OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

UNIVERSITÀ DEGLI STUDI
DI GENOVA

NUOVI TARGET EMERGENTI

Carlo Genova

U.O.C. Clinica di Oncologia Medica

Dipartimento di Medicina Interna e Specialità Mediche (Di.M.I.)

IRCCS Ospedale Policlinico San Martino

Università degli Studi di Genova

Carlo.genova@hsanmartino.it

DISCLOSURES

Honoraria:

- Amgen, Astra Zeneca, Boehringer Ingelheim, Bristol-Myers-Squibb, Eli Lilly, Merck-Sharp-Dohme, Sanofi, ThermoFisher, Roche

Advisory boards:

- Astra Zeneca, Bristol-Myers-Squibb, Merck-Sharp-Dohme, Roche, Takeda, Sanofi

Research grants:

- Bristol-Myers-Squibb; Ministero della Salute

EGFR

ALK

ROS1

BRAF

RET

K-RAS

MET

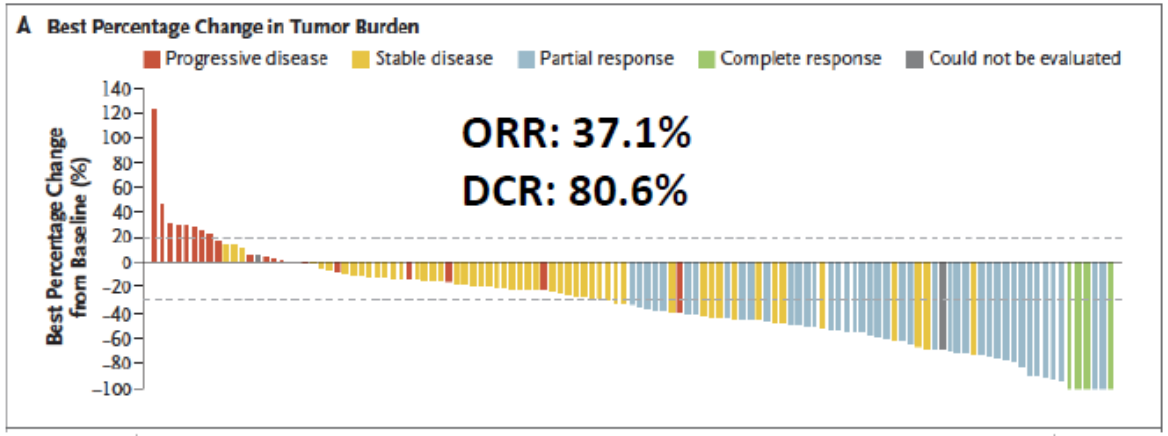
NTRK

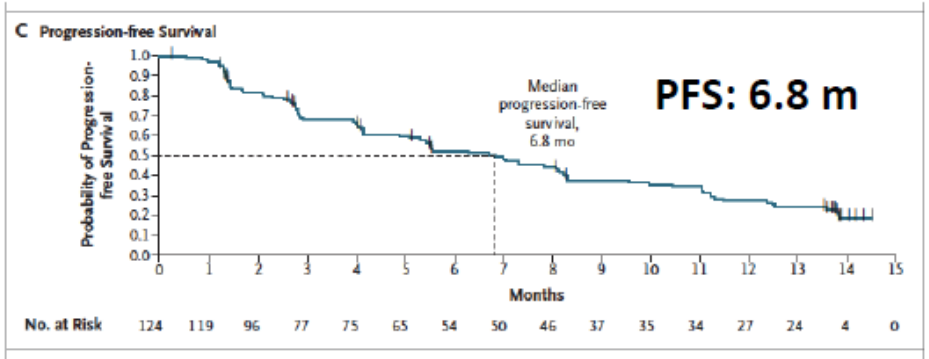
HER2

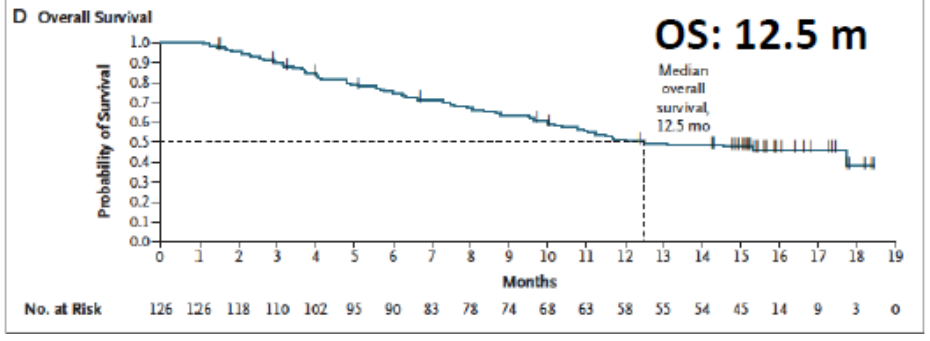
K-RAS IN NSCLC
An ongoing redemption arc

K-RAS PHASE I-II TRIALS

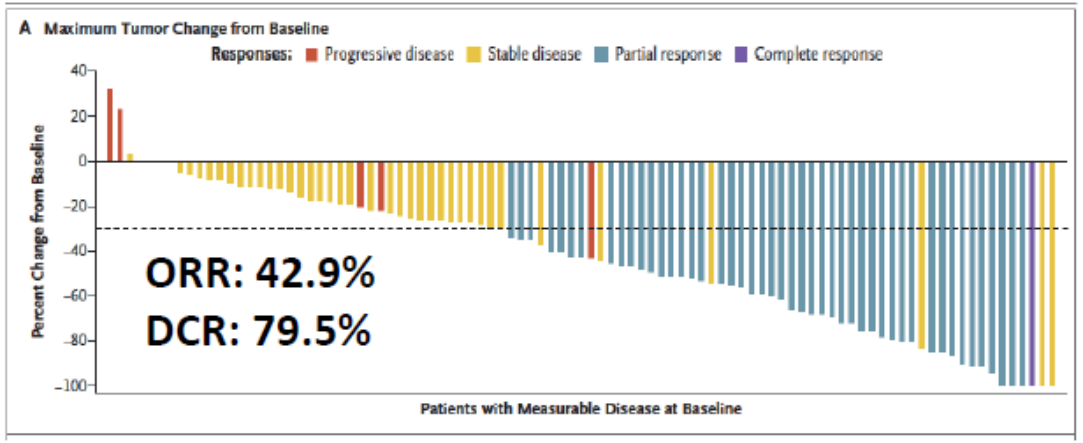
Sotorasib (CodeBreak-100)

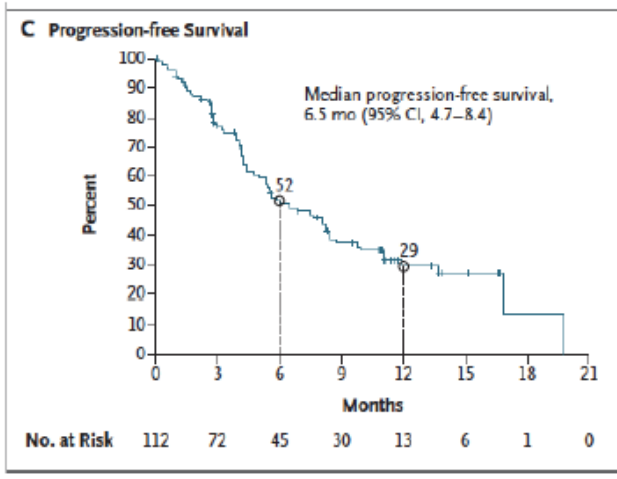




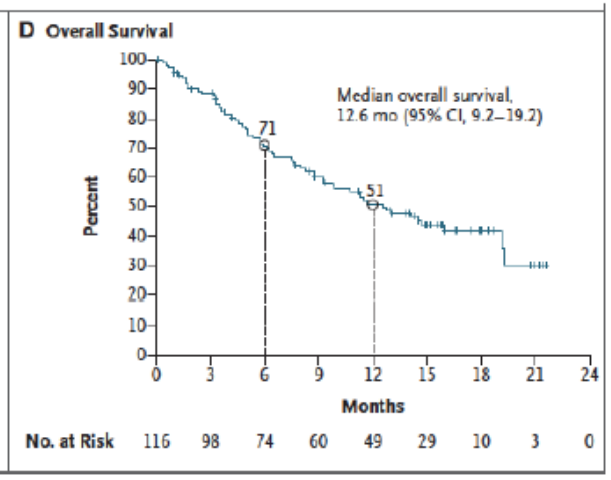


Adagrasib (KRYSTAL-1)





PFS: 6.5 m

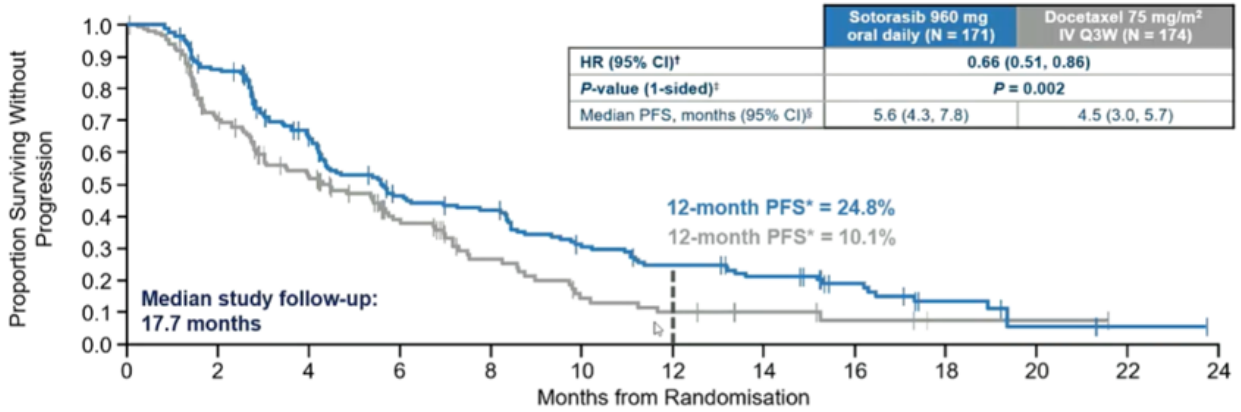


OS: 12.6 m

Skoulidis, NEJM 2021; Janne, NEJM 2022

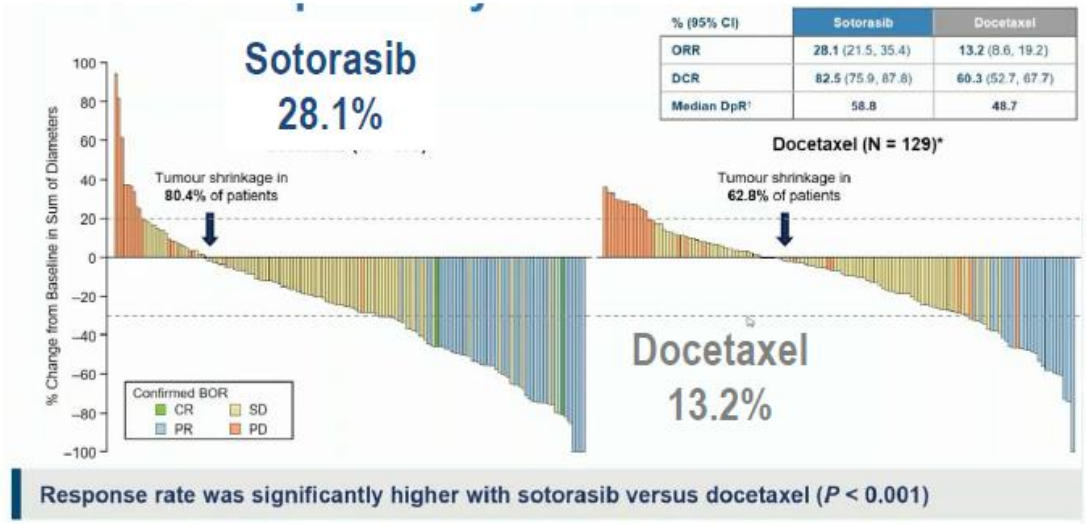
K-RAS – CODEBREAK 200

Primary Endpoint: PFS by BICR



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

PFS: 5.6 vs. 4.5 months; HR: 0.66; p= 0.002



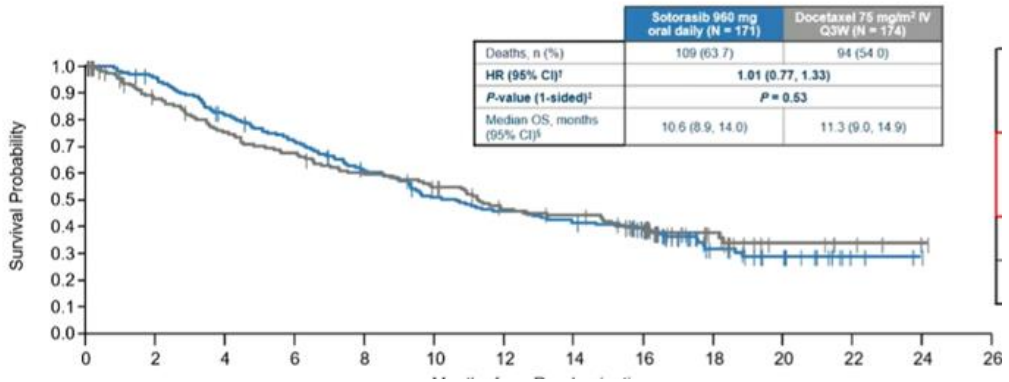
% (95% CI)	Sotorasib	Docetaxel
ORR	28.1 (21.5, 35.4)	13.2 (8.6, 19.2)
DCR	82.5 (75.9, 87.8)	60.3 (52.7, 67.7)
Median DpR†	58.8	48.7

Docetaxel (N = 129)*

Response rate was significantly higher with sotorasib versus docetaxel (*P* < 0.001)

OS: Sotorasib vs Docetaxel*

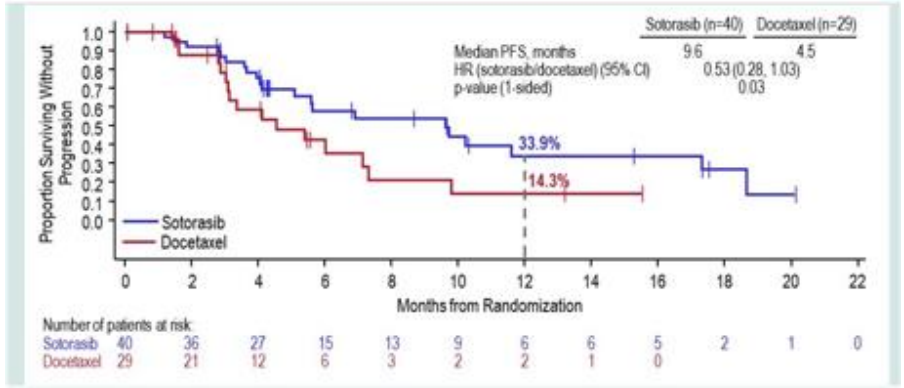
CROSS-OVER: 34%



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

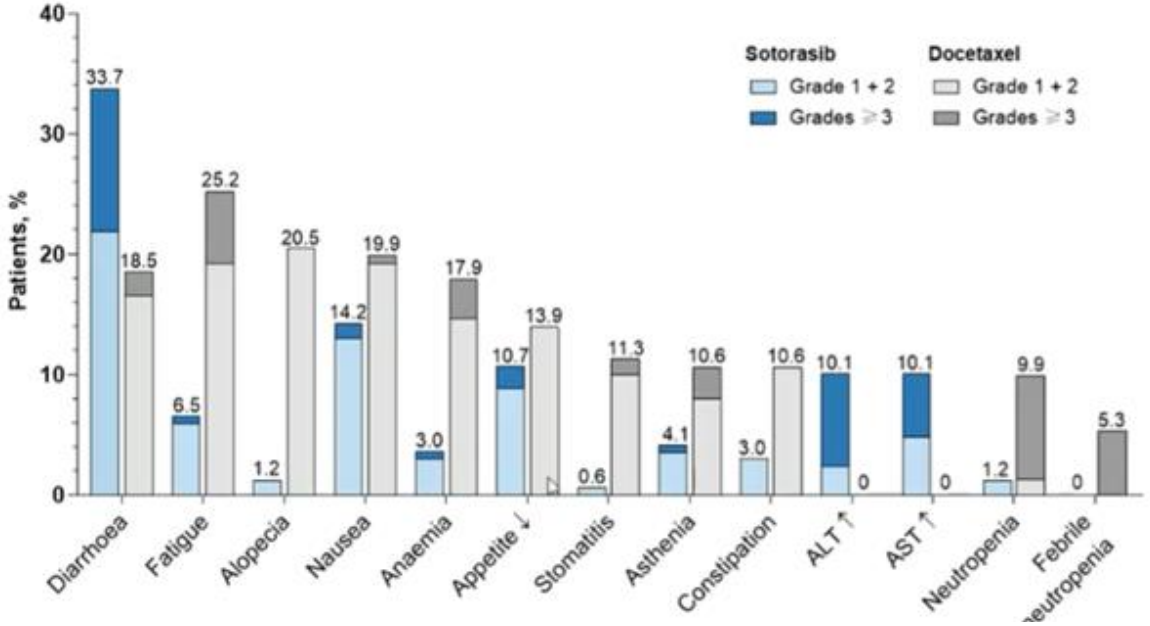
OS: 10.6 vs. 11.3 months; HR: 1.01; p= 0.53

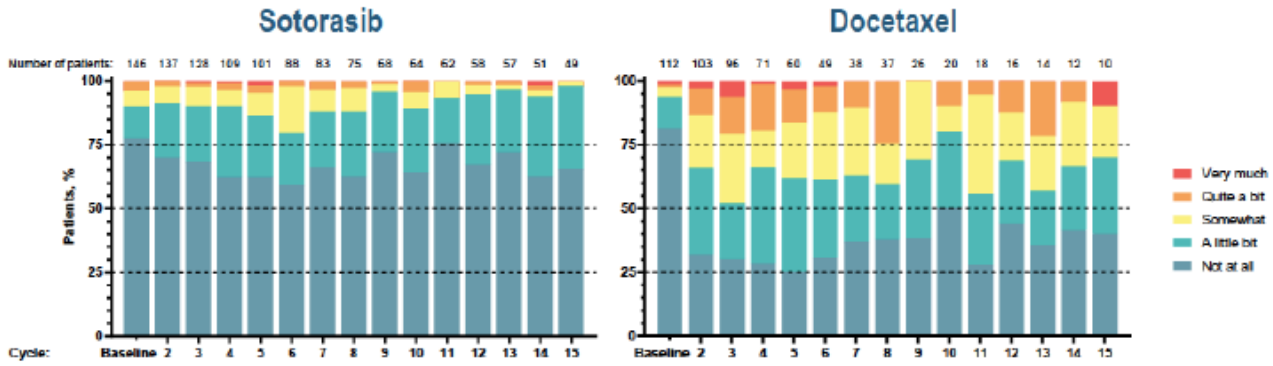
CNS Progression-Free Survival in Patients with CNS Lesions at Baseline



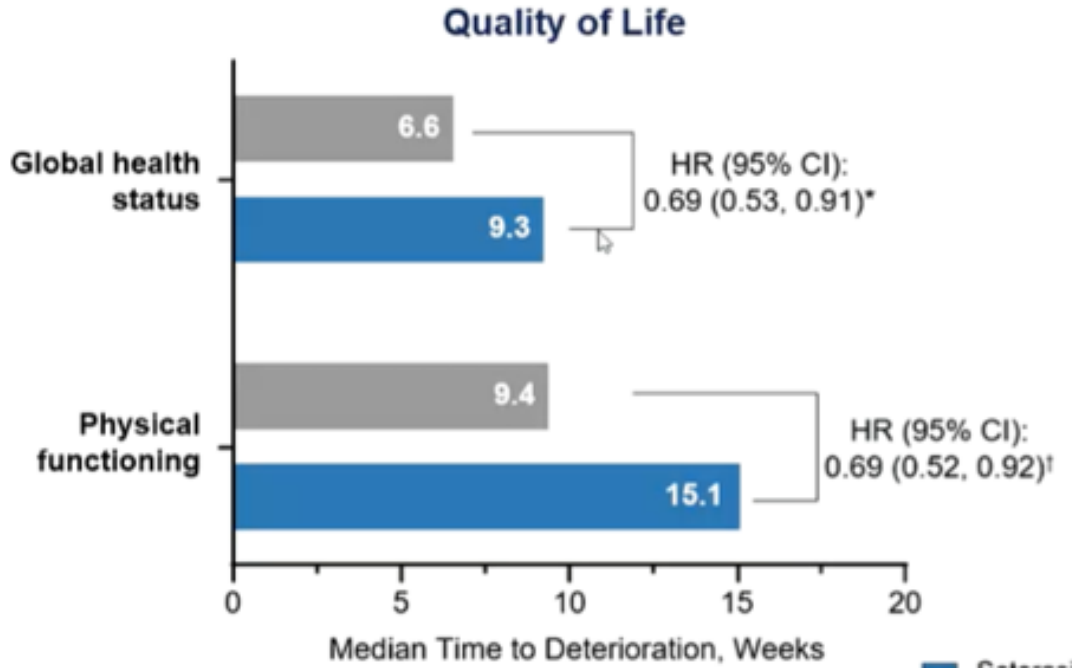
Median time to CNS progression or all-cause death was longer in patients treated with sotorasib compared with docetaxel (9.6 months vs 4.5 months; HR 0.53 [95% CI: 0.28, 1.03]; p=0.03)

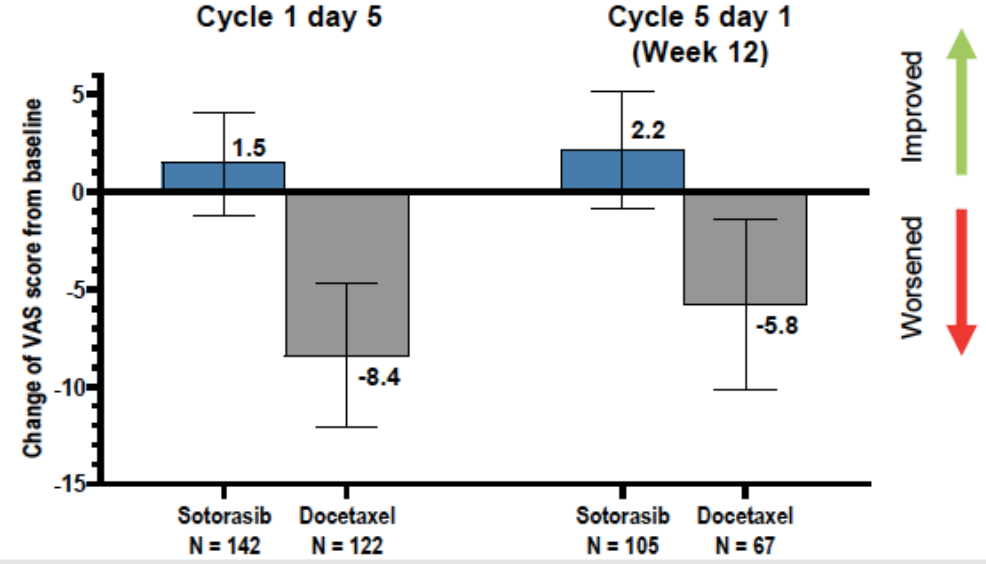
CODEBREAK 200 QoL





Patients in the sotorasib group were less severely bothered by side effects than those in the docetaxel group

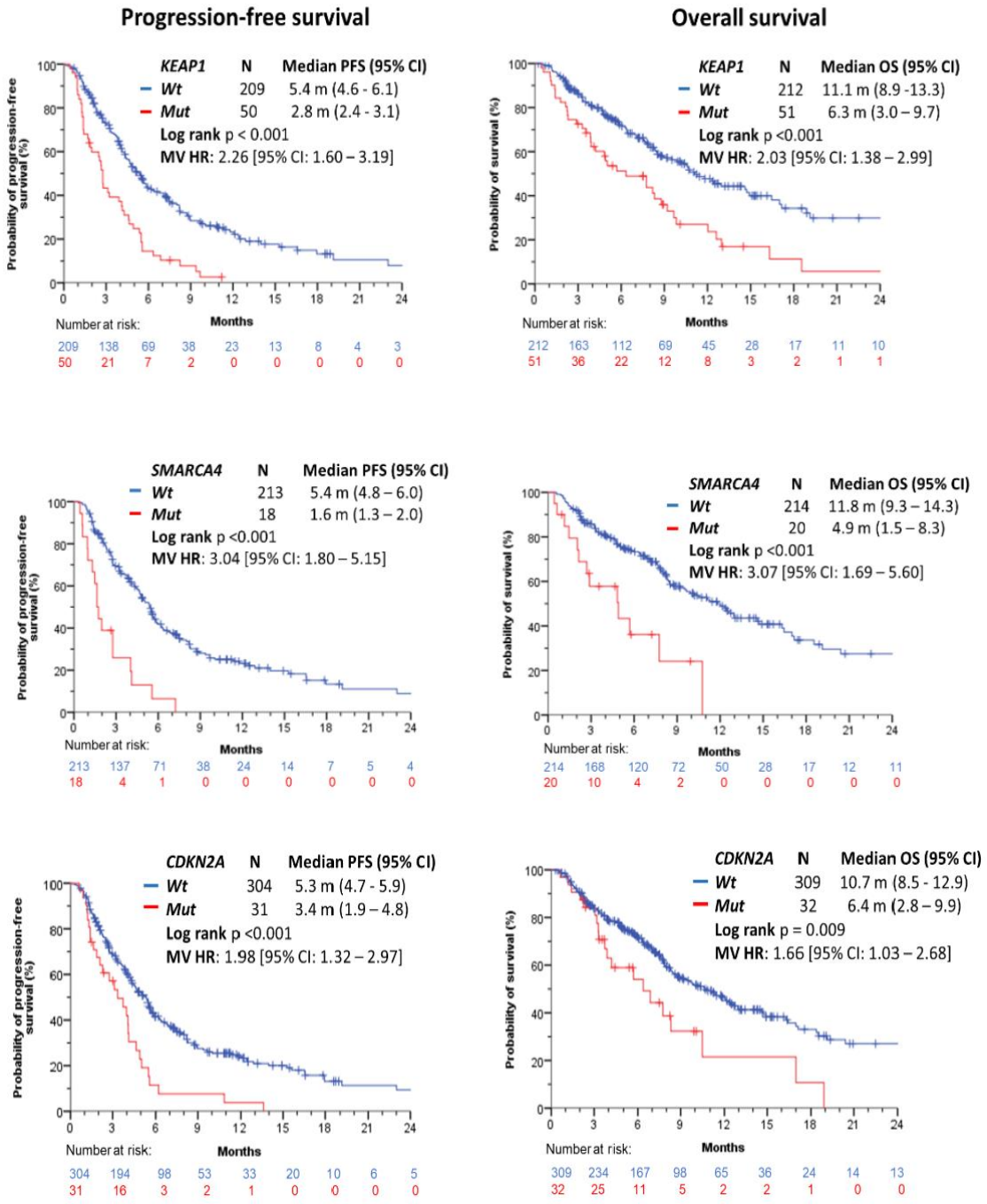




QOL worsened with docetaxel, while remaining stable with sotorasib

Johnson M, ESMO 2022; Waterhouse, ELCC 2023

CO-ALTERATIONS ASSOCIATED WITH WORSE OUTCOMES IN K-RASm NSCLC (SOTORASIB – ADAGRASIB)



KEAP-1 (25%)

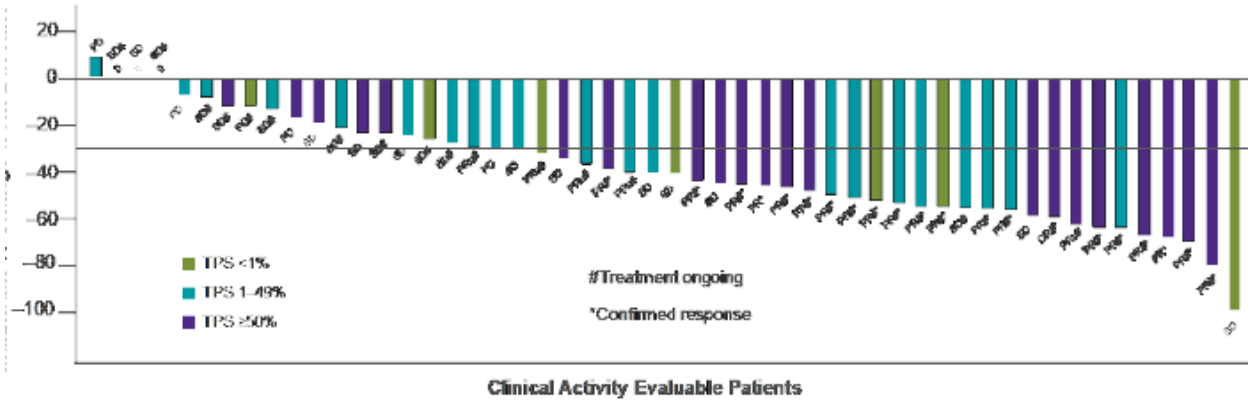
SMARCA-4 (10%)

CDKN2A (10%)

Negrao MV et al., *Cancer Discov*, 2023

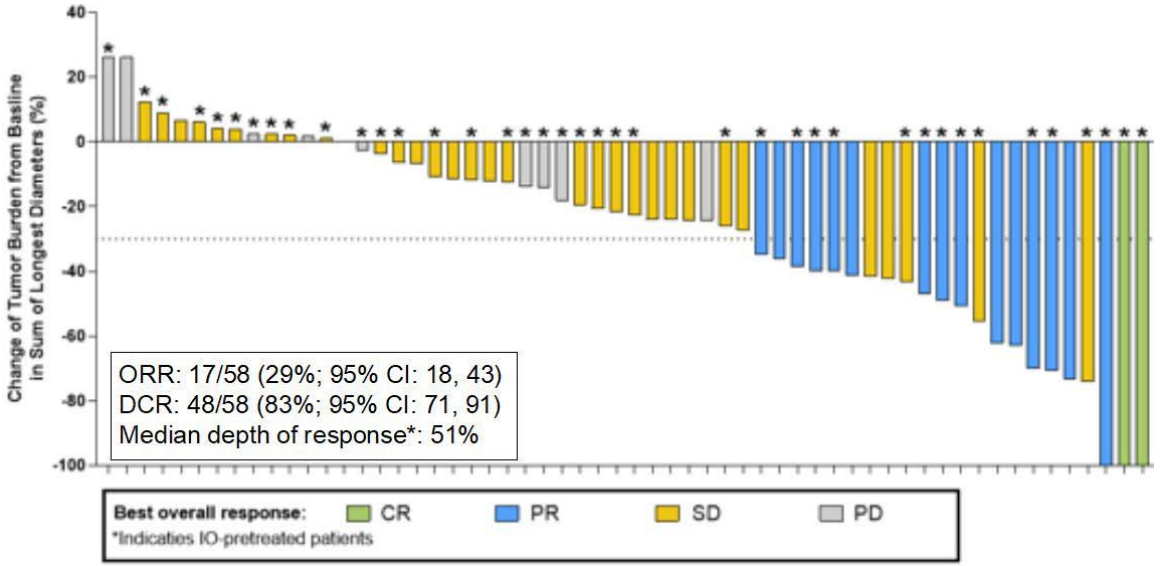
K-RAS + IMMUNE CHECKPOINT INHIBITORS

KRYSTAL 07
ADAGRASIB + PEMBRO



ORR: 49% DCR: 89%

CODEBREAK 101
SOTORASIB + PEMBRO/ATEZO



ORR: 29% DCR: 83%

Janne, ESMO-IO 2022

Falchook, WCLC 2022

K-RAS + CHEMOTHERAPY

Phase 1b CodeBreaK 101 Study

Key eligibility criteria
- *KRAS* G12C–mutated advanced NSCLC, identified through molecular testing
- Measurable disease per RECIST v1.1
- ECOG ≤ 2
- No active brain metastases

→

Induction phase

Sotorasib: 960 mg oral daily
+
Carboplatin: AUC 5 IV Q3W*
+
Pemetrexed: 500 mg/m² IV Q3W

→

Maintenance phase†

Sotorasib: 960 mg oral daily
+
Pemetrexed: 500 mg/m² IV Q3W

→

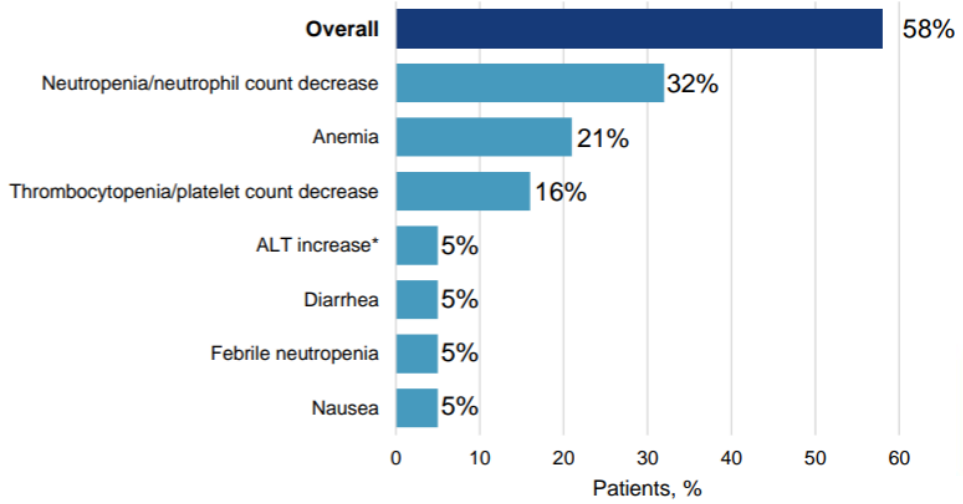
Data were pooled and analyzed by exposure to prior therapy in the locally advanced/metastatic setting‡

First-line (n = 25)

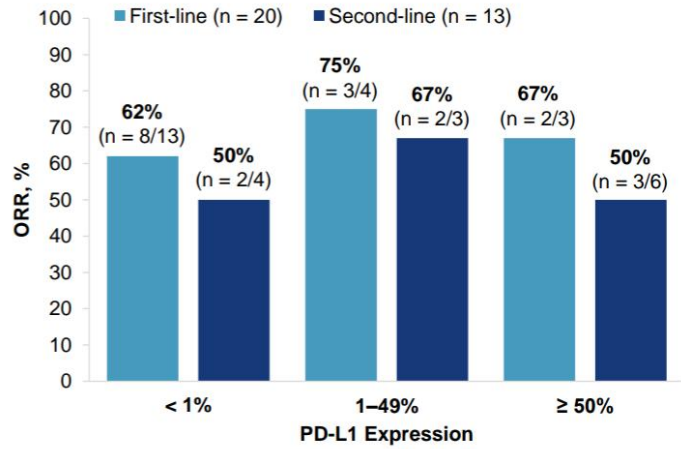
Second-line (n = 13)

Primary Endpoints: Safety and tolerability (including DLT)
Secondary Endpoints: Anti-tumor efficacy (ORR, DCR, DOR, TTR, OS, PFS, duration of SD) and PK

Grade 3–4 TRAEs occurring in ≥ 5% of all patients



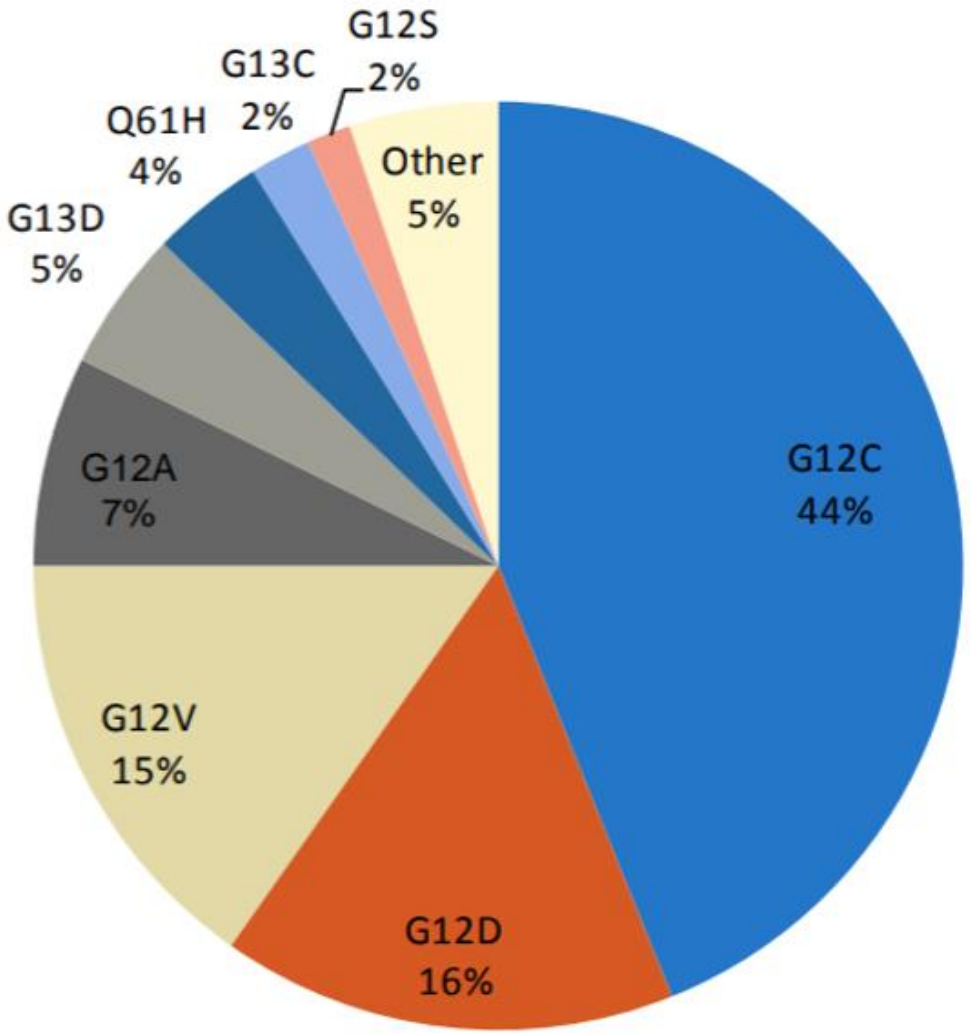
Response by Investigator Assessments*	Sotorasib + Carboplatin + Pemetrexed	
	First-line (n = 20)	Second-line (n = 13)
ORR, n (%)	13 (65)†	7 (54)
Best overall response, n (%)		
Complete response	0	1 (8)
Partial response	13 (65)	6 (46)
Stable disease	7 (35)	4 (31)
Progressive disease	0	1 (8)
Not evaluable / not done	0	1 (8)
DCR (95% CI)	20 (100) (83.2, 100)	11 (85) (54.6, 98.1)

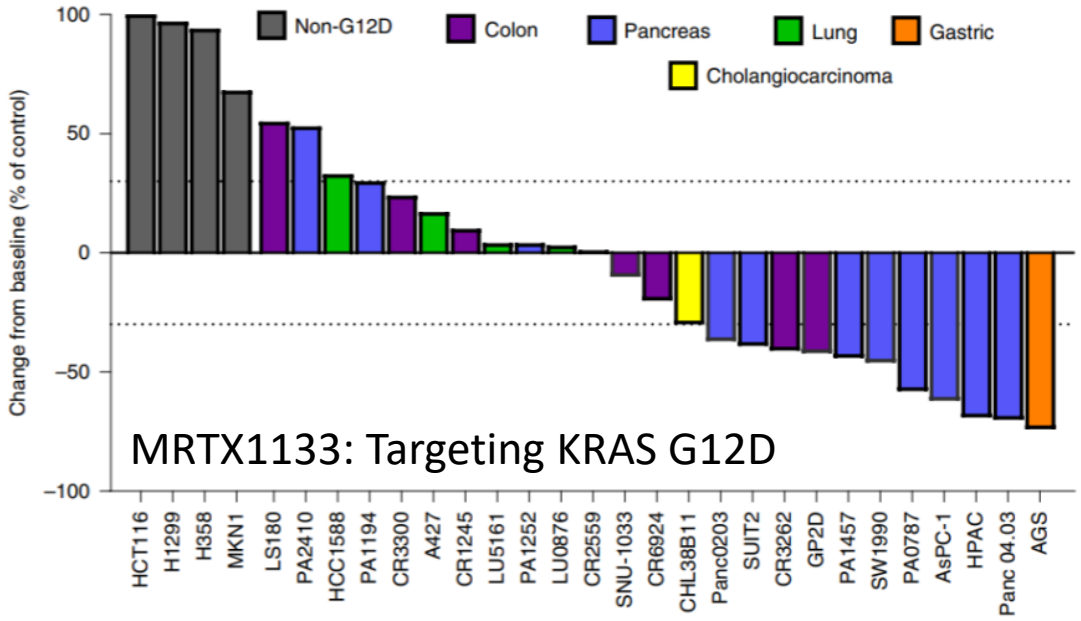


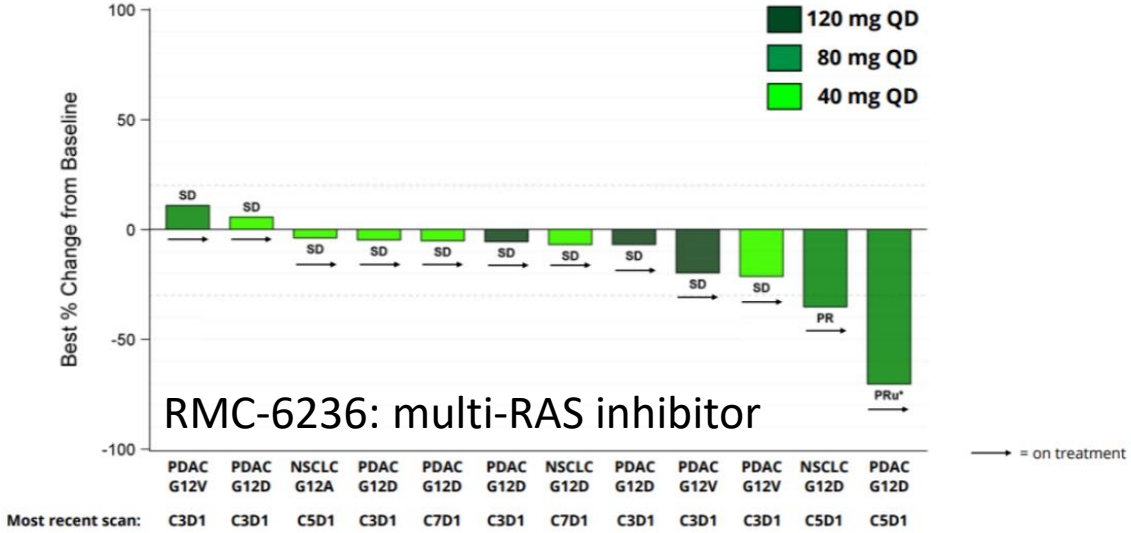
- **ORR was 65% in the first-line setting and 54% in the second-line setting**
- **ORR was similar across PD-L1 expression levels**

Clarke JM; WCLC 2023

K-RAS NON-G12C

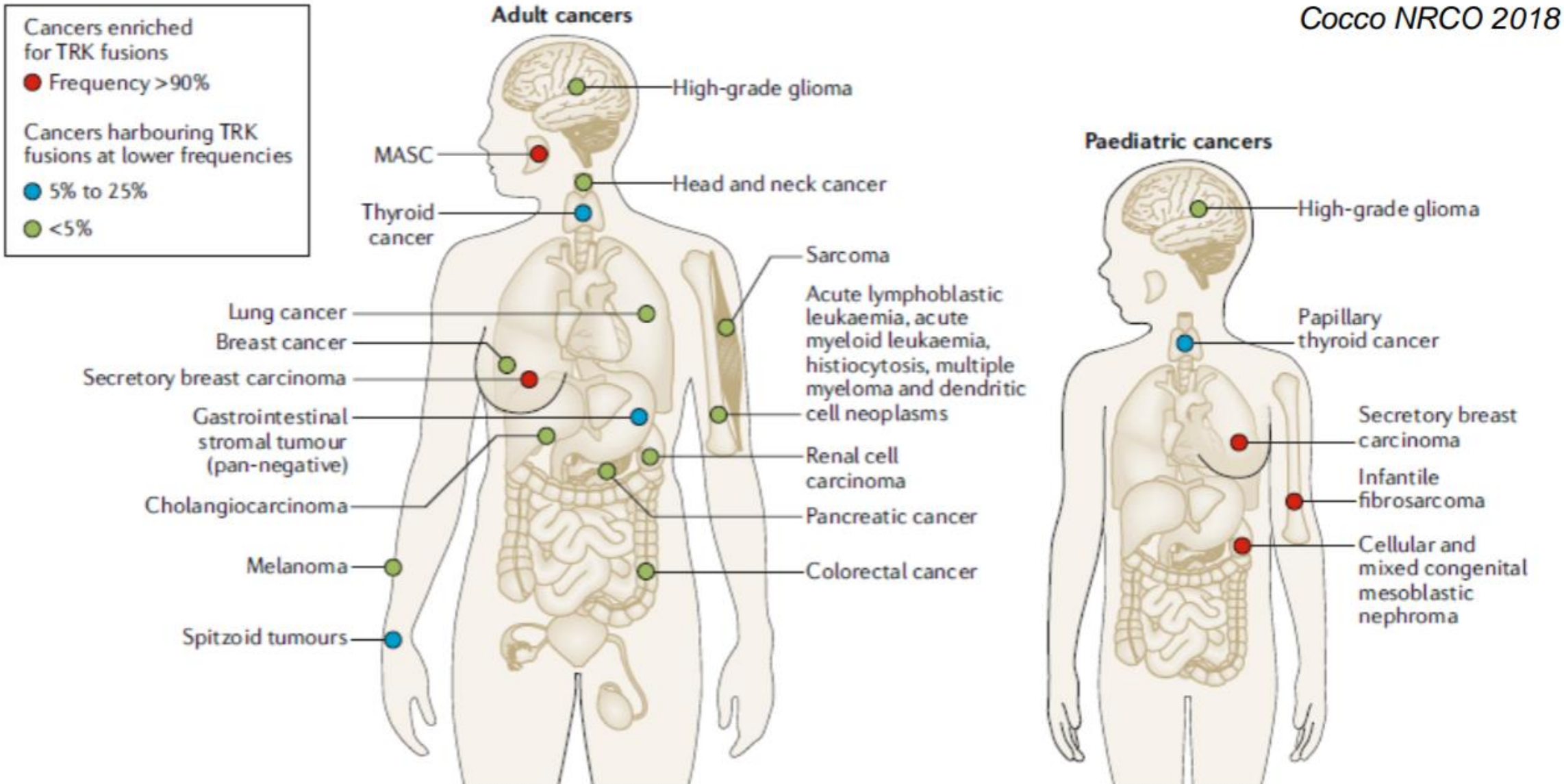






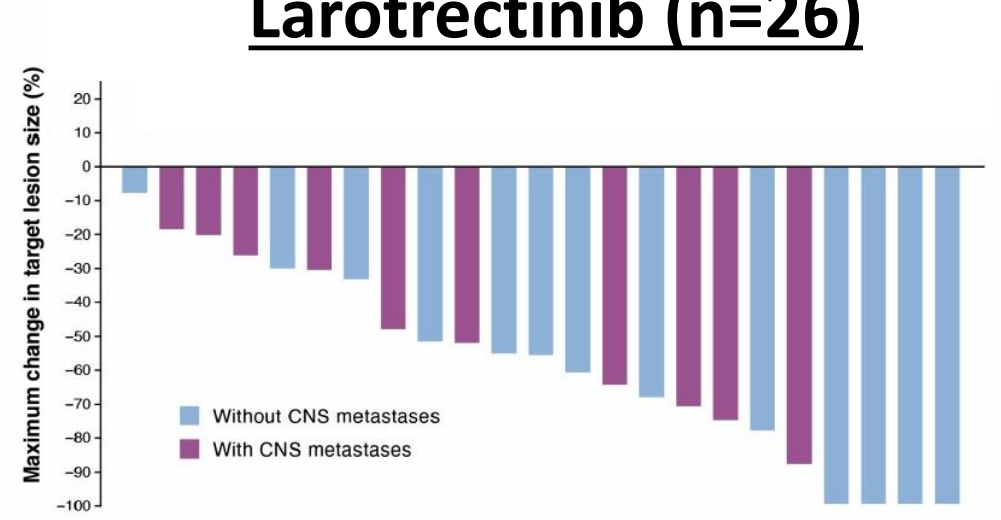
Jordan et al. Cancer Discovery. 2017; Arbour et al. CCR. 2018; Hallin et al. Nature. 2021; Arbour K; WCLC 2023

NTRK FUSIONS



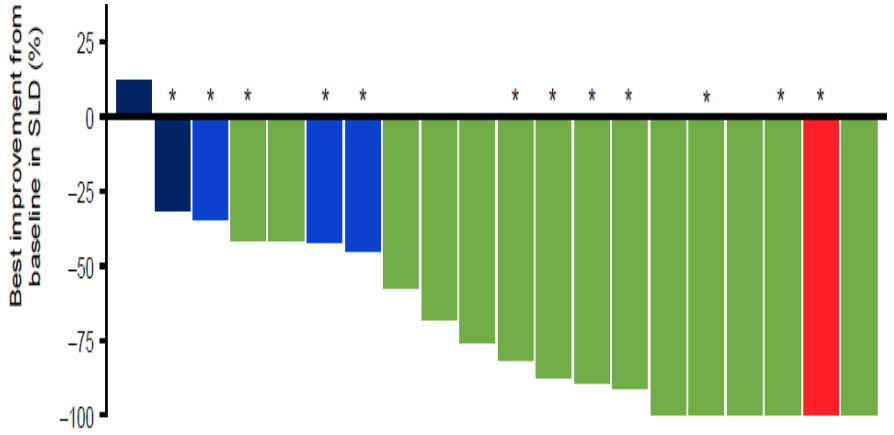
NTRK+ NSCLC

Larotrectinib (n=26)



ORR, % (95%, CI)	**83% (61-95)**
Median PFS, mo (95% CI)	**NR** (9.9–NR)
Median DoR, mo (95% CI)	**NR** (9.5–NR)
Median OS, mo (95% CI)	**40.7** (19.4-NE)

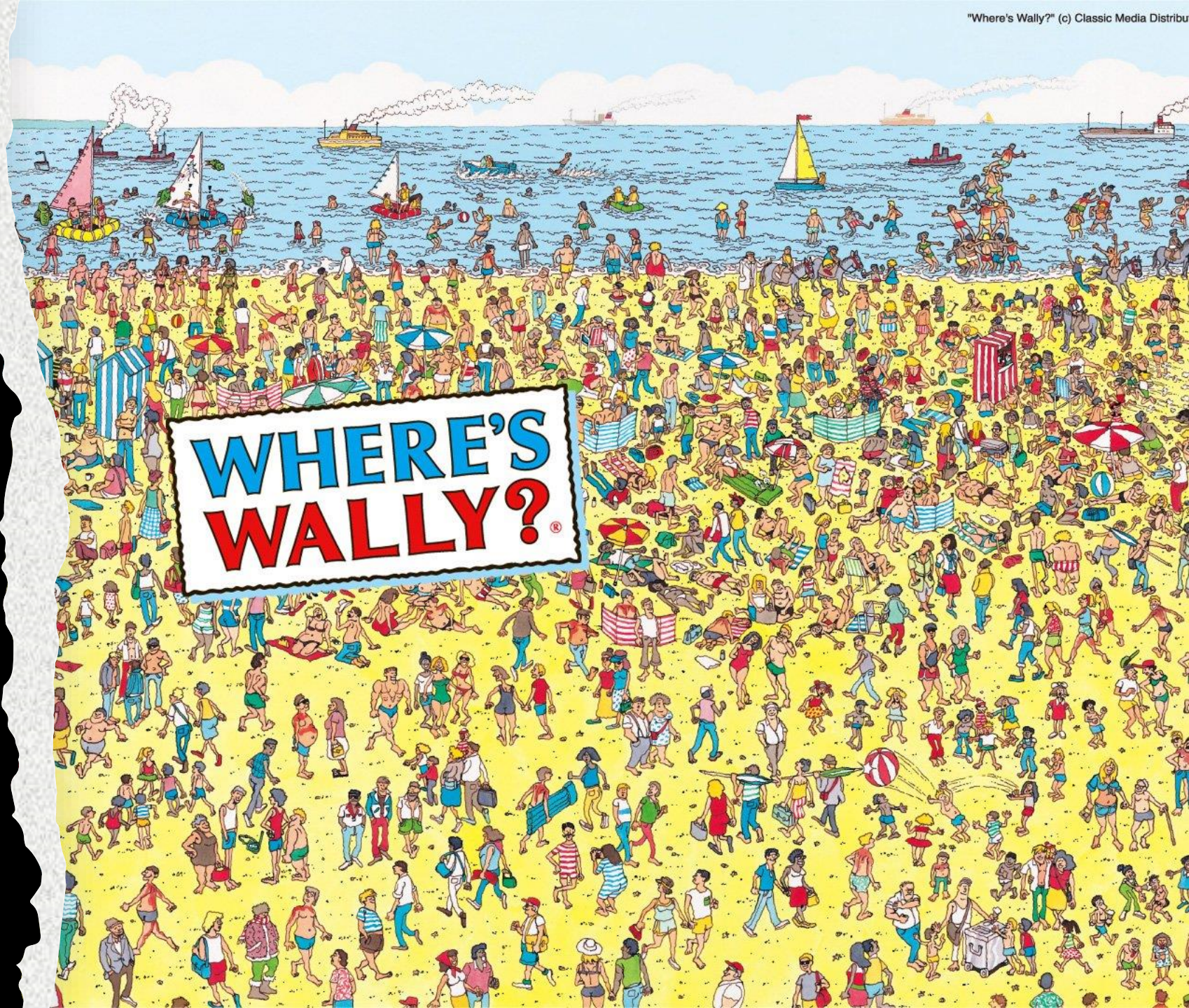
Entrectinib (n=22)



ORR, % (95%, CI)	**63.6% (40.7-82.8)**
Median PFS, mo (95% CI)	**14.9** (6.5–30.4)
Median DoR, mo (95% CI)	**19.9** (10.4-29.4)
Median OS, mo (95% CI)	**NE** (20.8-NE)

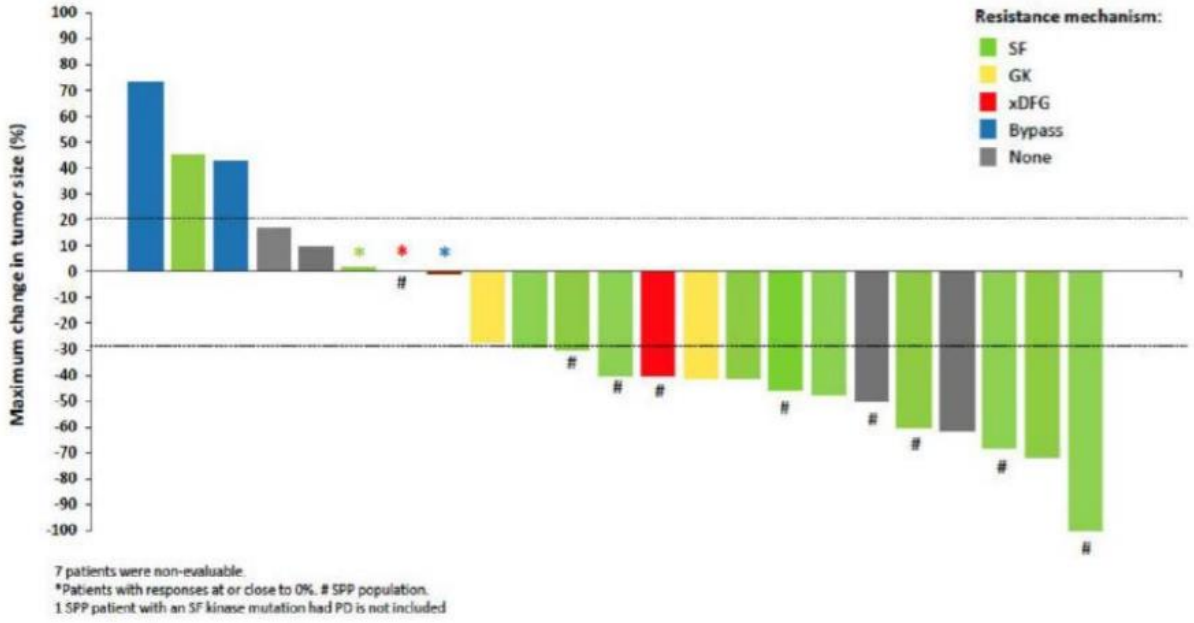
Drilon ASCO 2022, Cho ELCC 2022

NTRK FUSIONS ACCOUNT FOR 0.1-0.3% OF NSCLC !

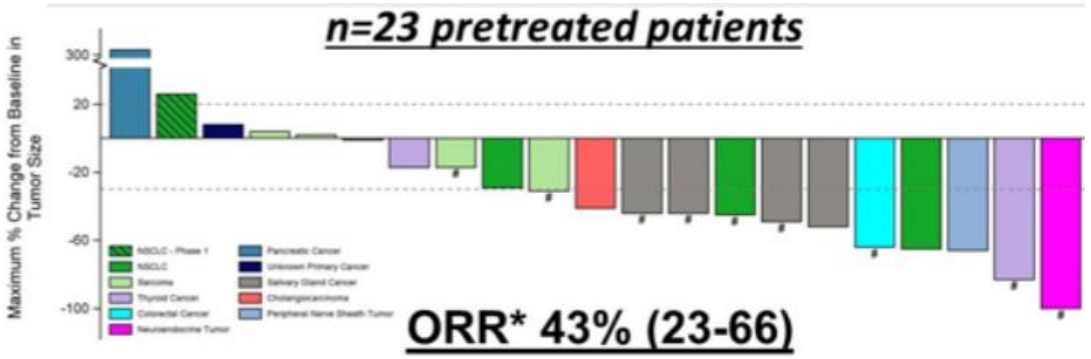


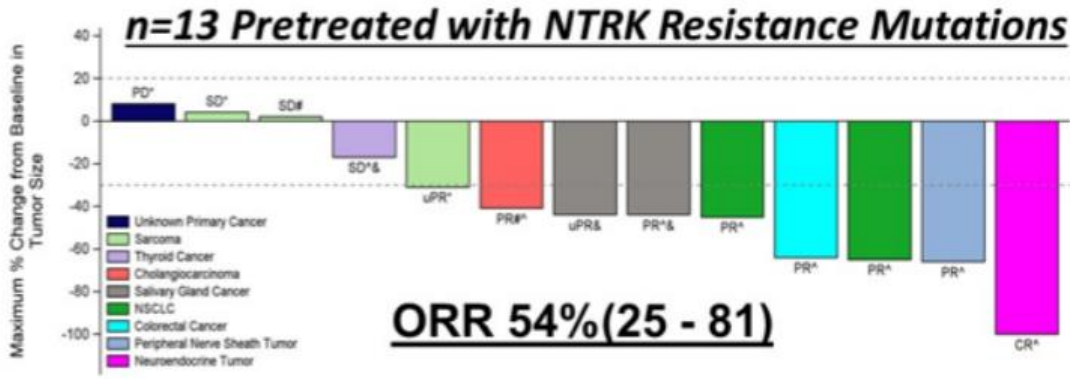
SECOND-GENERATION NTRK TKIs

SELITRECTINIB (n=20 all histology pretreated with TRK TKIs)
ORR = 45%
No activity in off target resistance



REPOTRECTINIB – TRIDENT1
(n=23 all hystology pretreated with TRK TKIs)
ORR = 43%

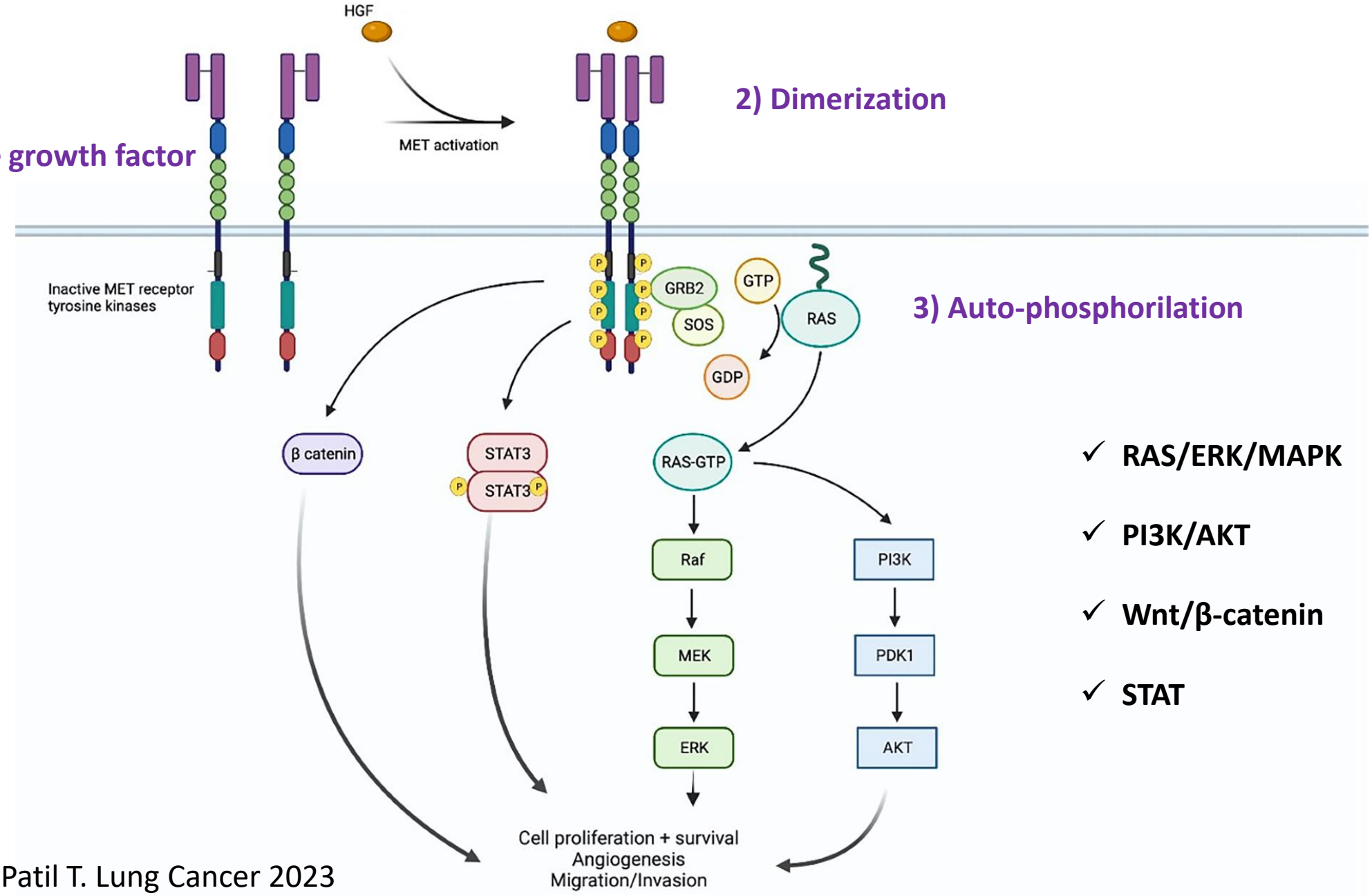




Hyman AACR 2019,Besse AACR EORTC NIH 2021

MET

1) Hepatocyte growth factor



2) Dimerization

3) Auto-phosphorilation

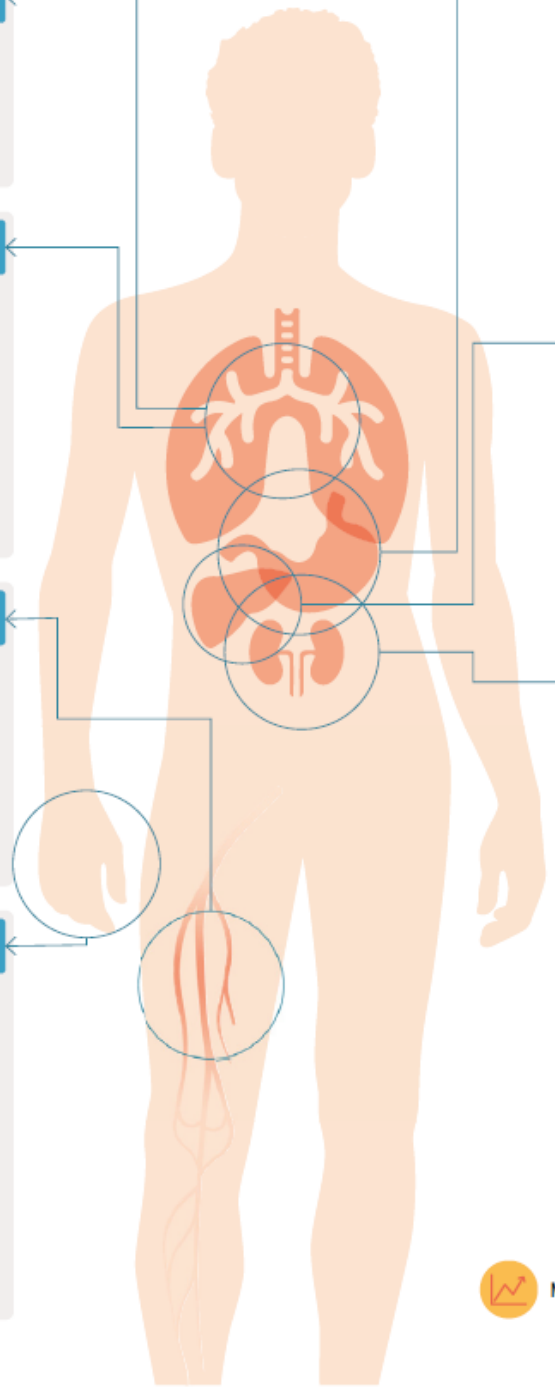
- ✓ RAS/ERK/MAPK
- ✓ PI3K/AKT
- ✓ Wnt/β-catenin
- ✓ STAT

Sakamoto M, Patil T. Lung Cancer 2023

MET –ex14 INHIBITORS

	Non-Selective		Selective TKI							
	CRIZOTINIB PROFILE 1001	ENSARTINIB	CAPMATINIB GEOMETRY Mono-1		TEPOTINIB VISION (A+C) (TBx)		SAVOLITINIB		GLUMETINIB GLORY	
IC_{50} (nM)	26,5	7.9	0.6		3.0		2.1		0.42	
Dose	250 mg BID	225 mg QD	400 mg BID		500 mg QD		400-600 mg QD		300 mg QD	
Line	≥1	1	1	≥2	1	≥2	1	≥2	1	≥2
N	69	29	60	100	111	97	28	42	46	38
RR (%)	32	67	68.3	44	56.8	49.5	46.4	40.5	71	60
DoR (mo.)	9.1	6.8	16.6	9.7	46.4	10.2	5.6	9.7	15.0	8.2
PFS (mo.)	7.3	6.1	12.5	5.5	15.3	11.5	6.9	6.9	11.7	7.6
OS (mo.)	20.5	NR	25.5	13.6	25.9	20.4	10.9	19.4	NE	16.2
Comments	Shorter PFS in ctDNA positive at baseline	Better intracranial activity than crizotinib	Higher activity in 1st *vs.* ≥2nd line		The RR regardless Age, line & type of previous therapy		Sarcom. *vs.* others RR: 40% *vs.* 44% PFS: 5.5 *vs.* 6.9		Higher activity in 1st *vs.* ≥2nd line	

Drilon –Nature Med 2020 * Xia – Cancer Letter 2023 * Wolf –ELCC 2022 * Wolf – ASCO 2021 * Thomas – WCLC 2022 * Lu – Lancet Resp Med 2021 * Lu – ELCC 2022 * Yu– eClinicalMedicine 2023



Pleural effusion

- Conduct thoracentesis and cytological testing to rule out malignant effusion.
- Other concomitant therapies and/or treatments should be considered as potential sources of pleural effusion.

ILD

- Although rare, monitor patients for signs of ILD throughout treatment duration and beyond, and consider previous treatments.
- Rule out other causes of ILD; evaluate lung function, bronchiolar lavage, bronchoscopy.
  Discontinue MET inhibitor treatment.
  Initiate steroids.
  Consider a referral to pulmonary specialists.
- Rule out other causes of ILD.
  Consider ethnicity – Japanese patients may be more likely to develop ILD than non-Japanese patients.

Hypoalbuminemia

- Monitor for reductions in albumin without stabilization.
- High protein diets may not be effective.
  Albumin transfusion or furosemide may provide transient benefits and/or prevent deterioration.
- Etiology unknown.

Peripheral edema

- Monitor all patients for asymptomatic edema following MET inhibitor initiation.
  Monitor skin for erosions.
  Consider prophylactic measures.
- Consider MET inhibitor dose reduction, and interruption or intermittent dosing.
  Consider diuretic and/or corticosteroid treatment.
  Lymphatic drainage (manual or mechanical) may be required.
- Peripheral edema is a cumulative, late-onset adverse event.
  Consider whether other medications might cause peripheral edema.
  Rule out systemic causes of edema.

GI disturbances

- GI events may be reduced when MET TKIs are taken with food.
  Diarrhea can usually be managed by standard antidiarrheal therapies.
  Ensure that there are no underlying reasons for GI disturbance, and treat non-MET TKI-related causes of GI disturbance appropriately as needed.
- Although symptoms are usually low grade, proactive management should be considered to minimize the impact on quality of life.

Increased liver transaminases and phosphatases

- Proactively monitor liver function.
- Consider MET inhibitor dose reduction or interruption if necessary.
  Switch MET inhibitors.
- Most events are low grade and reversible.
  In asymptomatic patients, transaminase increase may not require dose reduction or interruption.

Increased creatinine

- Transient MET inhibitor-related increased creatinine may indicate creatinine transporter inhibition rather than renal impairment.
  Consider methods other than creatinine-driven GFR to assess renal function and guide therapy.
  Close and frequent monitoring in early months of therapy will help identify clinically relevant increases in creatinine.
- Before deciding on an intervention based upon increased creatinine levels, check GFR using non-creatinine measures.
  Consider MET inhibitor dose reduction or interruption if clinically relevant increases in creatinine levels, or impaired renal function, is identified.
  Refer to a nephrologist for assistance with determining GFR.
- Non-clinically relevant increases and plateau in creatinine levels might be expected with MET inhibitor use.

Monitoring Management Other considerations

CHRYSALIS Study Design

- As of June 19, 2023, 97 patients had been enrolled in the *MET*ex14 cohort, with a median follow-up of 10.0 months

Dose-escalation phase

RP2D was identified:
Amivantamab
1050 mg IV
(1400 mg if ≥80 kg)

Dose-expansion cohorts

- **Cohort A:** Post–any EGFR TKI (T790M+, C797S+)
- **Cohort B:** Post–any EGFR TKI (T790M–, C797S–)
- **Cohort C:** Post-osimertinib (C797S+)
- **Cohort D:** *EGFR* Ex20ins[a]
- **Cohort MET-1:** Post–any EGFR TKI (*MET* amplified)
- **Cohort MET-2:** *MET*ex14[b]
- **Cohorts WT:** *EGFR* wild-type status

Endpoints

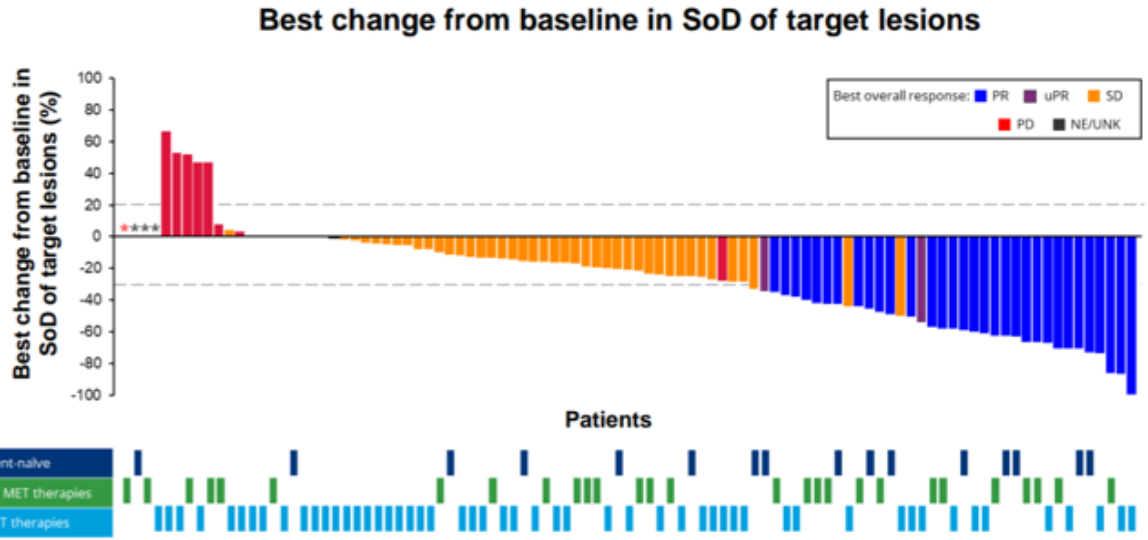
- Objective response rate (primary)
- Duration of response
- Clinical benefit rate[c]
- Progression-free survival
- Overall survival
- Adverse events

Focus of this presentation

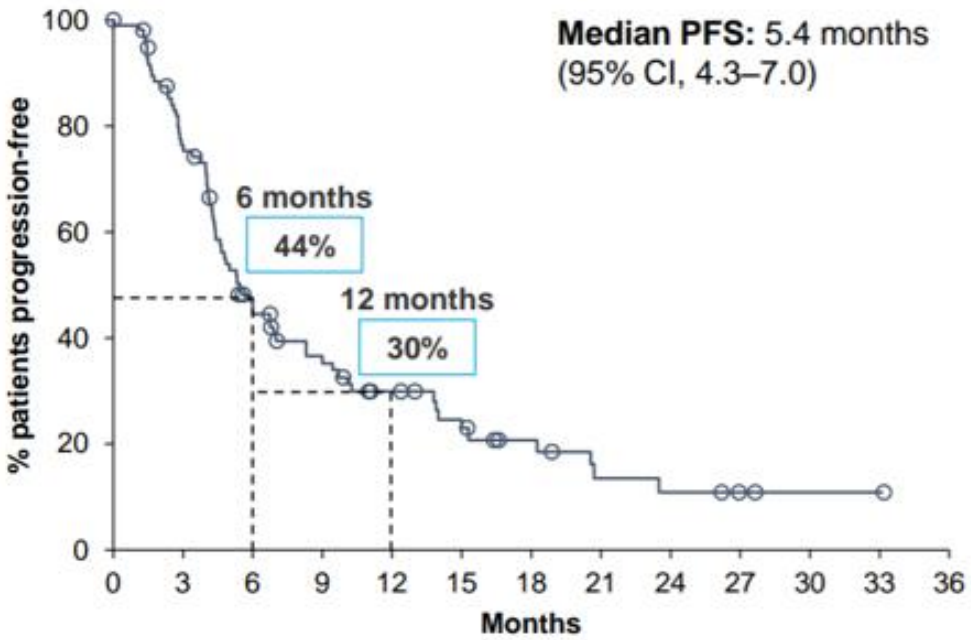
All cohorts are now closed

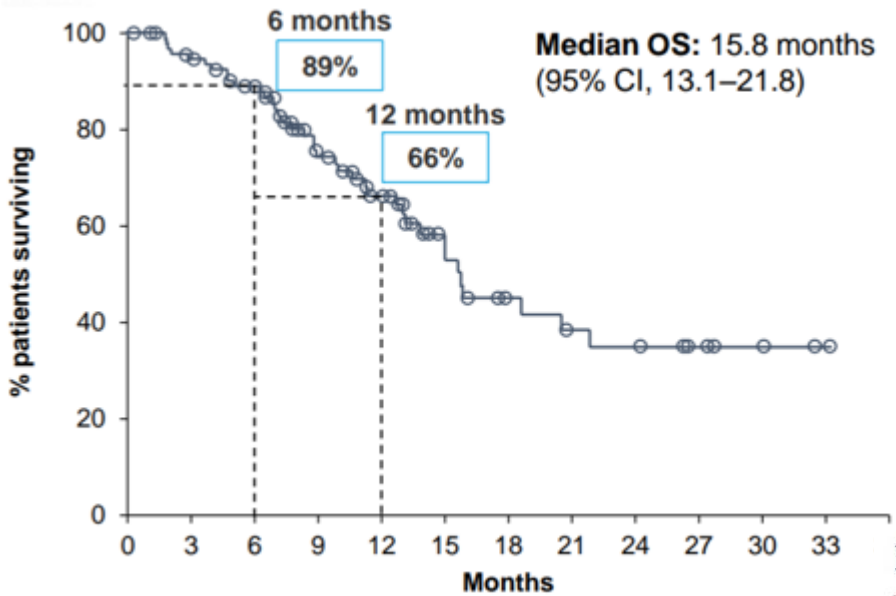
CHRYSALIS also included 2 additional combination cohorts:

- *Amivantamab + lazertinib*
- *Amivantamab + carboplatin-pemetrexed*



ORR	Treatment-naive	No prior MET	Prior MET
33% (32/97)	50% (8/16)	46% (16/28)	21% (11/53)





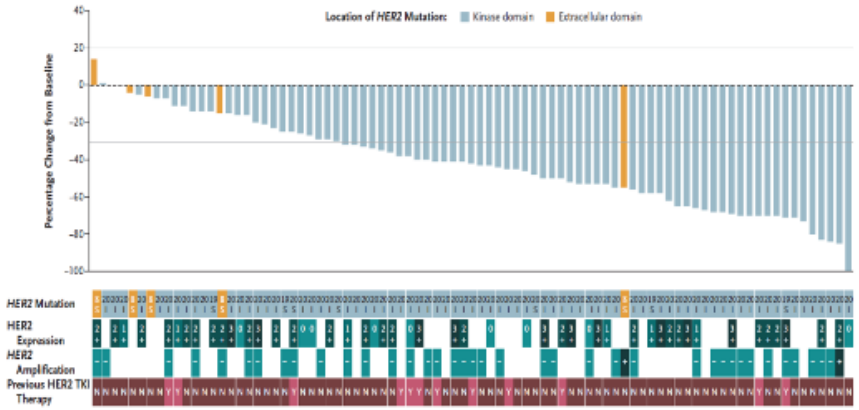
Leighl NB, WCLC 2023

HER2-DIRECTED TKIs

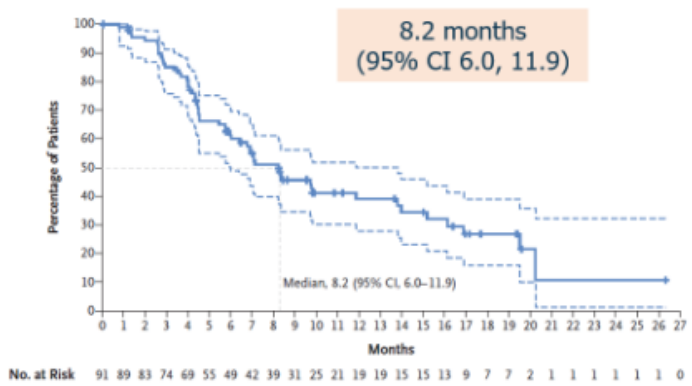
Drug	Target Pop	N	ORR	mPFS	Toxicities
Afatinib[1]	HER2^{mt}	13	8%	16 weeks	Diarrhea, vomiting, rash, paronychia, fatigue, mucositis
Afatinib[2]	HER2^{mt}	27	13%	3 mo	Diarrhea/GI toxicity, skin rash.
Neratinib[3]	HER2^{mt}	26	4%	5.5 mo	Diarrhea (74%), Nausea (43%), Vomiting (41%)
Dacomitinib[4]	HER2^{mt}	26	12%	3 mo	Diarrhea (90%), rash (73%)
Mobocertinib[5]	HER2^{mt}	5	1/5 (20%)		83% Diarrhea, 50% Anorexia
Pyrotinib[6]	HER2^{mt}	60	30%	6.9 mo	92% Diarrhea; 30% Creatinine increase
Poziotinib[7]	HER2^{mt}, Pretreated	90	28%	5.5 mo	49% Gr 3 Rash; 25.6 % Gr 3 Diarrhea
Poziotinib[8]	HER2^{mt}, First-line	48	44%	5.6 mo	49% Gr 3 Rash; 25.6 % Gr 3 Diarrhea

DESTINY-Lung01: Cohort 2 | HER2-mutated

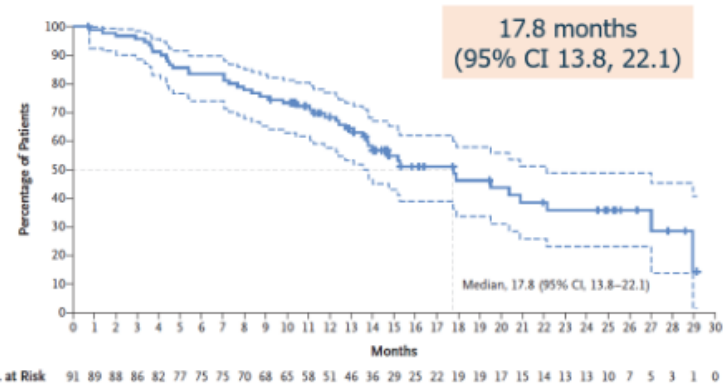
Best Change in Tumor Size



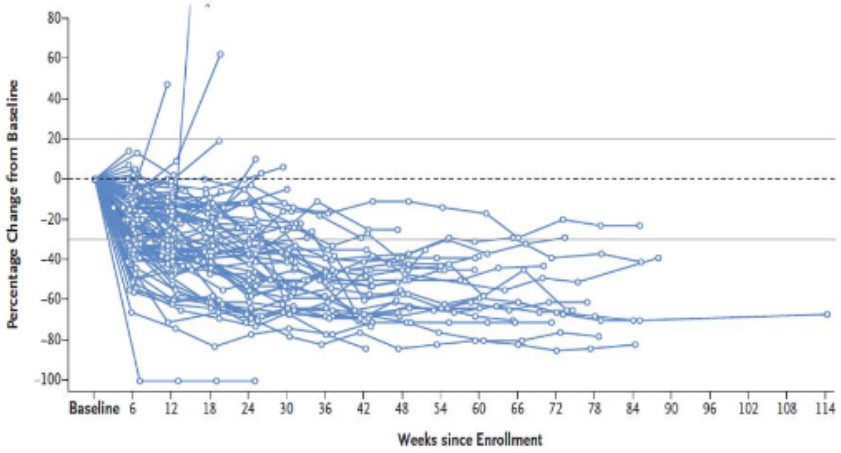
Median PFS



Median OS



Responses Over Time



Key data

- ORR of 55%
- DCR of 92%
- mPFS of 8,2 months
- mOS of 17,8 mohnts
- ILD occurred in 26,4% (any grade)

Li BT, et Al. NEJM 2022

TRASTUZUMAB DERUXTECAN

DESTINY-Lung02

Blinded, randomized, multicenter, international, noncomparative, phase 2 trial (NCT04644237)

Background

- T-DXd 5.4 mg/kg and 6.4 mg/kg showed robust antitumor activity in multiple cancer types; however, T-DXd 5.4 mg/kg has not been evaluated in patients with previously treated *HER2*-mutant (*HER2*m) mNSCLC
- DESTINY-Lung02 assessed the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in patients with *HER2*m mNSCLC
  - In the interim analysis, T-DXd showed deep and durable responses and an acceptable and generally manageable safety profile[1]
- Herein, we report the **primary analysis results** of DESTINY-Lung02

Statistical considerations

- Statistical hypothesis testing for the primary analysis was performed by comparing the lower limit of the 95% Clopper-Pearson CI of confirmed ORR of a T-DXd dose with the benchmark ORR of 26.4% (upper limit of the ORR 95% CI in the ramucirumab plus docetaxel arm of the REVEL trial)[2]
- The study was not powered to statistically compare between arms

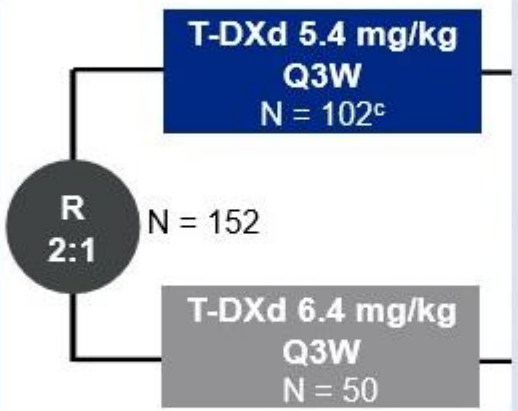
Key Eligibility Criteria[a]

- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:

- Prior anti–PD-(L)1 treatment

Study Design



Primary Endpoint

- Confirmed ORR by BICR

Secondary Endpoints

- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

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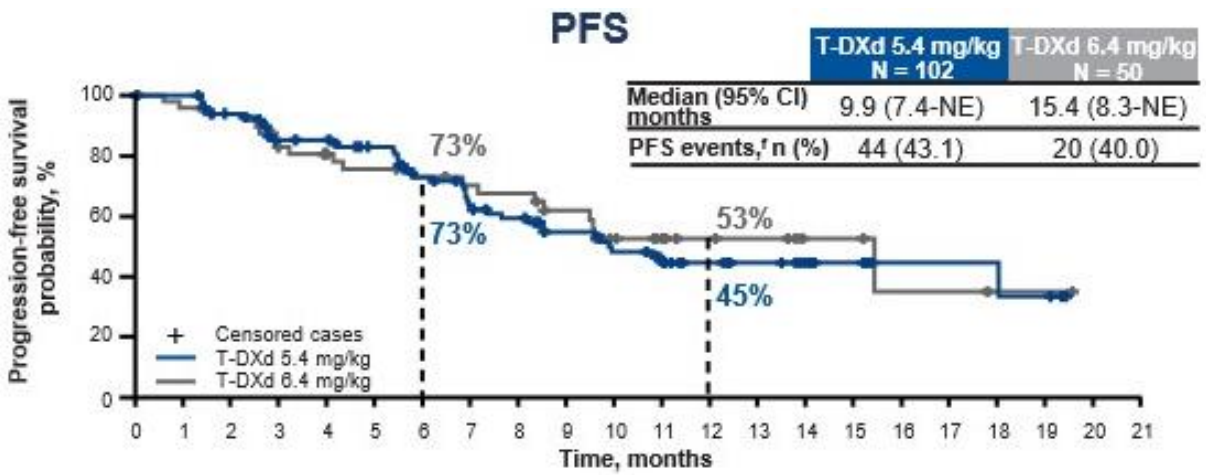
TRASTUZUMAB DERUXTECAN

Baseline Characteristics

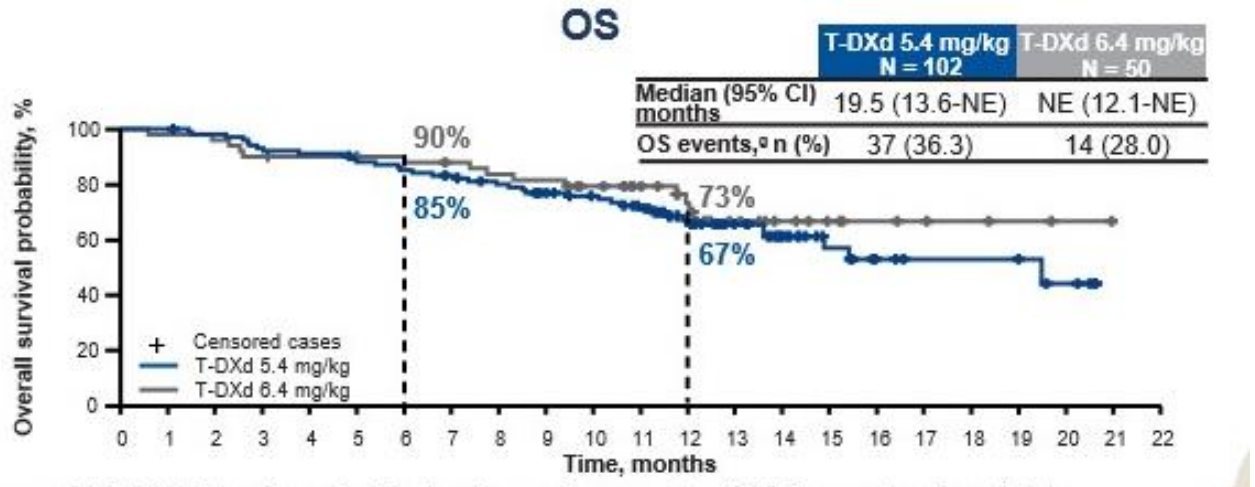
In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively:

- **Median age** was 59.4 years (range, 31-84) and 61.3 years (range, 28-86)
- Most patients were **female** (63.7% and 68.0%), **from Asia** (61.8% and 60.0%), had **never smoked** (53.9% and 58.0%), and **received prior anti–PD-(L)1 therapy** (73.5% and 78.0%)
- *HER2* mutations were primarily in the **kinase domain** (97.1% and 100%)
- **Baseline CNS metastasis** was present in 34.3% and 44.0% of patients
- **Median prior lines of treatment** was 2 (range, 1-12) and 2 (range, 1-7)

Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,[a] n (%) [95% CI]	**50 (49.0)** [39.0-59.1]	**28 (56.0)** [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable[b]	3 (2.9)	2 (4.0)
DCR,[c] n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DoR,[d,e] months (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR,[d] months (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, months (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)



9.9 months; 15.4 months



19.5 months; NE

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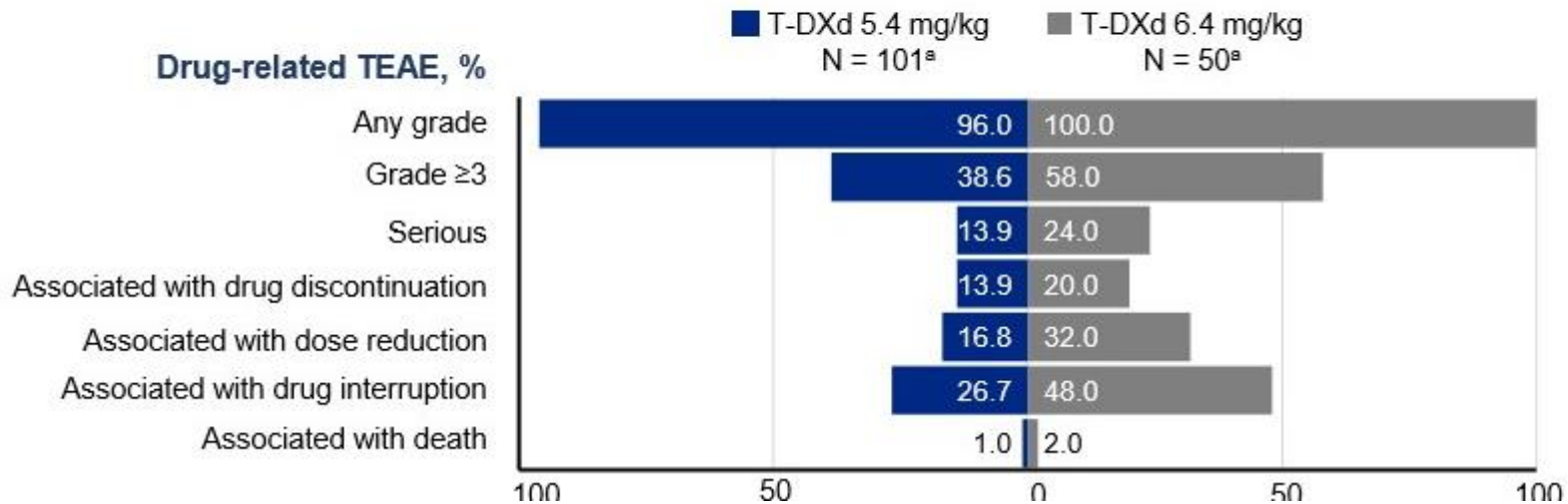
TRASTUZUMAB DERUXTECAN

Overall Safety Summary

Overall Safety



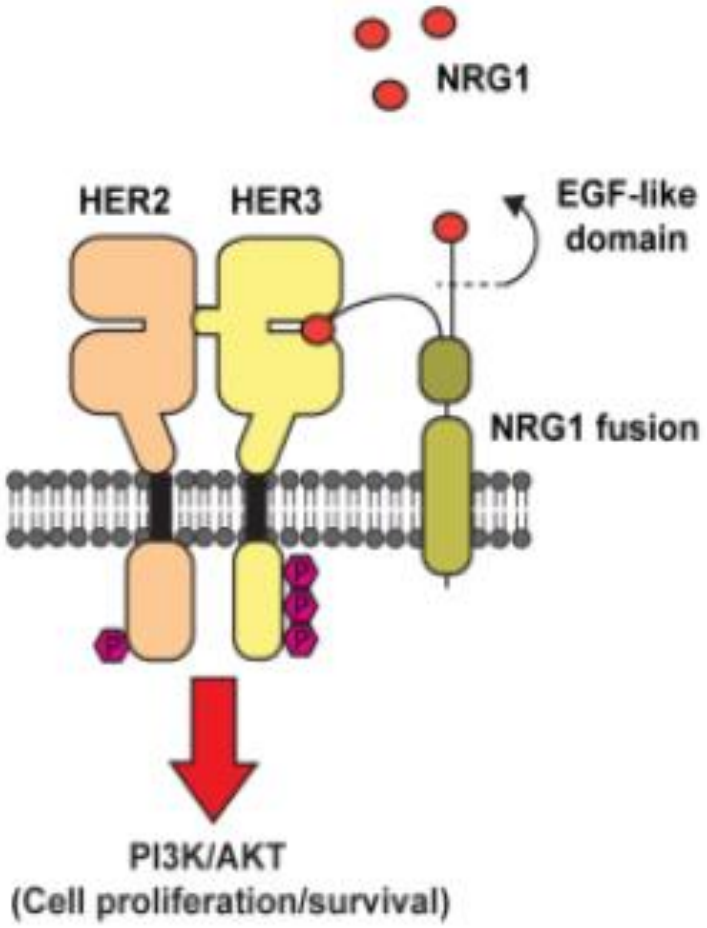
Adjudicated Drug-Related ILD

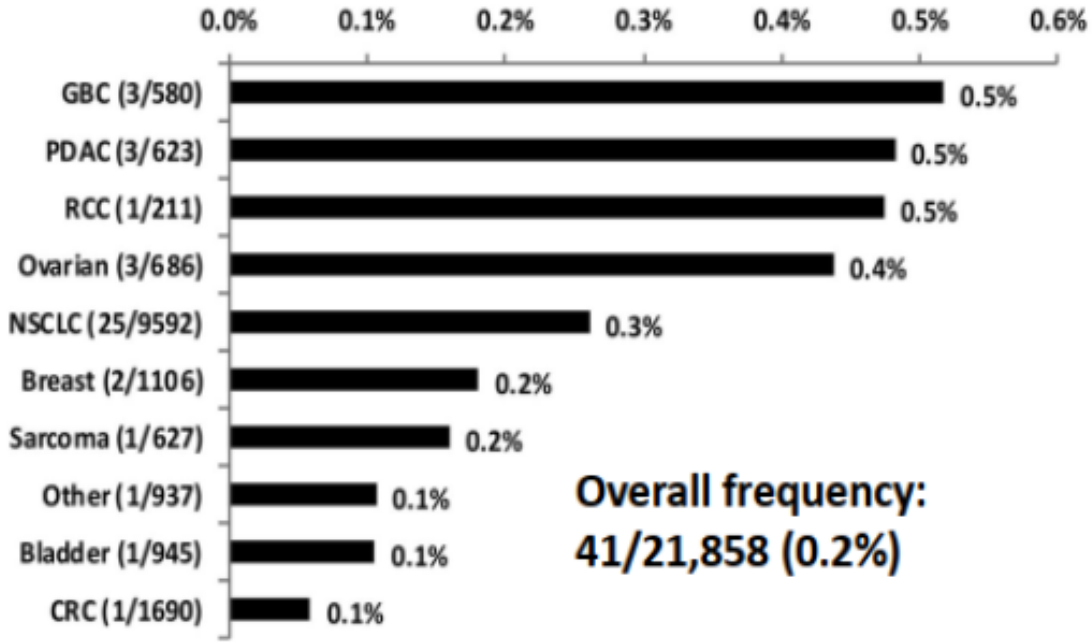
Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

- **Median treatment duration** was 7.7 months (range, 0.7-20.8) with T-DXd 5.4 mg/kg and 8.3 months (range, 0.7-20.3) with T-DXd 6.4 mg/kg
- The **most common any-grade TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **nausea** (67.3% and 82.0%), **neutropenia** (42.6% and 56.0%), and **fatigue** (44.6% and 50.0%)
- The **most common grade ≥3 TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **neutropenia** (18.8% and 36.0%) and **anemia** (10.9% and 16.0%)

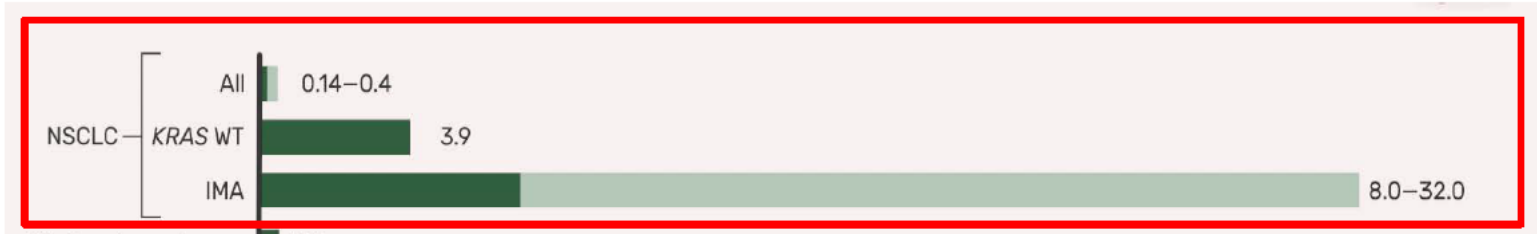
JANNE PA, WCLC 2023

NEUREGULIN 1 (NRG1)

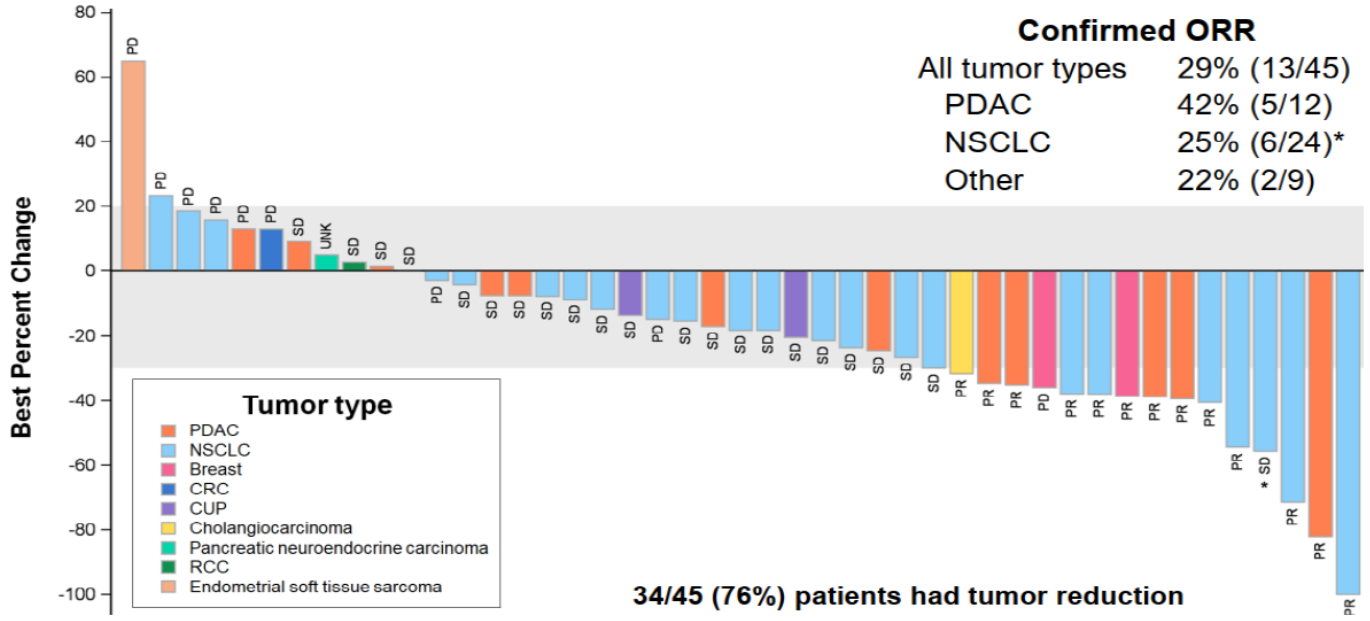




Fernandez-Cuesta et al. Cancer Discov. 2014;4:415-22
Schram et al. J Clin Oncol. 2019;37:3129
Jonna et al. J Clin Oncol. 2020;38:3113
Jonna et al. Clin Cancer Res. 2019;25:4966–7

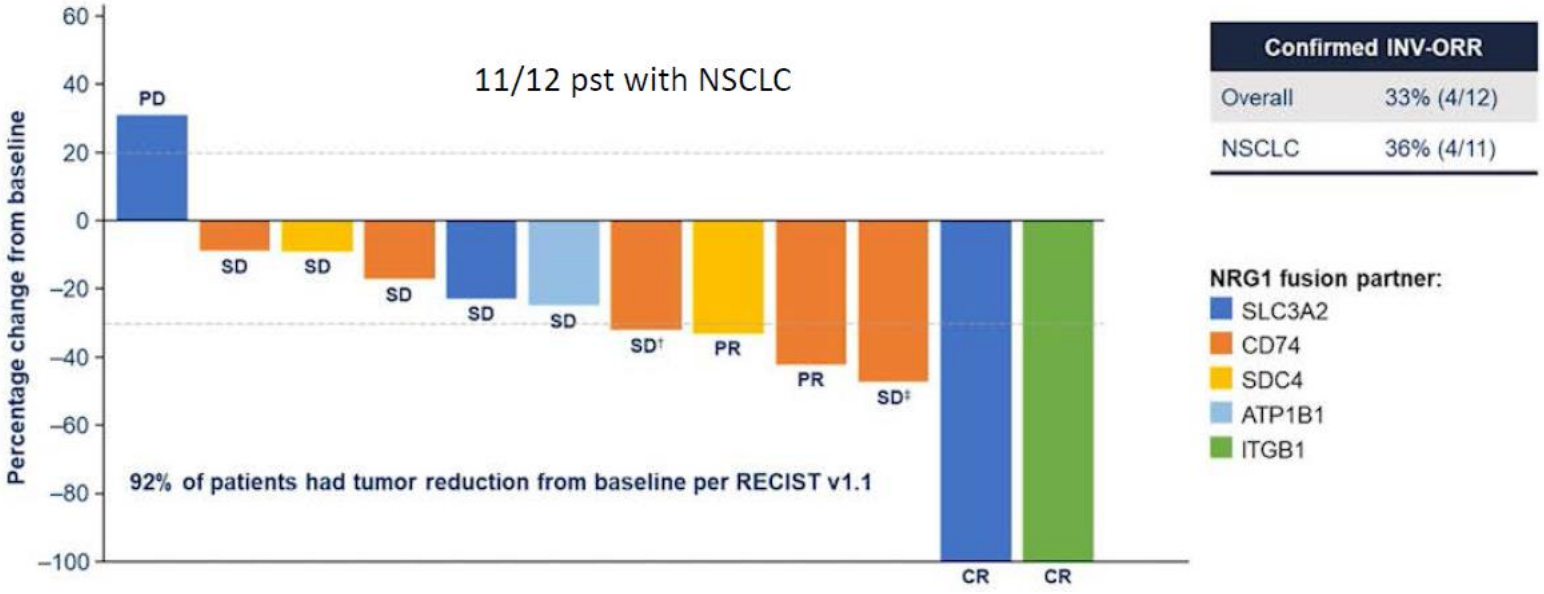


Best Percent change in Target Lesions from Baseline



* One additional PR confirmed after the cutoff date: NSCLC ORR 29% (7/24)

ZENOCUTUZUMAB

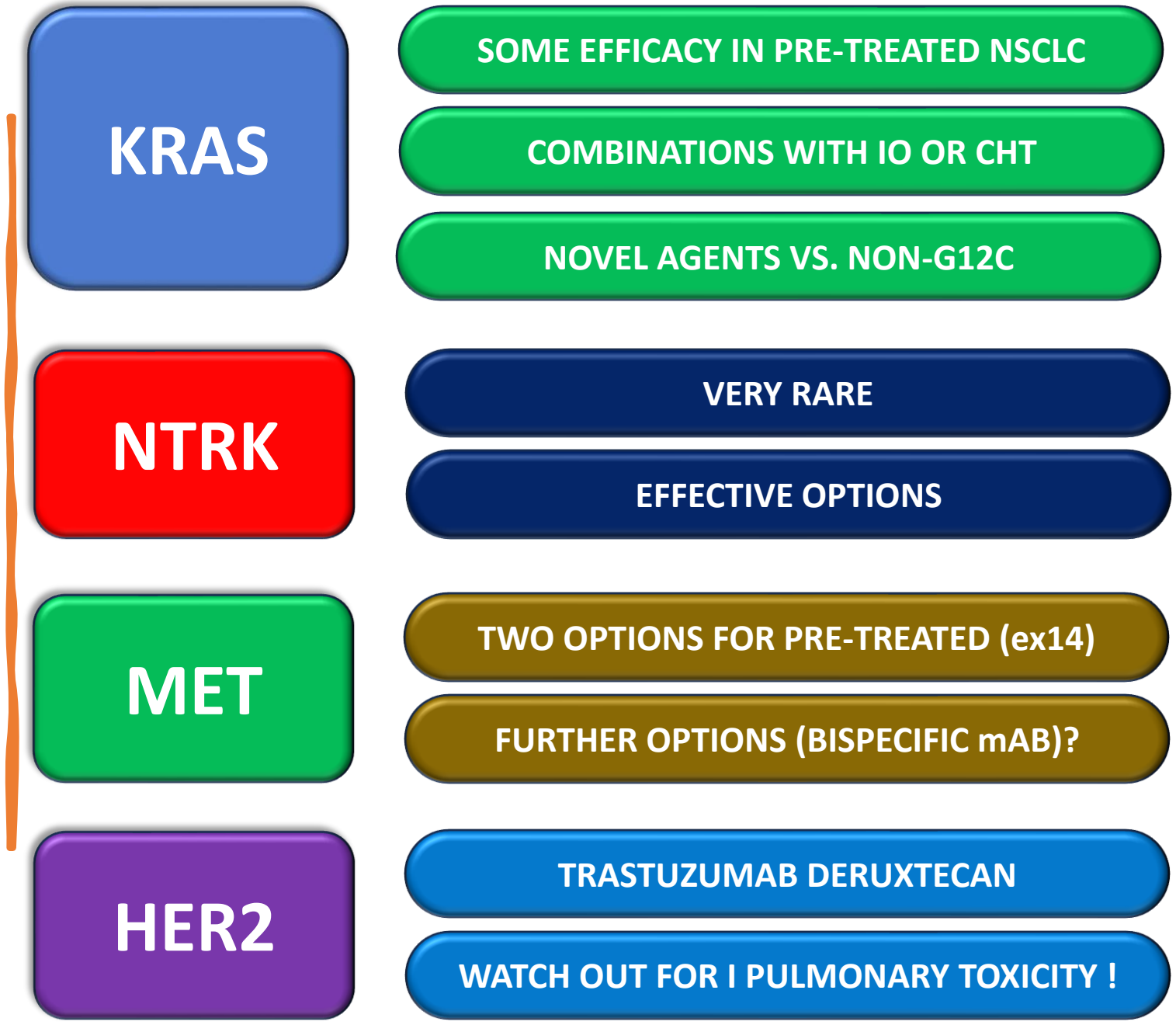


Confirmed INV-ORR	
Overall	33% (4/12)
NSCLC	36% (4/11)

SERIBANTUMAB

Schram AM et al. ASCO2022
Carrizzosa DR et al ASCO 2022

TAKE HOME MESSAGES



OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

UNIVERSITÀ DEGLI STUDI
DI GENOVA

GRAZIE PER L'ATTENZIONE !

Carlo Genova

U.O.C. Clinica di Oncologia Medica

Dipartimento di Medicina Interna e Specialità Mediche (Di.M.I.)

IRCCS Ospedale Policlinico San Martino

Università degli Studi di Genova

Carlo.genova@hsanmartino.it