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BSMO

Belgian Symposium on the Integration of Molecular Biology
Advances into Oncology Clinical Practice

Molecularly segmented NSCLC

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La Hulpe, Belgium
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Outline

- Overview
- ~~The *classic* drivers (*EGFR classic mutations, ALK & ROS1 fusions)*~~
- *Emergent* drivers (*EGFR* exon 20, *HER2, KRAS* G12C, *MET, RET, BRAF, NTRK*)
- A *new kid* in the block (*NRG1*)
- Conclusions

Overview

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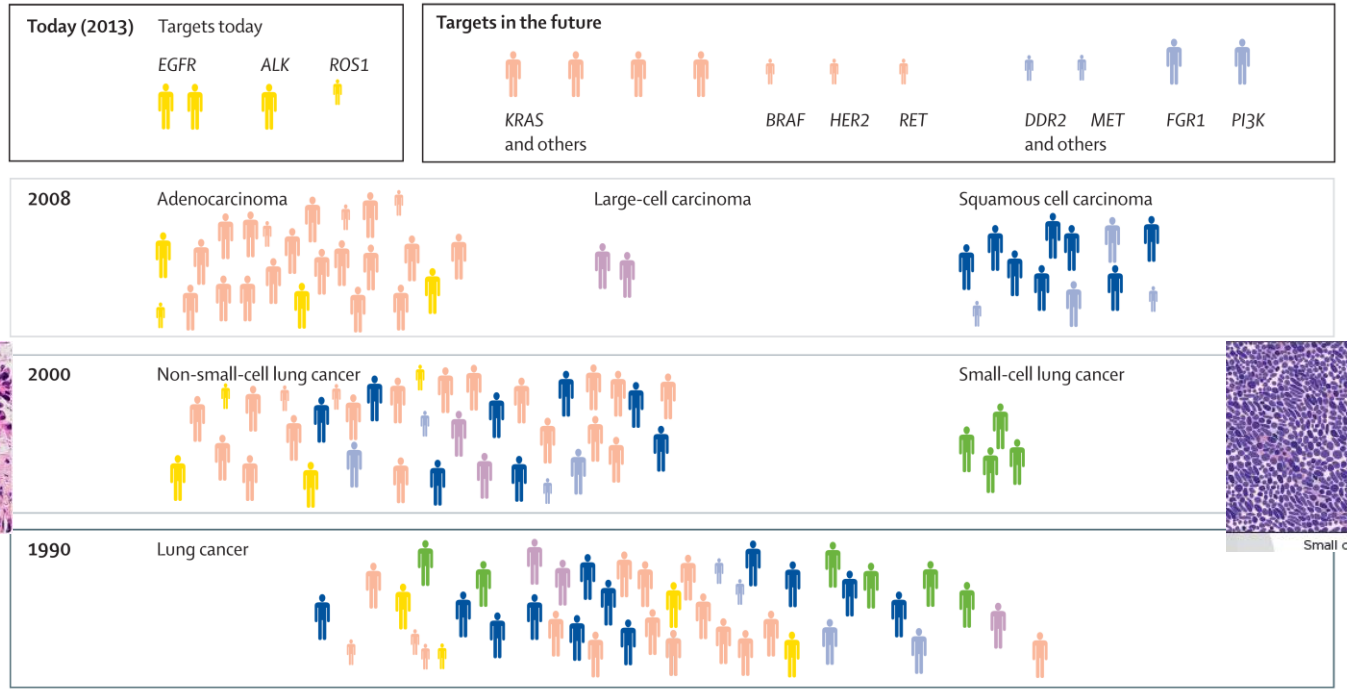
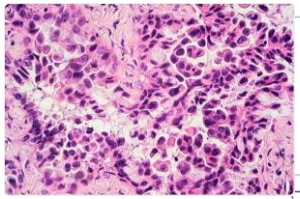
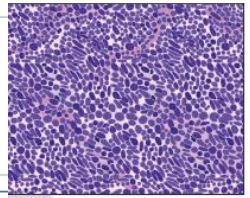
Lung cancer is *not* a single disease







Small cell carcinoma

Reck et al., The Lancet 2013

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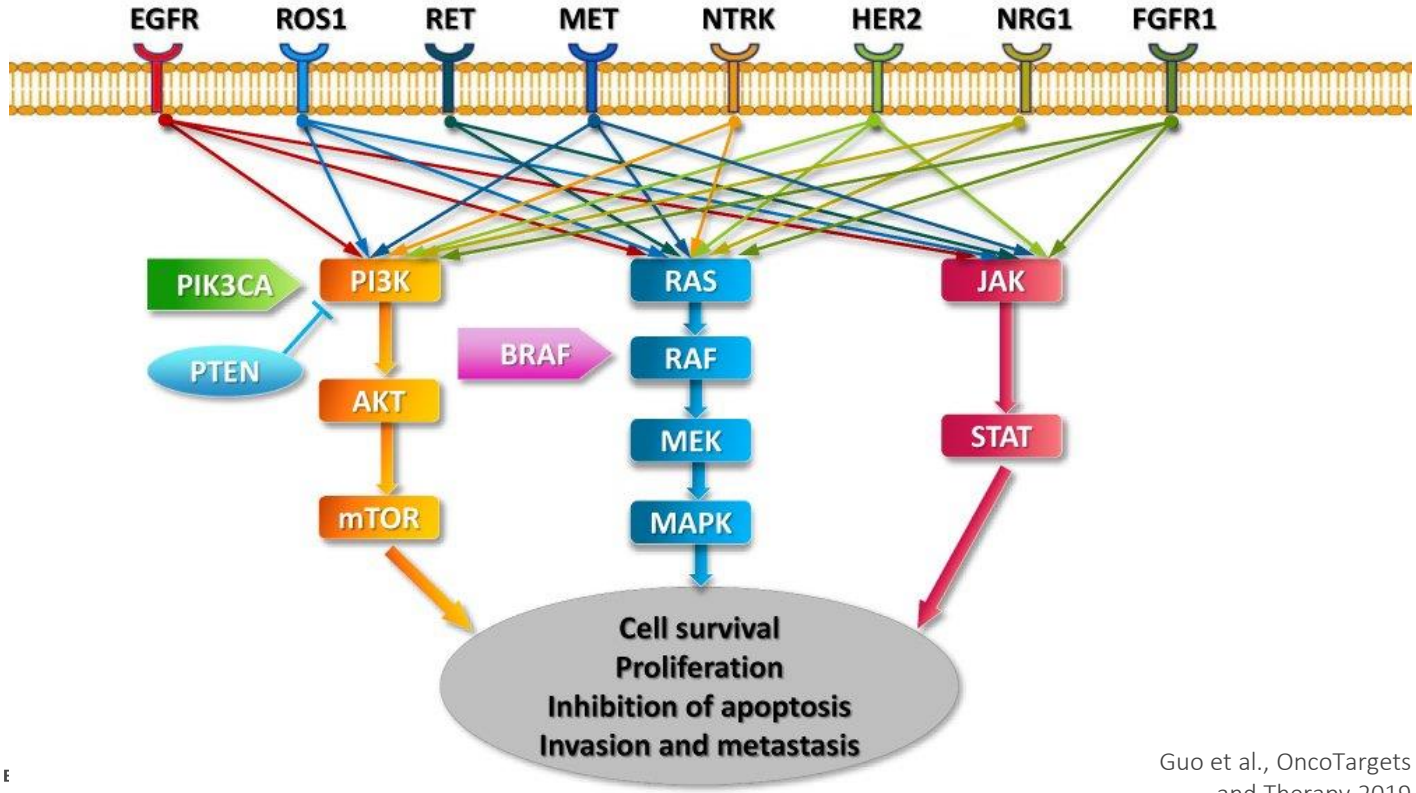
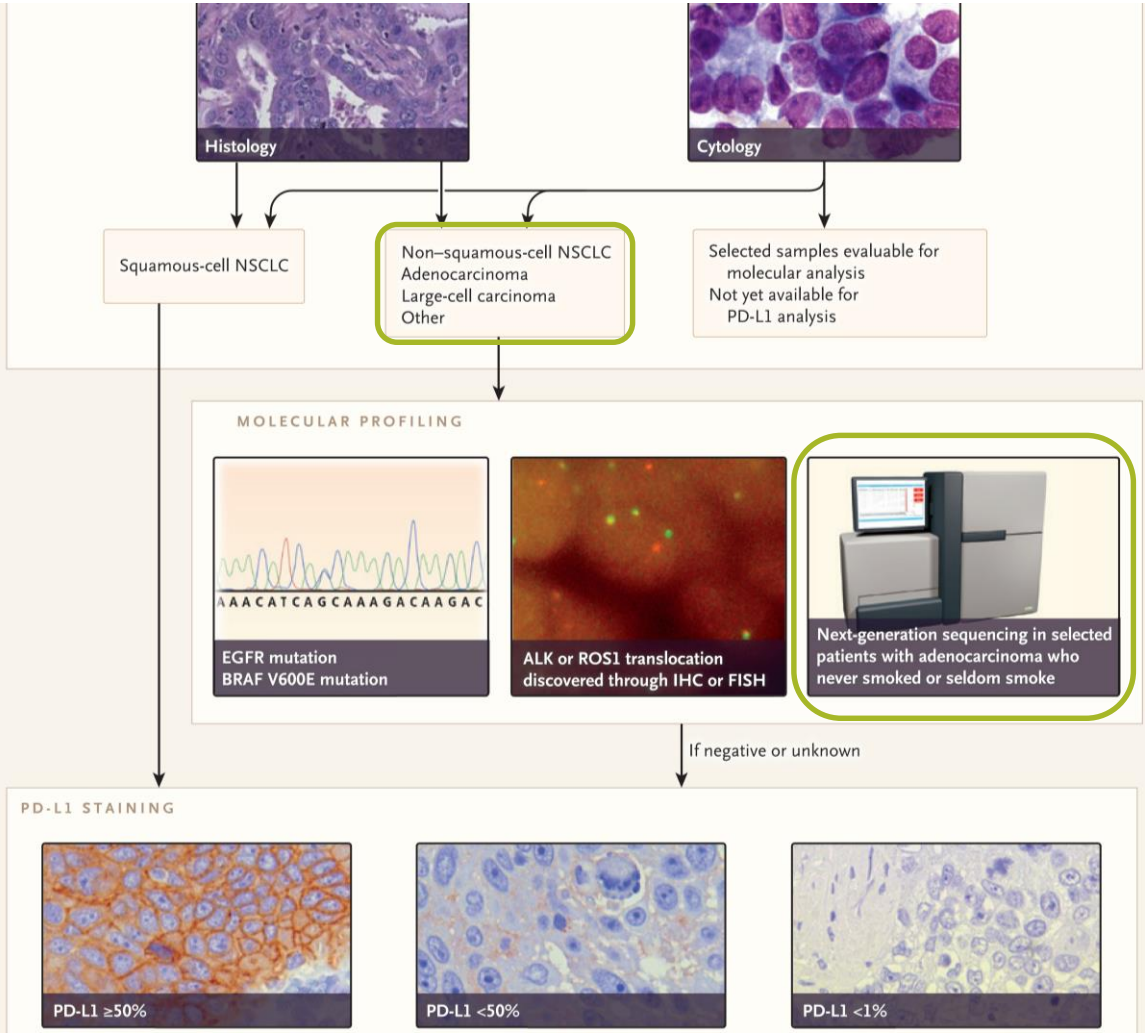
Oncogene drivers in NSCLC



Guo et al., OncoTargets and Therapy 2019

NSCLC



Reck et al., NEJM 2017

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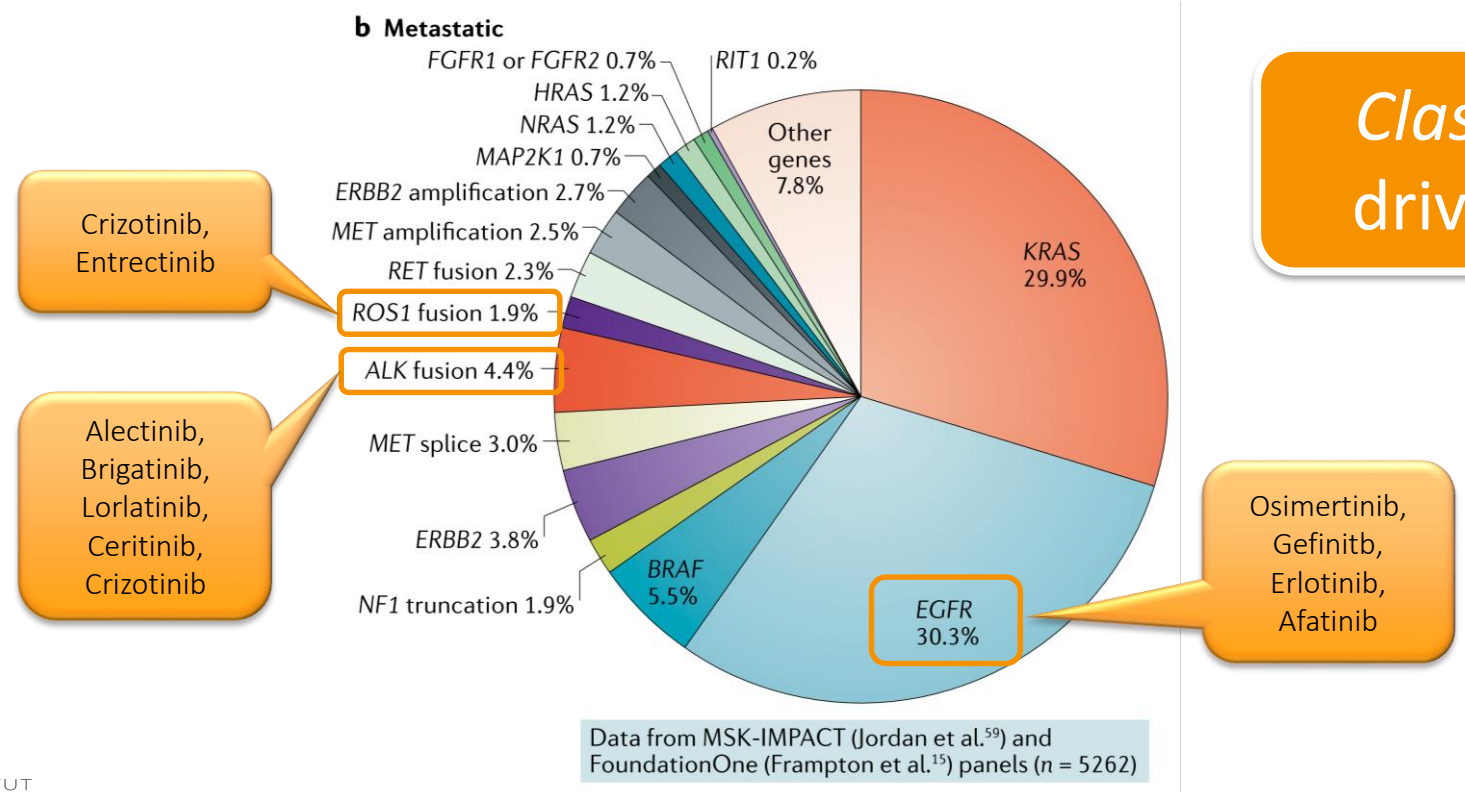
Genomic landscape of non-squamous NSCLC



Classic drivers

Skoulidis et al., Nat Rev Cancer. 2019

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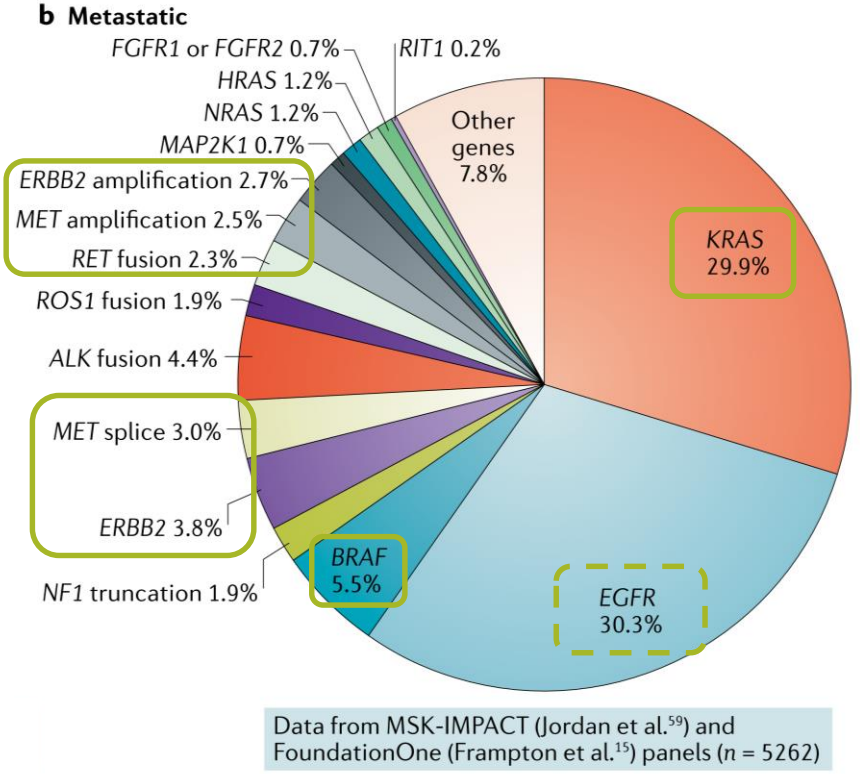
Genomic landscape of non-squamous NSCLC

Emergent drivers



Skoulidis et al., Nat Rev Cancer. 2019

Emergent molecular drivers

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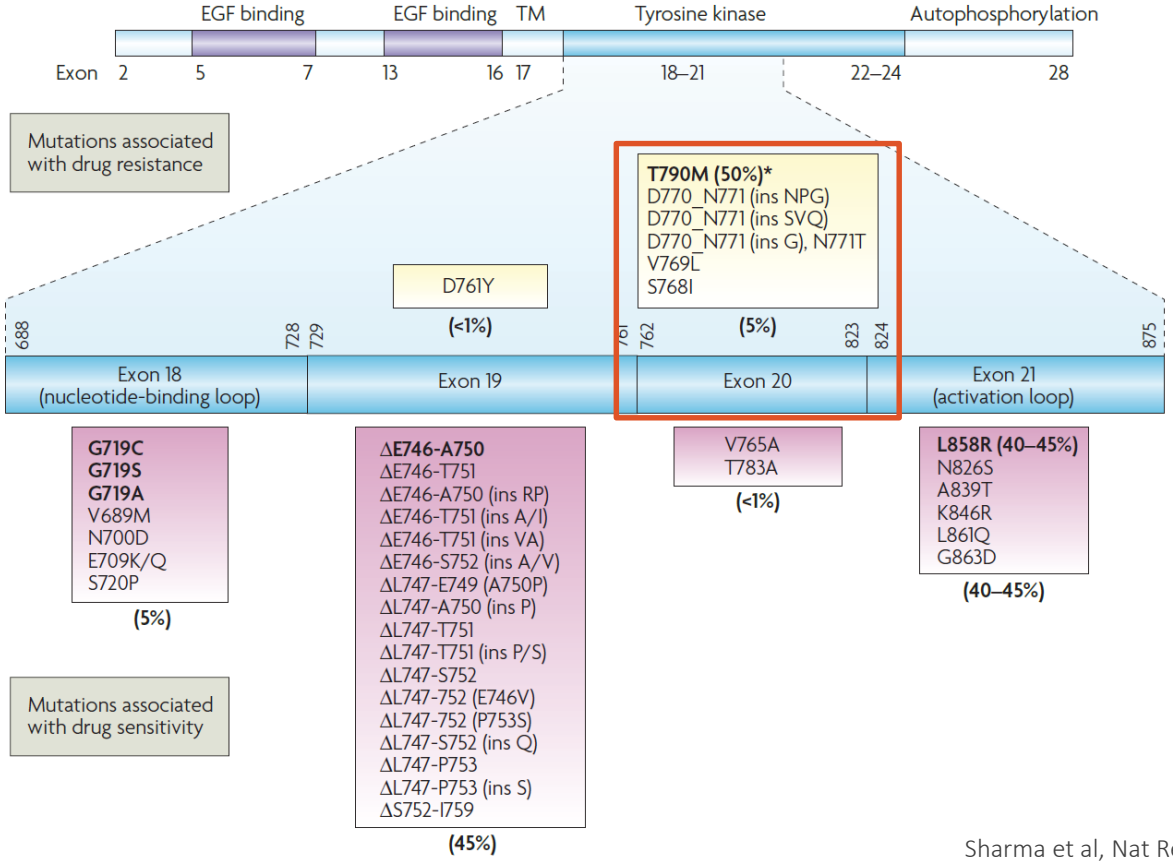
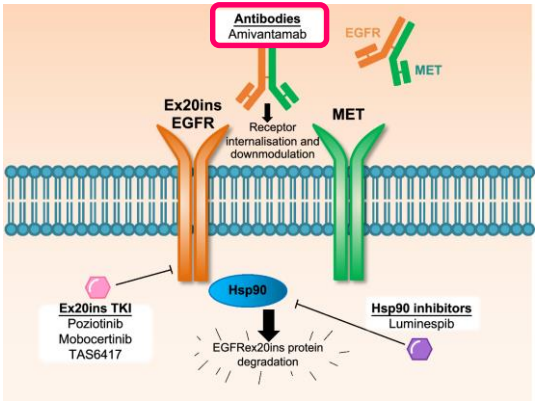
EGFR+ NSCLC → exon 20 insertion mutations



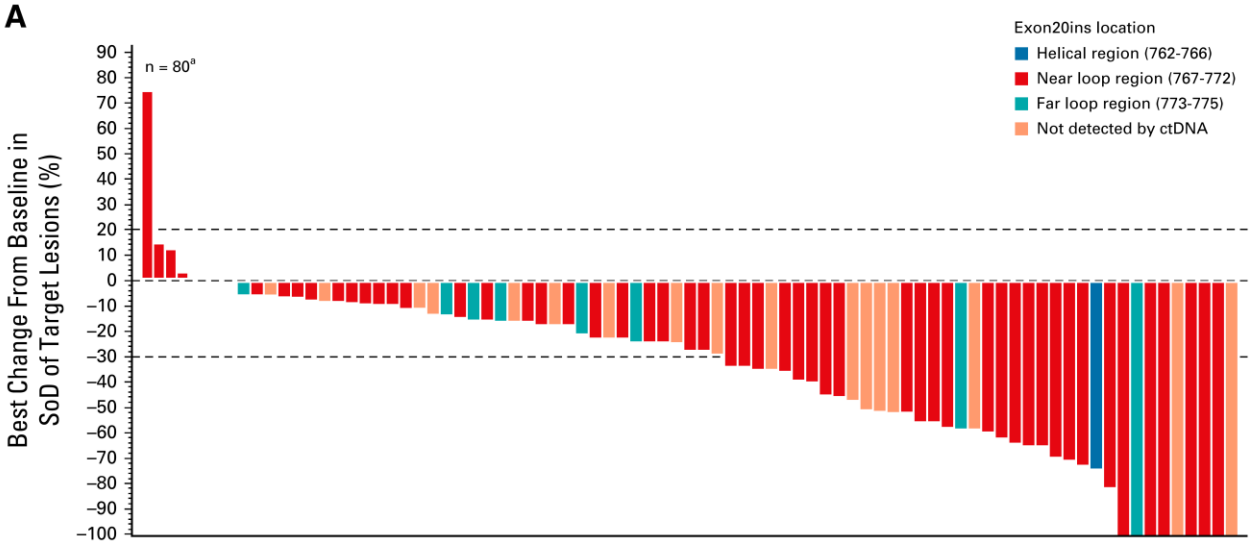
Sharma et al, Nat Rev Cancer 2007

EGFR exon 20 mutations (2%)

EMA APPROVED



- **Amivantamab**: EGFR-MET bispecific antibody
- **CHRYSALIS study** (phase I/II): 81 pts progressing on platinum-based chemotherapy
- Median of 2 previous tx lines (range 1-7)



ORR 40%

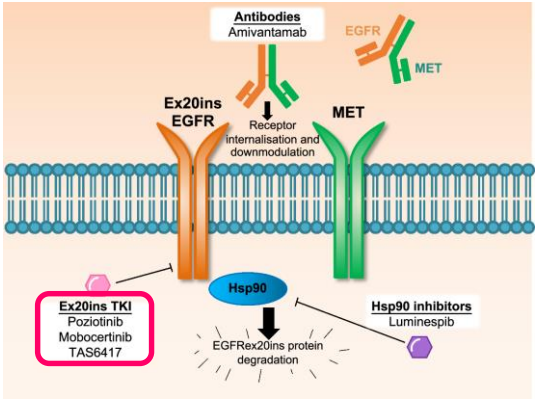
DCR 74%

mPFS 8.3 m

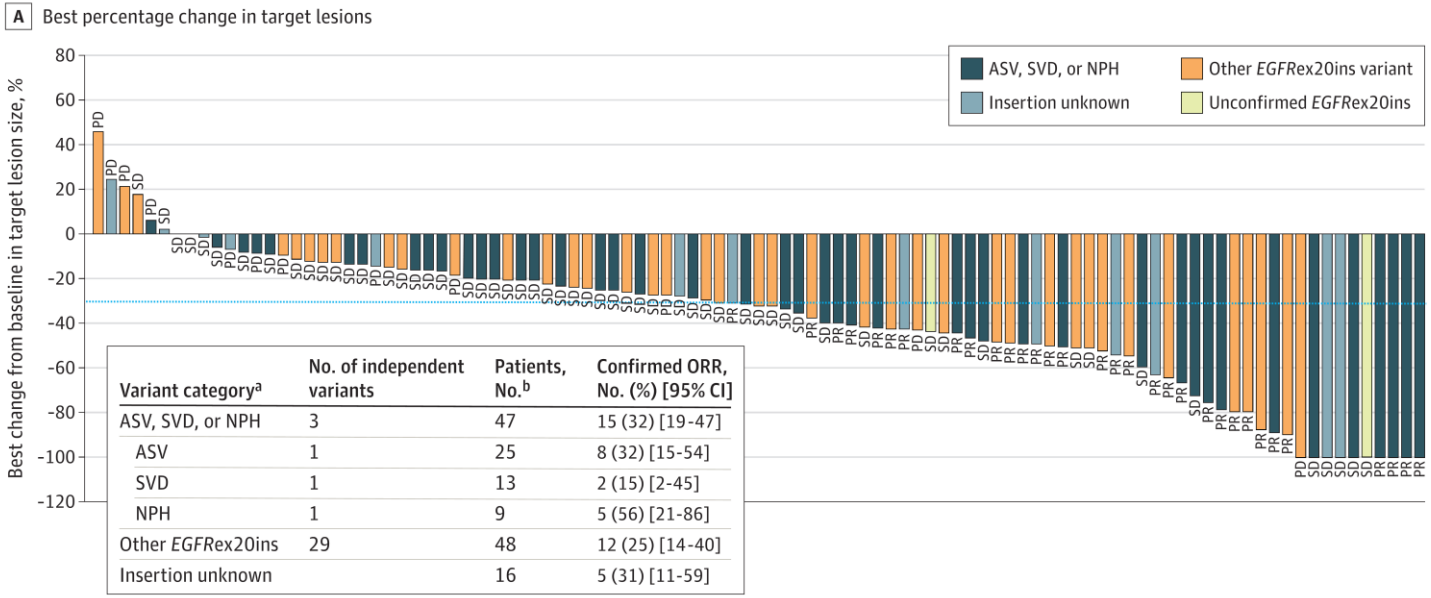
mOS 22.8 m

Park et al., J Clin Oncol 2021

EGFR exon 20 mutations (2%)



- **Mobocertinib**: oral TKI
- **EXCLAIM study** (phase I/II): 210 pts progressing on platinum-based chemotherapy; 1/3 with brain metastases at enrolment



Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR, No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	13	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]

ORR 28%

DCR 78%

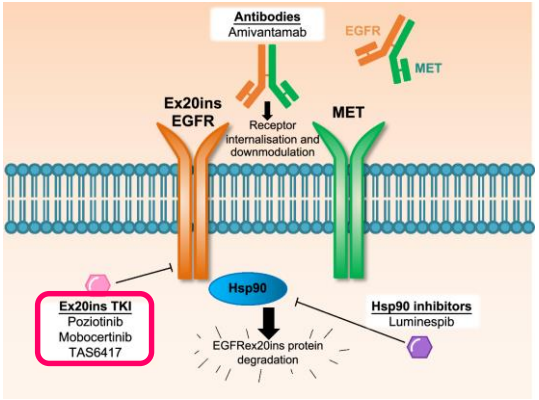
mPFS 7.3 m

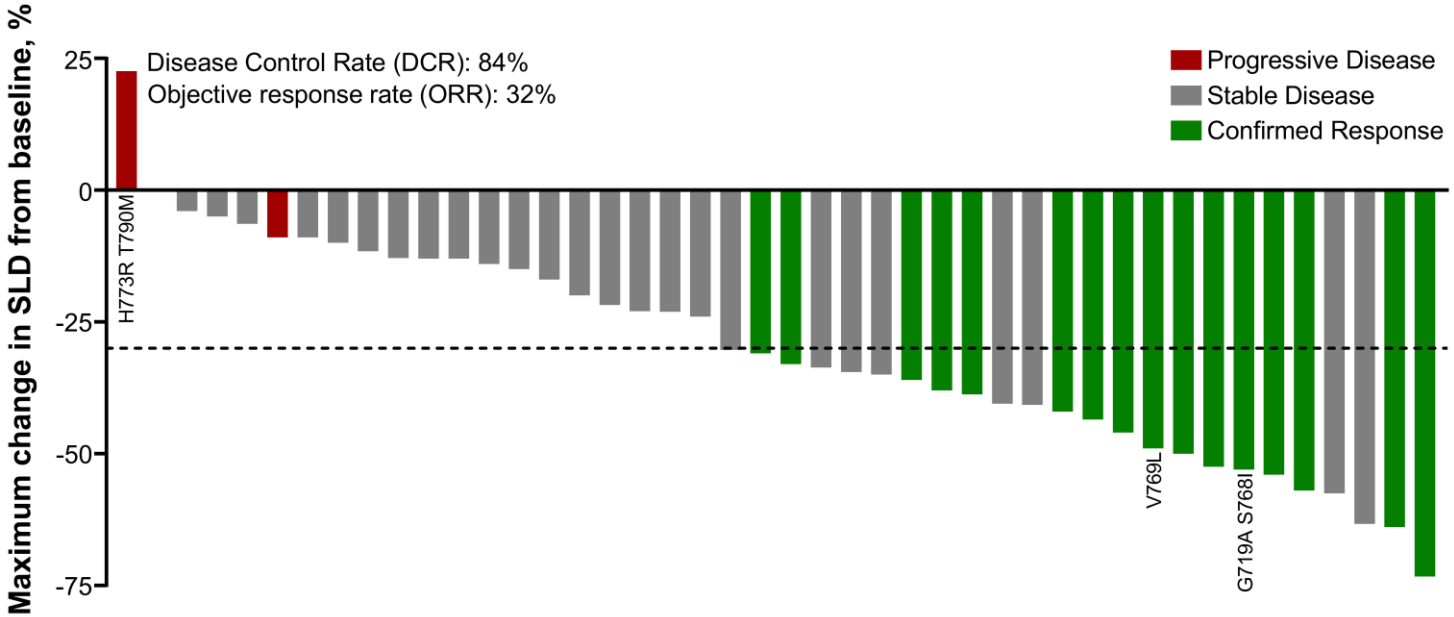
mOS 24.0 m

Zhou et al.,
JAMA Oncol 2022

EGFR exon 20 mutations (2%)

- **Poziotinib**: oral TKI
- **ZENITH20-1 study** (phase I/II): 50 pts, treatment naive or previously treated





ORR 32%

DCR 84%

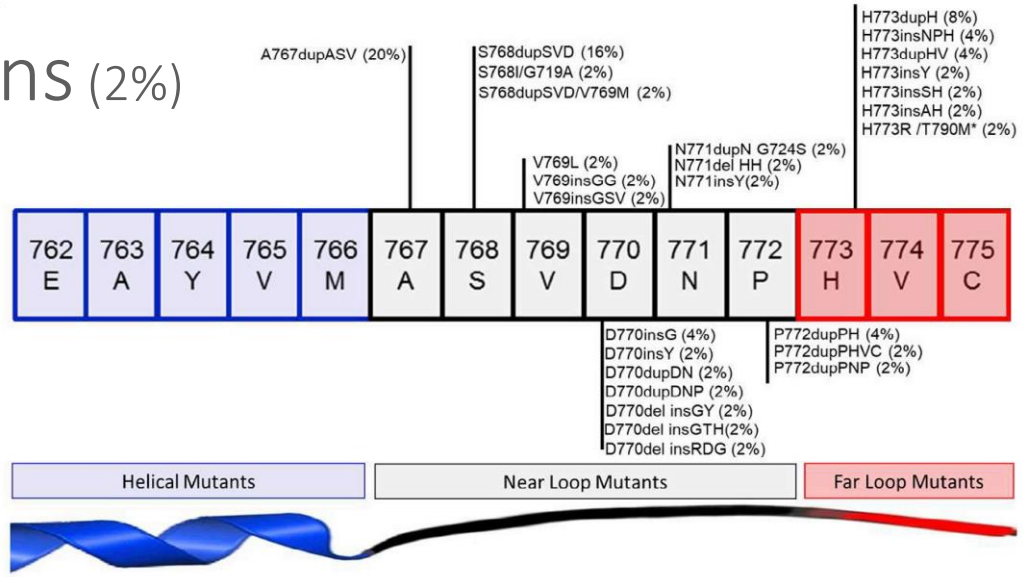
mPFS 5.5 m

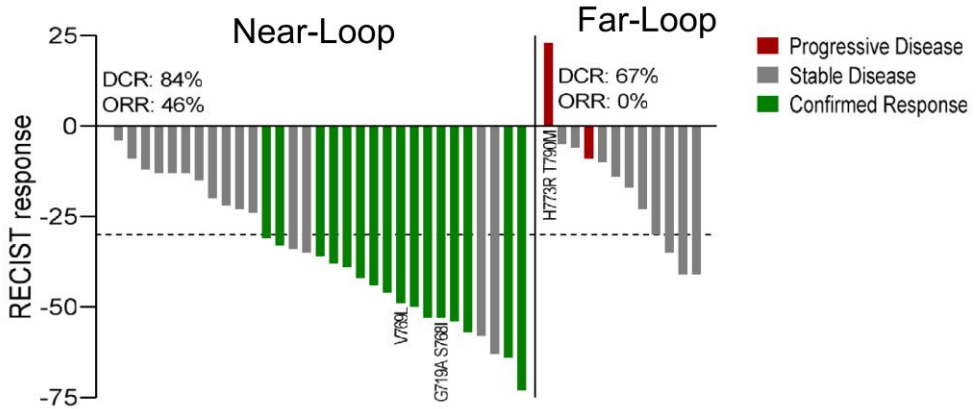
Elamin et al., Cancer Cell 2022

EGFR exon 20 mutations (2%)

- **Poziotinib**: oral TKI

- *"Location of the insertion at the C-terminal end of the alfa-C helix influences the orientation of distinct residues of the P loop that stabilize EGFR TKIs and influence drug binding affinities"*





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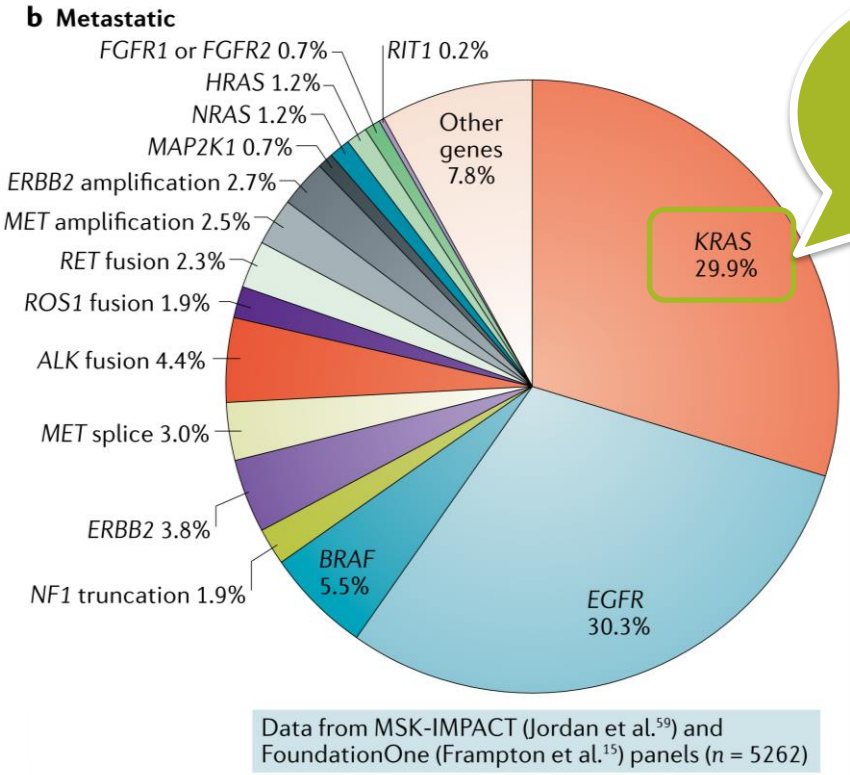
Elamin et al., Cancer Cell 2022

EGFR exon 20 mutations

Trial Name (First Author, Year)	Molecular Alteration	Study Type Line of Therapy	Regimen(s)	Evaluable patients, n	Overall response rate[a], % (95 % CI)	Median Duration of Response, months HR (95 % CI), [range]	Median progression free survival, months HR (95 % CI)	Median overall survival, months HR (95 % CI)
ECOG-ACRIN 5162 [53]	*EGFR* exon 20 insertions	Phase II Advanced 2nd line+	High-dose osimertinib 160 mg daily	21	23.5	NE (4.7–NE)	9.6 (4.1–10.7)	NR
RAIN-701 [54]	*EGFR* Exon 20 insertions	Phase II Stage IIIB/IIIC/IV or recurrent 1st line+	Tarloxotinib 150 mg/m^2 weekly	11	0	NR	NR	NR
ZENITH20−1 [55,56]	*EGFR* exon 20 insertions	Cohort 1 Phase II Stage IIIB/IV EGFR pre-treated	Poziotinib 16 mg daily	115	19.3 (11.7–29.1)	7.4 (3.7–9.7)	4.1 (3.7–6.6)	NR
		Cohort 3 Phase II Stage IIIB/IV 1st line	Poziotinib 16 mg daily	79	27.8 (18.4–39.1)	6.5	7.2	NR
EXCLAIM [57]	*EGFR* Exon 20 insertions	Phase I/II Stage IIIB/IV 2nd line (41%) 3rd line+ (59%)	Mobocertinib (TAK-788) 160 mg daily	96	25.0 (17–35)	NE (5.6–NE)	7.3 (5.5–9.1)	NR
CHRYSALIS [58]	*EGFR* Exon 20 insertions	Phase I Advanced 2nd line+ (100%)	Amivantamab 1050−1400 mg q1w x4 then q2w	81	40 (29–51)	11.1 (6.9–NYR)	8.3 (6.5–10.9)	22.8 (14.6–NYR)

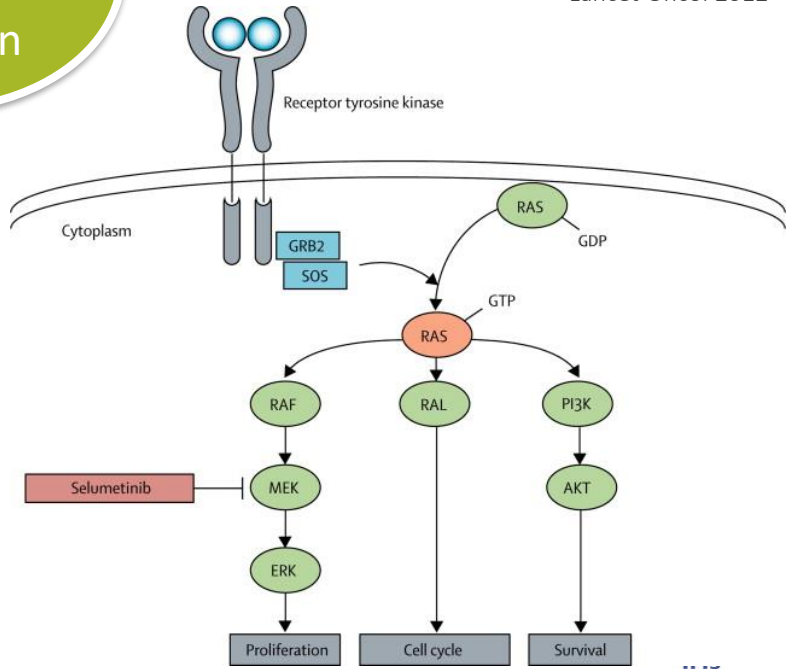
KRAS G12C mutation



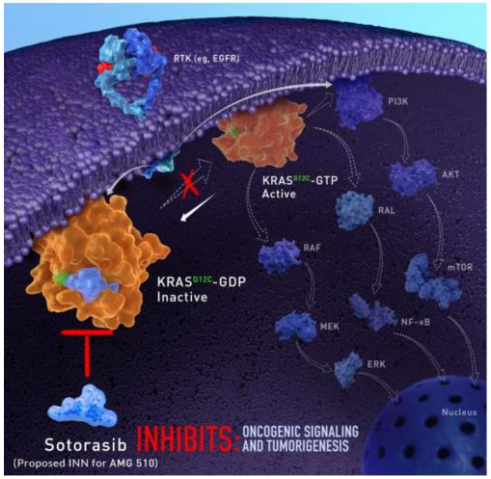
Skoulidis et al., Nat Rev Cancer. 2019

~13%:
KRAS G12C mutation

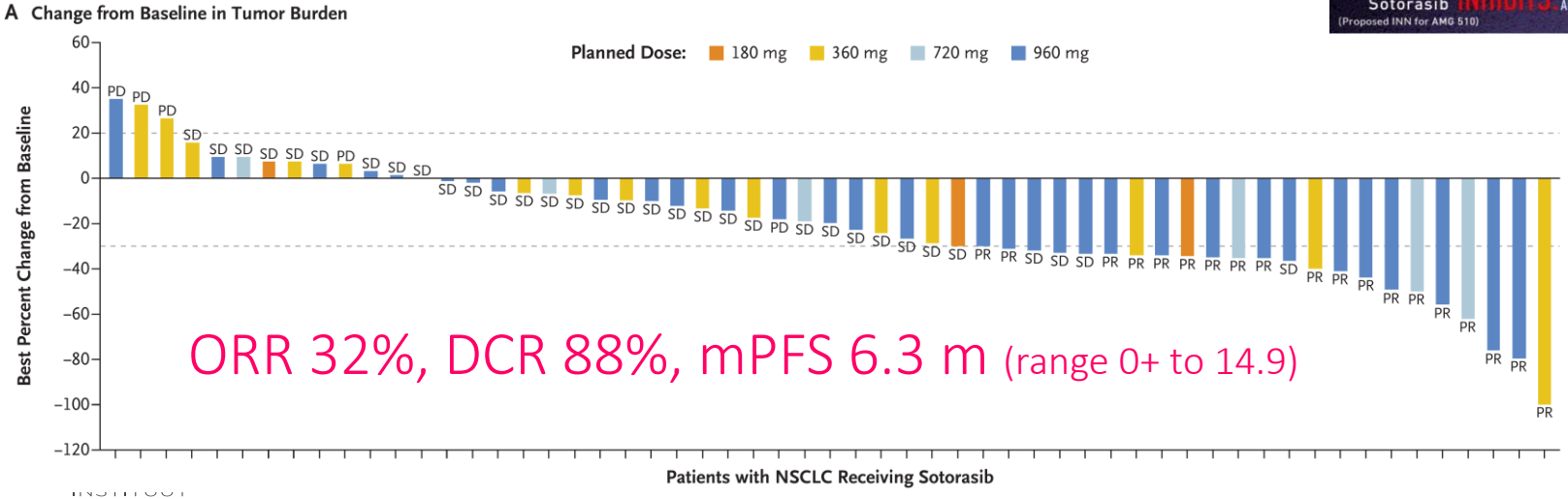
Goldberg et al.,
Lancet Oncol 2012



KRAS G12C mutation (13%)



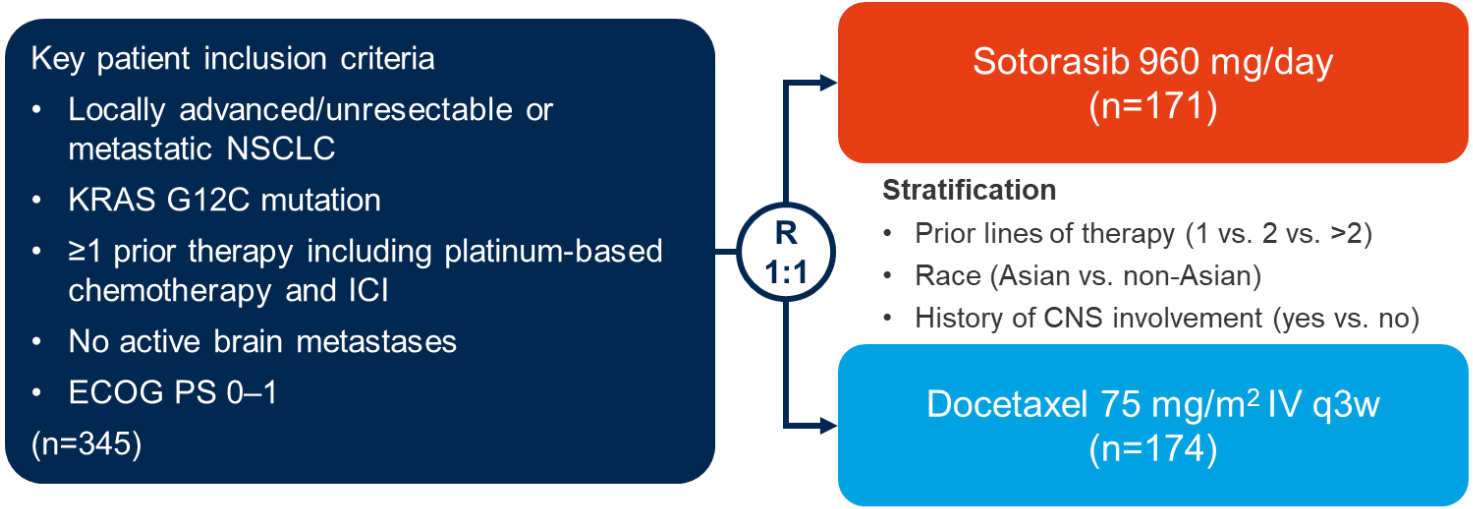
- **Sotorasib**: selective, irreversible and first-in-class KRAS^{G12C} inhibitor
- **CodeBreaK 100 study** (phase I/II): 129 patients with *KRAS* p.G12C mutant advanced solid tumors → *59 with NSCLC*
- Overall: median of 3 previous tx lines (NSCLC: ≥1 mandatory)



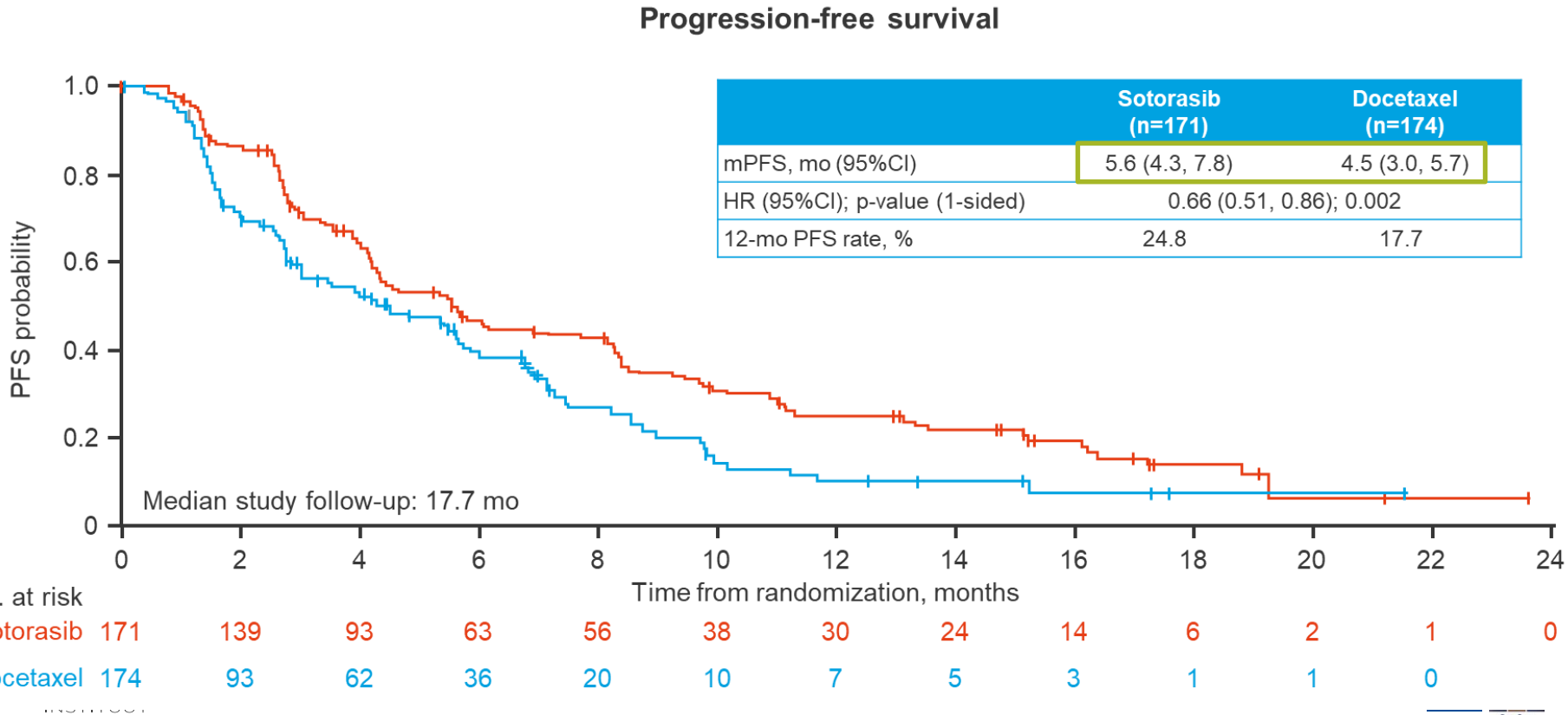
ORR 32%, DCR 88%, mPFS 6.3 m (range 0+ to 14.9)

Hong et al., NEJM 2020

KRAS G12C mutation (13%) – CodeBreak 200 study

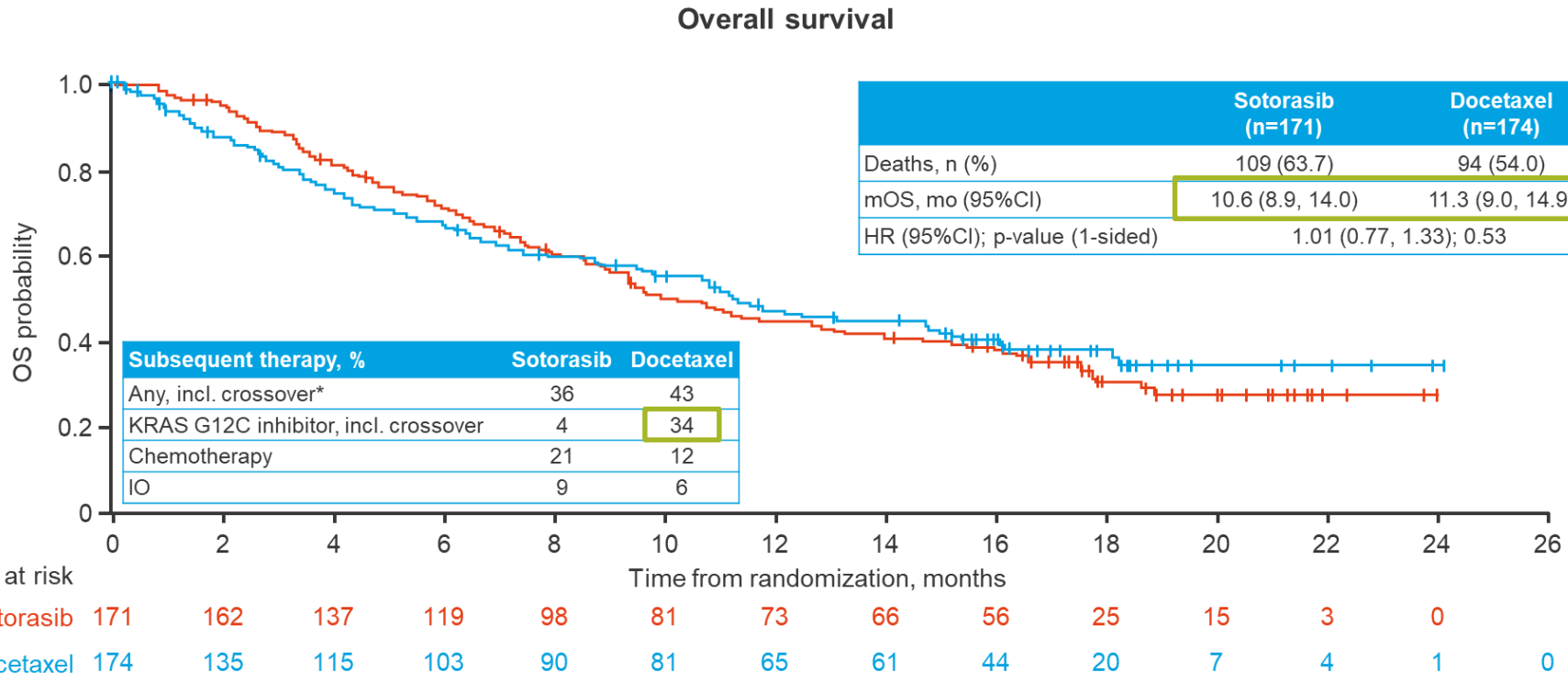


KRAS G12C mutation (13%) – CodeBreak 200 study



	Sotorasib (n=171)	Docetaxel (n=174)
mPFS, mo (95%CI)	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)
HR (95%CI); p-value (1-sided)	0.66 (0.51, 0.86); 0.002	
12-mo PFS rate, %	24.8	17.7

KRAS G12C mutation (13%) – CodeBreak 200 study



	Sotorasib (n=171)	Docetaxel (n=174)
Deaths, n (%)	109 (63.7)	94 (54.0)
mOS, mo (95%CI)	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)
HR (95%CI); p-value (1-sided)	1.01 (0.77, 1.33); 0.53	

Subsequent therapy, %	Sotorasib	Docetaxel
Any, incl. crossover*	36	43
KRAS G12C inhibitor, incl. crossover	4	34
Chemotherapy	21	12
IO	9	6

*16.4% and 5.2% of patients in the sotorasib and docetaxel arms, respectively, were treated beyond progression

KRAS G12C mutation (13%) – CodeBreak 200 study

Outcomes	Sotorasib (n=158)*	Docetaxel (n=129)*
ORR, % (95%CI)	28.1 (21.5, 35.4)	13.2 (8.6, 19.2)
DCR, % (95%CI)	82.5 (75.9, 87.8)	60.3 (52.7, 67.7)
Tumour shrinkage, %	80.4	62.8
Responders, n	48	23
mTTR, mo (range)	1.4 (1.2–8.3)	2.8 (1.3–11.3)
mDoR, mo (95%CI)	8.6 (7.1, 18.0)	6.8 (4.3, 8.3)

TRAEs, n (%)	Sotorasib (n=169)	Docetaxel (n=151)
Any grade	119 (70.4)	130 (86.1)
Grade ≥3	56 (33.1)	61 (40.4)
Serious	18 (10.7)	34 (22.5)
Led to dose interruption	60 (35.5)	23 (15.2)
Led to dose reduction	26 (15.4)	40 (26.5)
Led to discontinuation	16 (9.5)	17 (11.3)
Led to death	1 (0.6)	2 (1.3)

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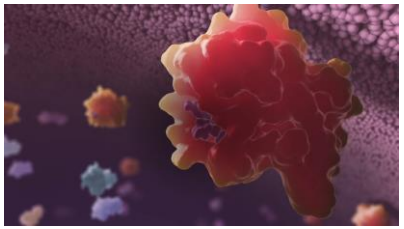
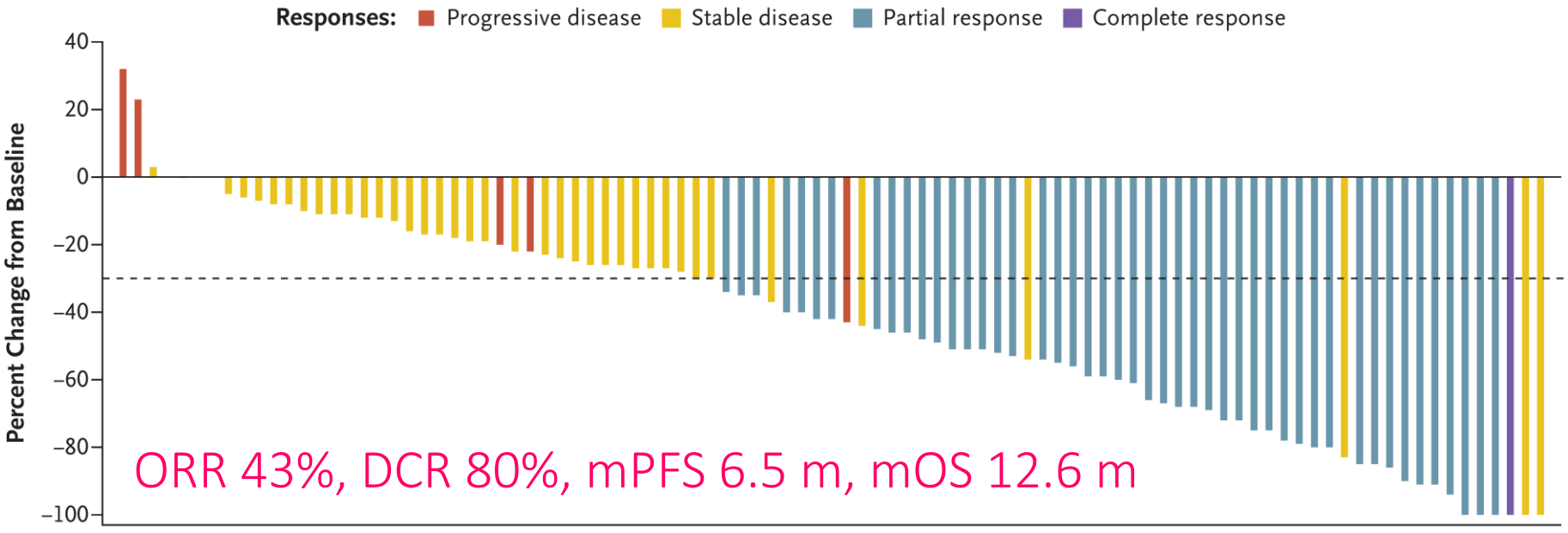
KRAS G12C mutation (13%) – KRYSTAL-1 study

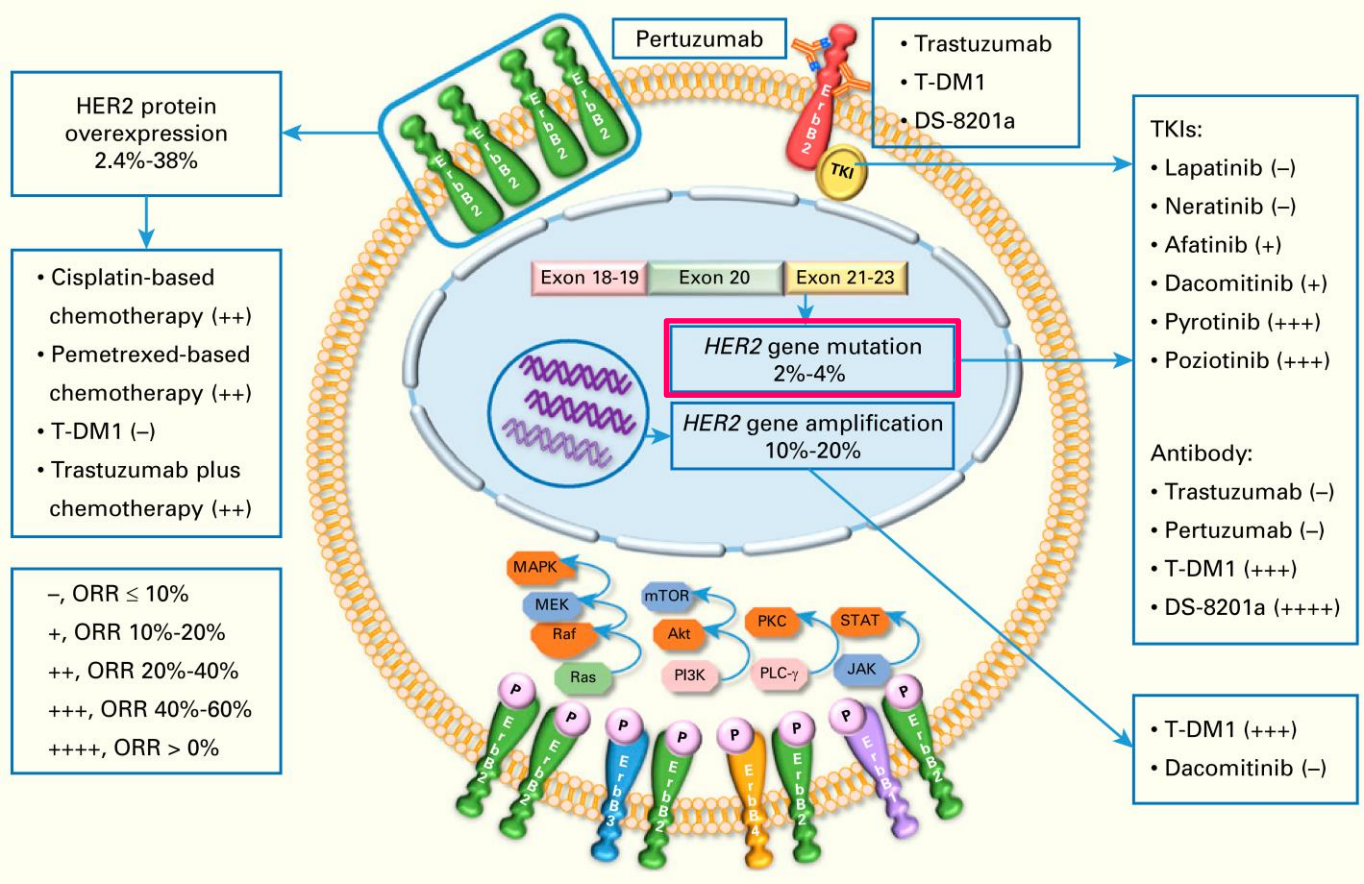


- **Adagrasib**: selective, irreversible KRAS^{G12C} inhibitor
- **KRYSTAL-1 study** (phase I/II): 116 patients previously treated with platinum-based chemotherapy + anti-PD-(L)1



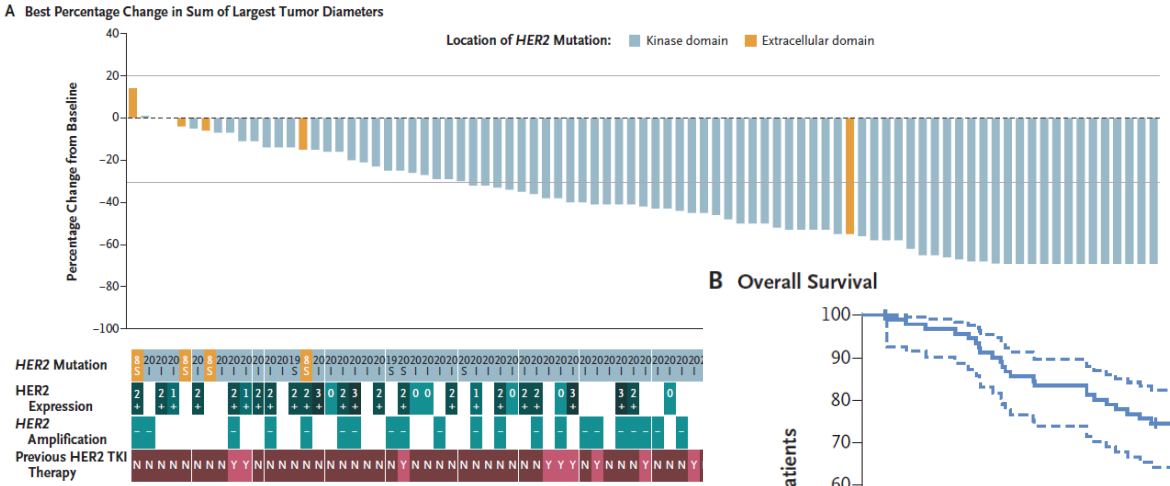
Zhao et al., JPO 2020

HER2 mutation

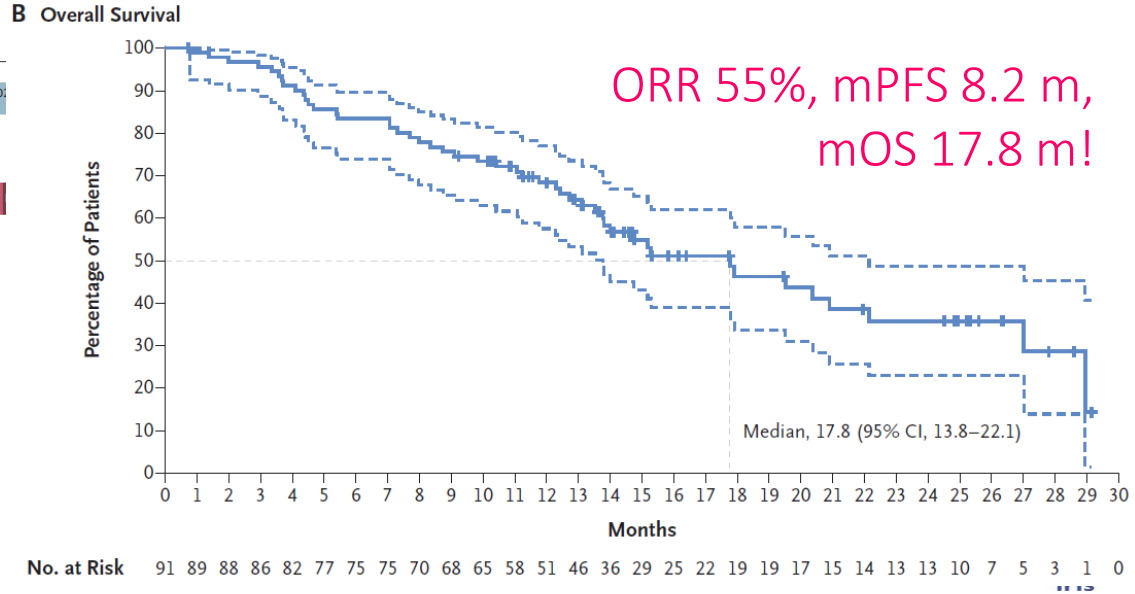


Li et al., NEJM 2022

HER2 mutations (3%)



DESTINY-Lung01 study with *Trastuzumab Deruxtecan*: antibody–drug conjugate against HER2 with a topoisomerase I inhibitor payload



ORR 55%, mPFS 8.2 m, mOS 17.8 m!

26% of Pneumonitis!!

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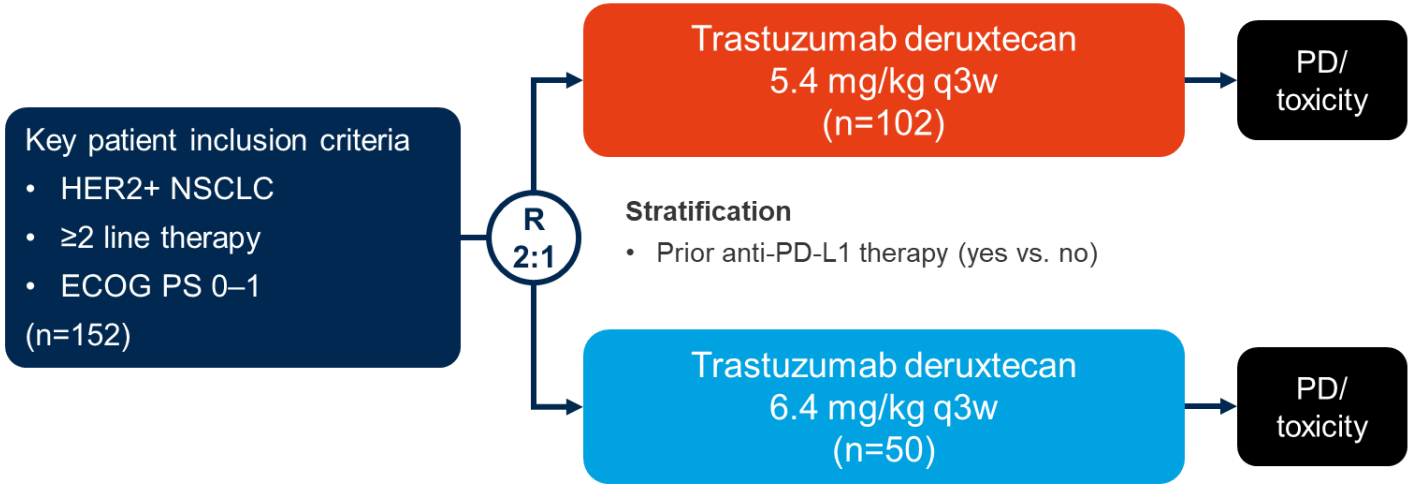
HER2 mutations (3%) – DESTINY-Lung02 study

- **Study objective**
  - To evaluate the efficacy and safety of two doses of trastuzumab deruxtecan in previously treated patients with advanced HER2-mutated NSCLC in the phase 2 DESTINY-Lung02 study



Primary endpoint

- ORR (BICR)

Secondary endpoints

- OS, PROs, PK, safety

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HER2 mutations (3%) – DESTINY-Lung02 study

- **Key results**

Response assessment by BIRC in the pre-specified early cohort

	Trastuzumab deruxtecan 5.4 mg/kg (n=52)	Trastuzumab deruxtecan 6.4 mg/kg (n=28)
Confirmed ORR, n (%) [95%CI]	28 (**53.8**) [39.5, 67.8]	12 (**42.9**) [24.5, 62.8]
BOR, n (%)		
CR	1 (1.9)	1 (3.6)
PR	27 (51.9)	11 (39.3)
SD	19 (36.5)	14 (50.0)
PD	2 (3.8)	1 (3.6)
NE	3 (5.8)	1 (3.6)
DCR, n (%) [95%CI]	47 (90.4) [79.0, 96.8]	26 (92.9) [76.5, 99.1]
mDoR, mo (95%CI)	NE (4.2, NE)	5.9 (2.8, NE)
Median time to initial response, mo (range)	1.4 (1.2–5.8)	1.4 (1.2–3.0)
Median follow-up, mo (range)	5.6 (1.1–11.7)	5.4 (0.6–12.1)

  - Trastuzumab deruxtecan 5.4 mg/kg did not reach mDoR at the time of cut-off, therefore, an additional 90-day follow-up was conducted and the ORR (confirmed by BIRC) was 57.7% (95%CI 43.2, 71.3)

HER2 mutations (3%)

TRAEs, %	Trastuzumab deruxtecan 5.4 mg/kg (n=101)	Trastuzumab deruxtecan 6.4 mg/kg (n=50)
Any grade	92.1	100
Grade ≥3	**31.7**	**58.0**
Led to drug discontinuation	**7.9**	**16.0**
Led to drug reduction	9.9	26.0
Led to drug interruption	13.9	30.0
Leading to death	1.0	2.0

Adjudicated drug-related ILD, n (%)	Trastuzumab deruxtecan 5.4 mg/kg (n=101)	Trastuzumab deruxtecan 6.4 mg/kg (n=50)
Any grade	6 (5.9)	7 (14.0)
Grade 1	3(3.0)	1 (2.0)
Grade 2	2 (2.0)	6 (12.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)
Median time to onset, days (range)	67.5 (40–207)	41.0 (36–208)

Ongoing study: *Destiny-Lung-04*
Trastuzumab Deruxtecan vs Carboplatin-Pemetrexed-Pembrolizumab in 1st line

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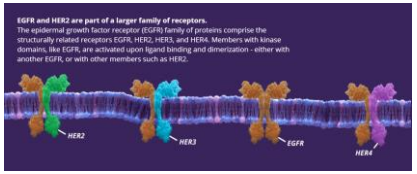
Le et al., J Clin Oncol 2022

HER2 exon 20 mutations (3%) – ZENITH20-2 trial

- **Poziotinib**: oral TKI
- **ZENITH20-2 study** (phase I/II): 90 pts, previously treated
- Median: 2 prior lines of therapy (range 1-6)

- Clinical benefit regardless of lines and types of prior therapy, presence of CNS metastasis, and types of HER2mutations



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Melosky et al., Lung Cancer 2021

HER2 mutations

Trial Name (First Author, Year)	Molecular Alteration	Study Type Line of Therapy	Regimen(s)	Evaluable patients, n	Overall response rate[a], % (95 % CI)	Median Duration of Response, months HR (95 % CI), [range]	Median progression free survival, months HR (95 % CI)	Median overall survival, months HR (95 % CI)
HER2-altered								
ZENITH20−1 [61]	*HER2* exon 20 insertions	Cohort 2 Phase II Advanced 2nd line+	Poziotinib 16 mg daily	74	35.1 (24.4–47.1)	5.1 [1–12.3+]	5.5 [1–13.1+]	NR
NCT02834936 [62]	*HER2* mutation	Phase II 2nd line (58.3%) 3rd line+ (41.7%)	Pyrotinib 400 mg daily	60	30.0 (18.8–43.2)	6.9 (4.9–11.1)	6.9 (5.5–8.2)	14.4 (12.3–21.3)
RAIN-701 [54]	*HER2* mutation	Cohort B Phase II Stage IIIB/IIIC/IV or recurrent 2nd line+ (prior platinum)	Tarloxotinib 150 mg/m^2 weekly	9	22.2	NR	NR	NR
NCT02289833 [63]	HER2 overexpression	Phase II Stage IIIb/IV 2nd line (26.5%) 3rd line+ (69.4%)	T-DM1 3.6 mg/kg q3w	IHC 2+: 29 IHC 3+: 20	0 (0.0–11.9) 20.0 (5.7–43.7)	NR NR	2.6 (1.4–2.8) 2.7 (1.4–8.3)	12.2 (3.8–23.3) 15.3 (4.1–NE)
DESTINY-Lung01 [64,65]	HER2 overexpression (IHC2+/3+)	Cohort 1 Phase II Stage IIIB/IV 2nd line+ Prior PD-1/PD-L1 (73.5 %)	T-DXd 6.4 mg/kg q3w	49	24.5 (13.3–38.9)	6.0 (3.2–NE)	5.4 (2.8–7.0)	11.3 (7.8–NE)
	HER2 mutation	Cohort II Phase II Stage IIIB/IV 2nd line+ Prior PD-1/PD-L1 (54.8 %)	T-DXd 6.4 mg/kg q3w	42	61.9 (45.6–76.4)	NYR (5.3–NE)	14.0 (6.4–14.0)	NYR (11.8–NE)

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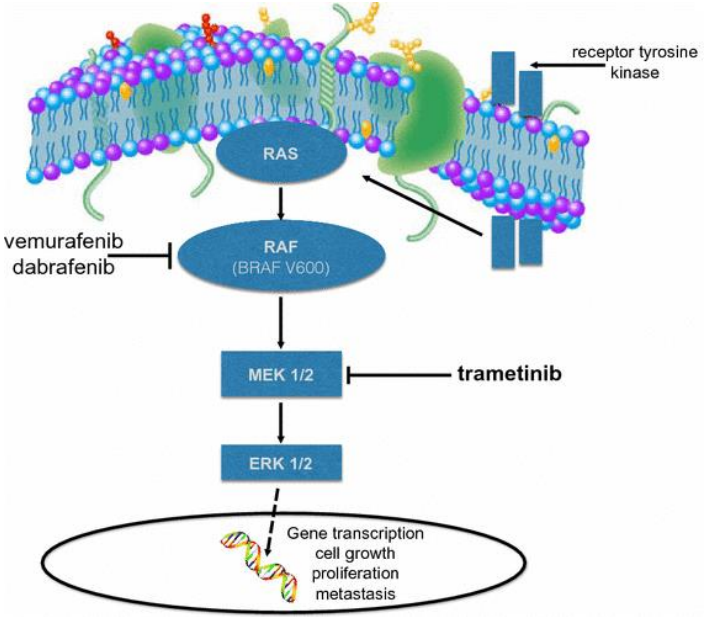
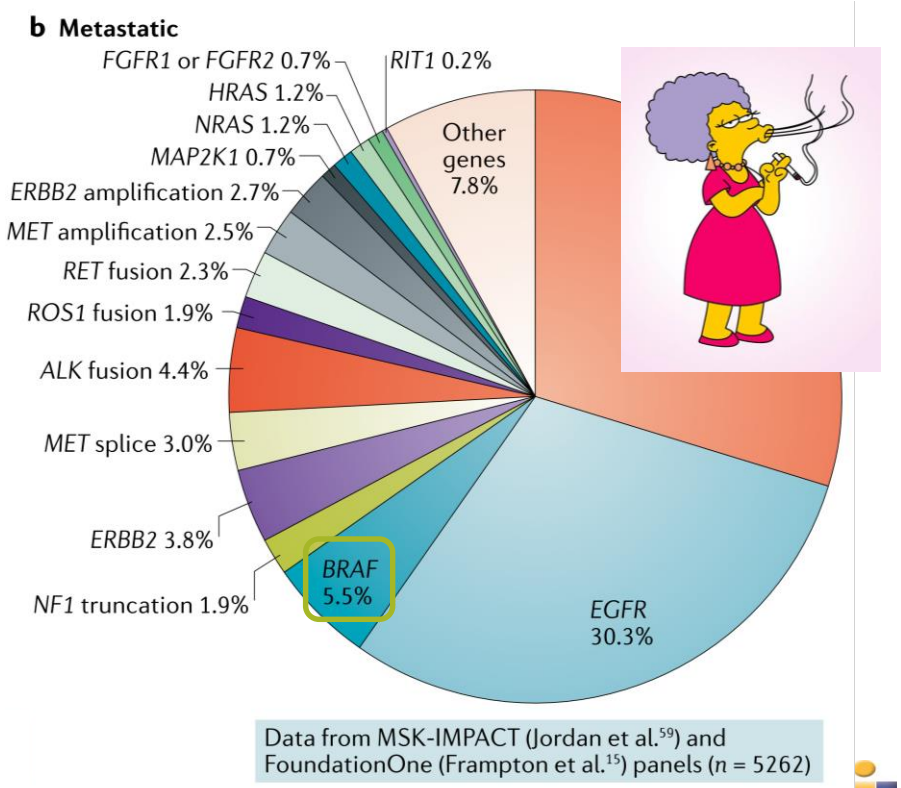
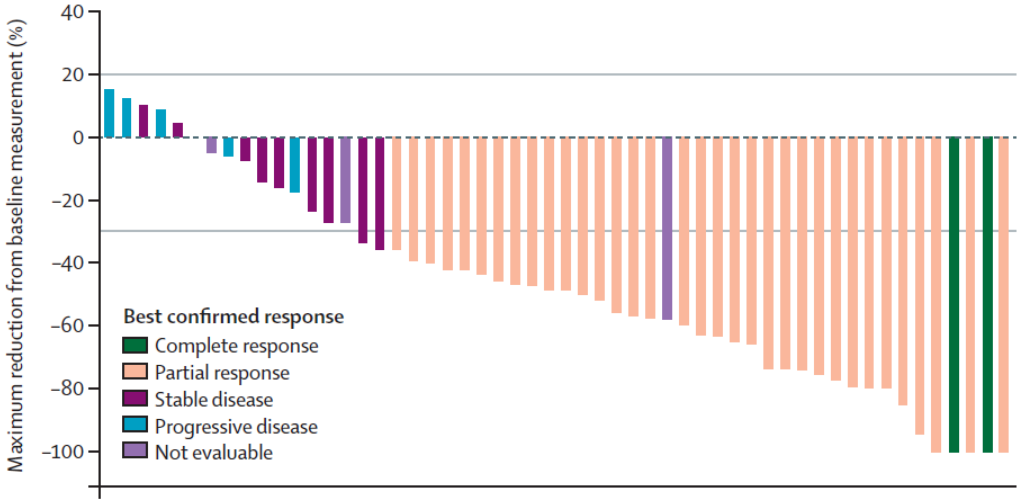
BRAF mutations → V600 mutation (~50%)

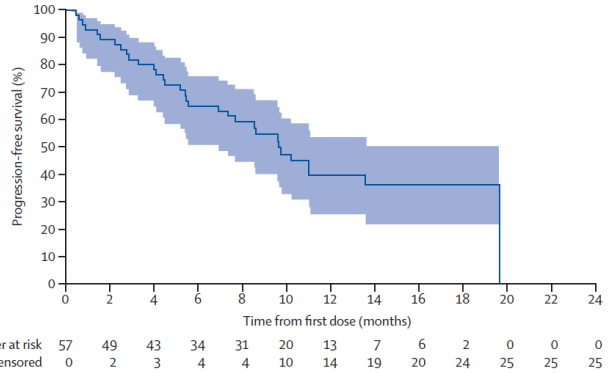




Skoulidis et al., Nat Rev Cancer. 2019

BRAF V600 mutation: Dabrafenib + Trametinib (1st line)





	Investigator assessment (n=57)
Best response	
Complete response	2 (4%)
Partial response	34 (60%)
Stable disease	9 (16%)
Progressive disease	7 (12%)
Non-complete response/ non-progressive disease	0
Not assessable	5 (9%)
Overall response (complete response + partial response)	36 (63·2%; 49·3–75·6)
Disease control (complete response + partial response + stable disease)	45 (78·9%; 66·1–88·6)
Progression-free survival (months)	9·7 (6·9–19·6)
Duration of response (months)	9·0 (6·9–18·3)

Data are n (%), n (%; 95% CI), or median (95% CI).

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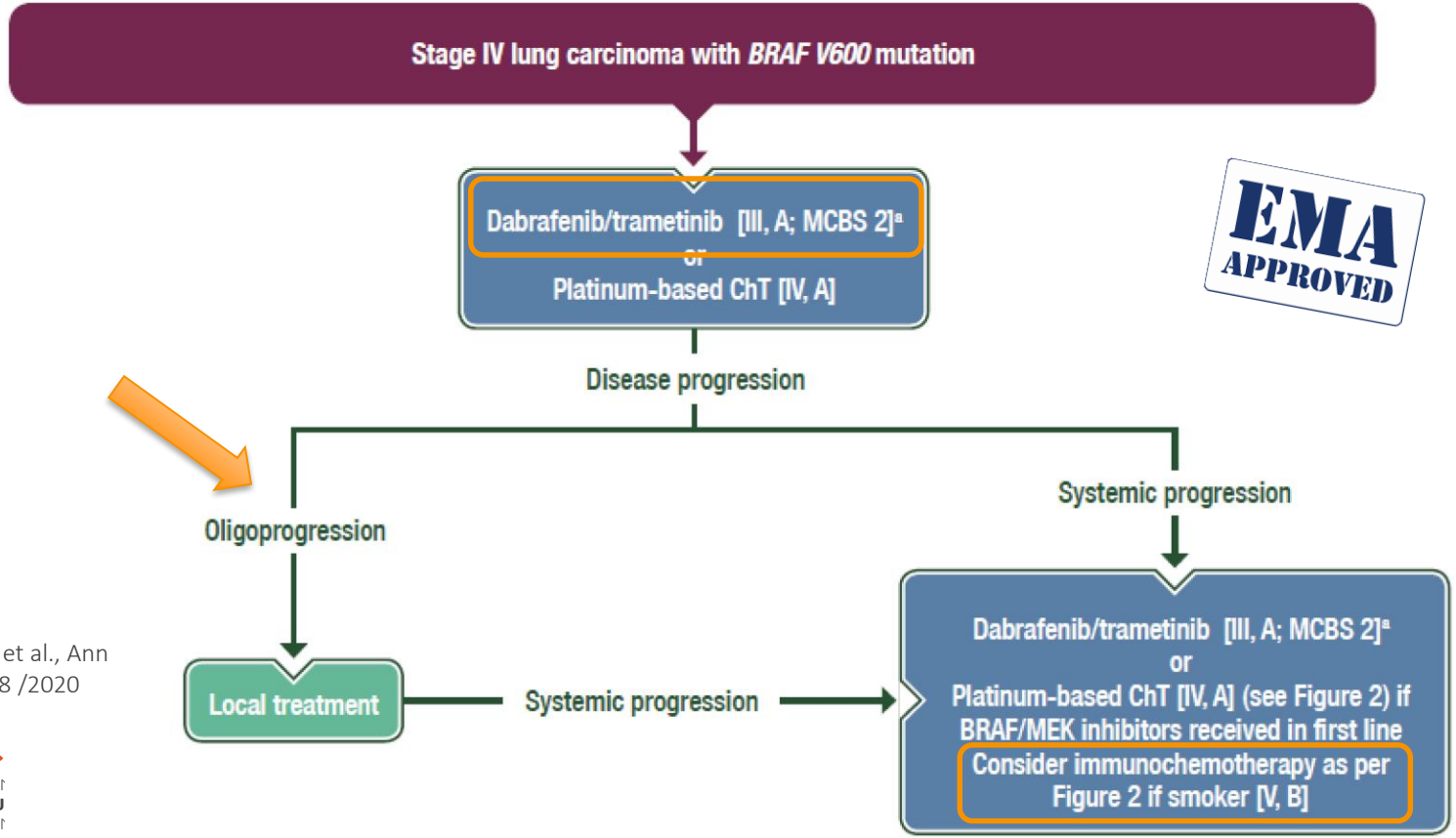
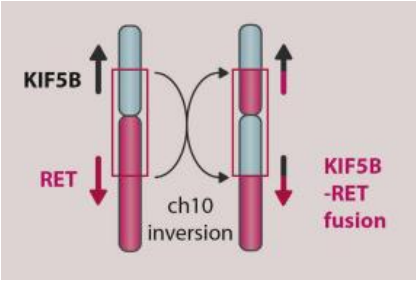
Planchard et al., Lancet Oncol 2016

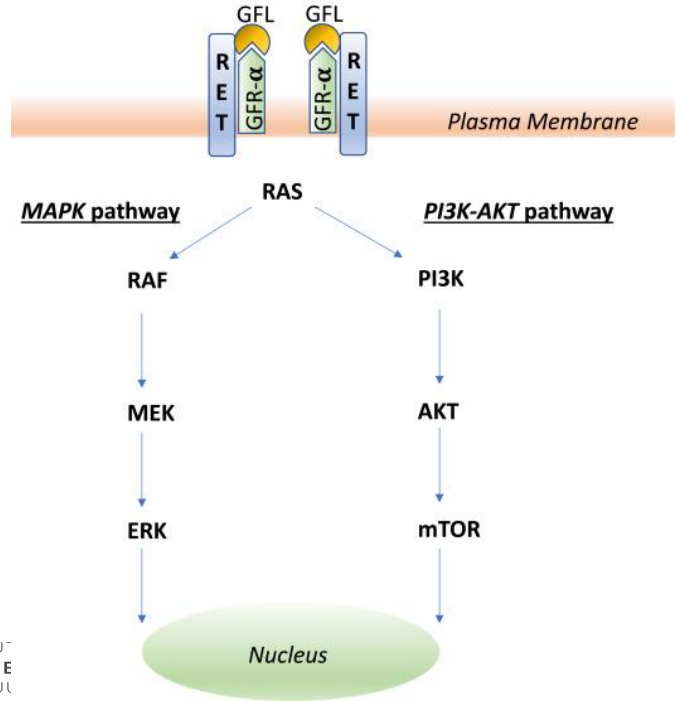
Advanced NSCLC with *BRAF V600* mutation

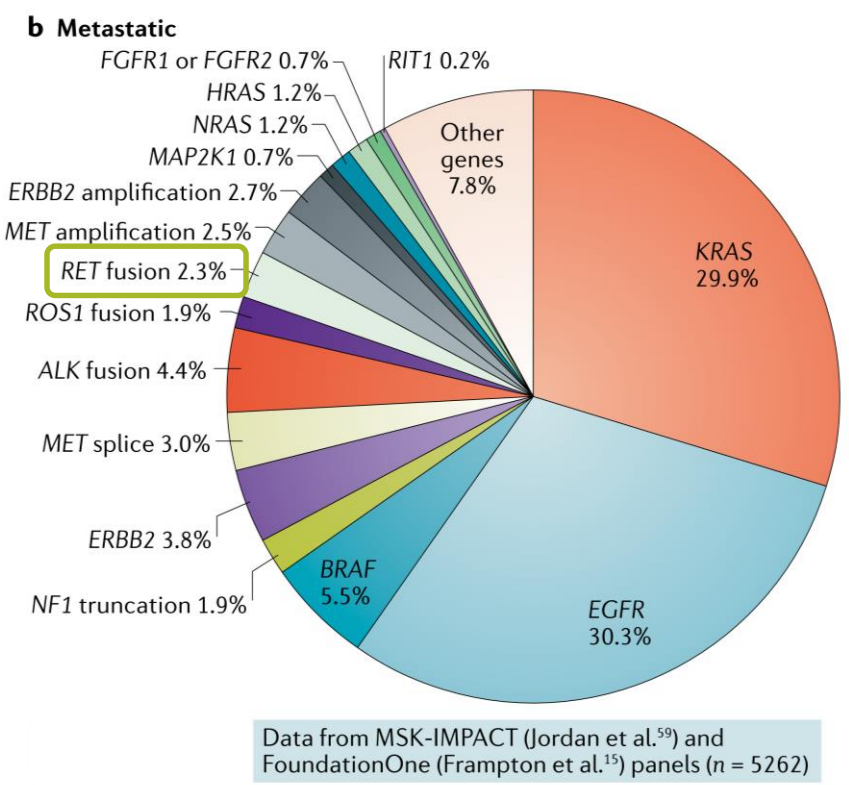


Planchard et al., Ann Oncol 2018 /2020

RET fusions







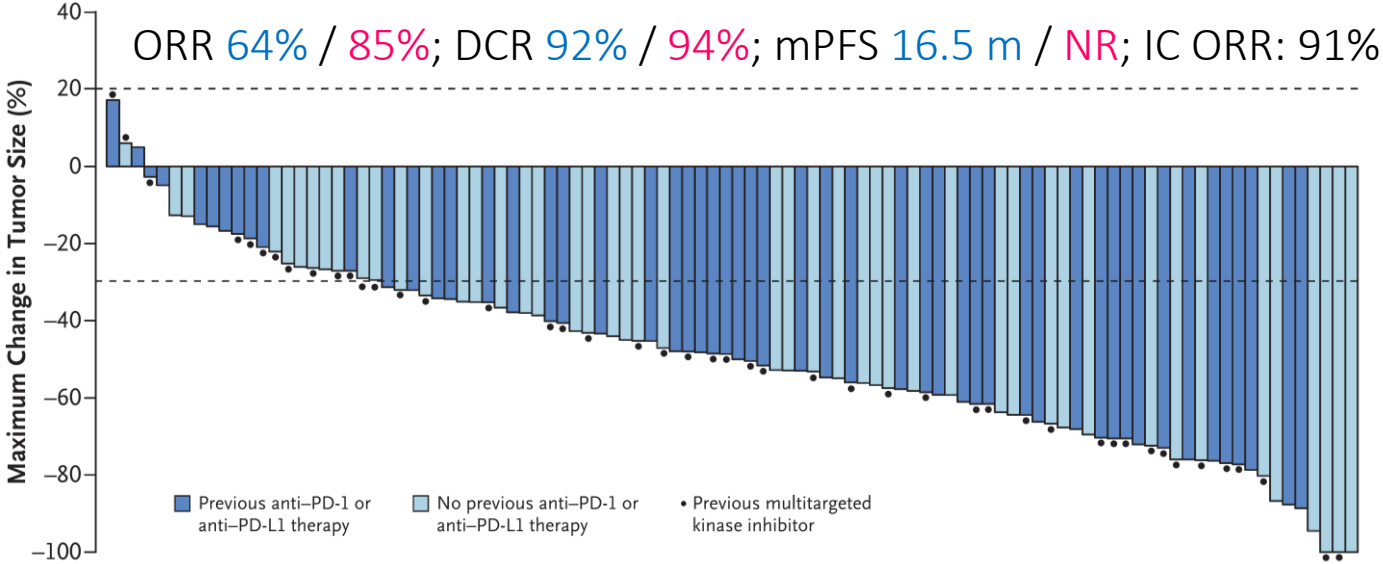
Skoulidis et al., Nat Rev Cancer. 2019

RET fusions (1-2%) – LIBRETTO-001 trial

EMA APPROVED

- **Selpercatinib** (LOXO-292): ATP-competitive, highly selective small-molecule inhibitor of RET kinase; passes the BBB
- **LIBRETTO-001** trial: 105 NSCLC patients previously treated (median: 3 lines tx) + 39 untreated

ORR 64% / 85%; DCR 92% / 94%; mPFS 16.5 m / NR; IC ORR: 91%



Drilon et al., NEJM 2020

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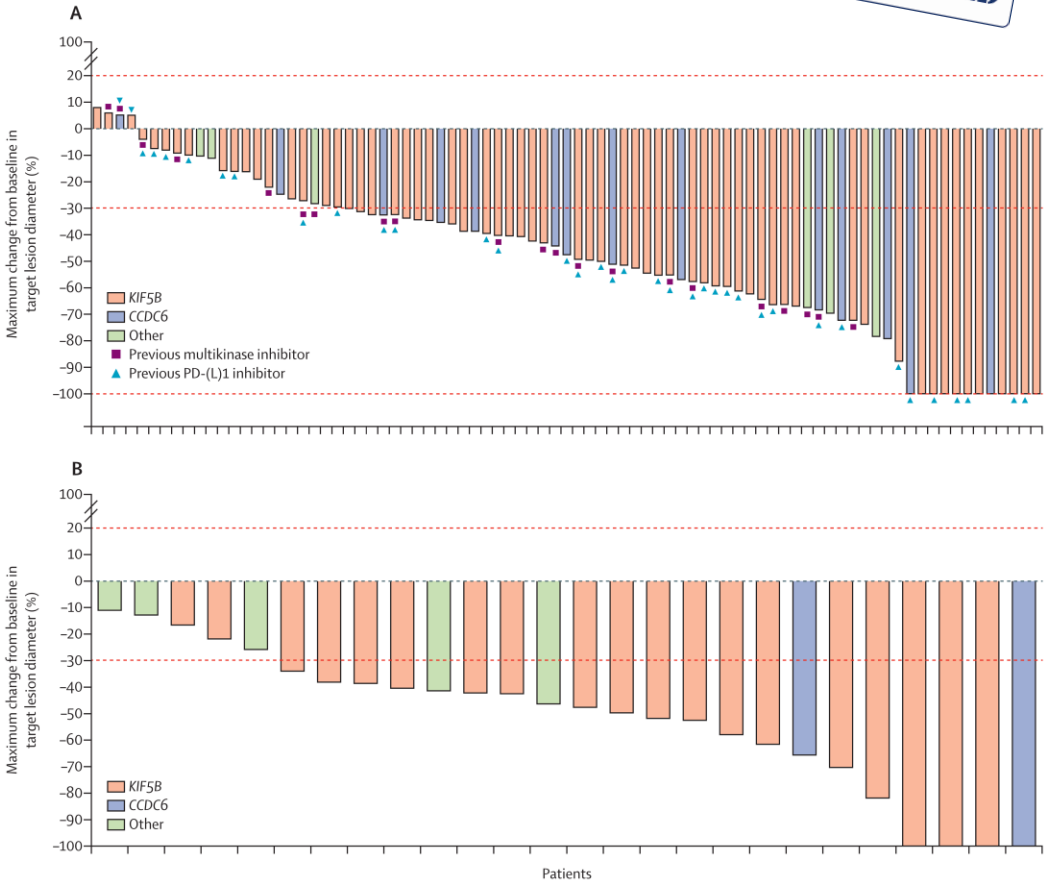
RET fusions (1-2%) – ARROW trial

EMA APPROVED

- **Praseltinib**: highly selective small-molecule inhibitor of RET kinase
- **ARROW** trial: 92 previously treated (platinum-based CT) + 29 untreated

ORR 61% / 70%; DCR 91% / 85%; mPFS 17.1 m



Gainor et al.,
Lancet Oncol 2021

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RET fusions (1-2%)

Trial Name (First Author, Year)	Molecular Alteration	Study Type Line of Therapy	Regimen(s)	Evaluable patients, n	Overall response rate[a], % (95 % CI)	Median Duration of Response, months HR (95 % CI), [range]	Median progression free survival, months HR (95 % CI)	Median overall survival, months HR (95 % CI)
ARROW [59]	*RET* fusion	Cohort A Phase I/II 1st line+	Pralsetinib 400 mg daily	26	73 (52–88)	NYR (11.3–NYR)	NR	NR
		Cohort B Phase I/II 2nd line (prior platinum)	Pralsetinib 400 mg daily	80	61[f] (50–72)			
LIBRETTO-001 [60]	*RET* fusion	Phase II dose expansion Stage IIIB/IV 1st line	Selpercatinib (Loxo292) 160 mg BID	39	85 (70–94)	NE (12.0–NE)	NE (13.8–NE)	NR
		Phase II dose expansion Stage IIIB/IV 2nd line+ (prior platinum)	Selpercatinib (Loxo292) 160 mg BID	105	64 (54–73)	17.5 (12.0–NE)	16.5 (13.7–NE)	NR

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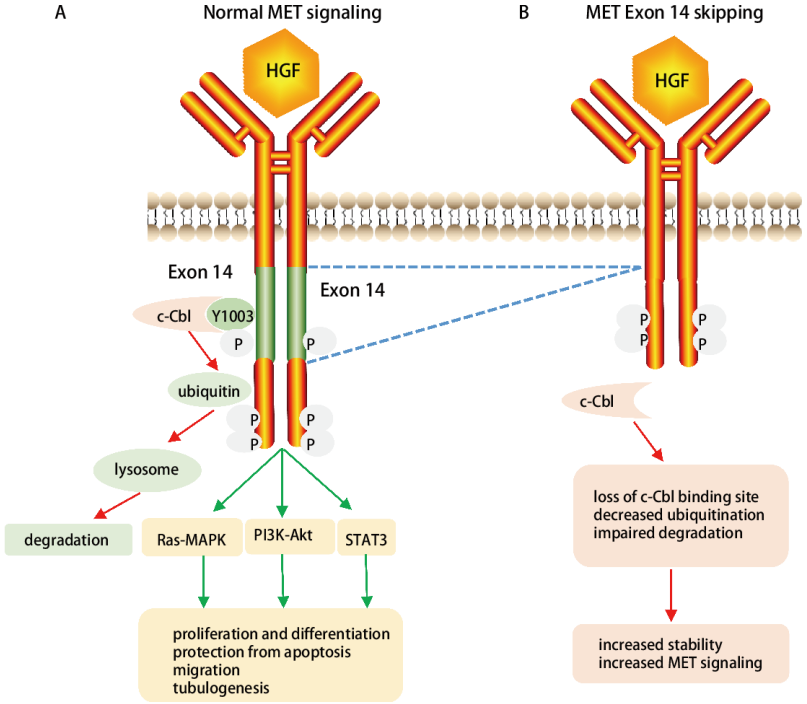
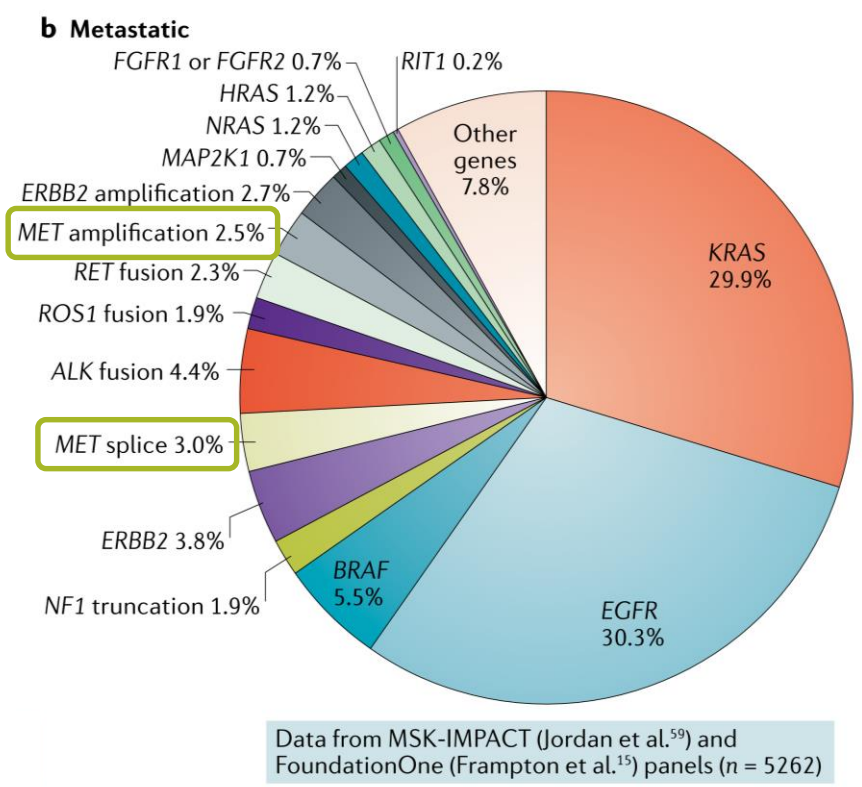
MET dysregulation





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Skoulidis et al., Nat Rev Cancer. 2019

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MET dysregulation

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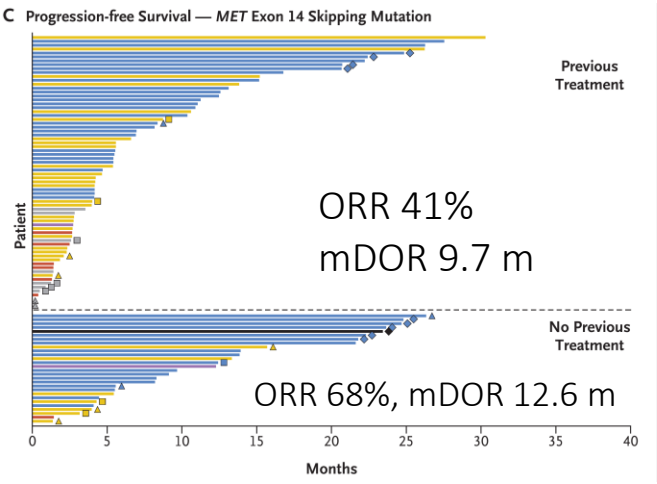
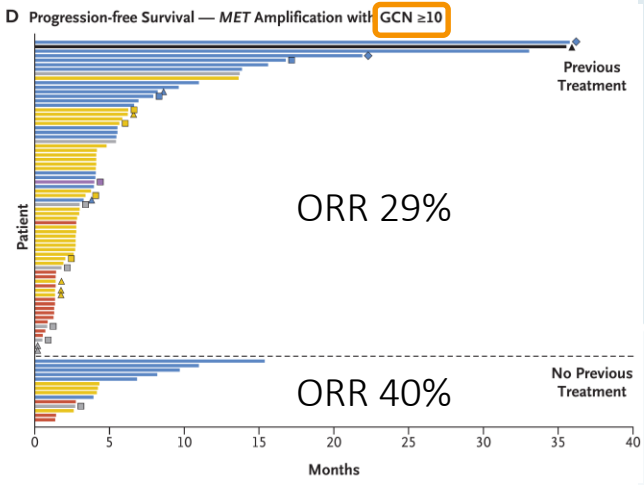
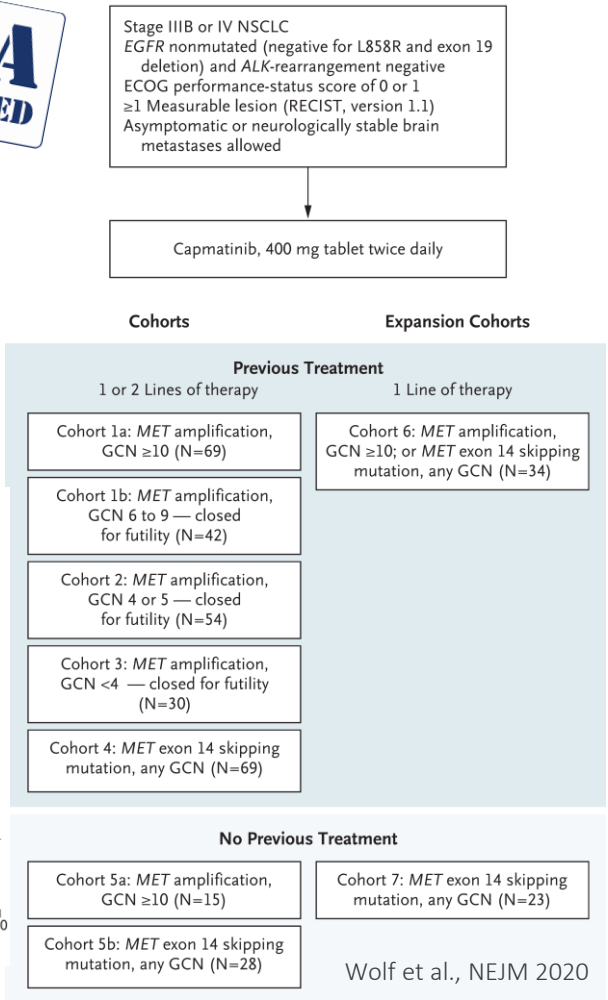
- **GEOMETRY mono-1** study: *MET* exon 14 skipping mutation or *MET* amplification – total n=364
- Capmatinib (INC280): highly potent and selective inhibitor of the MET receptor that crosses the BBB







Wolf et al., NEJM 2020

MET dysregulation

EMA APPROVED

N=6708

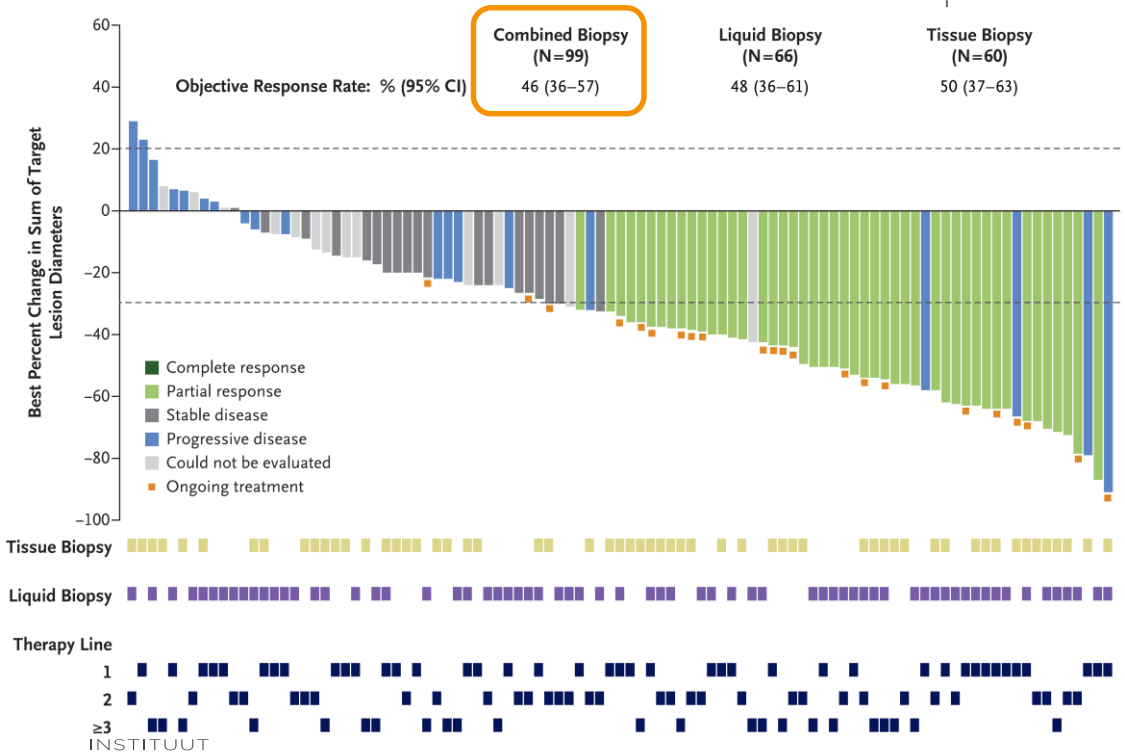
Pre-screening:
MET exon 14 skipping or amplification by liquid or tissue biopsy

Screening:
–28 days to –1 days; confirmation of eligibility criteria, which includes:
- Locally advanced or metastatic NSCLC
- *EGFR*-negative and *ALK*-negative
- ECOG PS 0 or 1
- 0–2 lines of prior therapy

Cohort A: *MET* exon 14 skipping
Tepotinib 500 mg daily (21-day cycles)

Cohort B: *MET* amplification
Tepotinib 500 mg daily (21-day cycles)

Cohort C: *MET* exon 14 skipping (*confirmatory for Cohort A*)
Tepotinib 500 mg daily (21-day cycles)



VISION study (**Tepotinib**):
Cohort A: *MET* exon 14 skipping mutation only, n=152
→ n=99 with ≥9 m of FU

mPFS: 8.5 m (6.7-11.0)

Molecular response (by cfDNA): 67% of patients

Paik et al., NEJM 2020

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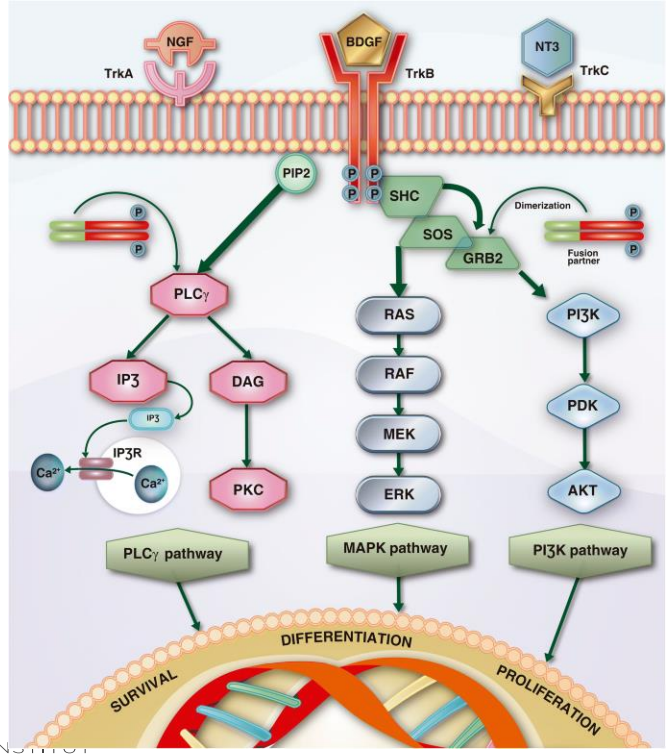
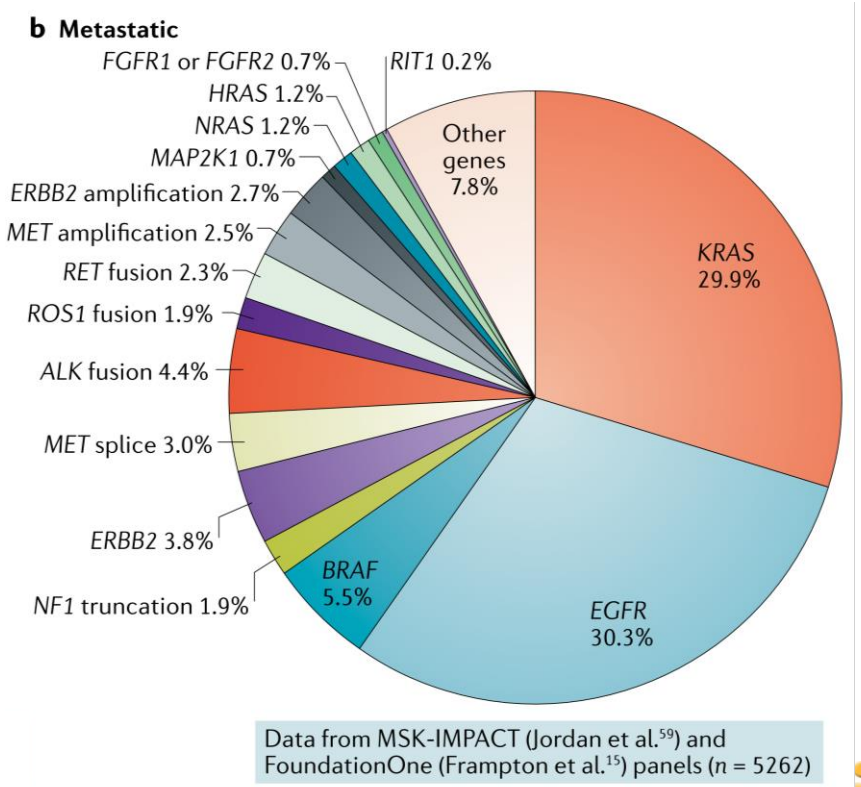
Trial Name (First Author, Year)	Molecular Alteration	Study Type Line of Therapy	Regimen(s)	Evaluable patients, n	Overall response rate[a], % (95 % CI)	Median Duration of Response, months HR (95 % CI), [range]	Median progression free survival, months HR (95 % CI)	Median overall survival, months HR (95 % CI)
NCT02897479 [51]	MET Exon 14 skipping mutation	Phase II Stage IIIB/IV 1st line (40.0%) 2nd line+ (60.0%)	Savolitinib 400 or 600 mg daily	70	49.2 (36.1–62.3)	9.6 (5.5–NYR)	6.9	14.0
GEOMETRY mono-1 [46]	MET exon 14 skipping mutation	Cohort 5b Phase II Stage IIIB/IV 1st line	Capmatinib 400 mg BID	28	68 (48–84)	12.6 (5.6–NE)	12.4 (8.2–NE)	NR
		Cohort 4 Phase II Stage IIIB/IV 2nd/3rd line	Capmatinib 400 mg BID	69	41 (29–53)	9.7 (5.6–13.0)	5.4 (4.2–7.0)	NR
PROFILE 1001 [48]	*MET* exon 14 mutation	Phase I Advanced 1st line (37.7%) 2nd line+ (62.3%)	Crizotinib 250 mg BID	65	32 (21–45)	9.1 (6.4–12.7)	7.3 (5.4–9.1)	NR
AcSé [24]	MET exon 14 or 16−19 mutation	Cohort B Phase II Advanced 2nd line+ (>95%)	Crizotinib 250 mg BID	28	10.7	NR	2.4 (1.6–5.9)	8.1 (4.1–12.7)
NLMT [44]	MET exon 14 skipping mutation	Phase II umbrella Advanced 2nd line	Crizotinib 250 mg BID	12	65 (39–86)[d]	NR	12.5 (6.4–29.7)	NR
VISION [49,50]	MET Exon 14 skipping mutation	Phase II Stage IIIB/IV 1st line (44.5%) 2nd line+ (55.5%)	Tepotinib 500 mg daily	146	45.2 (37.0–53.6)	11.1 (8.4–18.5)	8.9 (8.2–11.0)	17.1 (12.0–26.8)[e]

Melosky et al., Lung Cancer 2021

NTRK 1-3 fusions (<1%)



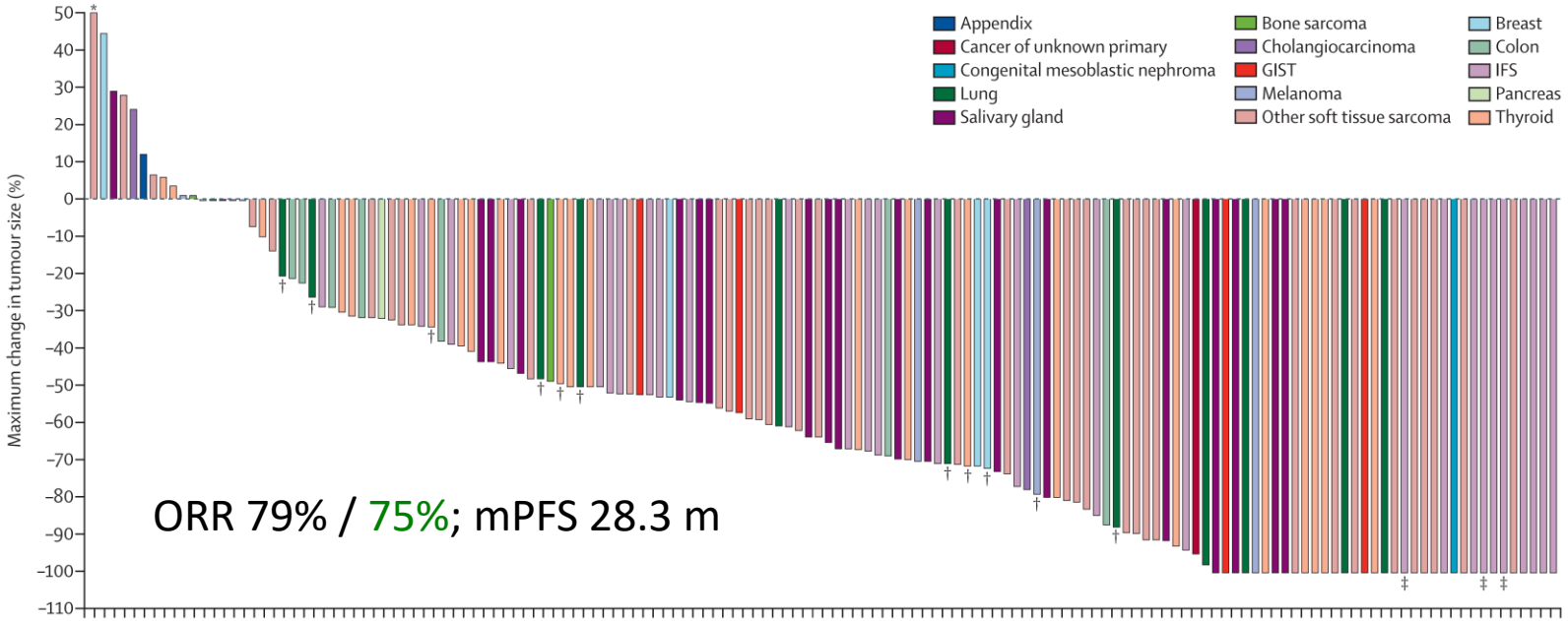


Skoulidis et al., Nat Rev Cancer. 2019

NTRK1-3 fusions (<1%)

EMA APPROVED

- **Larotrectinib**: highly selective and potent TRK inhibitor
- Patients with locally advanced or metastatic solid tumor, with previous standard therapy, with a TRK (*NTRK1-3*) fusion (by NSG, FISH or RT-PCR) → n=159 → n=12 with lung cancer



ORR 79% / 75%; mPFS 28.3 m

Hong et al., Lancet Oncol 2020

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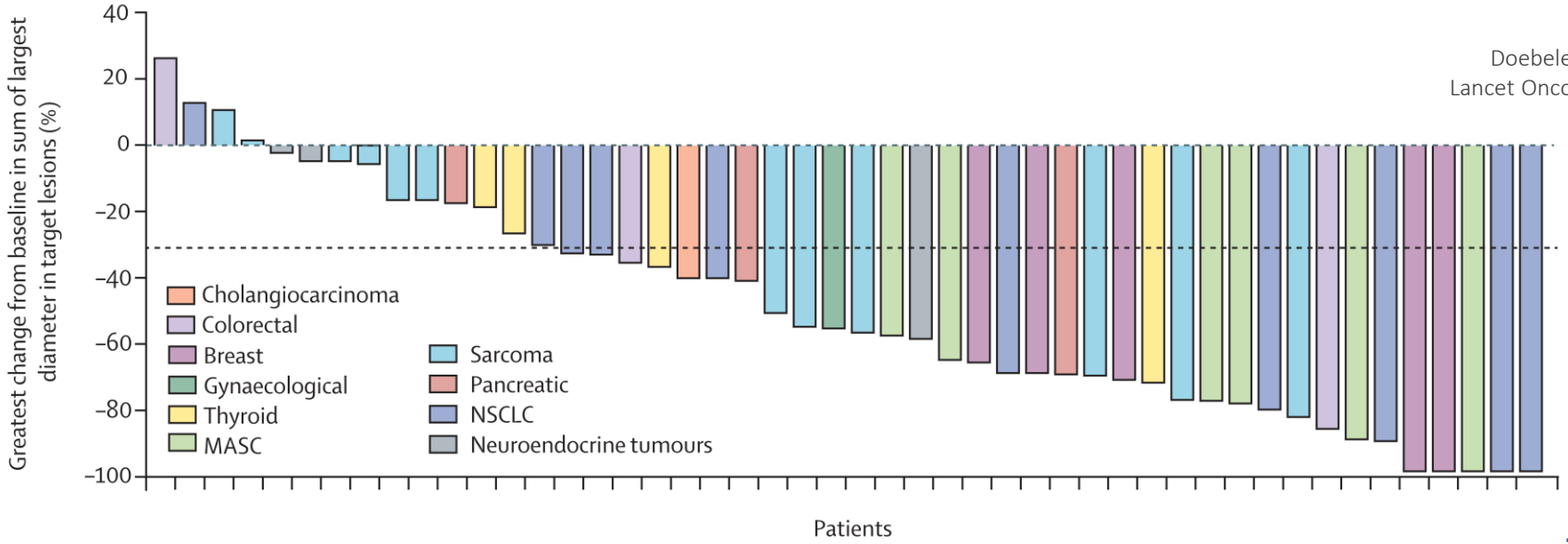
NTRK1-3 fusions (<1%)

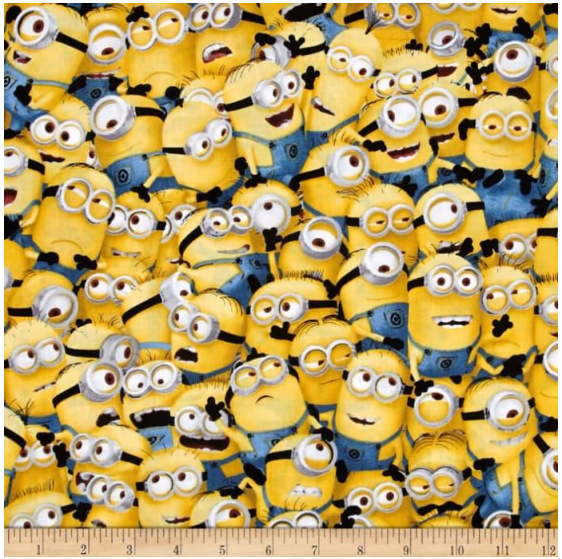
EMA APPROVED

- **Entrectinib**: potent inhibitor of TRK A, B, and C
- Pooled analysis of the ALKA-372-001, STARTRK-1, and STARTRK-2 trials
- 54 pts, n=10 (19%) with NSCLC – overall: 57% ORR



Doebele et al.,
Lancet Oncol 2020

A *new kid* in the block



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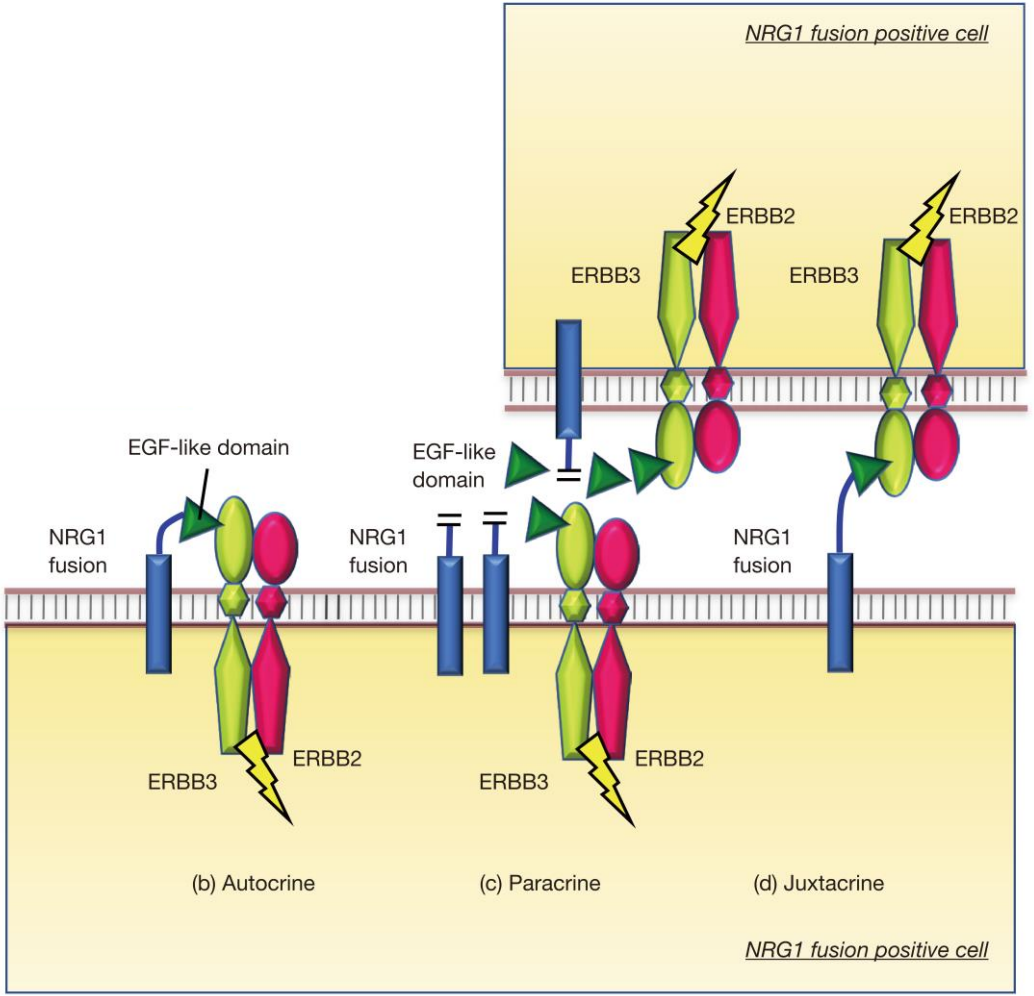
NRG1 fusions

- NRG1 is a ligand for ERBB3 and ERBB4 receptor tyrosine kinases → binding of the EGF-like domain of the NRG1 fusion to ERBB3 in an autocrine, paracrine, or juxtacrine fashion → activation of ERBB2/ERBB3 complex → downstream signaling

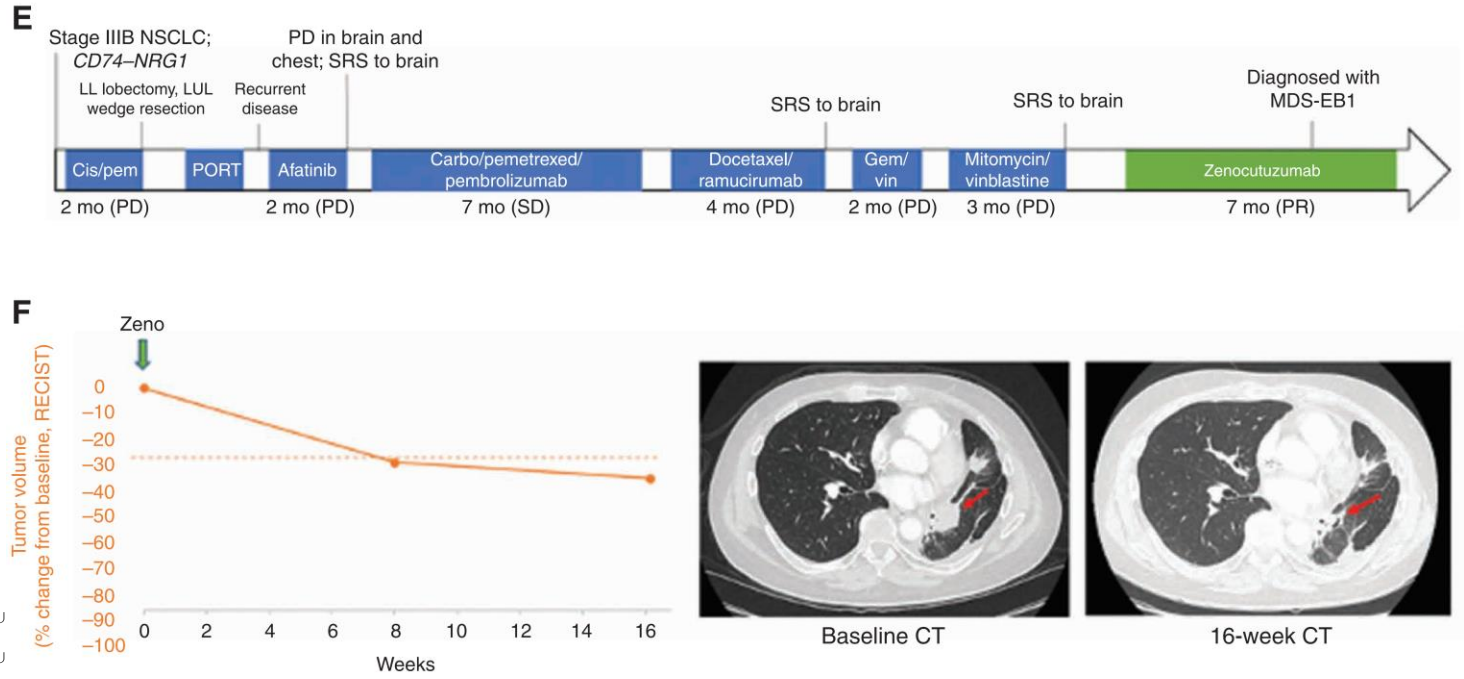


Suda et al., Transl Lung Cancer Res 2020

NRG1 fusions

Schram et al.,
Cancer Discov 2022

- **Zenocutuzumab**: a HER2xHER3 Bispecific Antibody
- Effective in cell lines → treatment of 4 pts with NRG1+ tumors (one with NSCLC)



Conclusions

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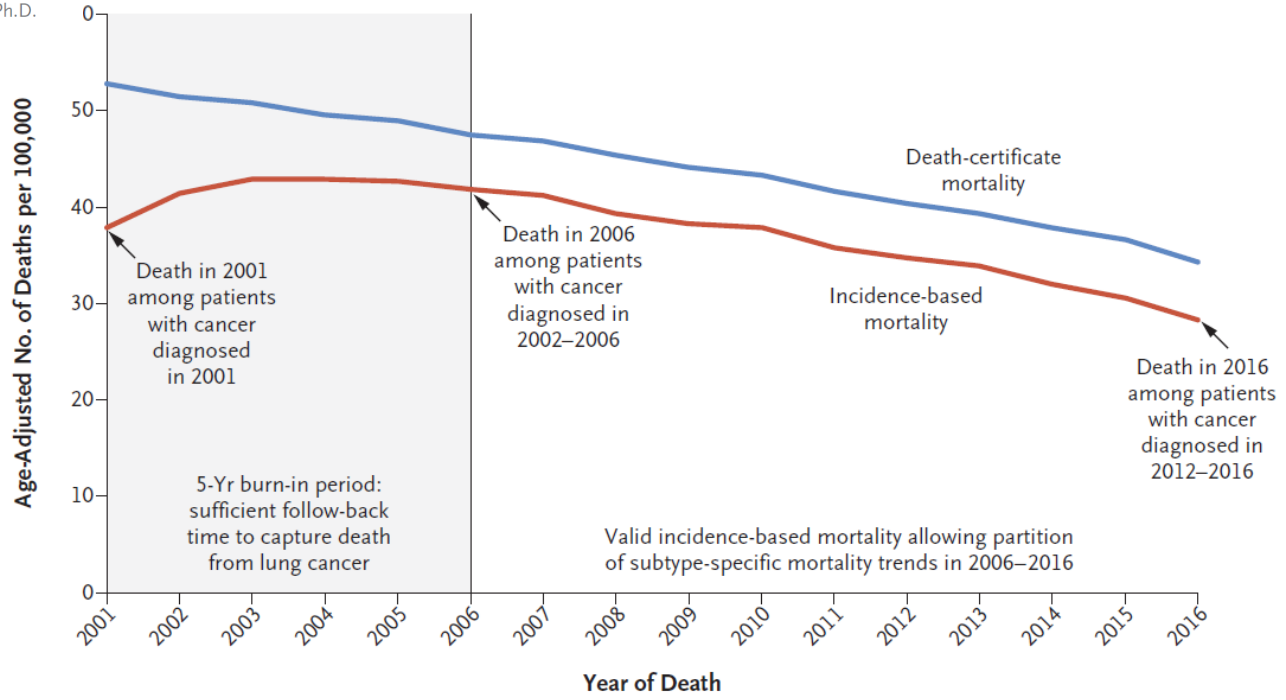
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Conclusions

The Effect of Advances in Lung-Cancer Treatment on Population Mortality

Nadia Howlader, Ph.D., Gonçalo Forjaz, D.V.M., Meghan J. Mooradian, M.D., Rafael Meza, Ph.D., Chung Yin Kong, Ph.D., Kathleen A. Cronin, Ph.D., Angela B. Mariotto, Ph.D., Douglas R. Lowy, M.D., and Eric J. Feuer, Ph.D.



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Gene	Alteration	EMA approved (in bold: reimbursed in BE; in italic: MNP in BE; 01/12/2022)	EMA pending (promising!)
EGFR	Exon 19-21 mutations	**Osimertinib, Gefinitb, Erlotinib, Afatinib**	
	Exon 20 insertions	*Amivantamab*	Mobocertinib*, Poziotinib
	Exon 20: T790M	**Osimertinib**	
ALK	Fusion	**Crizotinib, Alectinib, Brigatinib, Lorlatinib**	
ROS1	Fusion	**Crizotinib, Entrectinib**	
BRAF	V600 mutations	**Dabrafenib + Trametinib**	
NTRK 1-3	Fusion	**Larotrectinib, Entrectinib**	
RET	Fusion	**Selpercatinib**, Praseltinib	
HER2	Mutations		Trastuzumab-deruxtecan, Poziotinib
KRAS	G12C mutation	*Sotorasib*	Adagrasib
MET	Exon 14 skipping mutations	Capmatinib, Tepotinib	

Conclusions (1)

- There's an *explosion* of treatment approaches in oncogene driver NSCLC
- It is paramount to assess the *molecular characteristics* of the (advanced) tumor *before any systemic treatment*

- How to improve *patient selection*?
  - Minimal residual disease?
  - Tumor mutational burden?
- How to *decide* between the different treatment options?
  - Overall survival & QoL are needed!
  - Real-world data?
- *Incremental + Financial* toxicity?

Conclusions (2)

- If possible: **rebiopsy** for NGS at progression under targeted therapy
- Centralize cases, *refer for further treatment* before proposing chemo → *clinical trials*!!

- Medical Need Programs can provide *early access* to treatments (e.g. Sotorasib)

Thank you !

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