VII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN
Vigo, 20 y 21 de febrero de 2025

Cáncer de pulmón.
LO MEJOR DE 2024

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Disclosure Information

Consultant or Advisory Role: BMS, MSD, ROCHE, ASTRA ZENECA, BOEHRINGER INGELHEIM, NOVARTIS, Lilly, Sanofi, Regeneron, Gilead.

Lectures: BMS, MSD, ROCHE, ASTRA ZENECA, BOEHRINGER INGELHEIM, Lilly, Sanofi.

Grant support : BMS

Early stage and locally advanced NSCLC – Stages I, II and III

LAURA :Osimertinib is a new standard of care after CT/RT in unresectable *EGFR*-mutant NSCLC

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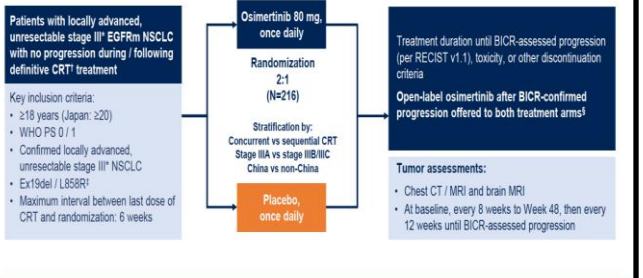
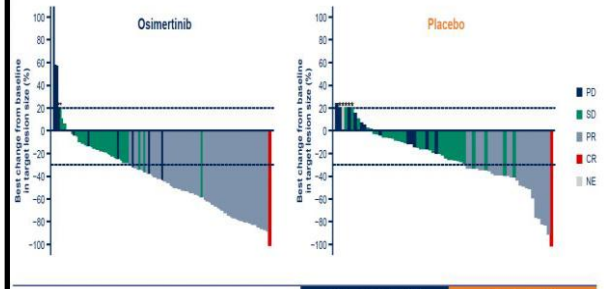
LAURA Phase 3 double-blind study design



Endpoints

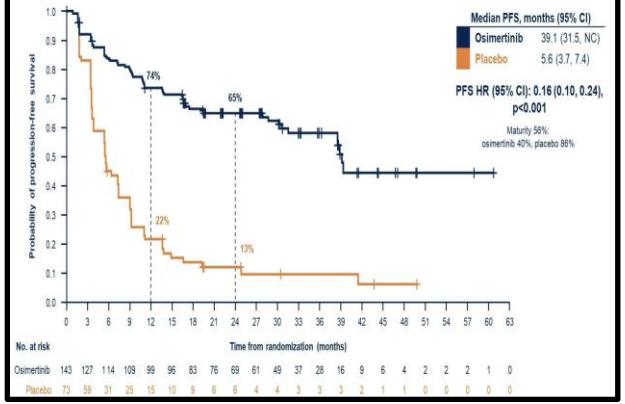
- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

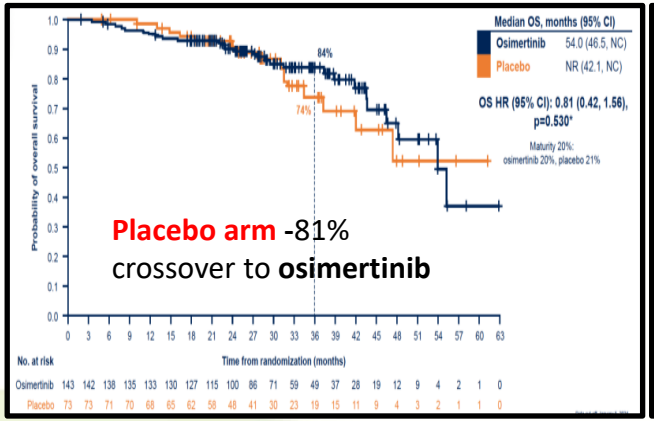
Tumor response by BICR



	Osimertinib (n=143)	Placebo (n=73)
Objective response rate, % (95% CI)	57 (49, 66)	33 (22, 45)
Disease control rate, % (95% CI)	89 (83, 94)	79 (68, 88)
Median duration of response, months (95% CI)	36.9 (30.1, NC)	6.5 (3.6, 8.3)

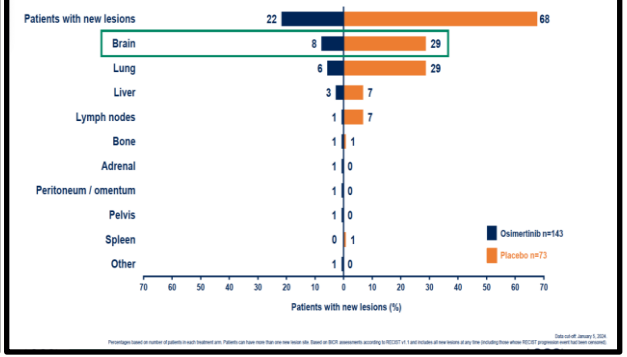
Progression-free survival by BICR





Placebo arm -81%
crossover to **osimertinib**

Sites of new lesions by BICR



All-causality adverse events (≥10%)*

The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable

Some reminders in toxicity:

- Radiation pneumonitis: 48% vs. 38%
- ILD: 8% vs. 1%
- Dose interruptions: 56% vs. 28%
- Dose reductions: 8% vs. 1%
- Discontinuation: 13% vs. 5%

Ramalingam, ASCO 2024; Lu S, NEJM 2024

POLESTAR study: Aumolertinib after Chemoradiotherapy in Unresectable

Key inclusion criteria:

- ≥18 years
- ECOG score 0 / 1
- EGFR Ex19del / L858R
- Locally advanced, unresectable stage III* NSCLC
- No progression during or following definitive CRT# treatment
- Interval between last dose of CRT and randomization: ≤6 weeks

2 : 1

Aumolertinib 110mg QD; (N=94)

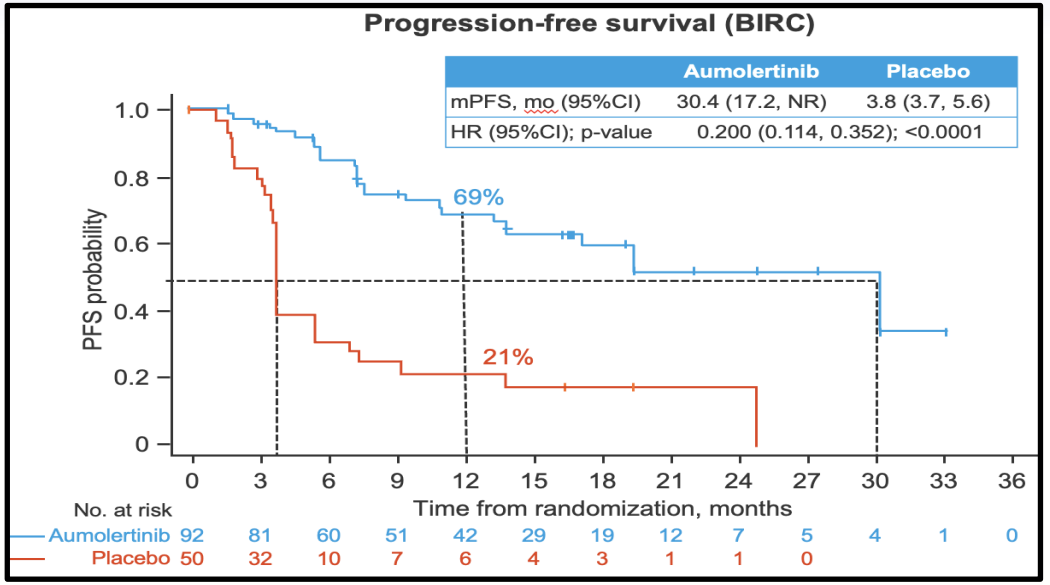
Placebo 110mg QD; (N=53)

N=147

Stratification by
- Ex19del vs L858R
- Stage IIIA vs Stage IIIB/IIIC
- cCRT vs sCRT

- Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria
- Tumor assessment: every 8 weeks to week 48, then every 12 weeks until progression
- Crossover§ is allowed for patients in placebo arm

- **Primary endpoint:** PFS assessed by BICR (sensitivity analysis: PFS assessed by Investigator)
- **Secondary endpoints:** OS, ORR, DCR, DoR, CNS PFS, TTDM, Safety



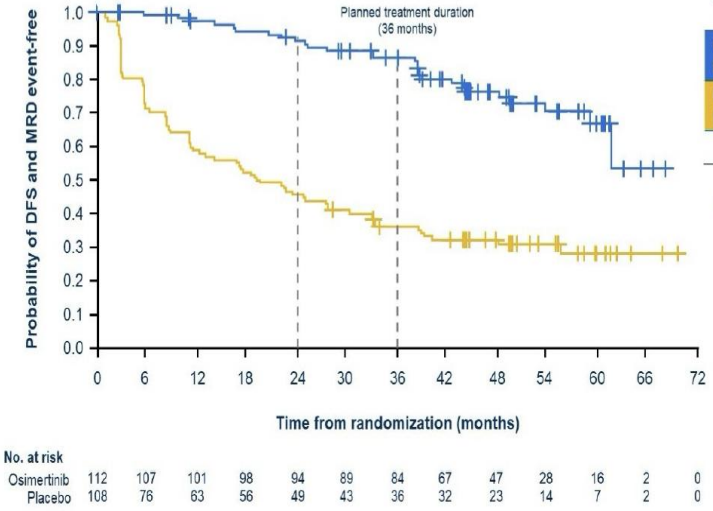
Outcomes	Aumolertinib (n=92)	Placebo (n=50)
ORR, % (95%CI)	57 (46, 67)	22 (11, 34)
mDoR, mo (95%CI)	16.59 (15.05, NR)	7.10 (1.71, 17.51)
mOS, mo (range)	16.6 (1.5–33.2)	14.9 (0.4–31.4)
CNS mPFS, mo (95%CI)	NR (NR, NR)	NR (NR, NR)
HR (95%CI); p-value	0.33 (0.12, 0.92); 0.027	
mTTDM, mo (95%CI)	NR (NR, NR)	NR, (3.84, NR)
HR (95%CI); p-value	0.21 (0.09, 0.49); <0.0001	

Safety

- The most common AE for aumolertinib was blood creatine phosphokinase increased; majority of the AEs were <Grade 3.
- Radiation pneumonitis was reported in 45% vs 30% for aumolertinib vs placebo, with none being Grade ≥3.
- Interstitial lung disease was not reported for aumolertinib, but reported in 1 patient (Grade 3) for placebo.

Meng et al. WCLC 2024

ADAURA: molecular residual disease (MRD)

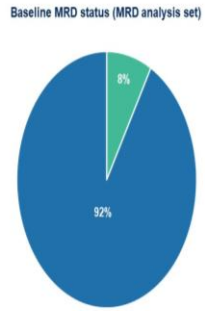


% (95% CI)	DFS and MRD event-free rate	
	24 months	36 months
Osimertinib (n=112)	91 (84, 95)	86 (78, 92)
Placebo (n=108)	46 (36, 55)	36 (27, 45)
HR (95% CI) 0.23 (0.15, 0.36)†		

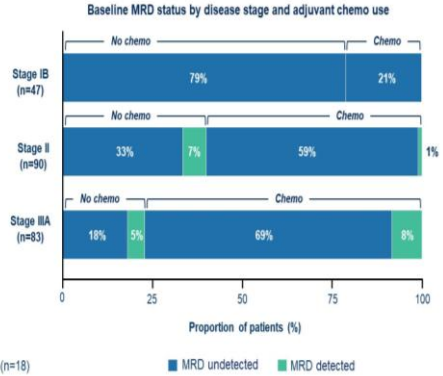
Median follow-up time, months (95% CI):
osimertinib 44.2 (42.4, 49.1), placebo 19.1 (11.1, 28.3)

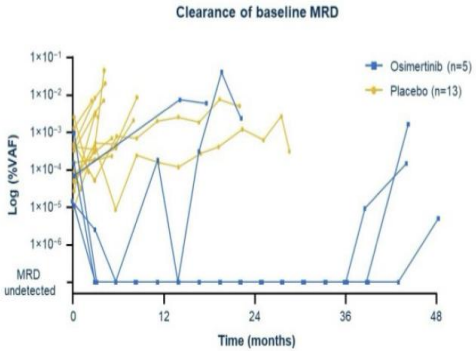
- Detected MRD at baseline was associated with poor outcomes
- Patients receiving osimertinib were more likely to be DFS and MRD event free vs placebo

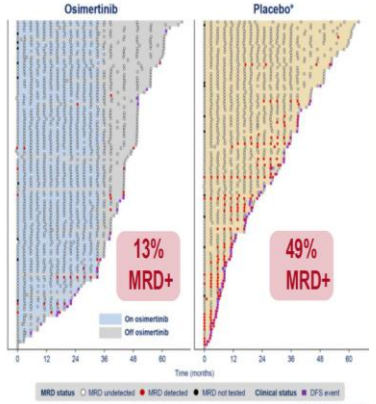
Majority of patients were MRD undetected at baseline



8% detected MRD







- Of 18 patients with detected MRD at baseline
  - 4 / 5 patients receiving osimertinib cleared MRD
  - 0 / 13 patients receiving placebo cleared MRD

John T, ASCO 2024

Advanced NSCLC

Not radically treatable stage III and stage IV

ALK--CROWN: lorlatinib versus crizotinib

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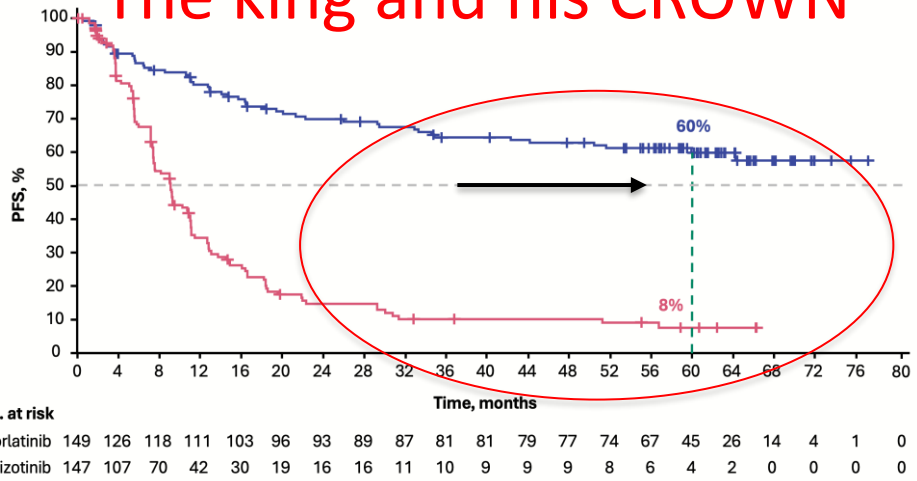
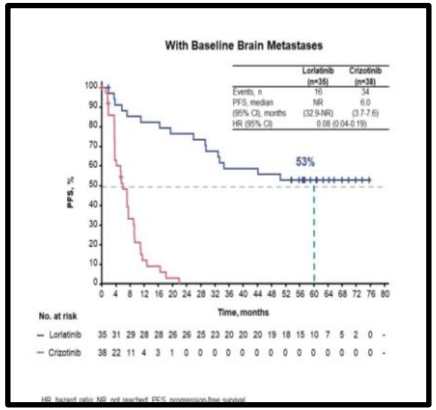
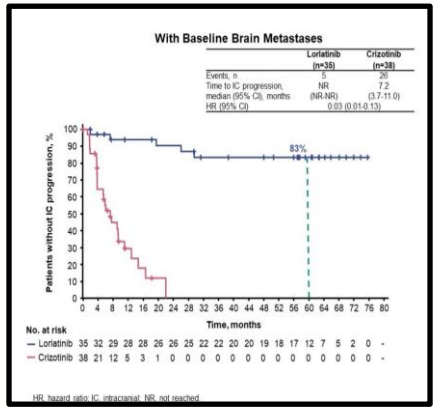
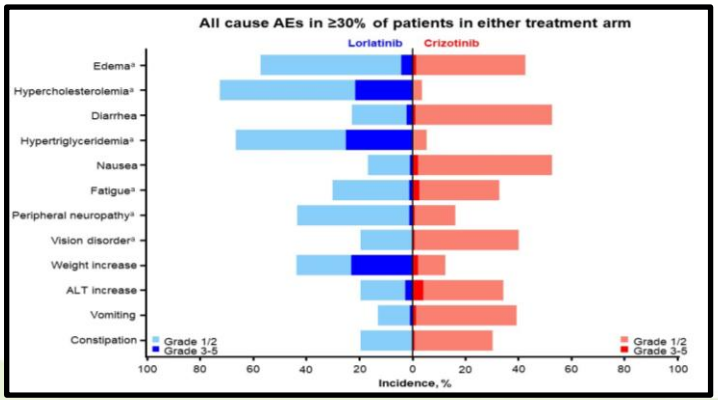
The king and his CROWN

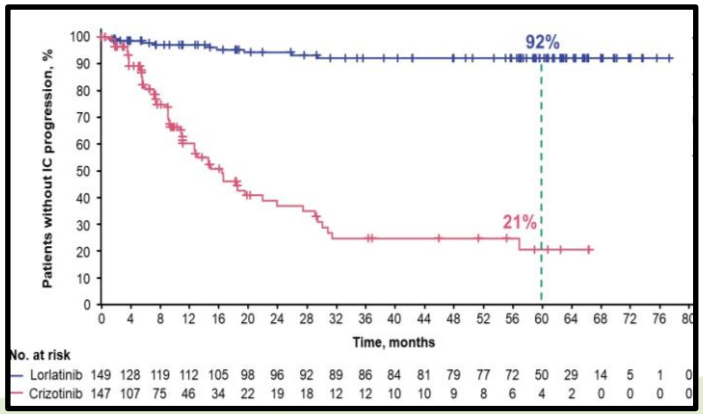






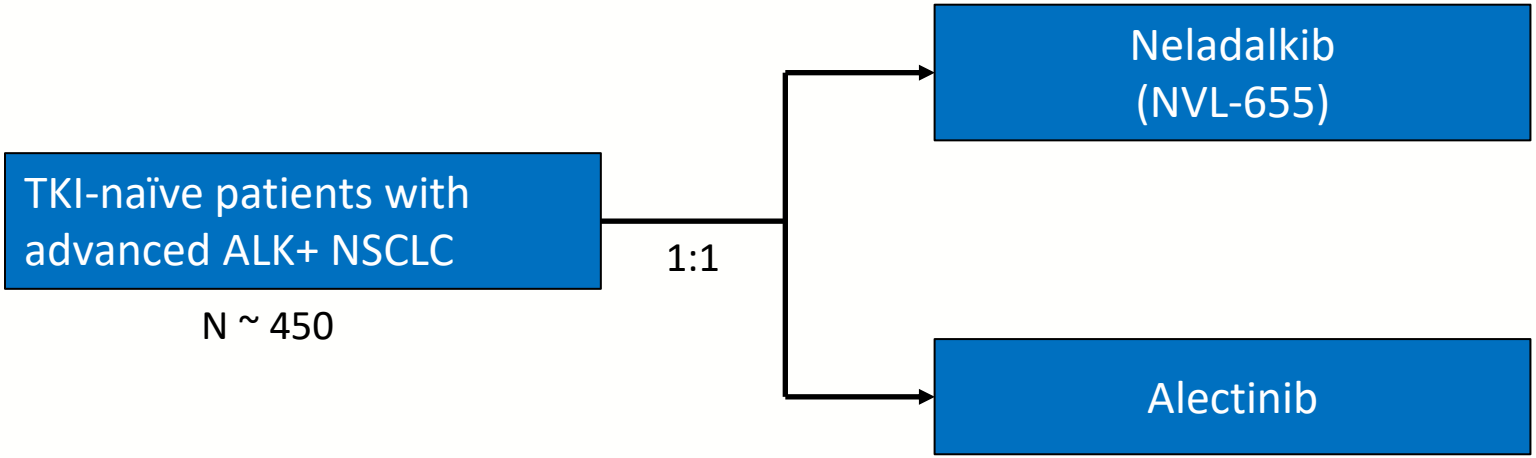


Time to intracranial progression in pts without BMs



Solomon BJ et al., ASCO 2024

On the Horizon: 4th Gen ALK TKI Neladalkib (NVL-655)

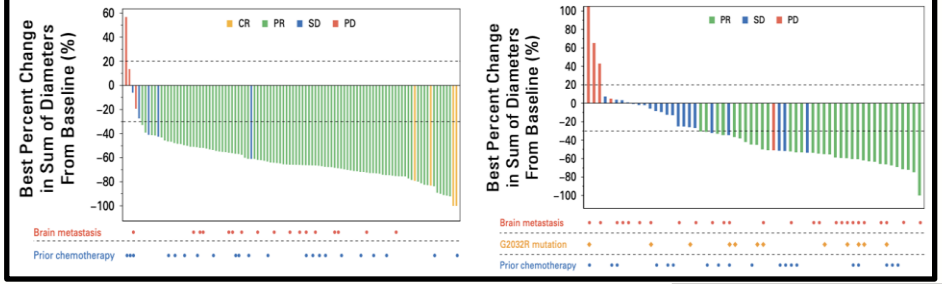


Primary endpoint: PFS per BICR
Secondary endpoints: PFS per investigator assessment, BICR-ORR, IC-ORR, OS, safety

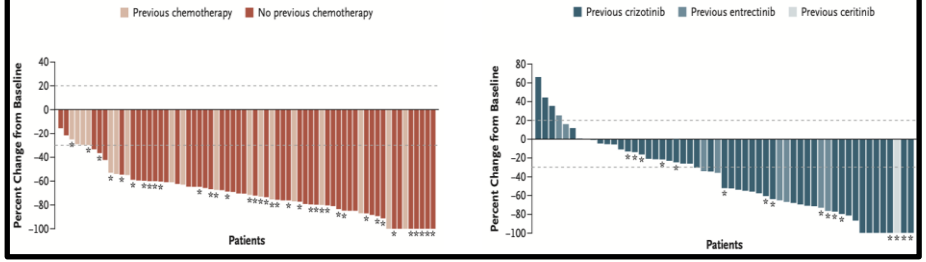
Nuvalent press release

ROS1 Inhibitors

- Taletrectinib (TRUST-I)
  - TKI naïve: RR 91%, intracranial RR 88%
  - Post-crizotinib: RR 52%, DOR 10.6m, PFS 7.6m, icRR 73%



- Repotrectinib, TRIDENT
  - Treatment naïve: RR 79%, DOR 34.1m, PFS 35.7m
  - Prior ROS1 TKI: RR 38%, DOR 14.8m, PFS 9.0m
    - In presence of known ROS1 G2032R, RR 59%

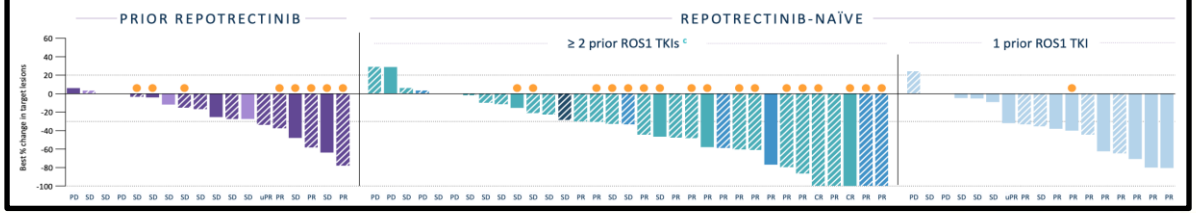


Zidesamtinib (NVL-520, ARROS-1)

- Potent, CNS-active, selective ROS1 inhibitor
- Early results in heavily pretreated population

All NSCLC Response Evaluable Patients ± chemotherapy	Any Prior ROS1 TKI (range 1-4)				≥ 2 prior ROS1 TKIs			1 prior ROS1 TKI (crizotinib)
	All	Repotrectinib-naive	ROS1 G2032R Resistance Mutation [b]		All	Prior Lorlatinib	Repotrectinib-naive	
			Prior Repotrectinib	Repotrectinib-naive				
RECIST 1.1 ORR % (n/n) [a]	44% (31/71)	51% (27/53)	38% (3/8)	72% (13/18)	41% (21/51)	44% (17/39)	47% (17/36)	73% (8/11)
CR [a]	2	2	-	2	2	2	2	-

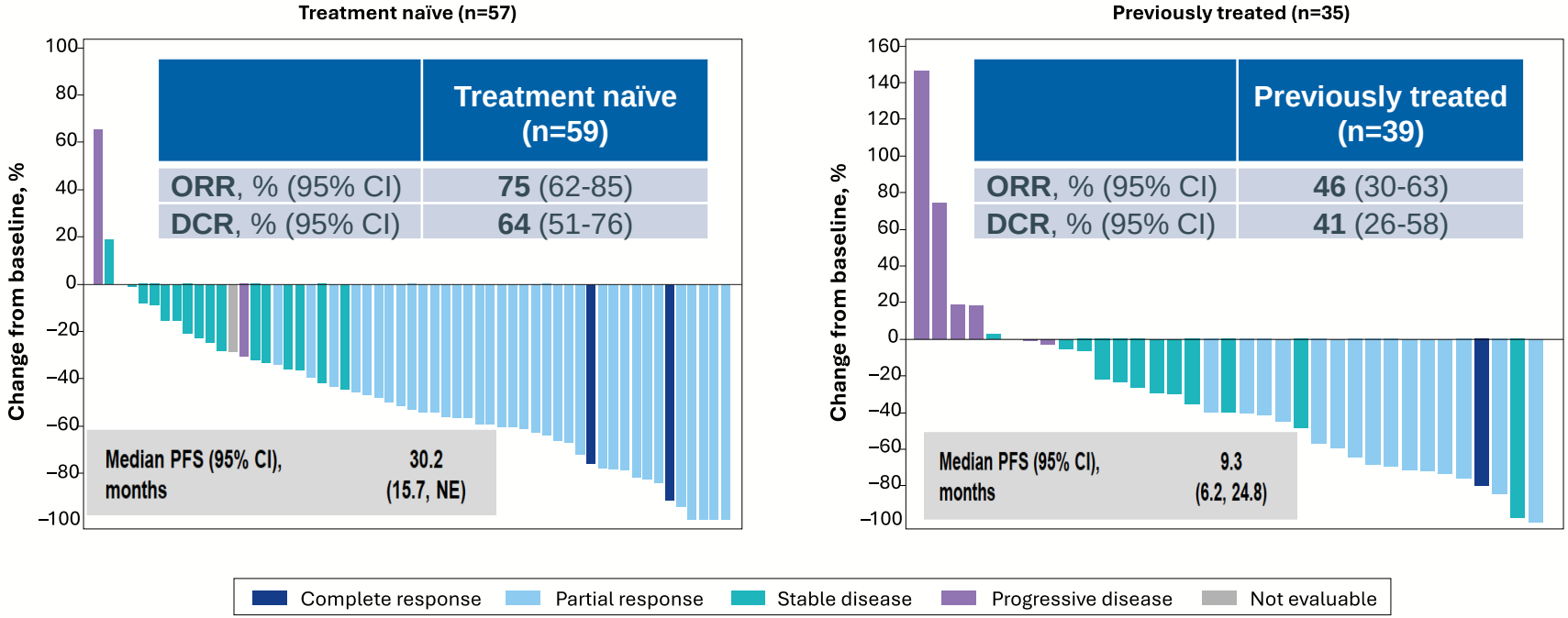
[a] 2 confirmed CRs ongoing with DOR 19.3+ and 26.3+ months. 5 additional CRs observed among patients without measurable disease (2 prior ROS1 TKIs [n=2], 1 prior ROS1 TKI (crizotinib [n=1], entrectinib [n=2])), all ongoing with DOR 3.6+, 3.7+, 13.8+, 13.9+, and 18.5+ months.



Wei Li. ASCO-24. Drilon, NEJM 2024. Besse, ESMO 2024

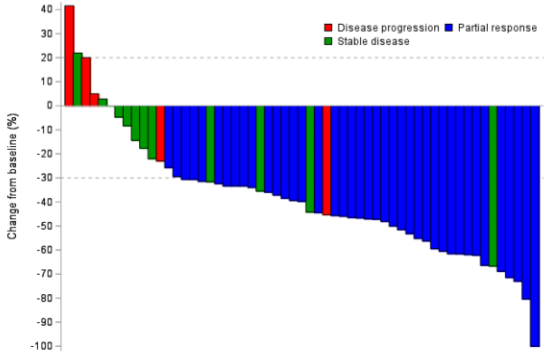
BRAF

Clinical Benefit with Encorafenib + Binimetinib in BRAF V600E NSCLC
Phase 2 PHAROS Study



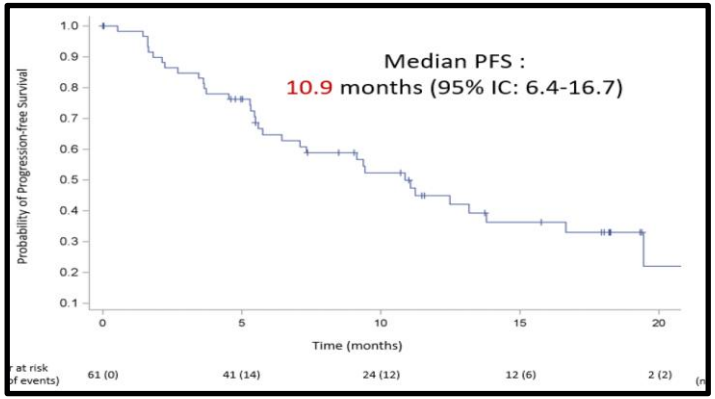
Riely GJ, et al. J Clin Oncol. 2023;41(21):3700-3711. Cutoff Apr 1, 2024, presented at ESMO 2024

Phase 2 trial (IFCT-1904ENCO-BRAF): Encorafenib plus binimetinib in patients with previously untreated



	Cohorte A (n=61)
Overall response confirmed, n (%) [95% CI]	**40 (65.6%)** [53.7% - 77.5%]
Partial response, n (%)	40 (65.6%)
Stable disease, n (%)	12 (19.7%)
Progressive disease, n (%)	5 (8.2%)
Not evaluable*, n (%)	4 (6.6%)
DOR, median [95% CI], months	**13 months** [9.1-NR]
DCR , % [95% CI]	**85.2%** [76.3% - 94.1%]

* 4 patients were not evaluable



	≥2nd line				1st line		
	BRF113928 Dabrafenib (n=78)	BRF113928 Dabrafenib + trametinib (n=57)	PHAROS* Encorafenib + binimetinib (n=39)	ENCO-BRAF Encorafenib + binimetinib (n=59)	BRF113928 Dabrafenib + trametinib (n=36)	PHAROS* Encorafenib + binimetinib (n=59)	ENCO-BRAF Encorafenib + binimetinib (n=64)
Never smokers, n(%)	29 (37%)	16 (28%)	11 (28%)	--	10 (28%)	18 (31%)	23 (36%)
cORR, % (IC 95%)	33% (23-45)	68% (55-80)	46% (62-85)	--	64% (46-79)	75% (62-85)	**66% (54 – 77)**
PFS, median months (IC 95%)	5.5 (3.4-7.3)	10.2 (6.9-16.7)	9.3 (6.2-NA)	--	10.8 (7.0-14.5)	NA (15.7-NA)	**10.9** (6.4-16.7)
OS, median months (IC 95%)	12.7 (7.3-16.3)	18.2 (14.3-28.6)	--	--	17.3 (12.3–40.2)	--	**NR** (20.7-NR)

*cORR and PFS according to an independent radiology review

ESMO24 Updated Efficacy and Safety. G.J.Riely et al

KRAS G12C- Phase III clinical trial: KRYSTAL-12

Key eligibility criteria
- Locally advanced or metastatic NSCLC with *KRAS*^{G12C} mutation[b]
- Prior treatment with platinum-based chemotherapy and anti-PD-(L)1 therapy[c]
- ECOG PS 0-1
- Stable brain metastases allowed

N = 453
R 2:1

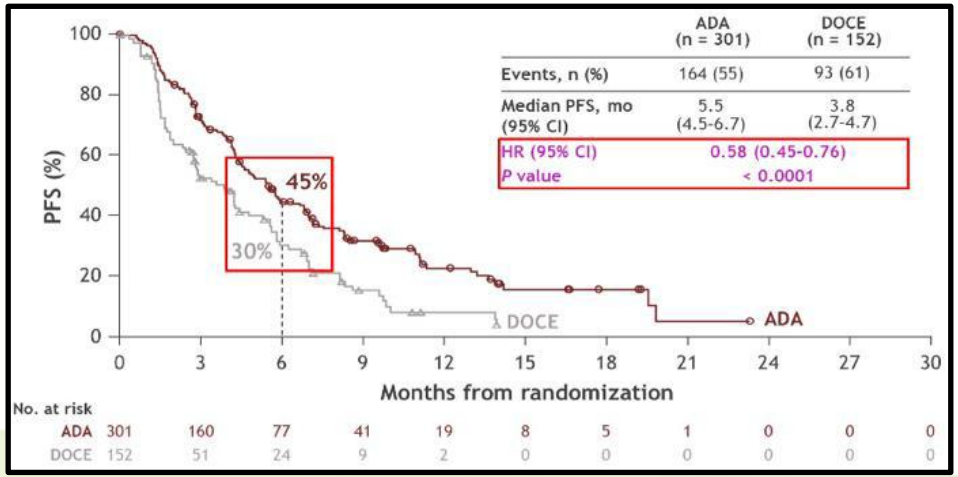
- **ADA** 600 mg BID PO[d]
- **DOCE** 75 mg/m² Q3W IV

Crossover from DOCE to ADA was allowed in cases where disease progression per RECIST v1.1 was confirmed by real-time BICR[e]

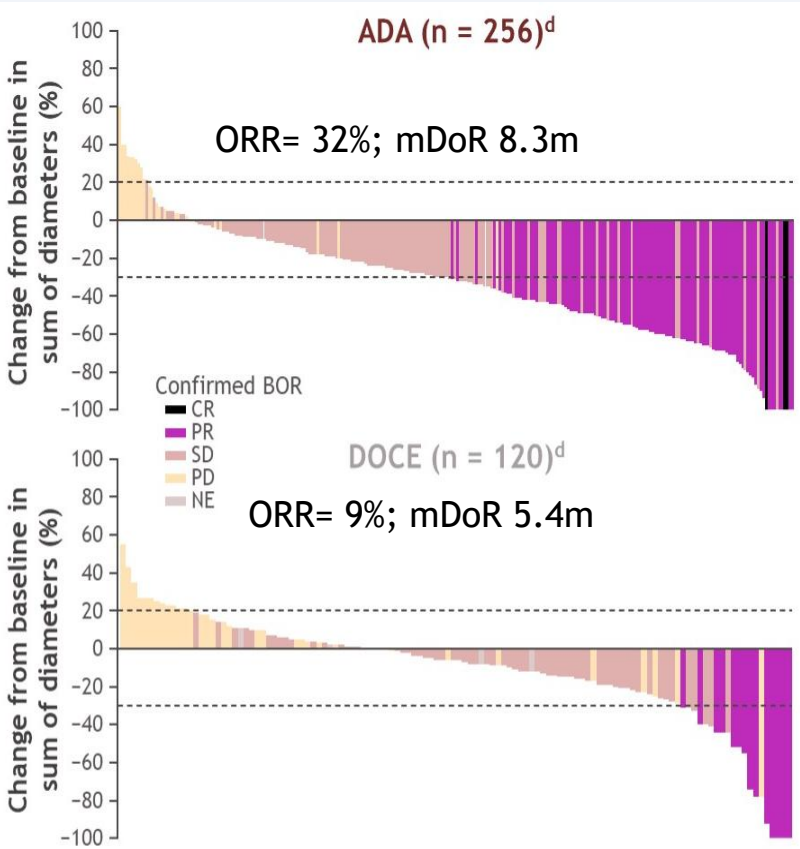
Stratified by:
- Region (non-Asia-Pacific vs Asia-Pacific)
- Prior treatment (sequential vs concurrent chemotherapy and immunotherapy)

Primary endpoint
- PFS by BICR (RECIST v1.1)

Secondary endpoints
- ORR by BICR (RECIST v1.1)
- DOR
- OS
- Safety
- Patient-reported outcomes



	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	



Mok et al. ASCO 2024

Secondary Insights from the PAPILLON

PAPILLON: Ami + Chemo in Frontline EGFR Ex20ins

Key Eligibility Criteria
- Treatment-naïve,[a] locally advanced or metastatic NSCLC
- Documented *EGFR* Exon 20 insertion mutations — Local
- ECOG PS 0 or 1

Stratification Factors
- ECOG PS
- History of brain metastases[b] — 23%
- Prior EGFR TKI use[a] — 1%

1:1 Randomization (N=308)

- Amivantamab-Chemotherapy (n=153)
- Chemotherapy (n=155)

Dosing (in 21-day cycles)

Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at week 7 (first day of cycle 3)

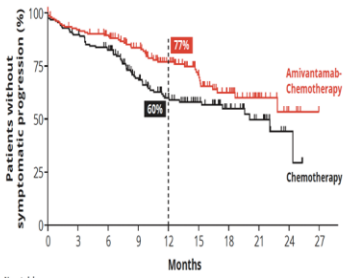
Chemotherapy on the first day of each cycle:
- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² until disease progression

Primary endpoint: Progression-free survival (PFS) by BICR according to RECIST v1.1[c]

Secondary endpoints:
- Objective response rate (ORR)[c]
- Duration of response (DoR)
- Overall survival (OS)[c]
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[d]
- Time to subsequent therapy[d]
- Safety

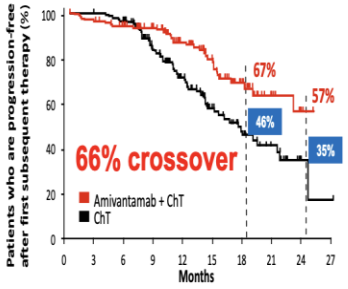
Optional crossover to 2nd-line amivantamab monotherapy[e] — 66%

Time to Symptomatic Progression (TTSP)[2]



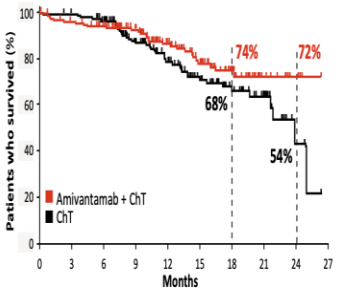
Ami + ChT	NE (18.6–NE)	HR, 0.67 p=0.04
ChT	20.1 (13.1–NE)	

PFS after First Subsequent Therapy (PFS2)[1]



Ami + ChT	NE (22.8–NE)	HR, 0.49 p=0.001
ChT	17.2 (14.0–21.5)	

Early Interim OS (33% data maturity)[3]



Ami + ChT	NE (NE–NE)	HR, 0.67 p=0.11
ChT	24.4 (22.1–NE)	

EMA & FDA APPROVED EMA & FDA

PAPILLON

1L Amivantamab + ChT (mPFS 11 mo; HR 0.40 vs. ChT)

2024

ESMO · NCCN National Comprehensive Cancer Network®

UPFRONT AMI + ChT

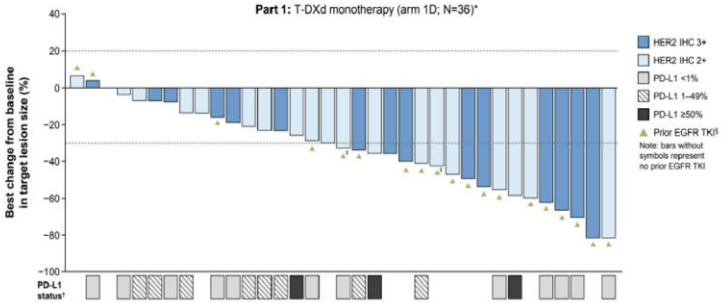
RECOMMENDED BY GUIDELINES

1.- Paz-Ares L, ELCC 2024; 2.--Felip E et al. ELCC 2024; 3.- Girard N et al. ESMO 2023

HER2 NSCLC

HER2 Overexpressing NSCLC IHC 2/3 + (Expansion Cohort T-DXd 5,4 mg/kg)

Best percentage change from baseline in target lesion size



DESTINY-Lung03

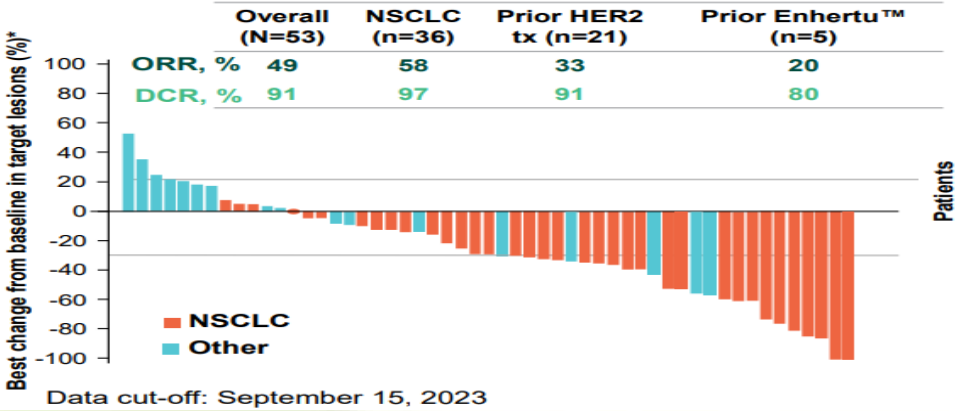
ORR IHC 3+, 56.3%
ORR IHC 2+, 35%

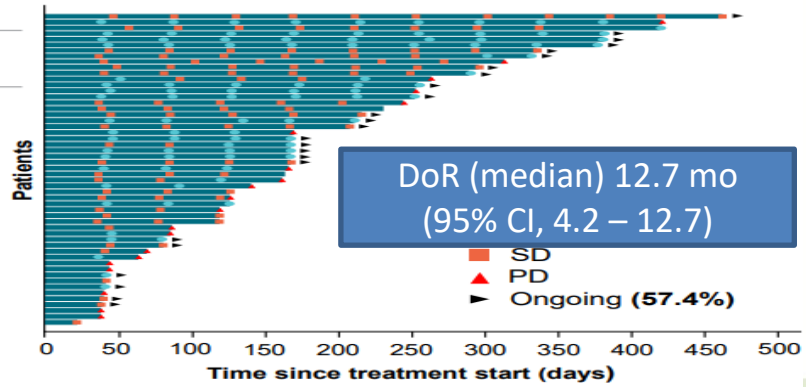
PFS (median) 8.2 mo

T-DXd FDA First Tumor Agnostic HER2 Therapy for previously treated metastasic HER2+ solid tumors

Beamion LUNG-1: Zongertinib

The overall median (range) duration of treatment with zongertinib at data cut-off was 4.8 (<1–18.7) months, with 35 patients ongoing

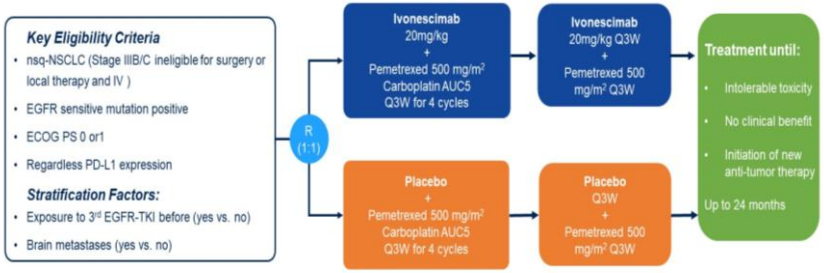




DoR (median) 12.7 mo
(95% CI, 4.2 – 12.7)

Advanced NSCLC pretreated

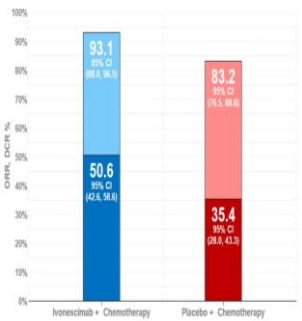
HARMONi-A trial



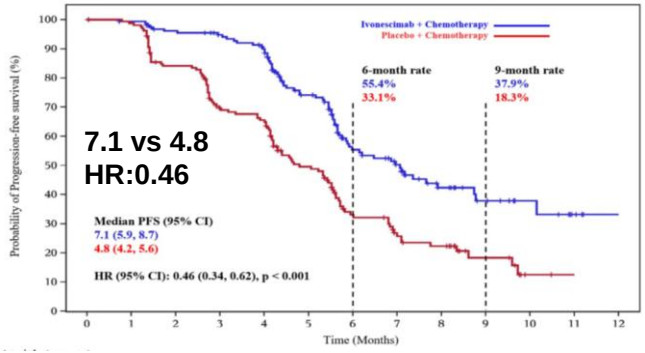
Endpoints

- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

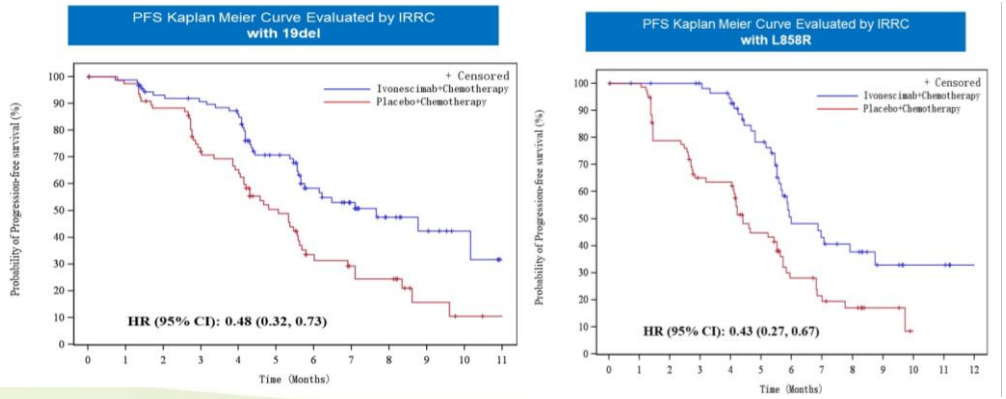
ORR, DCR and DoR per IRRC



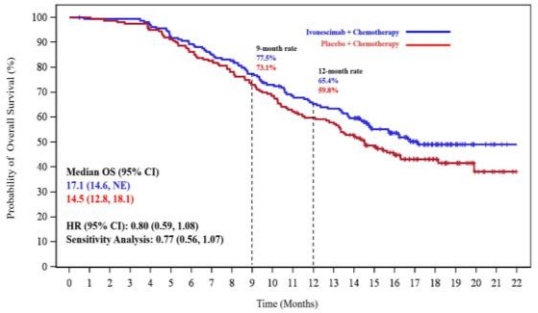
Study Met Primary Endpoint of PFS per IRRC



PFS of 19del and L858R



Overall Survival (at 52% of Data Maturity)



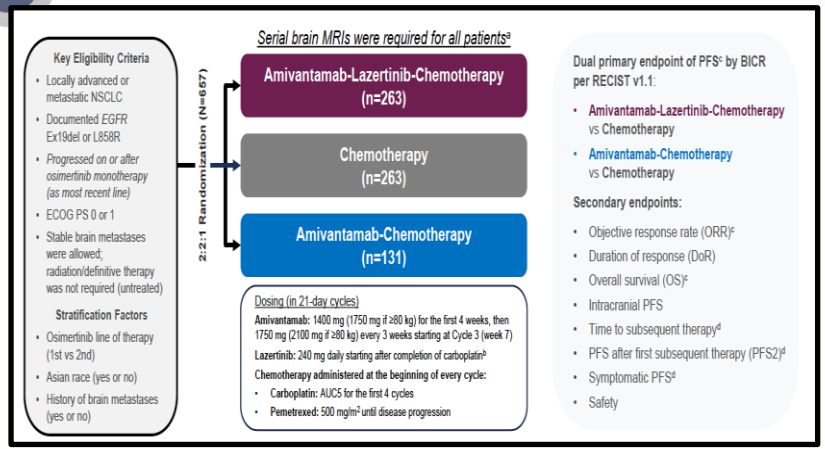
HR: 0.80 (0.59, 1.08) after 52% of data maturity

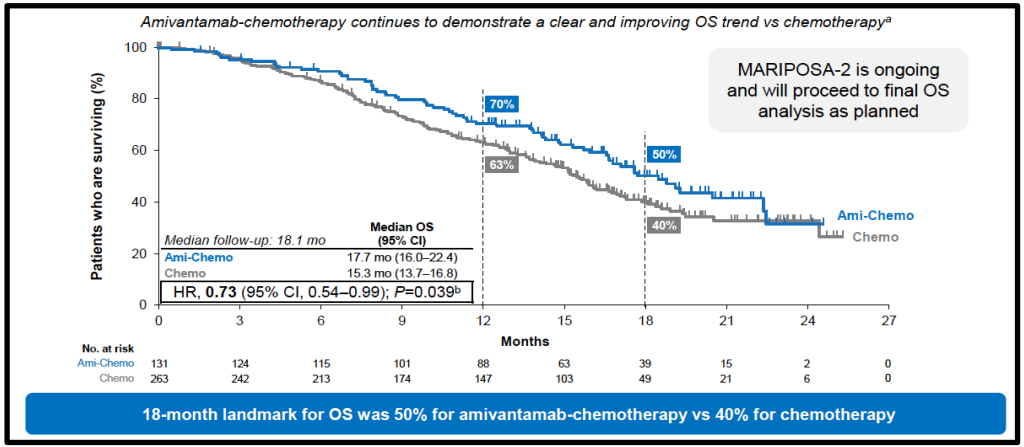
OS is consistent for both analysis

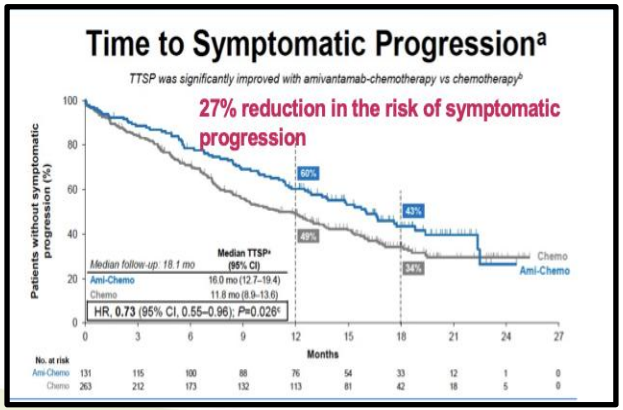
Data cutoff date: December 2023 (median follow-up of 17.6 months)

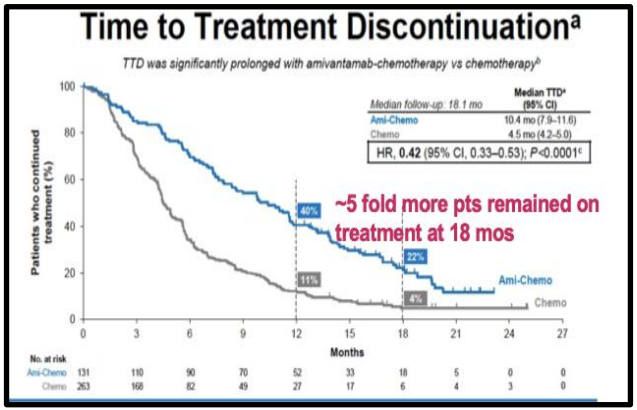
Li Zhang. ASCO 2024.

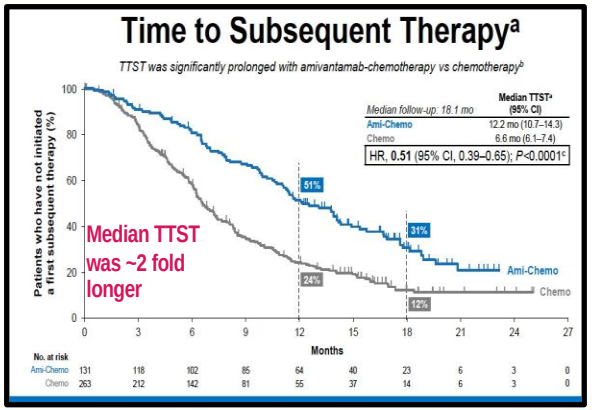
MARIPOSA-2: OS updated data for ami-chemo arm











Popat S, et al. ESMO 2024

Recoged ahora las rosas de la vida pues el tiempo jamás detiene su vuelo y esa flor que hoy se abre mañana estará marchita.

Carpe Diem

Oh capitán mi capitán!!