Comprehensive Hematology & Oncology Review : Metastatic NSCLC

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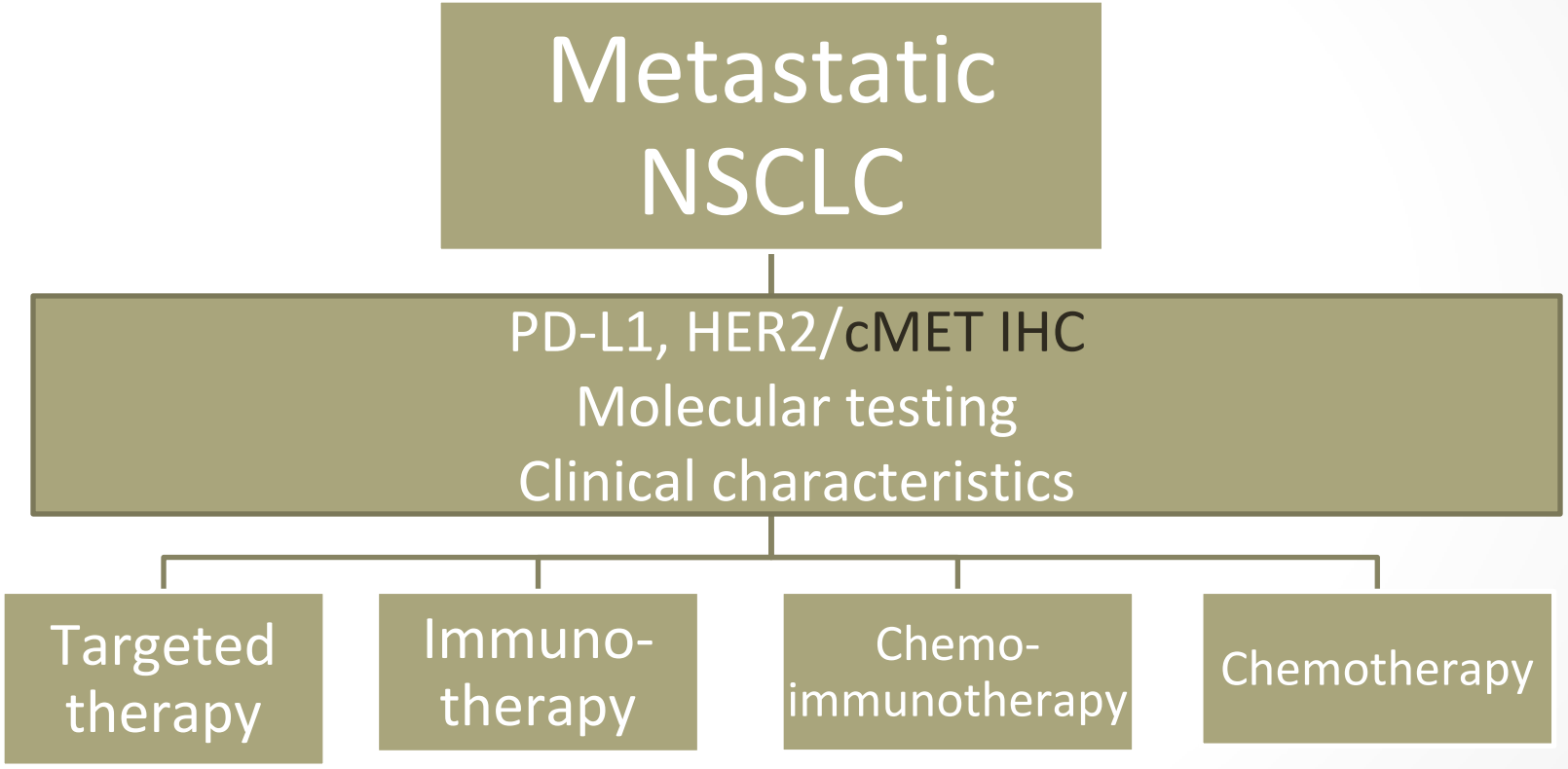
New FDA approvals for metastatic NSCLC (fall 2024-fall 2025)

- Ensartinib for ALK fusion
- Taletrectinib for ROS1 fusion
- Zongertinib for HER2 activating mutation
- Datopotomab Dxd for EGFR mutation
- Telisotuzumab vedotin for cMET over-expressed
- Sunvozertinib for EGFR 20 insertion
- Zenocutuzumab for NRG fusion

First line treatment decision in metastatic NSCLC

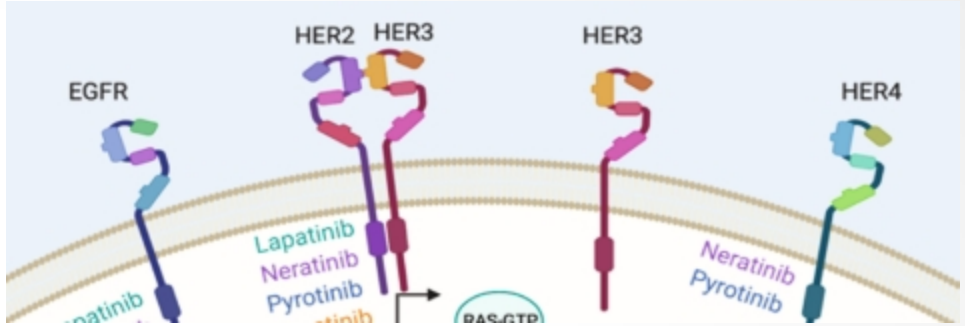


TARGETED THERAPY

Actionable molecular subtypes in NSCLC (i.e. available FDA approved drugs in October 2025)

Alteration	Prevalence (estimates)
EGFR mutations, non-exon20 ins	15-20%
EGFR exon 20 ins	2-3%
KRAS G12C	10-13%
ALK fusion	3-5%
ROS1 fusion	1-2%
BRAF V600E mutation	1-2%
NTRK fusion	<1%
MET exon 14 skipping mutation	3-4%
RET rearrangement	1-2%
HER2 fusion	1-2%
NRG fusion	<1%

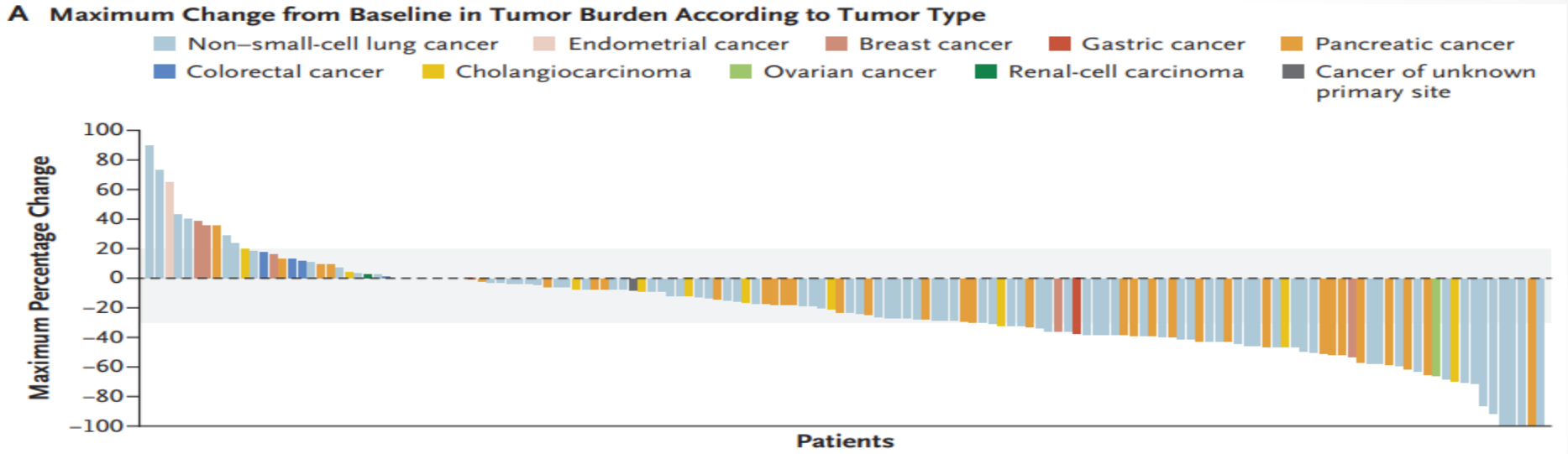
NRG fusion



- NRG1 = Encodes for neurogulin 1 protein, involved in neural development
  - NRG1 fusion abnormally actives HER3 and activates heterodimerization of HER2-HER3
- Prevalence of NRG1 fusion <1% in solid tumors
  - Enriched in mucinous adenocarcinoma of the lung and KRAS WT pancreatic cancer
- Zenocutuzumab-zbco:
  - Bispecific antibody against HER2 and HER3, IV q2week
  - Blocks interaction of NRG1 fusion protein with HER3 and HER2-HER3 dimerization
  - Approved in Dec 2024 for advanced NRG fusion-positive NSCLC or pancreatic adenocarcinoma
- NSCLC (n=94): ORR 29% (20-39), mDOR 12.7 mos
- Pancreatic adeno (n=36): ORR 42% (25-59); mDOR 7.4 mos

Schram et al. NEJM 2025; 392:566

NRG1 fusion

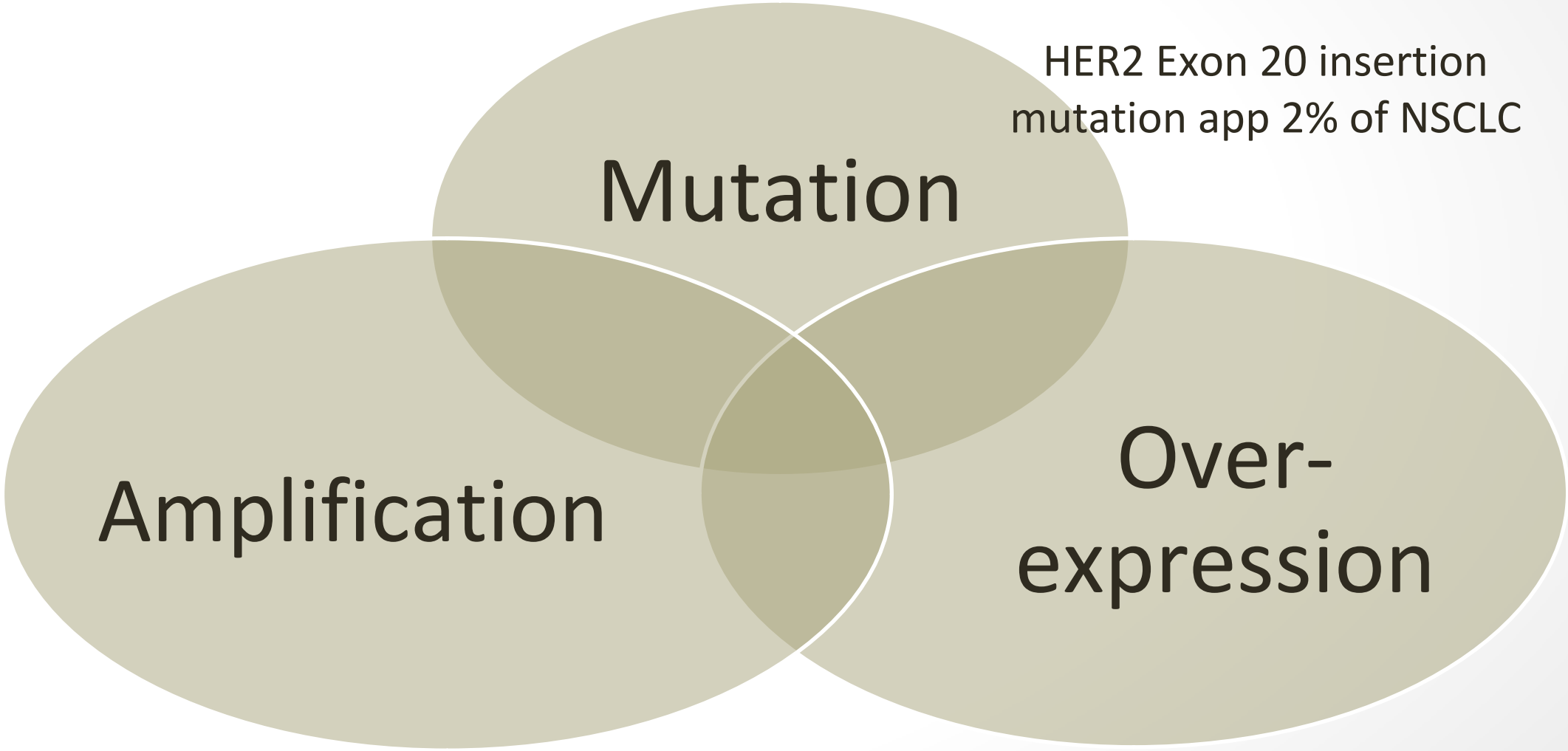


Adverse events occurring in ≥10% of patients				
Diarrhea	60 (29)	4 (2)	37 (18)	3 (1)
Fatigue	42 (21)	5 (2)	24 (12)	0
Nausea	40 (20)	4 (2)	23 (11)	2 (1)
Anemia	34 (17)	10 (5)	9 (4)	3 (1)
Dyspnea†	33 (16)	5 (2)	4 (2)	0
Constipation	28 (14)	0	7 (3)	0
Vomiting	28 (14)	2 (1)	12 (6)	1 (<1)
Abdominal pain‡	26 (13)	4 (2)	3 (1)	1 (<1)
Alanine aminotransferase increased	25 (12)	6 (3)	7 (3)	1 (<1)
Cough§	24 (12)	1 (<1)	3 (1)	0

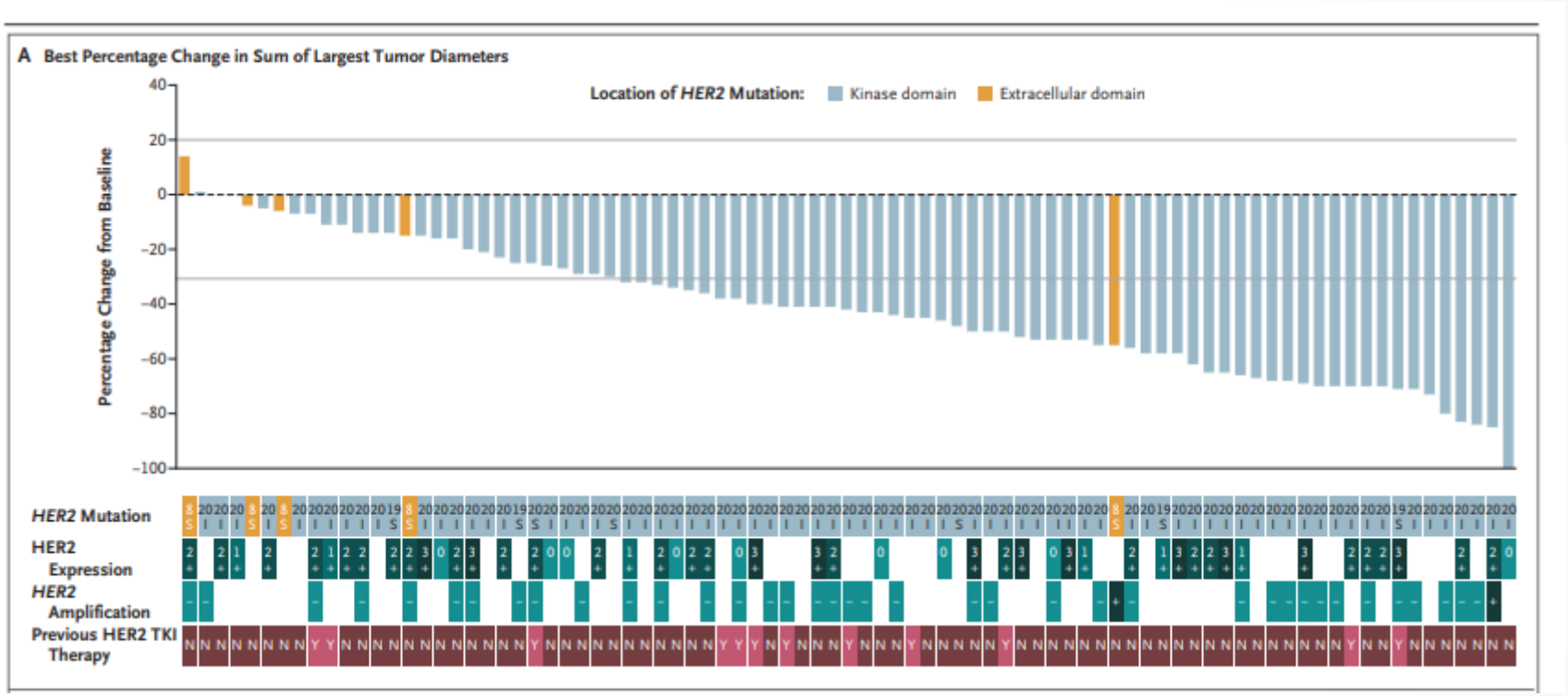
Schram et al. NEJM 2025; 392:566

HER2 alterations in NSCLC

HER2 Exon 20 insertion mutation app 2% of NSCLC



HER2 mutation: Trastuzumab deruxtecan



- Anti-HER2 antibody drug conjugate
- Studied in patients who have had prior chemo
- ORR 55% (95% CI 44-65)
- Duration of response: 9.3 mos (95% CI 5.7-14.7)
- mPFS: 8.2 mos (95% CI 6.0-11.9)
- FDA approved in post-platinum setting

Li et al. DESTINY Lung-01. NEJM 2021

HER2 mutation: Zongertinib

	Cohort 1 (previously treated)	Cohort 5 (previous HER2 ADC)	Cohort 3 (non-TKD)
n	75	31	20
ORR, % (95% CI)	71 (60-80)	48 (32-65)	30 (15-52)*
Disease control, % (95% CI)	96 (89-99)	97 (84-99)	65 (43-82)
mPFS (mos)	12.4 (8.2-NE)	6.8 (5.4-NE)	Not mature
Intracranial RR, % (95% CI)	41 (25-59), n=41	N/A	N/A

* Responders in non-TKD Cohort: S310F (extracellular), V659E (transmembrane)

Heymach *et al*. NEJM 2025;doi:10.1056

Zongertinib - toxicities

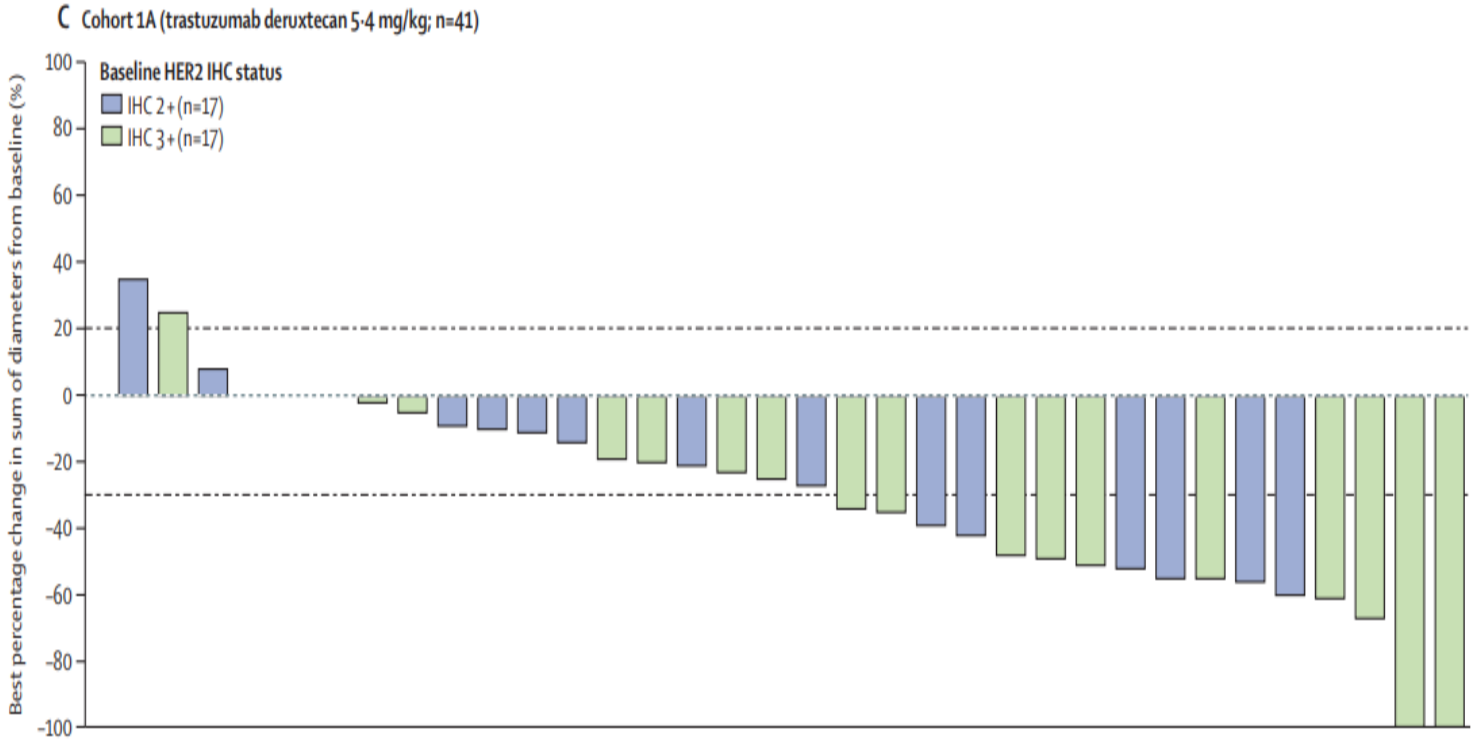
Table 3. Safety Summary and the Most Common Drug-Related Adverse Events among the 75 Patients in Cohort 1 Treated with Zongertinib at a Dose of 120 mg.

Event	All	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Any drug-related adverse event§	73 (97)	27 (36)	33 (44)	12 (16)	1 (1)	0
Diarrhea¶	42 (56)	36 (48)	5 (7)	1 (1)	0	0
Rash‖	25 (33)	18 (24)	7 (9)	0	0	0
Increased aspartate aminotransferase	18 (24)	11 (15)	3 (4)	4 (5)	0	0
Increased alanine aminotransferase	16 (21)	9 (12)	1 (1)	5 (7)	1 (1)	0
Nausea	11 (15)	10 (13)	1 (1)	0	0	0
Dry skin	11 (15)	11 (15)	0	0	0	0
Pruritus	10 (13)	9 (12)	1 (1)	0	0	0
Decreased white-cell count	10 (13)	5 (7)	5 (7)	0	0	0
Anemia	9 (12)	6 (8)	3 (4)	0	0	0
Decreased neutrophil count	9 (12)	3 (4)	5 (7)	1 (1)	0	0
Nail disorder	8 (11)	8 (11)	0	0	0	0

Dose reduction 7%
Discontinuation 3%

Heymach *et al*. NEJM 2025;doi:10.1056

T-Dxd in HER2 over-expressed NSLC



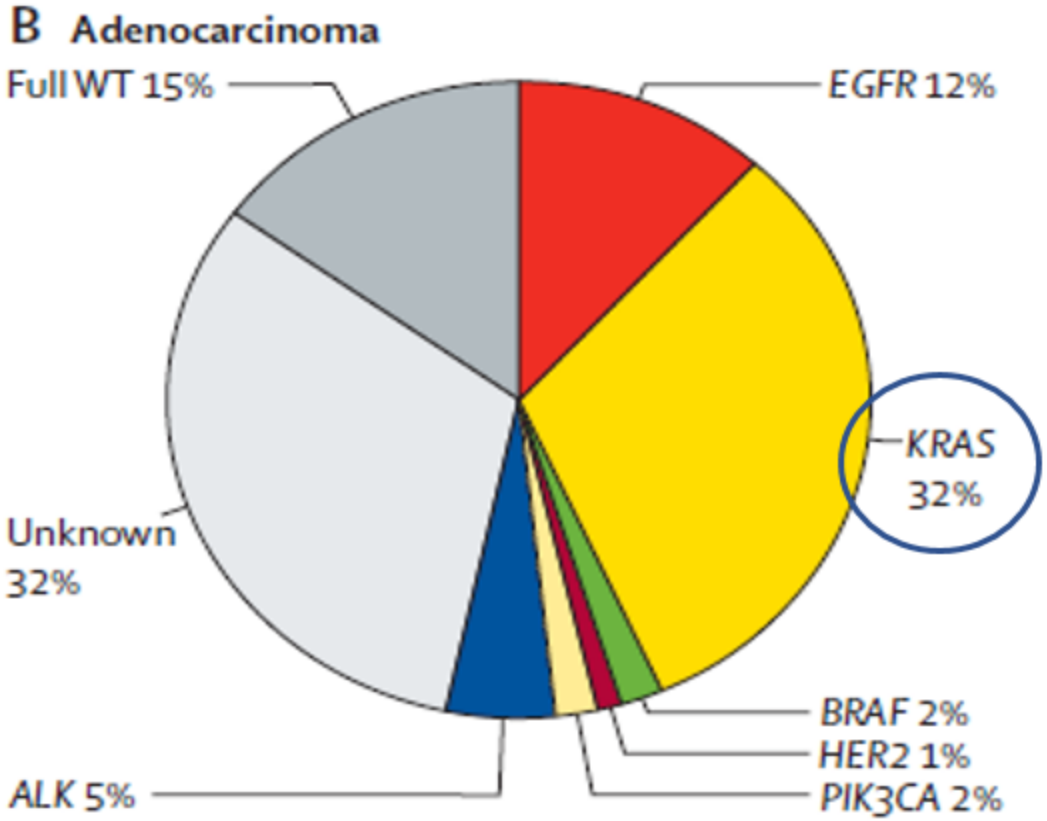
FDA approved dose 5.4mg/kg for 3+ HER2 solid tumor, who have had prior systemic therapy

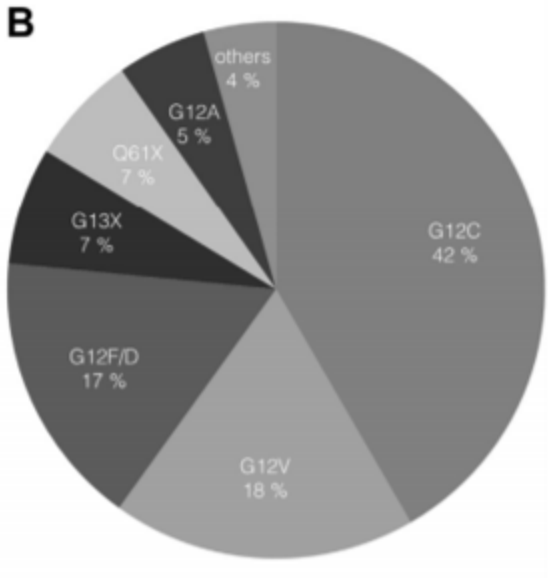
5.4mg/kg lung cohort (n=41), HER2 2-3%

- ORR 34% (21-51)
- PFS 6.7 mos (4.2-8.4)

Smit et al. LancetOncol 2024

KRAS G12C





KRAS G12C: App 10-13% of all NSCLC

Barlesi et al. Lancet 2016;387:1415-26 Hong et al. NEJM 2020;383:1207 Scheffler et al. JTO 2019; 14(4):606-616

KRAS G12C: Approved post-chemo

Table 2. Tumor Response to Sotorasib Therapy According to Independent Central Review.*

Variable	Patients (N = 124)
Objective response — % (95% CI)†	37.1 (28.6–46.2)
Disease control — % (95% CI)‡	80.6 (72.6–87.2)
Best response — no. (%)	
Complete response	4 (3.2)
Partial response	42 (33.9)
Stable disease	54 (43.5)
Progressive disease	20 (16.1)
Could not be evaluated	2 (1.6)
Missing scan	2 (1.6)
Median duration of objective response (95% CI) — mo§	11.1 (6.9–NE)
Kaplan–Meier estimate of objective response (95% CI) — %	
At 3 mo	90.5 (76.7–96.3)
At 6 mo	70.8 (54.3–82.2)
At 9 mo	57.3 (40.4–71.0)

PFS 6.9mos

Sotorasib

Table 2. Overall Efficacy Summary According to Blinded Independent Central Review.*

Variable	Cohort A (N=112)†
Objective response‡	
No. of patients	48
Percent (95% CI)	42.9 (33.5–52.6)
Best overall response — no. (%)	
Complete response	1 (0.9)
Partial response	47 (42.0)
Stable disease	41 (36.6)
Progressive disease	6 (5.4)
Not evaluable	17 (15.2)
Disease control	
No. of patients	89
Percent (95% CI)	79.5 (70.8–86.5)
Median duration of response (95% CI) — mo	8.5 (6.2–13.8)
Median progression-free survival (95% CI) — mo	6.5 (4.7–8.4)
Median overall survival (95% CI) — mo§	12.6 (9.2–19.2)

Adagrasib

Skoulidis et al. NEJM June 2021; Janne et al NEJM 2022

Table 3. Adverse Events.*

Event	All Patients (N=126)				
	Any Grade	Grade 1 or 2	Grade 3	Grade 4	Fatal
	number of patients (percent)				
Adverse event	125 (99.2)	48 (38.1)	53 (42.1)	4 (3.2)	20 (15.9)
Treatment-related adverse event	88 (69.8)	62 (49.2)	25 (19.8)	1 (0.8)	0
Treatment-related adverse event leading to dose modification	28 (22.2)	8 (6.3)	20 (15.9)	0	0
Treatment-related adverse event leading to discontinuation of therapy	9 (7.1)	4 (3.2)	4 (3.2)	1 (0.8)	0
Treatment-related adverse event of any grade occurring in >5% of the patients or that was grade ≥3					
Diarrhea	40 (31.7)	35 (27.8)	5 (4.0)	0	0
Nausea	24 (19.0)	24 (19.0)	0	0	0
Alanine aminotransferase increase	19 (15.1)	11 (8.7)	8 (6.3)	0	0
Aspartate aminotransferase increase	19 (15.1)	12 (9.5)	7 (5.6)	0	0
Fatigue	14 (11.1)	14 (11.1)	0	0	0

Sotorasib

Table 3. Adverse Events Reported during Treatment (Safety Population).*

Event	Any Grade	Grade ≥3
	no. of patients (%)	
Any adverse event	116 (100)	95 (81.9)
Adverse event leading to dose reduction or interruption	96 (82.8)	—
Adverse event leading to discontinuation of therapy	18 (15.5)	—
Adverse event of any grade that occurred in >10% of patients or that was grade ≥3 in >1 patient†		
Diarrhea	82 (70.7)	1 (0.9)
Nausea	81 (69.8)	5 (4.3)
Fatigue	69 (59.5)	8 (6.9)
Vomiting	66 (56.9)	1 (0.9)
Anemia	42 (36.2)	17 (14.7)

Adagrasib

Transaminitis in about 25%

KRAS G12C

- Sotorasib and adagrasib currently FDA approved after prior systemic therapy
- Many other G12C inhibitors in development
- Combinations are being evaluated: MEK inhibitor, immune checkpoint inhibitor, EGFR antibody, SHP2 inhibitor, chemotherapy, etc
- What about non-G12C? Various approaches being evaluated (select):
  - BDTX-4933: RAF/ RAS inhibitor (NCT05786924)
  - Cellular therapies (e.g. G12V TCR)
  - MEK inhibition with SHP2 inhibition (NCT03989115)
  - FASN (Fatty acid synthase) inhibitor, TVB-2640 (NCT03808558)
  - panKRAS inhibitor, BI1701963 (NCT04111458)

EGFR mutation+ NSCLC (non-exon 20)

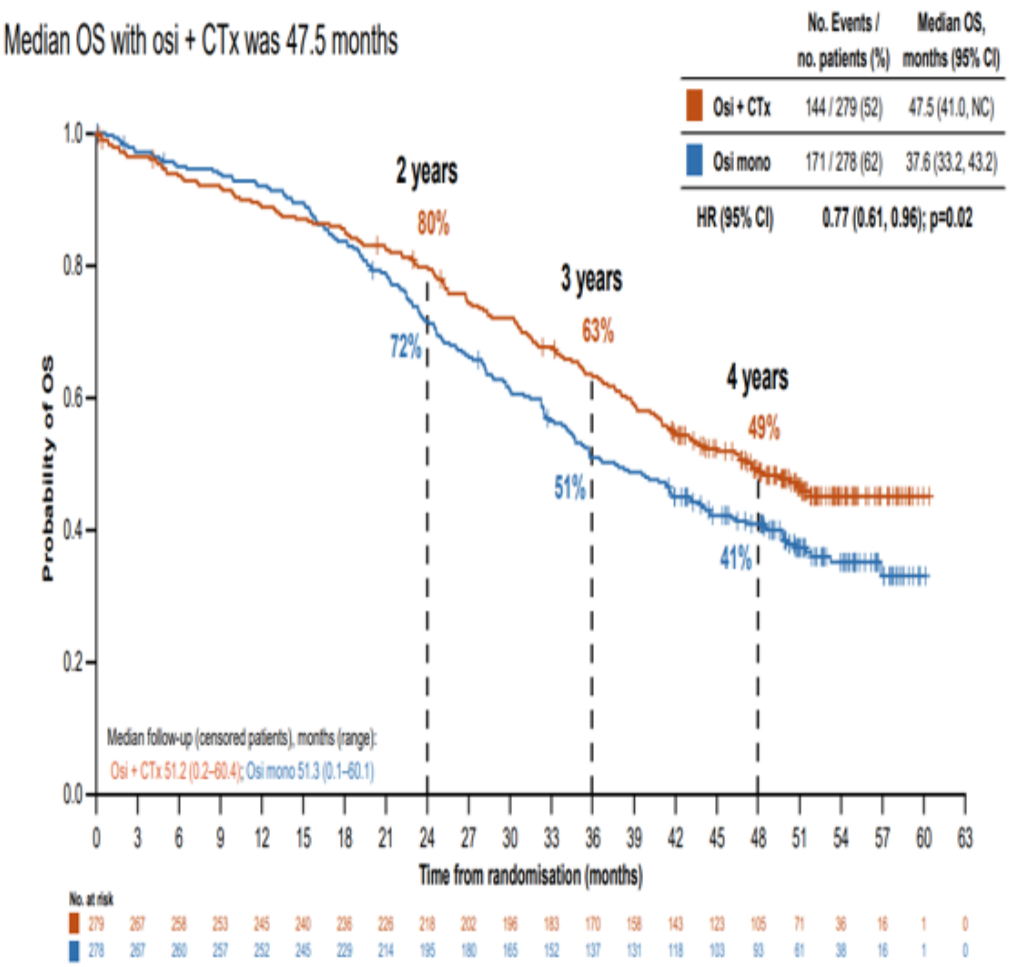
- Most common (i.e. classical) mutations: Exon 19 deletion and exon 21 L858R
- Other atypical mutations (e.g. G719X) have modest sensitivity to 3rd gen EGFR inhibitor

FDA approved first-line regimens	
Erlotinib +/- ramucirumab	Osimertinib
Gefitinib	Osimertinib + platinum pemetrexed
Afatinib	Lazertinib + amivantamab
Dacomitinib	

56% of osi pts with PD received platinum doublet

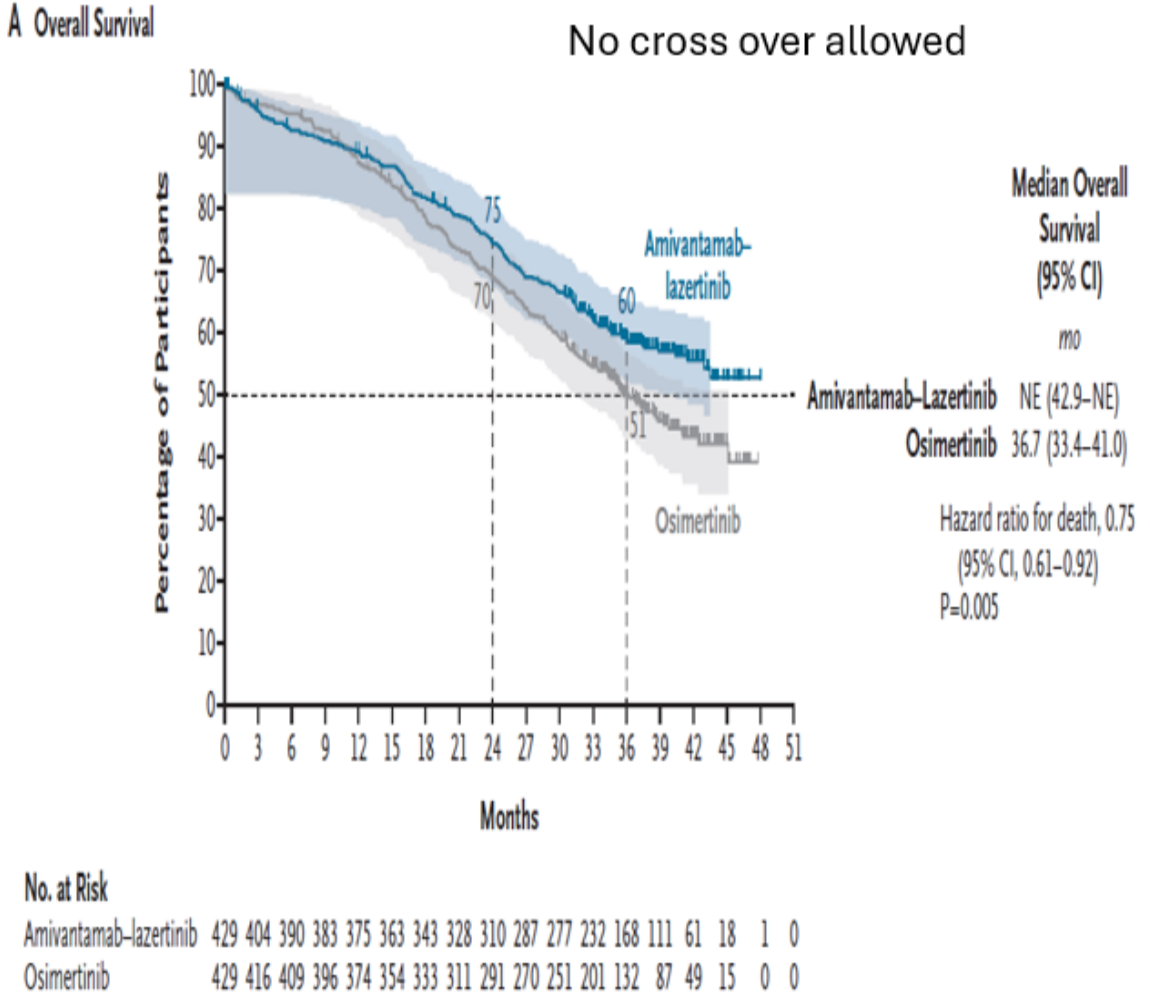
FLAURA2: Overall survival

Median OS with osi + CTx was 47.5 months



MARIPOSA

No cross over allowed



MARIPOSA Yang NEJM 2025 Planchard WCLC 2025

First line selection in EGFR+ NSCLC

- Osimertinib → Amivantamab + chemo (MARIPOSA2 regimen)?
- Osimertinib → Amivantamab → chemo?
- Osimertinib + chemo → Amivantamab?
- Amivantamab + Lazertinib → chemo?
- Erlotinib + ramucirumab → osi if T790M+ → ami + chemo?

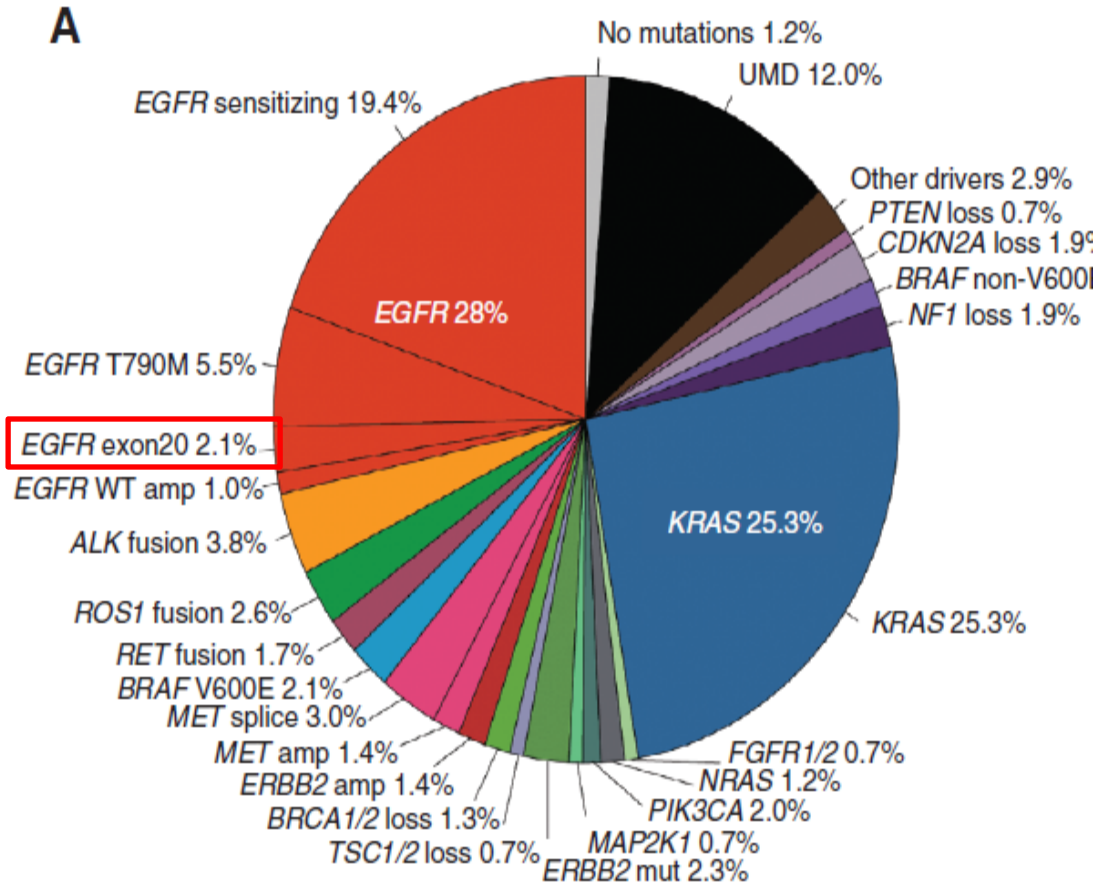
- ❑ Combination result in better PFS and OS than osimertinib but unknown if sequential therapy be as good
- ❑ Ongoing debate as to when to offer combination vs monotherapy but may be reasonable to offer combination in high risk patients
- ❑ Other regimens in trials (MET TKI for MET amplified / EGFR mutated, ADCs, etc)

Later line EGFR: Datopotomab Dxd

- Trop2 antibody drug conjugate; no biomarker selection
- FDA approved for EGFR-mutated NSCLC in June 2025, post EGFR directed therapy and platinum based chemotherapy
- Efficacy (n=78, Tropion Lung-05. Sands et al. JCO 2025):
  - 43.6% ORR; DCR 82.1%, mDOR 7.0 mos (4.2-10.2), PFS 5.8 mos (5.4-8.3)

	N = 137, No. (%)			
Adverse Event	Any Grade	Grade 3	Grade 4	Grade 5
TRAEs	129 (94.2)	38 (27.7)	1 (0.7)	0
Dose adjustments because of TRAEs				
Dose reductions	27 (19.7)	10 (7.3)	0	0
Dose delay	29 (21.2)	11 (8.0)	0	0
Treatment discontinuation	7 (5.1)	1 (0.7)	1 (0.7)	0
Serious TRAEs	11 (8.0)	6 (4.4)	1 (0.7)	0
AESIs				
Oral mucositis/stomatitis	90 (65.7)	15 (10.9)	0	0
Mucosal inflammation	1 (0.7)[a]	0	0	0
Ocular surface events	36 (26.3)	3 (2.2)	0	0
Infusion-related reactions	22 (16.1)	0	0	0
Adjudicated ILD/pneumonitis	5 (3.6)	0	0	1 (0.7)

EGFR exon 20 insertion



Amivantamab FDA approved in May 2021

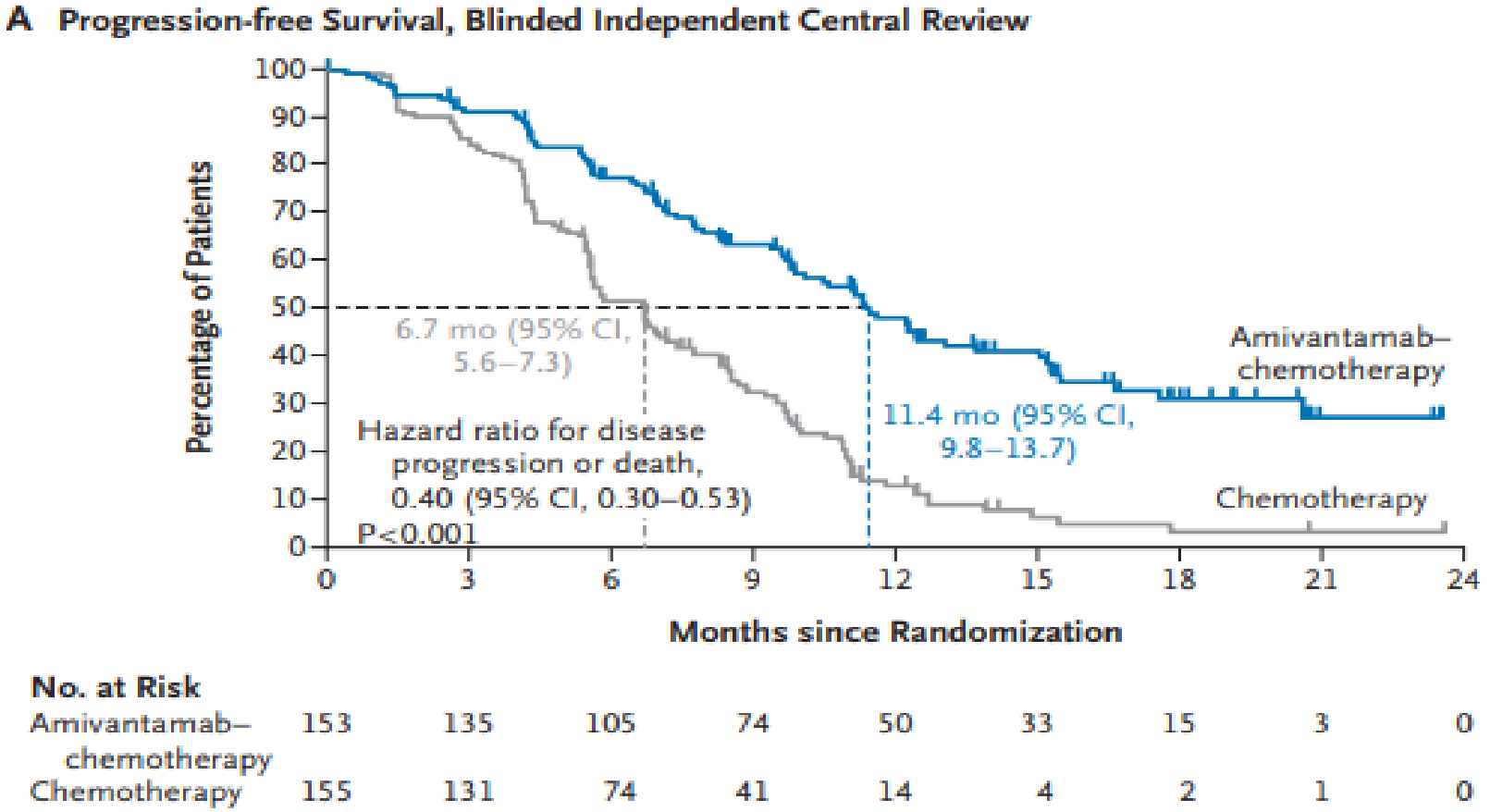
Bispecific antibody (IV) to EGFR and MET

RR % (95% CI)	mPFS, mos (95% CI)	DOR, mos (95% CI)
40 (29-51)	8.3 (6.5-10.9)	11.1 (6.9-NR)

Toxicities (%)	
Rash	86
Infusion reaction	66
Paronychia	45
Hypoalbuminemia	27
Edema	18

Jordan et al. Cancer Discovery 2017; 7(6):596-609 Sabari et al. WCLC 2021

Chemo vs Ami + chemo in EGFR exon 20



- FDA approved in 2024
- ORR 73% ami+chemo, 47% chemo
- Unknown whether better than sequential but a reasonable regimen
- 66% chemo arm received ami
- OS trending for benefit

Papillon Zhou et al NEJM2023

EGFR exon 20 insertion

- Sunvozertinib: Small molecule EGFR exon 20 inhibitor
- FDA approved after platinum based chemotherapy
- N=85 (200mg arm)
  - ORR 46% (35-57), DOR 11.1 mos
  - Prior Ami: 14% ORR
  - No prior Ami: 49% ORR
- Most common toxicities:
  - Diarrhea, CK increase, anemia, rash

Yang et al. WU-KONG1B. JCO 2025
FDA.gov accessed 8.11.2025

MET exon14 skipping mutation

Clinical characteristics

- 3-4% of NSCLC
- Older patients
- Often observed in patients with smoking history
- Present in 20-30% of sarcomatoid histology

Targeted therapy options

- Capmatinib and tepotinib

Characteristic	*MET* Exon 14 (n = 28)
Median age (range), years	72.5 (59-84)
Sex	
Male	9 (32)
Female	19 (68)
Smoking history, pack-years*	
Never-smoker	10 (36)
≤ 10	3 (11)
> 10	15 (53)
Race	
White, non-Hispanic	28 (100)
Asian	0 (0)
Black	0 (0)
White, Hispanic	0 (0)
Unknown	0 (0)
Histology	
Adenocarcinoma	18 (64)
Pleomorphic with adenocarcinoma component	4 (14)
NSCLC, poorly differentiated	5 (18)
Squamous	0 (0)
Adenosquamous	1 (4)

Drilon et al. JTO 2017; 12(1):15-26
Awad et al. JCO 2016; 34:721-730

MET inhibitor: Tepotinib

Patient characteristics (n=99)

Median age: 74 (41-94)

45% never smokers

	Both tx naïve/prev treated
Overall response %	46 (36-57)
Disease control rate %	89
DOR, mos	11 (7.2-NE)
CNS response %	55 (23-83), n=11

Most common treatment related Aes (%)		
	All	Grade 3 / 4
Peripheral edema	63	7
Nausea	26	1
Diarrhea	22	1
Elevated creatinine	18	1
Hypoalbuminemia	16	2
Amylase increase	11	2
Lipase	9	3

Paik et al. NEJM 2020; 383(1):931-943

MET inhibitor: Capmatinib

	Previously treated (n=69)	Treatment naïve (n=28)
ORR % (95% CI)	41 (29-53)	68 (48-84)
DCR % (95% CI)	78 (67-87)	96 (82-100)
DOR months (95% CI)	9.7 (5.6-13)	12.6 (5.6-NE)

ORR, overall response rate;
DCR, disease control rate; DOR, duration of response

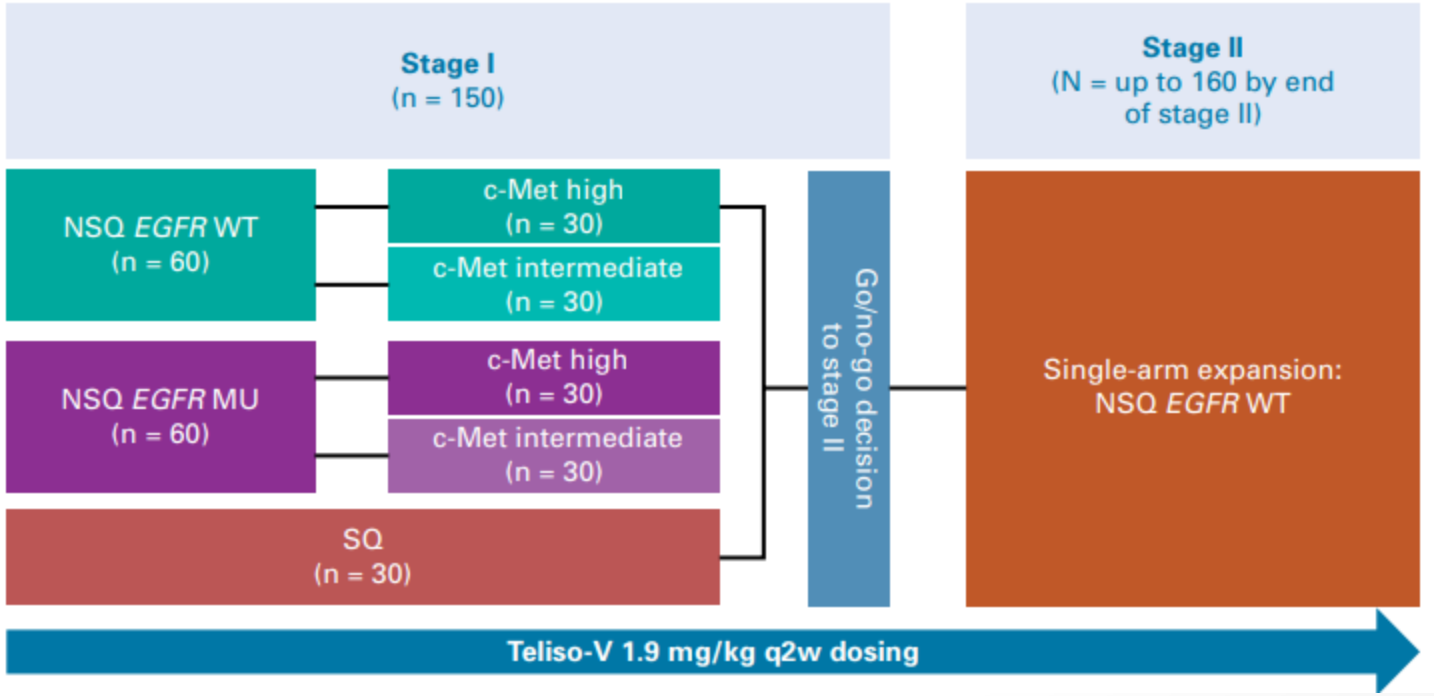
Several other MET inhibitors under investigation: e.g. savolitinib

Most common treatment related AEs (≥10%, all grades), n (%)	All Patients N = 334	
	All Grades	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea*	111 (33.2)	6 (1.8)
Increased blood creatinine†	65 (19.5)	0
Vomiting*	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Decreased appetite*	42 (12.6)	3 (0.9)
Diarrhea	38 (11.4)	1 (0.3)

Wolf et al. NEJM 2020

cMET ADC (Teliso-V)

- FDA approvced in cMET high expressed (Ventana SP44 IHC) metastatic non-squam NSCLC who received prior systemic therapy
- MET ADC IV, q2weeks



Camidge et al. JCO 2024

Teliso-V: Efficacy

- 1,954 evaluable samples submitted for prescreening in patients with nonsquam, EGFR WT:
  - 23.6% c-MET overexpressing; 13.5% cMET high

TABLE 2. Efficacy Summary in Patients With c-Met Protein–Overexpressing Nonsquamous *EGFR*-Wildtype NSCLC

Outcome	c-Met High (n = 78)	c-Met Intermediate (n = 83)	c-Met OE Total (N = 161)
ORR,[a] % (95% CI)	34.6 (24.2 to 46.2)	22.9 (14.4 to 33.4)	28.6 (21.7 to 36.2)
DCR,[a] % (95% CI)	60.3 (48.5 to 71.2)	57.8 (46.5 to 68.6)	59.0 (51.0 to 66.7)
DOR,[a] months, median (95% CI)	9.0 (4.2 to 13.0)	7.2 (5.3 to 11.5)	8.3 (5.6 to 11.3)
DOR ≥6 months,[a] n/no. of responders (%)	17/27 (63.0)	9/19 (47.4)	26/46 (56.5)
PFS,[a] median, months (95% CI)	5.5 (4.1 to 8.3)	6.0 (4.5 to 8.1)	5.7 (4.6 to 6.9)
6-month PFS,[a,b] % (95% CI)	45.8 (33.8 to 57.1)	50.1 (37.9 to 61.1)	48.0 (39.5 to 56.1)
OS, months, median (95% CI)	14.6 (9.2 to 25.6)	14.2 (9.6 to 16.6)	14.5 (9.9 to 16.6)
12-month OS,[b] % (95% CI)	57.0 (45.0 to 67.4)	55.0 (43.5 to 65.2)	56.0 (47.7 to 63.4)

Camidge et al. JCO 2024

Teliso-V: Toxicity

Event	c-Met High (n = 84), No. (%)	
	Any Grade	Grade ≥3
TEAE	83 (98.8)	50 (59.5)
TRAE	68 (81.0)	25 (29.8)
TRAEs occurring in >5% of patients in the NSQ *EGFR* WT NSCLC population		
Peripheral sensory neuropathy	24 (28.6)	5 (6.0)
Peripheral edema	17 (20.2)	2 (2.4)
Fatigue	11 (13.1)	3 (3.6)
Decreased appetite	7 (8.3)	0
Increased alanine aminotransferase	8 (9.5)	2 (2.4)
Pneumonitis[a]	11 (13.1)	3 (3.6)
Hypoalbuminemia	10 (11.9)	0
Nausea	6 (7.1)	0
Vision blurred	11 (13.1)	1 (1.2)
Increased aspartate aminotransferase	7 (8.3)	0
Asthenia	4 (4.8)	1 (1.2)
Anemia	7 (8.3)	1 (1.2)
Increased gamma-glutamyltransferase	5 (6.0)	1 (1.2)
Keratitis	5 (6.0)	0
Peripheral neuropathy	6 (7.1)	1 (1.2)

Camidge et al. JCO 2024

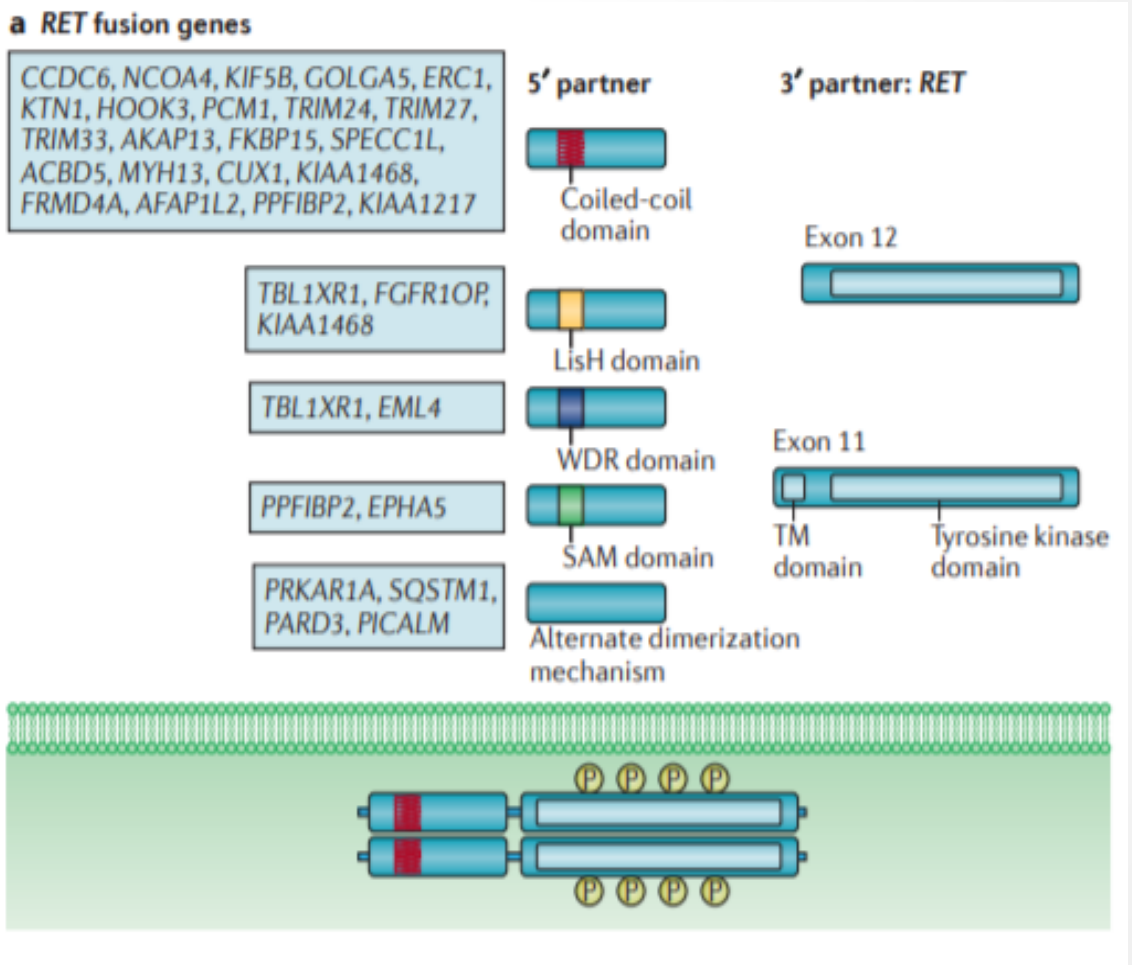
RET rearrangement

Clinical characteristics

- 1-2% of all NSCLC
- Mostly seen in never / minimal smokers

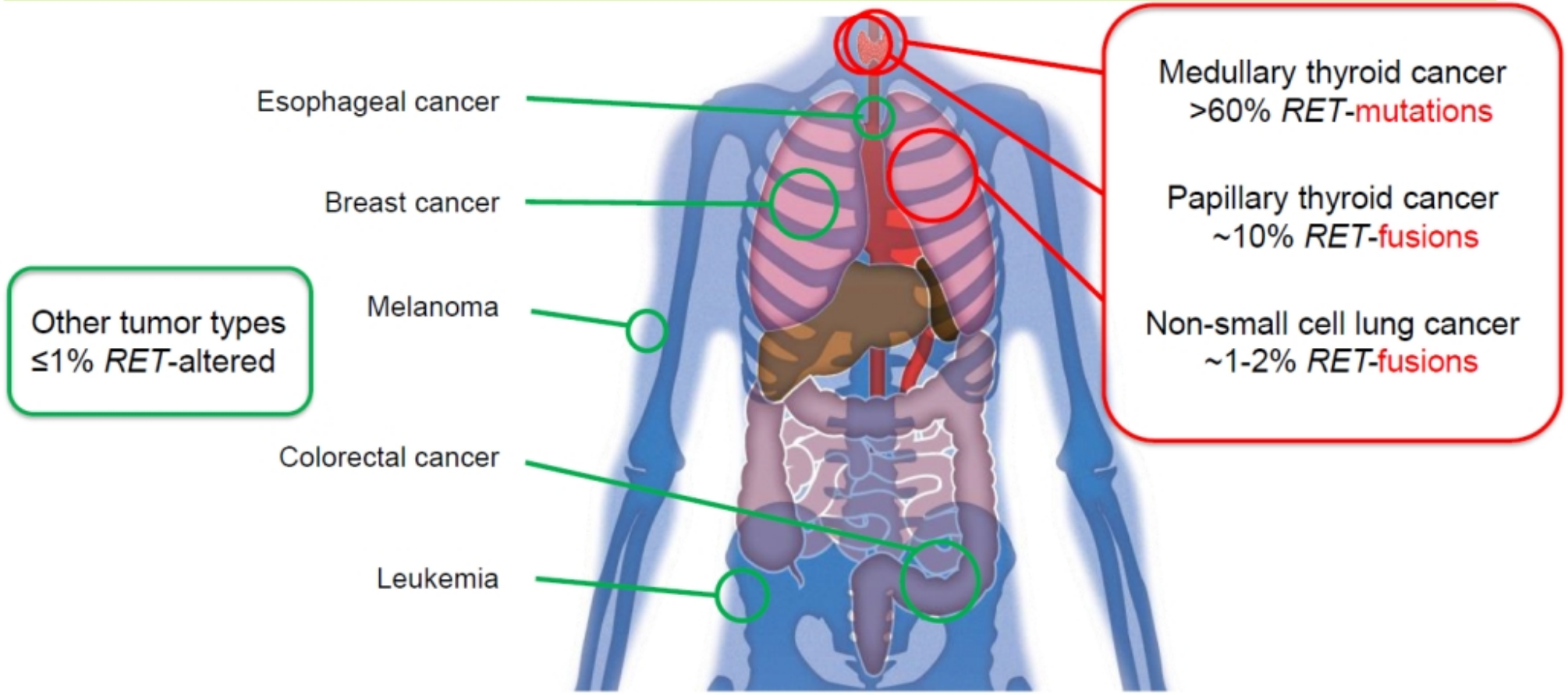
Mechanism of action

Receptor protein fuses with partner protein, inducing dimerization and activation



Drilon et al. Nat Rev Clin Onc 2018; 15:151

RET is a rare driver of multiple, diverse tumor types[1,2]



1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67 2.Kato S, et al. *Clin Cancer Res* 2017;23:1988-1997.

Subbiah et al. AACR 2018

Selective RET inhibitors

	Selpercatinib	Pralsetinib
Dose, frequency	Oral BID: >50kg 160mg, <50kg 120mg	Oral daily, 400mg
Never smoker % (in trials)	72	62
Median age (in trials)	61 (23-86)	60 (28-87)
RR %, treatment naive	85 (70-94), n=34	66 (46-82), n=29
RR %, previously treated	64 (54-73), n=105	65 (55-73), n=92
Disease control rate %	93	90
Progressive disease as best response %	4	4
Duration of response, mos	17.5 (12-NR) in prev treated	NR (11.3-NR) overall
CNS RR %	91 (59-100), n=11	56, n=9
Adverse events, ≥grade 3	Hypertension (14%) Transaminitis (12-14%) Lymphopenia (6%)	Hypertension (10%) Neutropenia (10%) Anemia (8%)
Drug discontinuation rate %	2	4

Drilon et al. NEJM 2020; 383(9):813-824 Gainor et al. ASCO 2020. Abs 9515

ALK rearranged NSCLC (3-5% NSCLC)

FDA approved ALK inhibitors		
1st generation	2nd generation	3rd generation
Crizotinib	Alectinib	Lorlatinib
	Ceritinib	
	Brigatinib	
	Ensartinib	

General principles

- Second generation TKIs are active after crizotinib but unclear if active after another 2nd gen TKI (although there is some data for brigatinib after alectinib)
- Lorlatinib active after crizotinib and modestly active after second generation TKIs
- All of the above TKIs are approved as first line therapy

ALK first line therapy

Drug	Progression free survival (median, mos)
Crizotinib (1)	10.9
Ceritinib (2)	16.6
Alectinib (3,4)	~ 35
Brigatinib (5,6)	~24-29
Ensartinib (8)	~ 26
Lorlatinib (7)	Not reached

(1) Solomon *et al*. NEJM 2014; 371: 2167-2177
(2) Soria *et al*. Lancet 2017;389:917-29
(3) Peters *et al*. NEJM 2017. DOI: 10.1056/NEJMoa1704795
(4) Camidge *et al*. JTO 2019; 14(7): 1233-1243
(5) Camidge *et al*. DOI: 10.1056/NEJMoa191071
(6) Camidge et al. Doi.org/10.1200/JCO.20.00505
(7) Solomon et al. DOI.org/10.1200/JCO.24.00581
(8) Horn et al. JAMA 2021 Oncol vol7, No11

First line lorlatinib (CROWN)

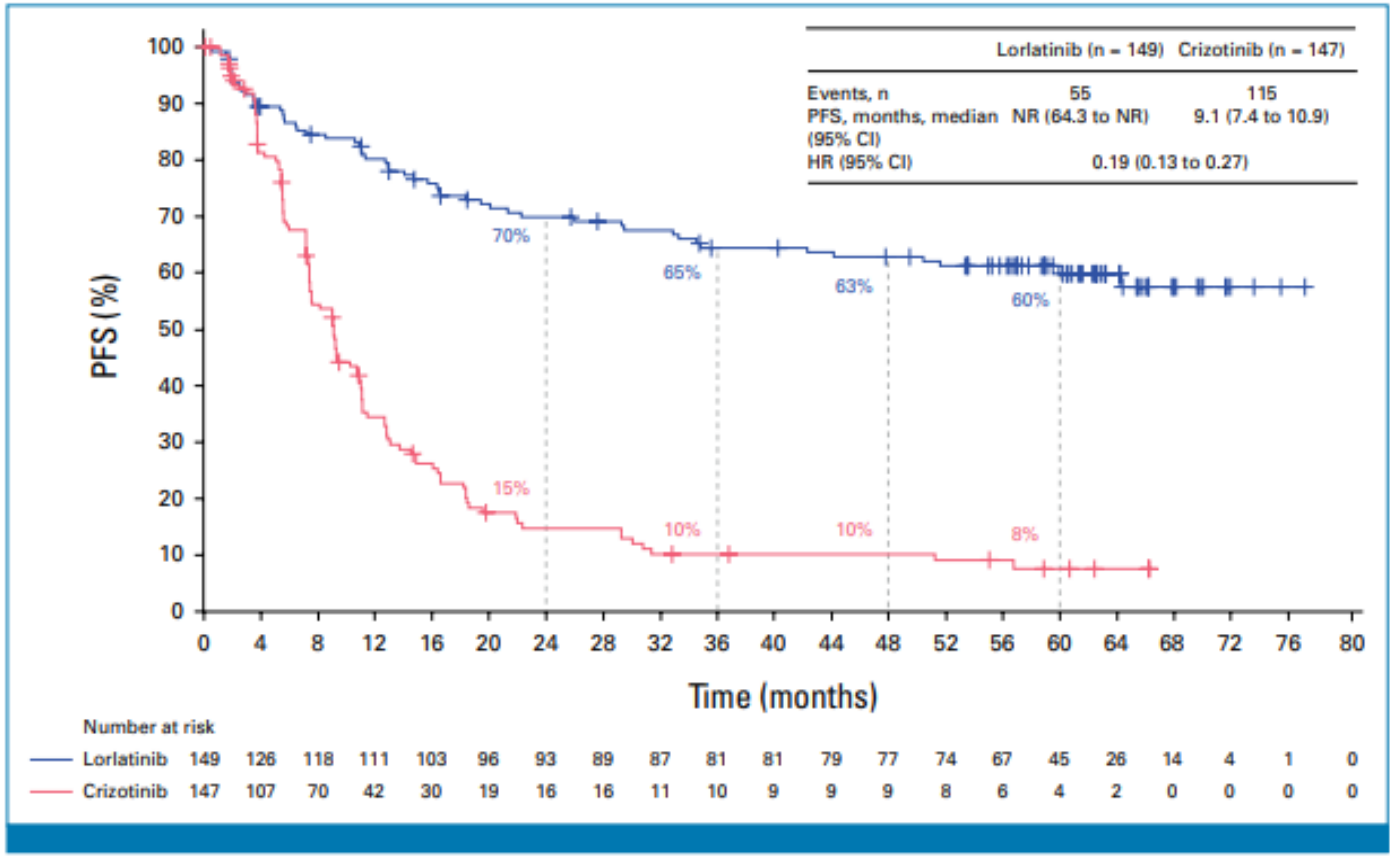


FIG 2. PFS by investigator assessment in the intention-to-treat population. HR, hazard ratio; NR, not reached; PFS, progression-free survival.

Unique toxicities to lorlatinib:
-Cognitive
-Hyperlipidemia

Solomon et al. JCO 2024

ROS1 rearranged NSCLC (1-2% NSCLC)

- First line options: Crizotinib, Entrectinib, Repotrectinib, taletrectinib

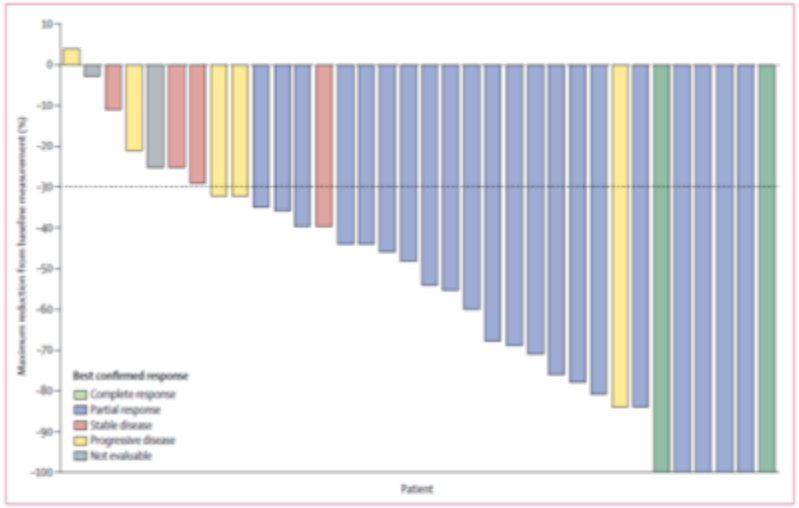
	RR, %	PFS, mos	CNS RR
Crizotinib (n=50)	72 (58-84)	19 (14.4-NR)	N/A
Entrectinib (n=53)	77 (64-88)	19 (12.2-36.6)	79% (n=19)
Repotrectinib (n=71)	79 (68-88)	36 (27.4-NE)	89% (52-100)
Taletrectinib	89 (83-93)	46 (29-NR)	77% (50-93)

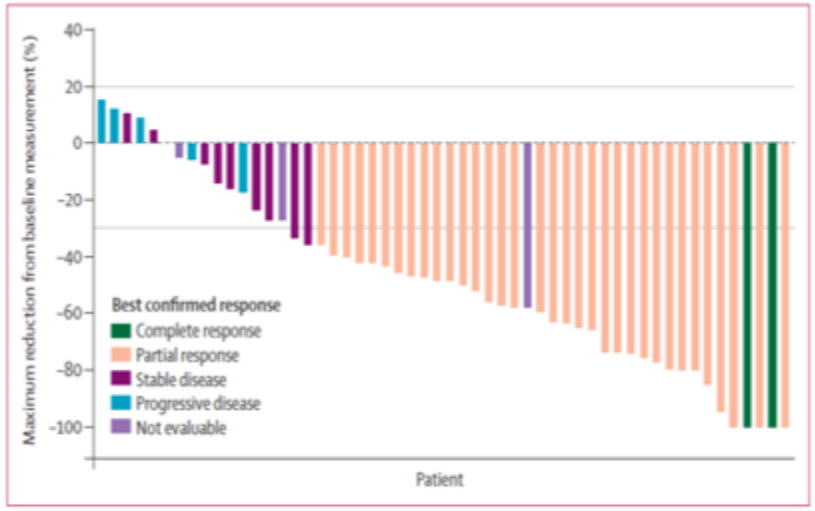
- Second line
  - Entrectinib not active in crizotinib pre-treated
  - Repotrectinib post one previous ROS1 TKI:
    - ORR 38% (25-52), PFS 9.0mos (6.8-20)
  - Lorlatinib active after crizotinib but not FDA approved (ORR 26.5, 12.9-44.4; median PFS 8.5mos)

Shaw et al. NEJM 2014; 371: 1963 Doebele et al. OA02.01 WCLC 2018 Ou et al. WCLC 2018 Dziadziusko et al. JCO 2021 Drilon NEJM 2024 Perol JCO 2025

BRAF V600E

- Occur in 1-4% of NSCLC
- Present regardless of smoking history
- Two available options
  - Dabrafenib (BRAFi) + trametinib (MEKi)
  - Encorafenib (BRAFi) + binimetinib (MEKi)

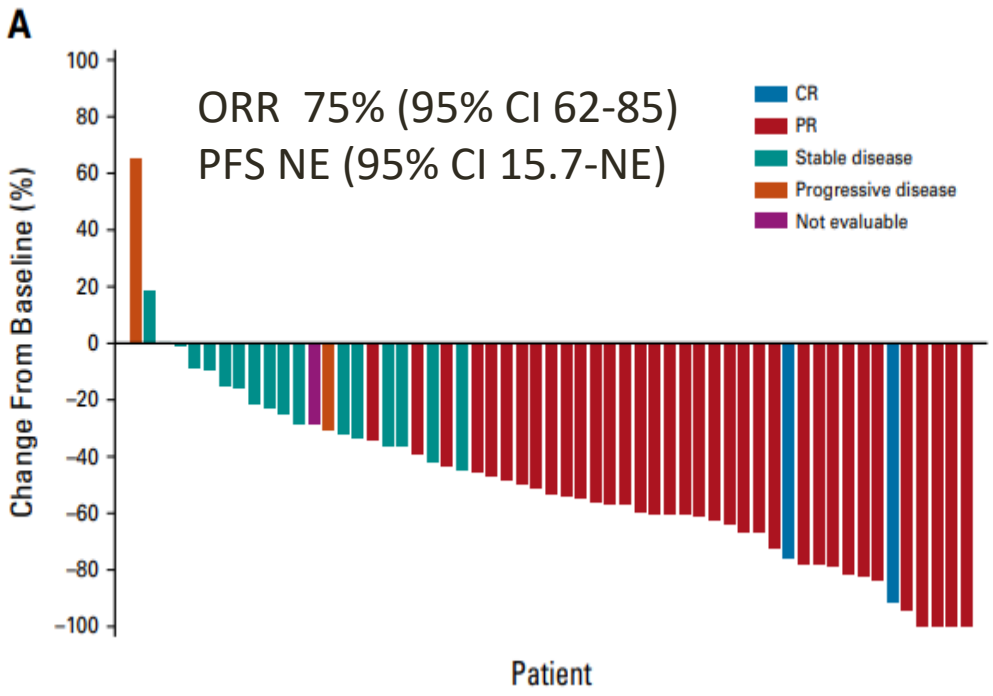




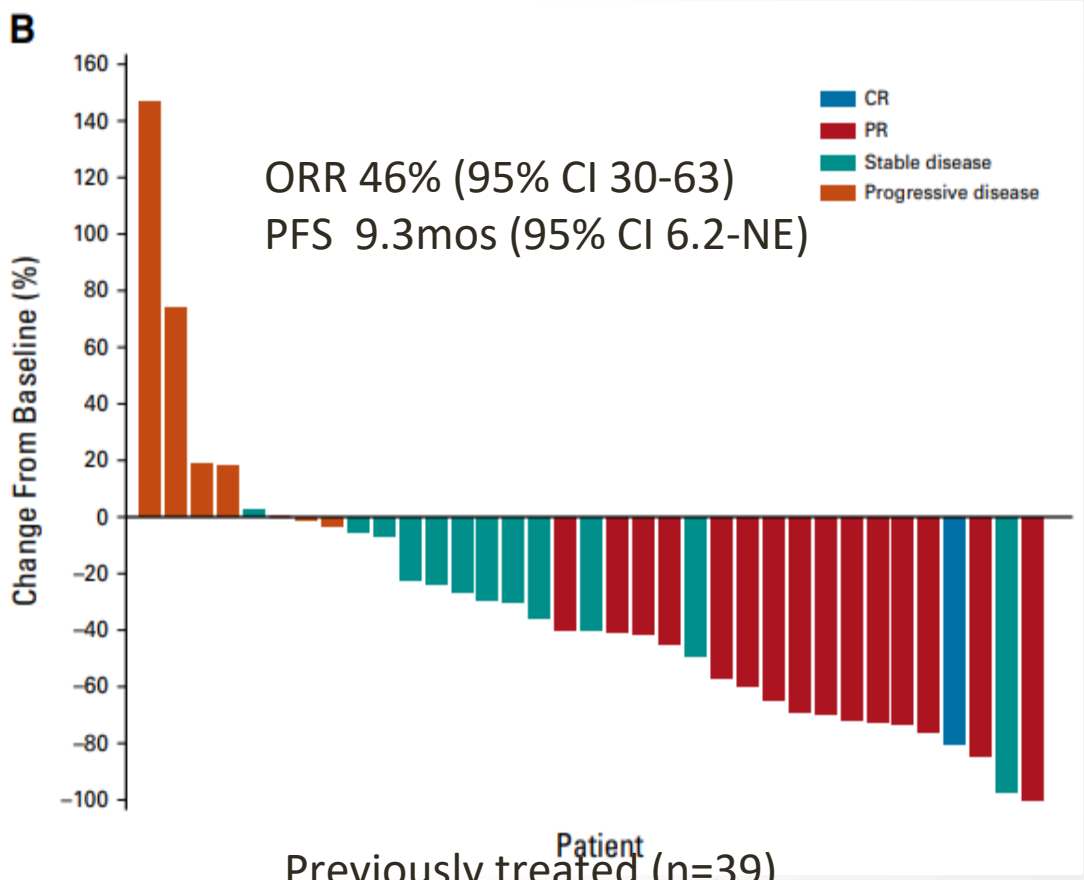
Treatment naïve patients
RR = 64% (95% CI 46-79)
PFS = 10.4 (invest); 15.2 mos (indep)
Planchard *et al*. Lancet Oncol 2017

Previously treated patients
RR = 63% (95% CI 49-76)
PFS = 9.7 mos (95% CI 7-20)
Planchard *et al*. Lancet Oncol 2016

Encorafenib/binimetinib



Treatment naïve (n=59)



Previously treated (n=39)

Riely et al. JCO 2023

Notable toxicities

- Pyrexia (app 45% dab/tram, 22% Enco/bini)
- Ejection fraction decrease >=10% from baseline: D+T 6%, E+B 7-11%
- Bleed
  - D+T 17%, E+B 19% (Rare fatal cases have been observed)
  - Hold drug / dose reduce if persistent
- Squamous cell carcinoma of the skin
  - Rare with combination therapy
  - Education on skin exam, lesions to be recognized

NTRK rearrangement

- NTRK+ NSCLC is rare (<1%), although not clearly characterized
  - DNA based next-generation sequencing is often used but likely limited sensitivity
  - Limited data on clinical characteristics but seen more commonly in light smokers but also observed in patients with smoking history
- Three FDA approved drugs (for all solid tumor with NTRK fusion without resistance mutations):
  - **Larotrectinib** (ORR 66%, 95% CI 47-81; PFS around 22 mos in lung cohort. Drilon *et al*. NEJM 2018; Drilon et al ASCO 2024)
  - **Entrectinib** (ORR 57%, 95% CI 43-71; PFS 11.2 mos, 95% CI 8.0-14.9. Demetri *et al* ESMO 2018)
  - **Repotrectinib (**ORR 58%, 95% CI 41-73; PFS 30 mos (9.0-NE). Solomon et al ESMO 2023)

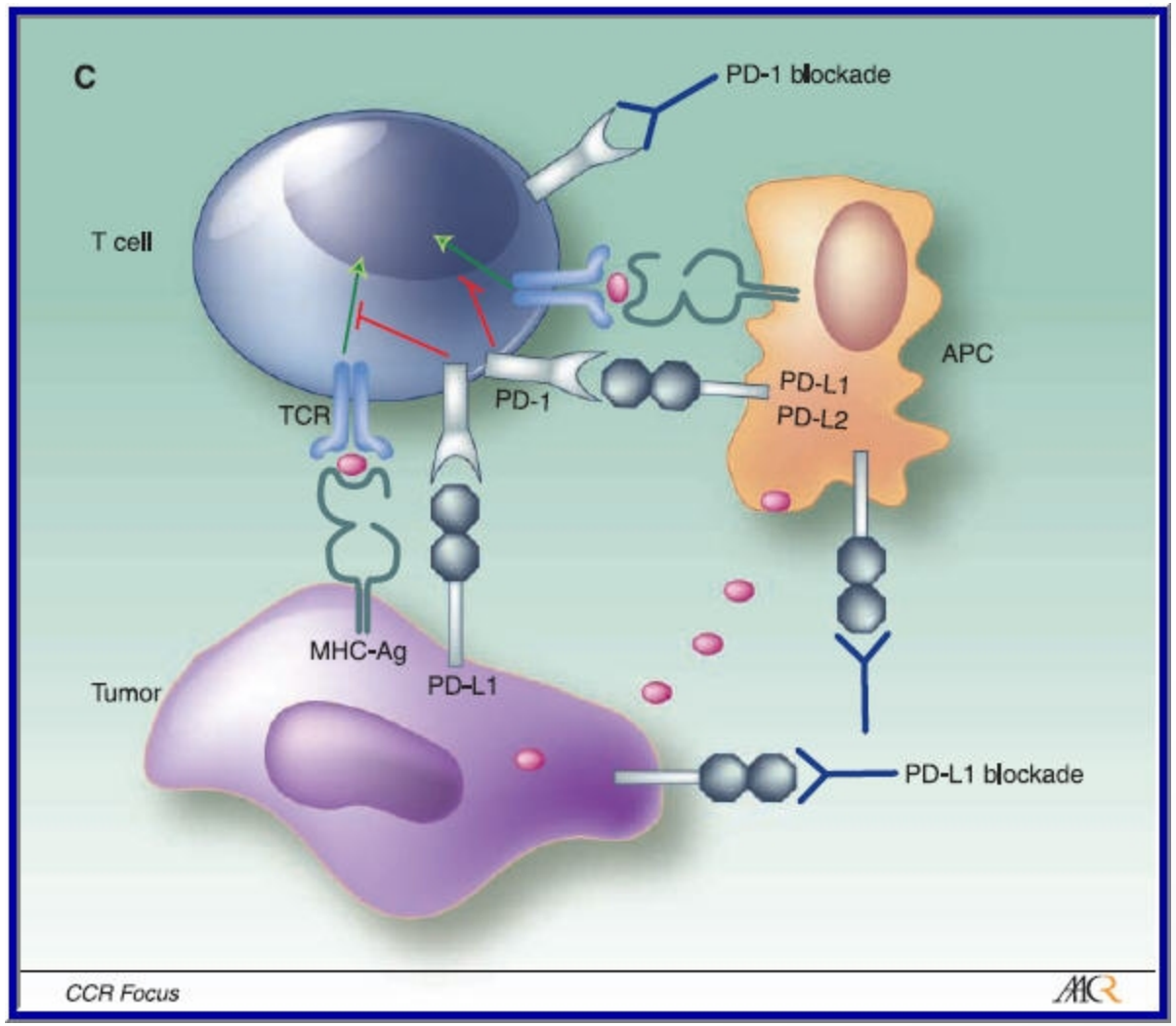
Targets with FDA approved drugs (as of October 2025)

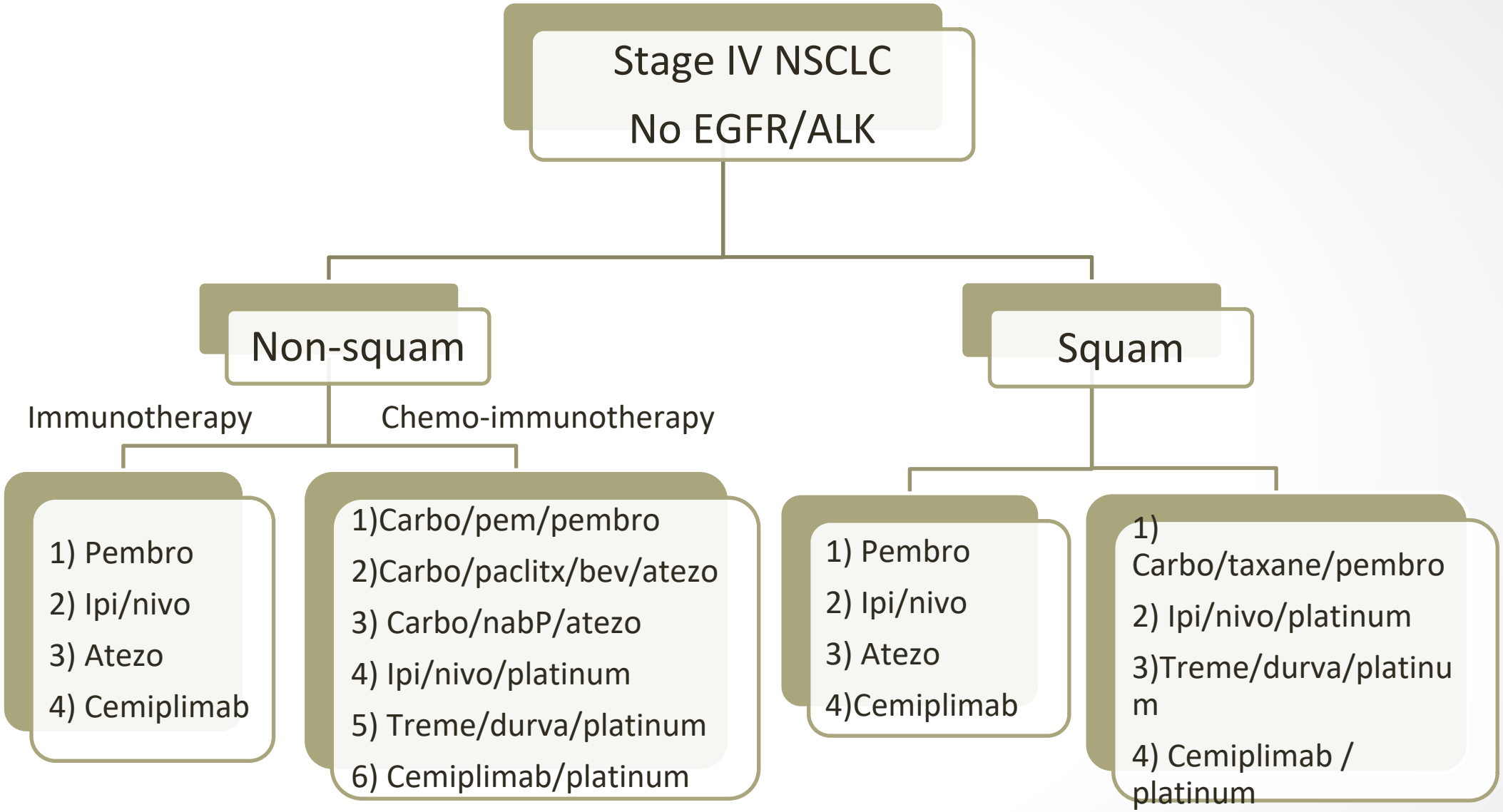
EGFR (non-exon20 ins)	EGFR (exon20 ins)	ALK fusion	ROS1 fusion	BRAF V600E	RET fusion
Erlotinib +/- ram Gefitinib Afatinib Dacomitinib Osimertinib+/- chemo Laz + amivantamab Dato Dxd	Amivantamab +/- chemo Sunvozertinib	Crizotinib Alectinib Ceritinib Brigatinib Lorlatinib Ensartinib	Crizotinib Entrectinib Repotrectinib Taletrectinib	Dabrafenib + trametinib Encorafenib+ binimetinib	Selpercatinib Pralsetinib

Targets with FDA approved drugs (as of October 2025)

NRG fusion	KRAS G12C	MET exon 14	NTRK fusion	HER2 mt/exp	HER2 overex	cMET overexpressed
Zenocutuzumab	Sotorasib Adagrasib	Capmatinib Tepotinib	Larotrectinib Entrectinib Repotrectinib	Trastuzumab deruxtecan Zongertinib	Trastuzumab deruxtecan	Teliotuzumab vedotin

Immune checkpoint inhibitors (ICIs)




Stage IV NSCLC
No EGFR/ALK
Non-squam
Squam
Immunotherapy
Chemo-immunotherapy
1) Pembro
2) Ipi/nivo
3) Atezo
4) Cemiplimab
1)Carbo/pem/pembro
2)Carbo/paclitx/bev/atezo
3) Carbo/nabP/atezo
4) Ipi/nivo/platinum
5) Treme/durva/platinum
6) Cemiplimab/platinum
1) Pembro
2) Ipi/nivo
3) Atezo
4)Cemiplimab
1) Carbo/taxane/pembro
2) Ipi/nivo/platinum
3)Treme/durva/platinum
4) Cemiplimab / platinum

Immune checkpoint inhibitor vs platinum doublet chemo

	PD-L1 (Assay)	ORR (%)	PFS (months)	OS (months)
Pembrolizumab (KYETNOE-24)	≥50% (22C3)	44 v 28	10.3 vs 6.0	30 vs 13 (HR 0.63, 0.47-0.86)
Pembrolizumab (KEYNOTE-42)	≥1% (22C3)	27 v 27	5.4 vs 6.5	16.7 vs 12.1 (HR 0.81,0.71-0.93)
Atezolizumab (IMPOWER-110)	≥50% TC or ≥10% IC (SP142)	38 v 29	8.1 vs 5.0	20 vs 13 (HR 0.59, 0.40-0.89)
Cemiplimab (EMPOWER-Lung1)	≥ 50% (22C3)	37 v 21	6.2 v 5.6	NR vs 14 (HR 0.57,0.42-0.77)
Ipi/nivo	≥1% (28-8)	36 v 30	5.1 vs 5.6	17.1 vs 14.9 (HR 0.79, 0.65-0.96)
(CheckMate-227)	<1%	27 v 23	5.1 vs 4.7	17.2 vs 12.2 (HR 0.62, 0.48-0.78)

TC, tumor cells IC, immune cells

Sezer et al Lancet 2021;397:592-604 Herbst et al NEJM 383:1328-39 Reck et al. NEJM DOI:10.1056/NEJMoa1606775
Mok et al. Lancet 2019;393:1819-30 Hellmann et al. NEJM 2019: 2020-31

Immune checkpoint inhibitor vs platinum doublet chemo

Summary points

- Pembrolizumab, atezolizumab, cemiplimab clearly better than chemo in PD-L1 high NSCLC (e.g. >=50% PD-L1 expression)
- In patients with intermediate PD-L1 expressed NSCLC (1-49% PD-L1), whether pembrolizumab is better than chemo is unclear (KN-42 trial included patients with >50% and survival benefit appears to be driven by these patients)
- Ipi / nivo is better than chemo in both PD-L1 positive (>=1%) and negative NSCLC, but FDA approval is limited to PD-L1 positive NSCLC
- In high PD-L1 (≥50%) NSCLC, anti-PD (L1) monotherapy without CTLA4 inhibition is likely adequate (pembro vs pembro/ipi resulted in similar outcomes in a trial of patient with PD-L1 >50%. KN-598 Boyer et al. JCO 2021)

Chemo-immunotherapy vs Chemo

Regimen	n	ORR (%)	PFS (mos)	OS (mos)
Non-squamous NSCLC				
Carboplatin / pemetrexed +/- pembrolizumab (KEYNOTE-189)	616	47.6 v 18.9	8.8 v 4.9 (HR 0.52,0.43-0.64)	22 vs 10.7 (HR 0.49, 0.38-0.64)
Carbo/paclitax/bevacizumab +/- atezolizumab (IMPOWER-150)	692	63.5 v 48	8.3 v 6.8 (HR 0.62, 0.52-0.74)	19.2 v 14.7 (HR 0.78, 0.64-0.96)
Carbo/nabP +/- atezo (IMPOWER-130)	724	49.2 v 31.9	7.0 v 5.5 (HR 0.64, 0.54-0.77)	18.6 v 13.9 (HR 0.79, 0.64-0.98)
Squamous NSCLC				
Carbo/paclitx or nabP +/- pembro (KEYNOTE-407)	559	57.9 v 38.4	6.4 v 4.8 (HR 0.56, 0.45-0.70)	15.9 v 11.3 (HR 0.64, 0.49-0.85)

nabP, *nab*-paclitaxel

Gandhi NEJM 2018;378:2078 Socinski NEJM 2018;378:2288 West et al LancetOnc 2019; 20:924
Paz-Ares NEJM 2018; 379:2040 Gadgeel et al. JCO 2020

Chemo-immunotherapy vs Chemo

Regimen	n	ORR (%)	PFS (mos)	OS (mos)
NSCLC, any histology				
Platinum chemo +/- cemiplimab (EMPOWER-Lung3)	466	43 v 23	8.2 v 5.0 (HR 0.56, 0.44-0.7)	21.9 v 13.0 (HR 0.71, 0.53-0.93)
Platinum chemo +/- ipi/nivo (i.e.CM-9LA)	719	38 v 25	6.7 v 5.0 (HR 0.68, 0.57-0.82)	15.6 v 10.9 (HR 0.66, 0.55-0.80)
Platinum chemo +/- tremelimumab and durvalumab (POSEIDON)*	1,013	39 v 24	6.2 V 4.8 (HR 0.72, 0.60-0.86)	14.0 v 11.7 (HR 0.77, 0.65-0.92)

* Chemo + durva vs chemo did not lead to significant survival benefit

Gogishvili et al. Nature Med 2022; 28:2374-2380 Paz-Ares et al. Lancet 2021; 21:198-221
Johnson et al. JCO 2022; doi.org/10.1200/JCO.22.00975

Summary - Immune checkpoint inhibitor

- Chemo-immunotherapy is superior to chemo, in any PD-L1 setting. Many regimens to choose from; efficacy likely similar across the different regimens
- No comparison between chemoIO vs IO
- Pembrolizumab / atezolizumab / cemiplimab monotherapy is a reasonable option for PD-L1 high tumors as first-line therapy (but no head-to-head data vs chemo-immunotherapy)
- In PD-L1 1-49% patients, I prefer chemo-immunotherapy or ipi/nivo since the benefit of pembro alone does not appear to be significantly better compared to chemo alone
- I prefer chemo-immunotherapy in high PD-L1 patients if high response rate is desired (e.g. symptomatic disease burden) or never smokers
- When to use ipi/nivo? Reasonable in patients intermediate / low PD-L1 expressed NSCLC who want to avoid chemo
- Ongoing studies using PD(L)1/VEGFi bispecific antibodies (e.g. ivonescimab) so stay tuned

Stage IV NSCLC – final thoughts

- Post-chemoIO? Docetaxel +/- ramucirumab remains standard. Also test for HER2 and cMET overexpression (IHC) as T-Dxd and Teliso-V would be options

- Complete molecular testing as much as possible
  - All non-squamous histology
  - Squamous histology if light smoking history, small specimen

- Blood based molecular testing is helpful but recognize that has limited sensitivity, especially in patients with low disease burden / intrathoracic only disease → complete tissue testing as much as possible if blood based test is negative

- Immunotherapy and targeted therapy options continue to expand and evolve. Stay tuned!

EXTRA SLIDES

Immune checkpoint inhibitors in oncogene+ NSCLC

As a rule of thumb, oncogene+ NSCLC enriched with never smokers have limited sensitivity to immunotherapy (e.g. EGFR / ALK / ROS1 / RET). Oncogene+ NSCLC seen in smokers have variable sensitivity to immunotherapy (e.g. BRAF, MET, KRAS, etc)

EGFR / ALK:

Increased risk of immune related toxicities if TKI given too soon after immune checkpoint inhibitor therapy (ideal washout 3-6 months)

KRAS G12C:

Giving sotorasib within 3 months of ICI increased risk of hepatitis (Rakshit et al. WCLC 2022)

BRAF:

Starting BRAF inhibitor soon after ICI probably safe based on the melanoma literature

Trastuzumab deruxtecan

- Original FDA approved dose: 6.4mg/kg (DESTINY-Lung01)
- Updated FDA approved dose: 5.4mg/kg (DESTINY-Lung02)

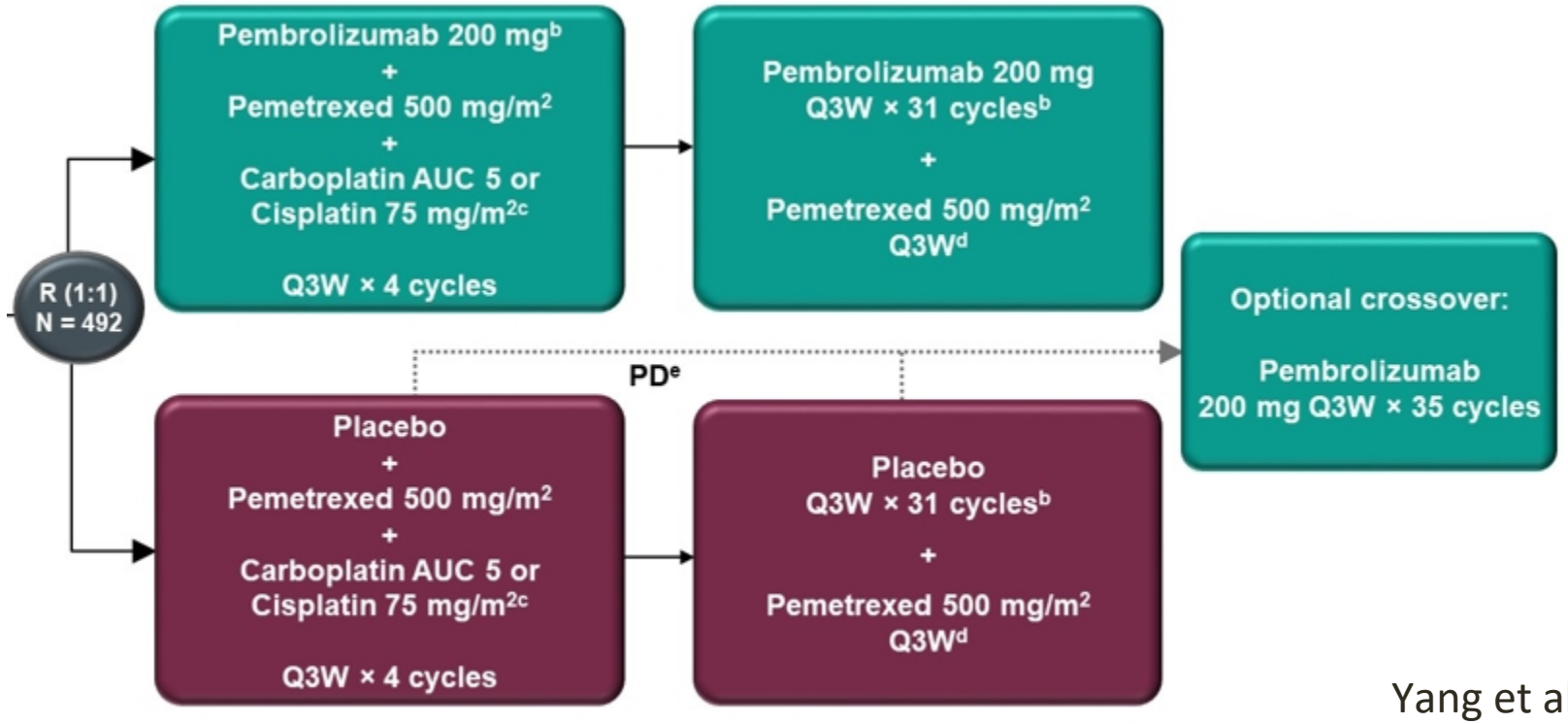
	5.4 mg/kg, n=52	6.4 mg/kg, n=28
ORR, % (95% CI)	49 (39-59)	56 (41-70)
Disease control rate, %	93	92
Duration of response, mos	16.8 (6.4-NE)	NE (8.3-NE)
PFS, mos	9.9 (7.4-NE)	15.4 (8.3-NE)
Dose reduction, %	18	32
Dose discontinuation, %	15	26
Dose interruption, %	45	62
ILD, any grade %	13	28
ILD grade >=3, %	2	2

Goto et al. JCO2023

Many HER2 small molecule inhibitors in development

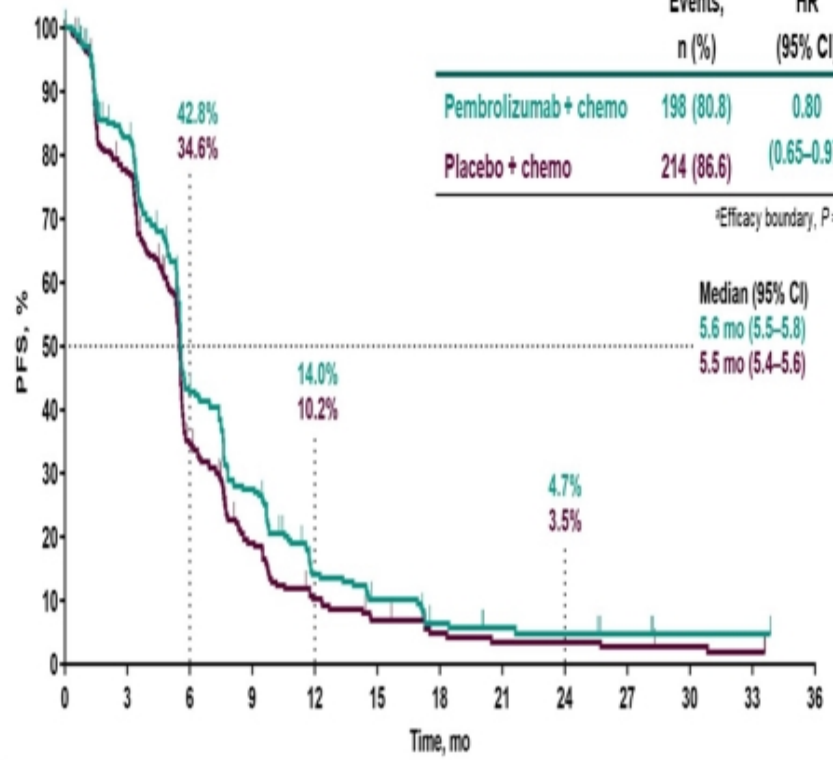
Chemo +/- pembrolizumab in EGFR+ NSCLC (KEYNOTE-789)

- Metastatic NSCLC, EGFR del19 or L858R
- Progressed on TKI
- No prior chemo or IO



Yang et al. ASCO 2023

Progression-Free Survival at IA2
(RECIST v1.1, BICR)

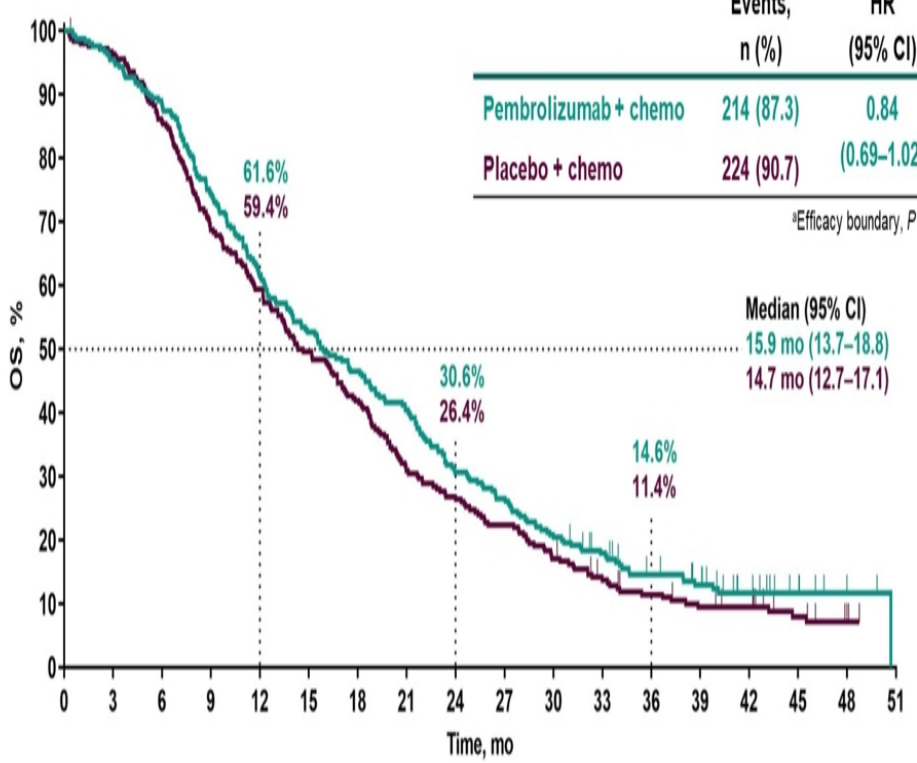


	Events, n (%)	HR (95% CI)	P value[a]
Pembrolizumab + chemo	198 (80.8)	0.80 (0.65–0.97)	0.0122
Placebo + chemo	214 (86.6)		

[a]Efficacy boundary, $P = 0.0117$ for PFS (IA2).

No. at risk													
Pembrolizumab + chemo	245	181	90	57	25	17	9	6	5	3	1	1	0
Placebo + chemo	247	184	75	37	19	12	7	5	5	4	3	2	0

Overall Survival at FA



	Events, n (%)	HR (95% CI)	P value[a]
Pembrolizumab + chemo	214 (87.3)	0.84 (0.69–1.02)	0.0362
Placebo + chemo	224 (90.7)		

[a]Efficacy boundary, $P = 0.0117$ for OS (FA).

No. at risk																		
Pembrolizumab + chemo	245	234	217	182	151	129	114	99	75	65	50	40	29	23	13	7	3	0
Placebo + chemo	247	237	211	169	146	122	103	76	65	55	42	31	24	19	17	10	3	0