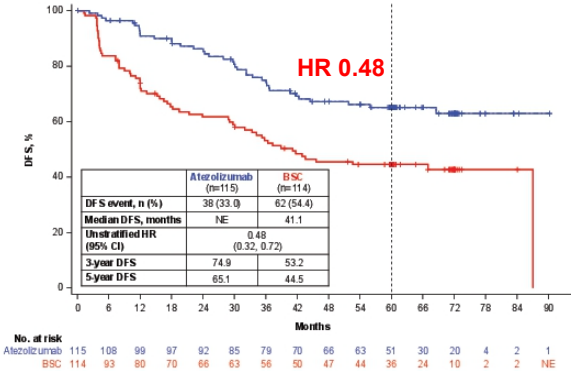
IMpower010: 5-yr follow-up data - DFS

DFS stage II-III, PD-L1 ≥1%



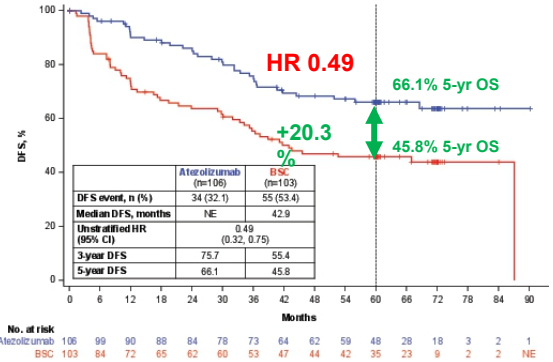
	Atezolizumab (n=248)	BSC (n=228)
DFS event, n (%)	113 (45.6)	127 (55.7)
Median DFS, months	68.5	37.3
Stratified HR (95% CI)	0.70 (0.55, 0.91)	
3-year DFS, %	62.7	52.1
5-year DFS, %	53.2	42.7

DFS stage II-III, PD-L1 ≥50%



	Atezolizumab (n=115)	BSC (n=114)
DFS event, n (%)	38 (33.0)	62 (54.4)
Median DFS, months	NE	41.1
Unstratified HR (95% CI)	0.48 (0.32, 0.72)	
3-year DFS	74.9	53.2
5-year DFS	65.1	44.5

DFS stage II-III, PD-L1 ≥50% EGFR/ALK WT

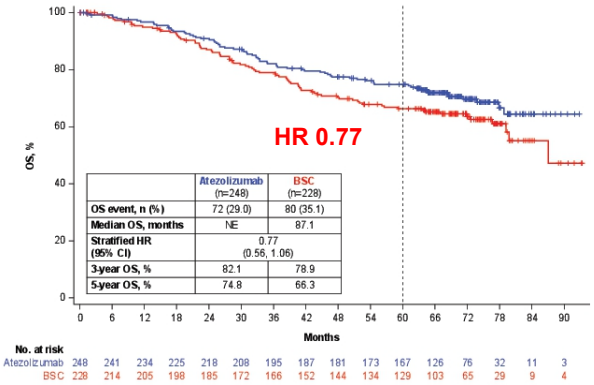


	Atezolizumab (n=106)	BSC (n=103)
DFS event, n (%)	34 (32.1)	55 (53.4)
Median DFS, months	NE	42.9
Unstratified HR (95% CI)	0.49 (0.32, 0.75)	
3-year DFS	75.7	55.4
5-year DFS	66.1	45.8

Wakelee H, et al. ASCO 2024

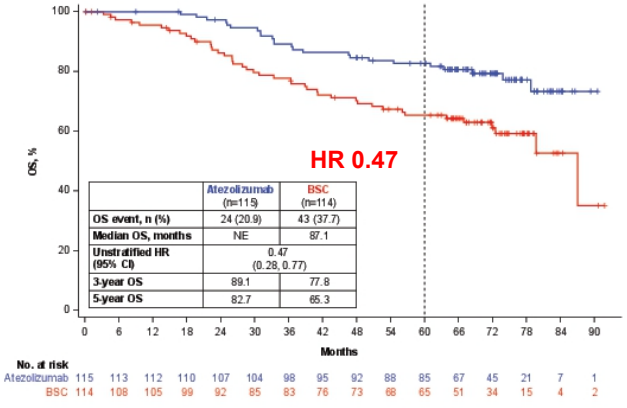
IMpower010: 5-yr follow-up data - OS

OS stage II-III, PD-L1 ≥1%



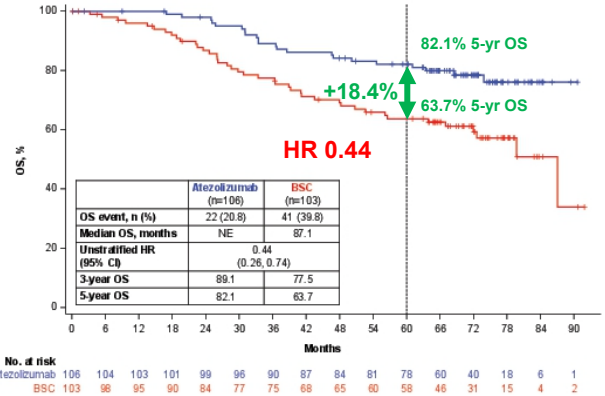
	Atezolizumab (n=248)	BSC (n=228)
OS event, n (%)	72 (29.0)	80 (35.1)
Median OS, months	NE	87.1
Stratified HR (95% CI)	0.77 (0.56, 1.06)	
3-year OS, %	82.1	78.9
5-year OS, %	74.8	66.3

OS stage II-III, PD-L1 ≥50%



	Atezolizumab (n=115)	BSC (n=114)
OS event, n (%)	24 (20.9)	43 (37.7)
Median OS, months	NE	87.1
Unstratified HR (95% CI)	0.47 (0.28, 0.77)	
3-year OS	89.1	77.8
5-year OS	82.7	65.3

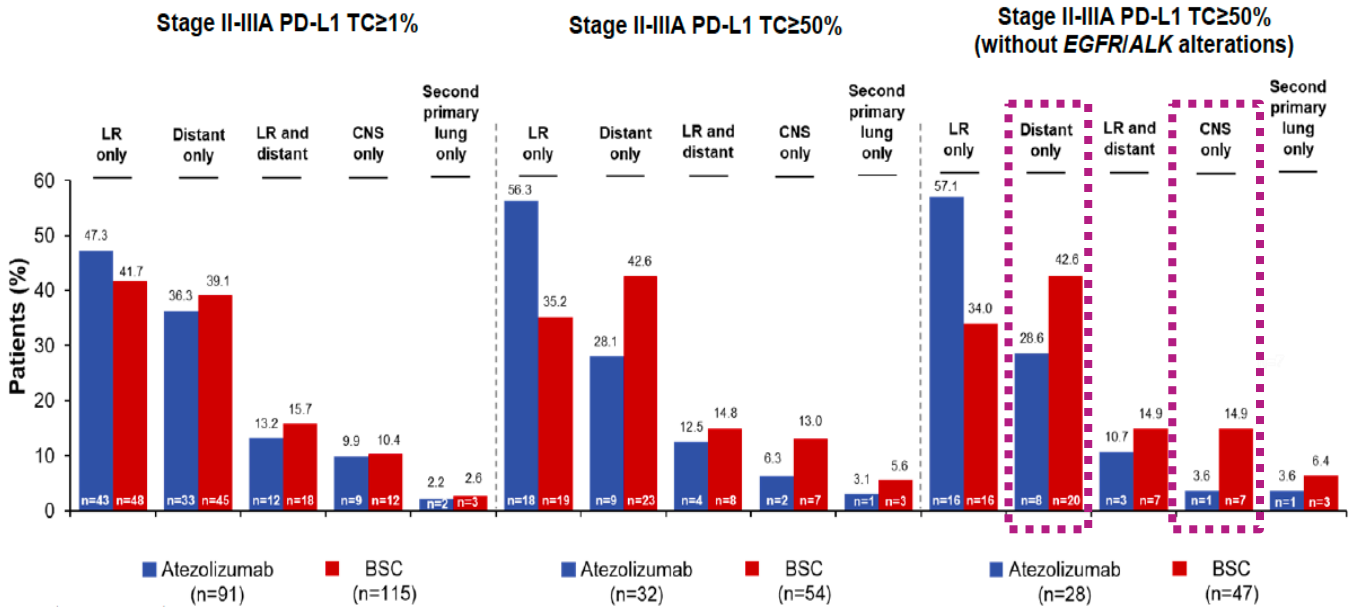
OS stage II-III, PD-L1 ≥50% EGFR/ALK WT



	Atezolizumab (n=106)	BSC (n=103)
OS event, n (%)	22 (20.8)	41 (39.8)
Median OS, months	NE	87.1
Unstratified HR (95% CI)	0.44 (0.26, 0.74)	
3-year OS	89.1	77.5
5-year OS	82.1	63.7

Wakelee H, et al. ASCO 2024

IMpower010: relapse patterns



Small numbers, but:

- ✓ Lower rates of PD-L1 high pts experienced relapse after atezo vs. BSC
- ✓ Lower proportion of pts with relapse had distant/CNS only recurrence after atezo vs. BSC

Felip E, et al. WCLC 2024

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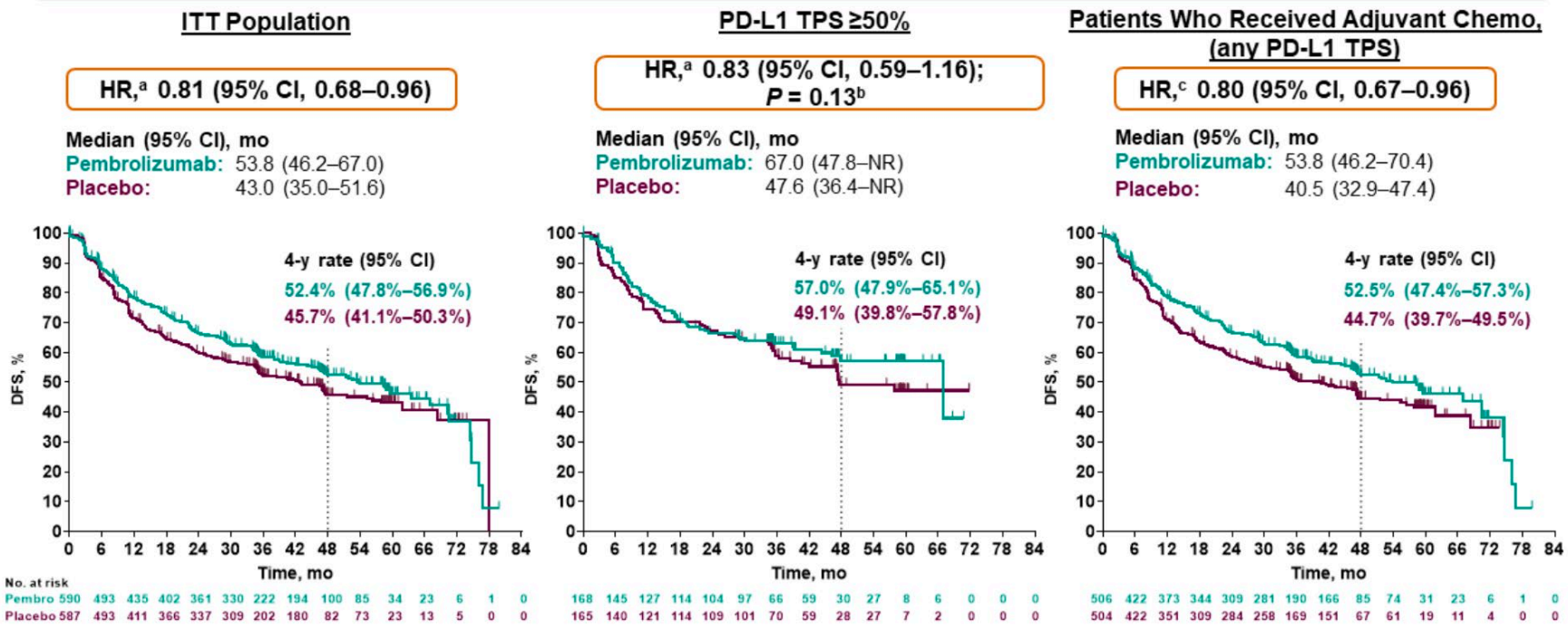
PEARLS Trial: DFS



Besse B. ESMO-IO 2023

CCTG BR.31

Study population:
- Stage IB (≥4 cm)–IIIA NSCLC (AJCC 7th ed.)
- Complete resection
- ECOG PS 0–1
- EGFRm/ALK+ pts eligible

Surgery → randomization ≥3 weeks

Platinum doublet
(Chemo ineligible, chemo intolerant, patients who refuse chemo may also be included)

N=1415 (all comers)
N=1219 EGFR−/ALK−

R[1]
2:1

Durvalumab
20 mg/kg Q4W x 12 months

Stratification
- Stage IB (≥4 cm) *vs* II *vs* IIIA
- PD-L1 status (0 *vs* 1–24% *vs* 25–49% *vs* ≥50%)[2]
- Adjuvant platinum-based chemotherapy (≥300 mg/m cisplatin/equiv *vs* <300 mg/m² vs no chemotherapy)
- Accruing center
- Nodal dissection according to ESTS[3] (yes *vs* no)

Placebo
20 mg/kg Q4W x 12 months

Primary endpoint
- DFS[4] (Investigator Assessed) in patients with PD-L1 TC ≥25% and EGFR−/ALK−

Key secondary endpoints
- DFS in patients with:
  - PD-L1 TC ≥1% and EGFR−/ALK−
  - All PD-L1 TC ≥25%
  - All randomized patients
  - PD-L1 all comers and EGFR−/ALK−
  - All PD-L1 TC ≥1%
- OS (six patient subpopulations)
- AEs
- QoL

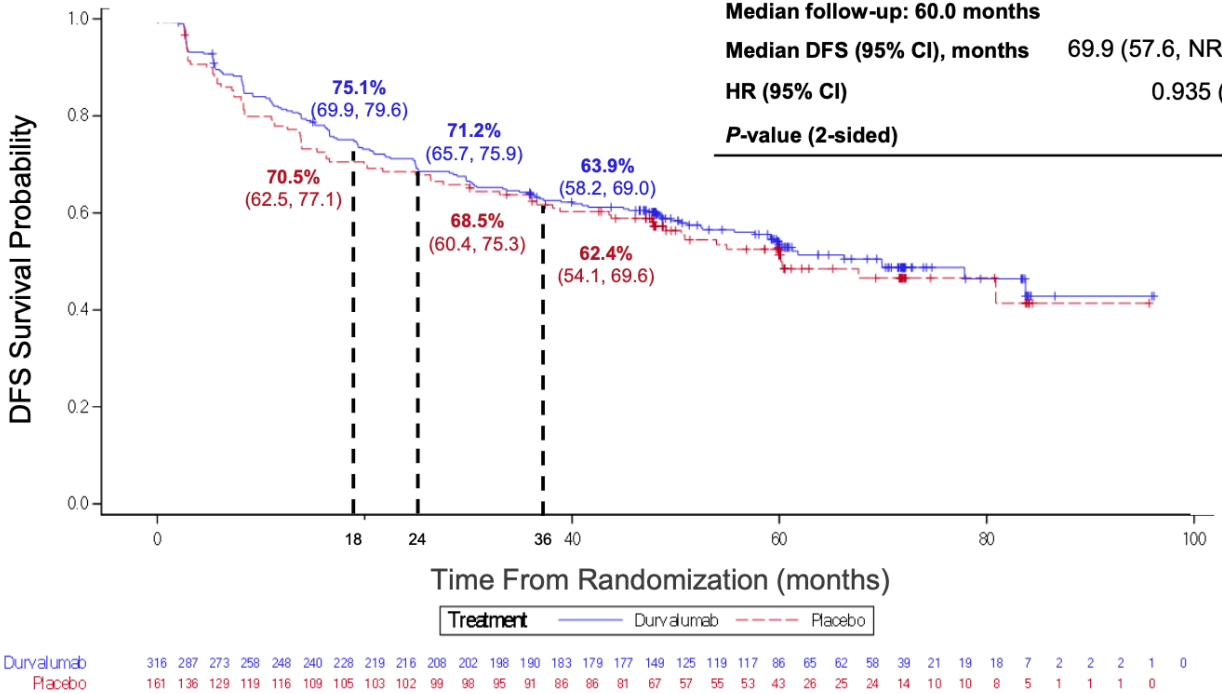
Today, we will present the final DFS analysis from three EGFR−/ALK− populations

Goss G. ESMO 2024

CCTG BR.31

DFS in PD-L1 ≥25% EGFR-/ALK-

	D arm n=316	PBO arm n=161
Median follow-up: 60.0 months		
Median DFS (95% CI), months	69.9 (57.6, NR)	60.2 (47.7, NR)
HR (95% CI)	0.935 (0.706, 1.247)	
***P*-value (2-sided)**	0.642	



Goss G. ESMO 2024

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Dissecting the differences between the three adjuvant IO studies

✓ Differences in patients characteristics?

	Mandatory postop CT	Patients receiving CT	Carboplatin allowed	Patients receiving carboplatin
IMpower010[1]	**Yes**	**100%**	**No**	-
KEYNOTE 091[2]	NO	86%	Yes	30%
CCTG BR.31[3]	NO	85%*	Yes	23.5%

*38% of patients received <300 mg/m^2 cisplatin

✓ Differences in tumor characteristics?

	Sq	PDL1 IHC assay	PDL1 <1%	PDL1 >1%	PDL1 ≥50%
IMpower010[1]	34%	**SP142 (R)** SP263 (A)	41%	54.6% (SP263)	23%
KEYNOTE 091[2]	35%	22C3	40%	-	**28%**
CCTG BR.31[3]	**28%**	SP263	42%	41%	26%

✓ Differences in resected pts populations?

	N	♀	Non-smoker	IB*	II	IIIA	pN2	Pneumonectomy rate
IMPOWER[1] 010	1005	34%	**23%**	12%	47%	**40%**	30%	16%
KEYNOTE[2] 091	1177	32%	15%	14%	56%	30%	21%	11%
CCTG[3] BR.31	1415	35%	11%	11%	57%	31%	23%	10%

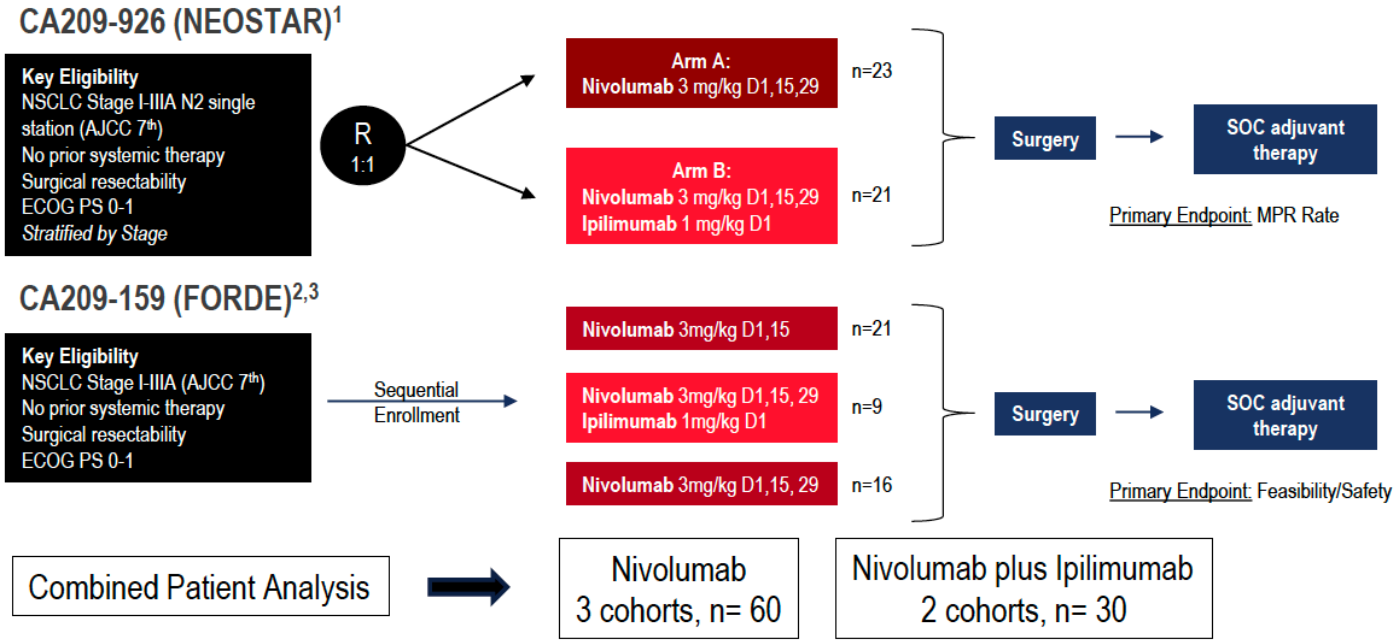
Garrido P. ESMO 2024

NSCLC

Neoadjuvant

NEOSTAR and CA209-159

Combined analysis of 5-year outcomes in resectable NSCLC



Reuss J. ESMO 2024

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Reuss J, et al. ESMO 2024

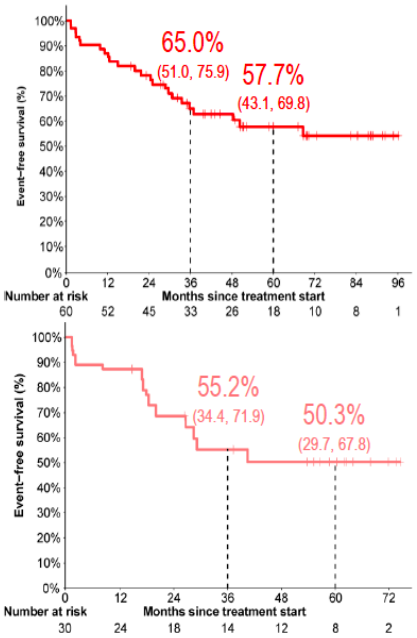
NEOSTAR and CA209-159

Combined analysis of 5-year outcomes in resectable NSCLC

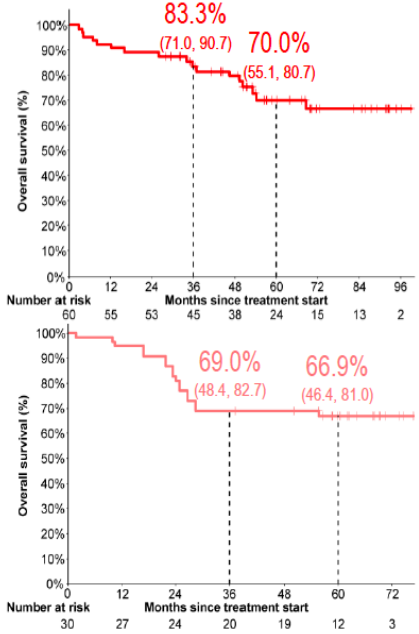
Nivo
n=60
Median f/u 68.4mo

Nivo plus Ipi
n=30
Median f/u 62.1mo

EFS



OS



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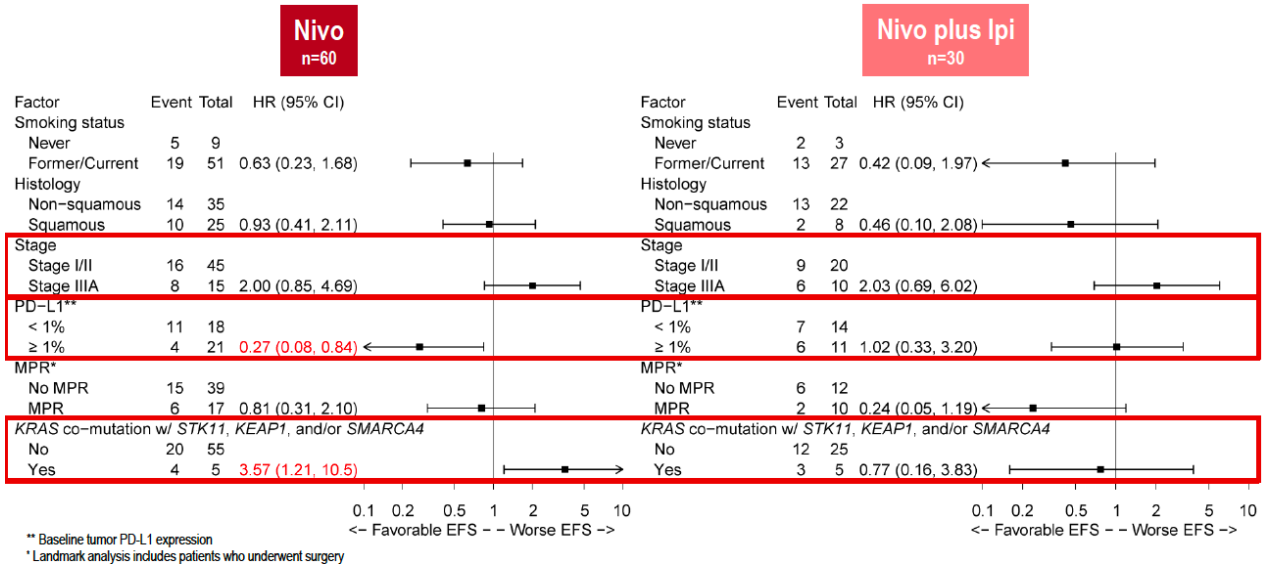
Reuss J. ESMO 2024

Reuss J, et al. ESMO 2024

NEOSTAR and CA209-159

Combined analysis of 5-year outcomes in resectable NSCLC



Pathologic Response Rates

	MPR (95% CI)	pCR (95% CI)
Nivo (n=60)	28.1% (17.4, 42.1)	8.3% (3.5, 18.5)
Nivo plus Ipi (n=30)	33.3% (19.0, 51.7)	26.7% (13.9, 45.0)
TOTAL (n=90)	30.0% (21.5, 40.2)	13.5% (6.6, 25.7)

Reuss J. ESMO 2024

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Reuss J, et al. ESMO 2024

All major neoadjuvant/perioperative IO trials have revealed a similar trend around surgical outcomes and pathological response

	Checkmate-816	KEYNOTE-671	AEGEAN	Checkmate-77T	NEOTORCH	RATIONALE-315
Patients received neo-IO	179	397	366	229	202	226
Cancelled surgery	15.6%	17.9%	19.4%	20.0%	17.8%	15.9%
Surgical delay	20.8%	4.9%	14.5%	-	-	16.3%
R0	83.2%	92.0%	94.7%	89.0%	95.8%	95.0%
MPR rate	36.9%	30.2%	33.3%	35.4%	48.5%	56.2%
PCR rate	24.0%	18.1%	17.2%	25.3%	24.8%	40.7%
PD-L1<1%	43.3%	36.3%	33.4%	40.3%	26.0%	38.2%
PD-L1 1-49%	27.4%	30.4%	37.4%	34.5%	33.9%	28.5%
PD-L1≥50%	22.3%	33.4%	29.2%	21.0%	31.7%	29.4%

Unmet needs

Risk of surgical cancellation and delay

40.1%
25.0%

Low response

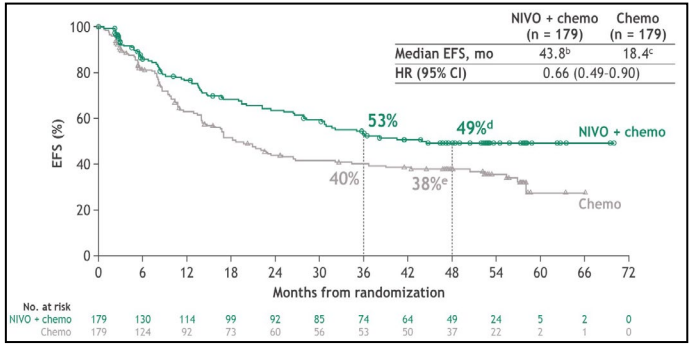
36.3%
32.0%

Large proportion of lower PD-L1 expression

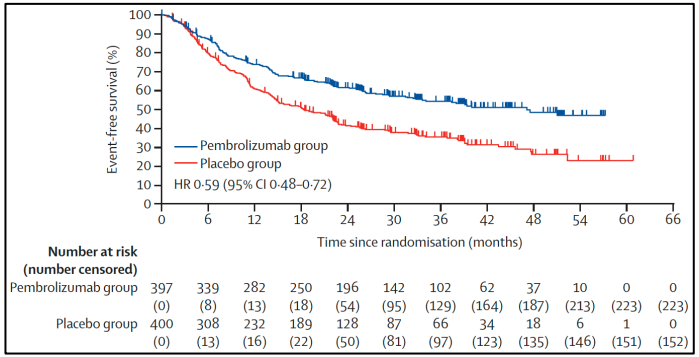
Wu N. WCLC 2024

We have equipoise! EFS HRs 0.59-0.69 across pivotal trials

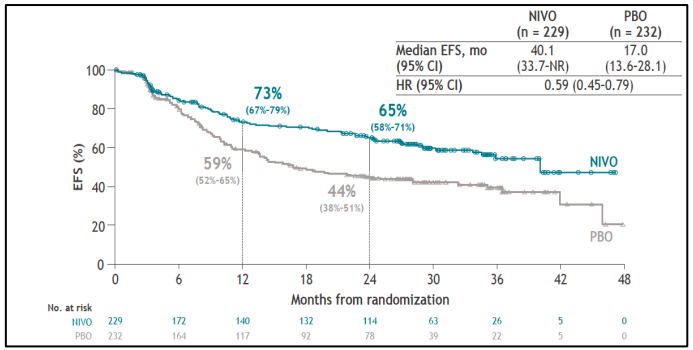
CheckMate816 (Spicer et al. ASCO 2024)



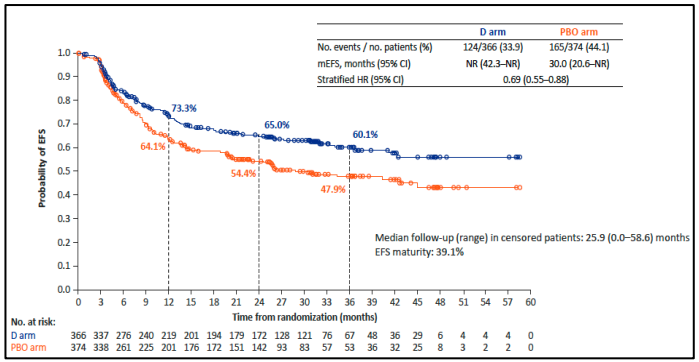
Spicer JD, et al. Lancet 2024 (KN-671)



CheckMate77T (Provencio M, et al. ESMO 2024)



AEGEAN (Heymach J, et al. WCLC 2024)



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Phase 3 ICPi clinical trials in peri-operative setting

Trial	Drugs	Setting	N	ADJ ICPi	Endpoint
CM77T	Nivo + platinum-doublet CT	Neoadjuvant, Stage IB–IIIB(N2), resectable NSCLC	461	Y	EFS
IMpower030	Atezo + platinum-doublet CT	Neoadjuvant, Stage II–IIIB (N2), resectable NSCLC	374	Y	MPR & EFS
KN-617	Pembro + platinum-doublet CT	Neoadjuvant, Stage II–IIIB (N2), resectable NSCLC	786	Y	EFS & OS
AEGAN	Durva + platinum-doublet CT	Neoadjuvant, Stage II–IIIB (N2), resectable NSCLC	802	Y	MPR & pCR
Rationale	Tisle + platinum-doublet CT	Neoadjuvant, Stage II–IIIA, resectable NSCLC	453	Y	MPR & EFS
Neotorch	Toripalib + platinum-doublet CT	Neoadjuvant, Stage II–IIIA, resectable NSCLC	500	Y + CT	MPR & EFS

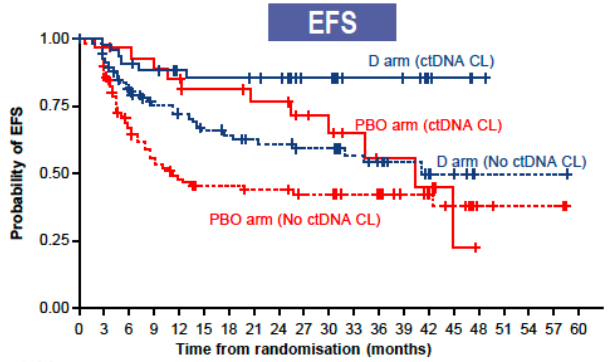
Neoadjuvant and Peri-operative trials of CT +/- IO in resectable NSCLC: summary of efficacy outcome results

	CM816 (CT +/- Nivo) NEJM'22	CM77T (CT +/- Nivo-> Adj Nivo) ESMO'23	KN 671 (CT +/- Pembro-> Adj Pembro) ESMO'23	AEGEAN (CT +/- Durva-> Adj durva) AACR'23 WCLC'24	Rationale (CT +/- Tisle-> Adj Tisle) ESMO'23	NEOTORCH (CT +/- Toripa-> Adj Toripa) ASCO'23
pCR	24.0 vs 2.2	25.3 vs 4.7	18.1 vs 4.0	17.2 vs 4.3	40.7 vs 5.7	24.8 vs 1.0
2Y EFS% (HR)	63.8 vs 45.3 (0.63)	65 vs 44 (0.59)	61.5 vs 41.4 (0.59)	63.3 vs 52.4 (0.68)	-	64.7 vs 38.7 (0.40)
3Y EFS% (HR)	57.0 vs 43.0 (0.68)	-	54.3 vs 35.4 (0.59)	60.1 vs 47.9 (0.69)	-	-
3Y OS% (HR)	78 vs 64 (0.62)	-	71.3 vs 64.0 (0.72)	67.1 vs 63.9 (0.89)	-	-

AEGEAN trial

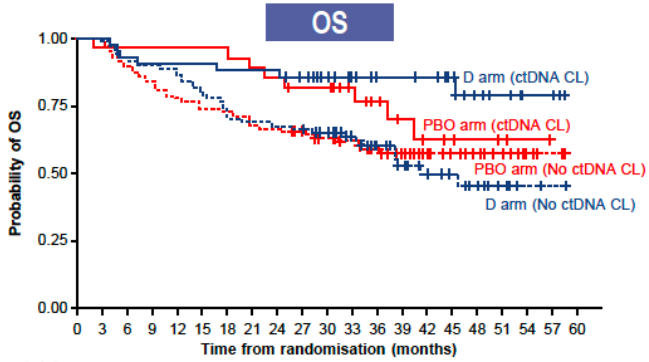
Associations of ctDNA clearance at Neoadjuvant C2D1 with EFS and OS

- As early as neoadjuvant C2D1, patients in the D arm with ctDNA clearance had longer EFS and OS compared to patients without clearance, and versus the PBO arm*



No. at risk

D arm (ctDNA CL)	41	40	37	35	32	31	31	30	29	21	21	14	14	13	9	7	1	0	0	0
PBO arm (ctDNA CL)	27	26	25	23	22	19	19	17	17	12	11	7	5	5	4	1	0	0	0	0
D arm (No ctDNA CL)	80	73	61	51	47	42	40	37	36	33	33	22	19	13	10	8	1	1	1	0
PBO arm (No ctDNA CL)	92	85	57	45	39	34	34	32	31	25	25	21	20	13	11	8	3	2	2	0



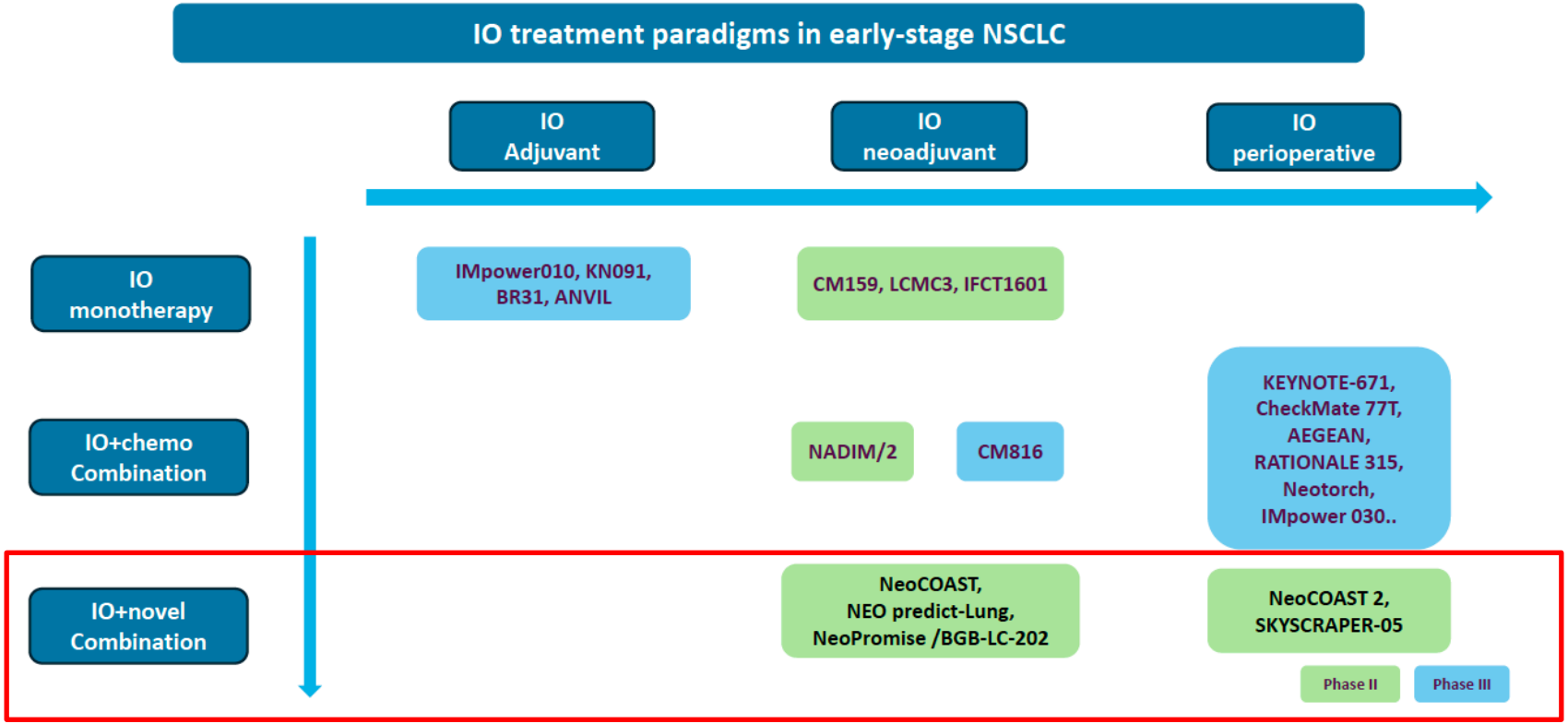
No. at risk

D arm (ctDNA CL)	41	41	38	37	37	37	36	36	36	32	26	22	19	18	17	14	8	6	3	3	0
PBO arm (ctDNA CL)	27	26	26	26	26	26	26	24	23	21	21	16	13	9	7	6	4	2	1	0	0
D arm (No ctDNA CL)	80	79	73	72	69	63	58	55	54	52	47	38	29	20	14	12	9	5	2	1	0
PBO arm (No ctDNA CL)	92	92	82	77	71	68	67	63	60	58	50	46	36	29	21	18	14	11	4	2	0

	D arm	PBO arm
EFS HR for ctDNA CL vs No ctDNA CL	0.30 (95% CI: 0.12–0.71)	0.53 (95% CI: 0.27–1.02)
EFS HR for the D vs PBO arm (ctDNA CL)	0.31 (95% CI: 0.11–0.85)	–
EFS HR for the D vs PBO arm (No ctDNA CL)	0.62 (95% CI: 0.40–0.97)	–

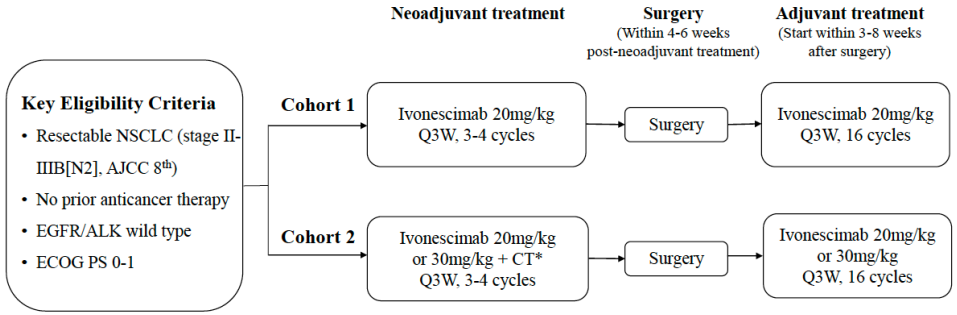
	D arm	PBO arm
OS HR for ctDNA CL vs No ctDNA CL	0.32 (95% CI: 0.14–0.72)	0.61 (95% CI: 0.28–1.31)
OS HR for the D vs PBO arm (ctDNA CL)	0.55 (95% CI: 0.20–1.52)	–
OS HR for the D vs PBO arm (No ctDNA CL)	1.07 (95% CI: 0.68–1.69)	–

Reck M, et al. ESMO 2024


IO treatment paradigms in early-stage NSCLC
IO Adjuvant
IO neoadjuvant
IO perioperative
IO monotherapy
IO+chemo Combination
IO+novel Combination
IMpower010, KN091, BR31, ANVIL
CM159, LCMC3, IFCT1601
NADIM/2
CM816
KEYNOTE-671, CheckMate 77T, AEGEAN, RATIONALE 315, Neotorch, IMpower 030..
NeoCOAST, NEO predict-Lung, NeoPromise /BGB-LC-202
NeoCOAST 2, SKYSCRAPER-05
Phase II
Phase III

A Phase II Study of Perioperative Ivonescimab Alone or Combined with Chemotherapy in Resectable NSCLC

Study Design



- **Primary Endpoints: MPR, Safety**
- **Secondary Endpoints: pCR, EFS, OS, ORR, the rate of R0 resection and downstaging**

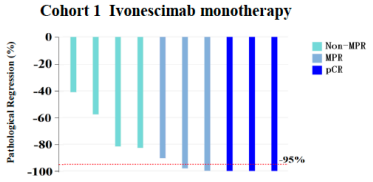
Characteristics		Cohort 1 Ivonescimab monotherapy (N=11)	Cohort 2 Ivonescimab + CT (N=49)	Total (N=60)
Dose level of Ivonescimab, n(%)	20mg/kg	11 (100.0)	24 (49.0)	35 (58.3)
	30mg/kg	0	25 (51.0)	25 (41.7)
Age, years	Median (range)	64 (50, 70)	64 (30, 74)	64 (30, 74)
Sex, n(%)	Male	9 (81.8)	42 (85.7)	51 (85.0)
ECOG, n(%)	PS=0	11 (100)	48 (98.0)	59 (98.3)
Smoking status, n(%)	Never	1 (9.1)	10 (20.4)	11 (18.3)
	Current or former	10 (90.9)	39 (79.6)	49 (81.7)
Histology, n(%)	Squamous	8 (72.7)	37 (75.5)	45 (75.0)
	Non-squamous	3 (27.3)	12 (24.5)	15 (25.0)
PD-L1 expression, n(%)	<1%	2 (18.2)	12 (24.5)	14 (23.3)
	≥1%	9 (81.8)	33 (67.3)	42 (70.0)
	Unknown	0	4 (8.2)	4 (6.7)
Clinical stage, n(%)	II	3 (27.3)	10 (20.4)	13 (21.7)
	III	8 (72.7)	39 (79.6)	47 (78.3)
N stage, n(%)	N0	3 (27.3)	3 (6.1)	6 (10.0)
	N1/2	8 (72.7)	46 (93.9)	54 (90.0)
	N1	0	12 (24.5)	12 (20.0)
	N2	8 (72.7)	34 (69.4)	42 (70.0)

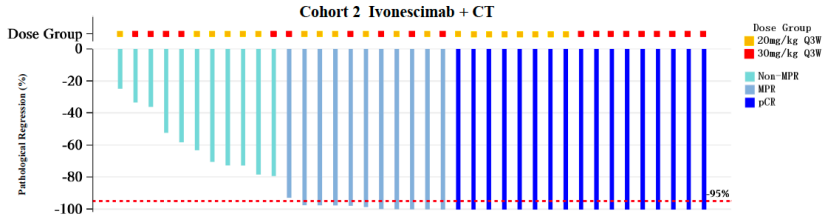
Wang C, et al. WCLC 2024

A Phase II Study of Perioperative Ivonescimab Alone or Combined with Chemotherapy in Resectable NSCLC

Pathological Response

	Cohort 1 (N=10)	Cohort 2 (N=39)
MPR (RVT≤10%)	60.0%	71.8%
- RVT* < 5%	50.0%	69.2%
pCR	30.0%	43.6%

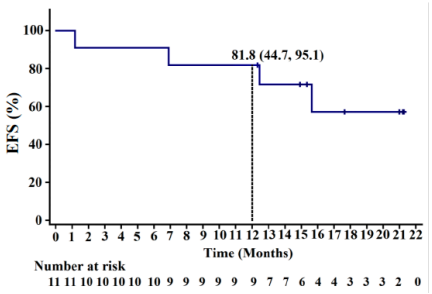




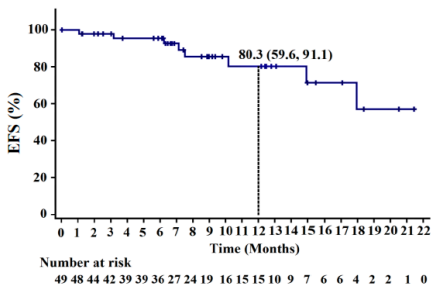
*RVT : residual viable tumor cells in both primary tumor and lymph nodes.

EFS

Cohort 1 Ivonescimab monotherapy (n=11)	
Median Follow-up (95% CI)	17.64 (12.3, 21.2)
No. of Events/No. of Patients (%)	4/11 (36.4%)
Median EFS (95% CI)	NR (6.9, NE)



Cohort 2 Ivonescimab + CT (n=49)	
Median Follow-up (95% CI)	8.94 (6.6, 12.2)
No. of Events/No. of Patients (%)	8/49 (16.3%)
Median EFS (95% CI)	NR (14.9, NE)



Remaining questions

- Impact of Ivo+CT on N2 and tumors with central location, cavitation and blood vessel encasement
- VEGF inhibition specific toxicity and toxicity by treatment phase

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Wang C, et al. WCLC 2024

NSCLC

Locally Advanced

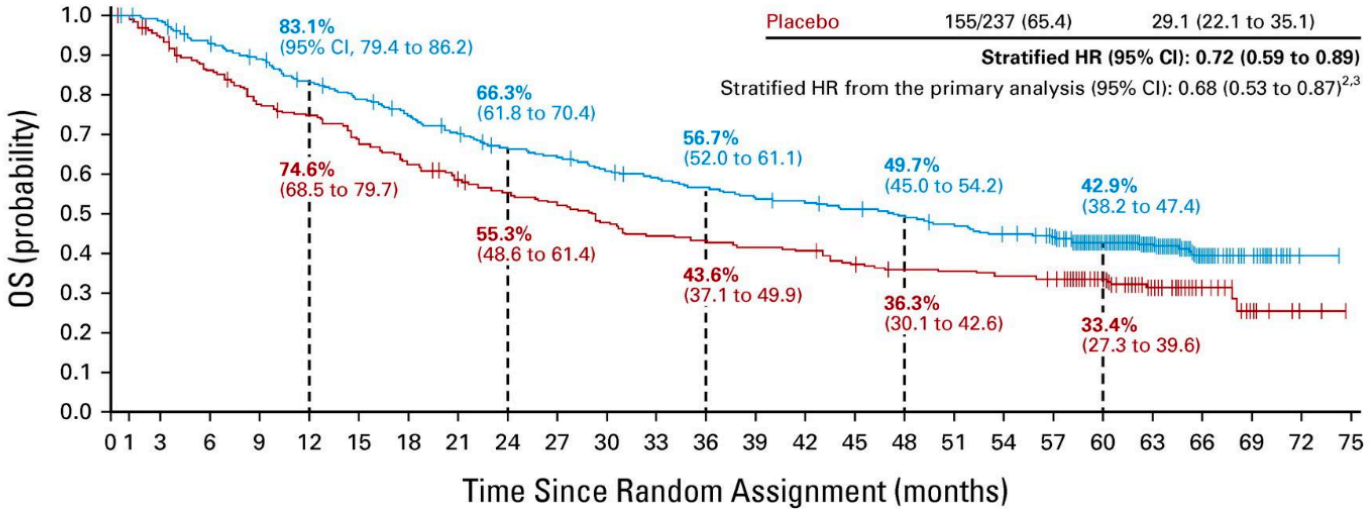
PACIFIC 5-YEARS OS ITT

Durvalumab for 1 year vs placebo after CT-RT

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



No. at risk:

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

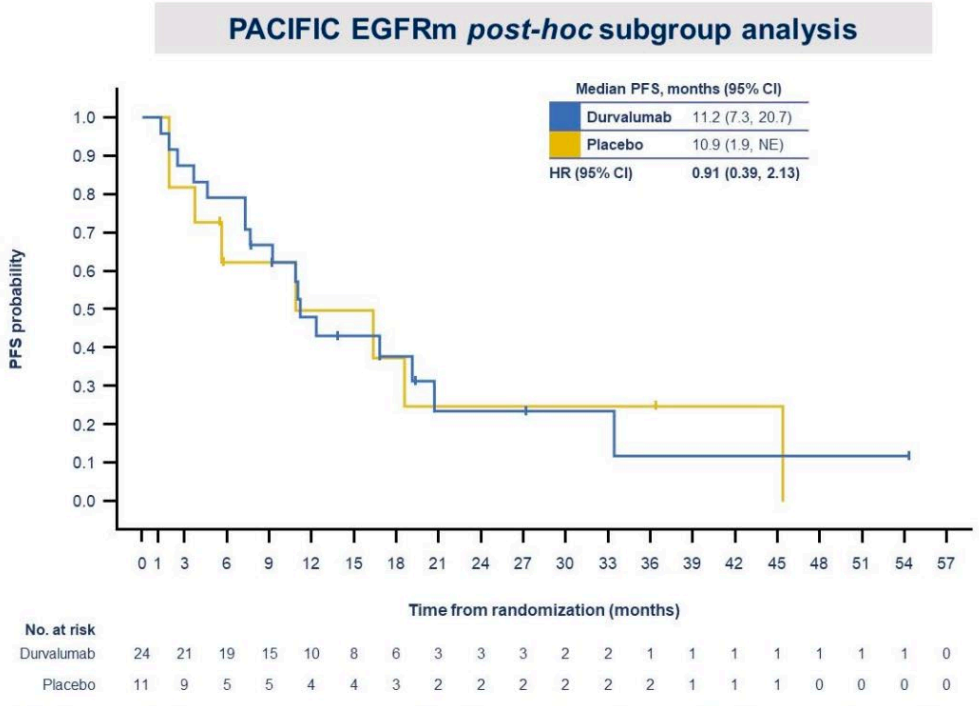
Spigel DR, JCO 2022

The James

The Ohio State University
Comprehensive Cancer Center

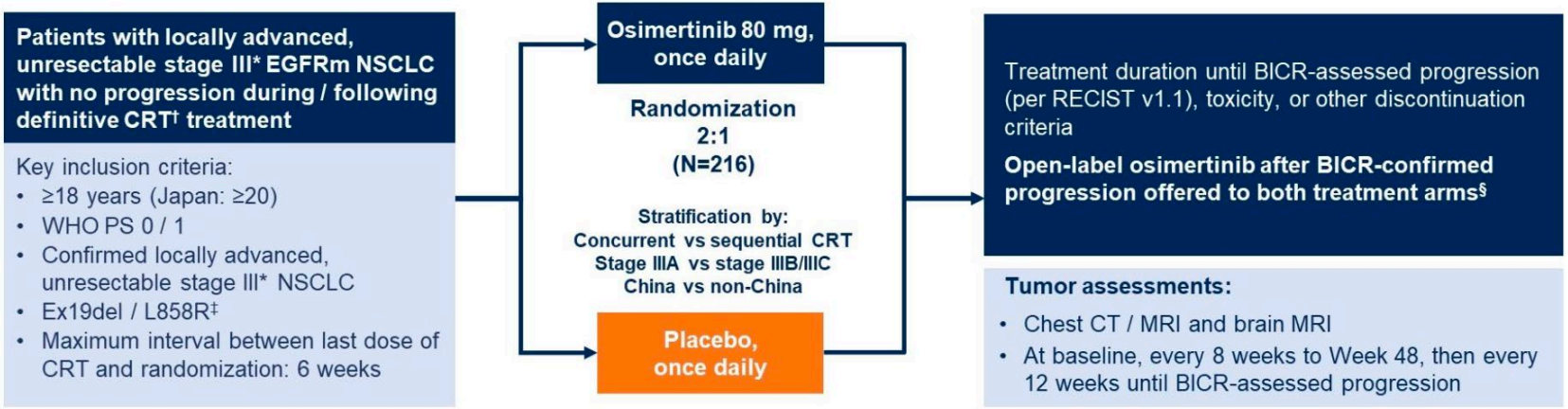
Unmet need in unresectable stage III EGFRm NSCLC

- In unresectable stage III NSCLC following CRT without progression, standard of care is consolidation durvalumab
- Benefit of consolidation durvalumab in EGFRm NSCLC is uncertain based on PACIFIC *post-hoc* subgroup analysis
- Efficacy of EGFR-TKIs is supported by the Phase 2 RECEL study and real-world data but prospective Phase 3 data are needed
- No approved targeted therapies for unresectable stage III EGFRm NSCLC



Ramalingam S.S. ASCO 2024

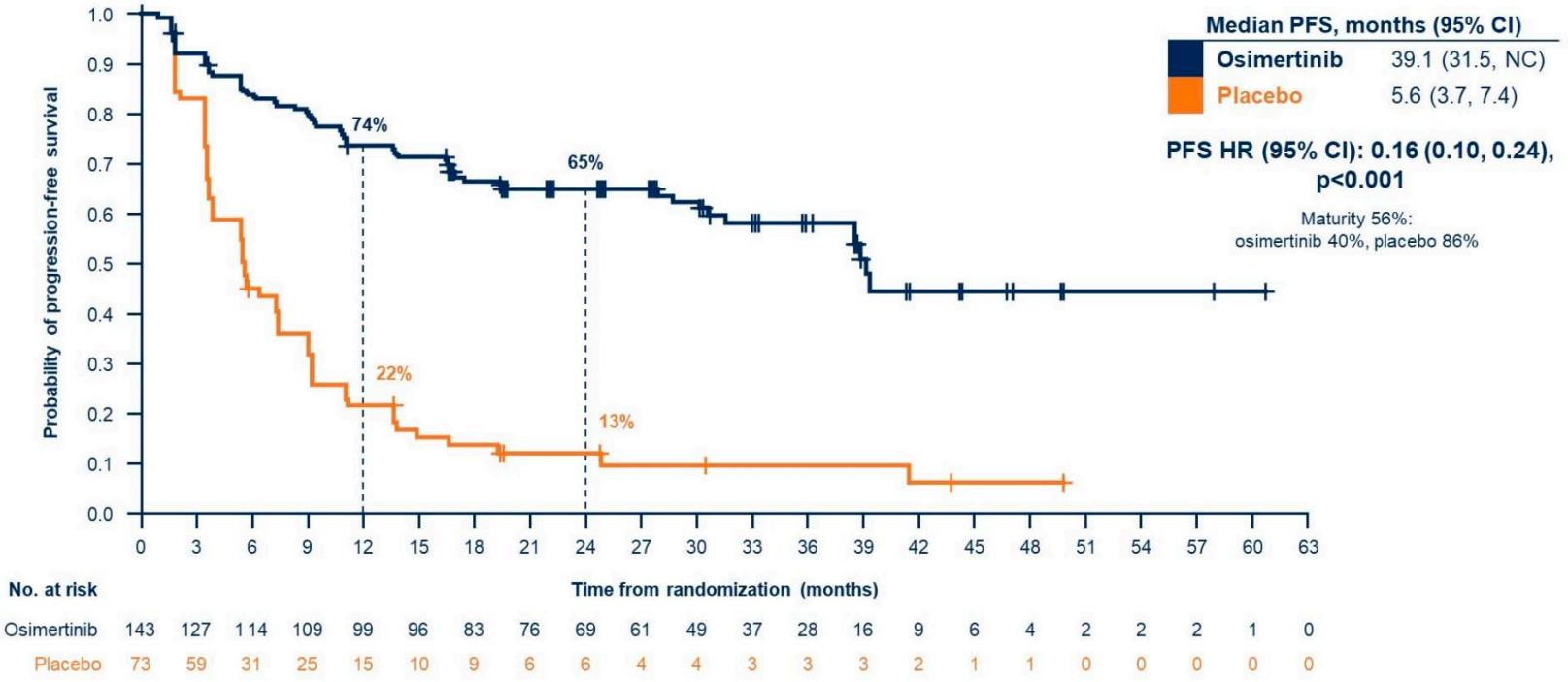
LAURA trial



Endpoints

- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

LAURA trial: PFS by BICR

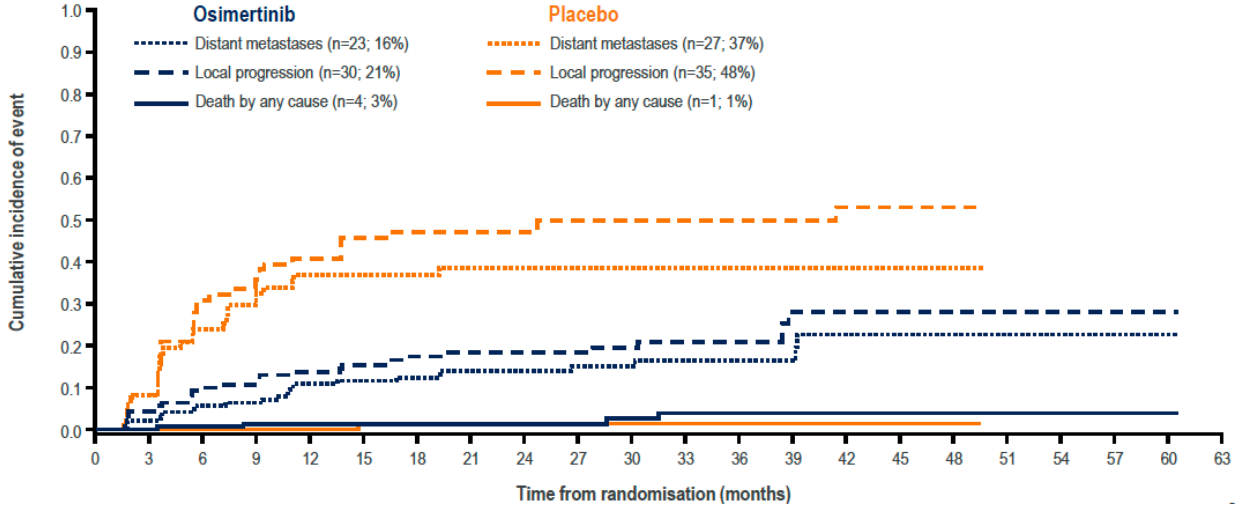


Ramalingam S.S. ASCO 2024

Osimertinib protects against CNS progression in the LAURA trial

Cumulative incidence of distant / non-distant (local) progression or death

- Cumulative incidence* of distant metastases was consistently lower with osimertinib vs placebo
- The cumulative incidence* rate of distant metastases at 12 months was 11% (95% CI 6, 17) with osimertinib vs 37% (95% CI 26, 48) with placebo



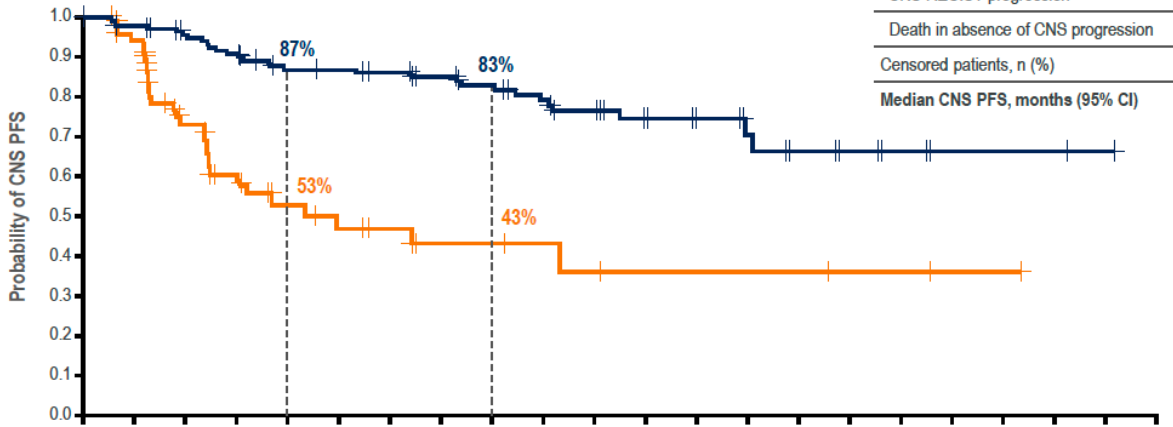
Lu S, et al. ESMO 2023

Osimertinib protects against CNS progression in the LAURA trial

CNS progression-free survival by neuroradiologist BICR*

- Reduced risk of CNS progression or death with osimertinib vs placebo

	Osimertinib (n=143)	Placebo (n=73)
Total CNS PFS events, n (%)†	29 (20)	30 (41)
CNS RECIST progression‡	18 (13)	26 (36)
Death in absence of CNS progression	11 (8)	4 (5)
Censored patients, n (%)	114 (80)	43 (59)
Median CNS PFS, months (95% CI)	**NR (NC, NC)**	**14.9 (7.4, NC)**



HR: 0.17 (0.09, 0.32), p<0.001 (nominal)

No. at risk

Osimertinib	143	130	121	115	105	104	94	84	74	63	49	37	28	17	9	6	4	2	2	2	1	0
Placebo	73	63	36	26	19	16	12	8	8	6	5	3	3	3	3	2	2	1	1	0	0	0

Lu S, et al. ESMO 2023

NSCLC

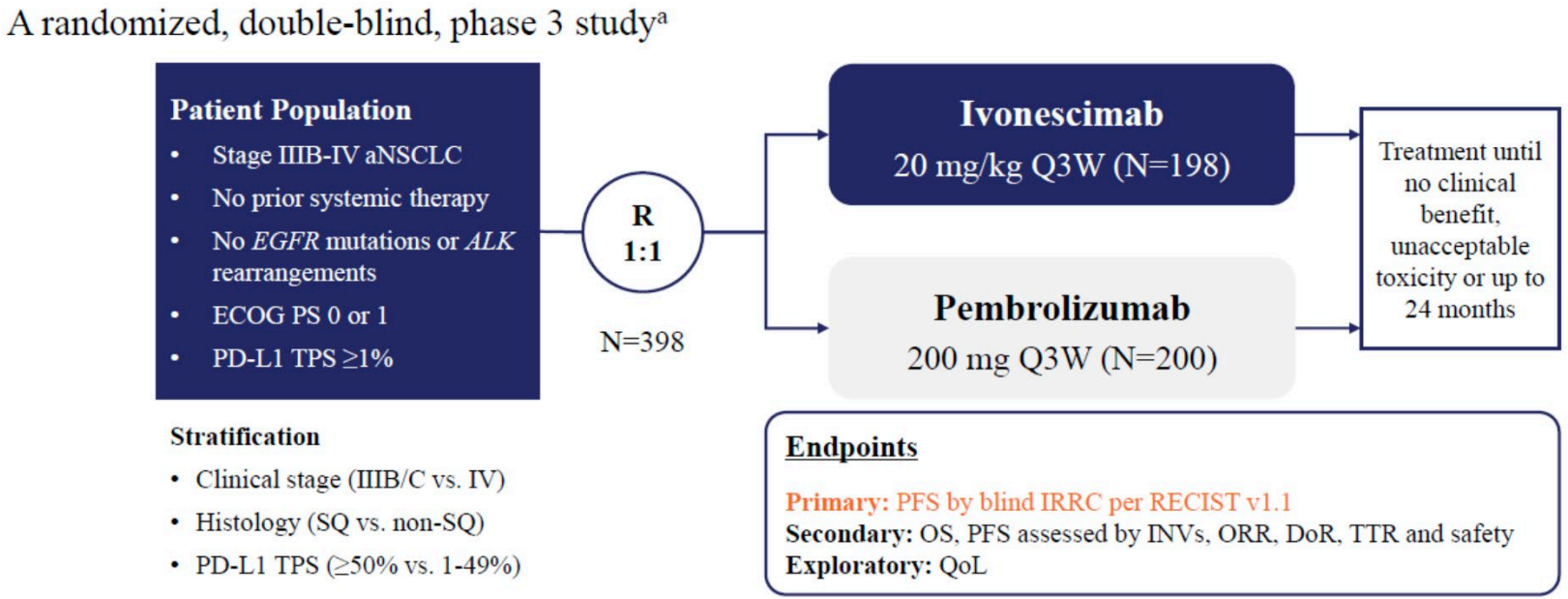
Metastatic non-oncogene addicted

Anti-PD-(L)1 «single agent» vs CT in A-NSCLC with PD-L1 > 50%: results of 1L RCT

	EMPOWER (cemiplimab)	IMpower110 (atezolizumab)	KN024 (pembrolizumab)
# Pts	563	205	305
RR%	20 vs 39	28.6 vs 38.3	27.8 vs 44.8
mPFS (months)	5.7 vs 8.2	5.0 vs 8.1	6.0 vs 10.3
HR (p value)	0.54 (0.0001)	0.63 (0.007)	0.63 (0.002)
mOS (months)	14.2 vs NR	13.1 vs 20.2	14.2 vs 30
OS (1YS%)	53.9 vs 72.4	50.6 vs 64.9	48.0 vs 69.8
HR (p value)	0.57 (0.0002)	0.59 (0.01)	0.60 (nr)
OS (5YS%)	29% vs 15%	NA	31.9 vs 16.3
G ≥ 3 TRAE %	37 vs 12	44.1 vs 12.9	53.3 vs 26.6

Sazer A et al, Lancet 2021; Herbst et al, NEJM 2020; Reck et al, NEJM 2016; Reck et al, JCO 2019

HARMONi-2

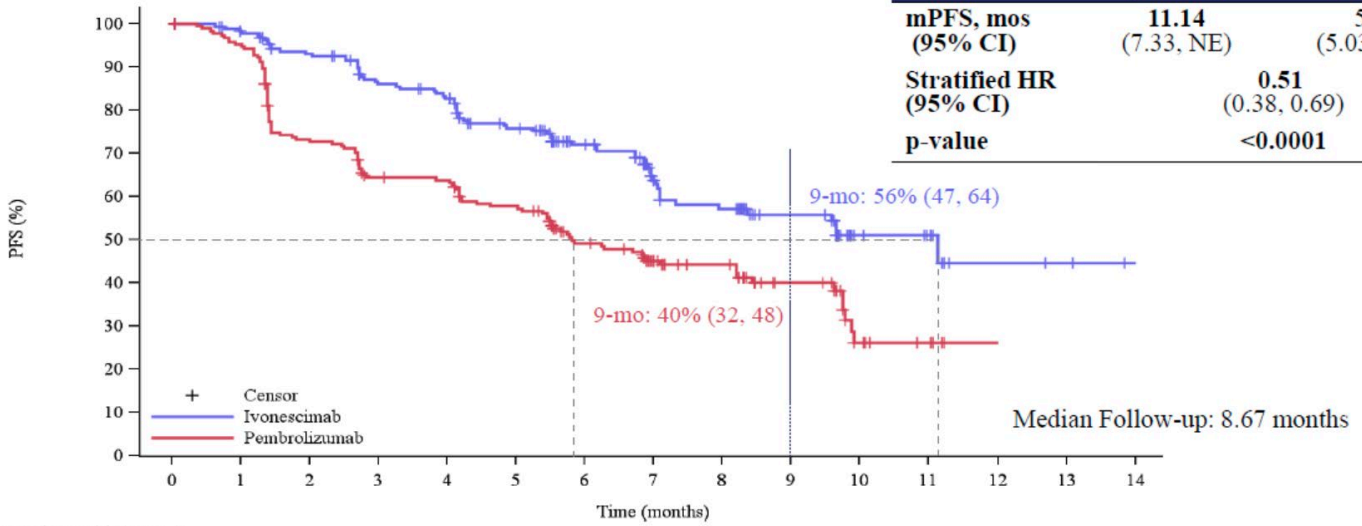


Zhou Caicun, WCLC 2024

HARMONi-2 trial

Primary Endpoint: PFS per IRRC

	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	**11.14** (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	**0.51** (0.38, 0.69)	
p-value	**<0.0001**	



Number at risk (Events)

Ivonescimab	198(0)	189(3)	175(13)	156(26)	148(32)	128(44)	99(50)	68(60)	59(67)	38(68)	14(71)	11(71)	3(72)	2(72)	0(72)
Pembrolizumab	200(0)	187(9)	141(52)	121(69)	119(70)	103(81)	74(95)	53(101)	45(102)	25(106)	9(112)	5(112)	0(112)		

Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

Zhou Caicun, WCLC 2024

TROPION-Lung 01

Study Design (NCT04656652)[1]

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without AGA*
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With AGA
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

Dato-DXd
6 mg/kg q3w
N=299

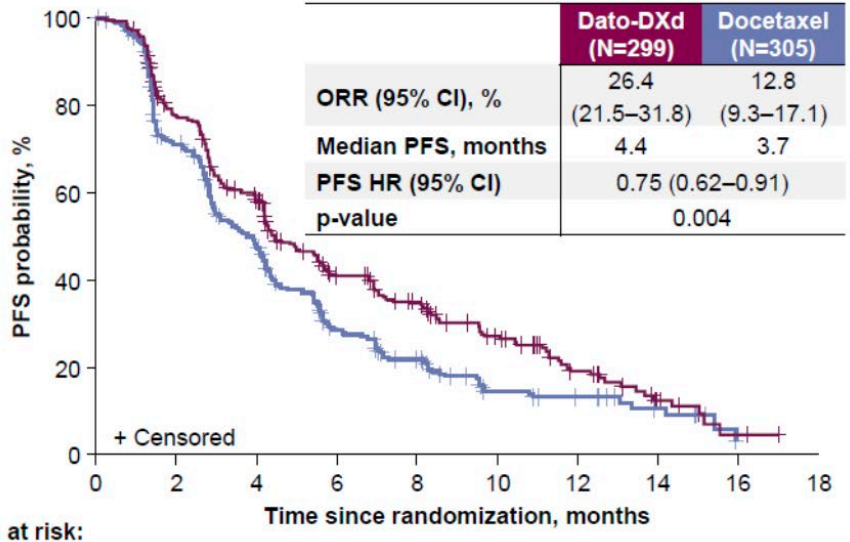
Docetaxel
75 mg/m² q3w
N=305

Stratified by:
Histology†, AGA‡, anti–PD-(L)1 mAb included in most recent prior therapy, geography§

Dual Primary Endpoints: PFS by BICR; OS
Secondary Endpoints: ORR by BICR; DOR by BICR; Safety

PFS by BICR and ORR[1]

	Dato-DXd (N=299)	Docetaxel (N=305)
ORR (95% CI), %	26.4 (21.5–31.8)	12.8 (9.3–17.1)
Median PFS, months	4.4	3.7
PFS HR (95% CI)	0.75 (0.62–0.91)	
p-value	0.004	

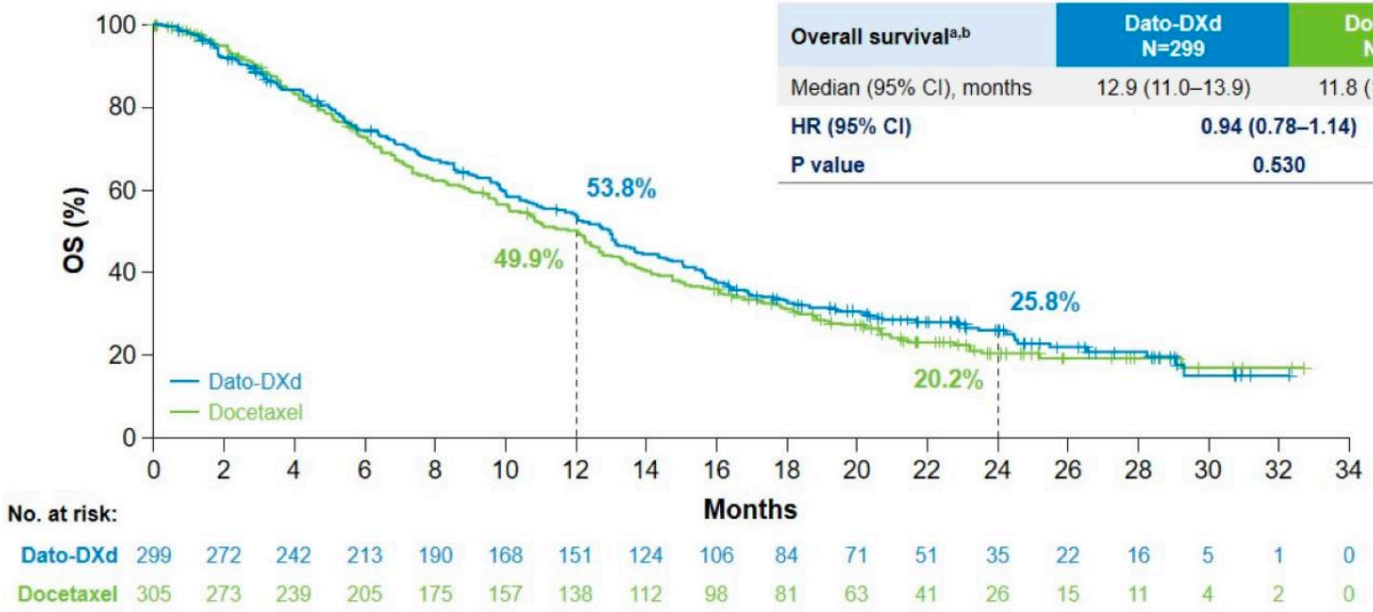


No. at risk:

Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0

TROPION-Lung 01

OS in ITT



Overall survival[a,b]	Dato-DXd N=299	Docetaxel N=305
Median (95% CI), months	12.9 (11.0–13.9)	11.8 (10.0–12.8)
HR (95% CI)	0.94 (0.78–1.14)	
P value	0.530	

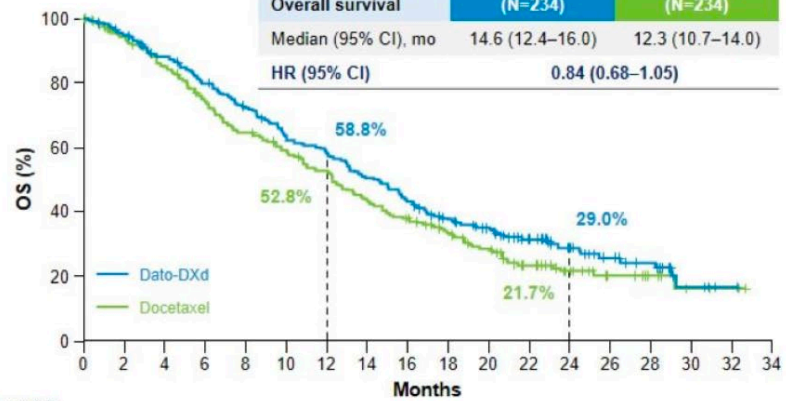
Garassino M.C. WCLC 2024

TROPION-Lung 01

OS by histology

Nonsquamous

Overall survival	Dato-DXd (N=234)	Docetaxel (N=234)
Median (95% CI), mo	14.6 (12.4–16.0)	12.3 (10.7–14.0)
HR (95% CI)	0.84 (0.68–1.05)	

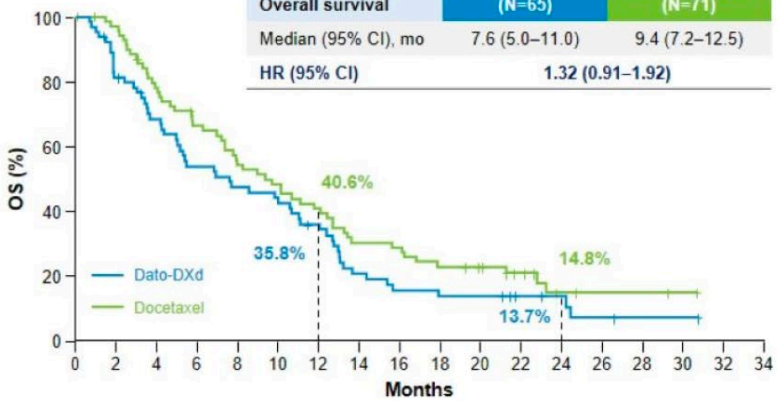


No. at risk:

Dato-DXd	234	220	200	180	161	141	130	112	97	76	63	46	31	20	15	4	1	0
Docetaxel	234	206	186	161	139	125	111	92	79	66	50	32	22	12	8	3	2	0

Squamous

Overall survival	Dato-DXd (N=65)	Docetaxel (N=71)
Median (95% CI), mo	7.6 (5.0–11.0)	9.4 (7.2–12.5)
HR (95% CI)	1.32 (0.91–1.92)	



	65	52	42	33	29	27	21	12	9	8	8	5	4	2	1	1	0	0
	71	67	53	44	36	32	27	20	19	15	13	9	4	3	3	1	0	0

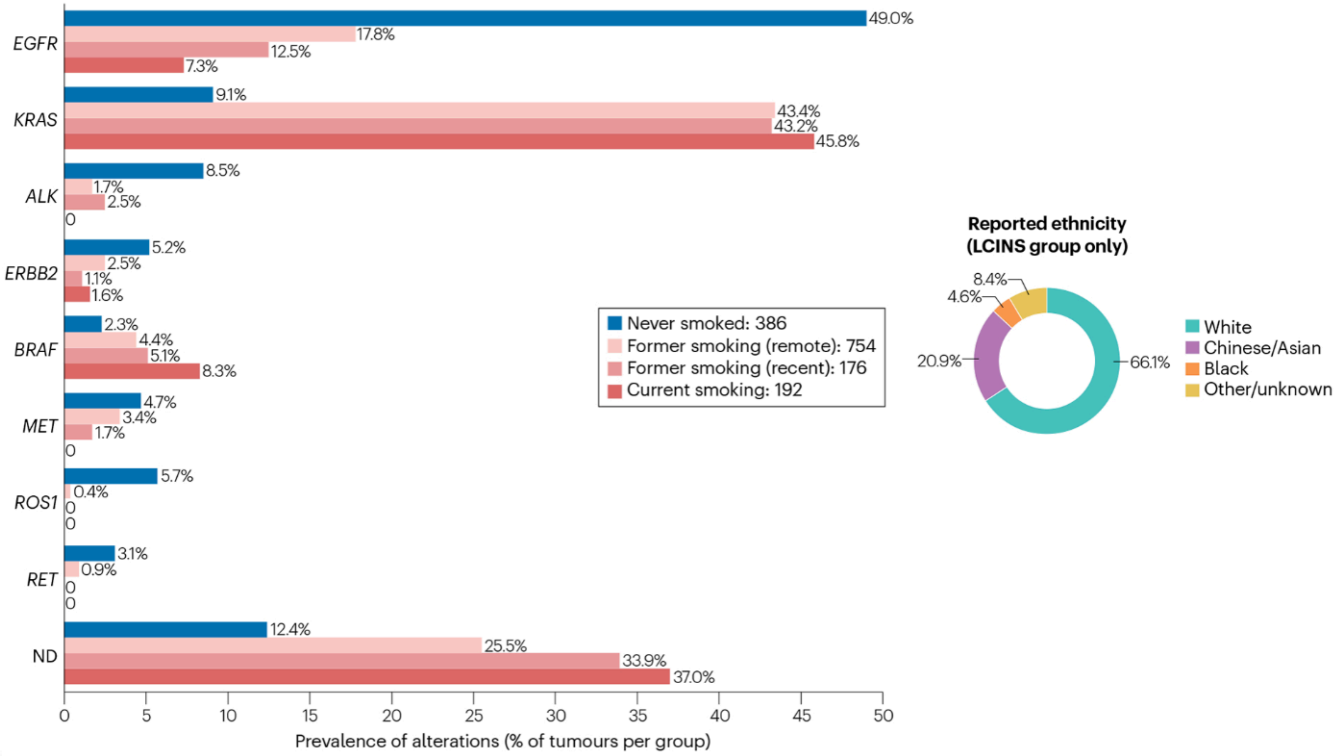
- In patients with NSQ histology, 16% risk reduction for death and 2.3-month improvement in median OS with Dato-DXd
- OS improvements in the NSQ subset were seen regardless of actionable genomic alteration status[a]:
  - **Present**: 15.6 vs 9.8 months (HR [95% CI], 0.65 [0.40–1.08]); **Absent:** 13.6 vs 12.3 months (HR [95% CI], 0.89 [0.70–1.13])

Garassino M.C. WCLC 2024

NSCLC

Metastatic NSCLC oncogene addicted

Lung cancer in never smoker

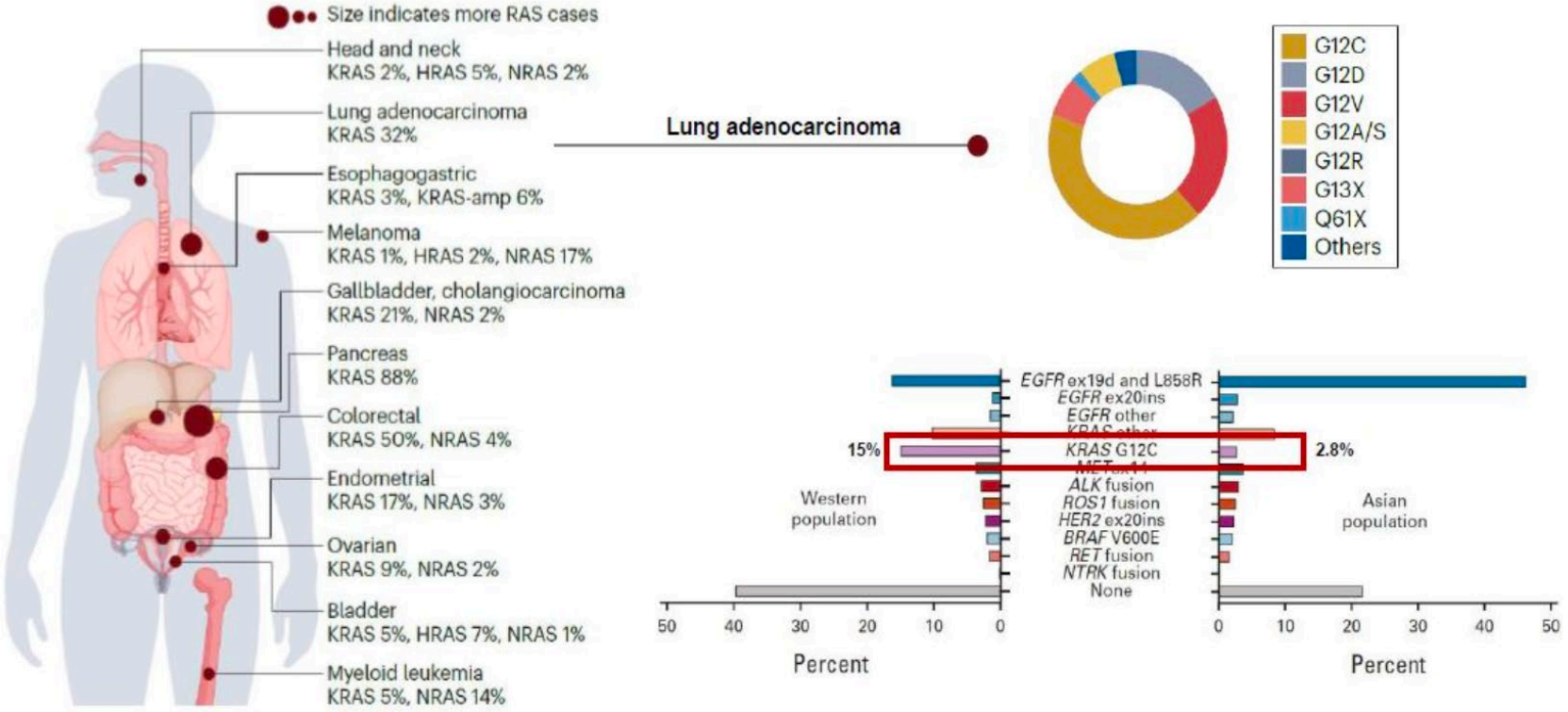


LoPiccolo, Nat Rev Clin Oncol 2024

The James

The Ohio State University
Comprehensive Cancer Center

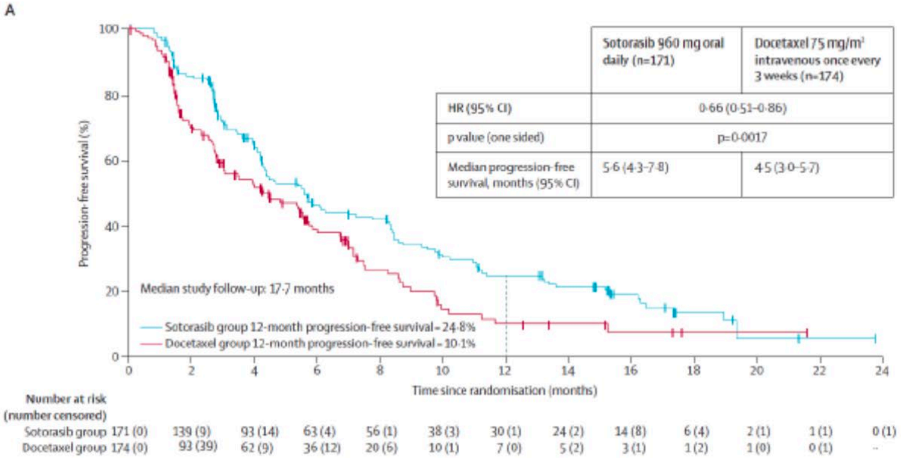
KRAS in NSCLC



Nat Med 2024

Can KRASG12C change the paradigm of 2L+ line in NSCLC?

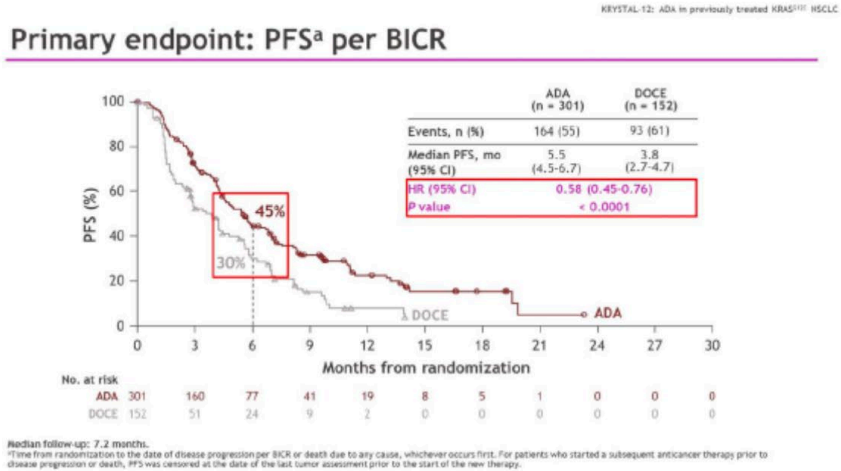
phase III CoreBreak200: Sotorasib vs Docetaxel



	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
HR (95% CI)	0·66 (0·51–0·86)	
p value (one sided)	p=0·0017	
Median progression-free survival, months (95% CI)	5·6 (4·3–7·8)	4·5 (3·0–5·7)

- **ORR 28.1% (37.1% in phase II) vs 13.1%**
- **mPFS showed clinical marginal benefit (5.6 vs 4.5 months, HR 0.66)**
- **yet "cannot reliably be interpreted" due to early censoring and overperformance of control group?**

phase III KRYSTAL-12: Adagrasib vs Docetaxel

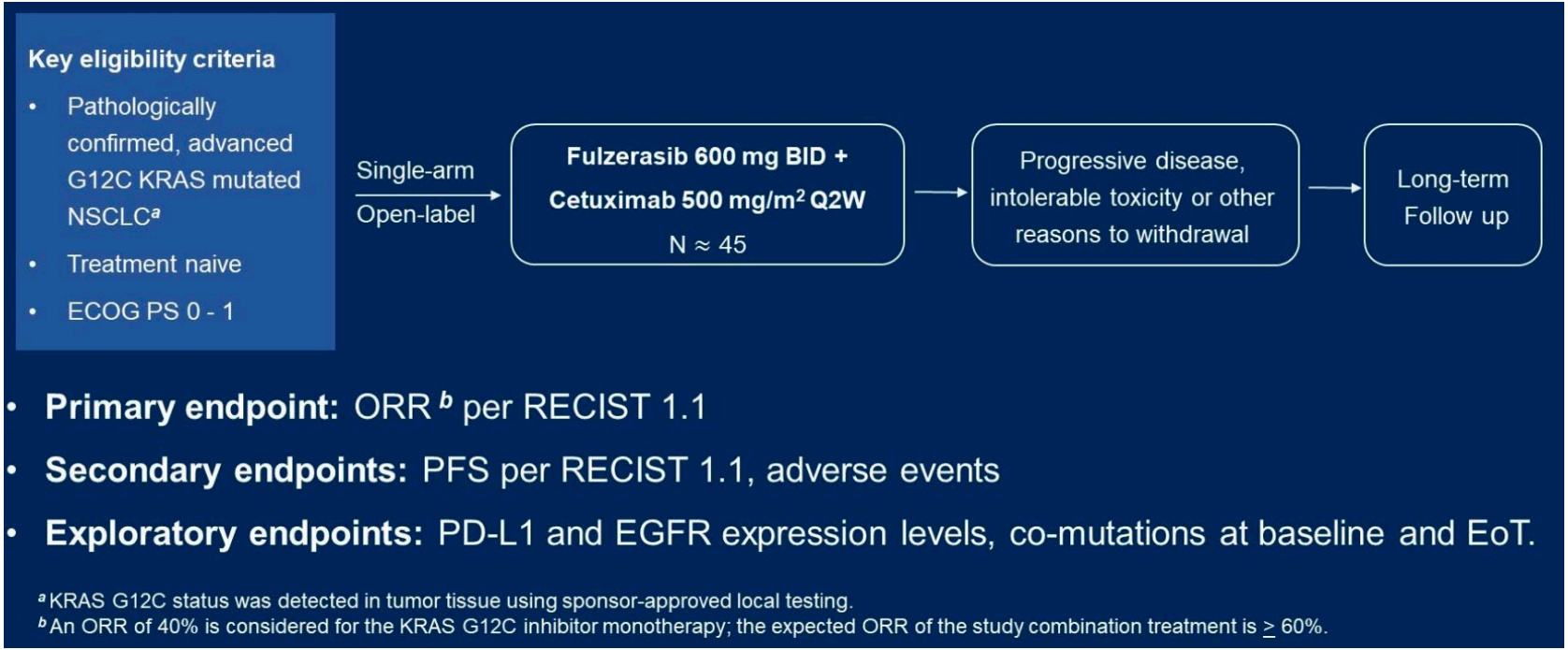


	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

- **ORR 32% (42.9% in phase II) vs 9%**
- **mPFS 5.5 vs 3.8 months, HR 0.58**
- **Potential CNS activity: intracranial response 24% (40% in CNS evaluable population)**

De Langen A.J. Lancet 2023; Tony Mok ASCO 2024

KROCUS trial

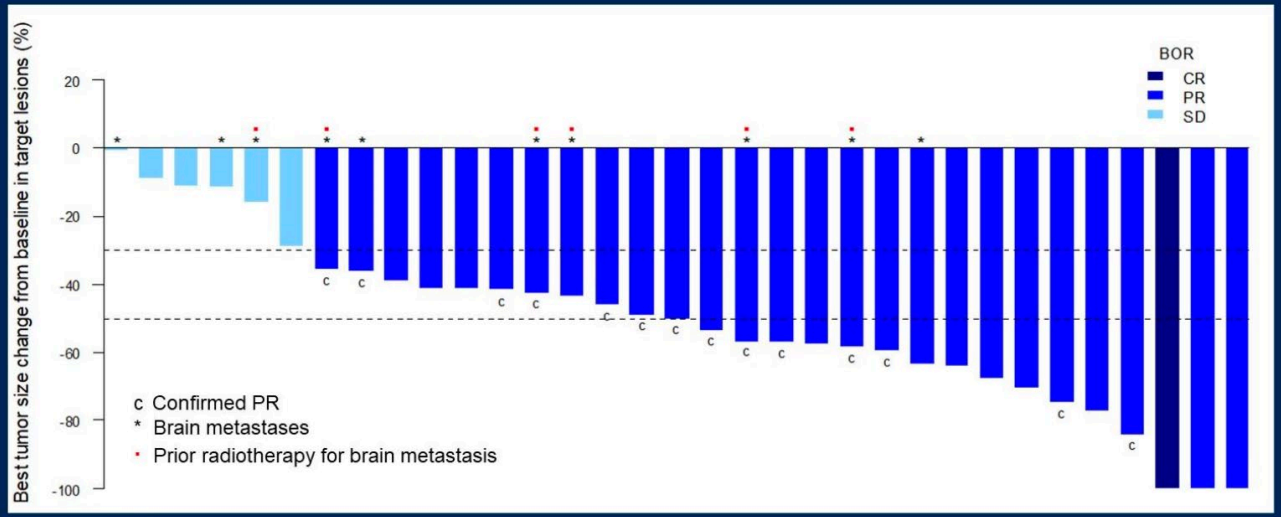


Gregorc Vanesa, ASCO 2024

KROCUS trial

Best Overall Response

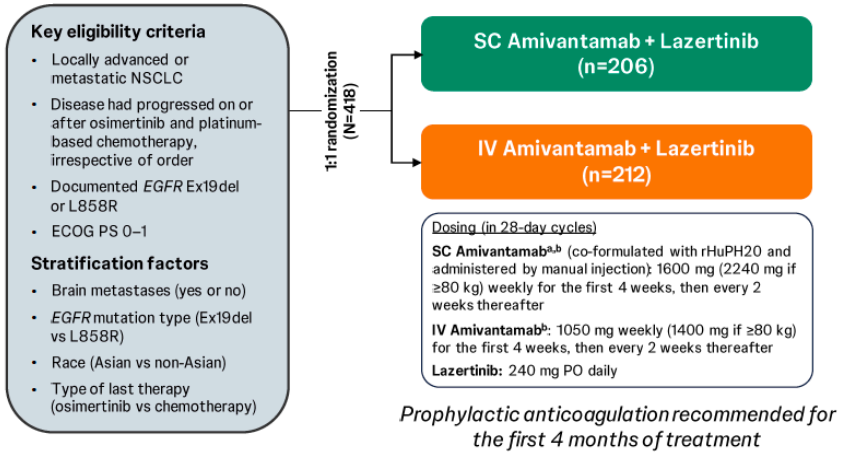
- A total of 33 pts had at least one available post-treatment tumor assessment as of data cut-off date.
- Investigator-assessed ORR was 81.8% (95% CI: 64.5, 93.0) and DCR was 100% (95% CI: 89.4, 100); in pts with brain mets ORR was 70%.



Gregorc Vanesa, ASCO 2024

PALOMA-3 trial: study design and ORR

Subcutaneous Amivantamab with Lazertinib in pretreated EGFRm+ NSCLCs:



Co-primary endpoints[c]:
- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

Secondary endpoints:
- ORR (noninferiority)
- PFS (superiority)
- DoR
- Patient satisfaction[f]
- Safety

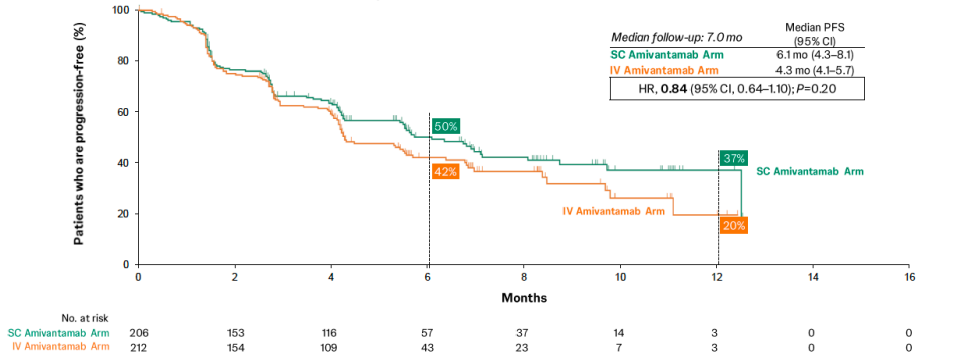
Exploratory endpoints:
- OS

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI)[a]		
All responders	30 (24–37)	33 (26–39)
	Relative risk, 0.92 (95% CI, 0.70–1.23); *P*=0.001	
Confirmed responders	27 (21–33)	27 (21–33)
	Relative risk, 0.99 (95% CI, 0.72–1.36); *P*<0.001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI)[b]	75 (69–81)	71 (64–77)
Median time to response (range), mo	1.5 (1.2–6.9)	1.5 (1.2–9.9)

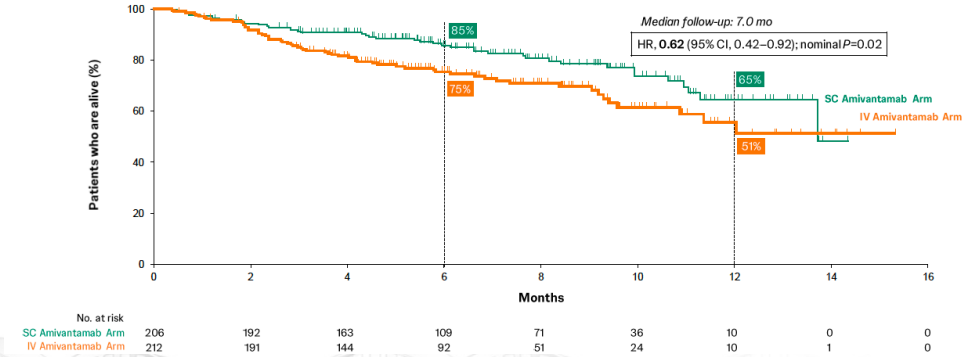
Leighl NB, et al. ASCO 2024

PALOMA-3 trial: study design and ORR

PFS was numerically longer with SC vs IV amivantamab, with an HR of 0.84

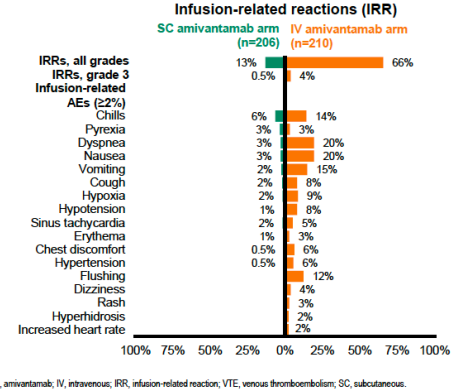


There was an OS benefit associated with SC amivantamab, with an HR of 0.62 compared to the IV amivantamab arm[a]

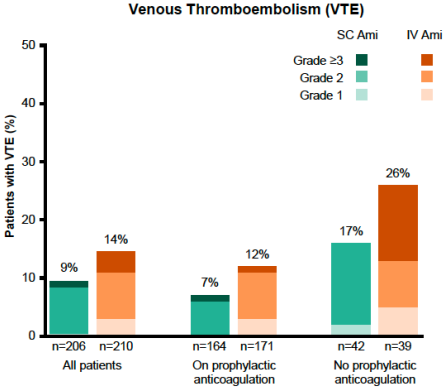


Leighl NB, et al. ASCO 2024

PALOMA-3 trial: exploratory analyses

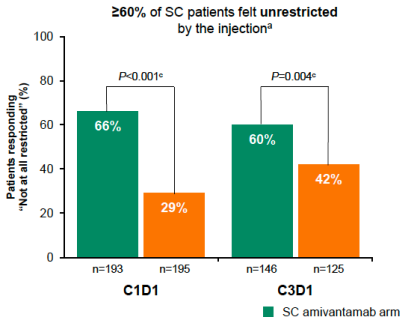


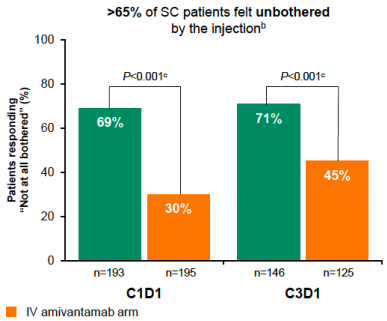
Ami, amivantamab; IV, intravenous; IRR, infusion-related reaction; VTE, venous thromboembolism; SC, subcutaneous.



Patient Convenience

Patient convenience as measured by mTASQ was substantially improved with SC vs IV amivantamab on C1D1 and C3D1





PALOMA-3
Ami + Lazi in
3L EGFR+ NSCLC

Alexander M, et al. WCLC 2024

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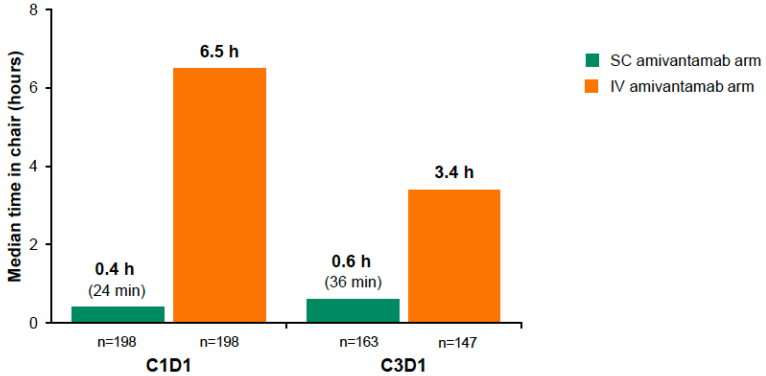
PALOMA-3 trial: exploratory analyses

Patient Time in Chair[a]

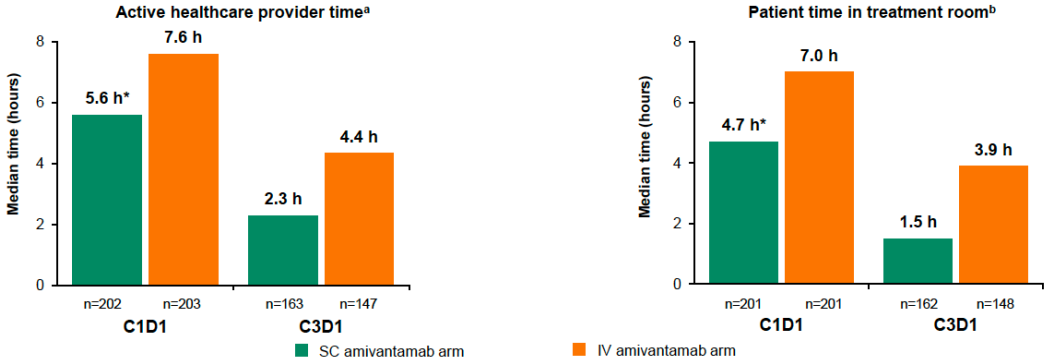
Patient time in chair was substantially lower with SC vs IV amivantamab on C1D1 and C3D1



Healthcare Resource Utilization

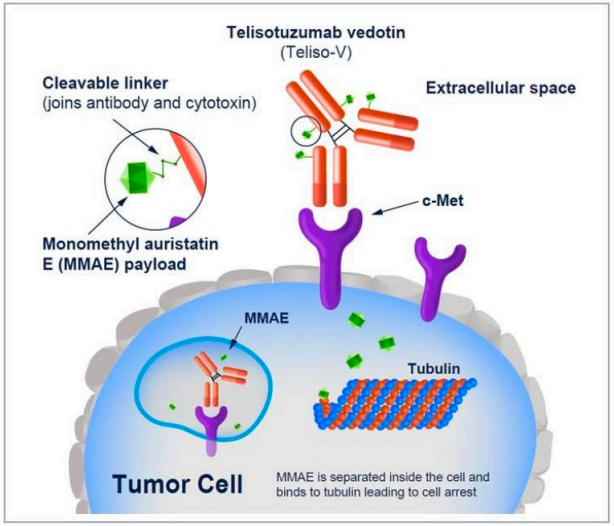
Healthcare resource utilization was substantially improved with SC vs IV amivantamab on C1D1 and C3D1

*Trial required mandatory observation period of 4 hours for SC amivantamab on C1D1



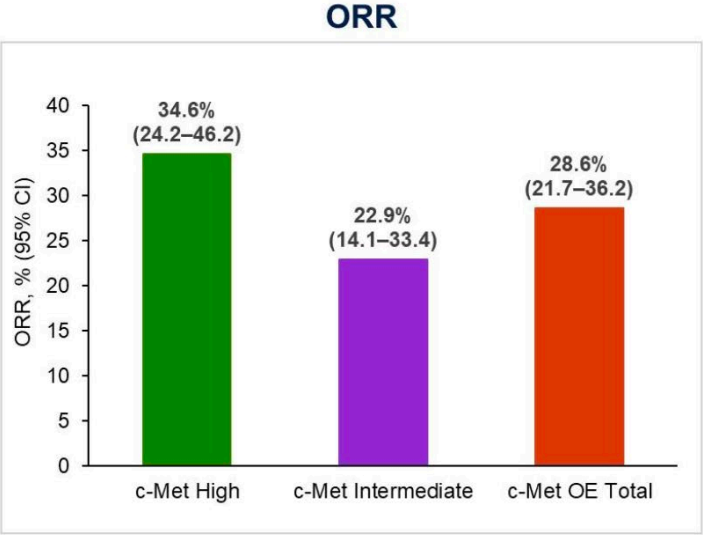
LUMINOSITY trial: Teliso-V, a first in class c-Met-targeting ADC

- Teliso-V is an ADC that kills c-Met OE tumor cells by delivery of the MMAE cytotoxic payload
- Approximately 25% of patients with NSQ *EGFR* WT NSCLC overexpress the c-Met protein by IHC[1a]
- Teliso-V was tested in the non-randomized, 2-stage, phase 2 LUMINOSITY trial,[2] which was designed to:
  - Identify the optimal c-Met protein–OE NSCLC population for treatment with Teliso-V (**stage 1**)
  - Expand the selected group for efficacy evaluation (**stage 2**)
- **This presentation will demonstrate**
  - Durable responses were observed in the NSQ *EGFR* WT population
  - Higher c-Met protein expression enriched for response rate
  - Tolerability was characterized by late-onset peripheral neuropathy



LUMINOSITY trial

ORR and DOR per ICR

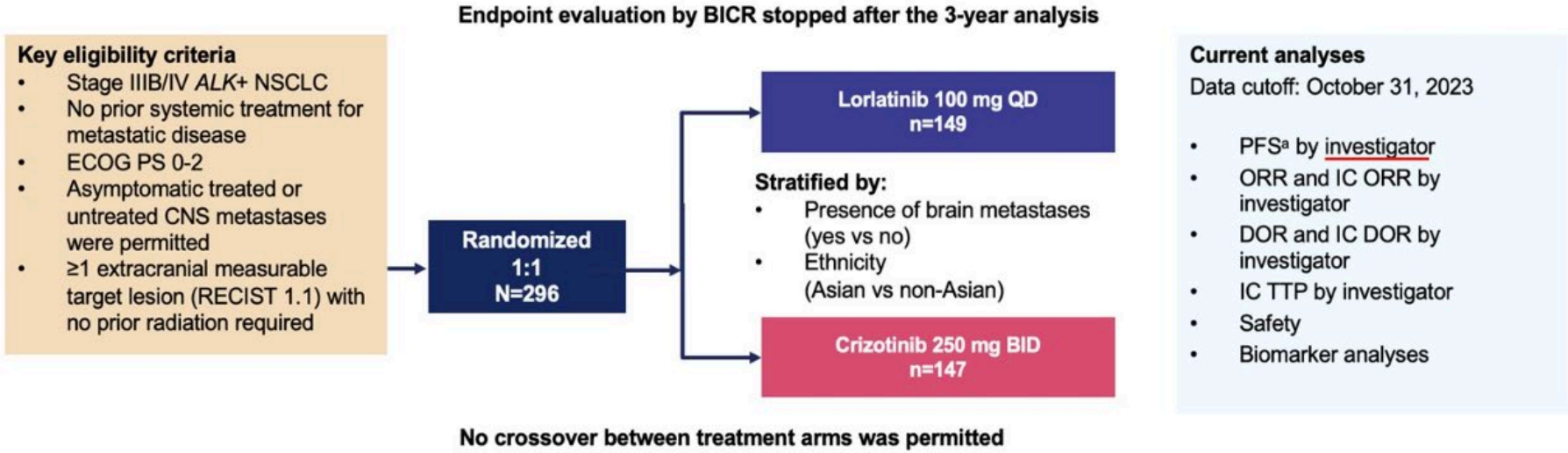


	c-Met High (n=78)	c-Met Intermediate (n=83)	c-Met OE Total (N=161)
Number of responders	27	19	46
Median DOR, months [95% CI]	9.0 [4.2, 13.0]	7.2 [5.3, 11.5]	8.3 [5.6, 11.3]
DOR ≥6 months, n (%)	17 (63.0)	9 (47.4)	26 (56.5)

- Median time to onset of response per ICR was 1.41 months (range 1.0–7.4) for c-Met OE total

CROWN trial

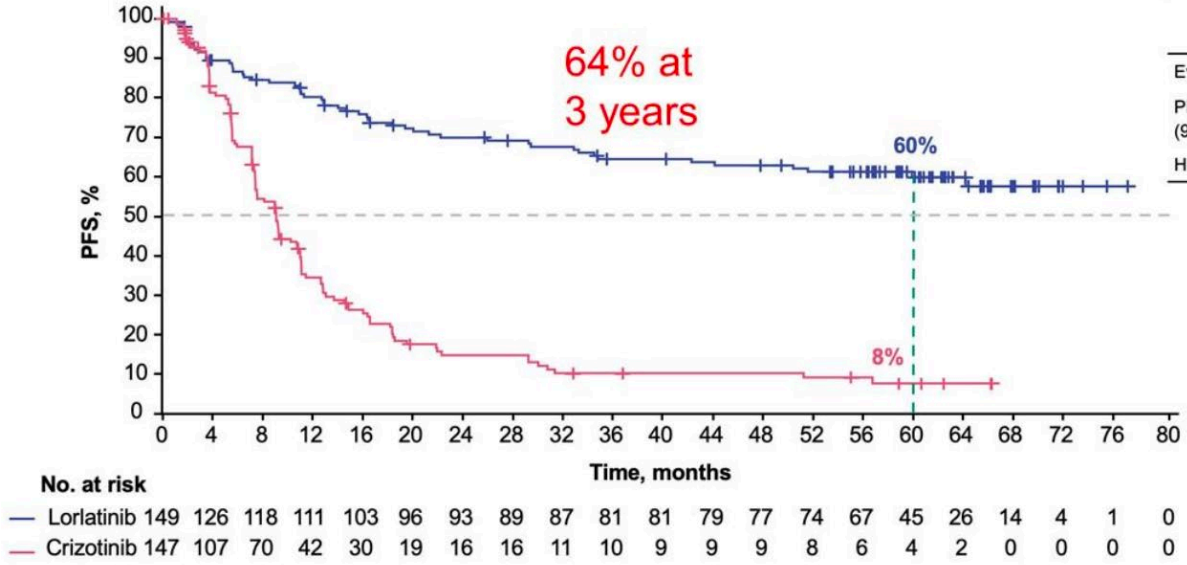
Study design



Ibiyai Dagogo-Jack et al., ASCO 2024

CROWN trial

5-y PFS (not reached)



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

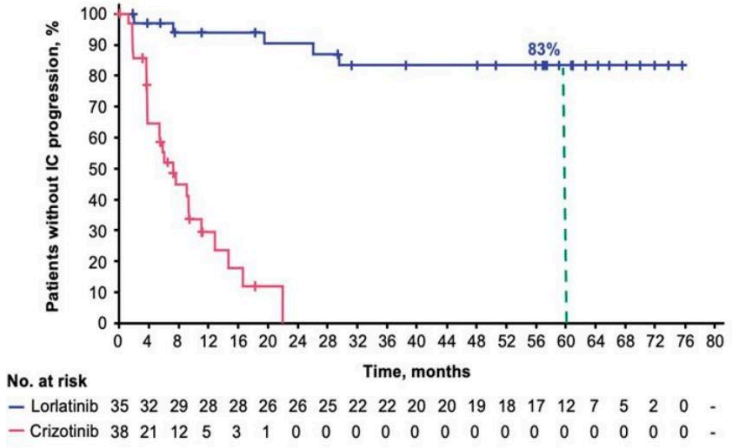
Ibiyai Dagogo-Jack et al., ASCO 2024

CROWN trial

5-y CNS outcome

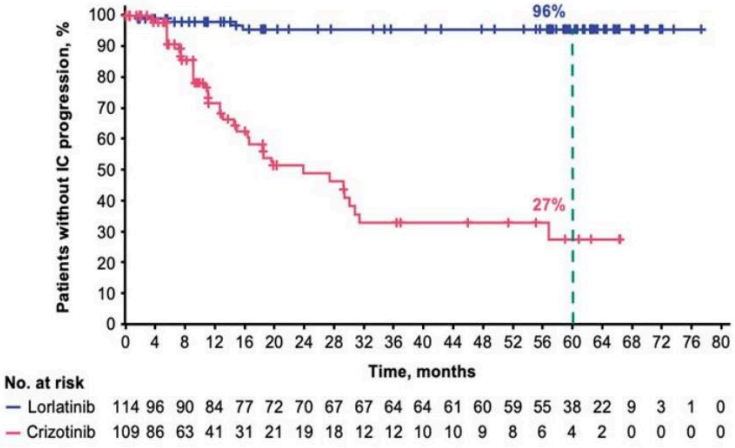
With Baseline Brain Metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, median (95% CI), months	NR (NR-NR)	7.2 (3.7-11.0)
HR (95% CI)	0.03 (0.01-0.13)	



Without Baseline Brain Metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	4	39
Time to IC progression, median (95% CI), months	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	0.05 (0.02-0.13)	



Ibiyai Dagogo-Jack et al., ASCO 2024

CROWN trial

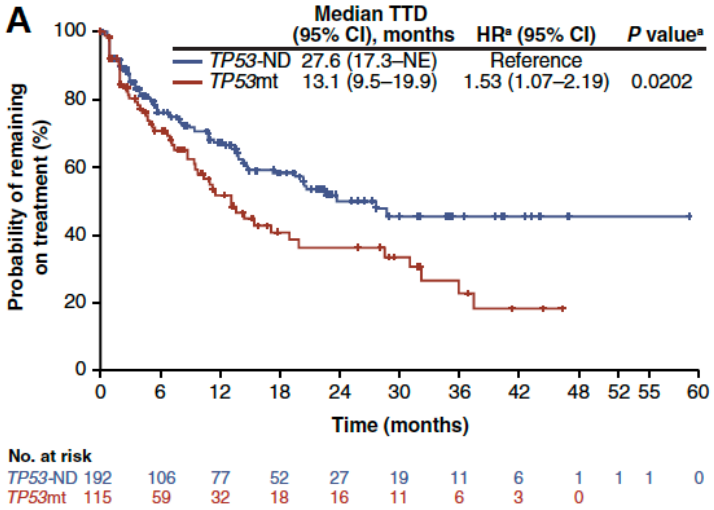
Co-mutations in TP53 gene and efficacy of ALK TKIs

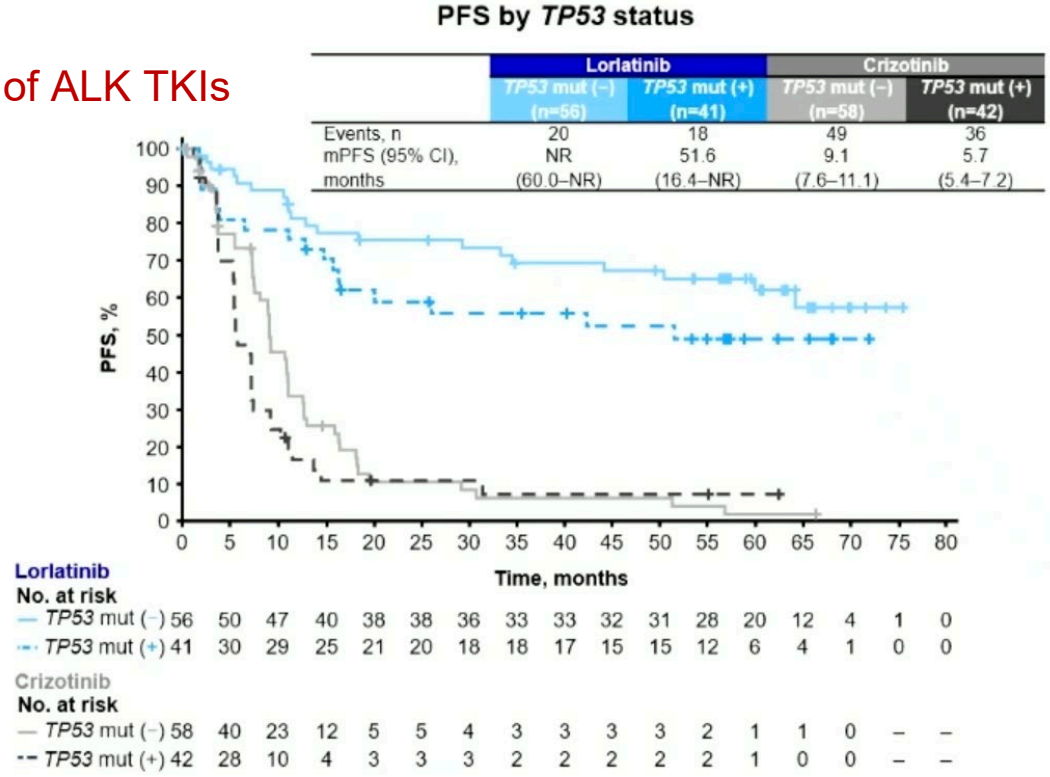
ORIGINAL ARTICLE

IASLC

Impact of *EML4-ALK* Variants and Co-Occurring *TP53* Mutations on Duration of First-Line ALK Tyrosine Kinase Inhibitor Treatment and Overall Survival in *ALK* Fusion-Positive NSCLC: Real-World Outcomes From the GuardantINFORM database

Kaushal Parikh, MD,[a,*] Anastasios Dimou, MD,[a] Konstantinos Leventakos, MD, PhD,[a] Aaron S. Mansfield, MD,[a] Mohamed Shanshal, MD,[a] Yin Wan, MS,[b] Huamao M. Lin, PhD,[b] Sylvie Vincent, PhD,[b] Jennifer Elliott, PhD,[c] Ioana R. Bonta, MD[d]





Parikh K, et al. JTO 2024; Solomon BJ, et al. JCO 2024

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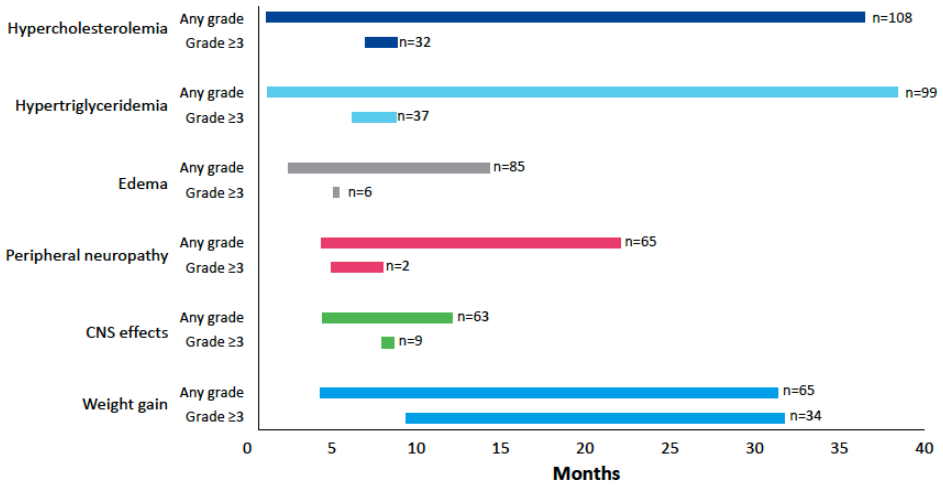
CROWN trial

Lorlatinib safety profile in the CROWN study: Onset, severity and management

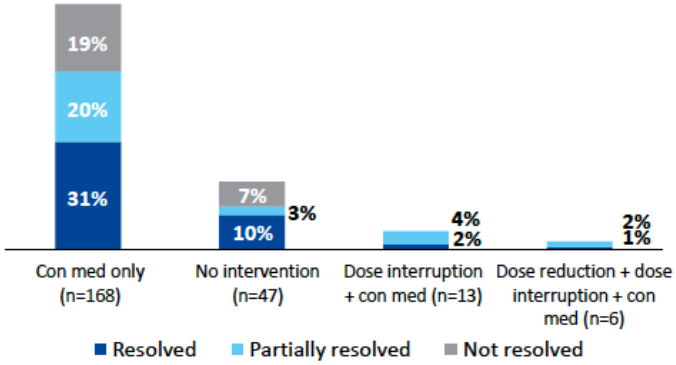
- For hyperlipidemia, median time to onset of any-grade AEs was 15 days, and median duration was ≈37 months; median time to onset of grade ≥3 AEs was ≈6 months
- For any grade edema, peripheral neuropathy, and CNS effects, median time to onset was 2-4 months, and median duration was 8-18 months
- Only weight gain showed grade ≥3 AE that lasted more than 3 months

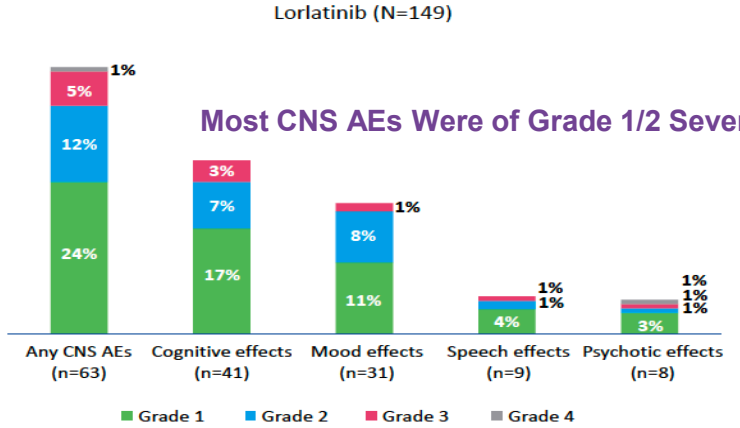


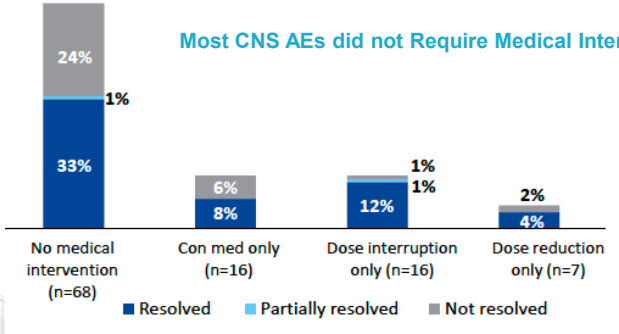
Most of the hyperlipidemia events were managed and controlled with lipid-lowering agents

CROWN trial

Lorlatinib safety profile in the CROWN study: Onset, severity and management







Bauer TM, et al. WCLC 2024

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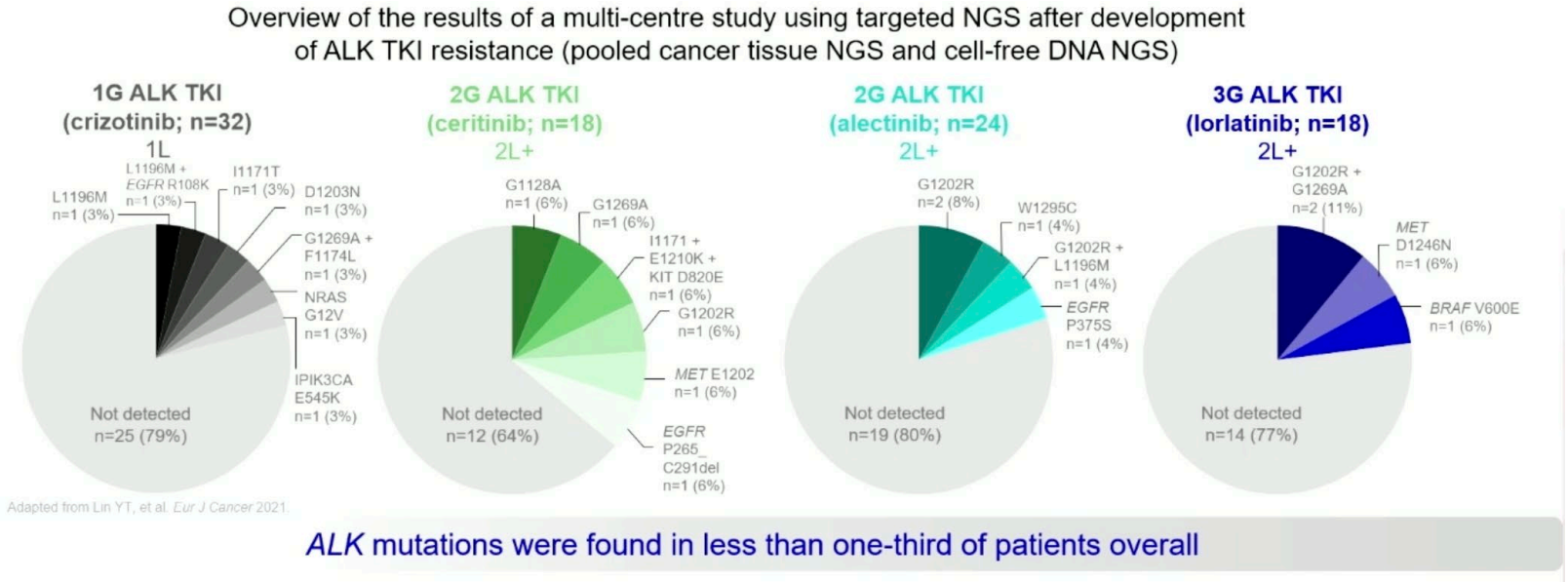
Variations of mechanisms of resistance to different generations of ALK TKIs

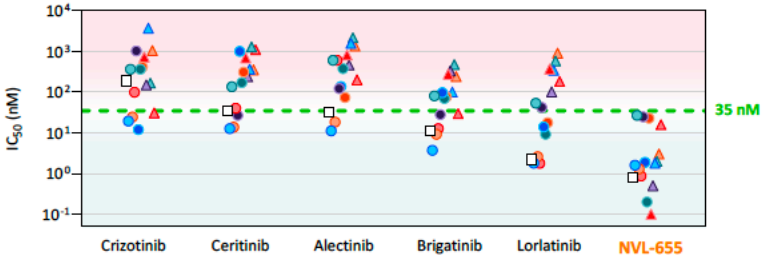


Mok TS. ESMO 2024

NVL-655: A Rationally Designed ALK-selective, TRK-sparing TKI

ALK Fusion and ALK Single/Compound Mutation Activity

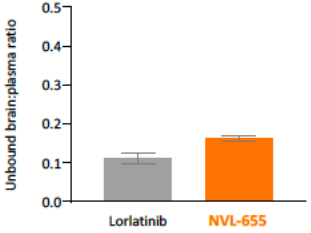
Potent activity (IC_{50} = 0.1 – 30 nM) against ALK-driven cell lines, including ALK single and compound mutants



Cell lines harboring EML4-ALK fusion
3-day cell viability assay

Brain Penetrance

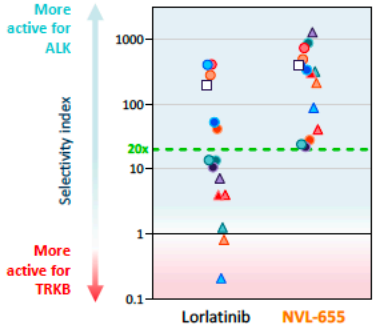
Preclinical pharmacokinetic data similar to lorlatinib



Wistar Han rats
10 mg/kg, single dose PO
1-hour timepoint

Avoidance of TRK Inhibition

Selective inhibition of ALK and ALK mutants over TRK



$$\text{Selectivity index} = \frac{IC_{50}\ (\text{pTRKB})}{IC_{50}\ (\text{Ba/F3 EML4-ALK})}$$

Cell viability 3-day IC_{50} (nM) of human cell lines (NCI-H2228, NCI-H3122) or of Ba/F3 cells expressing *EML4-ALK* V1 fusions

	Cell with *ALK* fusion	NUV-655	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
No kinase domain mutations	NCI-H2228 (*EML4-ALK* V3)	**0.70**	90	55	13	13	<1.1
	NCI-H3122 (*EML4-ALK* V1)	**2.0**	180	48	22	22	3.5
	Wild-type	**1.6**	270	90	25	42	4.2
G1202R+ mutations	G1202R	**<0.73**	950	570	1,600	400	120
	G1202R/L1196M	**7.0**	1,500	1,400	2,200	820	3,900
	G1202R/G1269A	**3.0**	1,100	350	1,300	240	970
	G1202R/L1198F	**2.0**	170	1,300	2,200	470	720

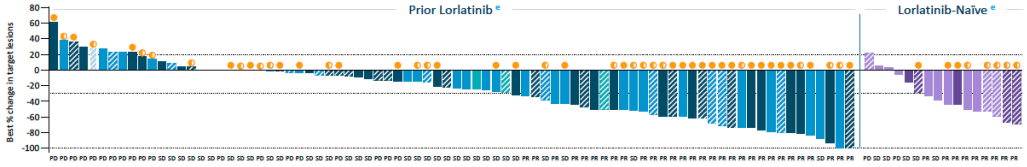
Adapted from Relish HE, et al. *Cancer Res* 2021

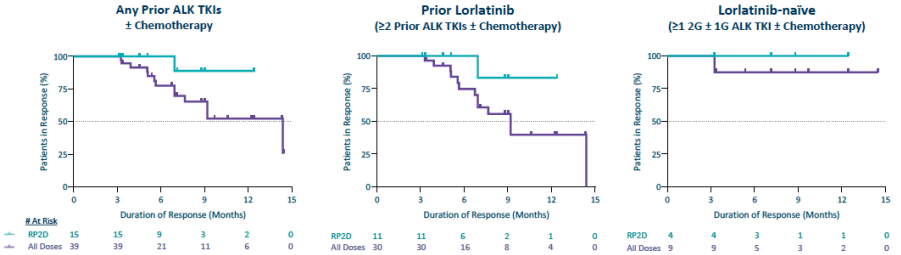
A Phase 1/2 clinical trial (ALKOVE-1) is underway in advanced NSCLC and other solid tumours harbouring *ALK* rearrangements or activating *ALK* mutations[2]

Drilon A, et al. ESMO 2024

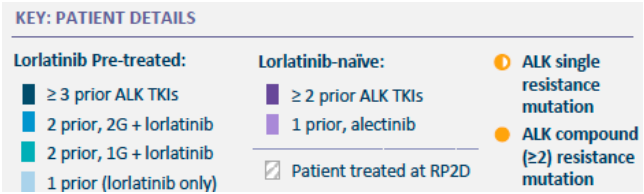
Phase 1/2 ALKOVE-1 study of NVL-655 in ALK-positive (ALK+) solid tumors

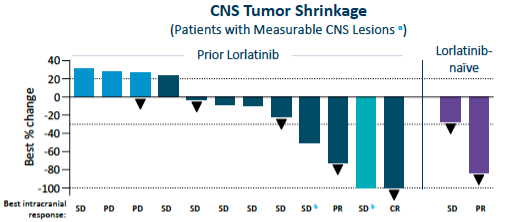
RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [a]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	38% (39/103)	52% (30/58)	69% (22/32) [d]	35% (30/85)	47% (23/49)	54% (15/28)	53% (9/17)	88% (7/8)
RP2D	38% (15/39)	55% (12/22)	71% (10/14)	35% (11/31)	50% (8/16)	64% (7/11)	57% (4/7)	80% (4/5)

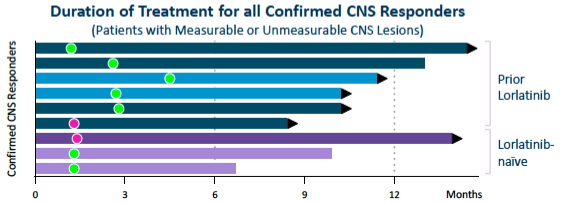




NSCLC Response-Evaluable	All Dose Levels	RP2D	All Dose Levels	RP2D	All Dose Levels	RP2D
Median DOR, m (95% CI)	14.4 (6.9, NE)	Not Reached (6.9, NE)	9.2 (6.9, NE)	Not Reached (6.9, NE)	Not Reached (3.3, NE)	Not Reached (NE, NE)
DOR ≥ 6 m [a] (95% CI)	78% (58, 89)	100% (100, 100)	75% (52, 88)	100% (100, 100)	88% (39, 98)	100% (100, 100)







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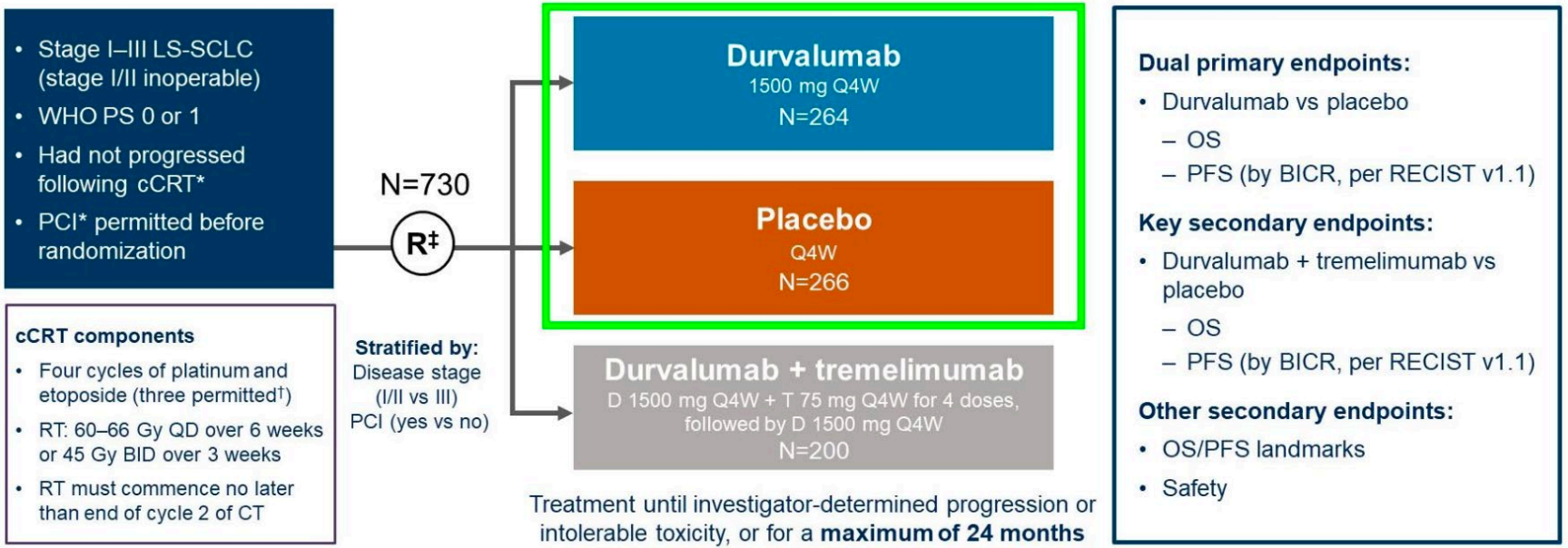
Drilon A, et al. ESMO 2024

SCLC

ADRIATIC trial

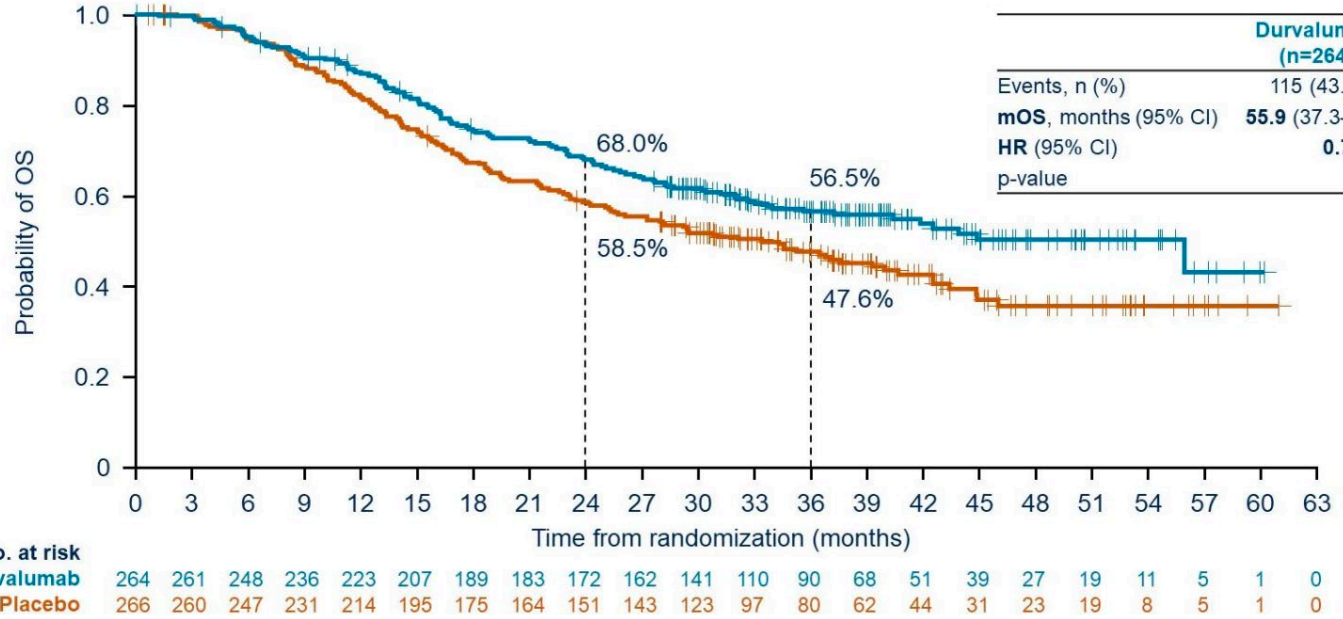
Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)



Spigel David, ASCO 2024

ADRIATIC trial
OS

- Median duration of follow up in censored patients: 37.2 months (range 0.1–60.9)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

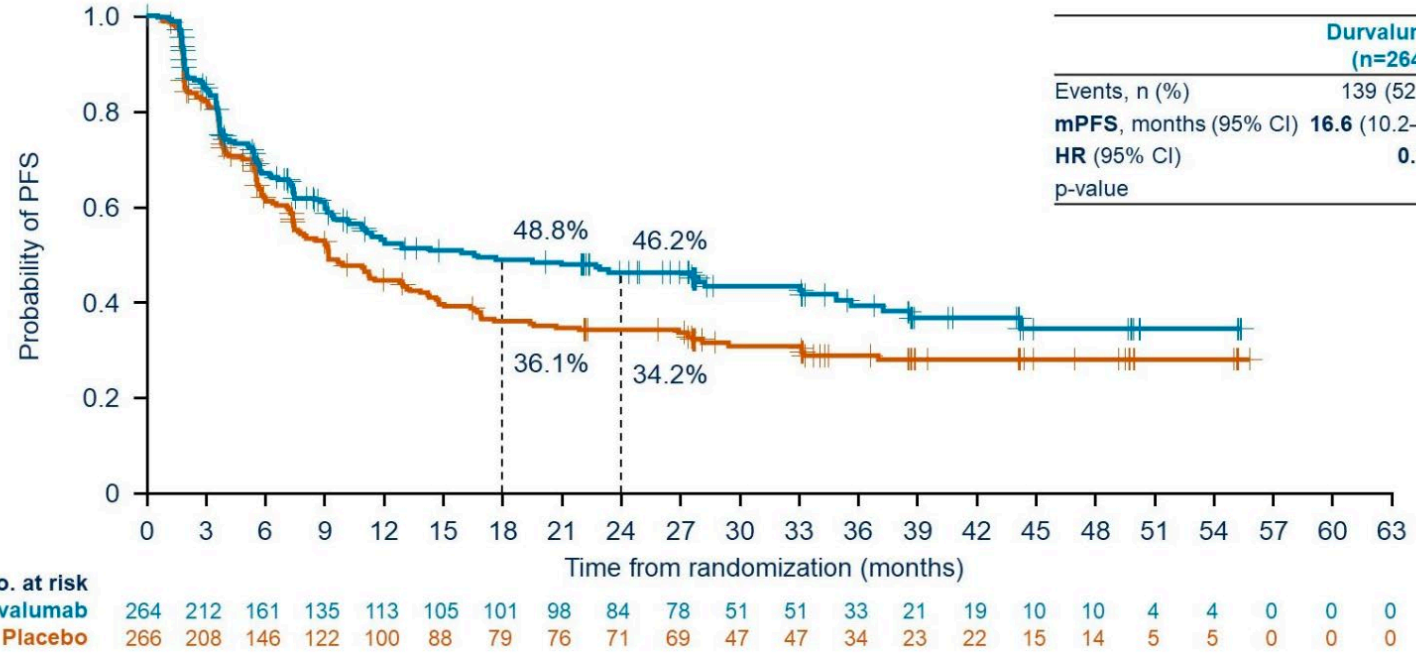
No. at risk																					
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

Spigel David, ASCO 2024

ADRIATIC trial

PFS

- Median duration of follow up in censored patients: 27.6 months (range 0.0–55.8)



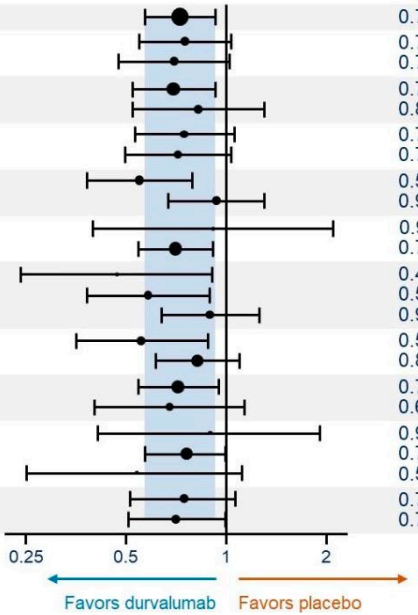
	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

Spigel David, ASCO 2024

ADRIATIC trial

OS Subgroup Analysis

		Events/Patients n/N		HR (95% CI)
		Durvalumab	Placebo	
All patients		115/264	146/266	0.73 (0.57–0.93)
Age	<65 years	69/160	83/162	0.76 (0.55–1.04)
	≥65 years	46/104	63/104	0.70 (0.48–1.02)
Sex	Male	79/178	108/188	0.70 (0.52–0.93)
	Female	36/86	38/78	0.83 (0.52–1.31)
Race	White	60/130	77/137	0.75 (0.53–1.05)
	Asian	53/131	64/121	0.72 (0.50–1.04)
→ **WHO performance status**	0	48/133	74/131	0.55 (0.38–0.79)
	1	67/131	72/135	0.94 (0.67–1.31)
AJCC disease stage at diagnosis	I/II	11/33	12/34	0.92 (0.40–2.11)
	III	104/231	134/232	0.71 (0.55–0.91)
→ **Time from end of cCRT* to randomization**	<14 days	14/32	24/32	0.47 (0.24–0.91)
	≥14 days to <28 days	37/79	51/80	0.59 (0.38–0.90)
	≥28 days	64/153	71/154	0.90 (0.64–1.27)
Prior chemotherapy regimen	Carboplatin-etoposide	31/ 91	46/88	0.56 (0.35–0.89)
	Cisplatin-etoposide	84/173	100/178	0.82 (0.61–1.10)
Prior radiation schedule	Once daily	92/195	107/187	0.72 (0.55–0.95)
	Twice daily	23/69	39/79	0.68 (0.40–1.14)
Best response to prior cCRT	Complete response	12/31	15/34	0.90 (0.41–1.92)
	Partial response	88/191	116/200	0.76 (0.57–1.00)
	Stable disease	15/42	15/32	0.54 (0.25–1.13)
Prior PCI	Yes	53/142	67/143	0.75 (0.52–1.07)
	No	62/122	79/123	0.71 (0.51–0.99)



*End of chemotherapy or radiotherapy, whichever was latest.
Intention-to-treat analysis stratified, subgroup analyses unstratified. Not all prespecified subgroups are included in the plot.
Size of circle is proportional to number of events across both arms.

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Conclusions

- Chemo-immunotherapy becomes the standard of care in early stages as a neoadjuvant/perioperative treatment.
- Osimertinib is effective as consolidation therapy post-chemotherapy/radiotherapy in locally advanced EGFR-mutated NSCLC.
- New TKIs and combination strategies for KRASG12C-mutated NSCLC (to be considered among oncogene-addicted diseases?).
- MoAbs, ADCs, and new TKIs for Ex20ins, MET positivity.
- Durvalumab is effective as consolidation therapy post-chemotherapy/radiotherapy in limited-stage SCLC.