Targeted Therapy Updates in NSCLC

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2024 MLS Cleveland Conference

April 2024

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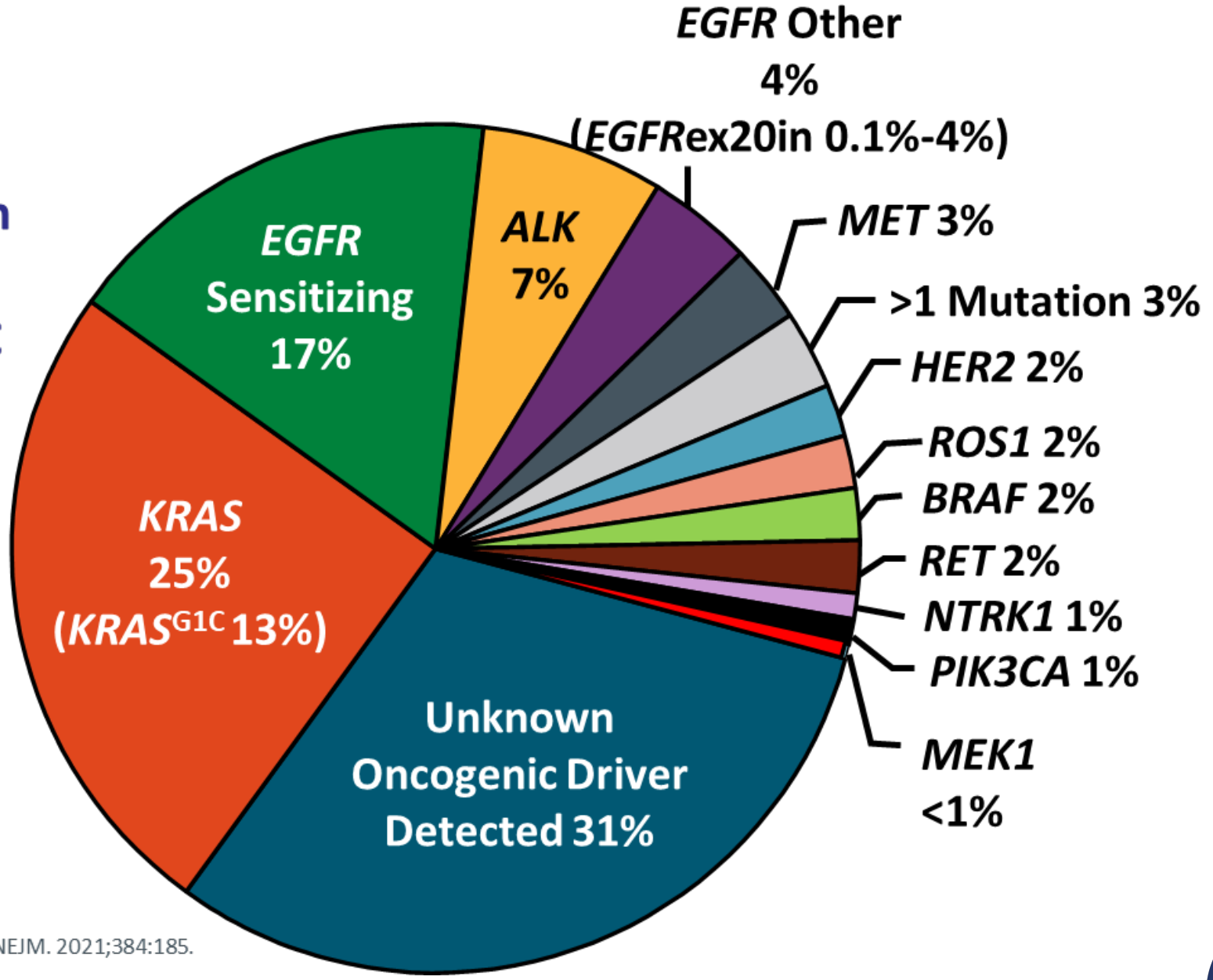
~52% of Patients With Advanced Nonsquamous NSCLC Have an Actionable Driver Mutation



Li. JCO. 2013;31:1039. Tsao. JTO. 2016;11:613.
Burnett. PLoS One. 2021;16:e0247620. Nassar. NEJM. 2021;384:185.

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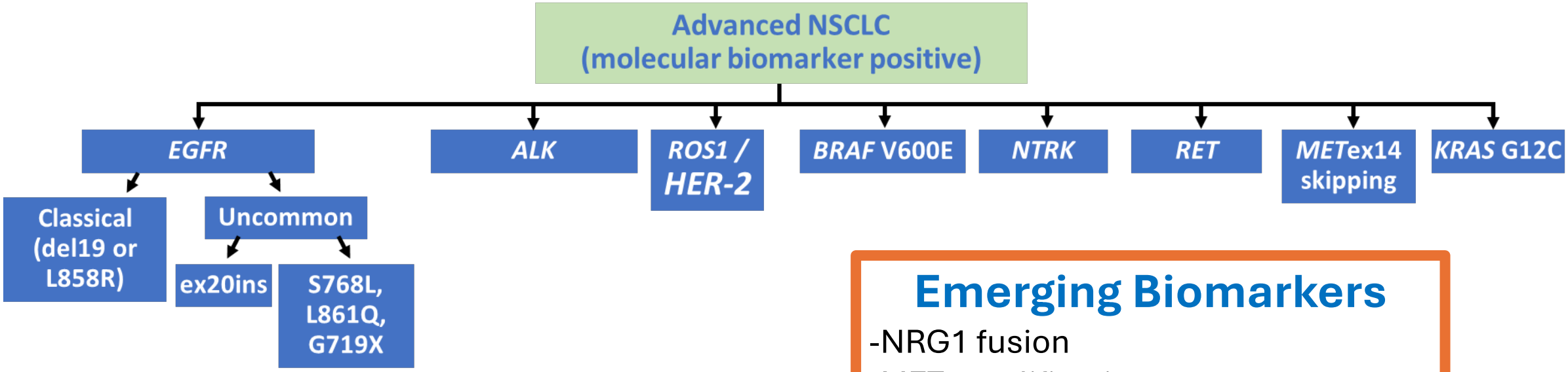
2023 Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC



Emerging Biomarkers

-NRG1 fusion
-MET amplification
-STK11
-KEAP-NF2l2
-FGFR

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2023 ASCO ANNUAL MEETING

Overall survival analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated (EGFRm) stage IB-IIIA non-small cell lung cancer (NSCLC)

Roy S. Herbst[1], Masahiro Tsuboi[2], Thomas John[3], Terufumi Kato[4], Margarita Majem[5], Christian Grohe[6], Jie Wang[7], Jonathan Goldman[8], Shun Lu[9], Wu-Chou Su[10], Filippo de Marinis[11], Frances A. Shepherd[12], Ki Hyeong Lee[13], Nhieu Thi Le[14], Arunee Oechaphunkul[15], Dariusz Kowalski[16], Lynne Poole[17], Marta Stachowiak[18], Yuri Rukazenkov[19], Yi-Long Wu[20]

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ADAURA Phase III Double-Blind Study Design

NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition. †Per, pre, or planned adjuvant therapy was allowed. ‡Centrally confirmed in tissue. §Patients received a CT scan of the chest and abdomen and brain ≤28 days prior to treatment. EGFR, epidermal growth factor receptor; IDMC, Independent Data Monitoring Committee; NCI, National Cancer Institute; WHO, World Health Organization.

Patients with completely resected stage IB, II, IIIA* NSCLC, with or without adjuvant chemotherapy

Key inclusion criteria:
- ≥ 18 years (Japan/Taiwan: ≥ 20)
- WHO performance status 0/1
- Confirmed primary nonsquamous NSCLC Ex19del/L858R‡
- Brain imaging, if not completed preoperatively
- Complete resection with negative margins§
- Maximum interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization 1:1 (N = 682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow-up:
- Until recurrence: week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Following IDMC recommendations, the study was unblinded early due to efficacy; all patients were followed up for at least 1 year.

End Points

- **Primary**: DFS, by investigator assessment, in stage II-IIIA patients; designed for superiority under the assumed DFS HR of 0.70.
- **Secondary**: DFS in the overall population, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life.

Presented by Dr. Roy S. Herbst, ASCO 2020, pending publication

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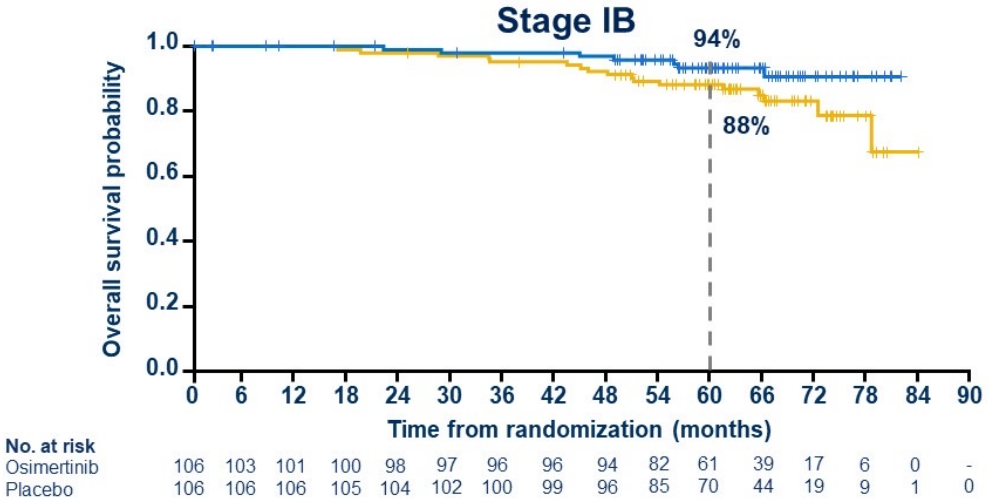
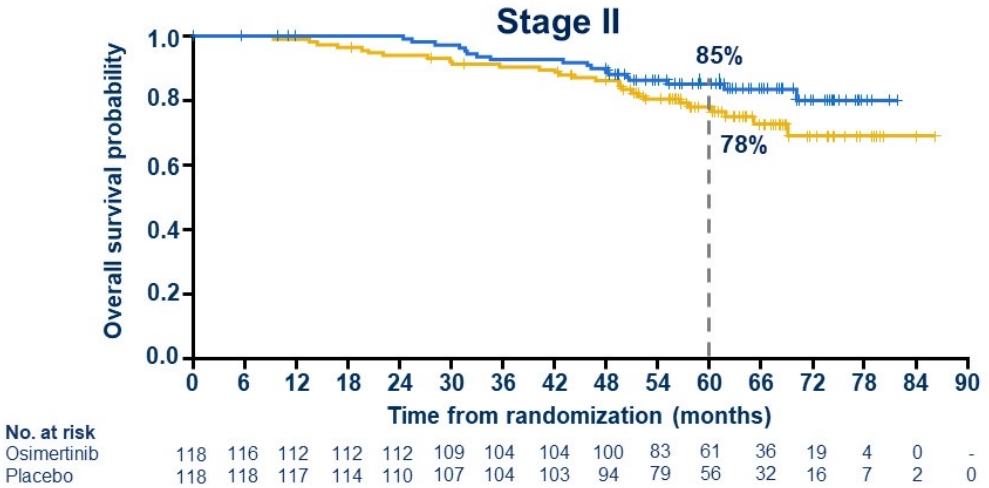
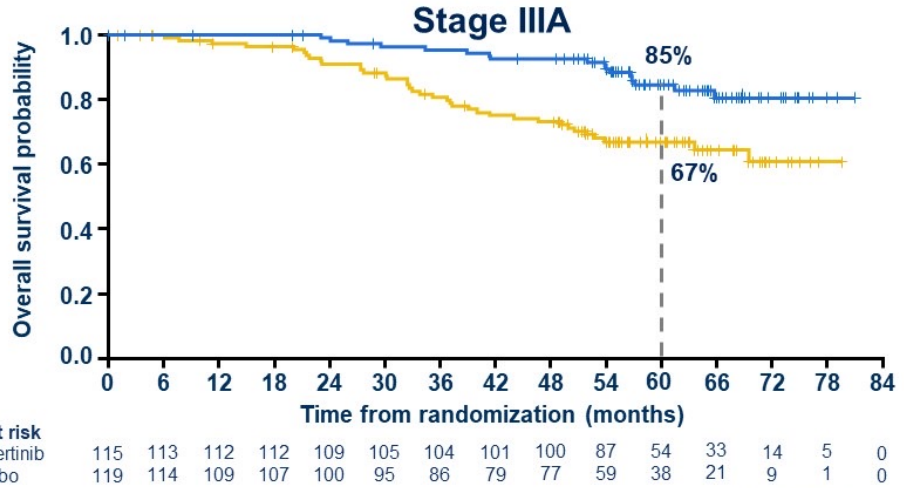
Overall survival by disease stage



	Stage IB	Stage II	Stage IIIA
5 year OS rate, % (95% CI)			
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	0.44 (0.17, 1.02)	0.63 (0.34, 1.12)	0.37 (0.20, 0.64)





2023 ASCO ANNUAL MEETING #ASCO23

PRESENTED BY: Roy S. Herbst

Data cut-off: January 27, 2023. Tick marks indicate censored data.
CI, confidence interval; HR, hazard ratio; OS, overall survival

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
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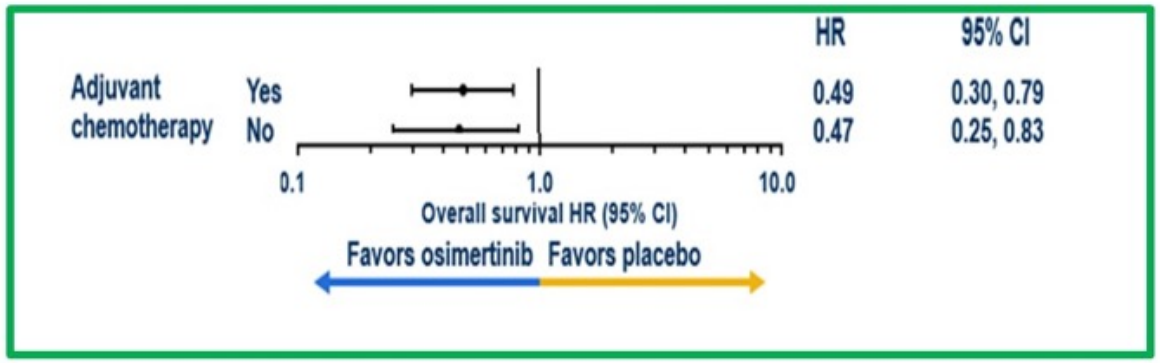
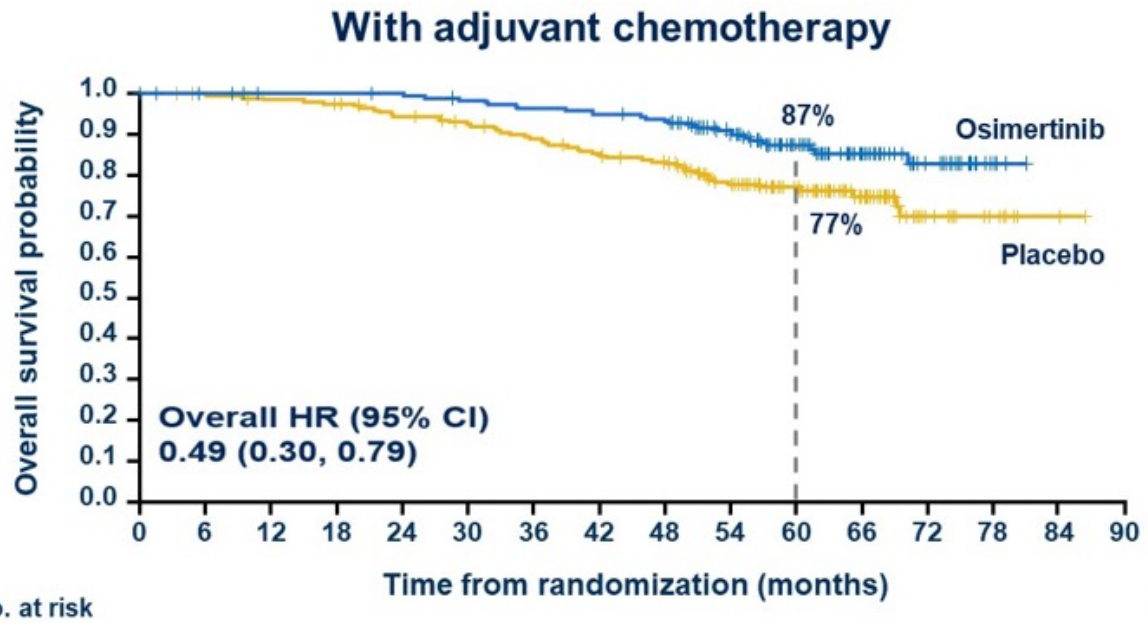
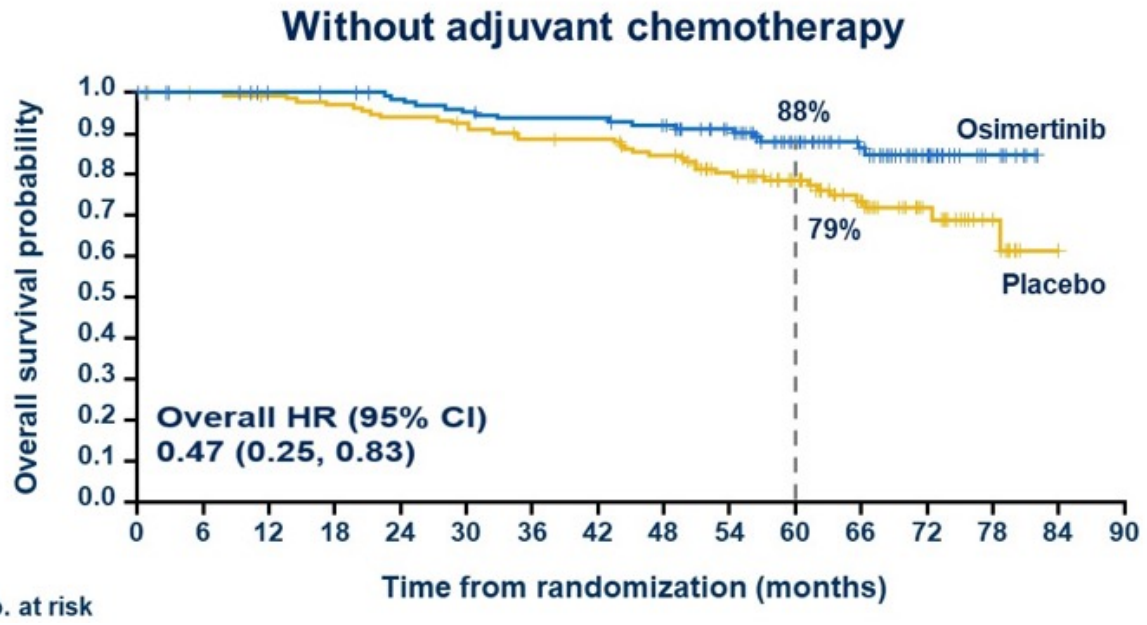
Benefit Regardless of Adjuvant Chemotherapy





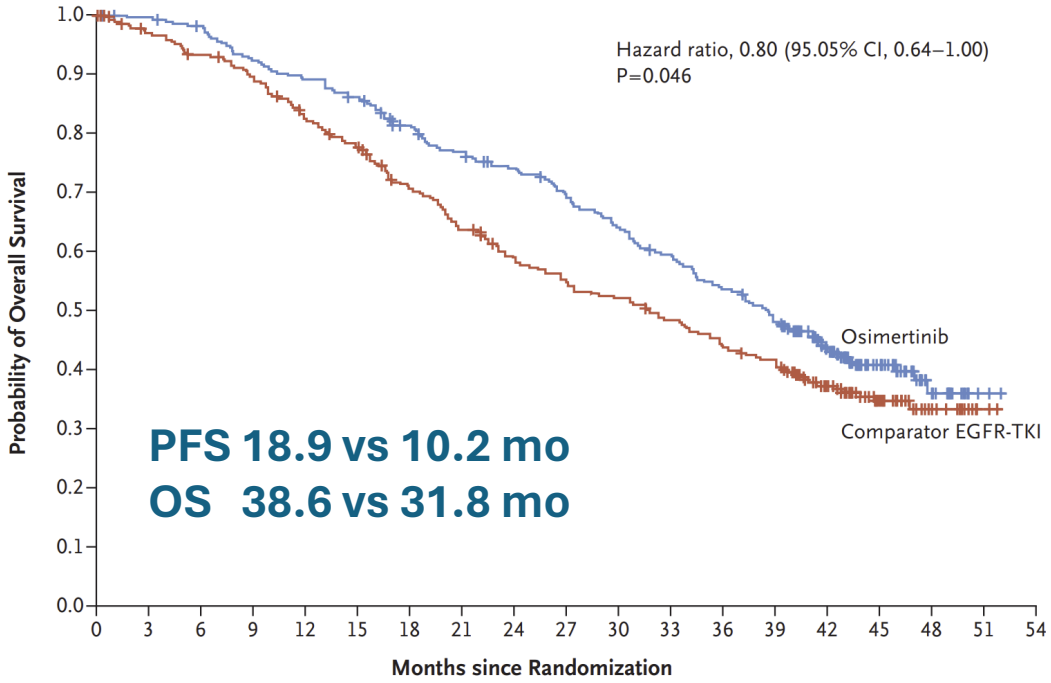


Slide courtesy of Dr. Benjamin Solomon

1L Treatment of EGFRm (L858R/del19) NSCLC until ~September 2023

Osimertinib Monotherapy

FLAURA: Osimertinib > 1st Gen



PFS 18.9 vs 10.2 mo
OS 38.6 vs 31.8 mo

1L Treatment of EGFRm NSCLC ~November 2023

+Chemo	**FLAURA2:** Osimertinib + Chemotherapy > Osimertinib
+EGFR/MET mAb	**MARIPOSA:** Amivantamab + Lazertinib > Osimertinib, Lazertinib
+VEGF	**RAMOS:** Osimertinib + anti-VEGFR
Exon 20ins	**PAPILLON (EGFR exon 20 insertions)** Amivantamab + Chemotherapy > Chemo

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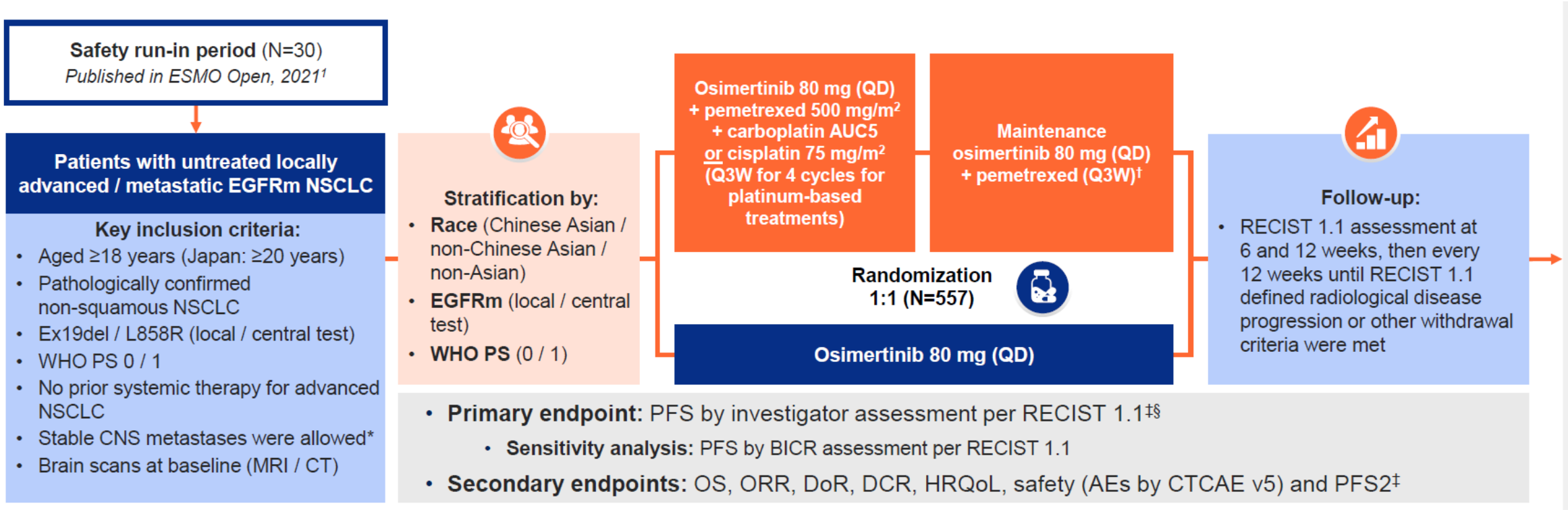
FLAURA2: 1L Osimertinib + Platinum Doublet for EGFR-mutated NSCLC



Presented by P. Janne, IASLC WCLC 2023, PL03.13

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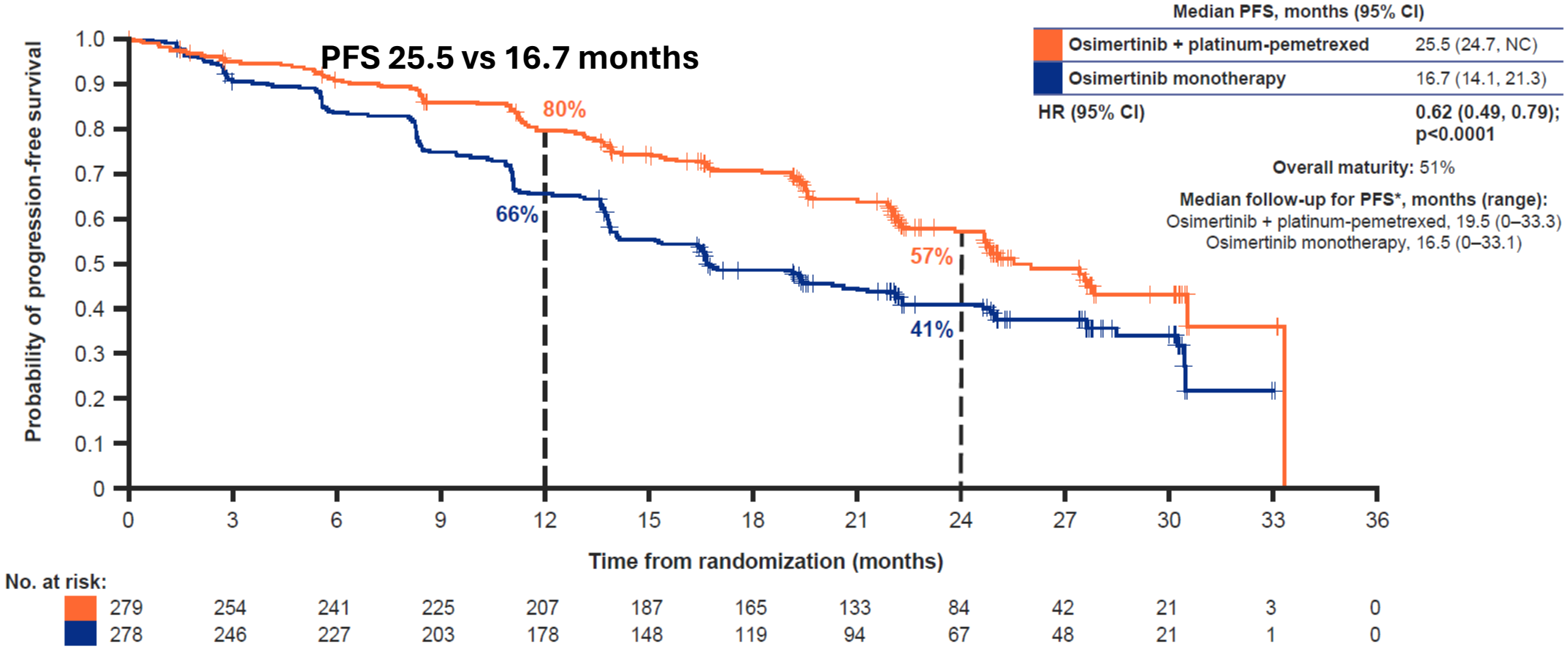
FLAURA2: PFS per Investigator



Presented by P. Janne, IASLC WCLC 2023, PL03.13

FDA APPROVED

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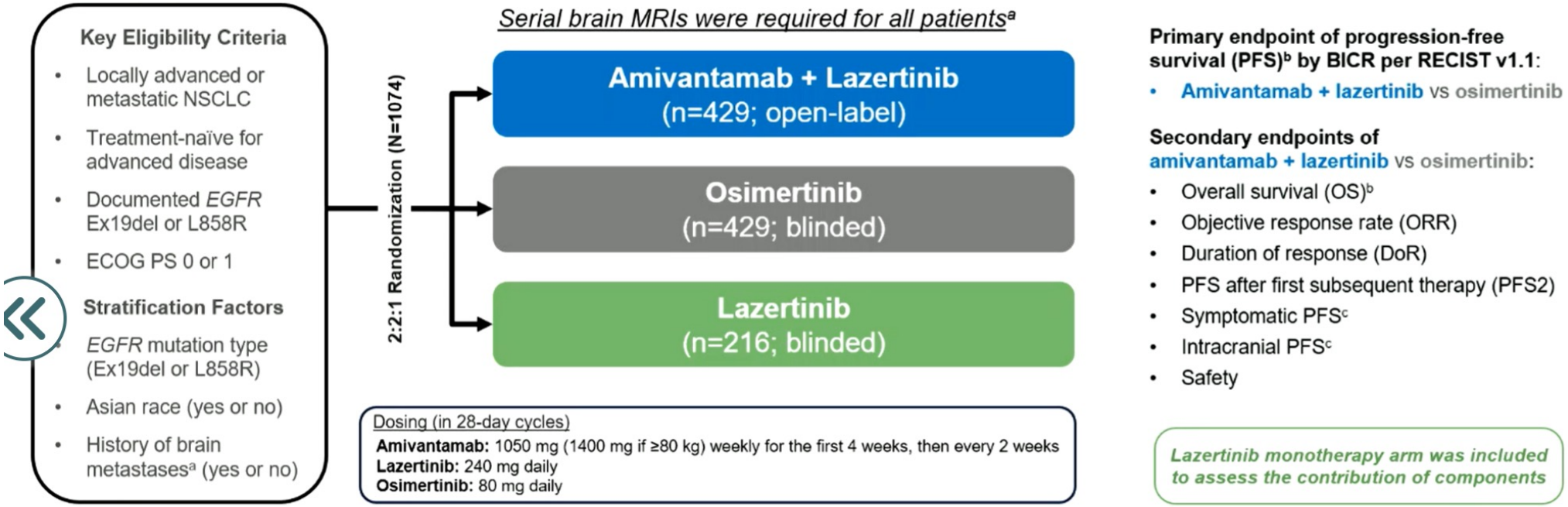
MARIPOSA: Amivantamab + Lazertinib 1L for EGFRm NSCLC



Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:

- **Amivantamab + lazertinib** vs osimertinib

Secondary endpoints of amivantamab + lazertinib vs osimertinib:

- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

[a]Baseline brain MRI was required for all patients and performed ≤28 days prior to randomization; patients who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis. Extracranial tumor assessments were conducted every 8 weeks for the first 30 months and then every 12 weeks until disease progression is confirmed by BICR.

[b]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS.

[c]These secondary endpoints (symptomatic and intracranial PFS) will be presented at a future congress.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

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Presented by B. Cho. ESMO 2023. LBA14

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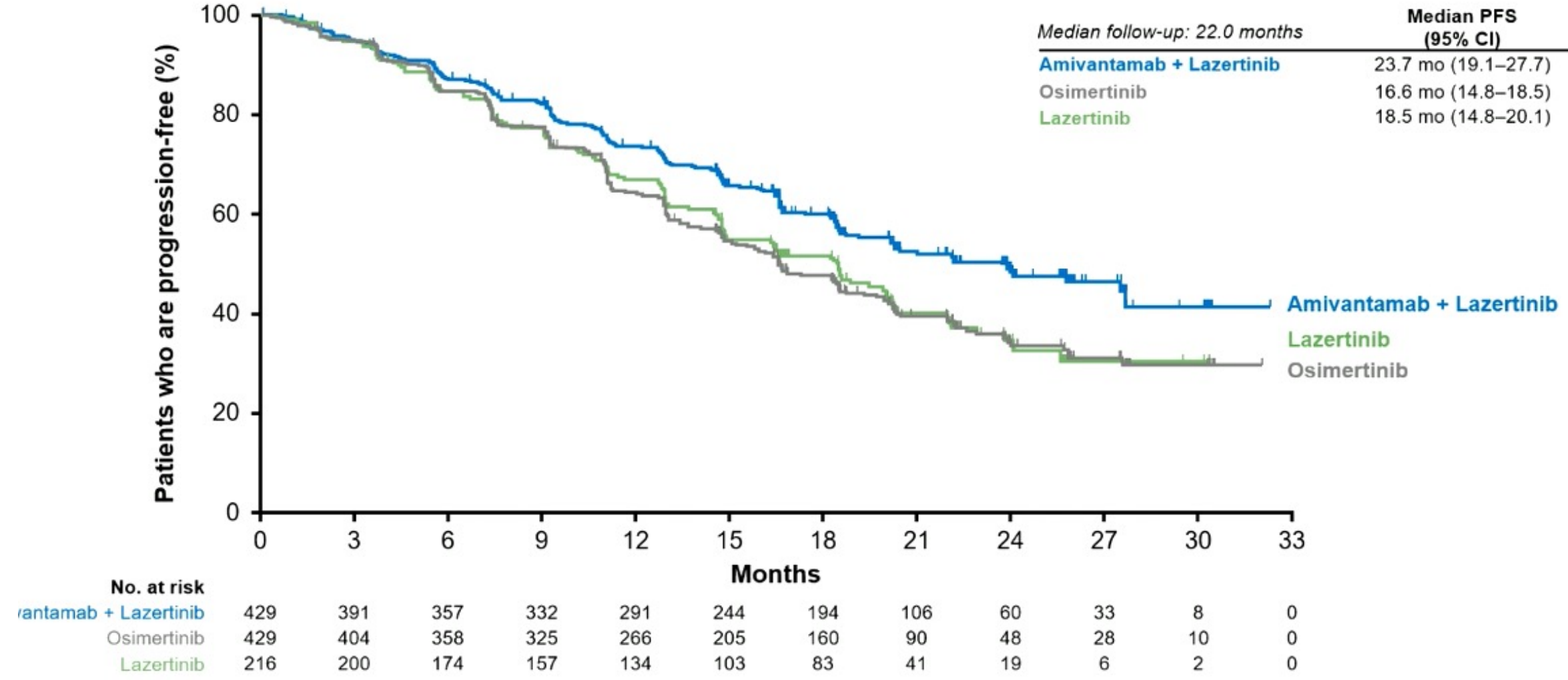
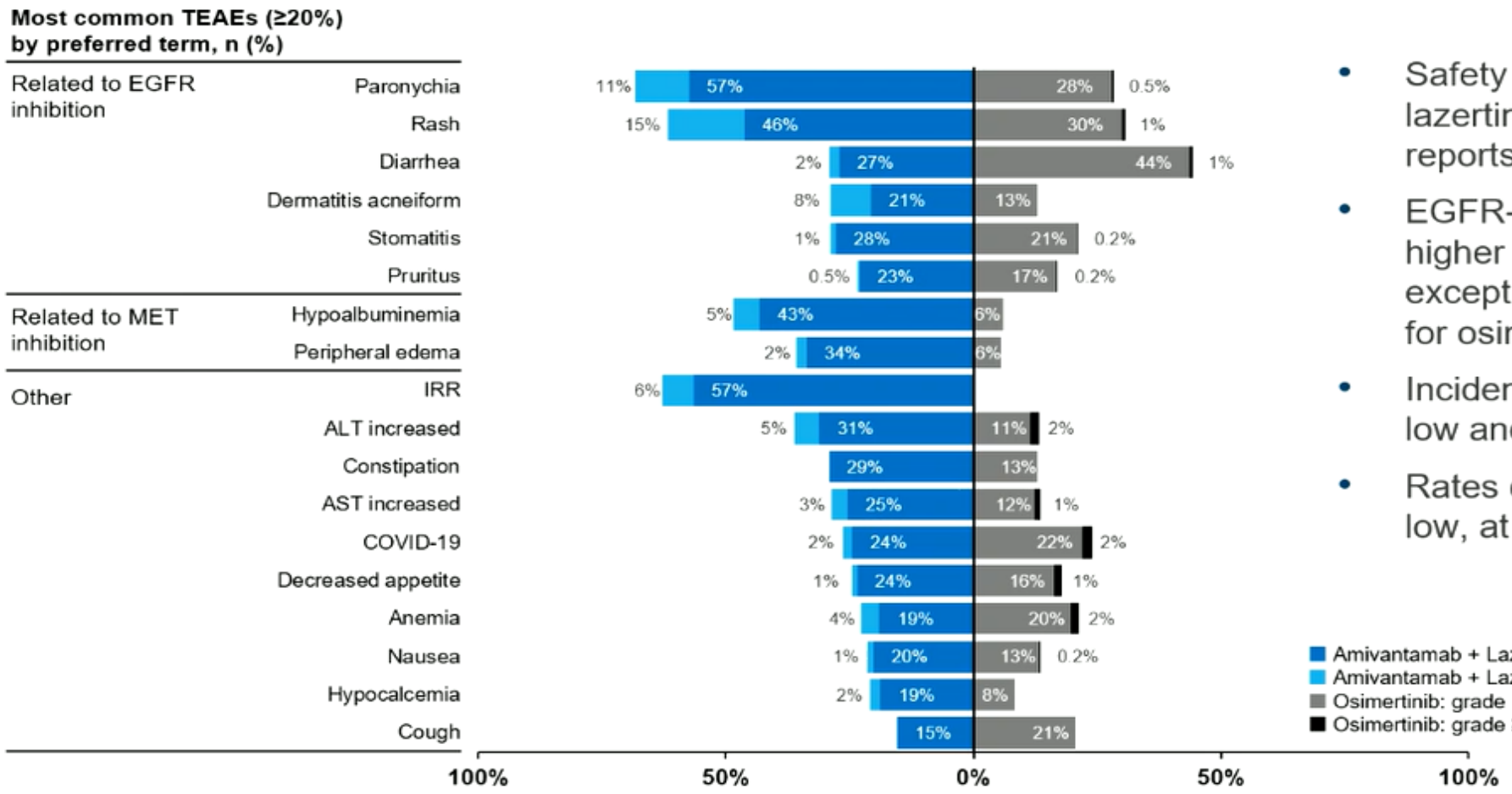
MARIPOSA: PFS by BICR



Presented by B. Cho. ESMO 2023. LBA14

Safety Profile



- Safety profile of amivantamab + lazertinib was consistent with prior reports, mostly grades 1-2
- EGFR- and MET-related AEs were higher for amivantamab + lazertinib except diarrhea, which was higher for osimertinib
- Incidence of grade 4-5 AEs was low and comparable between arms
- Rates of ILD/pneumonitis remained low, at ~3% for both arms

VTE 37% vs 9%
PPX indicated

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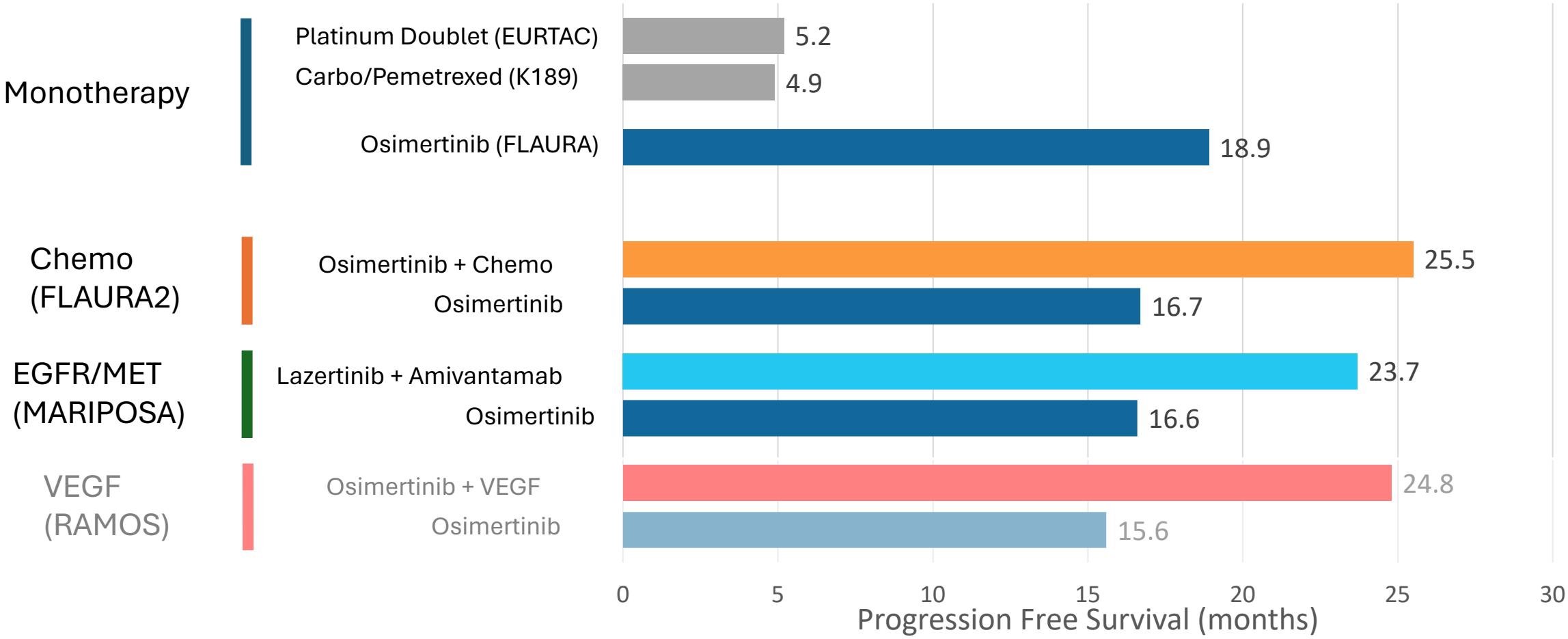
Firstline Combination Regimens for EGFR-mutated NSCLC



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Rosell et al. 2012; Soria et al. NEJM; Janne et al WCLC 2023; Gandhi et al, NEJM 2018, Le et al ESMO 2023; Cho et al ESMO 2023

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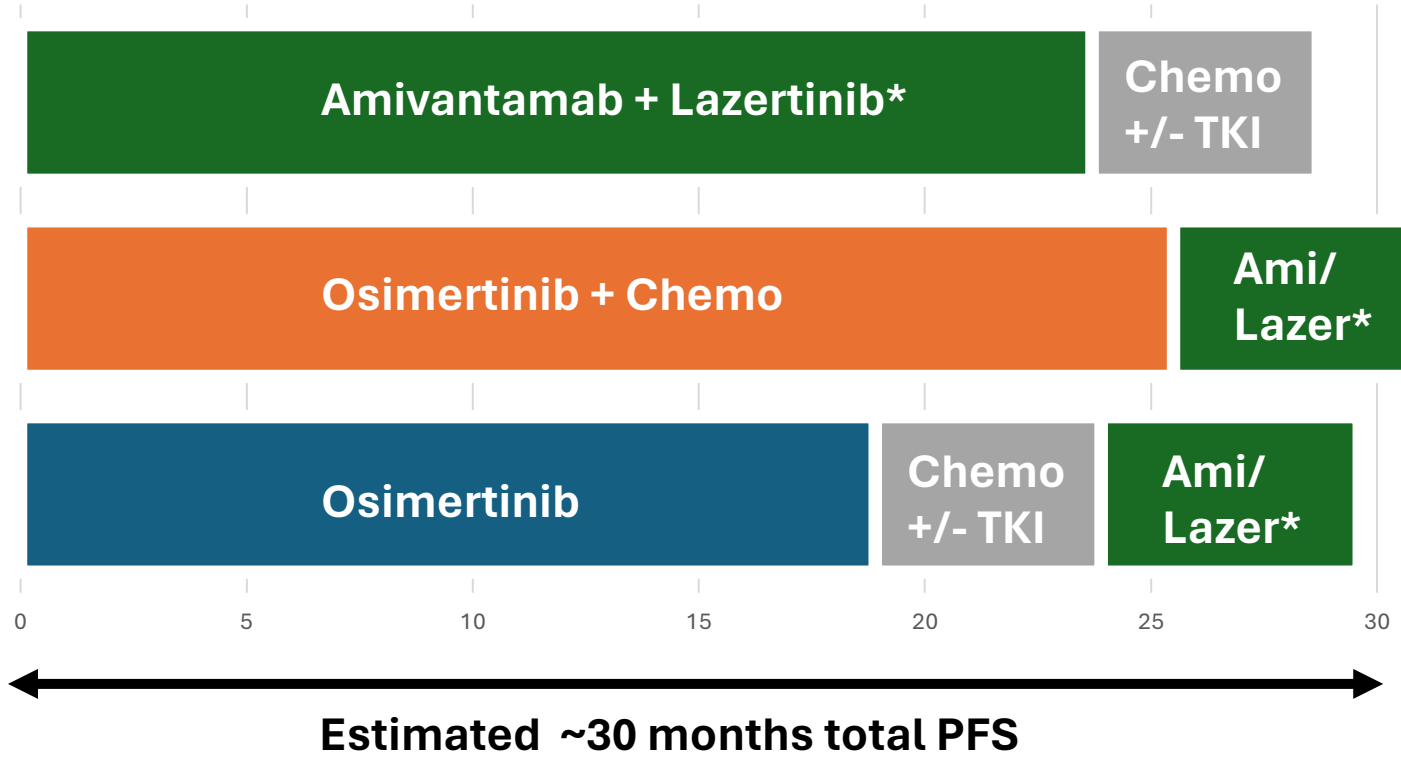
Sequencing Therapy in 1L EGFRm NSCLC



Q2W Infusions
Rash/IRR/VTE

Q3W Infusions
Nausea/fatigue/ cytopenias

**Regimen no FDA-Approved*
Adapted from Piotrowska et al and Rotow et al, ESMO 2023

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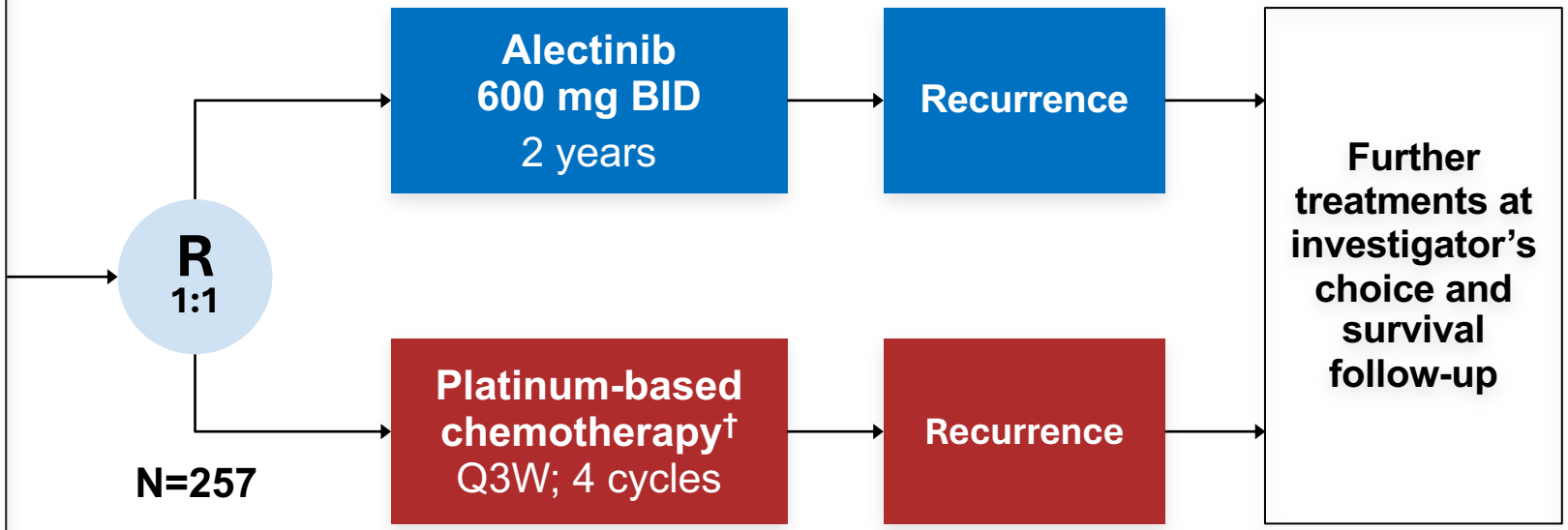
ALINA Study Design

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian



Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

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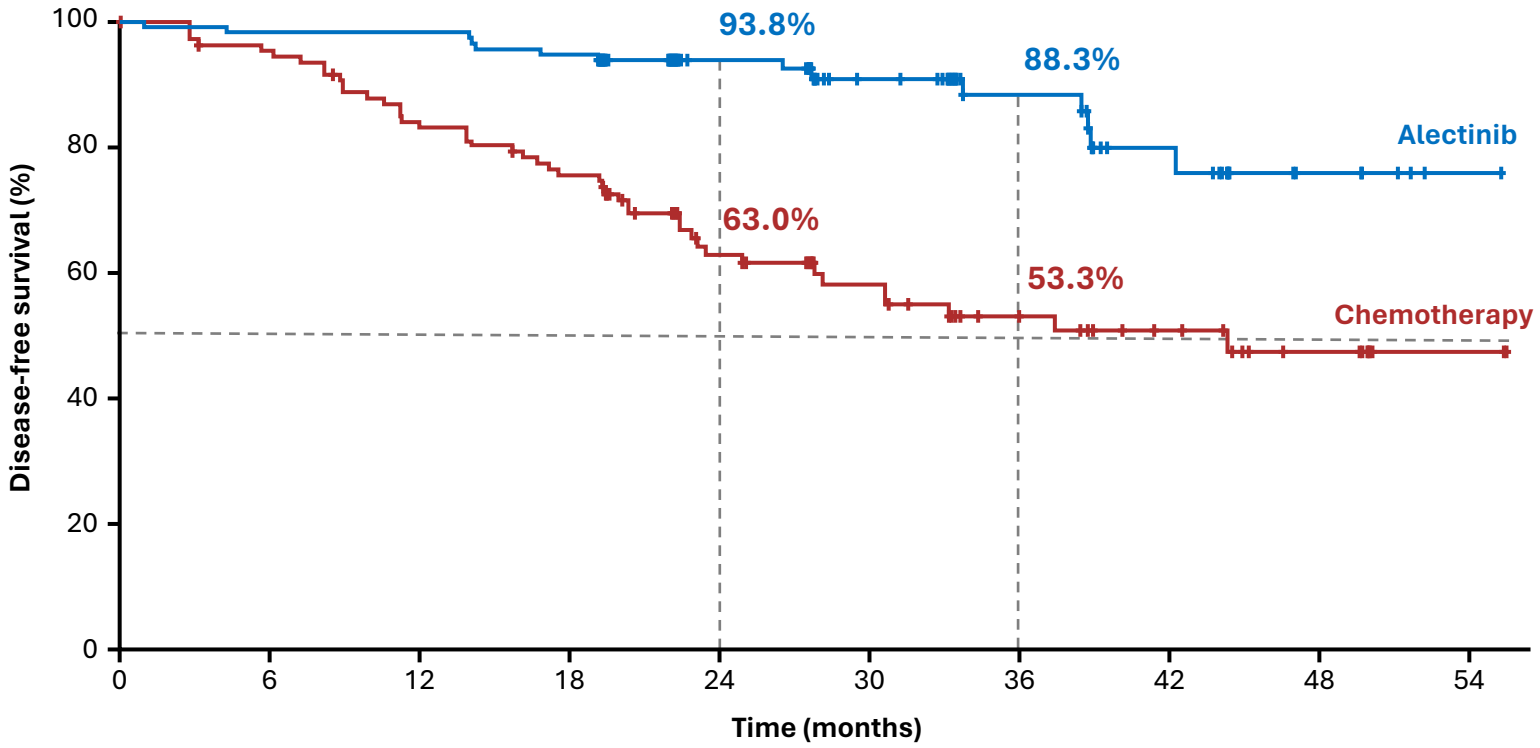
Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

Disease-free Survival: Stage II–IIIA



No. at risk

Alectinib	116	111	111	107	67	49	35	21	10	3
Chemo	115	102	88	79	48	35	23	17	10	2

	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

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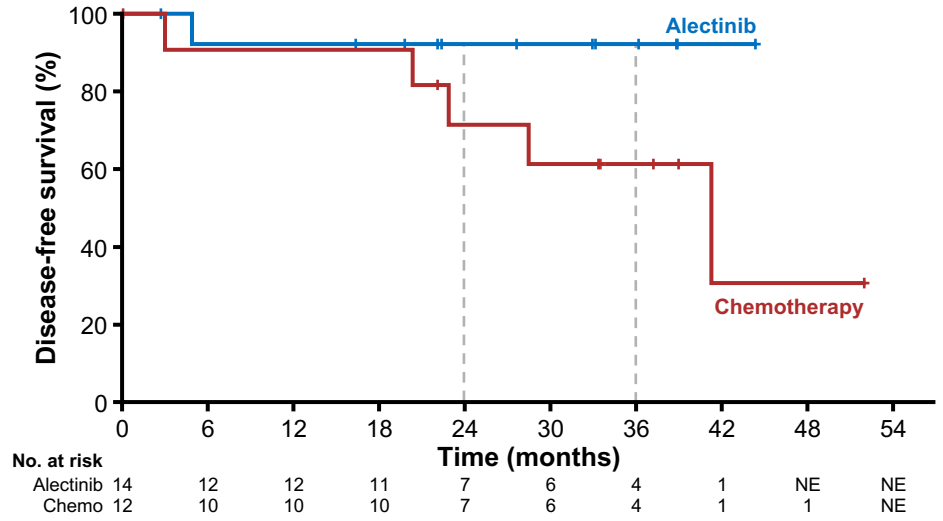
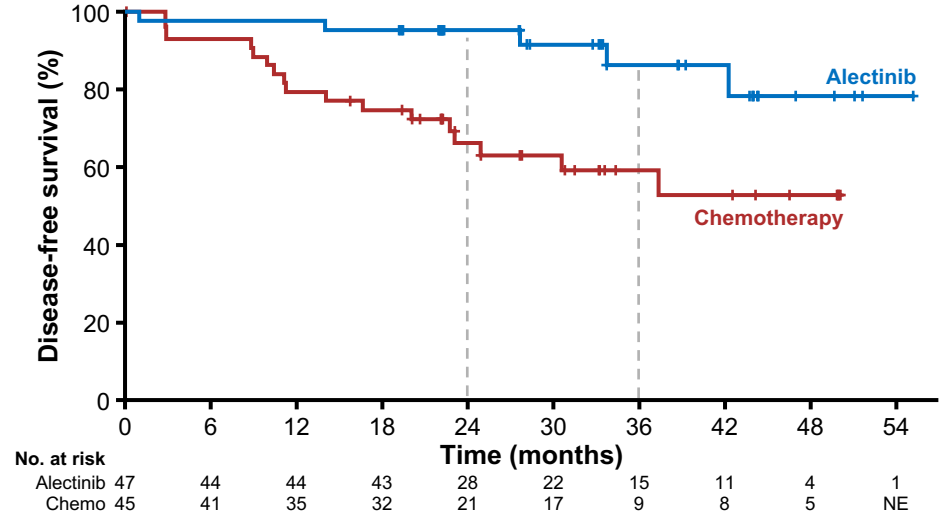
Disease-free Survival By Stage

Stage IB

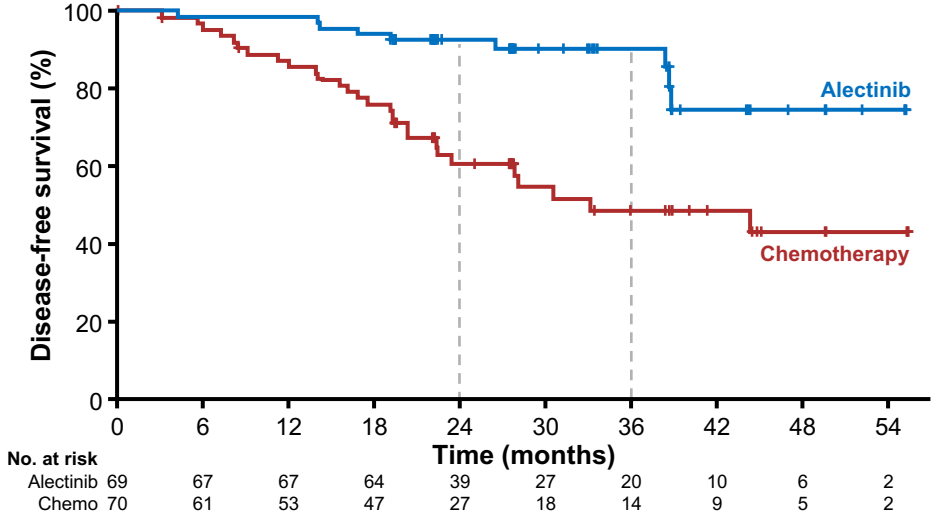


2-year DFS rate, % (95% CI)	Stage IB (n=26)	Stage II (n=92)	Stage IIIA (n=139)
Alectinib	92.3 (77.8, 100.0)	95.6 (89.5, 100.0)	92.7 (86.4, 98.9)
Chemotherapy	71.6 (44.2, 99.0)	66.3 (51.7, 81.0)	60.7 (47.9, 73.5)
HR† (95% CI)	0.21 (0.02, 1.84)	0.24 (0.09, 0.65)	0.25 (0.12, 0.53)

Stage II



Stage IIIA



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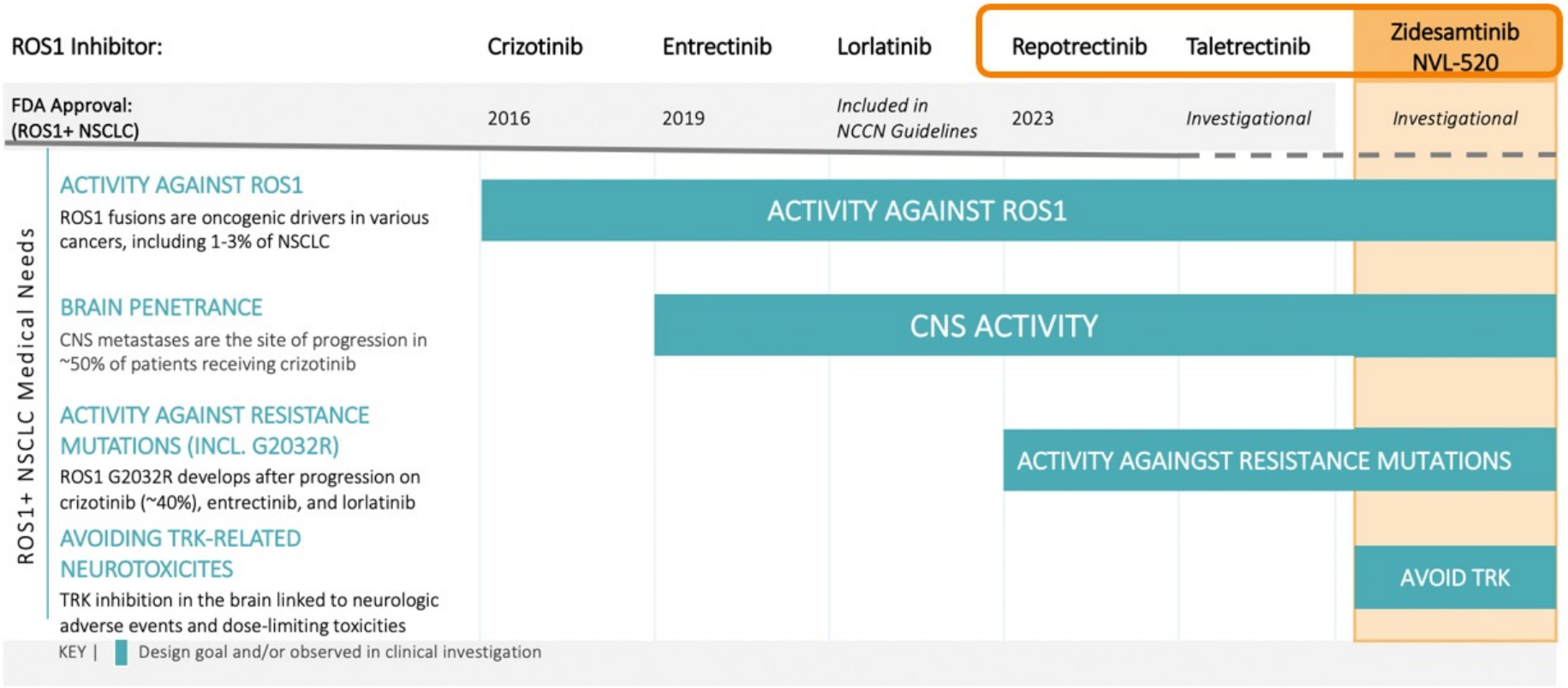
Data cut-off: 26 June 2023

*Per UICC/AJCC 7th edition; †Unstratified analysis

Targeting *ROS1+* Fusion NSCLC

ROS1 fusions makes up 1% of patients with advanced non squamous NSCLC

Entrectinib in ROS1 TKI naïve ORR 68%, icORR 80%, median PFS 15.7 months



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Slide courtesy of Dr. Cheema

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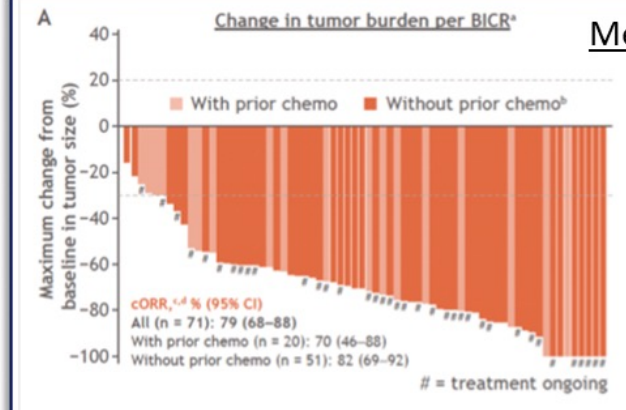
Repotrectinib | TRIDENT-: Phase I/II, ROS1+ NSCLC cohort

TKI naive (N=71)



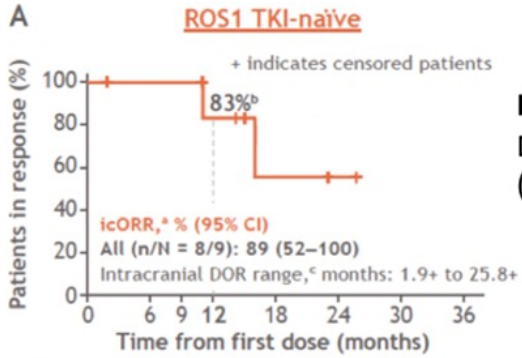
Median F/U: 24 months

cORR: 79 %

Median PFS: 35.7 (27.4- NE)
months (95% CI)
(n=71)

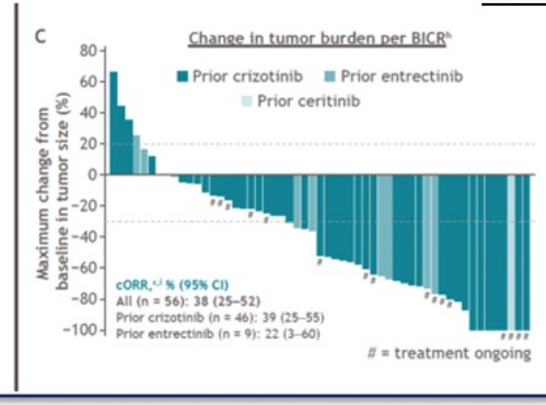
Median OS: NR
(95% CI:44.1-NE)

Measurable baseline brain metastases (N=9)



Intracranial ORR: 89% (52-100)
DOR: 83% at 12 months
(med F/U 24 mo. (range 14.2-66.6))

TKI pretreated (N=56)



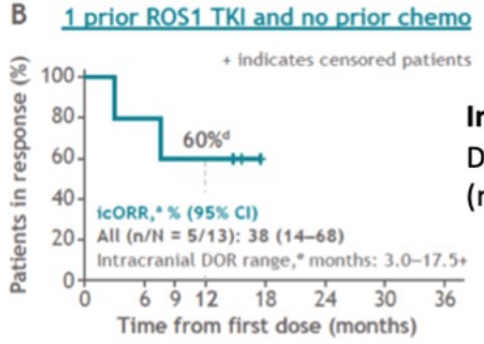
Median F/U: 21.5 months

cORR: 38%

Median PFS: 9.0 (6.8-19.6)
months (95% CI)
(n=56)
Prior Crizotinib (n=46): 9.0 (7.3-19.6)
Prior entrectinib (n=9): 4.5 (2.0-NE)

Median OS: 25.1 months
(95% CI, 17.8, NE)

Measurable baseline brain metastases (N=13)



Intracranial ORR (n/N=5/13) = **38%**
DOR: range 3.0-17.5, 60% @ 1 Year
(med F/U 21.5 months (14.2-58.6))

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Drilon, et al. NEJM 2024. Schneider JL, TTLC 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Repotrectinib in *ROS1* Fusion–Positive Non–Small-Cell Lung Cancer

A. Drilon, D.R. Camidge, J.J. Lin, S.-W. Kim, B.J. Solomon, R. Dziadziuszko, B. Besse, K. Goto, A.J. de Langen, J. Wolf, K.H. Lee, S. Popat, C. Springfeld, M. Nagasaka, E. Felip, N. Yang, V. Velcheti, S. Lu, S. Kao, C. Dooms, M.G. Krebs, W. Yao, M.S. Beg, X. Hu, D. Moro-Sibilot, P. Cheema, S. Stopatschinskaja, M. Mehta, D. Trone, A. Graber, G. Sims, Y. Yuan, and B.C. Cho, for the TRIDENT-1 Investigators*

Table 3. Adverse Events in the 426 Patients Who Received the Phase 2 Dose of Repotrectinib.*

Event	During Treatment Period		Related to Treatment	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	422 (99)	216 (51)	409 (96)	122 (29)
Event occurring in ≥15% of patients				
Dizziness	264 (62)	11 (3)	245 (58)	11 (3)
Dysgeusia	224 (53)	0	213 (50)	0
Constipation	162 (38)	1 (<1)	111 (26)	0
Anemia	160 (38)	33 (8)	111 (26)	16 (4)
Paresthesia	143 (34)	3 (1)	126 (30)	3 (1)
Dyspnea	117 (27)	27 (6)†	36 (8)	2 (<1)
Increased alanine aminotransferase level	99 (23)	8 (2)	76 (18)	6 (1)
Fatigue	95 (22)	4 (1)	70 (16)	3 (1)
Ataxia	90 (21)	1 (<1)	87 (20)	0
Increased aspartate aminotransferase level	89 (21)	9 (2)	75 (18)	6 (1)

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Drilon, et al. NEJM 2024

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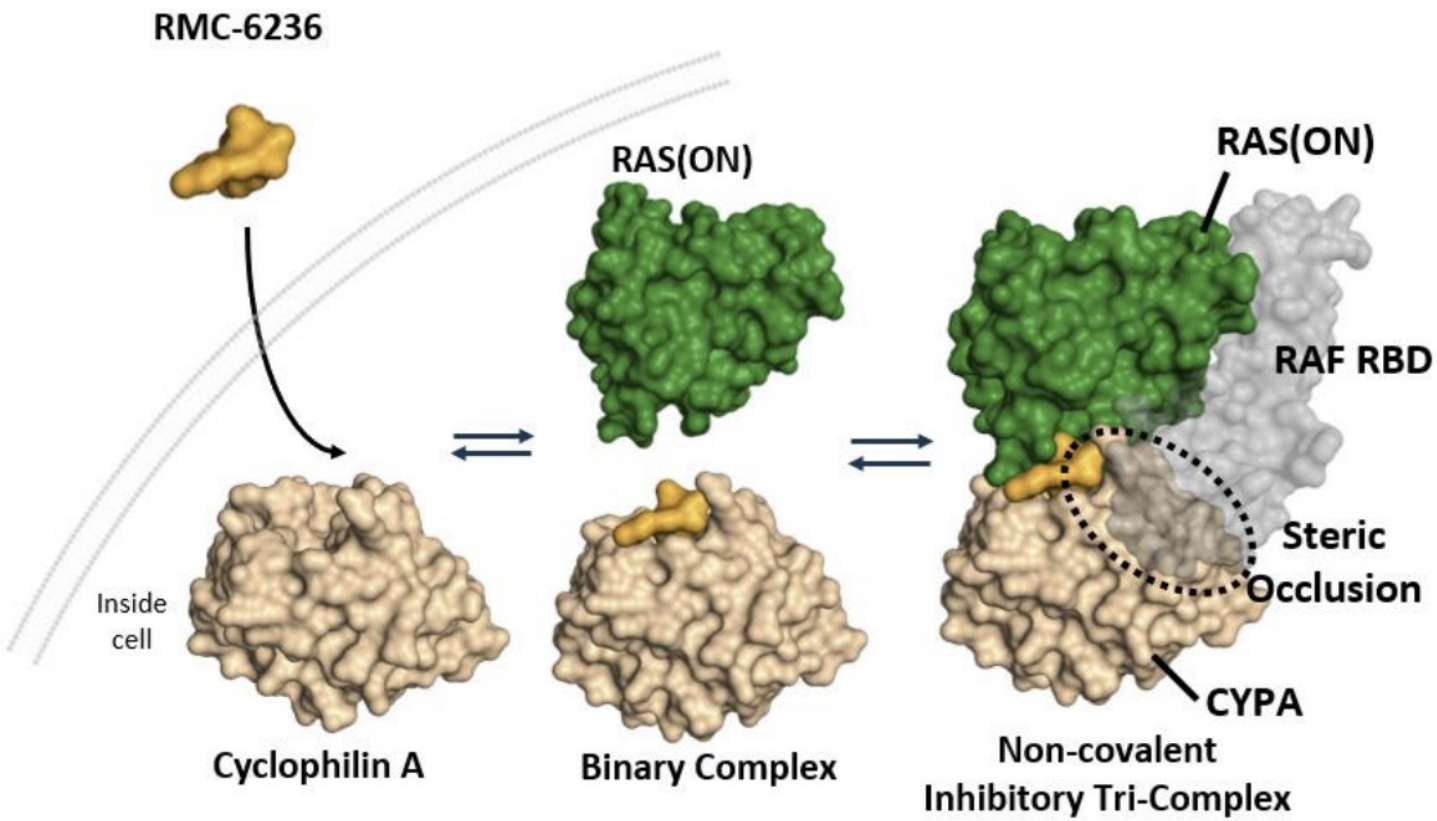
Honorary Mention
Still Under Development

RMC-6236 is a First-in-Class, RAS^{MULTI}(ON) Inhibitor

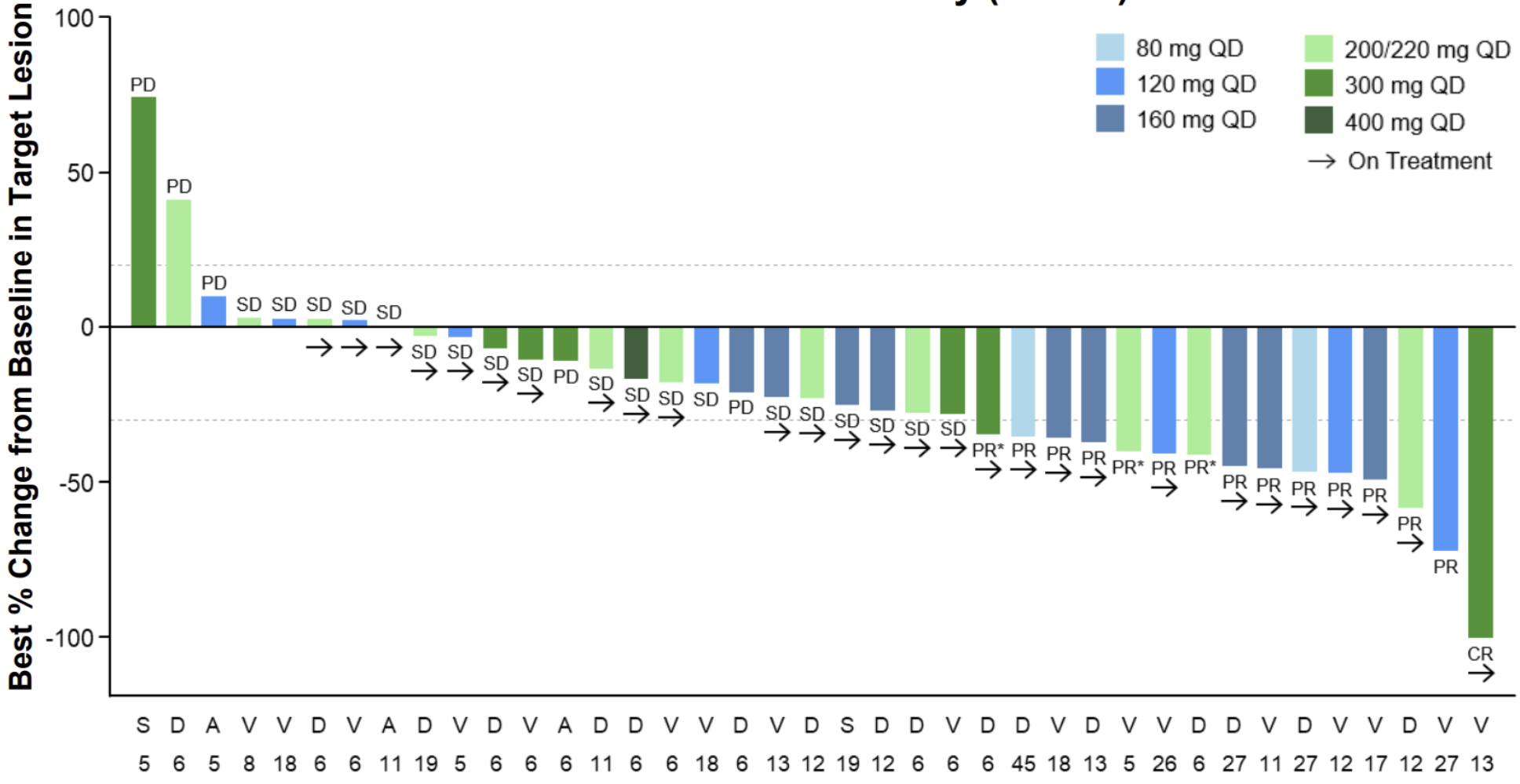
- RMC-6236 is a novel, oral, non-covalent RAS^{MULTI}(ON) inhibitor that is selective for the active, GTP-bound or ON state of both mutant and wild-type variants of the canonical RAS isoforms
- Preclinical studies have demonstrated deep and sustained regressions across multiple RAS^{MUT} tumor types, particularly PDAC and NSCLC harboring KRAS^{G12X} mutations



KRAS^{G12X} defined as mutation at codon 12 which encodes glycine (G) to X where X = A, D, R, S, or V.
CYPA, cyclophilin A; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma viral oncogene homolog; Mut, mutant; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RBD, RAS-binding domain.

KRAS^{G12X} NSCLC: Best Response

Evaluable for Efficacy (N = 40)[a]



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
CR	1 (3)
PR	14 (35)
SD	19 (48)
PD	5 (13)
NE[b]	1 (3)
ORR, n (%)	15 (38)
Confirmed, n	12
DCR (CR+PR+SD), n (%)	34 (85)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]One subject withdrew from study without post-baseline scans.

CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Data Extracted 12 Oct 2023

TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer with actionable genomic alterations

Luis Paz-Ares,[1] Myung-Ju Ahn,[2] Aaron Lisberg,[3] Satoru Kitazono,[4] Byoung Chul Cho,[5] George Blumenschein Jr,[6] Elaine Shum, [7] Elvire Pons Tostivint,[8] Yasushi Goto,[9] Kiyotaka Yoh,[10] Rebecca Heist,[11] Paul Baas,[12] David Planchard,[13] Maurice Pérol,[14] Enriqueta Felip,[15] Wu-Chou Su,[16] Hong Zebger-Gong,[17] Lan Lan,[18] Chelsea Liu,[18] Jacob Sands[19]

Screening

Key inclusion criteria

- Stage IIIB, IIIC, or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS of 0 or 1
- ≥1 line of targeted therapy
- 1 or 2 prior cytotoxic agent–containing therapies including platinum-based therapy in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

Dato-DXd
6 mg/kg
Q3W

Endpoints[a]

Primary: ORR by BICR

Secondary:

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

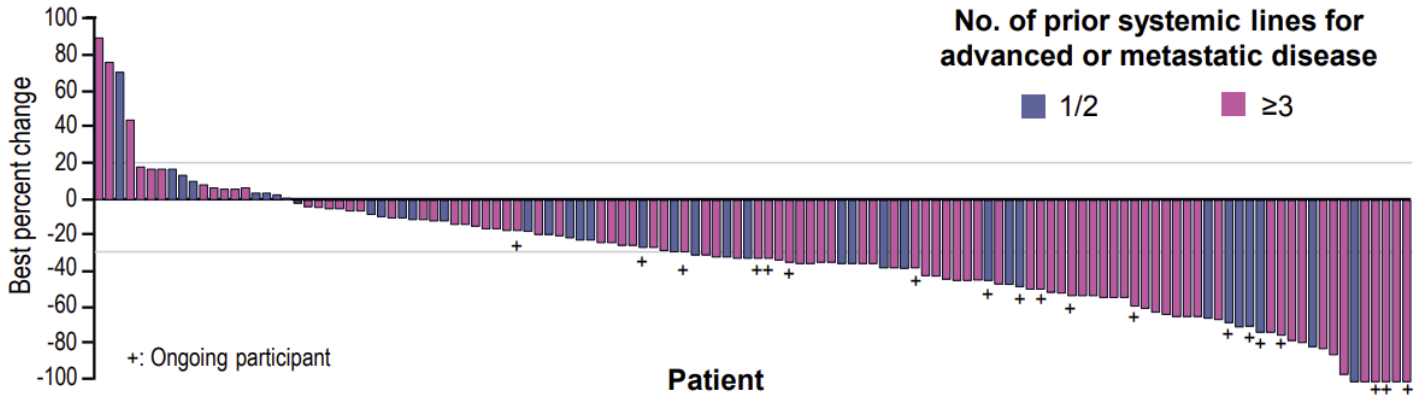
Efficacy Summary

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

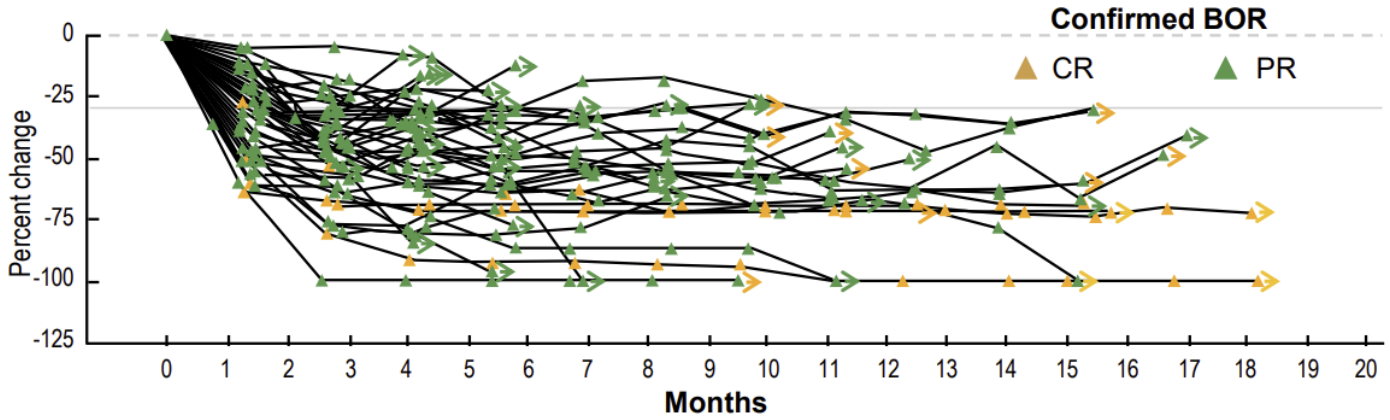
BOR: In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR

***EGFR* subset:** Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

Best Percent Change From Baseline in Sum of Diameters of Target Lesions

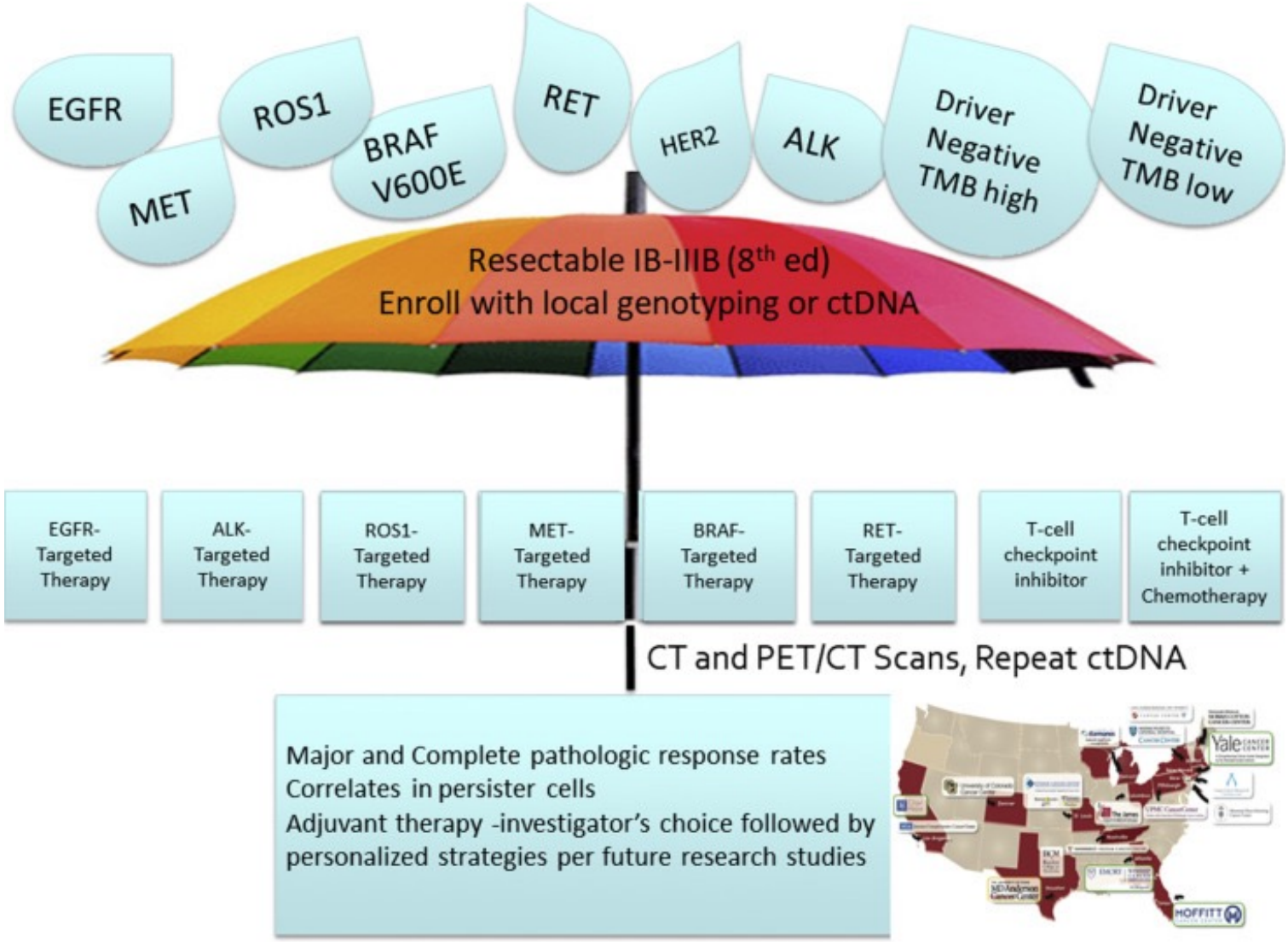


Percent Change From Baseline in Sum of Diameters of Target Lesions in Patients With Confirmed CR/PR[c]



BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

Innovative Trial Designs – Low Prevalence – Multi-Arms



- Nautika 1
- Orchard trial

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

Blumenthal et al, 2018 JTO

Florez Lab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