Lung Adenocarcinoma Updates

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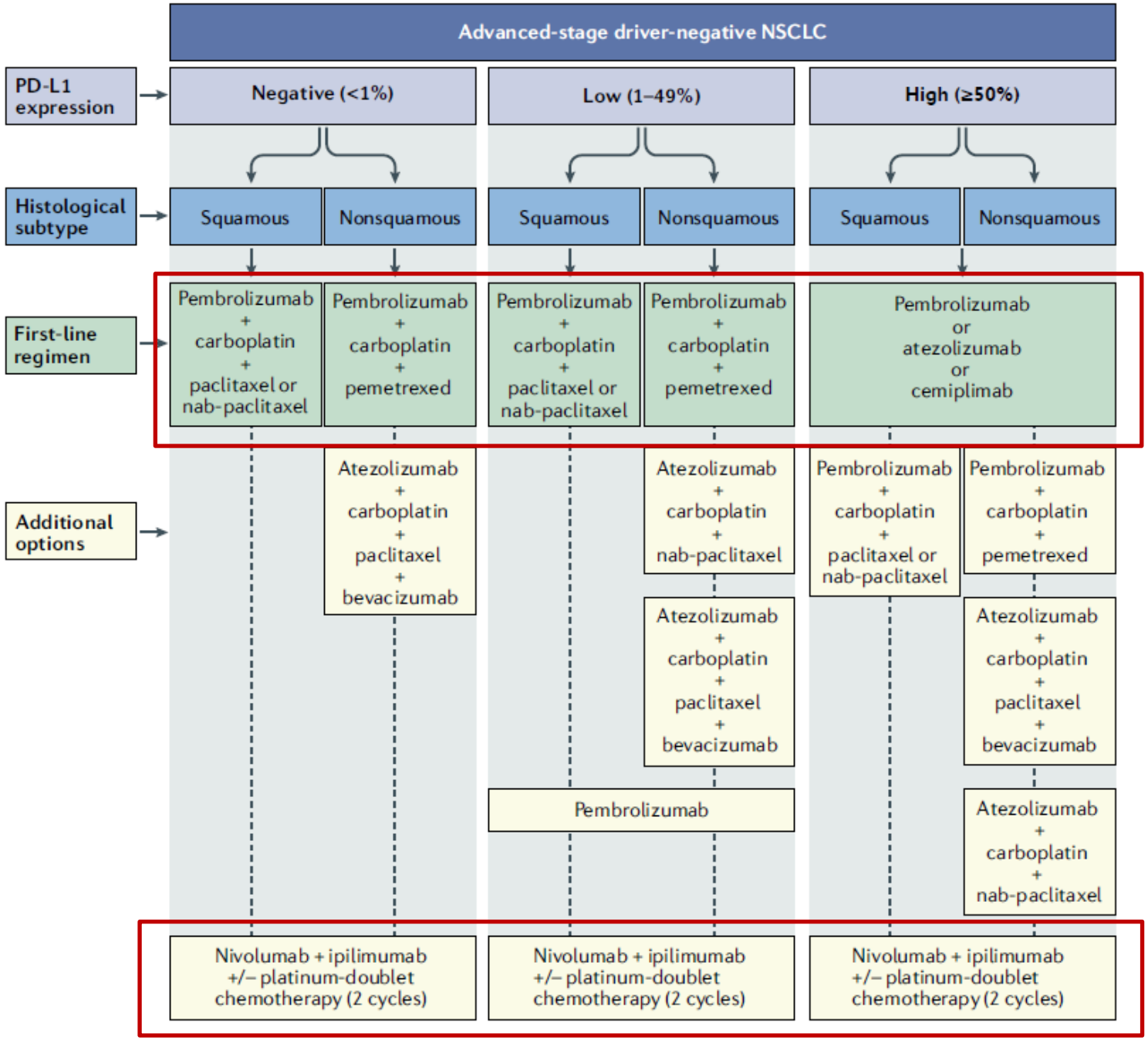
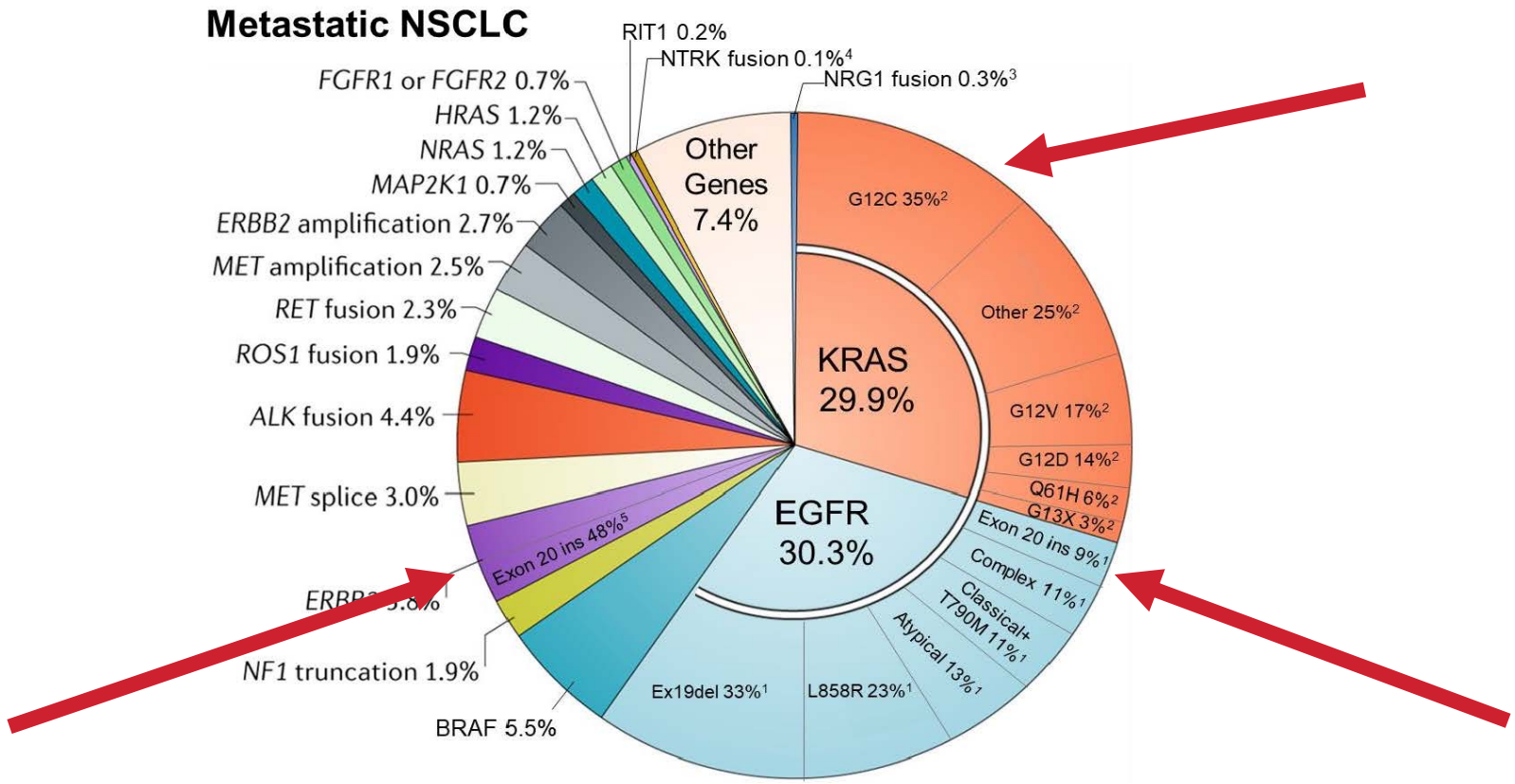


information.

Grant et al, Nat Reviews 2021

~43% of NSCLC patients have mutations that are targetable with approved agents



Adapted from Skoulidis and Heymach 2019 Nat Rev Can

[1] Robichaux et al 2020 WCLC

[2] Mack et al 2020 Cancer

[3] Jonna et al 2019 Clin Can Res

[4] Russo et al 2020 Precis Cancer Med

[5] Robichaux et al 2019 Cancer Cell

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Outline

- KRAS
- EGFR Exon 20
- HER2
- TROP2 for “Driver-negative” NSCLC

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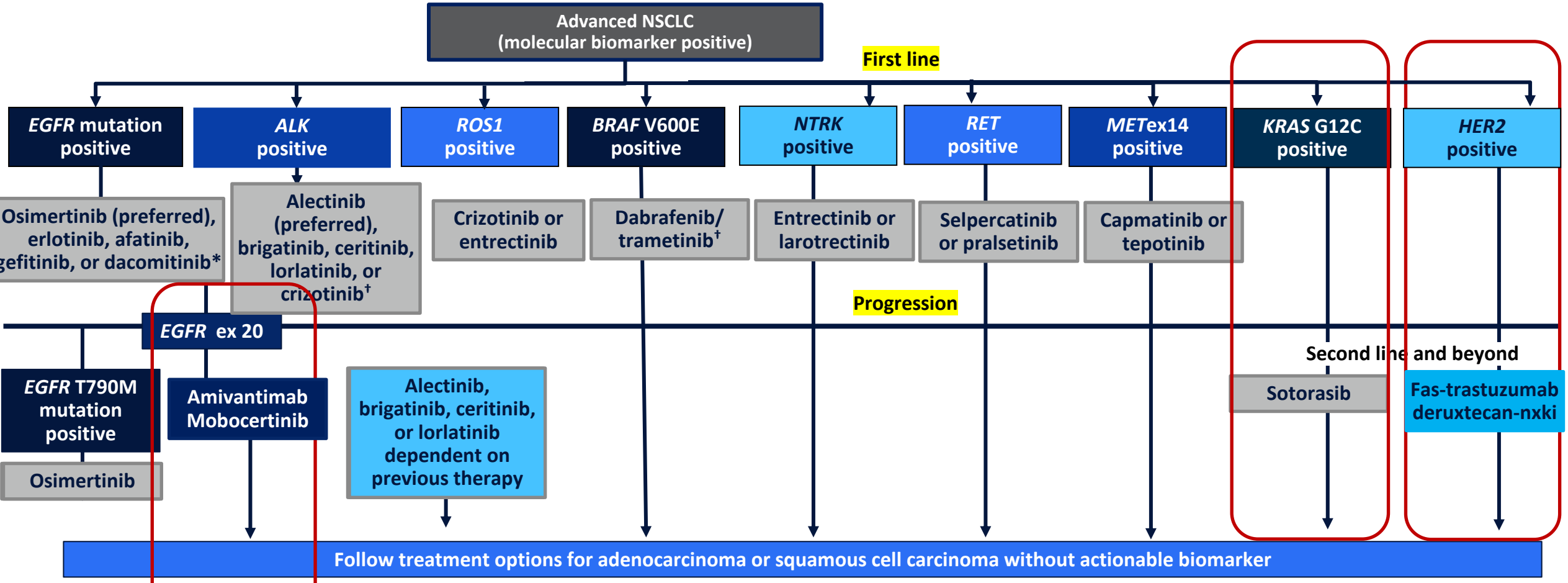
"Driver Mutations" Predict for Better Survival with FDA Approved Targeted Therapies



*Afatinib, dacomitinib, erlotinib, gefitinib, and osimertinib approved for *EGFR* exon19del, exon 21 L858R; afatinib for *EGFR* G719X, S768I, L861Q.

†Or as second-line after CT.

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KRAS G12C

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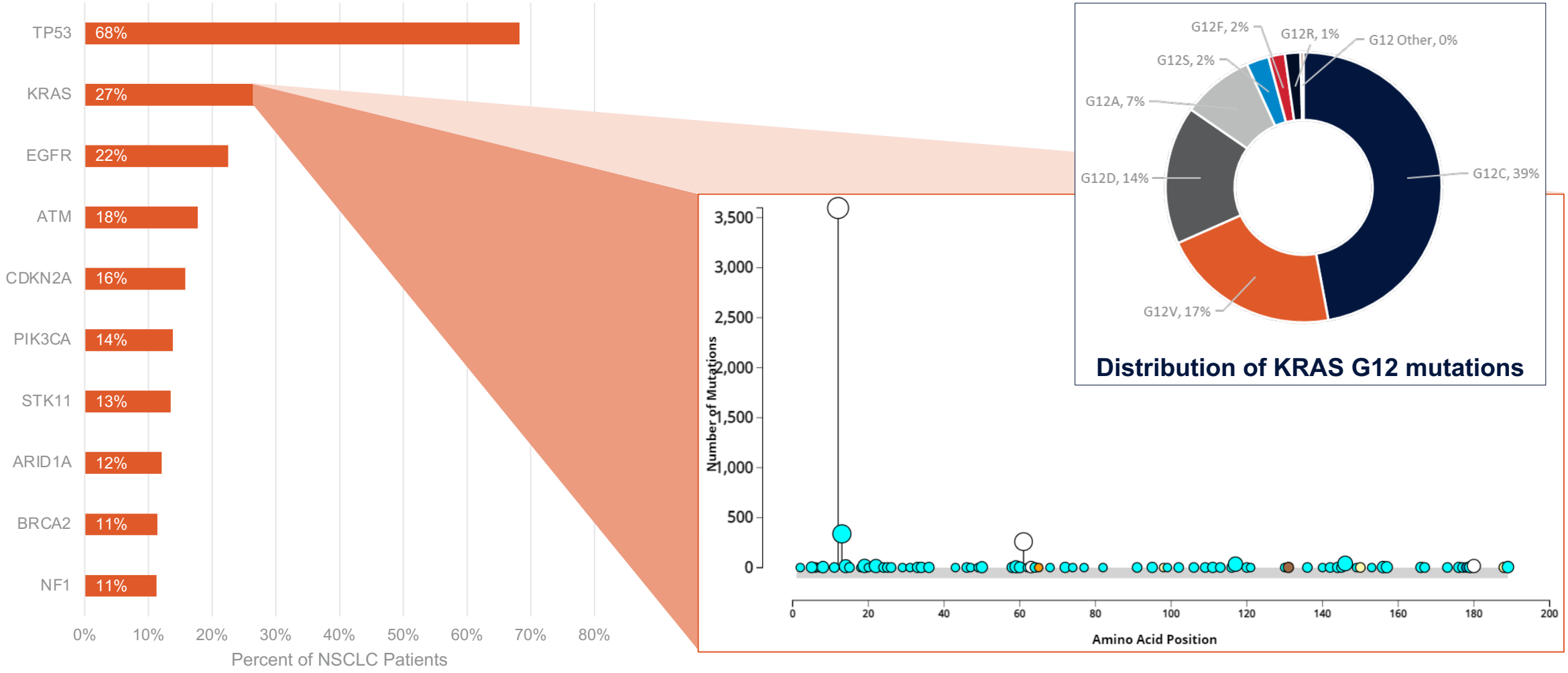
Frequency of KRAS Mutations in Lung Cancer

Sarah Cannon Network



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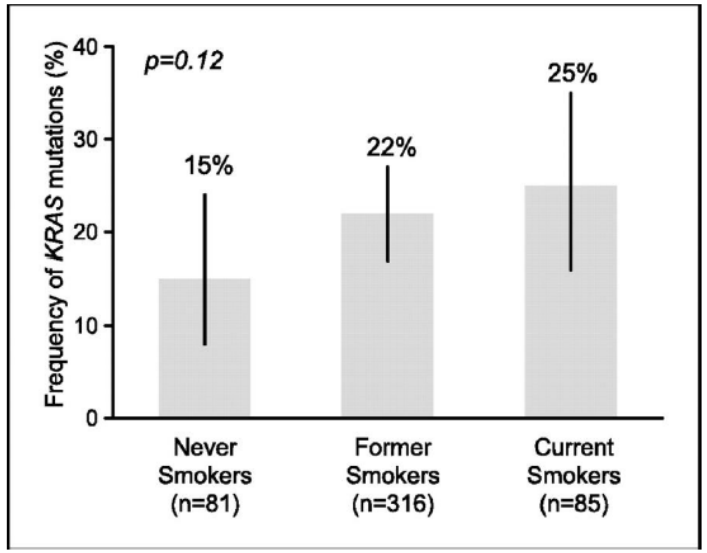
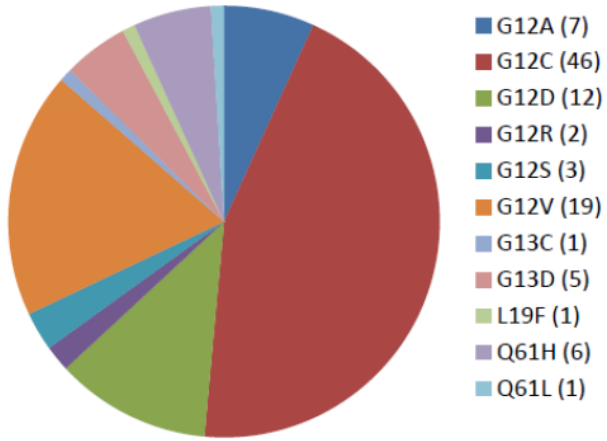
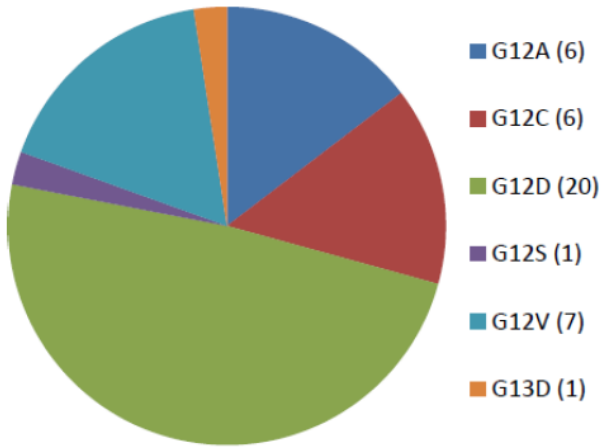
KRAS Mutations in NSCLC: Smokers vs. Never Smokers





Current/Former Smokers



Never Smokers

1. Biernacka A, et al. *Cancer Genet.* 2016;209:195-198. 2. Neumann J, et al. *Pathol Res Pract.* 2009;205:858-862. 3. Zhou L, et al. *Med Oncol.* 2016;33:32, Riely, G. et al. CCR 2008; Rediget al. ASCO 2016

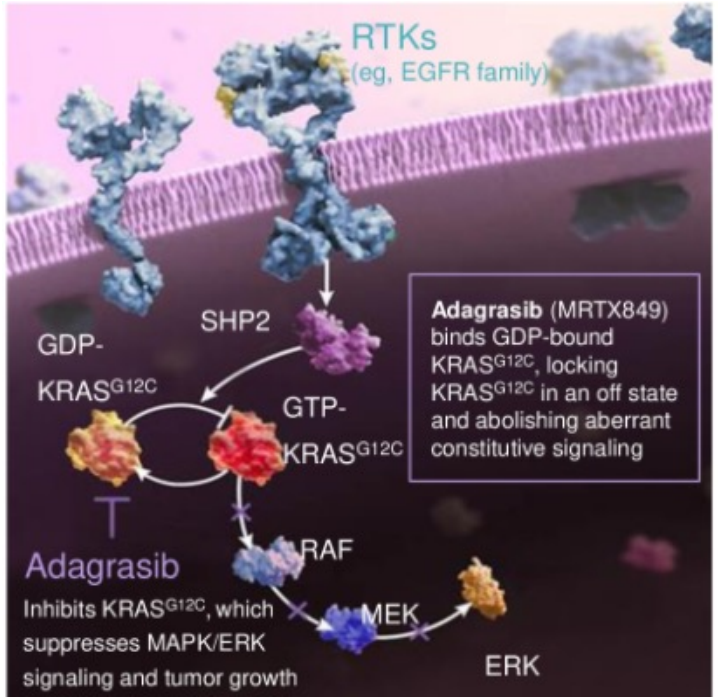
KRYSTAL-1: Adagrasib (MRTX849)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adagrasib in Non–Small-Cell Lung Cancer Harboring a *KRAS*^{G12C} Mutation

Pasi A. Jänne, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Shirish M. Gadgeel, M.D., Rebecca S. Heist, M.D., M.P.H., Sai-Hong I. Ou, M.D., Ph.D., Jose M. Pacheco, M.D., Melissa L. Johnson, M.D., Joshua K. Sabari, M.D., Konstantinos Leventakos, M.D., Ph.D., Edwin Yau, M.D., Ph.D., Lyudmila Bazhenova, M.D., Marcelo V. Negrao, M.D., Nathan A. Pennell, M.D., Ph.D., Jun Zhang, M.D., Ph.D., Kenna Anderes, Ph.D., Hirak Der-Torossian, M.D., Thian Kheoh, Ph.D., Karen Velastegui, B.Sc., Xiaohong Yan, Ph.D., James G. Christensen, Ph.D., Richard C. Chao, M.D., and Alexander I. Spira, M.D., Ph.D.



Key Eligibility Criteria

- Solid tumor with KRAS^{G12C} mutation[a]
- Unresectable or metastatic disease
- Prior treatment with a PD-1/L1 inhibitor in combination or following chemotherapy (NSCLC)[b]
- Treated and/or stable brain metastases[c]

Phase 1 Dose Escalation	Phase 1b Dose Expansion and Combination	Phase 2 Monotherapy Treatment
600 mg BID Expansion	**Adagrasib** monotherapy in solid tumors	**NSCLC**[g,h] (tumor tissue and/or ctDNA KRAS^{G12C})
1200 mg QD	**Adagrasib** brain metastases in solid tumors	
600 mg QD	**Adagrasib** NSCLC treatment-naive[e]	**CRC**[g,h] (tumor tissue and/or ctDNA KRAS^{G12C})
300 mg QD[d]	**Adagrasib** NSCLC prior KRAS^{G12C} inhibitor	**Other Solid Tumors**[h]
150 mg QD[d]	**Adagrasib** + pembro in NSCLC[f]	
	Adagrasib + afatinib in NSCLC	**NSCLC KRAS^{G12C} and STK11 Treatment-Naive**[g]
	Adagrasib + cetuximab in CRC[f]	

Mok et al, ASCO 2021
Mirati Investor Event, September 2021

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Adagrasib in NSCLC

Phase 2
NSCLC Monotherapy Treatment

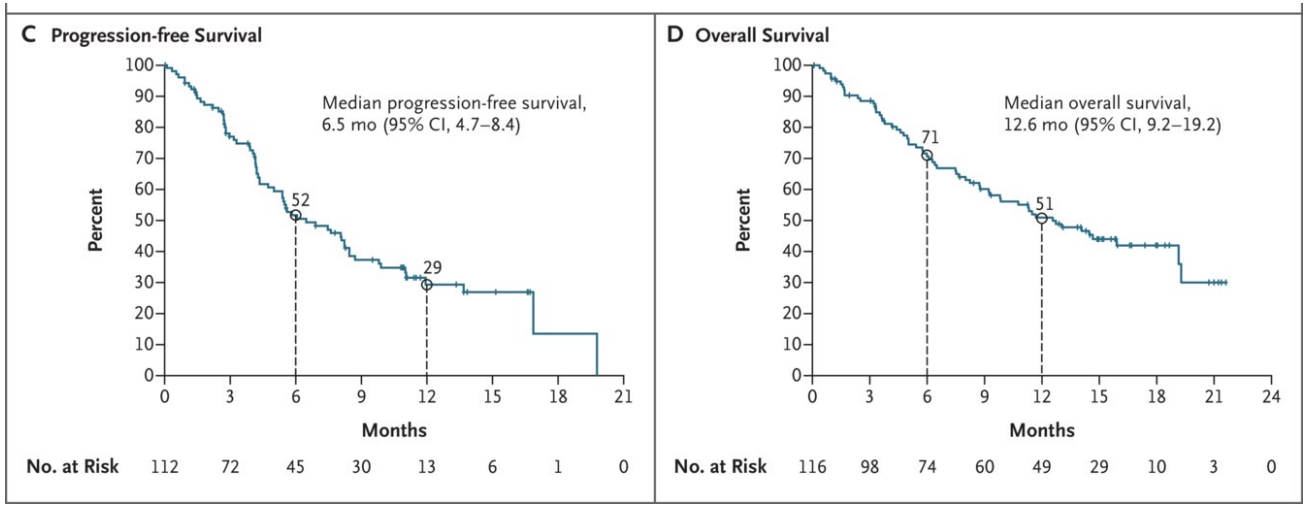
Key Eligibility Criteria

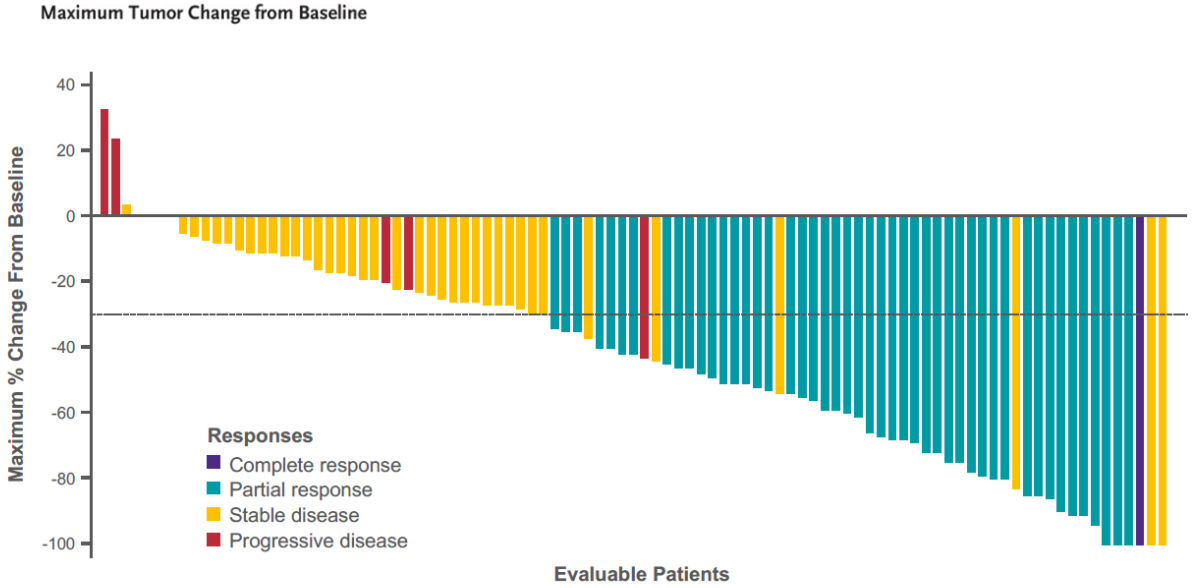
- NSCLC with $KRAS^{G12C}$ mutation[a]
- Unresectable or metastatic disease
- Prior treatment with a PD-1/L1 inhibitor in combination or in sequence with chemotherapy
- Treated, stable CNS metastases were allowed

Adagrasib 600 mg BID (Capsule, Fasted)

Study Objectives

- Primary endpoint: ORR (RECIST 1.1) per BICR
- Secondary endpoints: DOR, PFS, OS, safety





Efficacy Outcome	Adagrasib Monotherapy (n=112)[a]
Objective response rate, n (%)	48 (43%)
Best overall response, n (%)	
Complete response	1 (1%)
Partial response	47 (42%)
Stable disease	41 (37%)
Progressive disease	6 (5%)
Not evaluable	17 (15%)
Disease control rate, n (%)	89 (80%)

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CodeBreak100: Sotorasib

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 24, 2021 VOL. 384 NO. 25

Sotorasib for Lung Cancers with *KRAS* p.G12C Muta

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borgh
T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. A
Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. G

May 2021

- FDA grants accelerated approval in 2L+ KRAS G12C NSCLC

clinicaltrials.gov identifier: NCT03600883

Screening / Enrollment

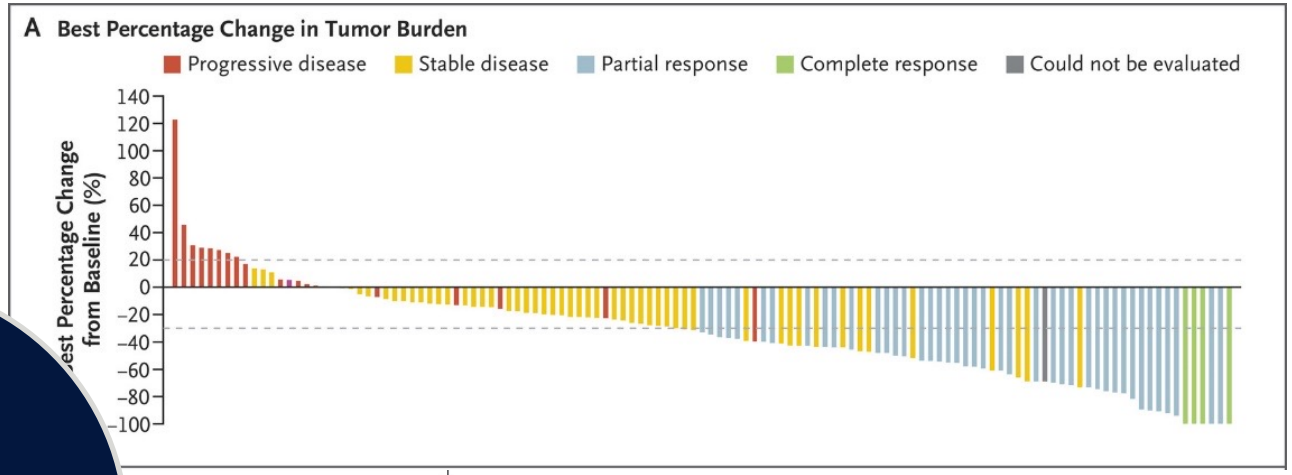
Key Eligibility:

- Locally advanced or metastatic NSCLC
- *KRAS* p.G12C mutation as assessed by central testing of tumor biopsies
- Progressed on prior standard therapies[a]
- No active brain metastases

Sotorasib was orally administered at 960 mg once dail until disease progression[b]

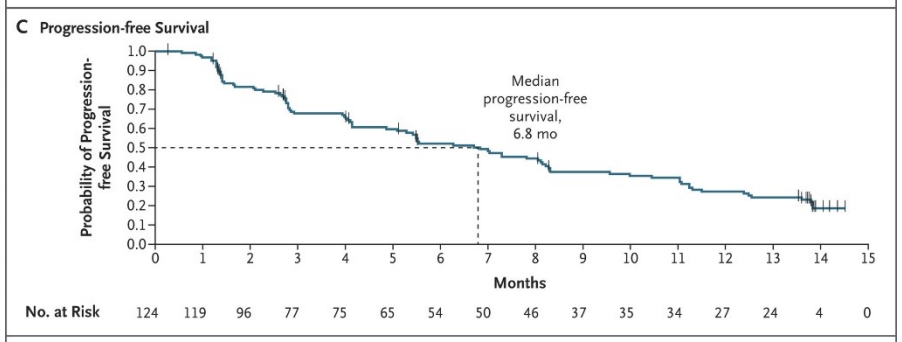
Radiographic scan every 6 weeks up to week 48 and once every 12 weeks thereafter

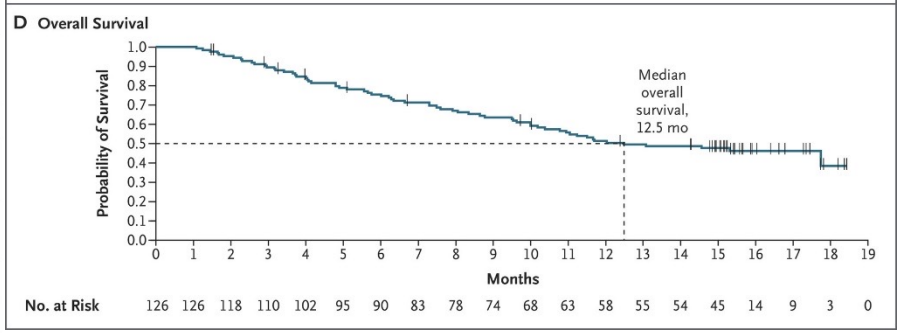
Primary endpoint: ORR (RECIST 1.1) by blinded independent central review
Key secondary endpoints: DoR; disease control rate; TTR; PFS; OS; safety
Exploratory endpoints: Evaluation of biomarkers (PD-L1, co-occurring mutations)



rapy According to Independent

	Patients (N = 124)
	37.1 (28.6–46.2)
	80.6 (72.6–87.2)
	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)





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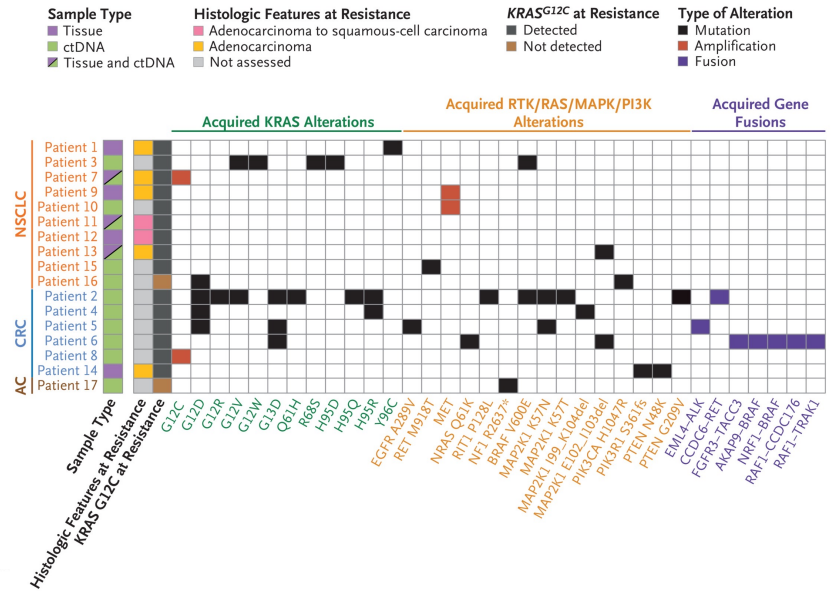
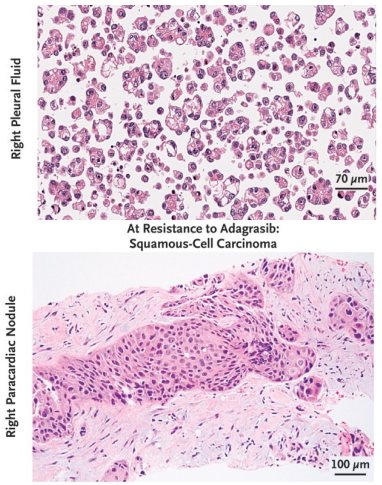
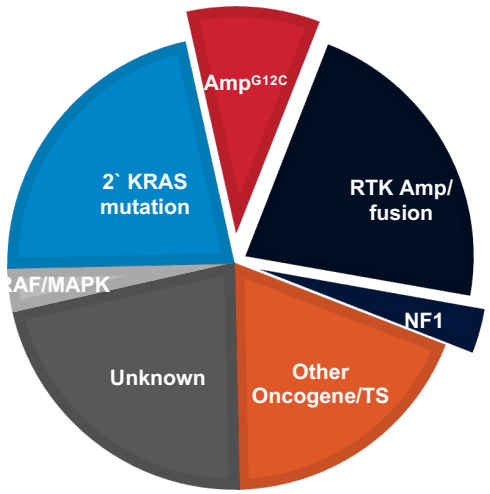
Acquired Resistance Mechanisms



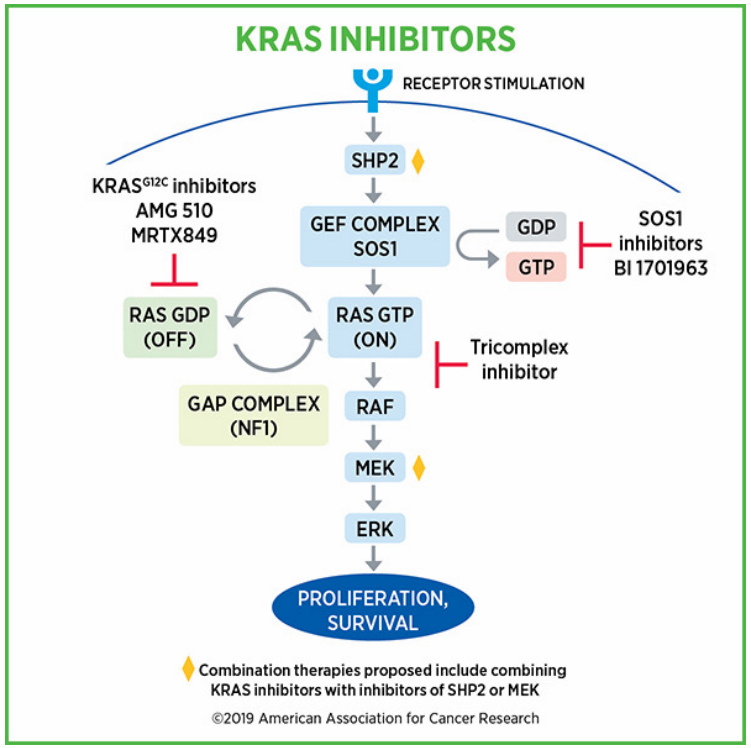




Zhao, Lito Nature 2021; graph courtesy of Kevin Webster, AACR 2022

Awad MM et al. *N Engl J Med* 2021;384:2382-2393

Can Up-front Combination Strategies Overcome AR?



SHP2 | SOS1 | Downstream MAPK

EGFR | PD1/PDL1

Hallin et al. Cancer Discov 2020;10:54–71; Canon et al. Nature 575 2019

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Sotorasib + RMC-4630 (SHP2 Inhibitor)

Screening/Enrollment

Key eligibility criteria*
- Locally advanced or metastatic *KRAS* p.G12C solid tumors
- Prior anti-PD(L)1 and/or platinum-based chemo and targeted therapy (NSCLC)
- Allowed prior KRAS^{G12C} inhibitor

→ **PART 1: Dose Exploration (N = 27)**

Sotorasib (960 mg PO daily) + RMC-4630 (PO) at:

- 200 mg at days 1 and 2 Q7D
- 140 mg at days 1 and 2 Q7D
- 100 mg starting dose at days 1 and 2 or days 1 and 4 Q7D

Variable, n (%)	Sotorasib + RMC-4630 (N = 27)*					
	Related to Sotorasib		Related to RMC-4630		Related to Sotorasib + RMC-4630	
	All Grades	Grade 3	All Grades	Grade 3	All Grades	Grade 3
Total TRAE	**15 (56)**	**6 (22)**	**17 (63)**	**6 (22)**	**17 (63)**	**6 (22)**
Edema†	7 (26)	0	6 (22)	0	8 (30)	0
Diarrhea	7 (26)	2 (7)	5 (19)	2 (7)	7 (26)	2 (7)
Dry mouth	3 (11)	0	2 (7)	0	3 (11)	0
Fatigue	3 (11)	0	3 (11)	0	3 (11)	0
AST increased	1 (4)	1 (4)	2 (7)	1 (4)	2 (7)	1 (4)
Ascites	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
Colitis	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
Dyspnea	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)
Hypertension	0	0	1 (4)	1 (4)	1 (4)	1 (4)
Pleural effusion	0	0	1 (4)	1 (4)	1 (4)	1 (4)

TRAEs consistent with known safety profile of sotorasib and RMC-4630
Edemas (peripheral and facial) were most common TRAE; all were Grade 1 or 2, and none led to discontinuation

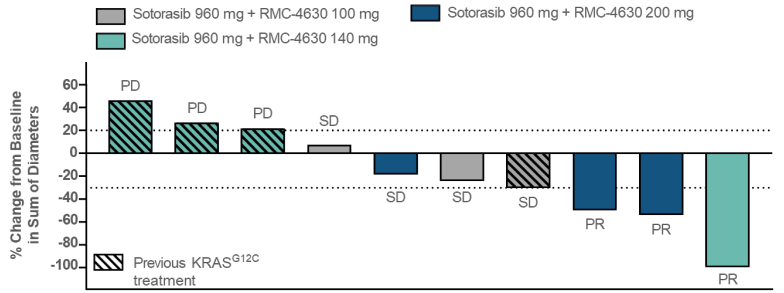
Response assessed by investigator	All enrolled (N = 11)	NSCLC KRAS^{G12C} inhibitor-naïve (N = 6)
ORR, % (95% CI)	**27 (6, 61)**	**50 (12, 88)**
Best overall response, n (%)		
Partial response	3 (27)	3 (50)
Stable disease	4 (36)	3 (50)
Progressive disease	4 (36)	0
Disease control rate, n (%)	**7 (64)**	**6 (100)**

Other tumor types: 8 CRC (5 SD; 3 PD); 1 ovarian cancer (PR with an 81% reduction in tumor burden); 1 pancreatic adenocarcinoma (SD), and 2 other solid tumors (1 SD, 1 NE).

- **Disease control in 7 of 11 patients with NSCLC and in all patients who were KRAS^{G12C} i-naïve**
- **Promising early efficacy observed in patients with NSCLC who were KRAS^{G12C} i-naïve**

Tumor Response* in NSCLC

At the two highest doses, responders included 3 of 4 patients who were KRAS^{G12C} i-naïve



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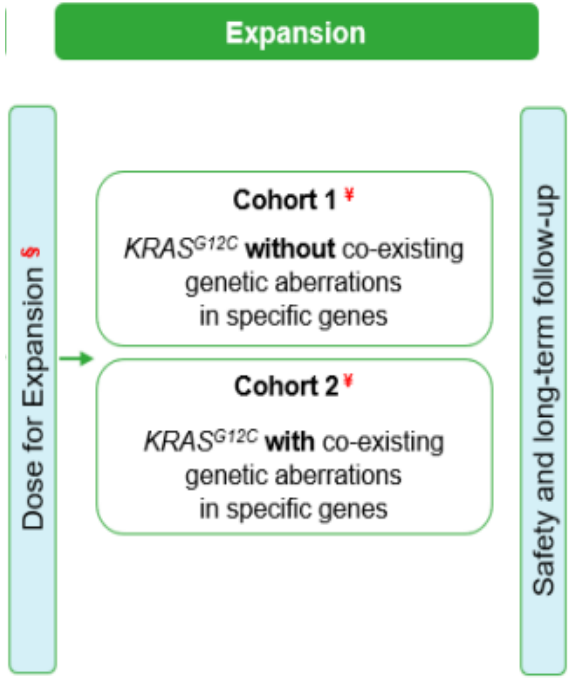
RMC-4630-03

Sotorasib (KRAS G12Ci) + RMC-4630 (SHP2i)

- 2-4L NSCLC
  - If an actionable alteration (EGFR, ALK, etc), must have received targeted tx
- KRAS G12C alteration; eligibility assessed based on prior genetic testing within 3 years
- No prior treatment with KRAS G12C inhibitor or SHP2 inhibitor



Co-mutations Include:
- STK11/LKB1
- KEAP1
- PIK3CA
- BRAF Class 1/2/unclassified
- ATRX
- BRCA2

"Promising clinical activity was observed"[1] in **CodeBreaK101c**

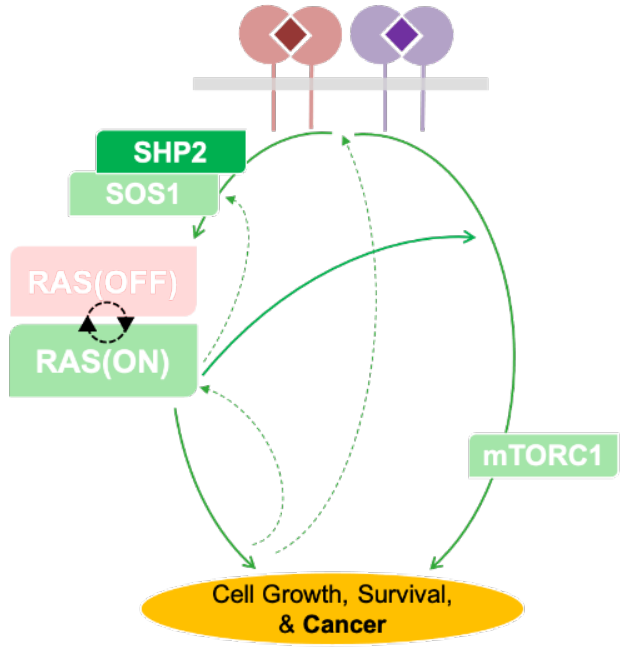
21 KRAS^{G12C} patients in dose/schedule exploration (all solid tumors, 100-200 mg twice weekly)[2]

"The combination of sotorasib with RMC-4630 was safe and tolerable"[1]

75%/ 100% ORR/DCR among KRAS^{G12C} inhibitor-naïve NSCLC patients treated at top two doses of RMC-4630 (n=4)

+ One patient with progression on sotorasib monotherapy achieved an unconfirmed PR on RMC-4630 combo

https://clinicaltrials.gov/ct2/show/NCT04185883



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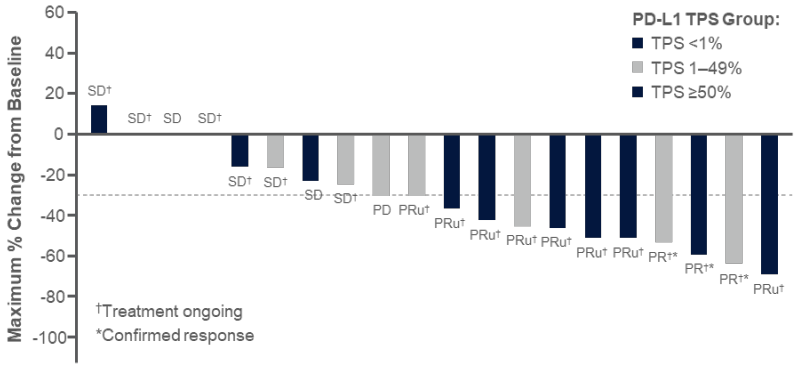
1L Adagrasib 400 mg BID + Pembrolizumab in KRAS^{G12C} Mutated NSCLC: Efficacy Outcomes

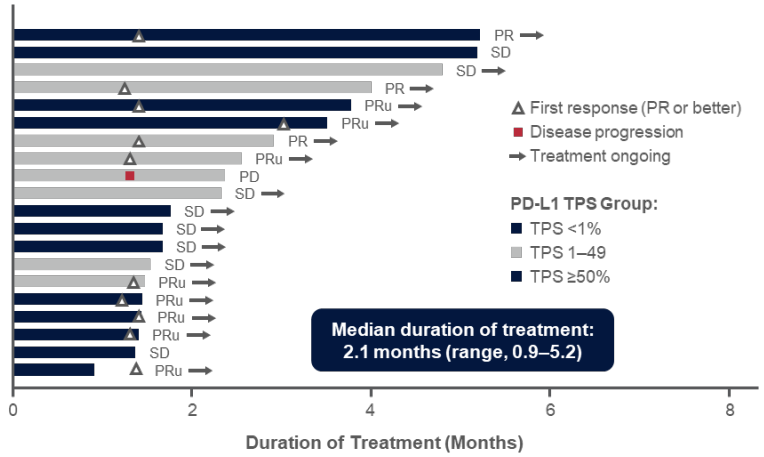
	Adagrasib 400 mg BID + Pembrolizumab[a]	
	Grade 1/2 (N=37)	Grade 3/4 (N=37)
Any treatment-related AE[b], n (%)	**12 (32.4%)**	**16 (43.2%)**
Diarrhea	10 (27.0%)	1 (2.7%)
Nausea	8 (21.6%)	4 (10.8%)
Amylase increased	8 (21.6%)	0
Fatigue	7 (18.9%)	1 (2.7%)
ALT increased	**6 (16.2%)**	**2 (5.4%)**
AST increased	**6 (16.2%)**	**2 (5.4%)**
Blood alkaline phosphatase increased	6 (16.2%)	0
Decreased appetite	5 (13.5%)	0
Edema peripheral	4 (10.8%)	0
Vomiting	4 (10.8%)	0
Lipase increased	3 (8.1%)	5 (13.5%)

- There were no grade 5 TRAEs
- TRAEs resulted in treatment discontinuations in 1/37 (2.7%) of patients

Best Tumor Change from Baseline[a]



Duration of Treatment[a]



- ORR was 77% (7/9) in patients with PD-L1 TPS ≥50%, and 50% (4/8) in patients with PD-L1 TPS 1–49%

[a]n=20; one additional patient with a TPS score of <1% did not have post baseline scan at time of data cutoff

Data as of April 1, 2022

Data courtesy of Jamie Christiansen, 6 June 2022

CodeBreaK 100/101: Sotorasib in combination with pembrolizumab or atezolizumab in *KRAS*^{G12C} NSCLC

Key Eligibility
- Advanced *KRAS* p.G12C-mutated NSCLC
- Received (or refused) prior standard therapies
- No prior KRAS^{G12C} inhibitor
- No active brain mets

Screening/Enrollment →

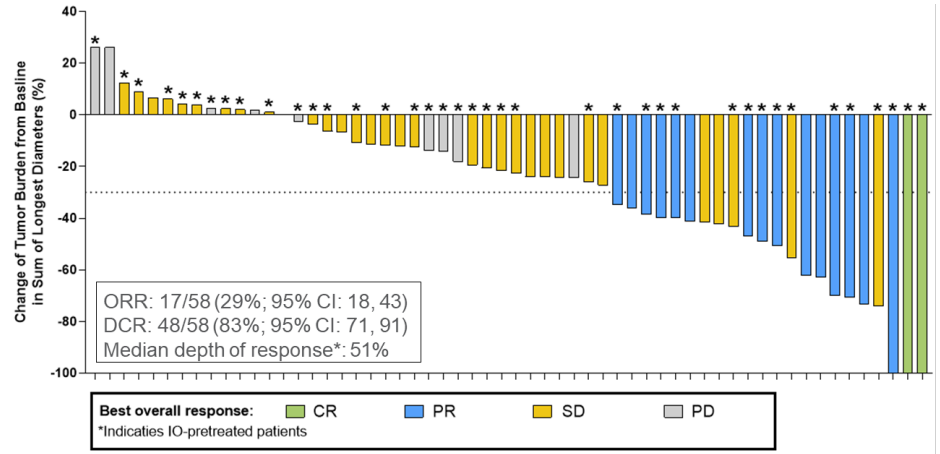
Sotorasib* (oral daily) at:	Sotorasib lead-in 21d or 42d then combination (N = 29)	Concurrent treatment (N = 29)
960 mg	Atezolizumab 1200 mg Q3W (N = 10)	Atezolizumab 1200 mg Q3W (N = 10)
720 mg		
360 mg	*OR*	*OR*
240 mg	Pembrolizumab 200 mg Q3W (N = 19)	Pembrolizumab 200 mg Q3W (N = 19)
120 mg		

Safety for Sotorasib Lead-in + Pembrolizumab

TRAE*, n (%)	Sotorasib 120 mg (N = 3)		Sotorasib 240 mg (N = 5)		Sotorasib 360 mg (N = 11)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	**3 (100)**	**3 (100)**	**3 (60)**	**1 (20)**	**9 (82)**	**6 (55)**
ALT increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	3 (27)
AST increased	2 (67)	2 (67)	1 (20)	1 (20)	6 (55)	2 (18)
ALP increased	2 (67)	0	0	0	3 (27)	2 (18)
Diarrhea	1 (33)	0	1 (20)	0	6 (55)	1 (9)
Arthralgia	1 (33)	0	0	0	2 (18)	0
Nausea	0	0	0	0	4 (36)	0
Fatigue	0	0	0	0	4 (36)	0
Hypokalemia	0	0	0	0	3 (27)	2 (18)
Decreased appetite	0	0	0	0	3 (27)	0
Headache	0	0	0	0	2 (18)	0
Hepatotoxicity	**2 (67)**	**2 (67)**	**2 (40)**	**1 (20)**	**6 (55)**	**5 (45)**

Overall safety data from lead-in and concurrent cohorts support lower dose sotorasib and lead-in administration for better tolerability

Response



- Deep and durable responses were observed for this combination across all cohorts, including at low doses
- Among the 17 responders, median duration of response was 17.9 months (95% CI: 5.6, NE)
- Response was similar in IO-naïve and IO-pretreated patients

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Future Opportunities: Combinatorial Clinical Trials in Solid Tumors

Closed
Open
Planned

Sotorasib

- Palbociclib (CDK4/6)
- Carboplatin-Pemetrexed (Chemo)
- RMC-4630 (SHP2)
- AMG 404 (PD-1)
- Trametinib (MEK)
- RMC-4630 (SHP2)
- Afatinib (TKI)
- Pembrolizumab (PD-1)
- Panitumumab (EGFR)
- Carboplatin (Chemo)
- Pemetrexed (Chemo)
- Docetaxel (Chemo)
- Atezolizumab (PD-L1)
- Everolimus (mTOR)
- Palbociclib (CDK4/6)
- Bevacizumab VEGF)
- TNO155 (SHP2)
- FOLFIRI (Chemo
- FOLFOX (Chemo)
- PD-1 (PD-1)
- Bevacizumab (VEGF)
- VS-6766 (MEK/RAF)
- Panitumumab (EGFR)
- BI 1701963 (Pan-KRAS SOS1)
- Osimertinib & BBP-298 (SHP2)
- BBP-398 (SHP2)

Adagrasib

- TNO155 (SHP2)
- Cetuximab (EGFR)
- Pembrolizumab (PD-1)
- BI 1701963 (Pan-KRAS SOS1)
- VS-6766 (MEK/RAF)
- RMC-4630 (SHP2)

GDC-6036

- Atezolizumab (PD-L1)
- Cetuximab (EGFR)
- Bevacizumab (VEGF)
- Erlotinib (EGFR)
- GDC-1971 (SHP2)
- RLY-1971 (SHP2)

JAB-21822

- Cetuximab (EGFR)
- JAB-3312 (SHP2)
- Cetuximab (EGFR)

BI 1823911

- BI 1701963 (Pan-KRAS SOS1)

MK-1084

- Pembrolizumab (PD-1)

RMC-6291

- RMC-4630 (SHP2)

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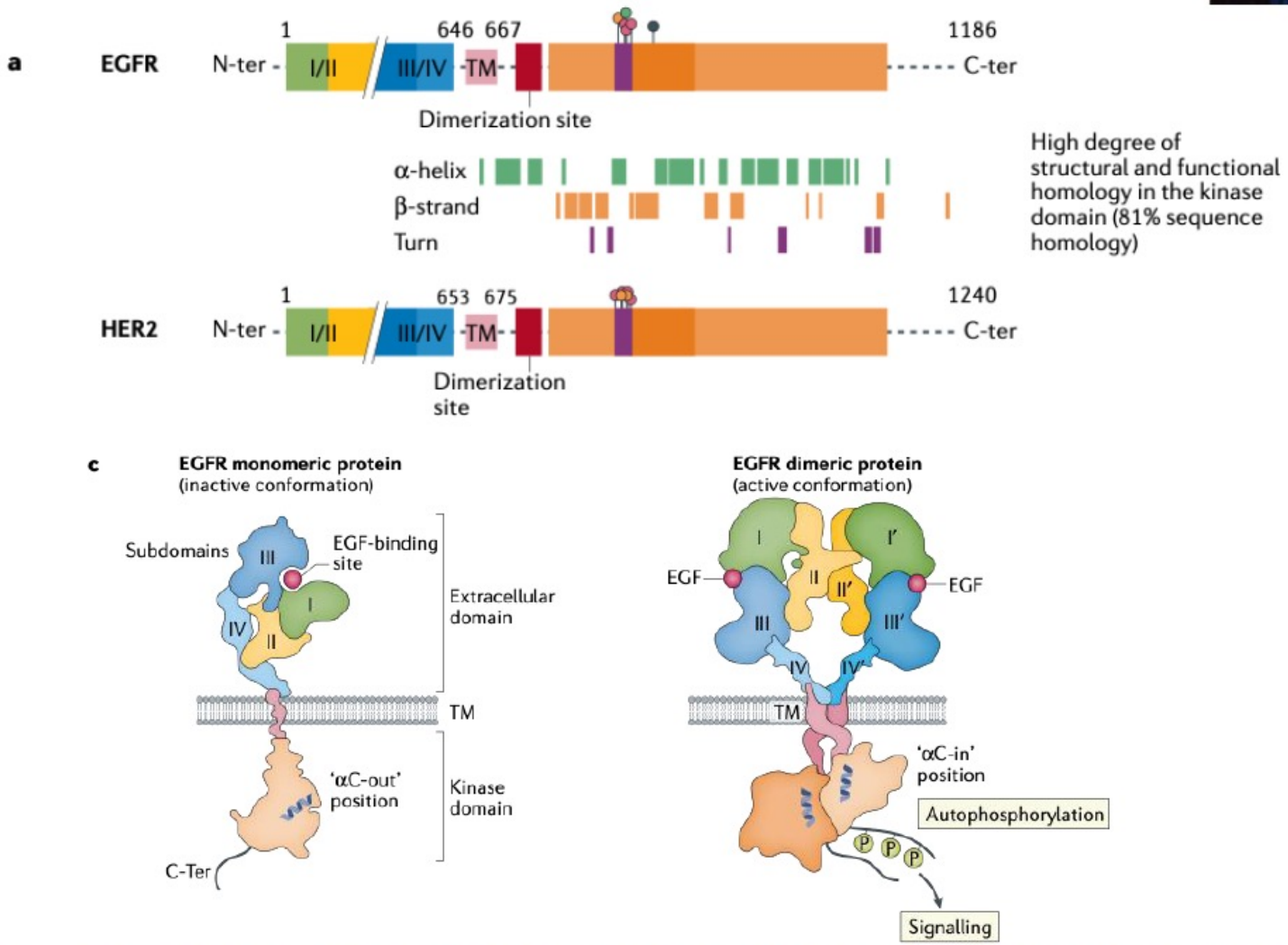
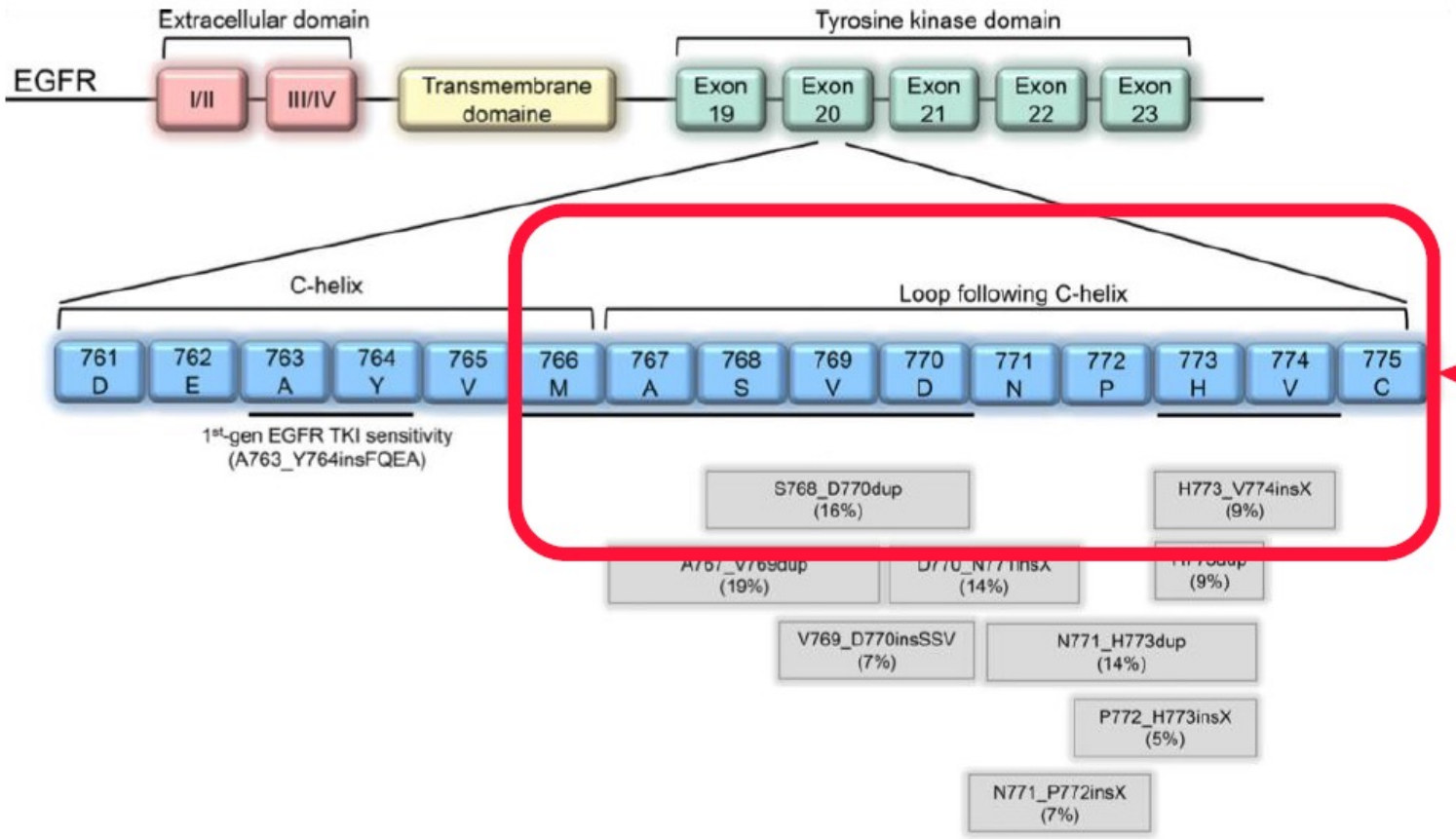
EGFR ex 20 and HER2



- EGFR and HER2 exon 20 regions share a high level of structural and functional homology (81%)[1]
- More than 90% of the insertion mutations are located between amino-acids 766 and 775 and usually involve insertions or duplications of 1-4 amino-acids
- Presence of the exon 20 insertion pushes the αC-helix in an "αC-in" conformation, resulting in constitutive activation and signaling

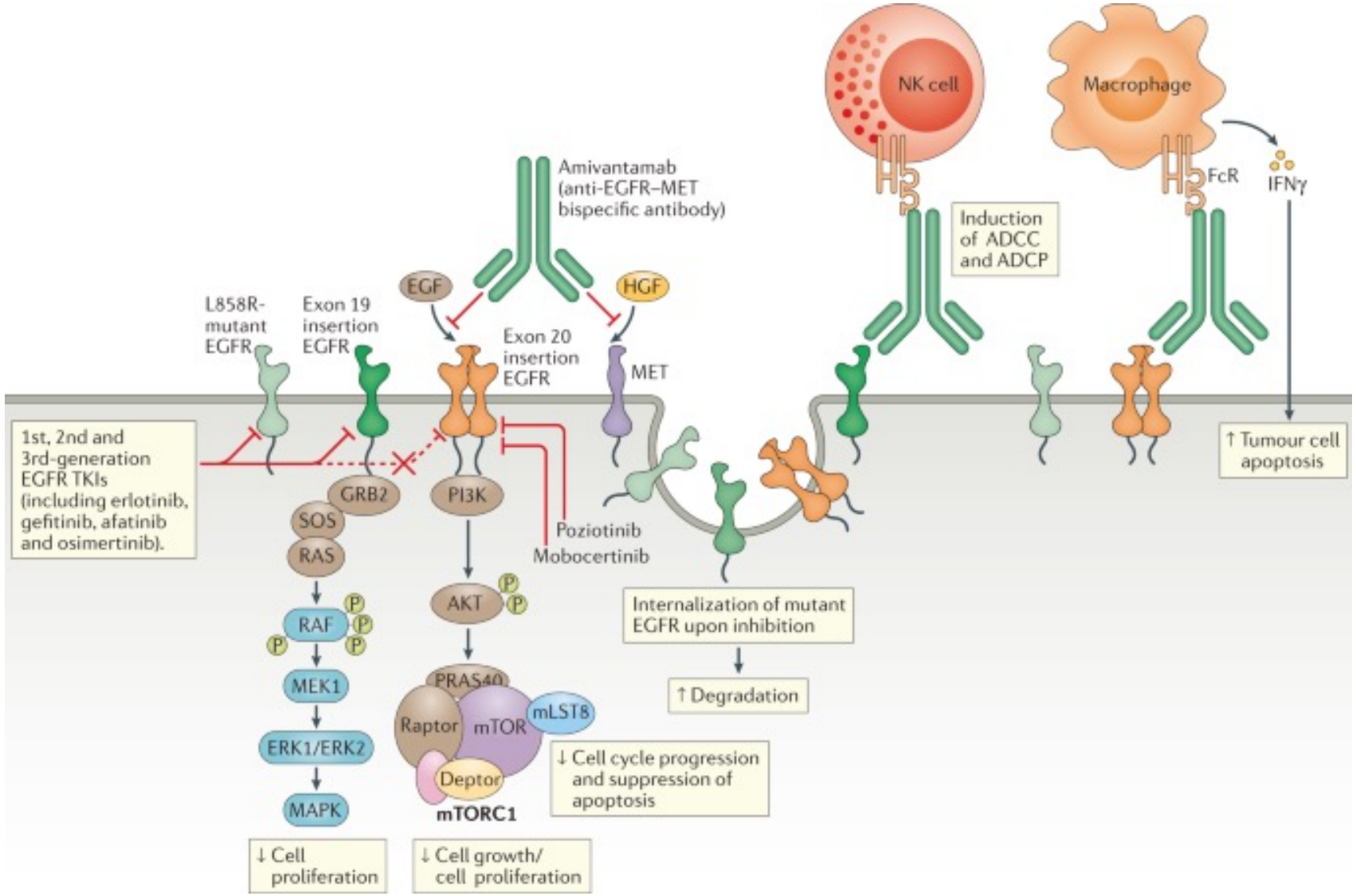
1. Friedlander A. et al. Nat Rev. Clin. Oncol 2021

Why are Exon 20 insertion mutations more difficult to target?



The vast majority of EGFR and HER2 exon 20 mutations are located in the loop which follows the C-helix (outside of the ATP binding pocket), meaning that most conventional TKIs binding in the ATP pocket are NOT active[1]

1. Meador et al. Cancer Discovery 2021



Friedlander A et al Nat Rev Clin Oncol 2021

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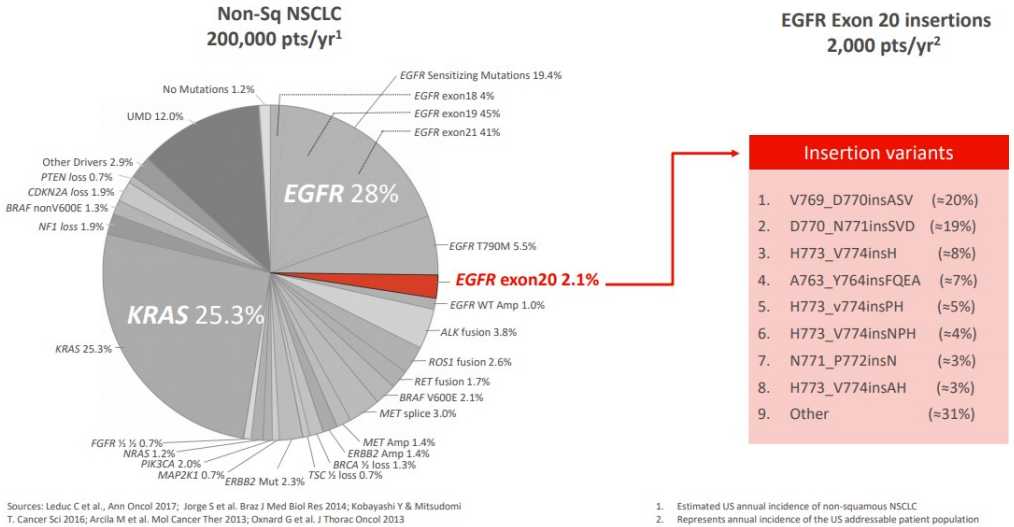
EGFR exon 20 insertions represent 2-12% of EGFR alterations and have a poor response to TKIs and PD-(L)1 therapy



EGFR Exon 20 insertions
2,000 pts/yr[2]

Insertion variants	
1. V769_D770insASV	(≈20%)
2. D770_N771insSVD	(≈19%)
3. H773_V774insH	(≈8%)
4. A763_Y764insFQEA	(≈7%)
5. H773_v774insPH	(≈5%)
6. H773_V774insNPH	(≈4%)
7. N771_P772insN	(≈3%)
8. H773_V774insAH	(≈3%)
9. Other	(≈31%)

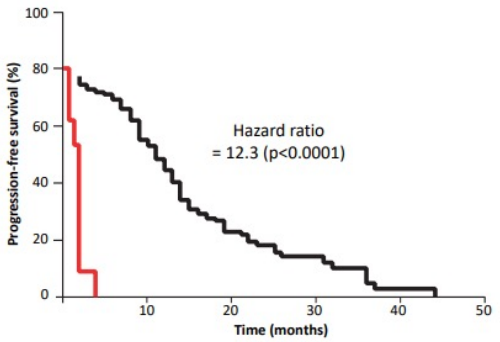
Sources: Leduc C et al., Ann Oncol 2017; Jorge S et al. Braz J Med Biol Res 2014; Kobayashi Y & Mitsudomi T. Cancer Sci 2016; Arcila M et al. Mol Cancer Ther 2013; Oxnard G et al. J Thorac Oncol 2013

1. Estimated US annual incidence of non-squamous NSCLC
2. Represents annual incidence of the US addressable patient population

2

POOR RESPONSE TO EXISTING TKIs [1]

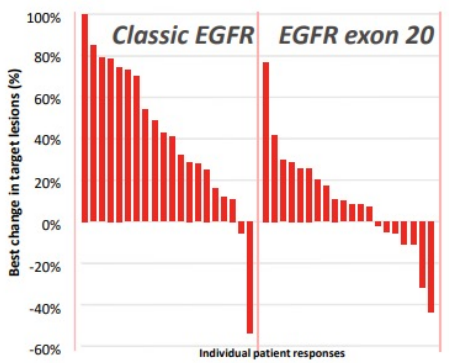
EGFR exon 20 insertions do not demonstrate significant PFS benefit with 1st and 2nd gen EGFR TKIs



Group	Median PFS (months)
EGFR exon 20 ins (n=9)	2.0
Classical EGFR mut (n=129)	12.0

POOR RESPONSE TO ANTI PD-1/PDL-1 THERAPY [2]

EGFR exon 20 ins patients demonstrate limited benefit to anti PD-1 directed therapy



Group	Median PFS (months)	PDL-1 expression ≥1%
EGFR exon 20 ins (n=20)	2.7 (1.7-3.8)	40%
Classical EGFR mut (n=22)	1.8 (1.2-2.4)	25%

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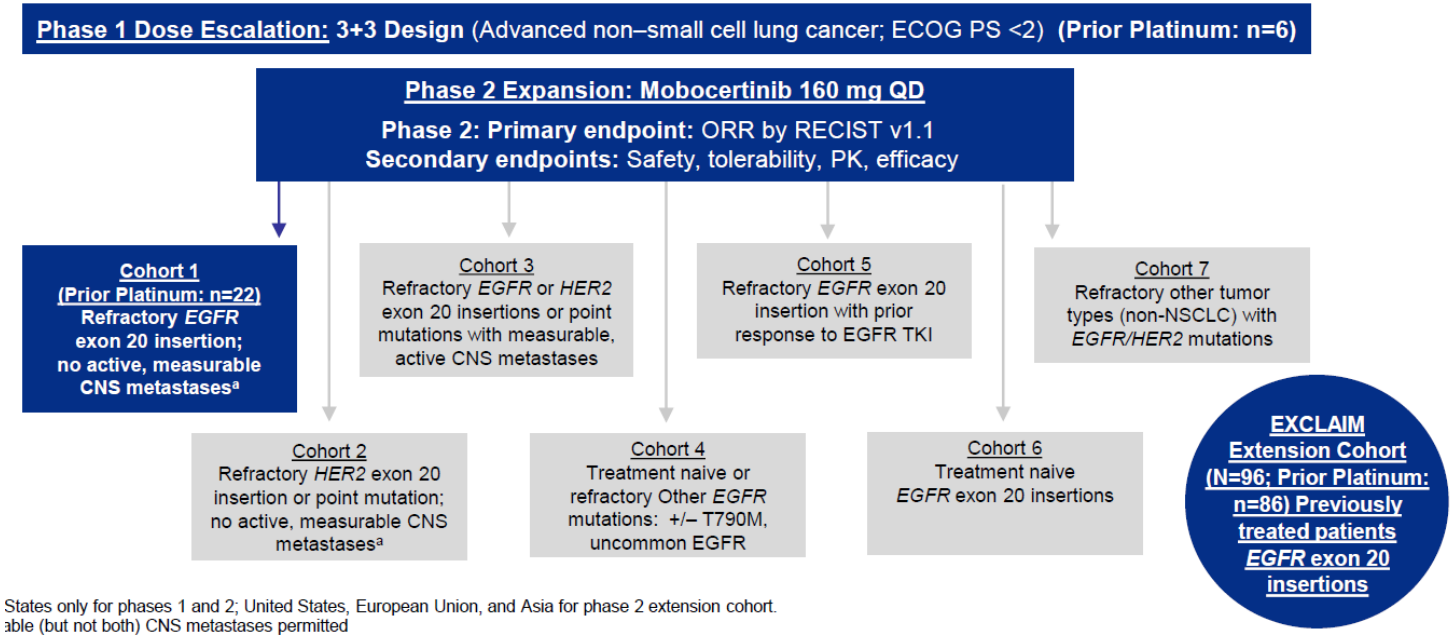
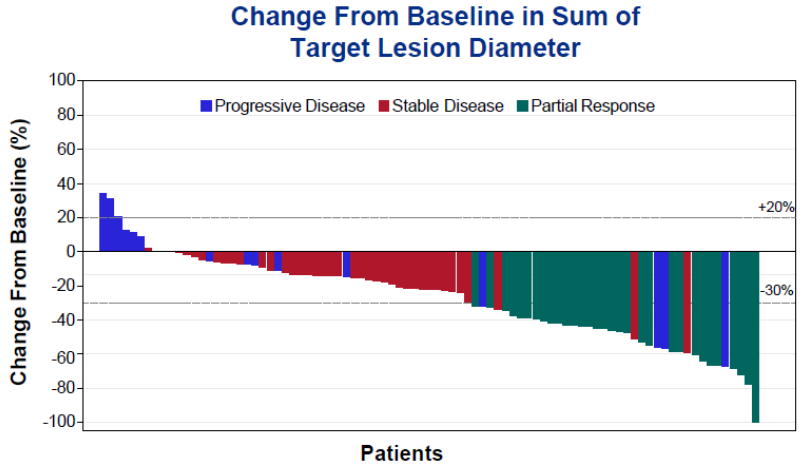
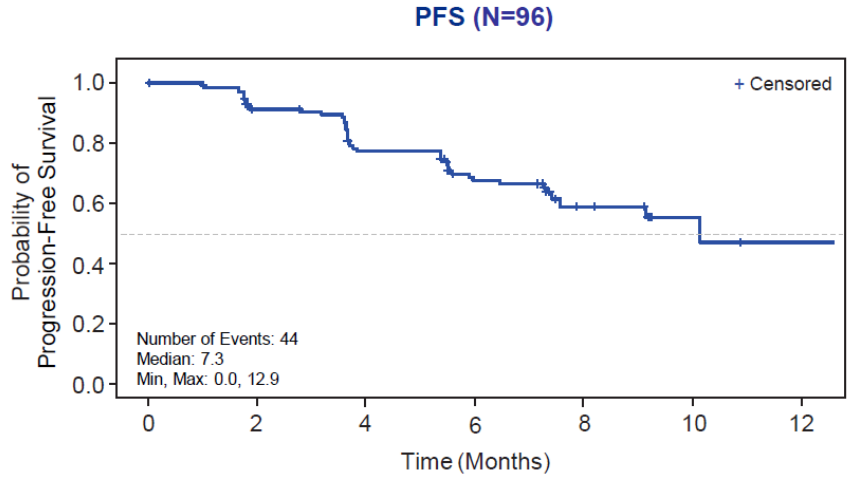
Mobocertinib: EXCLAIM Trial

TAK-788 is a highly selective EGFR/HER2 inhibitor





- 77 patients (80%) had a reduction from baseline in the sum of target lesion diameter



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Mobocertinib (TAK-788): Moving in the 1L Setting

April 2020: Breakthrough Therapy Designation

April 2021: FDA Grants Priority Review

NEW ACTIVATION: A TRIAL FOR NEWLY DIAGNOSED PATIENTS

Exclaim-2

2 year enrollment
Anticipated approval 2023

· Randomized, controlled, Phase 3 trial
· Treatment-naïve EGFR exon 20 insertion patients

- Advanced or metastatic
- Treatment-naïve patients diagnosed with NSCLC harboring EGFR exon 20 insertion mutations

R 1:1

TAK-788 at 160 mg qd

Platinum doublet

1. Median Progression Free Survival
2. Overall Response Rate
3. Duration of Response
4. Overall survival

Electronic patient reported outcomes

· ACTIVELY ENROLLING
· US, EU, LATIN AMERICA AND ASIA-PACIFIC

Source. https://clinicaltrials.gov/ct2/show/NCT04129502

9

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Amivantamab: CHRYSALIS Trial

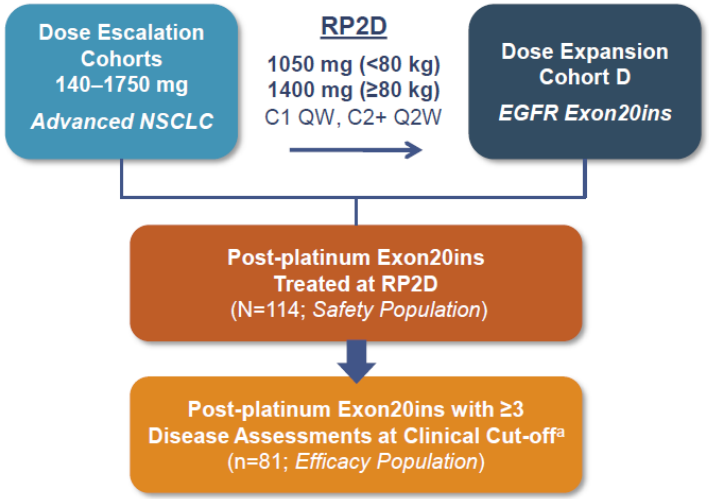
JNJ-6372 is an EGFR and MET bispecific antibody

Key Objectives

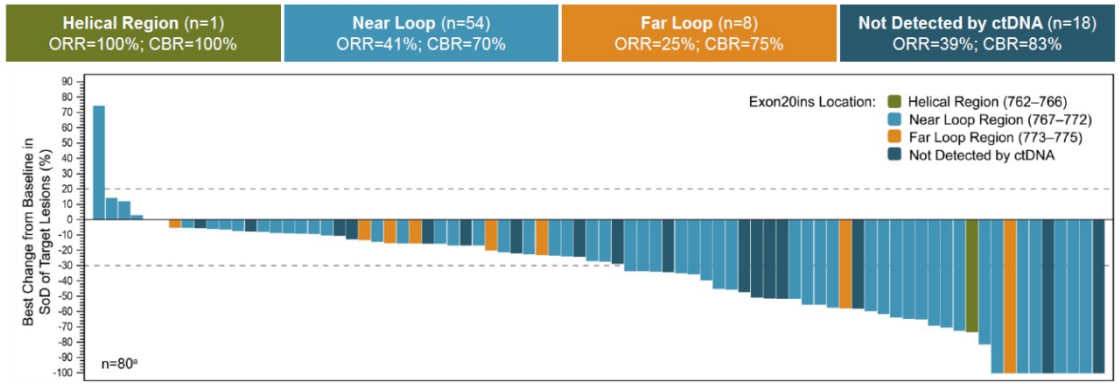
- Dose escalation: Establish RP2D
- Dose expansion: Assess safety and efficacy at RP2D

Key Eligibility Criteria for Post-platinum Population

- Metastatic/unresectable NSCLC
- EGFR Exon20ins mutation
- Progressed on platinum-based chemotherapy



Best ORR by Insertion Region of Exon 20 (detected by ctDNA)



25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

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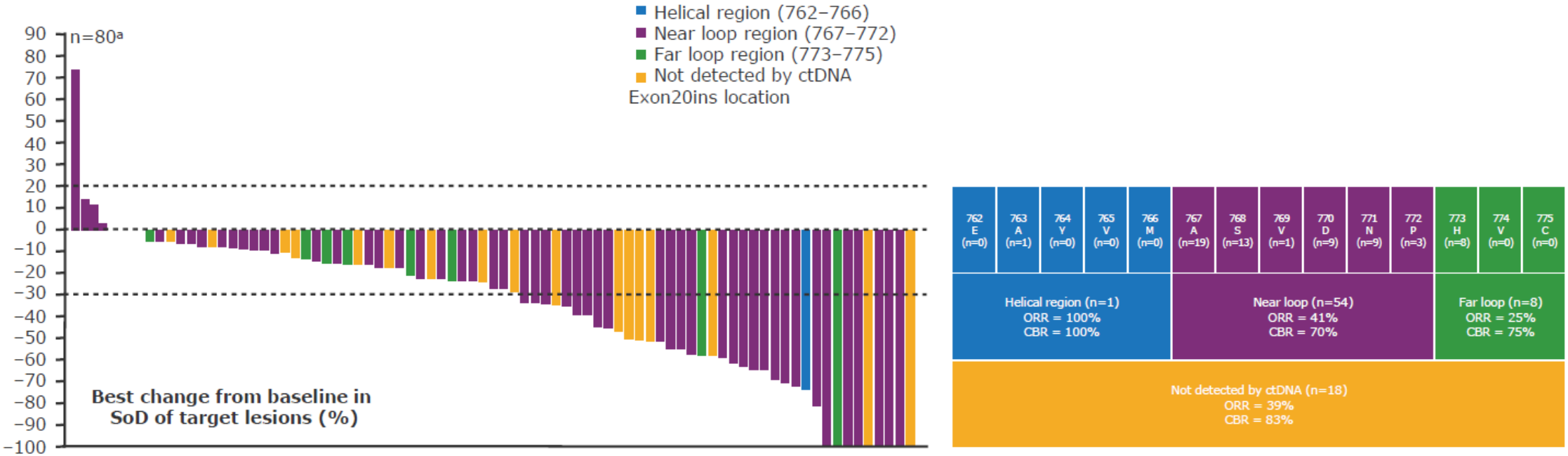
In the CHRYSALIS study, **antitumor responses were observed across the EGFR exon20ins**, in patients who harboured insertions within the **helical, near-loop, and far-loop regions of exon 20**[1]

Tumour reduction and responses in the efficacy population (n=80)[1]



One patient discontinued before any disease assessment and is not included in the plot. Dotted lines at 20% and −30% indicate thresholds for progressive disease and partial response, respectively, as per RECIST, v1.1.
CBR, clinical benefit rate; ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; Exon20ins, exon 20 insertion; ORR, overall response rate; SoD, sum of lesion diameters.

Park K, et al. *J Clin Oncol.* 2021;39(30):3391–3402;

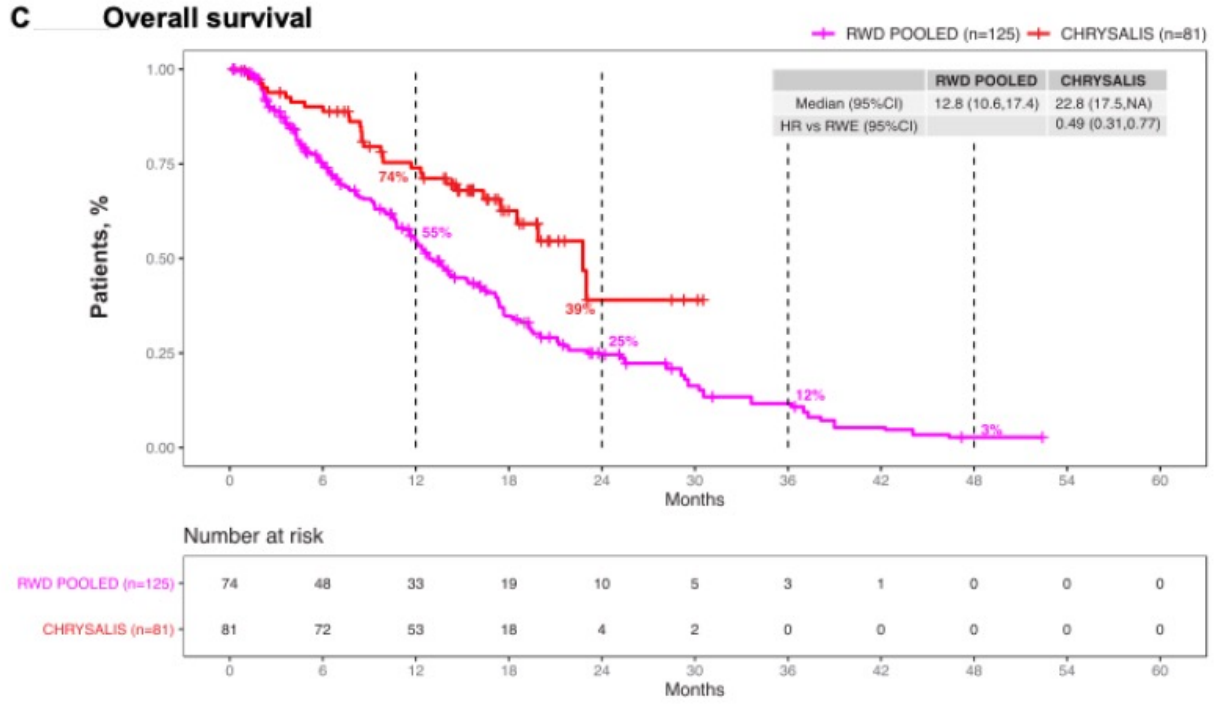
IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Amivantamab compared with real-world therapies in patients with advanced non-small cell lung cancer harboring EGFR exon 20 insertion mutations who progressed after platinum-based chemotherapy

Anna Minchom [a,*], Santiago Viteri [b,1], Lyudmila Bazhenova [c], Shirish M. Gadgeel [d], Sai-Hong Ignatius Ou [e], José Trigo [f], Joshua M. Bauml [g,2], Daniel Backenroth [h], Archan Bhattacharya [h], Tracy Li [i], Parthiv Mahadevia [i], Nicolas Girard [j]

[a] Drug Development Unit, Royal Marsden/Institute of Cancer Research, Sutton, United Kingdom
[b] Instituto Oncológico Dr Rosell, Centro Médico Teknon, Grupo QuironSalud, Barcelona, Spain
[c] University of California San Diego, San Diego, CA, USA
[d] Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI, USA
[e] University of California Irvine, Orange, CA, USA
[f] Hospital Universitario Virgen de la Victoria y Regional, IBIMA, Malaga, Spain
[g] Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[h] Janssen R&D, High Wycombe, United Kingdom
[i] Janssen R&D, Raritan, NJ, USA
[j] Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France



Indirectly compared using RWD, Amivantamab confers a median OS benefit of 10 months over conventional treatment strategies

Matching-Adjusted Indirect Comparison (MAIC) of Mobocertinib vs Amivantamab in Patients with Non-Small Cell Lung Cancer (NSCLC) with *EGFR* Exon 20 Insertions (ex20ins)

Sai-Hong I. Ou[1], Thibaud Prawitz[2], Huamao M. Lin[3], Jin-Liern Hong[3], Min Tan[2], Irina Proskorovsky[2], Luis Hernandez[4], Shu Jin[3], Pingkuan Zhang[3], Jianchang Lin[3], Jyoti Patel[5], Danny Nguyen[6], Joel W. Neal[7]

[1]Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA, USA; [2]Evidera, Inc, Lexington, MA, USA; [3]Takeda Development Center Americas, Inc, Lexington, MA, USA; [4]Takeda Pharmaceuticals America Lexington, MA, USA; [5]Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA; [6]City of Hope National Medical Center, Los Angeles, CA, USA; [7]Stanford Cancer Institute, Stanford University, Stanford, CA, USA

Mobocertinib (NCT02716116)[7,8]
(Individual-Level Data)

114 platinum-pretreated patients receiving mobocertinib 160 mg daily in a phase I/II single-arm study (data cut-off 1 Nov 2020)

Amivantamab (NCT02609776)[9]
(Published Aggregate-Level Data)

81 platinum-pretreated patients receiving amivantamab 1,050 mg (1,400 mg, ≥80 kg) with ≥3 disease assessments in CHRYSALIS, a phase I single-arm study (data cut-off 8 June 2020)

Mobocertinib patients

Amivantamab patients

1. MATCH the study populations

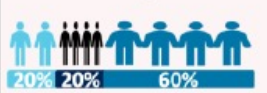
- The two trials had similar inclusion and exclusion criteria; thus, all patients from both trials were included for analysis.
- Different baseline characteristics of the two trial populations were observed (as shown in the hypothetical example).

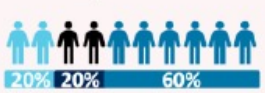
Apply weights

Published data (remain the same)

2. ADJUST for baseline characteristics

- Individual mobocertinib patients were re-weighted based on their characteristics at baseline to resemble those of amivantamab patients.
- MAIC weights were computed by propensity score models estimated by the generalized method of moments.[10]
- All baseline characteristics commonly available and similarly defined in both trials are listed in Table 1 and were adjusted. These variables were balanced after weighting.

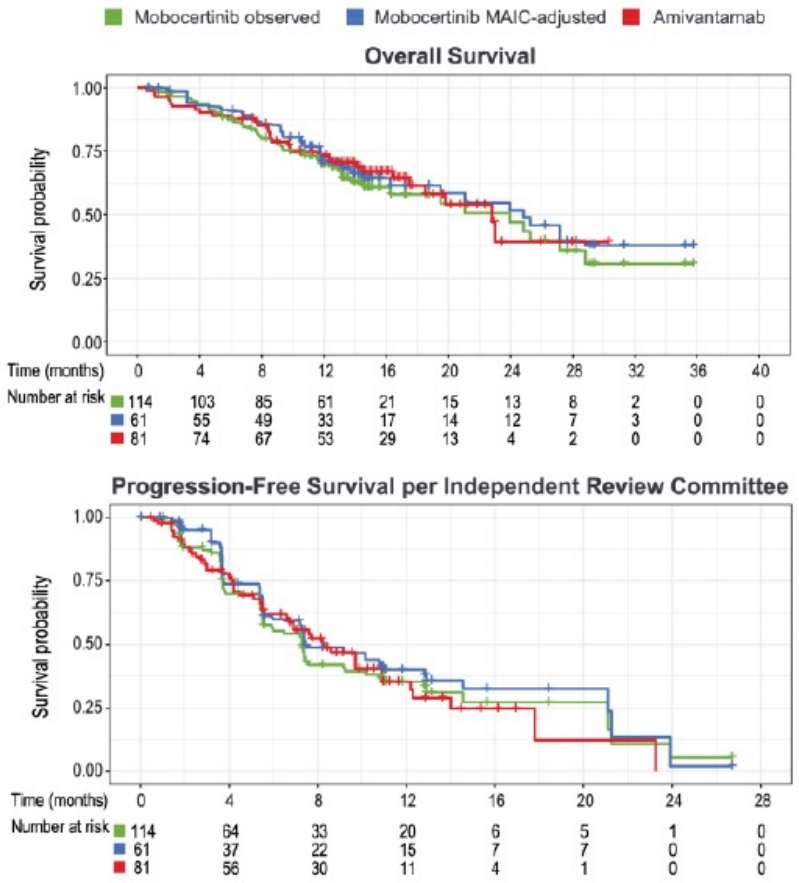




3. INDIRECT COMPARISON

- The outcomes were compared between the weighted mobocertinib patients and the amivantamab patients.
- Outcomes included confirmed overall response rate (cORR), progression-free survival (PFS), overall survival (OS), and duration of response (DoR).

Figure 1. Kaplan-Meier curves before and after weighting

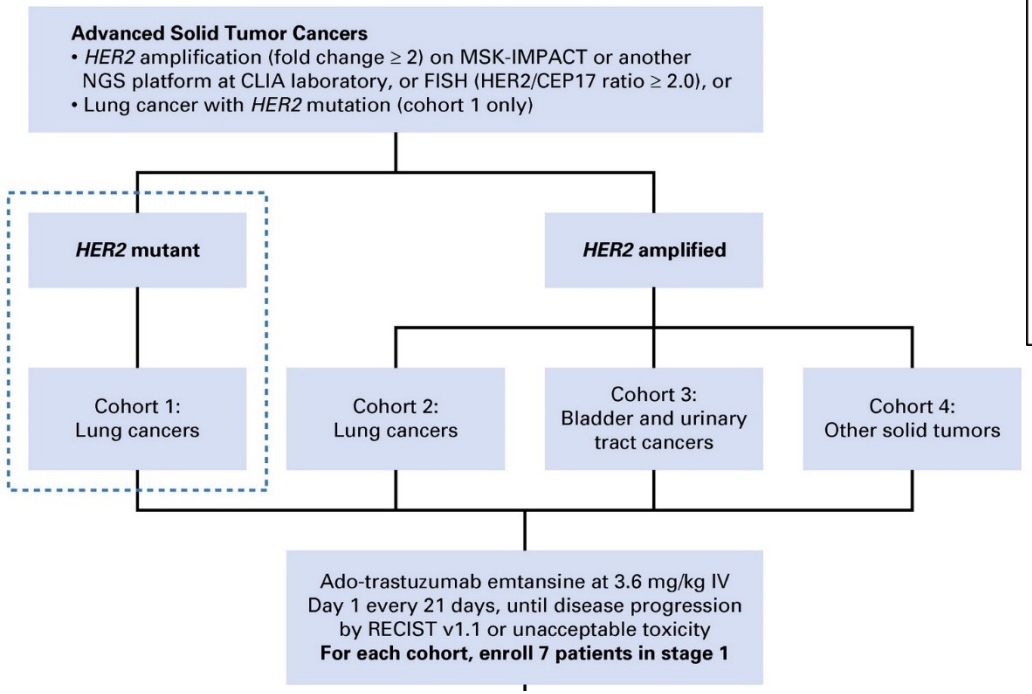


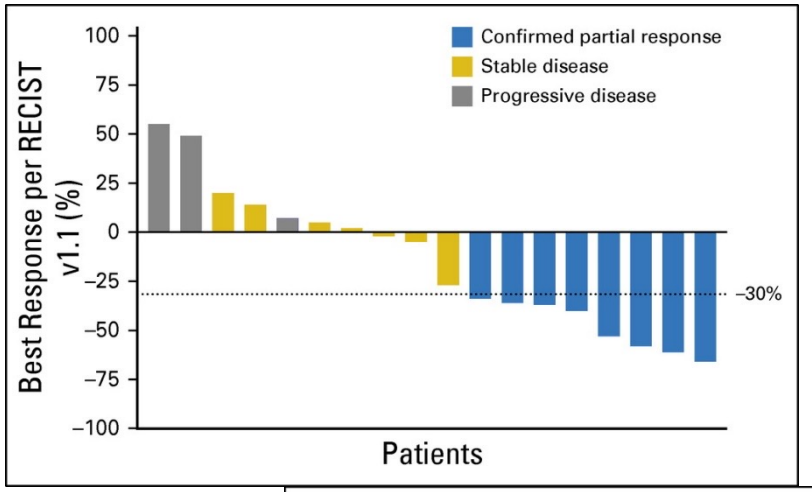
HER2

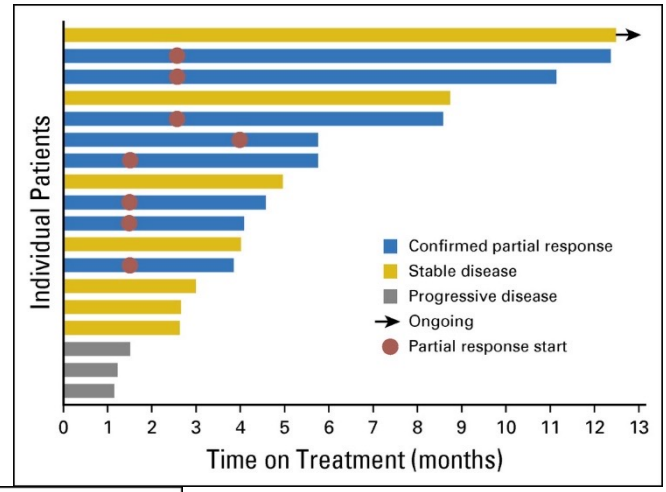
Conventional treatments exhibit modest activity in EGFR/HER2 exon 20 mutations

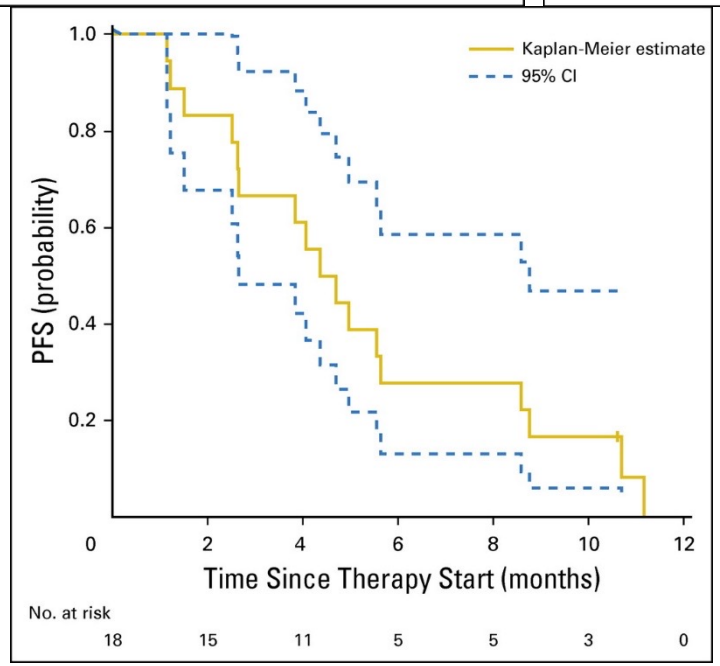
AGENT	TARGET	N	ORR (%)	mPFS (months)	mOS (months)	REF
Platinum+ Pemetrexed	EGFR Exon 20	152	NR	6.2	18.2	*Wu JY et al. Clin Lung Cancer 2019*
Afatinib	EGFR Exon 20	23	8.7	2.7	9.2	*Yang et al. Lancet Oncol 2015*
Osimertinib	EGFR Exon 20	21	25	9.7	-	*Piotrowska et al. J Clin Oncol 2020*
Afatinib	HER2 Exon 20	23	7.7	3.9	-	*Mazières et al. Ann. Oncol 2016*
Dacomitinib	HER2 Exon 20	26	11.5	3.0	9.0	*Kris et al. Ann Oncol 2015*
Pyrotinib	HER2 Exon 20	15	8.0	6.4	12.9	*Wang et al. Ann Oncol 2019*
Neratinib + Temsirolimus	HER2 Exon 20	14	21.0	4.0	-	*Besse et al. Ann Oncol 2014*

Ado-Trastuzumab Emtansine (T-DM1) in HER2-Mutant NSCLC









Li BT et al. *J Clin Oncol*. 2018;36(24):2532-2537
.Liu S. TTLC 2021. February 18, 2021;

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Trastuzumab Deruxtecan in HER2-Mutated mNSCLC: Interim Results of DESTINY-Lung01

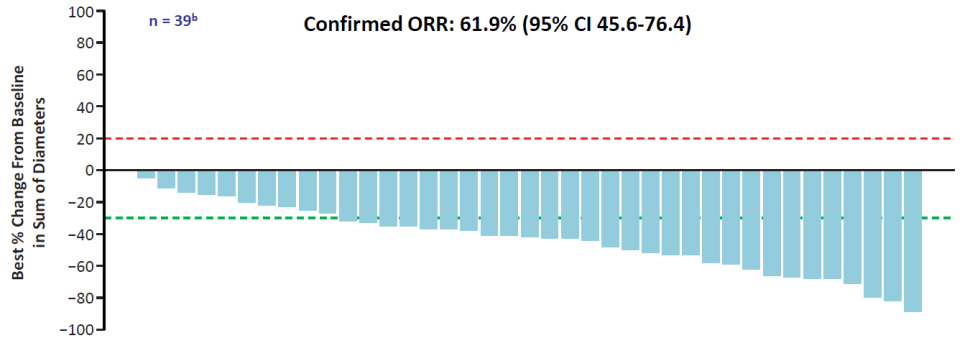
Key eligibility criteria

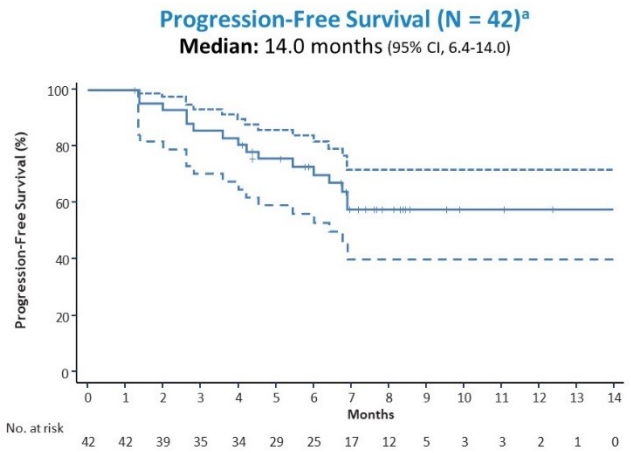
- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- ECOG PS of 0 or 1

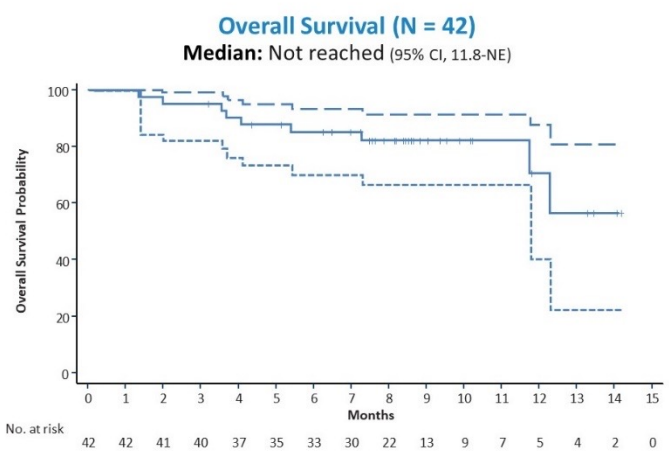
Cohort 1:
HER2-overexpressing[a]
(IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg q3w
n = 49

Cohort 2: HER2-mutated
T-DXd 6.4 mg/kg q3w
n = 42
(Encore to be presented at WCLC: abstract 1419)[b]

Best Percentage Change in Tumor Size[a] With T-DXd







Smit EF et al. *J Clin Oncol*. 2020;38(15_suppl):9504-9504.
Smit EF et al. 2020 WCLC. Abstract MA11.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer

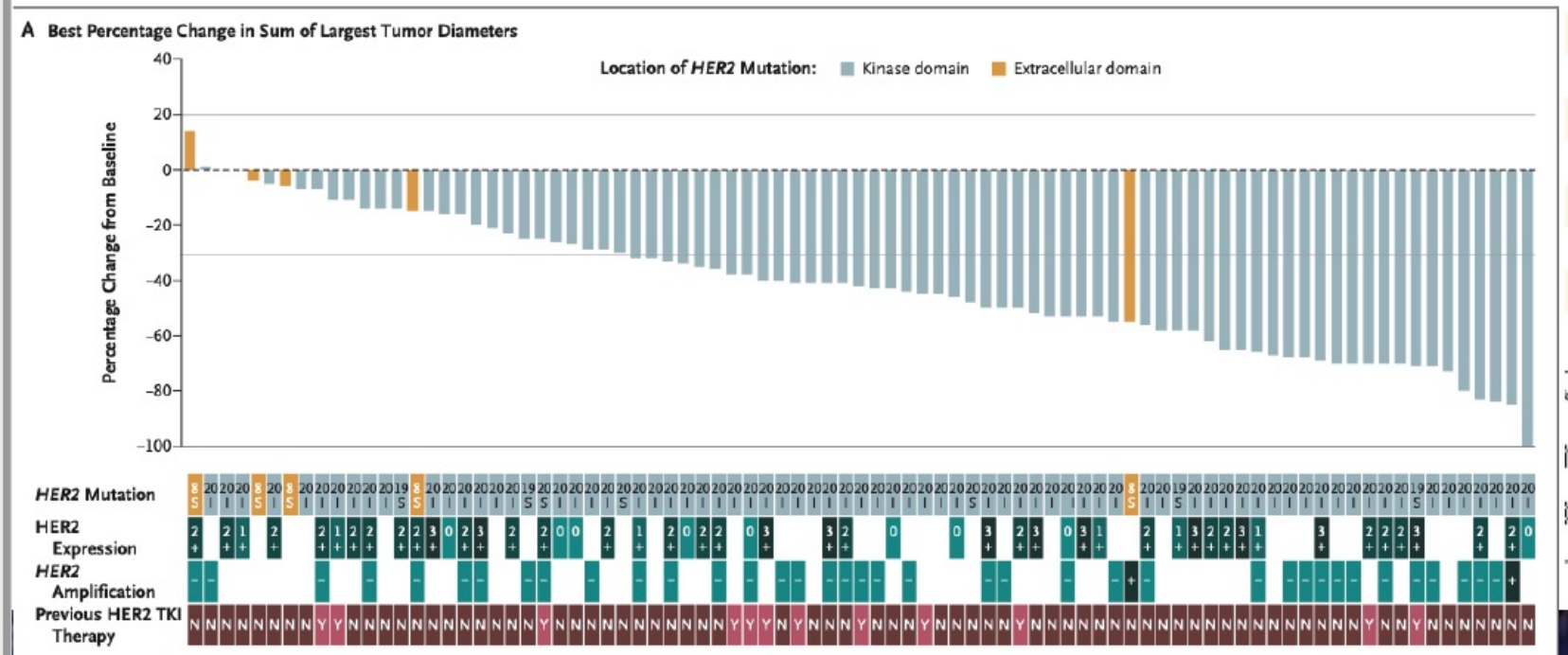

Table 2. Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review.

Response Assessment	Patients (N=91)
Confirmed objective response*	
No. of patients	50
Percentage of patients (95% CI)	55 (44–65)
Best response — no. (%)	
Complete response	1 (1)
Partial response	49 (54)
Stable disease	34 (37)
Progressive disease	3 (3)
Response could not be evaluated	4 (4)
Disease control†	
No. of patients	84
Percentage of patients (95% CI)	92 (85–97)
Median time to response (range) — mo‡	1.5 (1.2–9.3)
Median duration of response (95% CI) — mo‡	9.3 (5.7–14.7)

* Confirmed objective response was assessed by independent central review on the basis of the Response Evaluation Criteria in Solid Tumors, version 1.1.
† Disease control was defined as complete response, partial response, or stable disease at 6 weeks with no progression.
‡ Analyses of time to response and duration of response included only the patients with a confirmed objective response.

B. T. Li et al. N Engl J Med 2022

Patients should be closely monitored for signs and symptoms of ILD and treated aggressively according to guidelines

Table S5. Adjudicated Drug-related Interstitial Lung Disease.

	Patients (N = 91)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Adjudicated drug-related interstitial lung disease, n (%)*	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)†	24 (26.4)

CONCLUSIONS

Trastuzumab deruxtecan showed durable anticancer activity in patients with previously treated *HER2*-mutant NSCLC. The safety profile included interstitial lung disease that was fatal in two cases. Observed toxic effects were generally consistent with those in previously reported studies. (Funded by Daiichi Sankyo and AstraZeneca; DESTINY-Lung01 ClinicalTrials.gov number, NCT03505710.)

Driver Negative 2L+ NSCLC: TROP2

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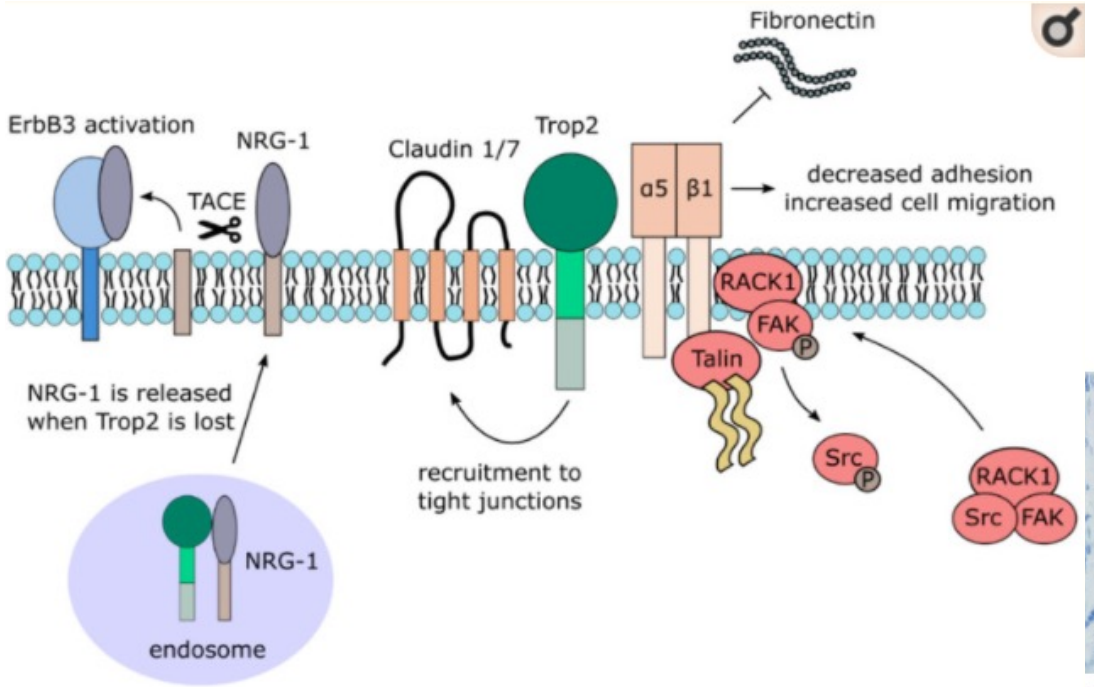
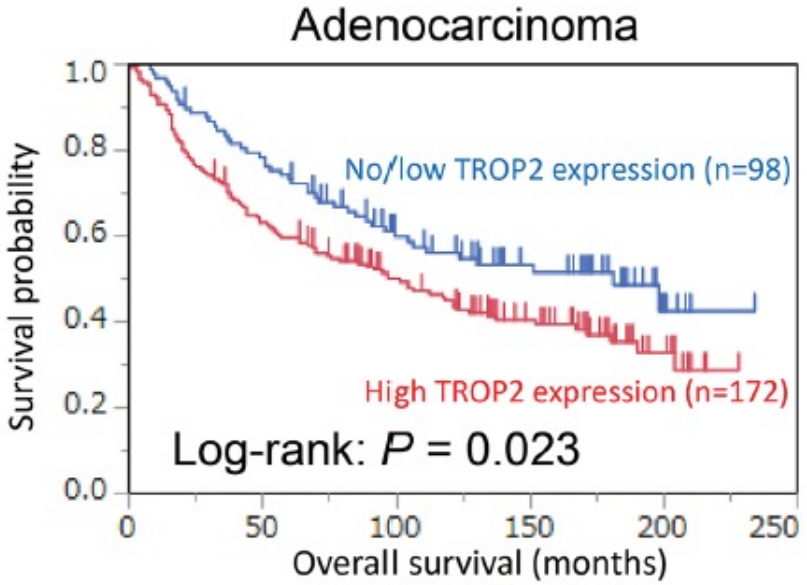
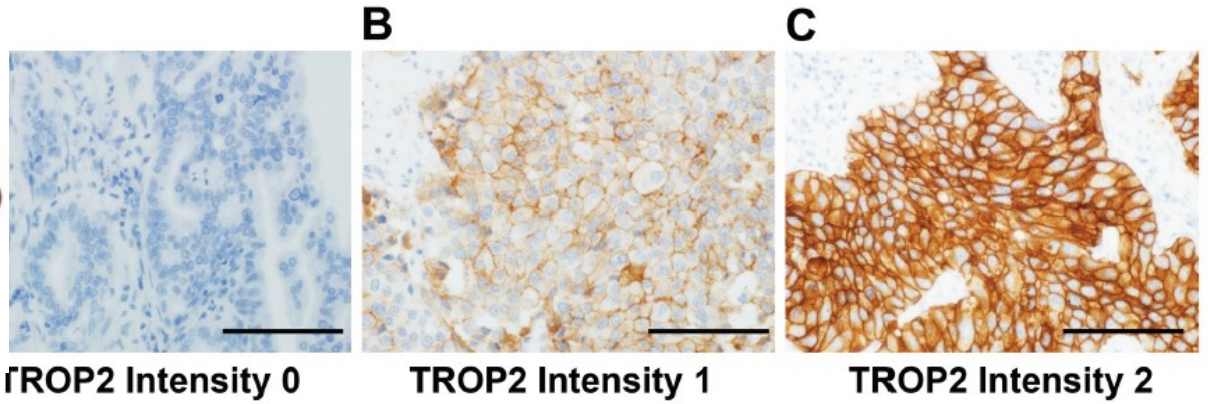
TROP2 in NSCLC

- TROP2, a transmembrane glycoprotein, is highly expressed in NSCLC and other solid tumors[1-5]
  - High TROP2 expression is associated with poor prognosis, making it a promising therapeutic target[6]





There is no current testing recommendation for TROP2 Identified by IHC (see below)



Lenart et al, Cancers 2020
Inamura et al. Oncotarget 2018
Jiang et al. Oncol Lett 2013

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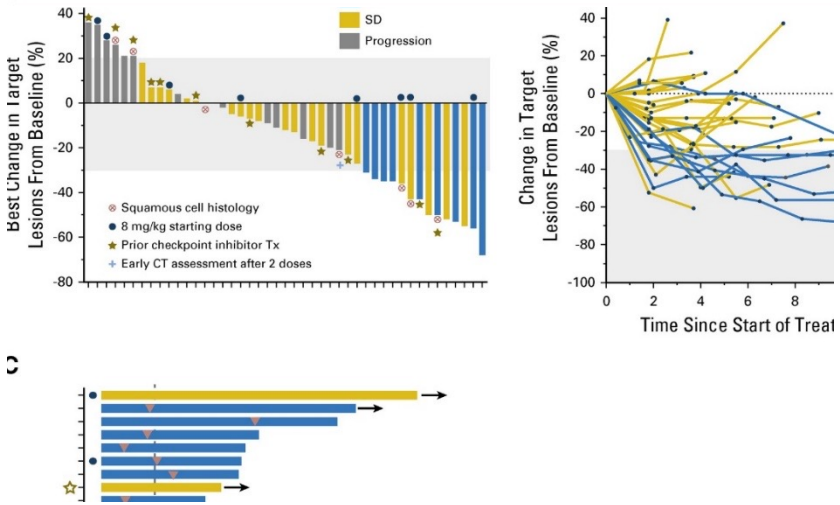
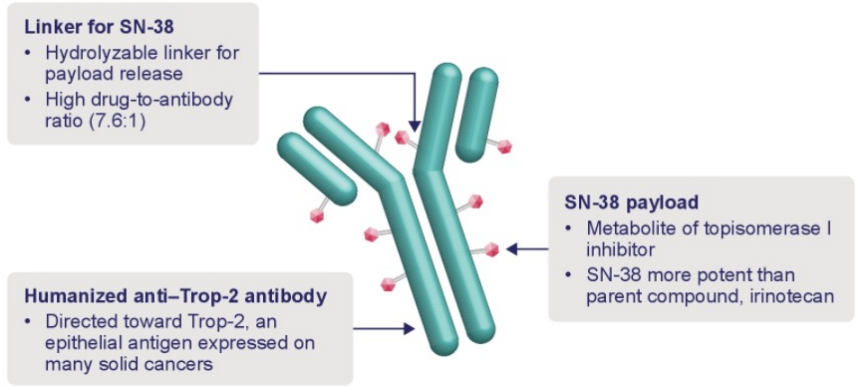
Sacituzumab govitecan

Table 2. Clinical Outcomes for Sacituzumab Govitecan in Metastatic NSCLC Irrespective of Trop-2 Expression[21]

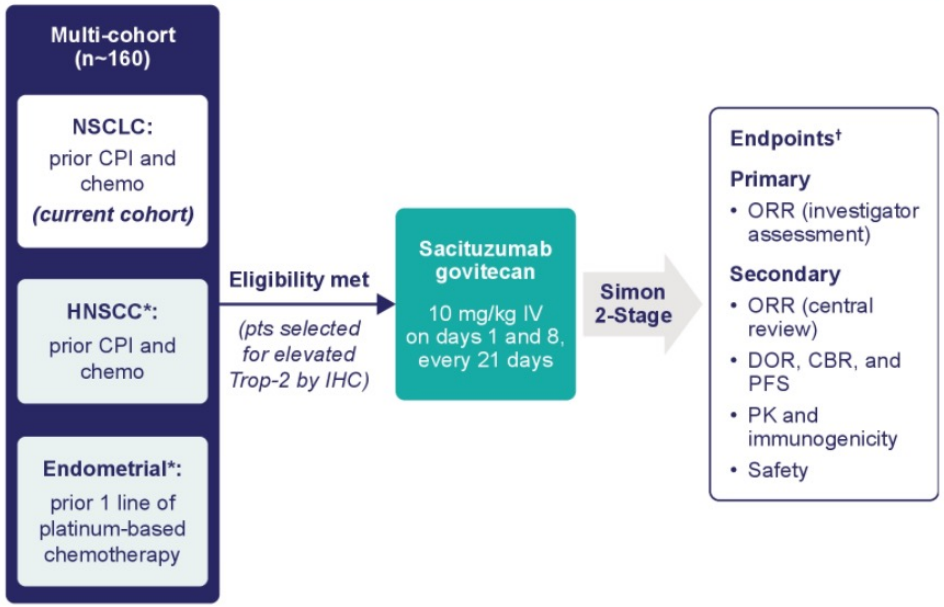
Clinical Outcomes	All NSCLC	Prior CPI
Response Outcomes*	**n=47; ITT**	**n=14**
ORR, n/n (%)	9/47 (19)	2/14 (14)
CR, n	0	0
PR, n	9	2
Median DOR, mo (95% CI)	6.0 (4.8-8.3)	NR
CBR (CR+PR+SD ≥4 mo), n/n (%)	20/47 (43)	5/14 (36)
Survival Outcomes	**N=54**	**n=14**
Median PFS, mo (95% CI)	5.2 (3.2-7.1)	5.2 (2.0-5.5)
Median OS, mo (95% CI)	9.5 (5.9-16.7)	14.6 (5.9-14.6)





Ongoing trial for TROP2+ Solid Tumors

Figure 2. TROPiCS-03: Phase 2, Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Solid Tumors (NCT03964727)



Goldenberg, Stein & Sharkey, Oncotarget 2018
Saxena et al, ASCO 2020

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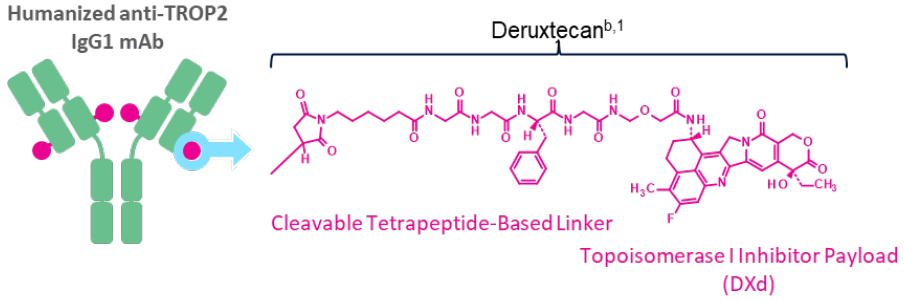
Datopotamab Deruxtecan (Dato-DXd; DS-1062)

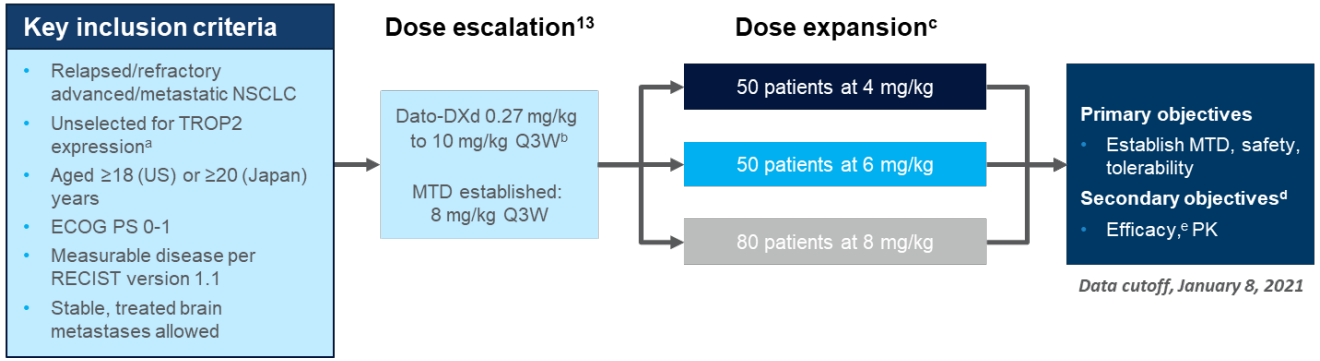


Designed With 7 Key Attributes:

- Payload mechanism of action: topoisomerase I inhibitor [a,7]
- High potency of payload [a,8]
- Optimized drug to antibody ratio ≈4 [a,c,7]
- Payload with short systemic half-life [a,c,8]
- Stable linker-payload [a,8]
- Tumor-selective cleavable linker [a,8]
- Bystander antitumor effect [a,8,12]

Tropion PanTumor01

Figure 2. Study Design



Data cutoff, January 8, 2021

Figure 4. Best Change in Sum of Diameters (BICR)

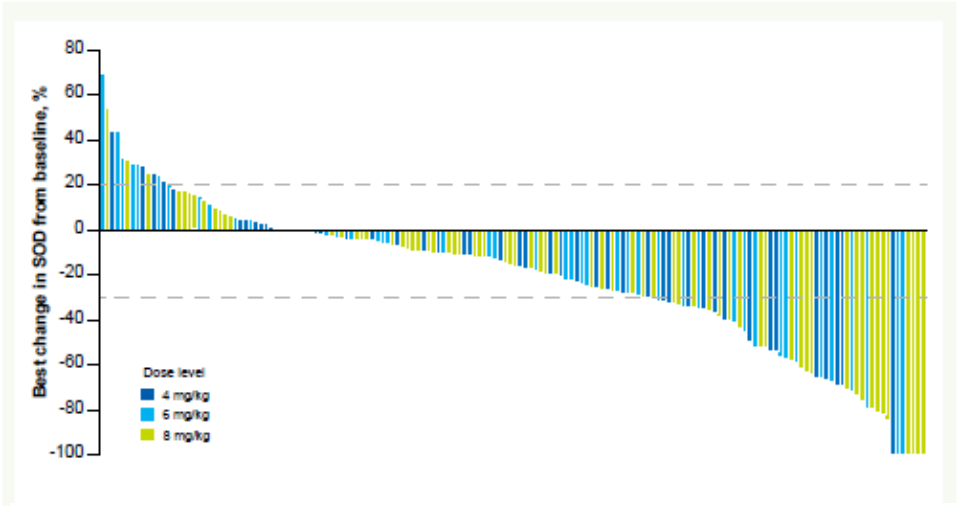


Table 4. Best Overall Response (BICR)

Patients[a]	Dato-DXd Dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)	12 (24)	13 (26)	19 (24)
CR/PR	10 (20)	11 (22)	19 (24)
CR/PR (too early to be confirmed)	2 (4)	2 (4)	0
DCR, n (%)	38 (76)	35 (70)	64 (80)
PD, n (%)	7 (14)	10 (20)	7 (9)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (4.1-NE)	9.0 (5.8-NE)
PFS, median (95% CI), mo[b]	4.3 (3.5-8.4)	6.9 (2.7-8.8)	5.2 (4.1-7.1)

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response.
[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] Median PFS was limited by immature duration of follow-up in the 4- and 6-mg/kg dosing cohorts.

TROPION-Lung02

Key eligibility

- Advanced/metastatic NSCLC
- Dose confirmation[b]: ≤2 lines of prior therapy[c]
- Dose expansion
  - ≤1 line of platinum-based CT (cohorts 1 and 2)[c]
  - No prior therapy (cohorts 3-6)[c]

	Dato-DXd IV Q3W	+	pembro IV Q3W	+	platinum CT IV Q3W	
Cohort 1 (n=20)[d]:	4 mg/kg	+	200 mg			"Doublet"
Cohort 2 (n=20)[d]:	6 mg/kg	+	200 mg			
Cohort 3 (n=17)[d]:	4 mg/kg	+	200 mg	+	carboplatin AUC 5	"Triplet"
Cohort 4 (n=20)[d]:	6 mg/kg	+	200 mg	+	carboplatin AUC 5	
Cohort 5 (n=7)[d]:	4 mg/kg	+	200 mg	+	cisplatin 75 mg/m²	
Cohort 6 (n=4)[d]:	6 mg/kg	+	200 mg	+	cisplatin 75 mg/m²	

In the overall population:

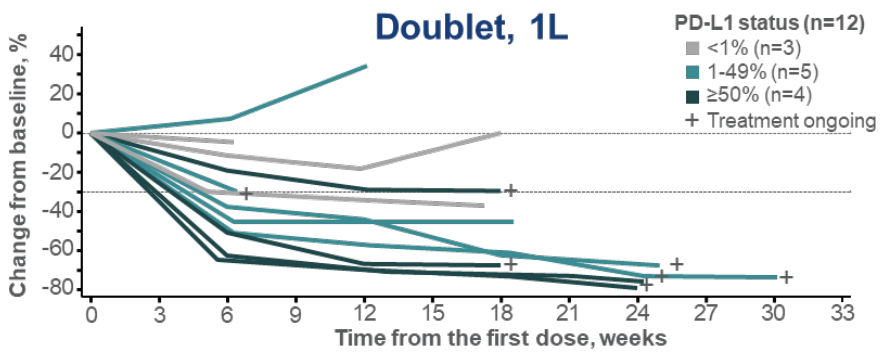
ORRs (confirmed + pending) of 37% and 41% were seen with doublet (n=38) and triplet (n=37) therapy, respectively; both groups had 84% DCR

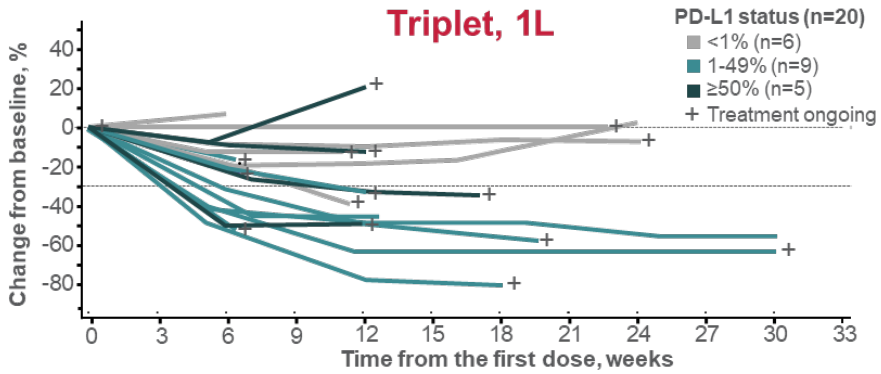
BOR With 1L Therapy For Advanced NSCLC[a,b]

Response, n (%)	Doublet (n=13)	Triplet (n=20)
ORR confirmed + pending	**8 (62%)**	**10 (50%)**
CR	0	0
PR confirmed	8 (62%)	7 (35%)
PR pending	0	3 (15%)
SD	5 (39%)	8 (40%)
DCR	13 (100%)	18 (90%)

- As 1L therapy, the doublet and triplet yielded ORRs (confirmed + pending) of 62% and 50%, respectively
- As 2L+ therapy, respective ORRs (confirmed + pending) were 24% and 29%

Percent Change in Sum of Diameters[a]





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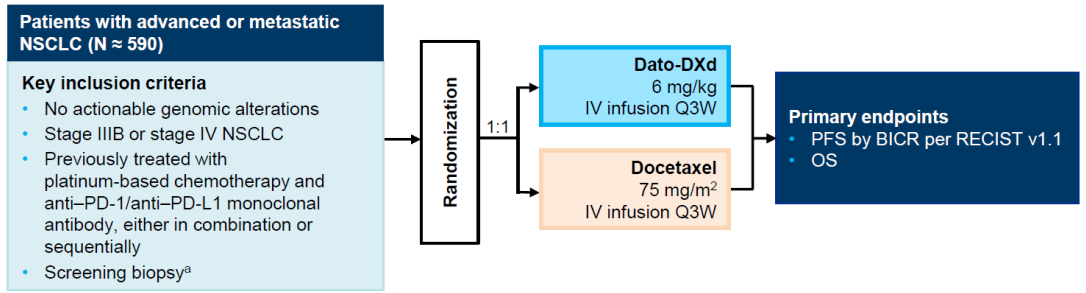
Ongoing TROPION-Lung Studies

As of Jun 2022			FY2021	FY2022	FY2023
NSCLC	All comers	Metastatic 2L/3L	TROPION-Lung01 monotherapy		
	ICI combination Without actionable mutations	Metastatic 1L/2L	TROPION-Lung02 pembrolizumab combination		
			TROPION-Lung04 durvalumab combination		
		Metastatic 1L		TROPION-Lung08 pembrolizumab combination	
	With actionable mutations	Metastatic 2L+	TROPION-Lung05 monotherapy		

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Phase 3 TROPION-Lung01 (NCT04656652) Study Design

- This phase 3 study is open for enrollment



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Conclusions

- ~ 40% NSCLC will have EGFR $^{ex\ 20}$, KRAS ^{G12C}, and HER2
- TROP2 is a promising target in NSCLC
- ADCs are the new TKIs! Lots to be hopeful about

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Thank You