University of California
San Francisco

PRIMO 2024

What's New in Targeted Therapy for NSCLC: Focus on EGFR, ALK, ROS1, and BRAF V600E

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February 9. 2024

What's New in Targeted Therapy in NSCLC

- Early-stage NSCLC
  - EGFR
  - ALK
- Advanced/Metastatic NSCLC
  - EGFR
    - EGFR exon 20 ins
  - BRAF V600E
  - ROS1

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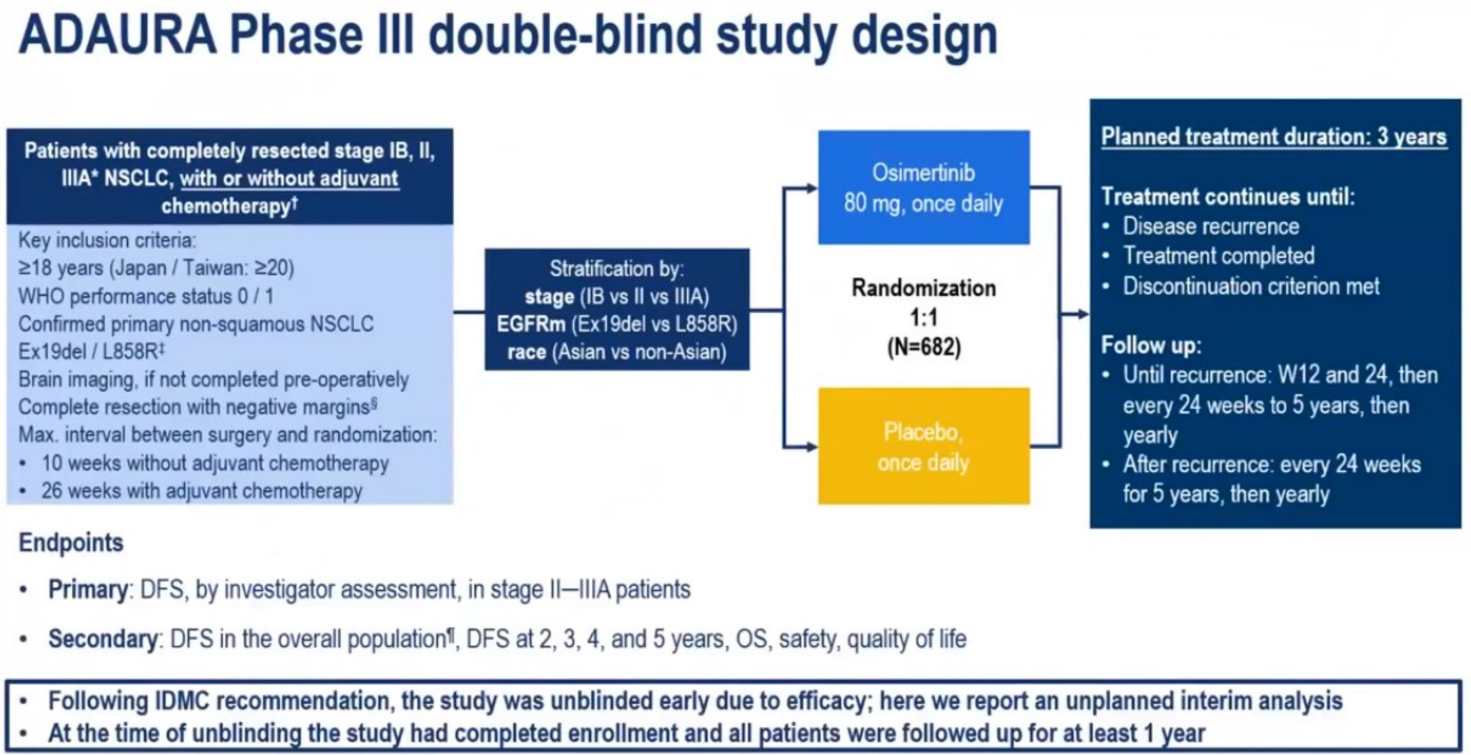
Early-stage EGFR: ADAURA



Herbst et al, ASCO 2020

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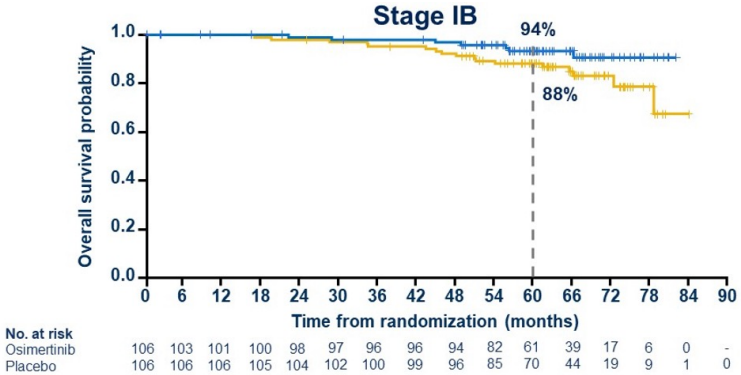
Early-stage EGFR: ADAURA

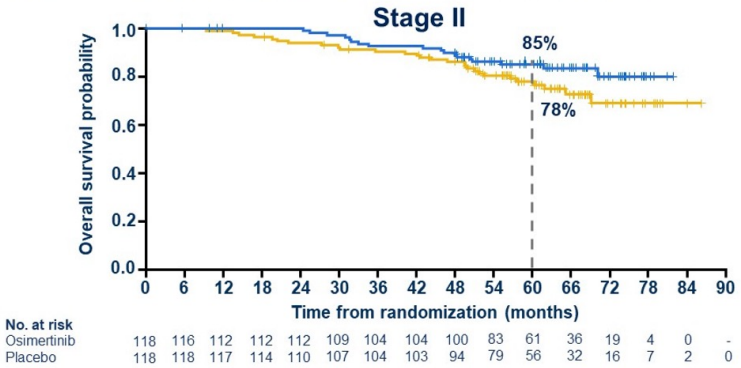
- Approved 12/20 for adjuvant use
  - ASCO 2020, NEJM 2020
  - DFS stage II-IIIA HR 0.17 (p<0.001), 90 vs 44% at 24 mos
  - DFS all comers HR 0.20 (p<0001), 89 vs 52% at 24 mos
- Question remained: Survival benefit?

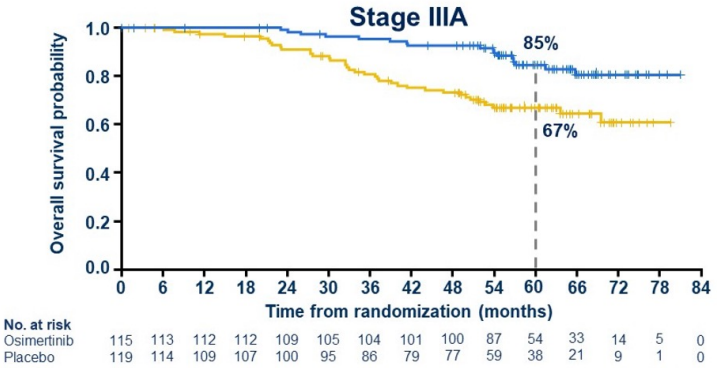
Wu et al, NEJM 2020

Early-stage EGFR: ADAURA Overall Survival



	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)**





Herbst et al, ASCO 2023

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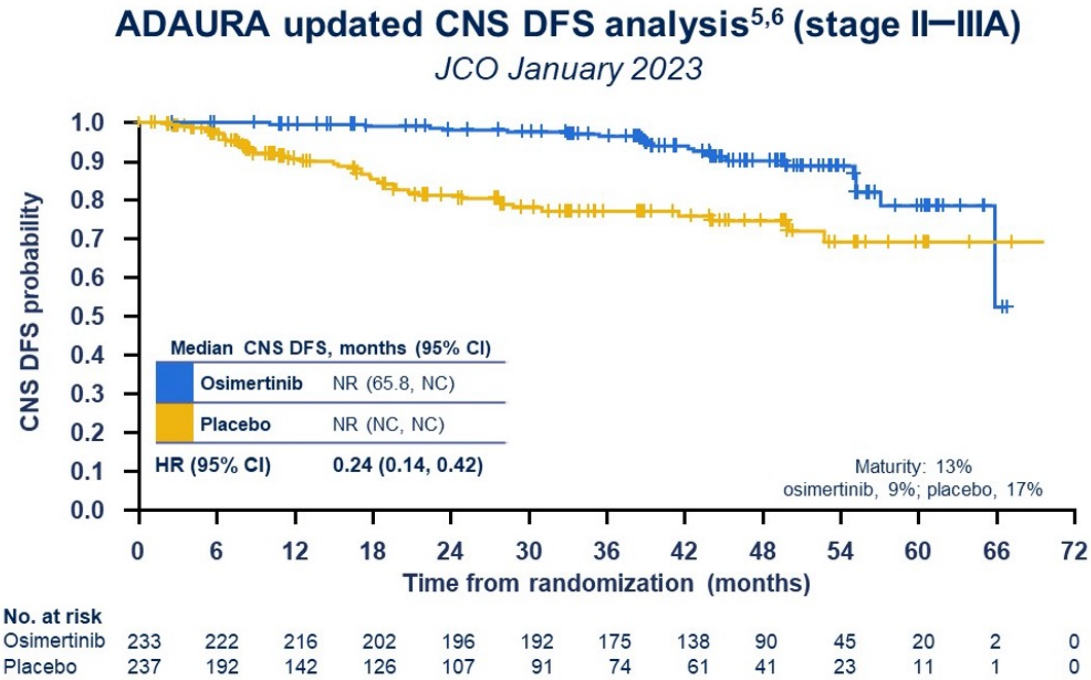
Early-stage EGFR: ADAURA CNS DFS



Herbst et al, ASCO 2023

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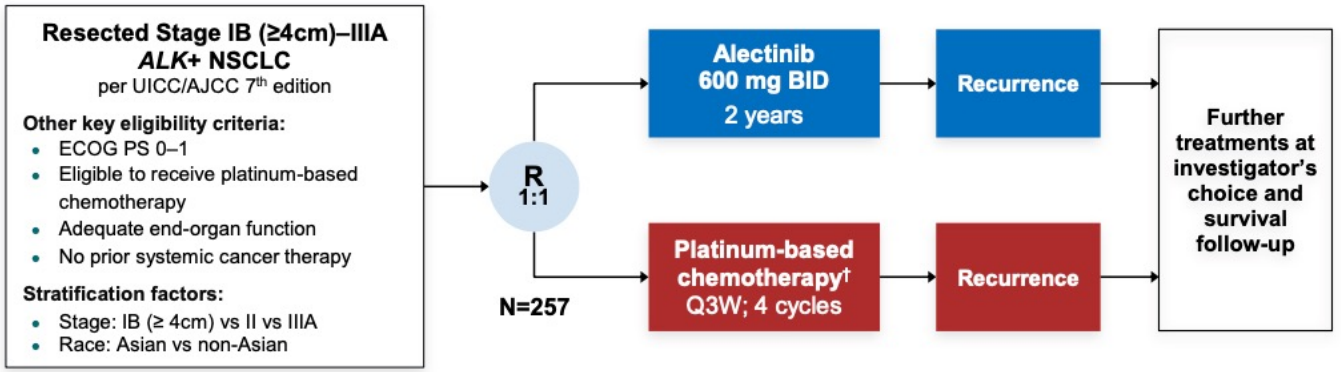
Early-stage ALK: ALINA



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

Solomon et al, ESMO 2023

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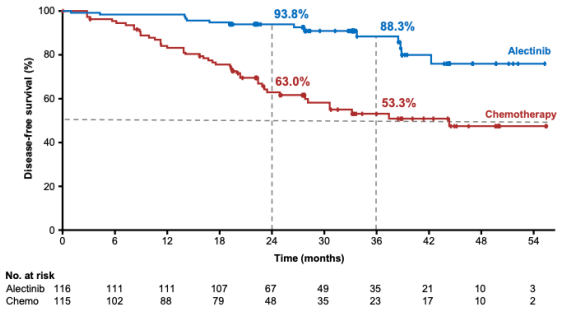
Early-stage ALK: ALINA DFS

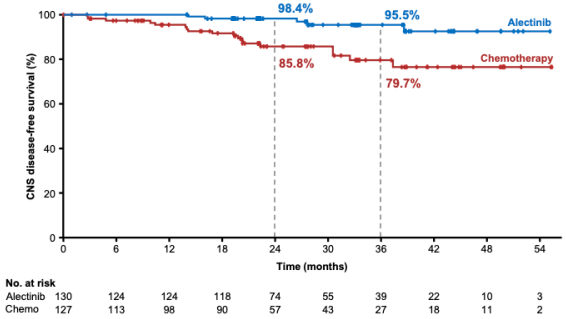
Overall: HR 0.24



	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

CNS: HR 0.22



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Brain recurrence	5 1 4	18 4 14
CNS-DFS HR* (95% CI)	**0.22** (0.08, 0.58)	

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  - ALK Alectinib x 2 years a potential new standard for resected disease
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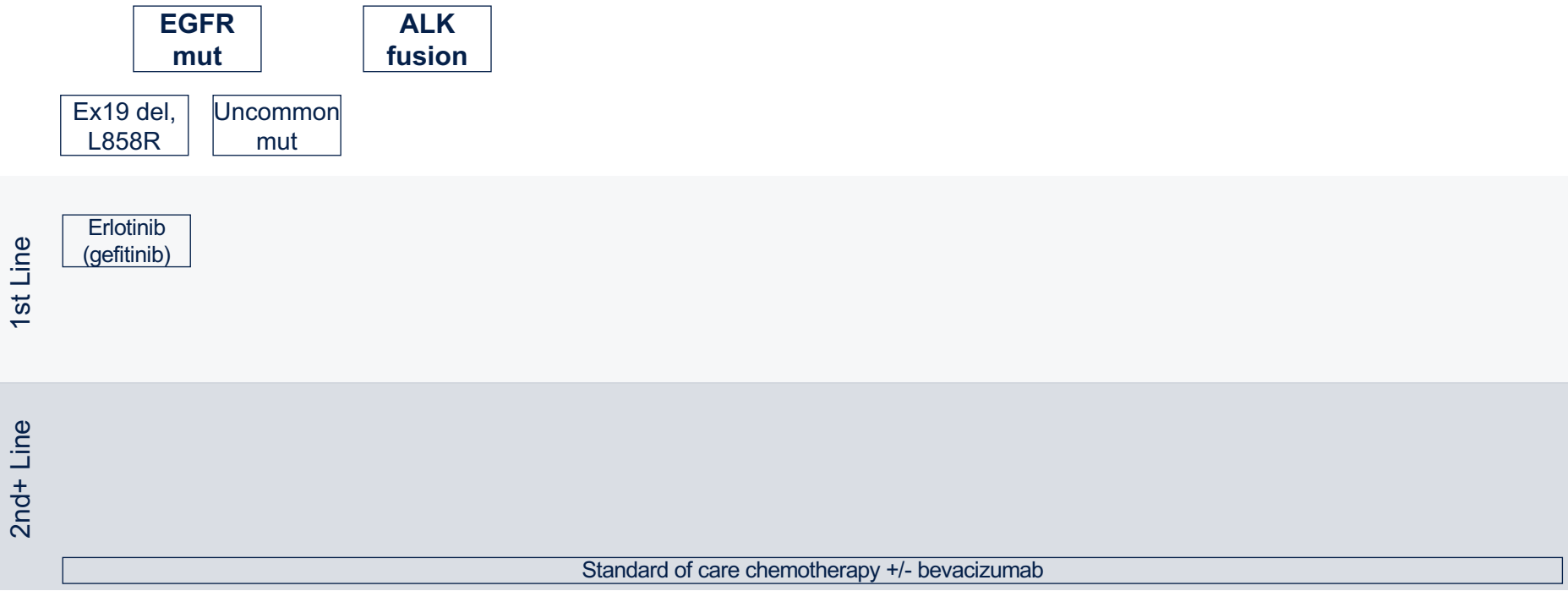
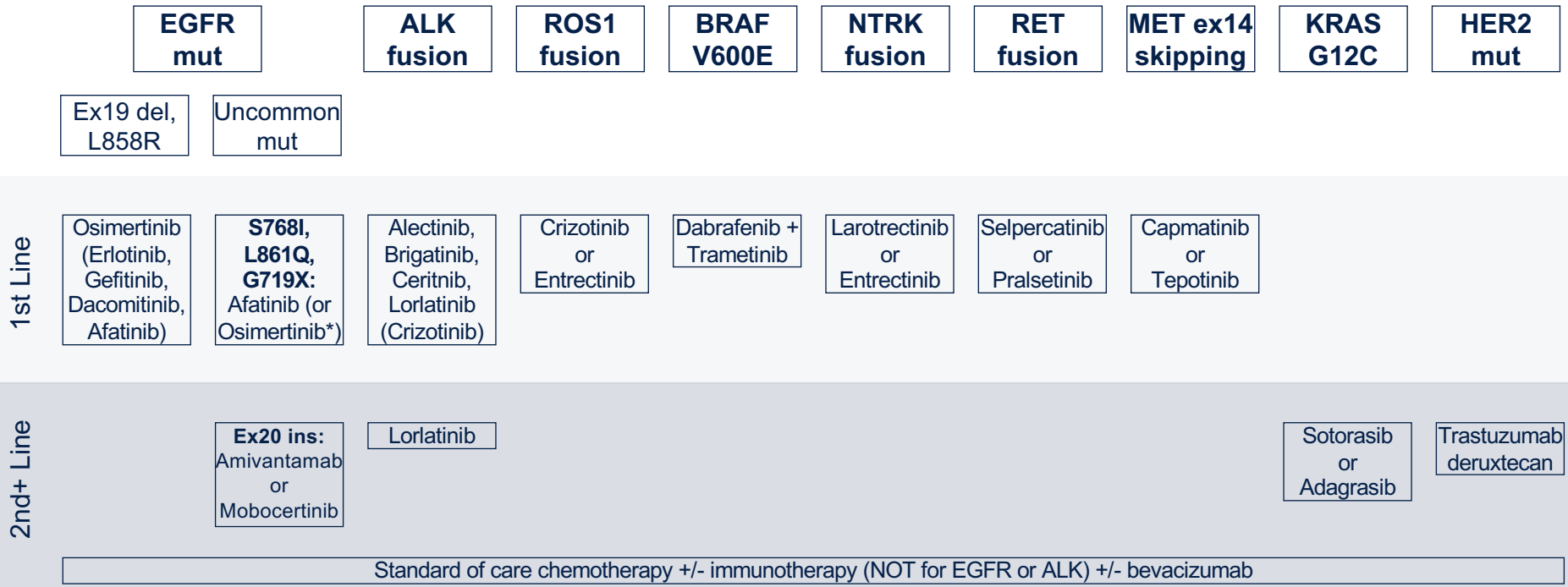
Molecular Biomarker-Positive Advanced NSCLC, 2008

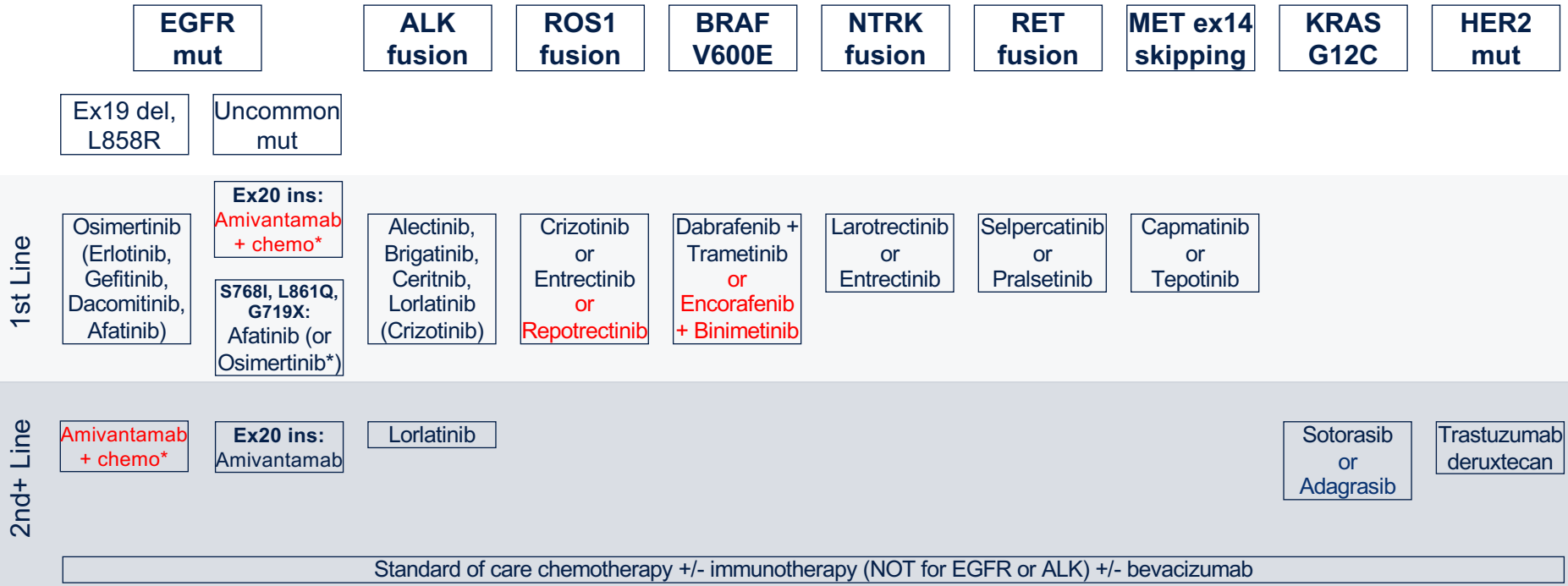


Molecular Biomarker-Positive Advanced NSCLC, 2022



*NCCN recommendation, not FDA approved

Molecular Biomarker-Positive Advanced NSCLC, 2/2024



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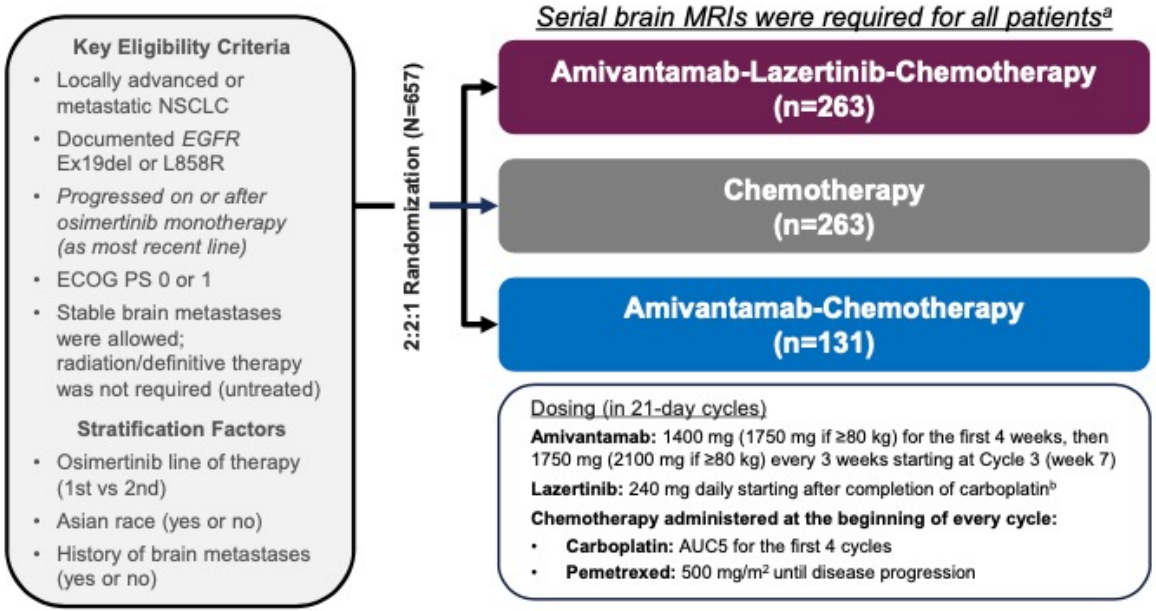
EGFR: MARIPOSA-2



Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:

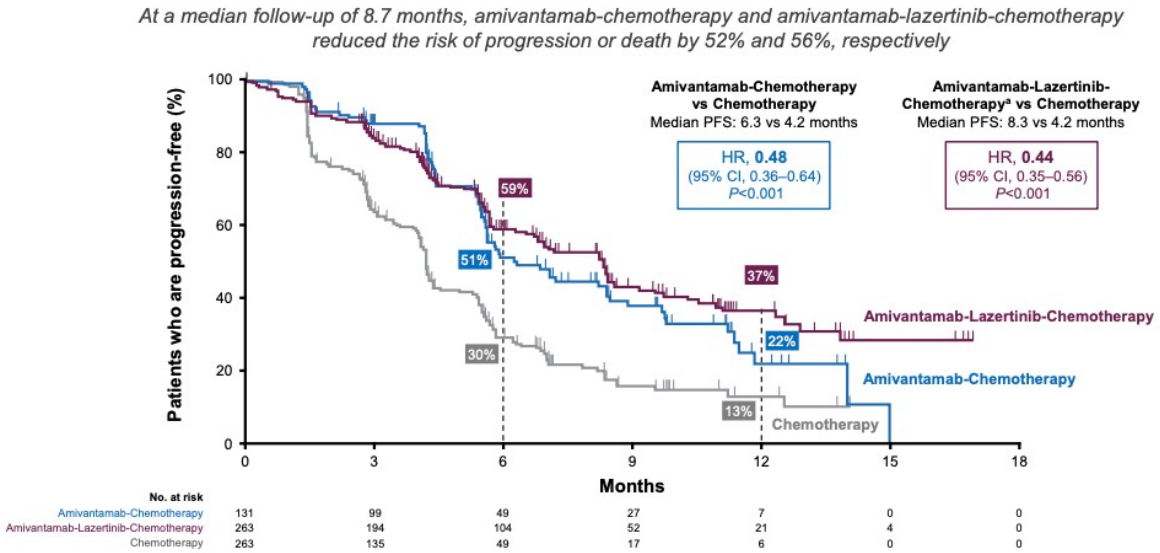
- **Amivantamab-Lazertinib-Chemotherapy** vs **Chemotherapy**
- **Amivantamab-Chemotherapy** vs **Chemotherapy**

Secondary endpoints:

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

Passaro et al, ESMO 2023

EGFR: MARIPOSA-2 PFS and ORR

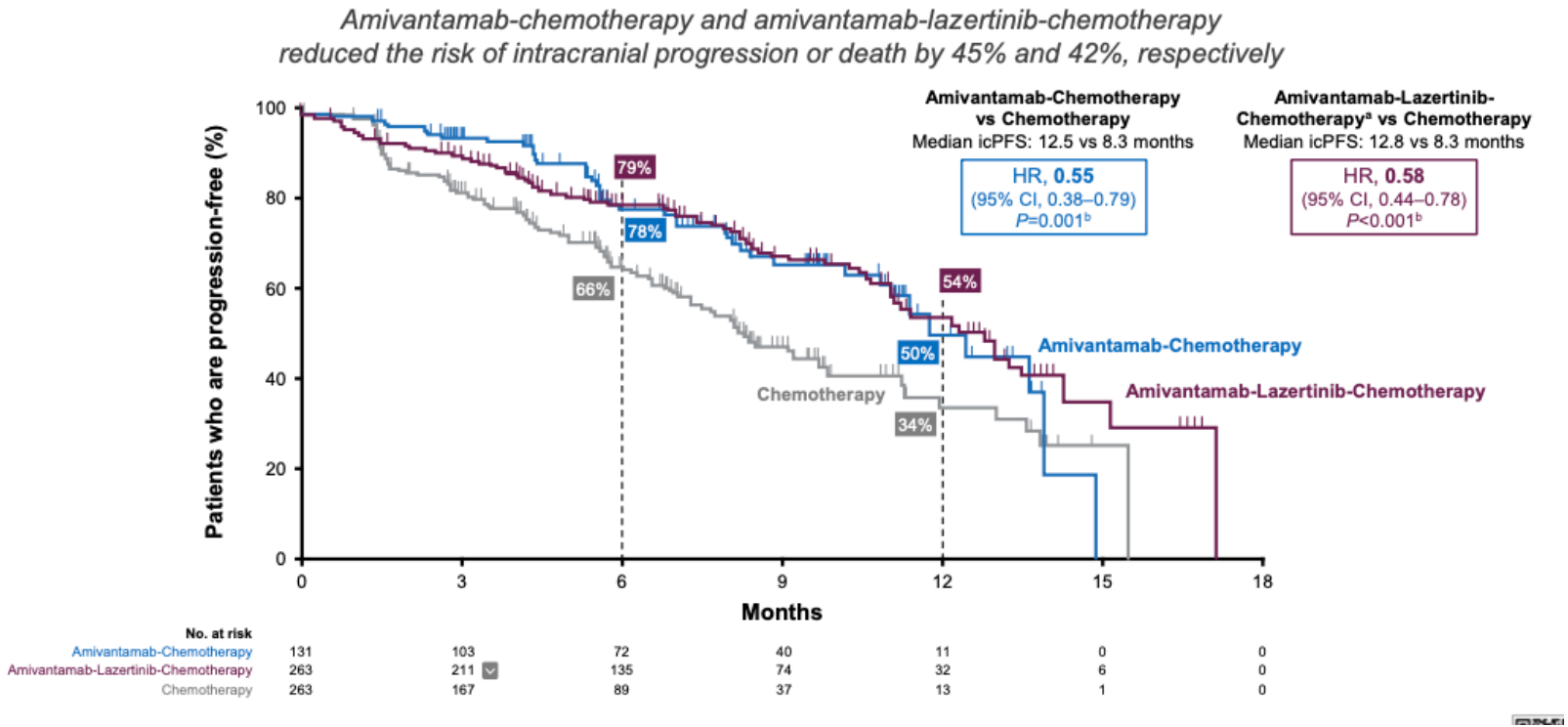


ORR

- 36% Chemo
- 64% Ami+chemo
- 63% Ami+Laz+chemo

Passaro et al, ESMO 2023

EGFR: MARIPOSA-2 Intracranial PFS



Passaro et al, ESMO 2023

EGFR: MARIPOSA-2 Safety

Most common TEAEs (≥25%) by preferred term, n (%)	Chemotherapy (n=243)		Amivantamab-Chemotherapy (n=130)		Amivantamab-Lazertinib-Chemotherapy[a] (n=263)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition						
Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
Stomatitis	21 (9)	0	41 (32)	1 (1)	120 (46)	24 (9)
Diarrhea	16 (7)	1 (0.4)	18 (14)	1 (1)	68 (26)	10 (4)
Associated with MET inhibition						
Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Associated with Chemotherapy						
Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Anemia	97 (40)	23 (9)	51 (39)	15 (12)	141 (54)	48 (18)
Leukopenia	68 (28)	23 (9)	37 (28)	26 (20)	106 (40)	71 (27)
Other						
Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)
Nausea	90 (37)	2 (1)	58 (45)	1 (1)	131 (50)	16 (6)
Constipation	72 (30)	0	50 (38)	1 (1)	96 (37)	3 (1)
Decreased appetite	51 (21)	3 (1)	40 (31)	0	85 (32)	7 (3)
Vomiting	42 (17)	1 (0.4)	32 (25)	1 (1)	76 (29)	10 (4)
Fatigue	47 (19)	4 (2)	36 (28)	4 (3)	69 (26)	15 (6)
Asthenia	40 (16)	5 (2)	34 (26)	1 (1)	67 (25)	14 (5)
Alanine aminotransferase increased	67 (28)	10 (4)	26 (20)	7 (5)	55 (21)	14 (5)
AESIs by grouped term, n (%)						
Rash[b]	30 (12)	0	92 (71)	13 (10)	197 (75)	40 (15)
VTE[c]	11 (5)	7 (3)	13 (10)	3 (2)	58 (22)	17 (6)
ILD	0	0	2 (2)	1 (1)	7 (3)	5 (2)

- Amivantamab-containing arms had higher rates of EGFR- and MET-related AEs
- Neutropenia and thrombocytopenia:
  - Mostly occurred during cycle 1
  - Low rates of febrile neutropenia (2%, 2%, and 8%)
  - Low rates of grade 3-4 bleeding[d] (0%, 1%, and 3%)
- VTE highest in amivantamab-lazertinib-chemotherapy arm
  - No grade 5 events
  - Rates of discontinuation due to VTE were low (0%, 1%, and 0.4%)
- Incidence of ILD was low in all arms (<3%)

Passaro et al, ESMO 2023

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    Consider adding amivantamab to chemo 2L (but check for resistance mechanisms)
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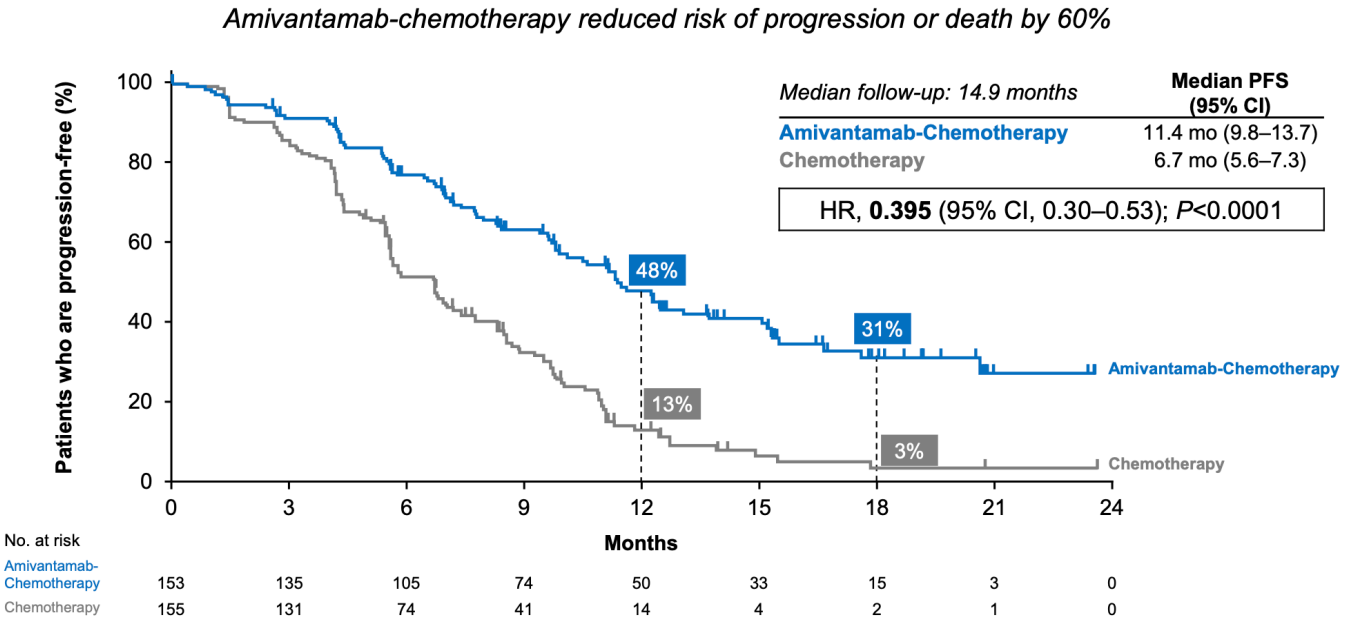
EGFR exon 20 ins

- Uncommon EGFR variant, resistant to approved EGFR TKIs
- Recent approvals in 2L:
  - Amivantamab, bispecific antibody targeting EGFR and MET
  - Mobocertinib, EGFR exon 20 ins TKI
- PAPILLON phase 3 study for 1L amivantamab + chemo vs chemo alone
  - N=308 pts
  - Crossover allowed to amivantamab for chemo arm
    - Amivantamab 1400mg (or 1750 if 80kg+) weekly x 4, then 1750mg (or 2100mg if 80kg+) every 3 weeks starting C3D1
    - Primary endpoint PFS

EGFR exon 20 ins: PAPILLON PFS



Interim OS: HR 0.675, p=0.106

Girard et al, ESMO 2023

EGFR exon 20 ins: Mobocertinib withdrawal

- Mobocertinib, EGFR exon 20 ins TKI
  - Accelerated approval pathway (phase 1/2 ORR 28%, PFS 7.3m)
  - Phase 3 EXCLAIM-2 trial: 1st line mobocertinib vs platinum-based chemo
    - Did not meet primary PFS endpoint (data not yet released)
- → Press release 10/2/23 announcing withdrawal from market

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EGFR: BRAF V600E dabrafenib+trametinib vs encorafinib+binimetinib

- Dabrafenib + trametinib approved in 2017 for NSCLC V600E (n=36 treatment-naïve)
  - ORR 64%
  - PI mDoR 10.4m, mPFS 10.9m
    - independent review mDoR 15.2m, mPFS 14.6m
- PHAROS trial of encorafinib + binimetinib (n=98, 58 treatment-naïve and 39 previously-treated)
  - ORR 75% treatment-naïve, 46% previously-treated
  - PI mDoR 18.2m in treatment-naïve (95% CI 16.4-22.3m) and 12.8m in previously-treated (9-19.8m)
    - independent review mDOR NE in treatment-naïve (95% CI 23.1 to NE), 16.7m in previously-treated (95% CI 7.4-NE)

Planchard et al, Lancet Oncology 2017. Riely et al, JCO 2023.

EGFR: BRAF V600E dabrafenib+trametinib vs encorafinib+binimetinib: Safety

	Dabrafenib + trametinib	Encorafinib + binimetanib
Grade 3 or 4	69%	41%
AE leading to d/c	22%	15%
AE leading to dose reduction	39%	24%
Pyrexia, any grade	64%	22%

Planchard et al, Lancet Oncology 2017. Riely et al, JCO 2023.

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ROS1 fusion

- Crizotinib– approved 2016: n=50, RR 66%, mDoR 18.3m
- Entrectinib– approved 2019: n=53, RR 77%, mDOR 24.6m

- Lorlatinib, not FDA approved: n=21 TKI-naïve, RR 62%, mDOR 25.3m
  - n=40 prior crizotinib, RR 35%, mDOR 13.8m
  - (NCCN recommended for subsequent therapy)

FDA approval for crizotinib, 2016. Drilon et al, Lancet Oncology 2019. Shaw et al, Lancet Oncology 2019.

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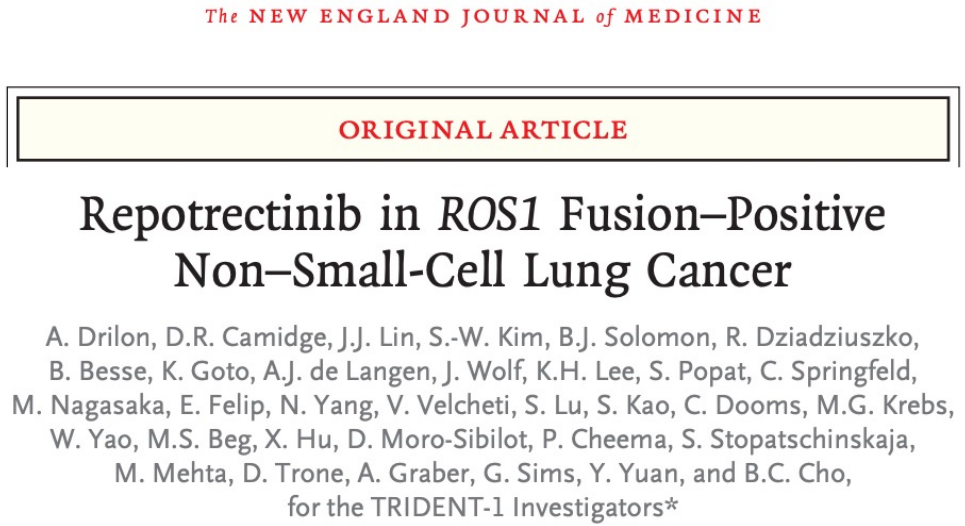
ROS1 fusion: Repotrectinib



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*

- Next gen TKI against ROS1 (and TRK)

Drilon et al, NEJM 2024

ROS1 fusion: Repotrectinib

	Treatment-naïve, n=71	Previously-treated with TKI not chemo, n=56
ORR	79%	38% (59% with G2032R)
mDOR	34.1m	14.8m
PFS	35.7m	

Drilon et al, NEJM 2024

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ROS1 fusion: Repotrectinib safety

- Most common adverse events:
  - Dizziness 62% (g3+ 3%)
    - No discontinuation, 11% dose reduction, 8% dose interruption
  - Dysguesia 53%
  - Constipation 38%
  - Anemia 38%
  - Paresthesia 34%
- Most common g3+ adverse events:
  - 29% overall
  - 5% neuro overall. (3% dizziness), 4% anemia, elevated creatine kinase

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)
Nausea	85 (20)	3 (1)	51 (12)	2 (<1)
Muscular weakness	85 (20)	8 (2)	59 (14)	6 (1)
Headache	79 (19)	0	42 (10)	0
Increased blood creatine kinase level	75 (18)	15 (4)	72 (17)	15 (4)
Weight increase	67 (16)	11 (3)	49 (12)	7 (2)
Memory impairment	65 (15)	1 (<1)	54 (13)	1 (<1)
Cough	64 (15)	1 (<1)	10 (2)	0
Event that led to treatment discontinuation	31 (7)	0	14 (3)	0
Event that led to dose reduction	163 (38)	0	149 (35)	0
Event that led to dose interruption	213 (50)	0	150 (35)	0
Any serious event	147 (35)	0	38 (9)	0
Death	19 (4)	0	0	0

Drilon et al, NEJM 2024

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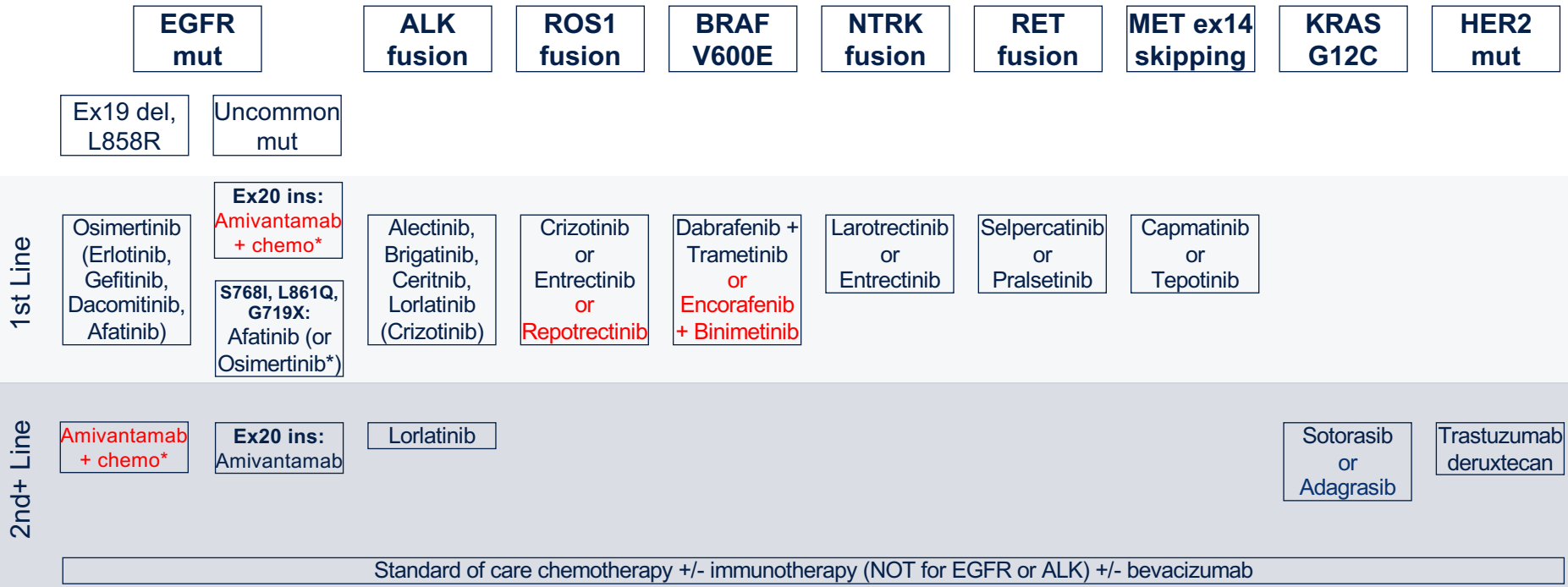
Molecular Biomarker-Positive Advanced NSCLC, 2/2024



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Thank you!