Can We Conquer KRAS Mutations?

Professor Tony Mok

Li Shu Fan Medical Foundation Professor of Clinical Oncology

The Chinese University of Hong Kong

COI Disclosure

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Board of Directors	AstraZeneca Ltd; HutchMed Ltd, Insigta Ltd.

Conquering KRAS mutations

Knowing KRAS

Conquering KRAS:
Our first attempt

Conquering KRAS:
Our future attempt

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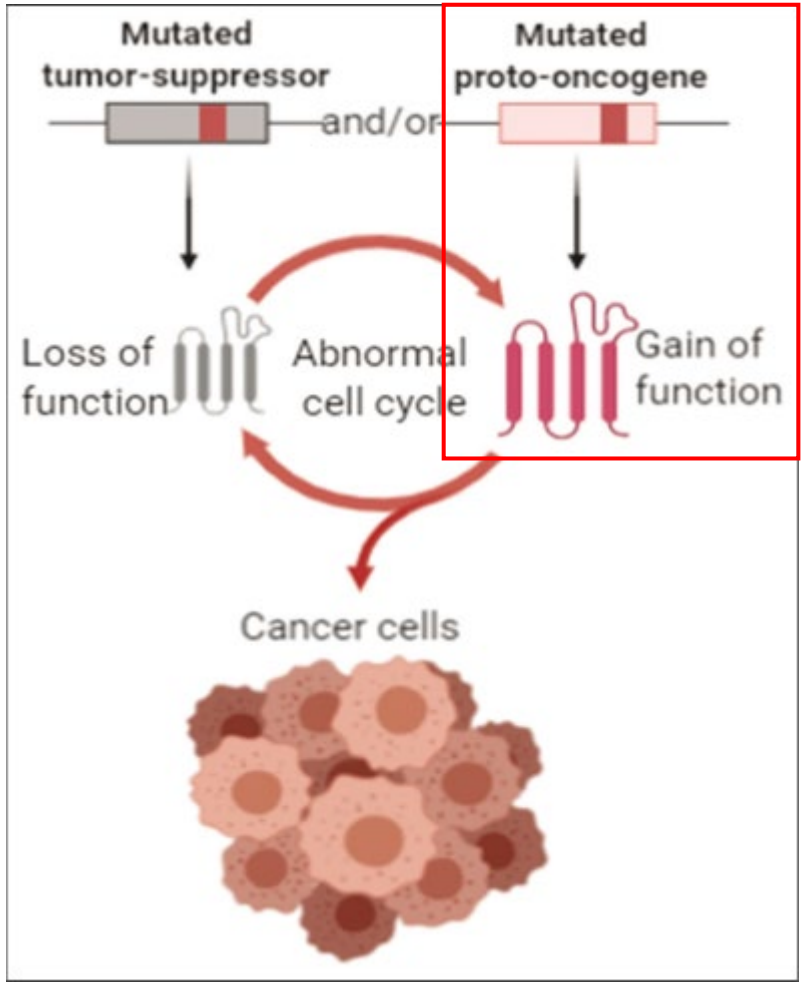
KRAS as a driver mutations

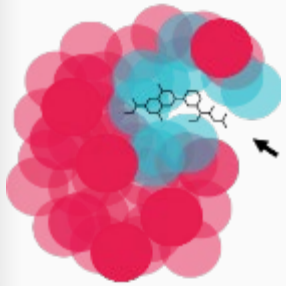


A term used to describe changes in the DNA sequence of genes that cause cells to become cancer cells and grow and spread in the body.

National Cancer Institute

Druggable versus undruggable

Classic protein-drug interaction



Functional pocket required for protein activity

Drug binding in the pocket inhibits protein activity

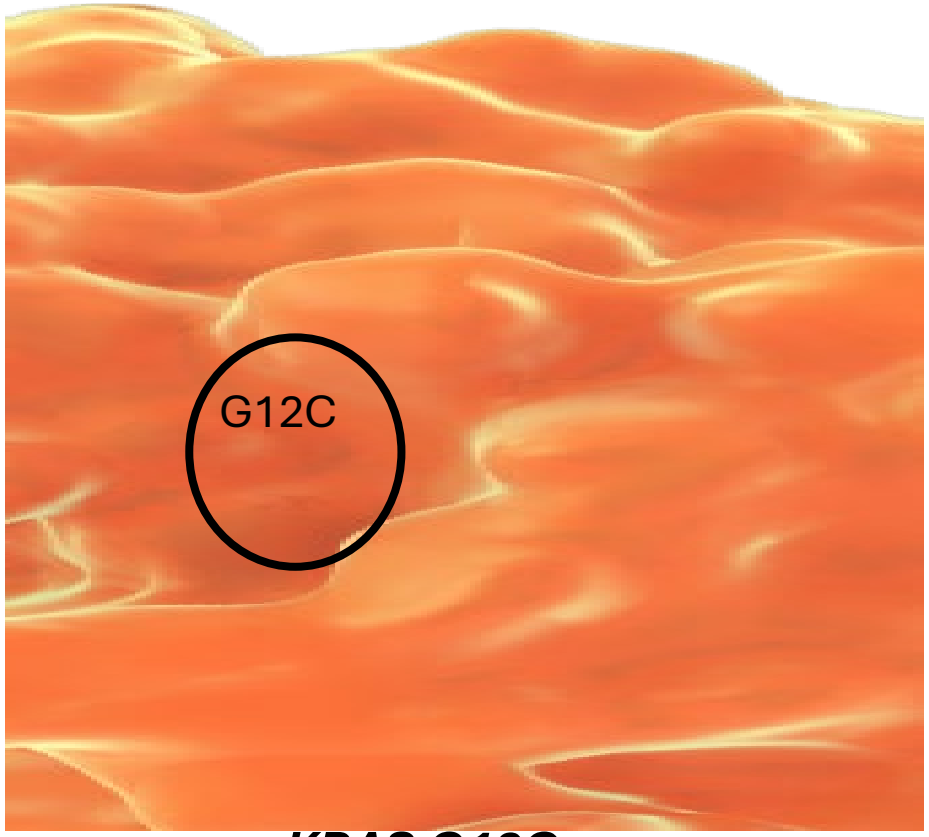
“Undruggable” proteins

No functional pocket
(~ 85% of human proteins)

KRAS was undruggable

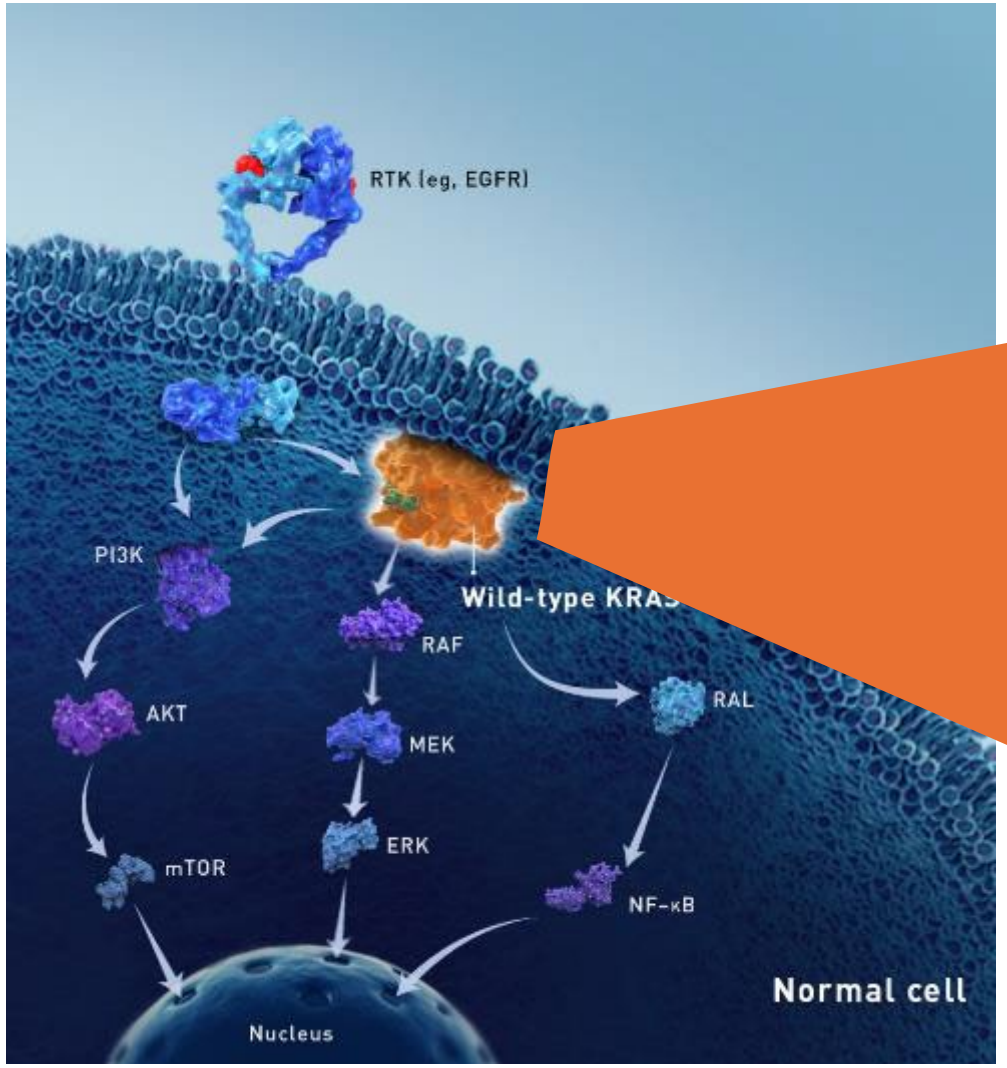
KRAS G12C is the first druggable KRAS mutation

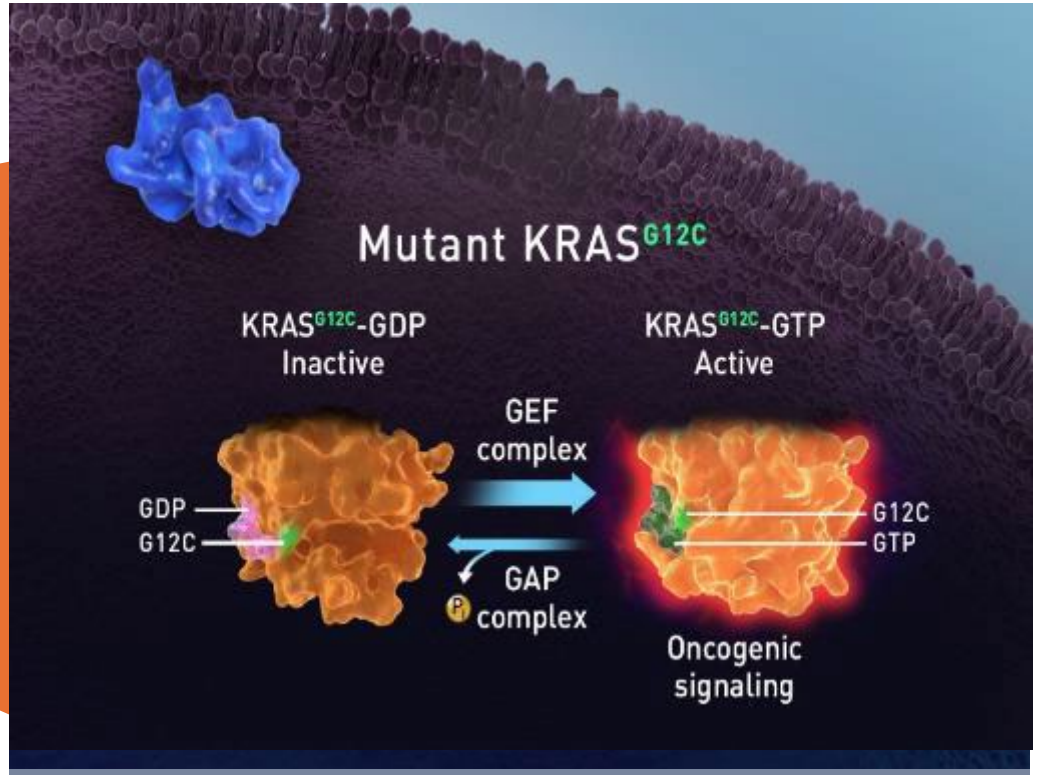
- Kirsten rat sarcoma viral oncogene homolog *(KRAS)* is one the most frequently mutated oncogenes in human cancers[1]
- *KRAS G12C* mutation (glycine to cysteine substitution at position 12) promotes tumorigenesis
- *KRAS G12C* mutation is found in approximately 13% of NSCLC, 3–5% of colorectal cancer, and 1%–3% of other solid tumors[2–7]



KRAS G12C

KRAS wild type versus mutation

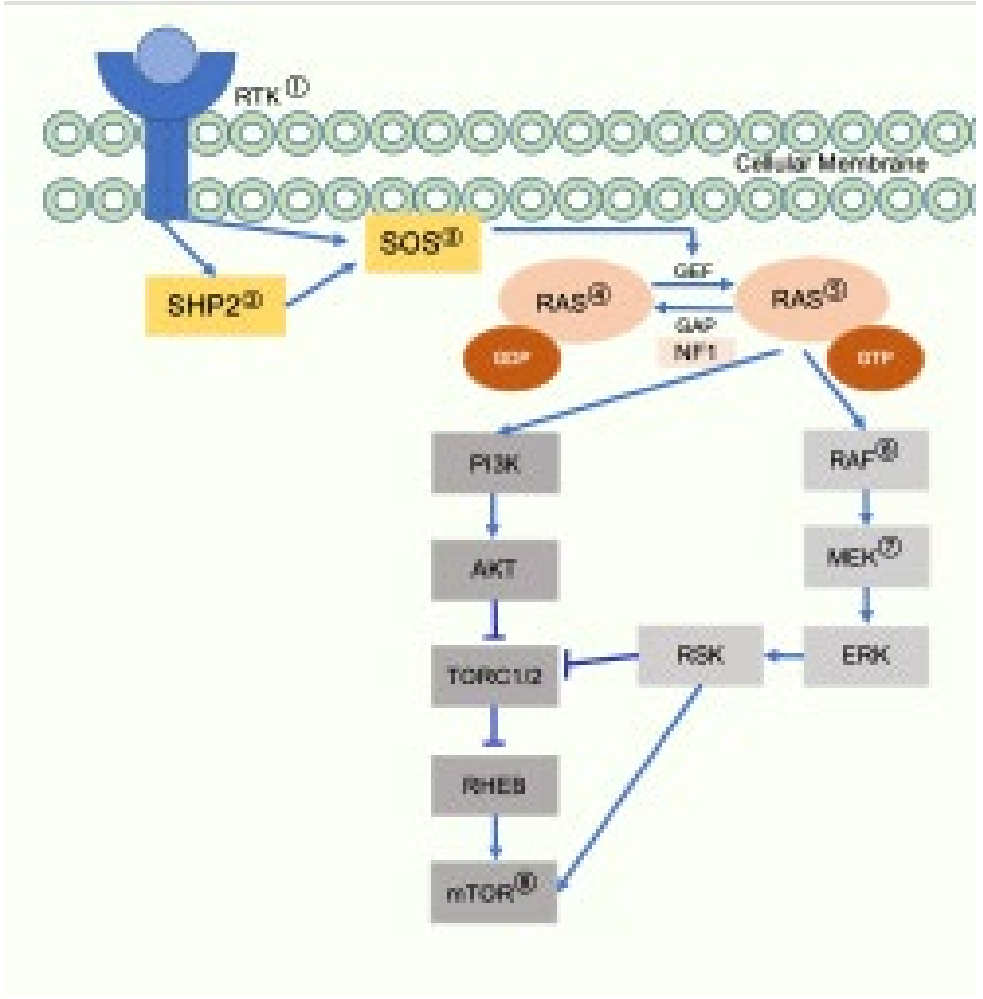




- The KRAS protein oscillated between inactive GDP and GTP states
- -Two major binding regions including the G domain and C terminal
- Guanine nucleotide exchange factor (GEFs) activate from GDP to GTP states

Palma et al Precision Oncology 2021

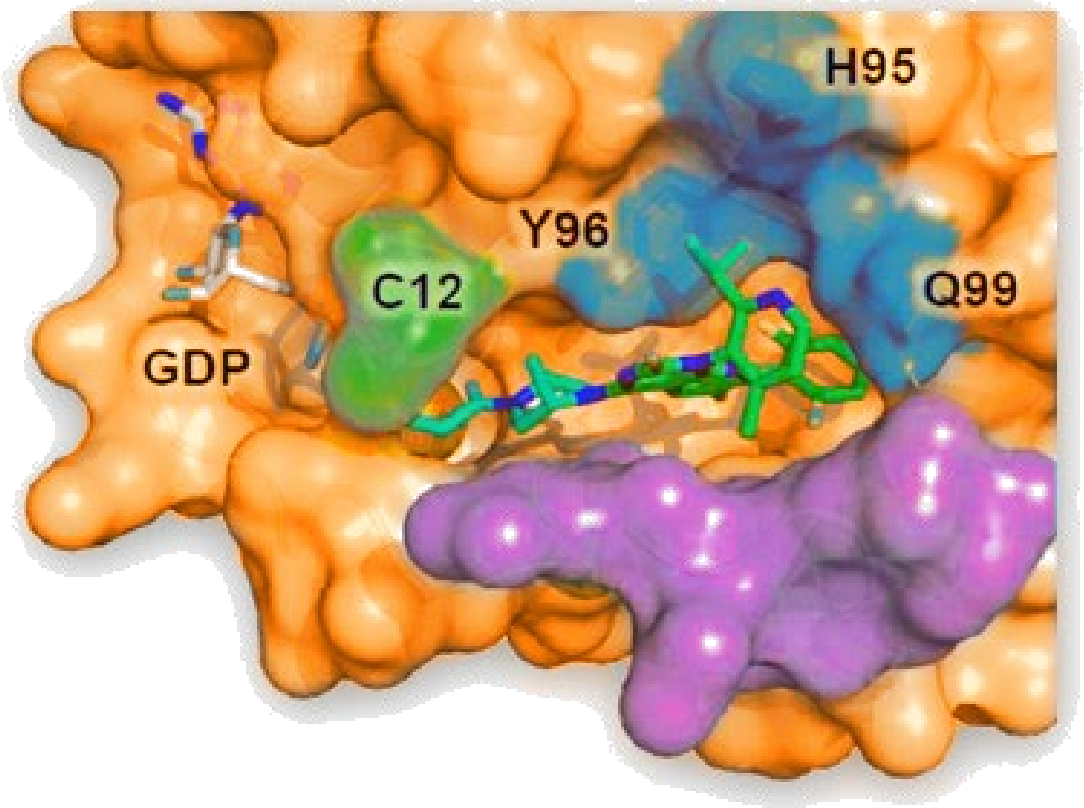
RAS at GTP state drives downstream signaling



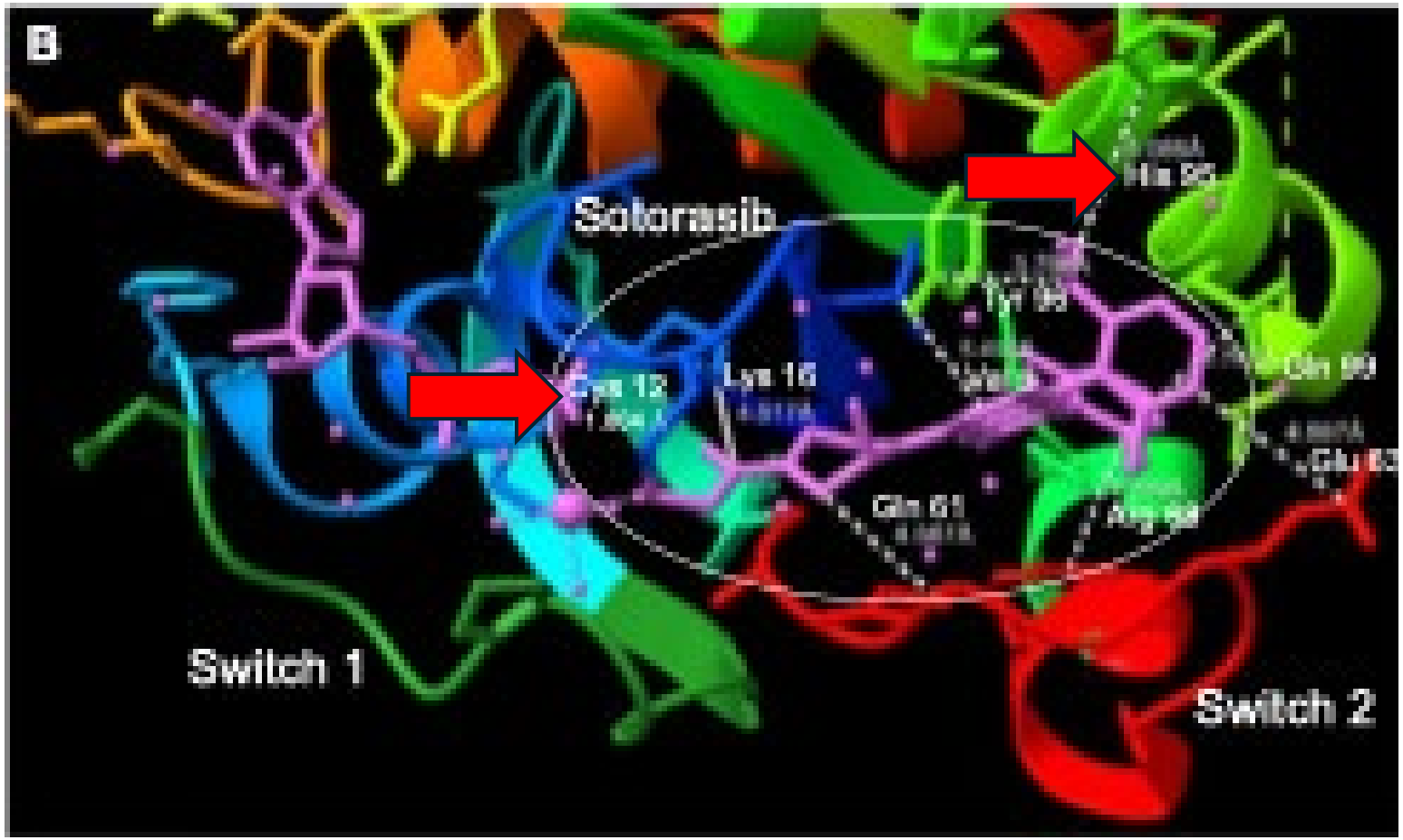
Palma et al Precision Oncology 2021

KRAS G12C as the first druggable mutations

- Binding at the allosteric pocket alternate the affinity of KRAS for GDP versus GTP nucleotide (thus stay inactive)
- Sotorasib is the first small molecule that bind covalently to C12 in proximity to switch 2
- It also utilizes the groove at histidine 95 (H95) for anchoring

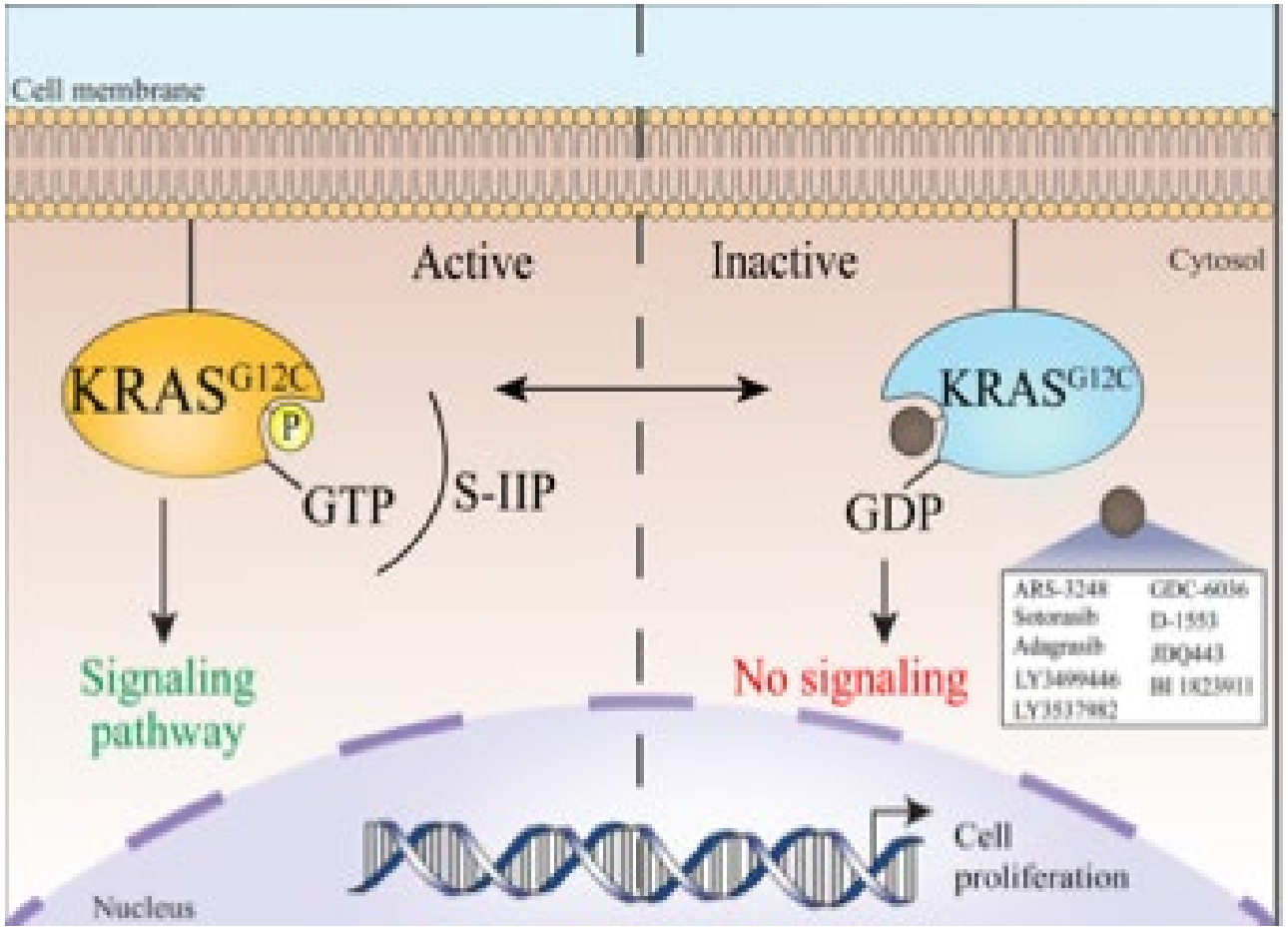


Crystalline protein structure



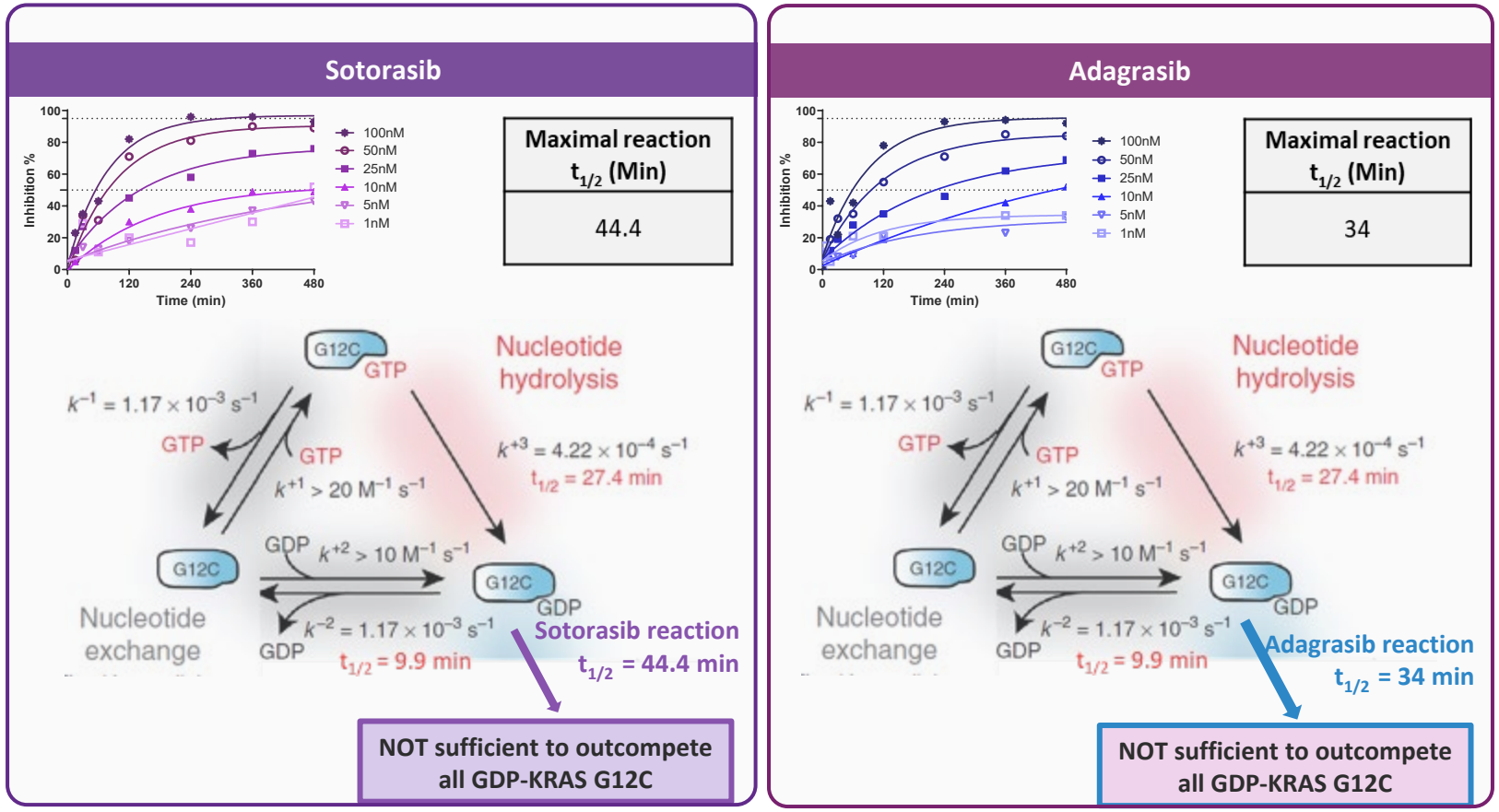
Palma et al Precision Oncology 2021

After all these jargons, this is the simplest way



Kwan et al Journal of Exp and Clin Can Res 2022

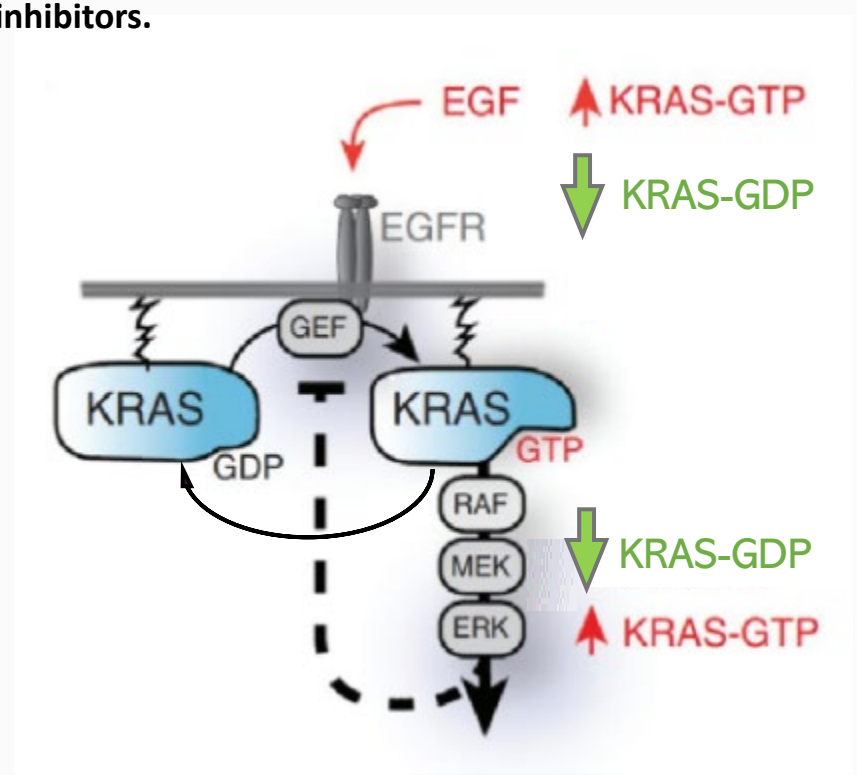
Factors that affect the G12C inhibitions: Potency and speed in target engagement (TE)



Cancer Discov 2020;10:1129–39

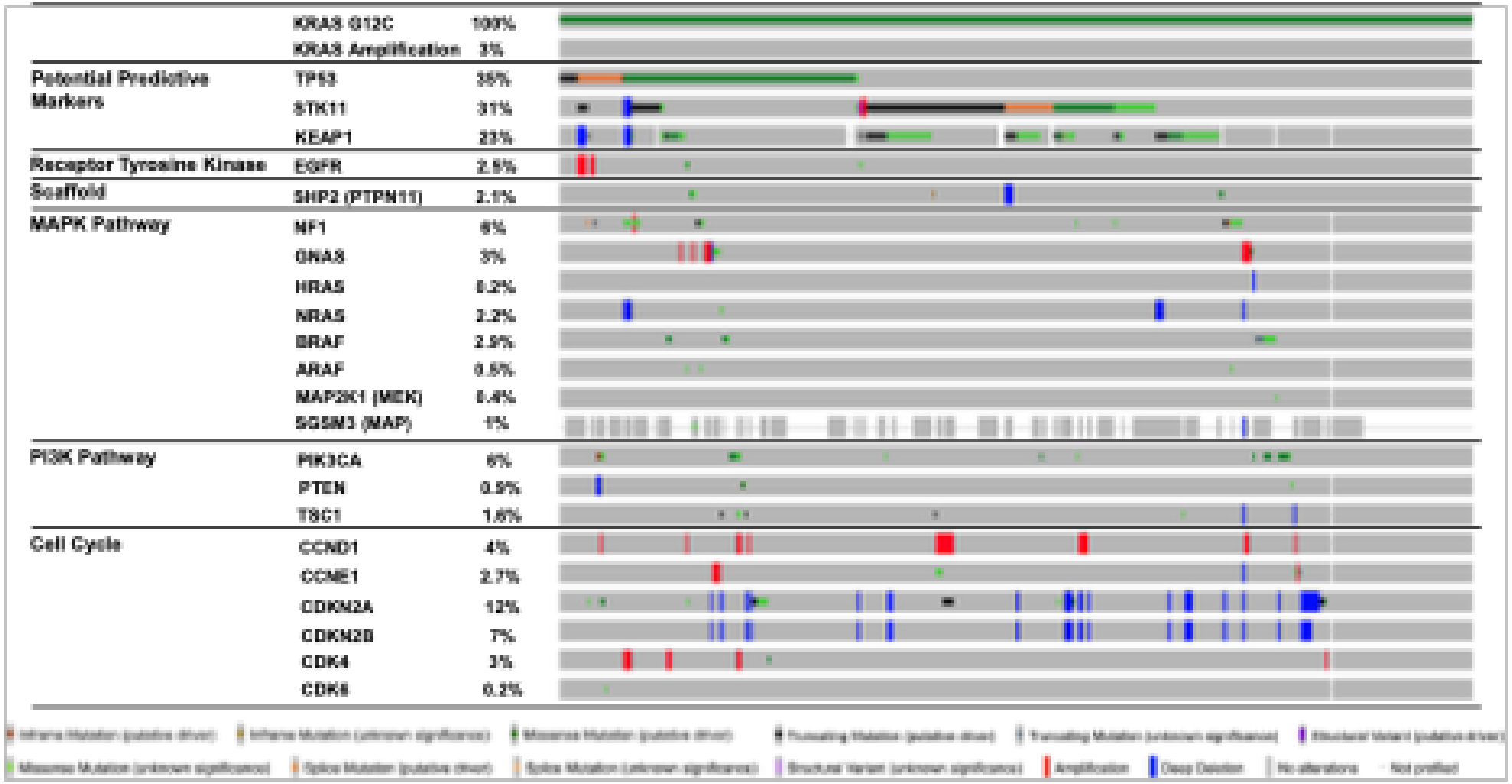
Factors that affect the G12C inhibitions: EGF function

- **Growth factors activate RTKs located upstream of KRAS, pushing the KRAS equilibrium in favor of its GTP-bound form, and compromising the activity of the GDP-bound KRAS G12C inhibitors.**



Cancer Discov 2020;10:1129–39

Factors that affect the G12C inhibitions: Co-mutations



Conquering KRAS mutations

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Our first attempt

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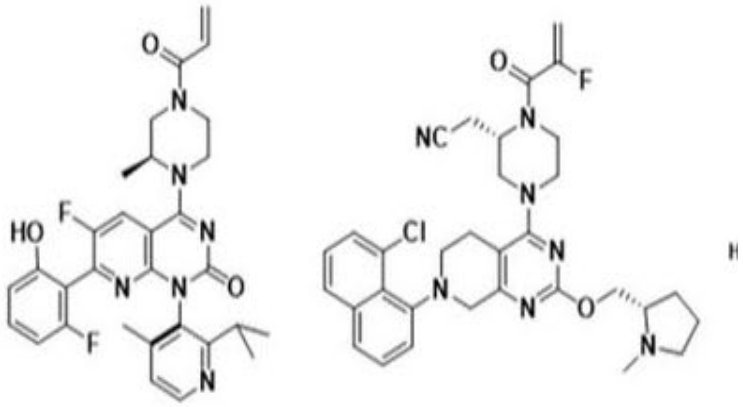
KRAS G12C inhibitors

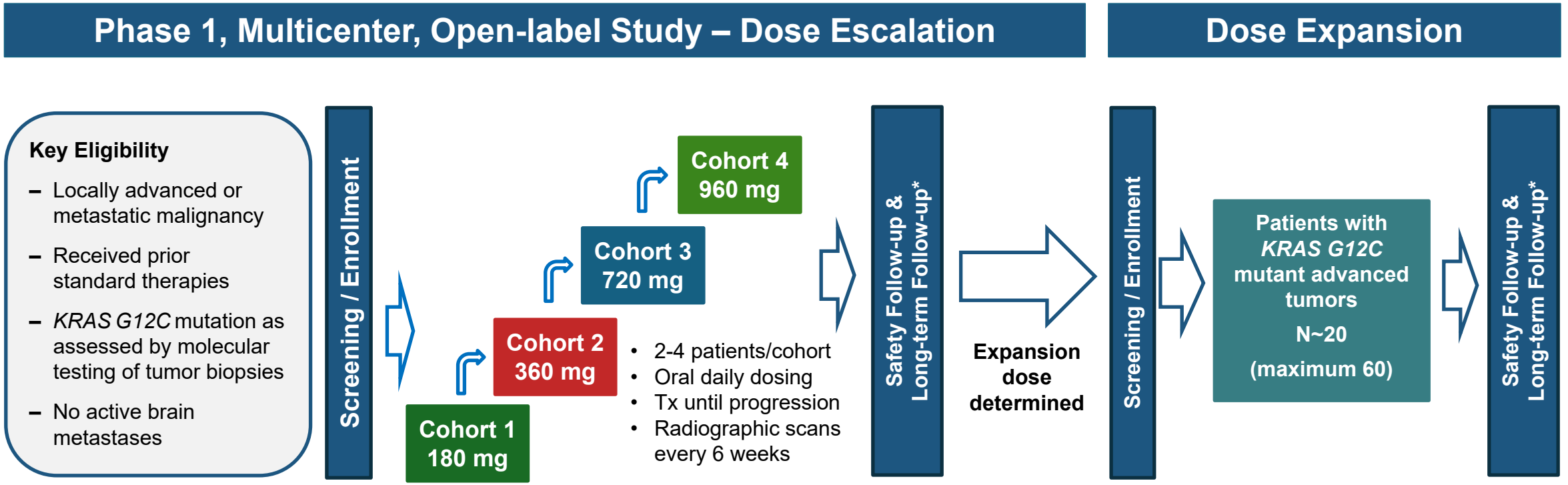
KRAS G12C Inhibitors in Clinical Trials and Representative Patent Examples



AMG510	MRTX849

Are these better?

CodeBreak 100: Phase 1 Study Design



Primary endpoint: Safety, including DLTs
Secondary endpoints include: PK; ORR; DOR; DCR; PFS; duration of SD

*30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long-term follow-up.

DCR, disease control rate; **DOR,** duration of response; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **ORR,** objective response rate; **PFS,** progression-free survival; **PK,** pharmacokinetic; **SD,** stable disease; **Tx,** treatment.

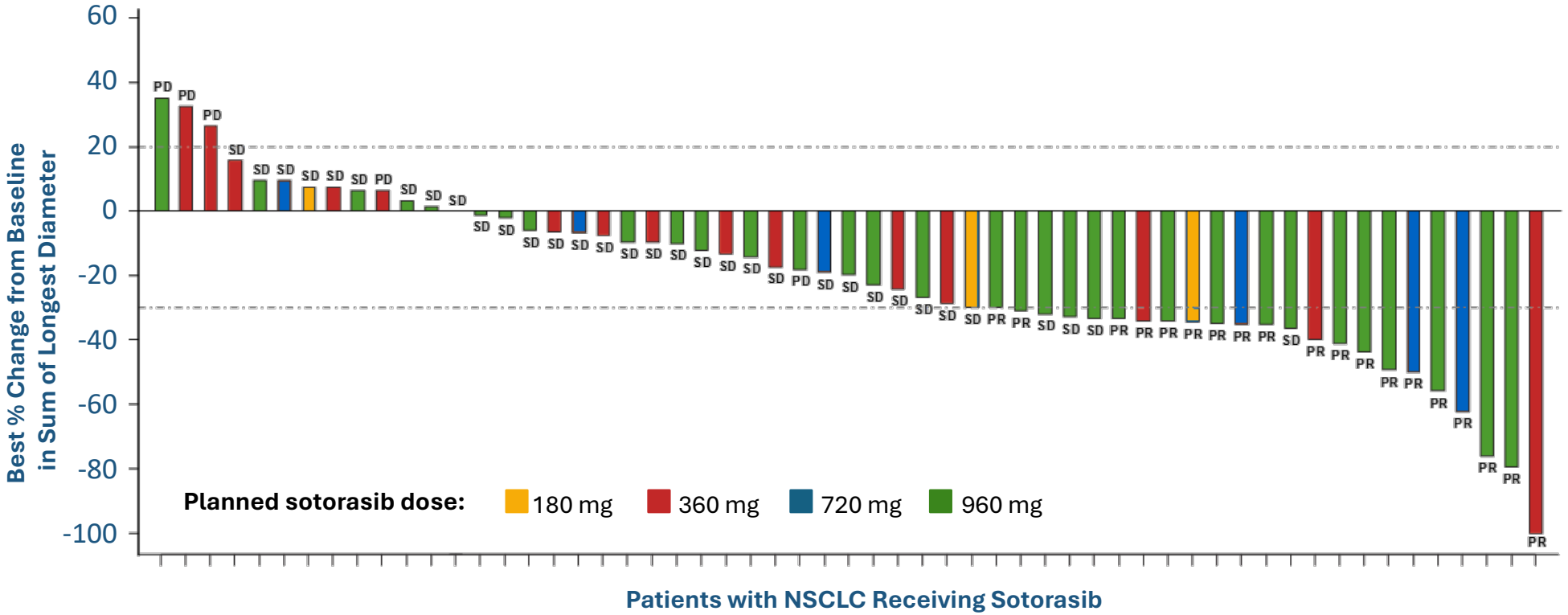
Hong DS. Oral presentation at European Society of Medical Oncology 2020 Virtual Congress, September 19-21, 2020.

Toxicity profile

Treatment-Emergent Adverse Events	All Patients (N = 129) n (%)			
	Any Grade	Grade ≥ 3	Grade ≥ 4	Grade 5
Diarrhea	38 (30)	5 (4)	0	0
Fatigue	30 (23)	3 (2)	0	0
Nausea	27 (21)	2 (2)	0	0
Vomiting	23 (18)	5 (4)	0	0
Abdominal pain	23 (18)	4 (3)	0	0
Dyspnea	21 (16)	3 (2)	1 (1)	1 (1)
Cough	20 (16)	0	0	0
Back pain	19 (15)	2 (2)	0	0
Decreased appetite	19 (15)	1 (1)	0	0
Headache	18 (14)	0	0	0

Treatment-Emergent Adverse Events	All Patients (N = 129) n (%)			
	Any Grade	Grade ≥ 3	Grade ≥ 4	Grade 5
AST increase	17 (13)	3 (2)	0	0
Anemia	17 (13)	6 (5)	0	0
Dizziness	17 (13)	0	0	0
ALT increase	15 (12)	6 (5)	1 (1)	0
Constipation	15 (12)	0	0	0
Pyrexia	14 (11)	0	0	0
Insomnia	14 (11)	0	0	0
Myalgia	13 (10)	0	0	0
Peripheral edema	13 (10)	0	0	0
Arthralgia	13 (10)	2 (2)	0	0

Tumor response



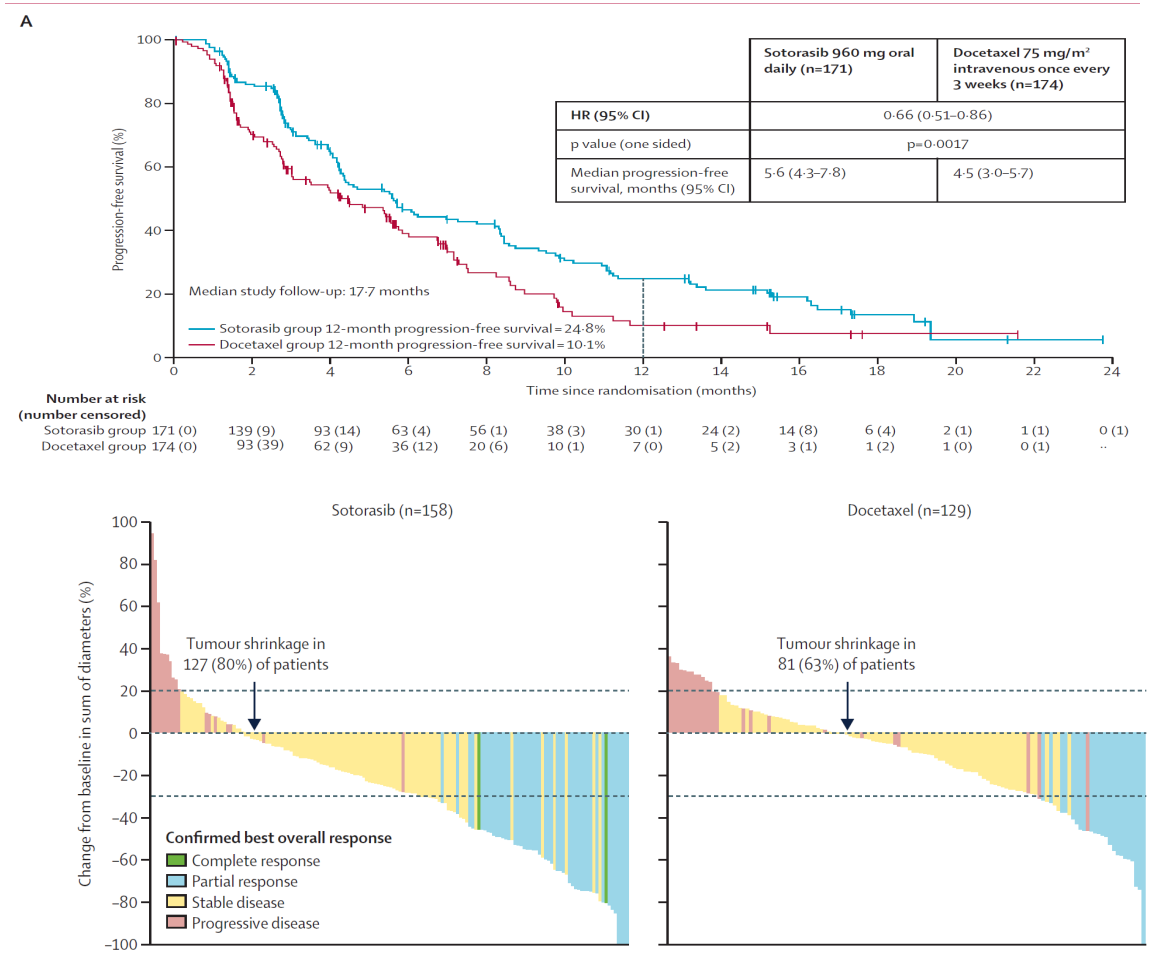
Tumor shrinkage was seen in most patients

Data cutoff: June 1, 2020.
*Patients with NSCLC who had available post-baseline tumor data (n = 57); Evaluation of response is based on modified RECIST 1.1.

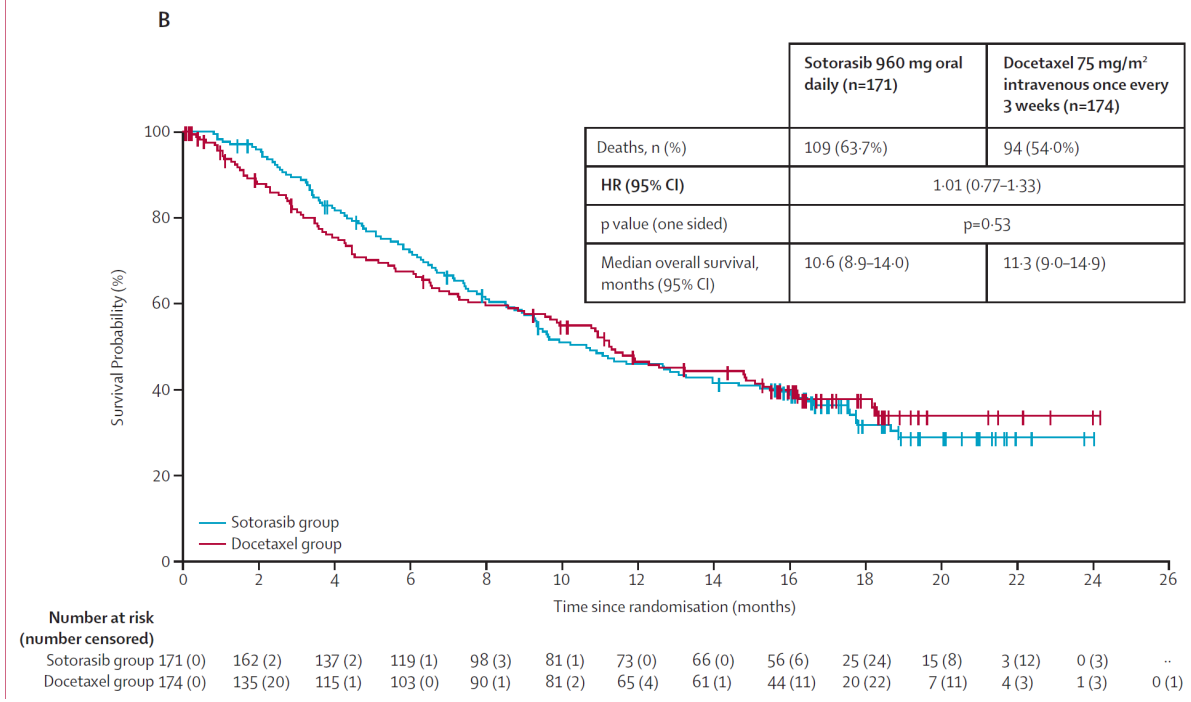
CR, complete response; **DCR,** disease control rate; **NSCLC,** non-small cell lung cancer; **ORR,** objective response rate; **PD,** progressive disease; **PR,** partial response; **RECIST,** response evaluation criteria in solid tumors; **SD,** stable disease.

Adapted from: Hong DS, et al. *N Engl J Med.* 2020; available online September 20, 2020.

CodeBreak 200: Sotorasib vs Docetaxel



	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
HR (95% CI)	0·66 (0·51–0·86)	
p value (one sided)	p=0·0017	
Median progression-free survival, months (95% CI)	5·6 (4·3–7·8)	4·5 (3·0–5·7)



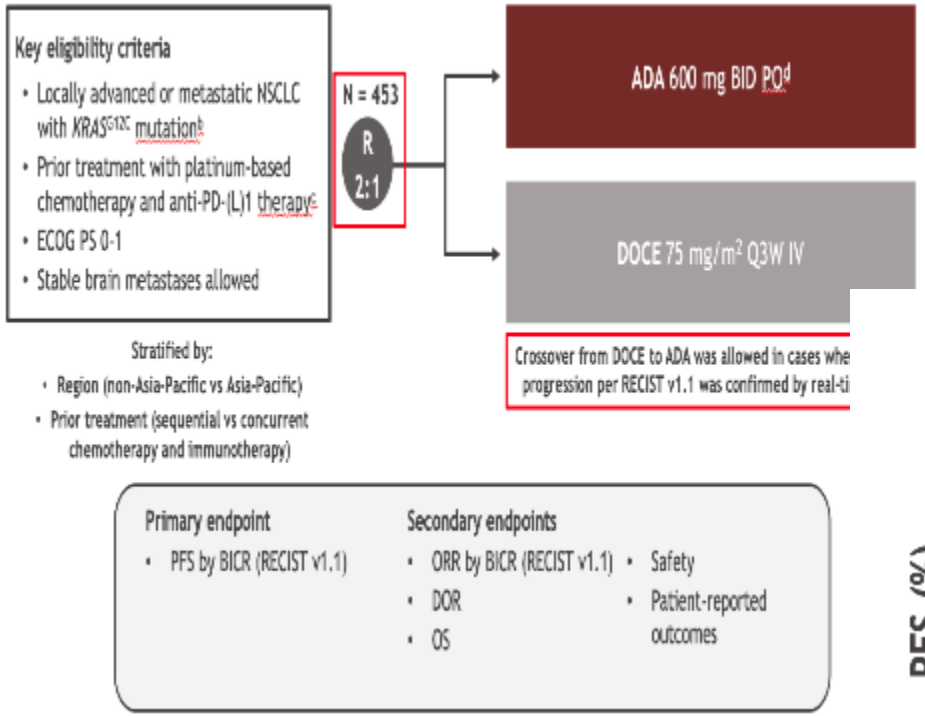
	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
Deaths, n (%)	109 (63·7%)	94 (54·0%)
HR (95% CI)	1·01 (0·77–1·33)	
p value (one sided)	p=0·53	
Median overall survival, months (95% CI)	10·6 (8·9–14·0)	11·3 (9·0–14·9)

De Langden et al Lancet 2023

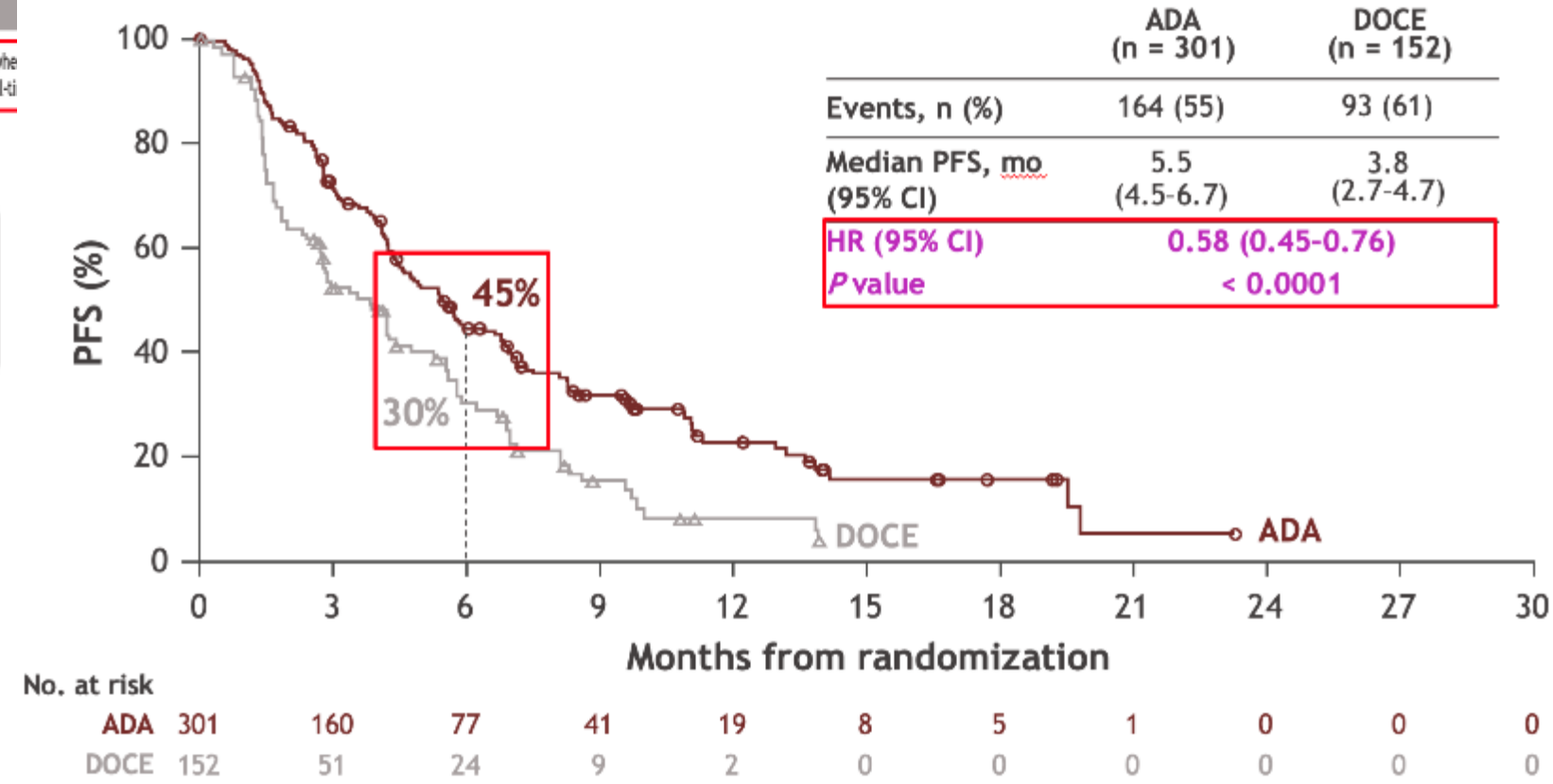
A quick history on sotorasib

May 2019: FDA granted orphaned drug status
Oct 2020: FDA granted breakthrough therapy designation
May 2021: FDA granted accelerated approval
Oct 2023: ODAC voted 10 to 2 that PFS of CodeBreak 200 is not reliable
Dec 2023: FDA denied full approval and requested new post-marketing requirement study by Feb 2028

KRYSTAL-12 (Phase 3): Adagrasib vs docetaxel among patients with advanced/metastatic *KRASG12C*- mutated NSCLC



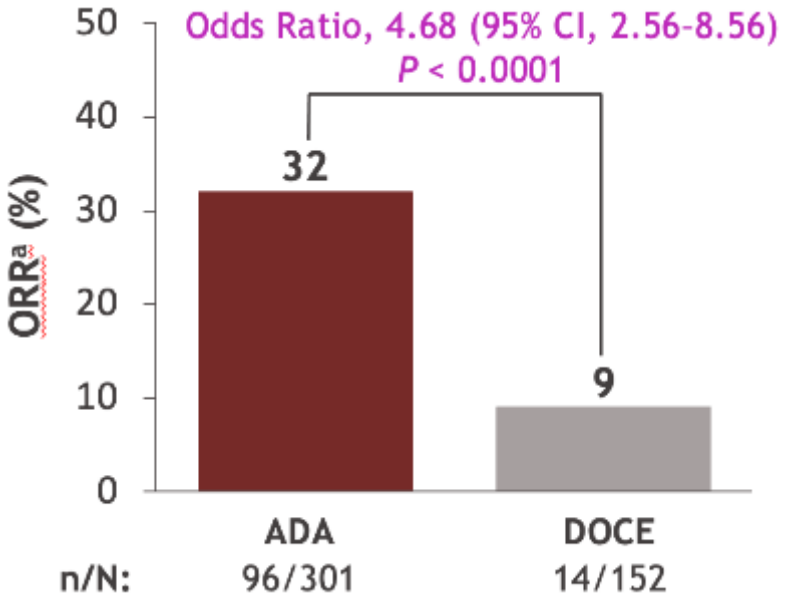
- Investigator assessment similar



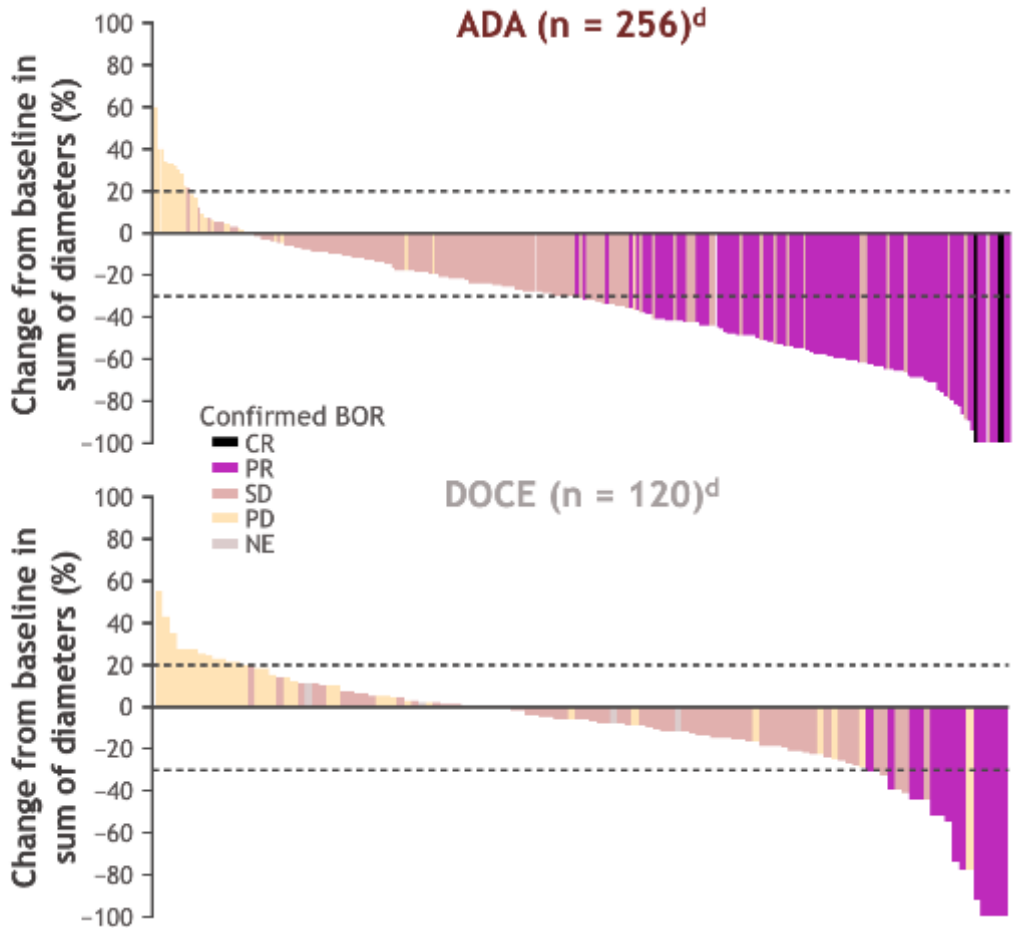
	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

Mok TSK, et al. ASCO 2024; Abstract LBA509.

KRYSTAL-12 (Phase 3): Adagrasib vs docetaxel among patients with advanced/metastatic *KRASG12C*- mutated NSCLC



Tumor response	ADA (n = 301)	DOCE (n = 152)
DCR,[b] n (%)	236 (78)	89 (59)
Median DOR,[c] mo (95% CI)	8.3 (6.1-10.4)	5.4 (2.9-8.5)
Remaining in response at 6 mo, %	64	39



Intracranial ORR

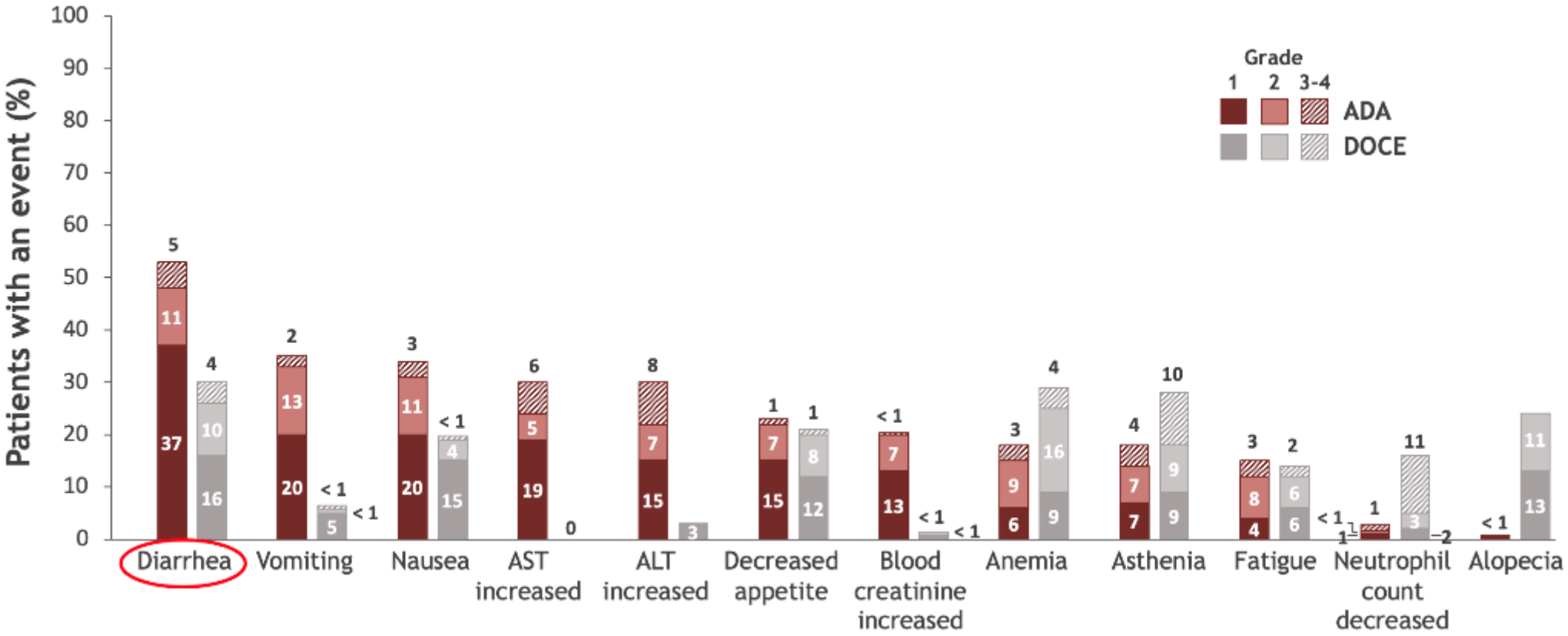
24%/11% ADA/Doce

In CNS evaluable:

40% ADA/11% doce

Mok TSK, et al. ASCO 2024; Abstract LBA509.

KRYSTAL-12 (Phase 3): Adagrasib vs docetaxel among patients with advanced/metastatic *KRASG12C*- mutated NSCLC



A phase 3 trial comparing first-line ADA plus pembrolizumab vs pembrolizumab alone is currently enrolling patients with advanced *KRAS*^{G12C}-mutated NSCLC and PD-L1 TPS ≥ 50% (KRYSTAL-7; NCT04613596)

Mok TSK, et al. ASCO 2024; Abstract LBA509.

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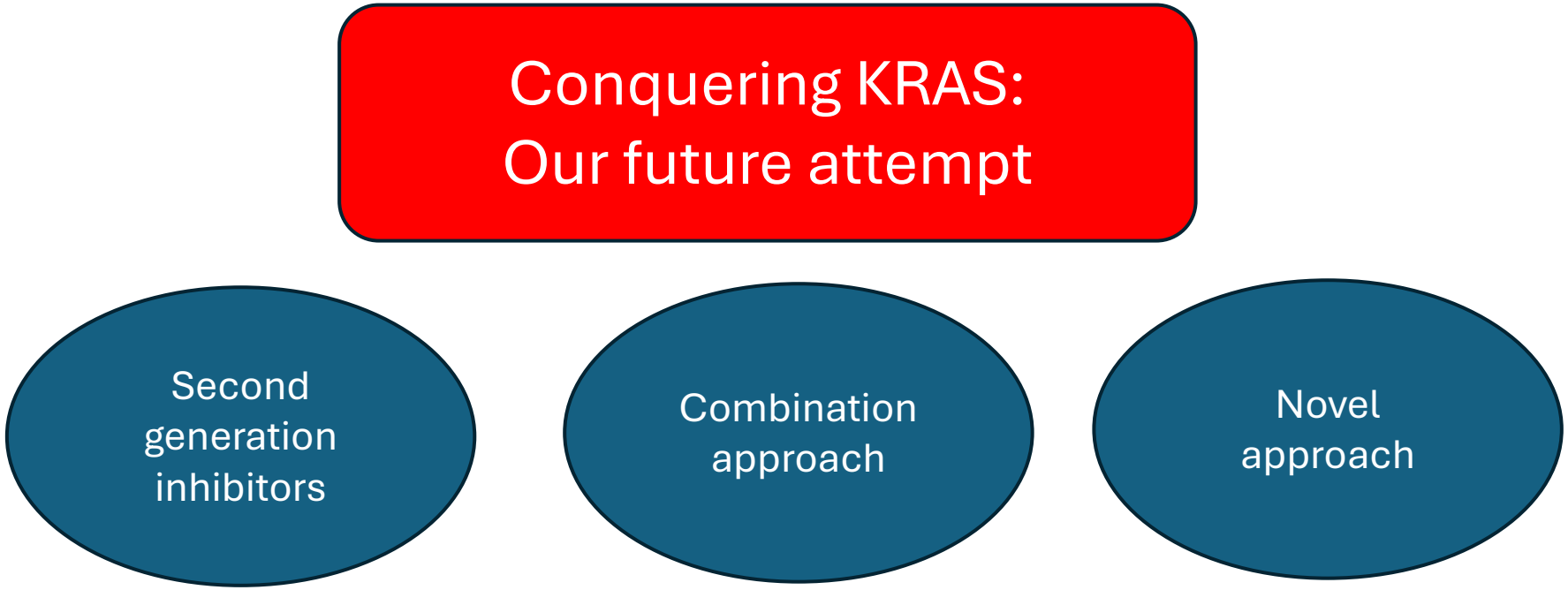
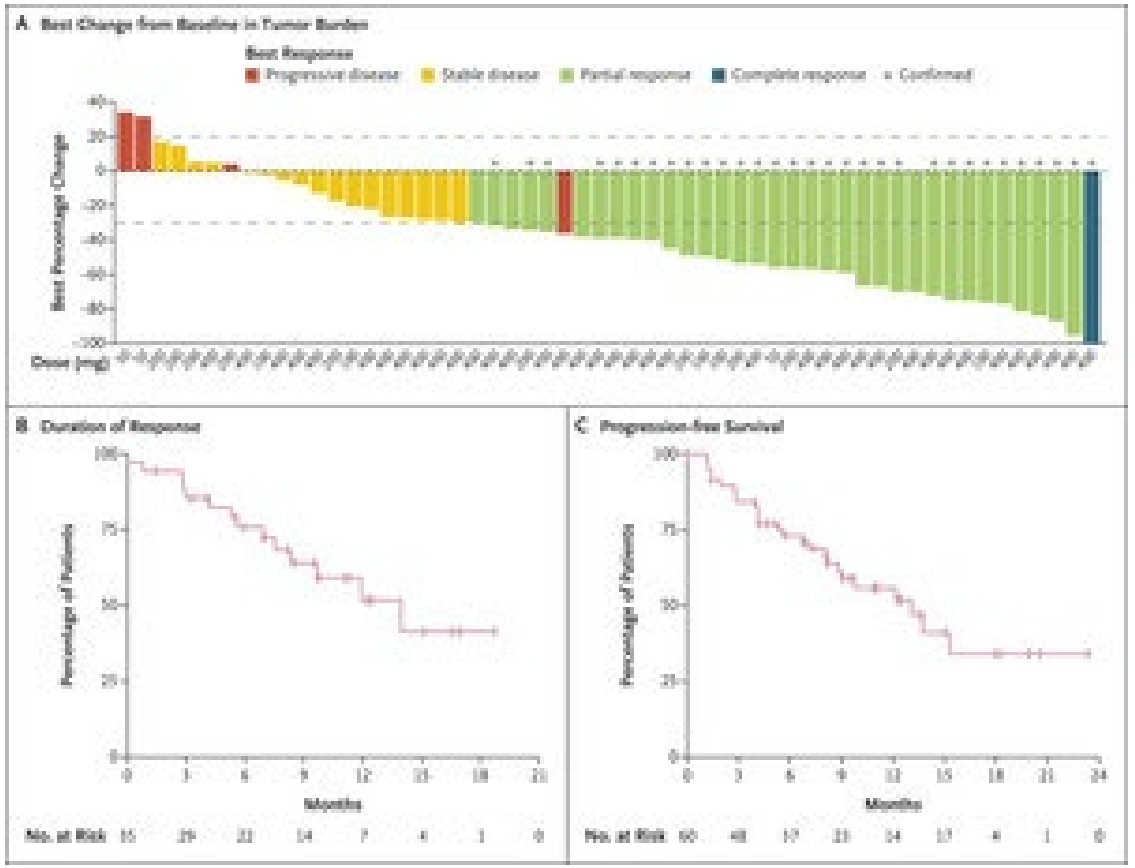


Short list of other KRAS G12C inhibitors

Company	Drug	Phase	Tumor type
Novartis[3]	JDQ443	3	**NSCLC**
Roche/Genentech[4]	GDC-6036	2/3	**NSCLC**
InventisBio[5]	D-1553	1/2	**NSCLC**, CRC
Genfleet Therapeutics[6]	GFH925	1/2	**NSCLC**, GI
Jacobio Pharmaceuticals[7]	JAB-21822	1/2	**NSCLC**, CRC, solid tumours
Shanghai YingLi[8]	YL-15293	1/2	Advanced solid tumours
Roche/Genentech[9]	GDC-6036	1	**NSCLC**, CRC, solid tumours
Boehringer Ingelheim[10]	BI 1823911	1	Solid tumours
Eli Lilly[11]	LY3537982	1	**NSCLC**, other tumor types

Divarasib: GDC6036

- Phase I study on 137 patients with KRAS G12C (NSCLC 60, CRC 55, Other 22)
- Confirmed RR at 53.4% for NSCLC
- Median PFS at 13.4 months for NSCLC
- Confirmed RR at 29.1% for CRC
- Median PFS at 5.6 months for CRC

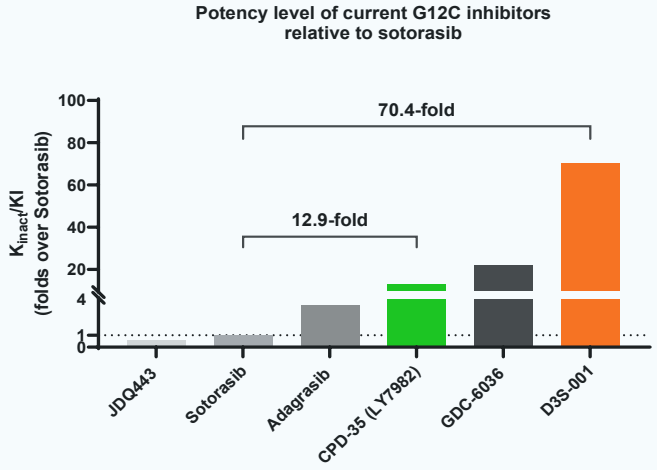


Sacher et al NEJM 2023

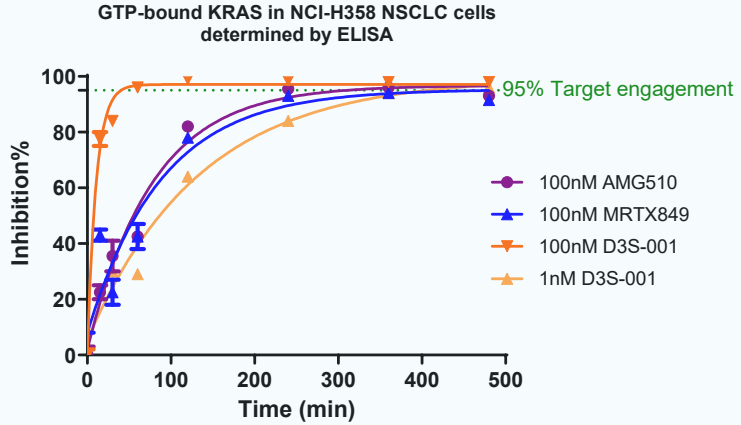
Overall preclinical feature summary for D3S-001 as a next generation GDP-bound KRAS G12C inhibitor

德昇济 D3 BIO

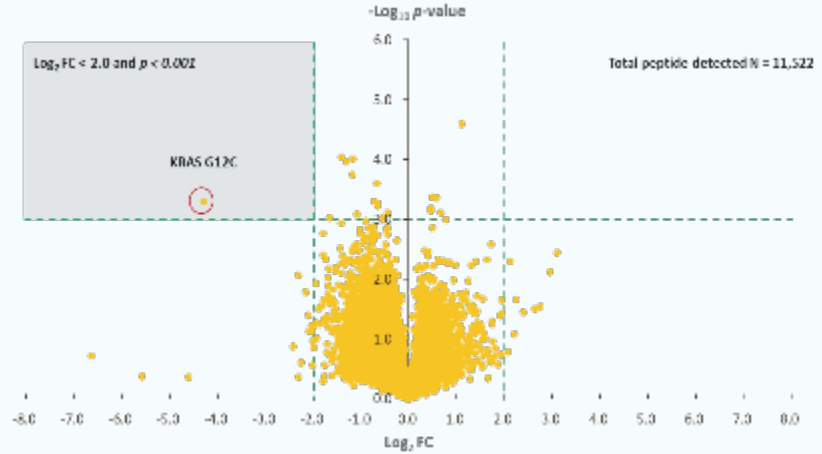
High covalent potency



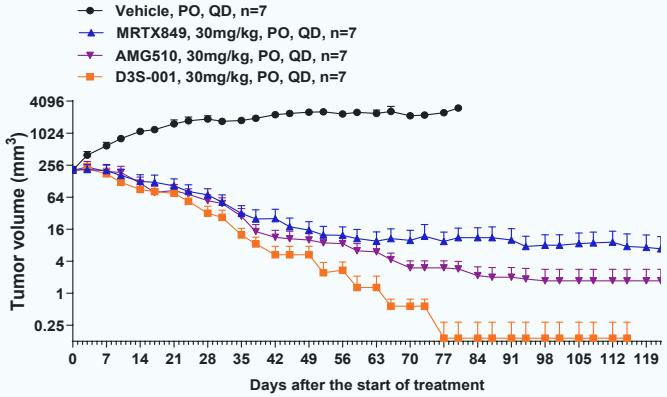
Rapid target engagement



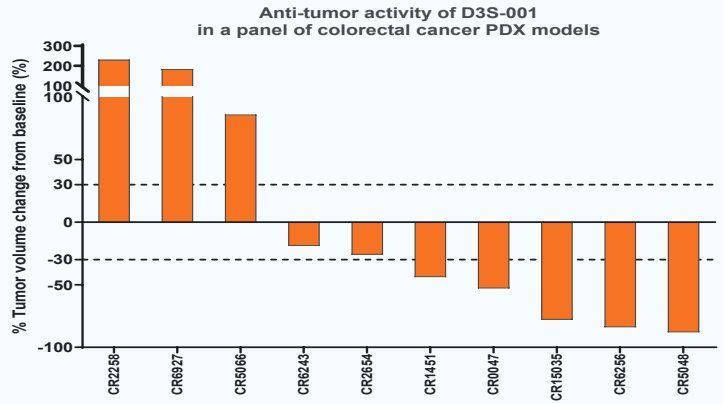
High selectivity



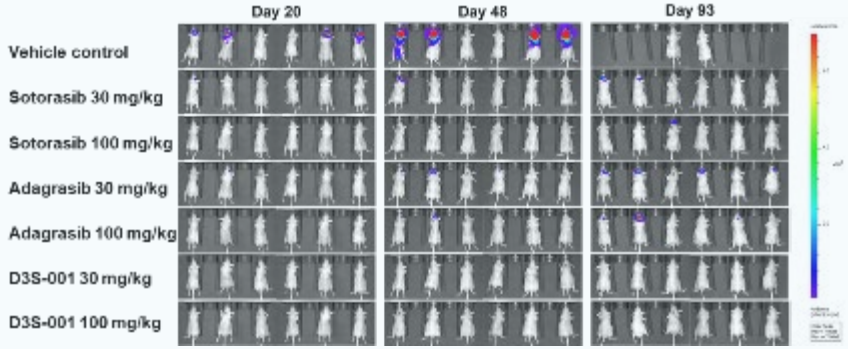
Deep and durable anti-tumor activity



More robust efficacy in CRC



CNS-penetrable



Zhang et al Cancer Discovery 2024

Phase 1/2 Study Design: D3S001

Key Eligibility

- Locally advanced or metastatic solid tumor
- Documented KRAS G12C mutation by a local test on tumor tissue or blood
- At least one line of prior systemic therapy
- Measurable disease per RECIST v1.1
- ECOG 0-1
- Treated/stable brain metastases allowed

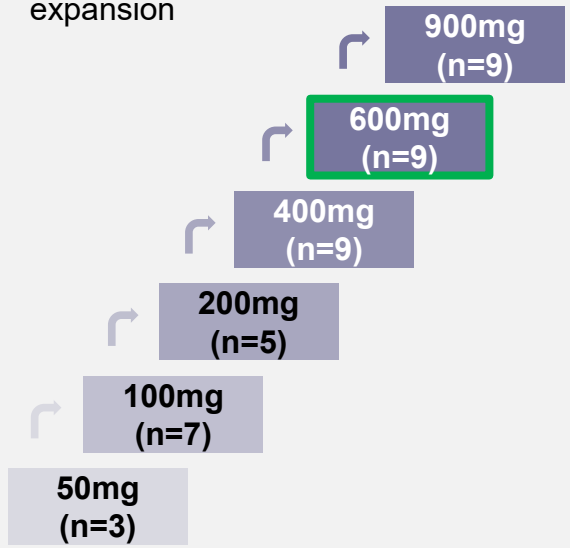
Key Endpoints

- Safety and tolerability
- Pharmacokinetics
- Anti-tumor activity

Dose Escalation

D3S-001 administered orally QD, 21-day per cycle

- Backfill allowed in cohorts >50mg QD
- KRAS G12Ci pre-treated allowed in cohorts 400-900mg QD
- 600mg QD selected as dose for expansion



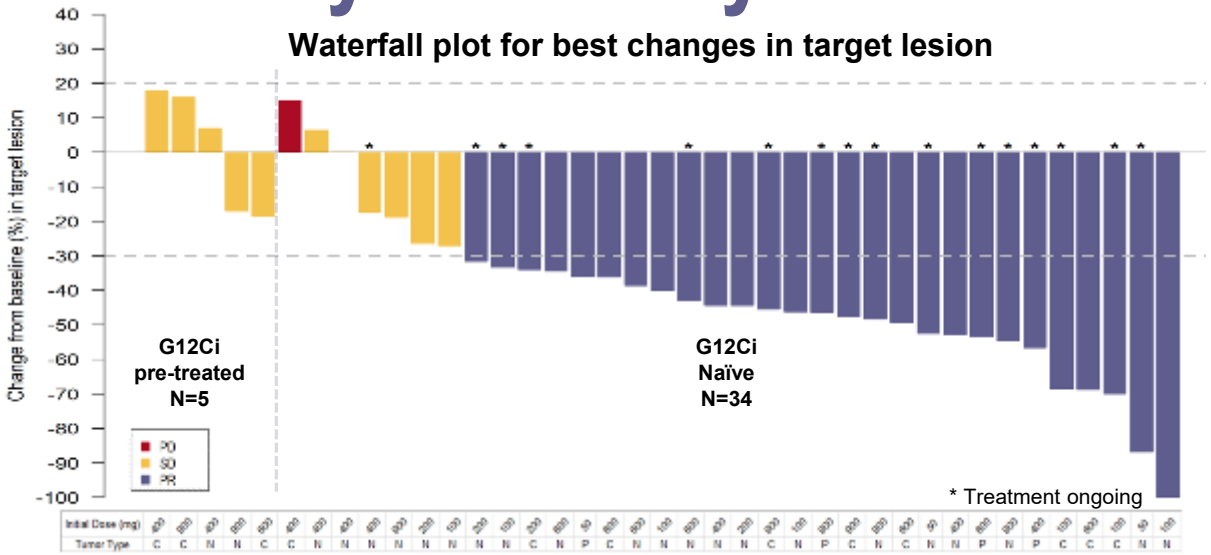
Characteristic	50mg n=3	100mg n=7	200mg n=5	400mg n=9	600mg n=9	900mg n=9	Total N=42
Median age, years	60	64	67	65	59	64	64
Male, n	3	6	2	6	7	8	32
Race, n							
White	1	1	1	0	1	0	4
Asian	2	6	4	8	8	9	37
Not reported	0	0	0	1	0	0	1
ECOG, n							
0	2	3	0	1	4	2	12
1	1	4	5	8	5	7	30
Primary diagnosis, n							
NSCLC	2	5	4	6	4	4	25*
CRC	0	2	1	2	4	4	13
PDAC	1	0	0	1	1	1	4
Numbers of lines in prior systemic therapy, n							
1 line	2	1	2	4	4	2	15
2 lines	1	2	3	1	1	1	9
≥3 lines	0	4	0	4	4	6	18
KRAS G12Ci pre-treated	0	0	0	2	2	2	6

Abbreviations:
KRAS = Kirsten rat sarcoma viral oncogene. RECIST = Response Evaluation Criteria in Solid Tumors. QD = once daily. G12Ci = G12C inhibitor. NSCLC = Non-small cell lung cancer. CRC = Colorectal cancer. PDAC = Pancreatic duct adenocarcinoma.
* Among 25 NSCLC subjects, 22 (88%) experienced at least one checkpoint inhibitor therapy; 20 (80%) experienced at least one platinum chemotherapy. 6 (24%) with brain metastases at baseline.

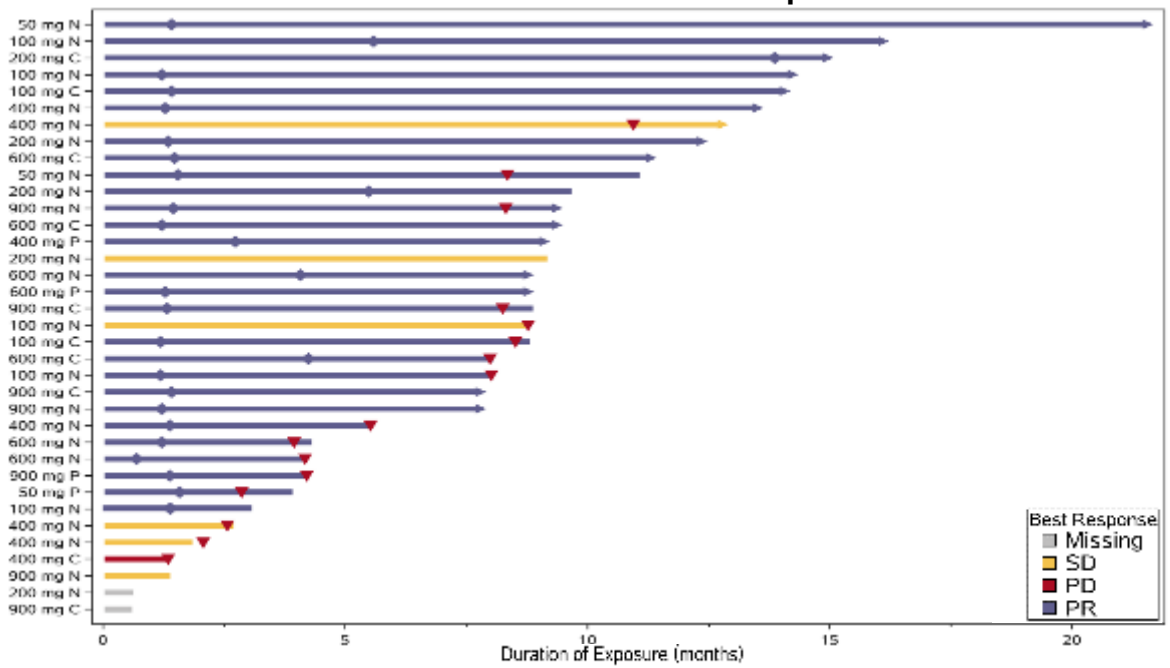
Data cut-off date: August 16, 2024

Efficacy Summary

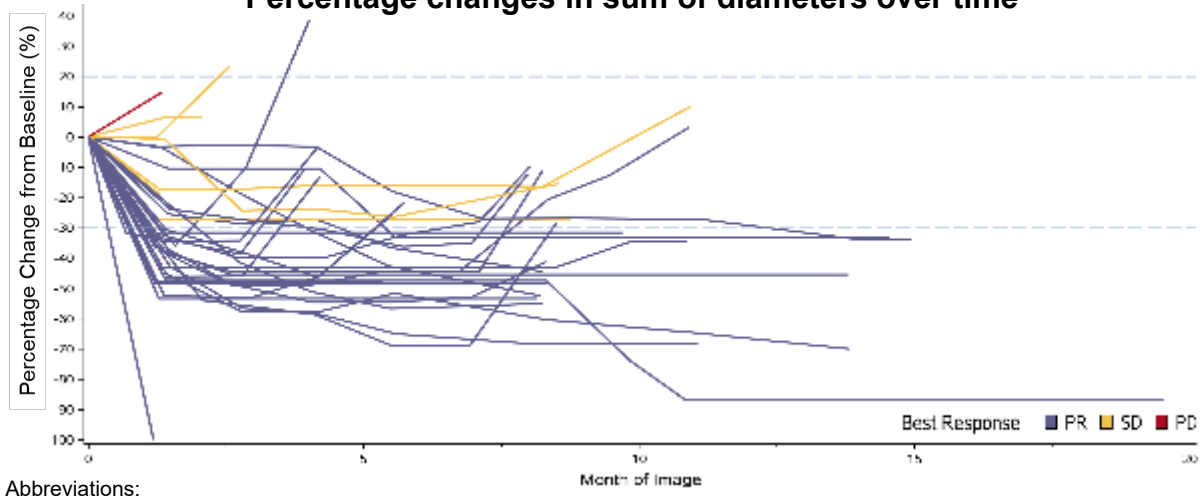
Waterfall plot for best changes in target lesion



Duration of treatment with response



Percentage changes in sum of diameters over time



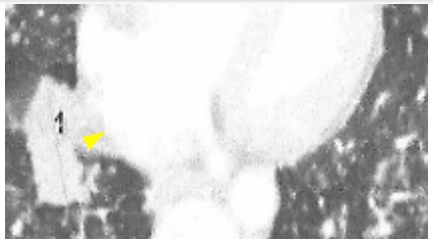
	All G12Ci naïve (N = 34)	NSCLC G12Ci naïve (N = 22)	CRC G12Ci naïve (N = 9)
ORR – confirmed (95% CI)	**73.5%** (55.6%, 87.1%)	**66.7%** (47.8%, 88.7%)	**88.9%** (51.8%, 99.7%)
DCR (95% CI)	**97.1%** (84.7%, 99.9%)	**100%** NC	**88.9%** (51.8%, 99.7%)
6m DoR rate (95% CI)	**78.4%** (55.6%, 90.4%)	**77.4%** (44.9%, 92.1%)	**85.7%** (33.4%, 97.9%)
6m PFS rate (95% CI)	**68.6%** (50.5%, 81.3%)	**66.5%** (42.2%, 82.4%)	**80.0%** (40.9%, 94.6%)

Abbreviations:
G12Ci = G12C inhibitor. ORR = Objective response rate. DCR = Disease control rate. DoR = Duration of response. PFS = Progression free survival. PR = Partial response. SD = Stable disease. PD = Progressive disease. N = Non-small cell lung cancer. C = Colorectal cancer. P = Pancreatic cancer.

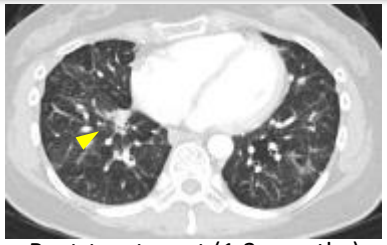
Case Reports and Molecular Responses

Non-small Cell Lung Cancer

- Prior 1st line with Platinum double chemo plus IO.
- Confirmed PR.
- On treatment 14 months (on-going).



Pre-treatment

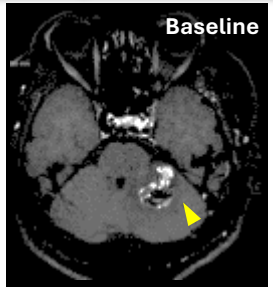


Post-treatment (1.3 months)

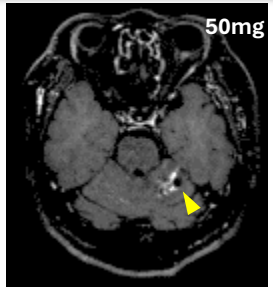
Non-small Cell Lung Cancer (CNS)

- Prior lines with Platinum chemo and IO.
- Prior treated/stable BM* at baseline.
- Confirmed PR.
- BM shrinkage observed at first dose and further shrinkage with higher doses.
- On treatment 22 months (on-going).

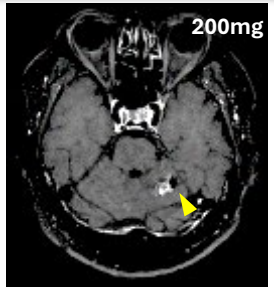
** Gamma Knife ~1.5 Yrs prior to study treatment*



Pre-treatment*



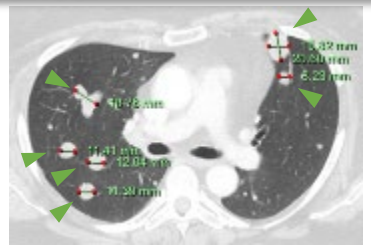
Post-treatment (5.6 months)



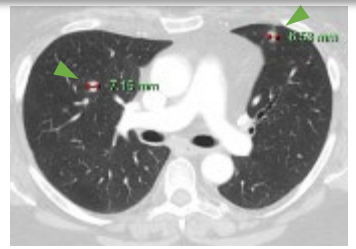
Post-treatment (10.8 months)

Colorectal Cancer

- CRC patient, previously 3 lines of systemic therapies.
- Confirmed PR (significant shrinkages of liver and lung lesions).
- CEA 1200 → 20; CA19.9 ~8000 → 264.
- On treatment 9 months.

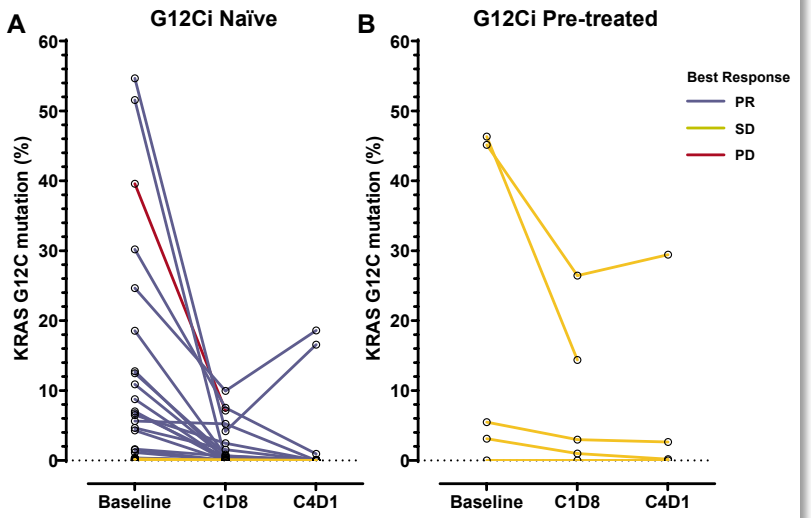


Pre-treatment



Post-treatment (1.2 months)

Molecular Response



A: G12Ci naïve pts

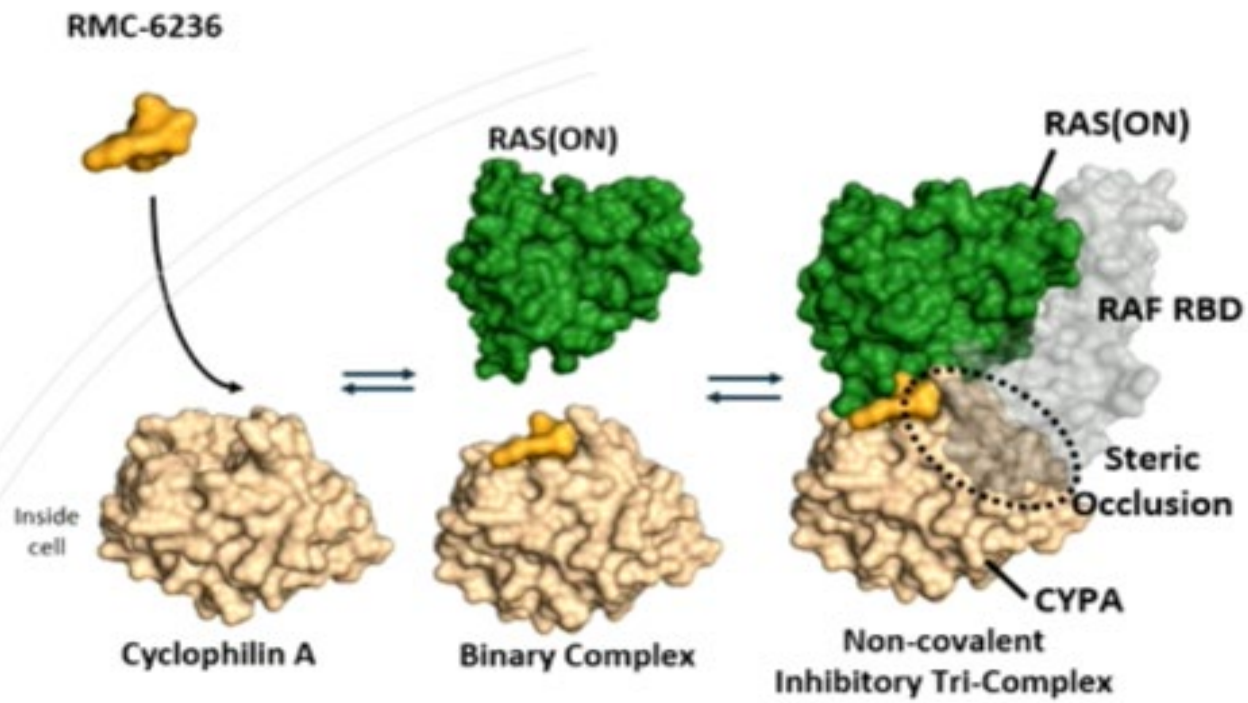
- 25 of 34 pts (73.5%) were KRAS G12C ctDNA (+) at baseline (14 NSCLC, 7 CRC, 4 PDAC)
- All 25 pts showed rapid reduction of G12C MAF as early as Cycle 1 Day 8 (23 >90% and 20 =100% as best reduction)
- Of the 25 ctDNA (+) pts, 22 (88%) achieved PR as the best overall response

B: G12Ci pre-treated pts

- 4 of 5 pts (80%) were KRAS G12C ctDNA (+) at baseline (1 NSCLC, 3 CRC)
- All 4 pts showed rapid reduction of G12C MAF, only 1 pt achieved >90% as best reduction.
- Of the 4 ctDNA (+) pts, all achieved SD as best overall response

RMC-6236 is a First-in-Class, RAS^{MULTI}(ON) Inhibitor

- RMC-6236 is a novel, oral, non-covalent RAS^{MULTI}(ON) inhibitor that is selective for the active, GTP-bound or ON state of both mutant and wild-type variants of the canonical RAS isoforms
- Preclinical studies have demonstrated deep and sustained regressions across multiple RAS^{MUT} tumor types, particularly PDAC and NSCLC harboring KRAS^{G12X} mutations



KRAS^{G12X} defined as mutation at codon 12 which encodes glycine (G) to X where X = A, D, R, S, or V.
CYPA, cyclophilin A; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma viral oncogene homolog; Mut, mutant; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RBD, RAS-binding domain.

Summary of Treatment-Related Adverse Events

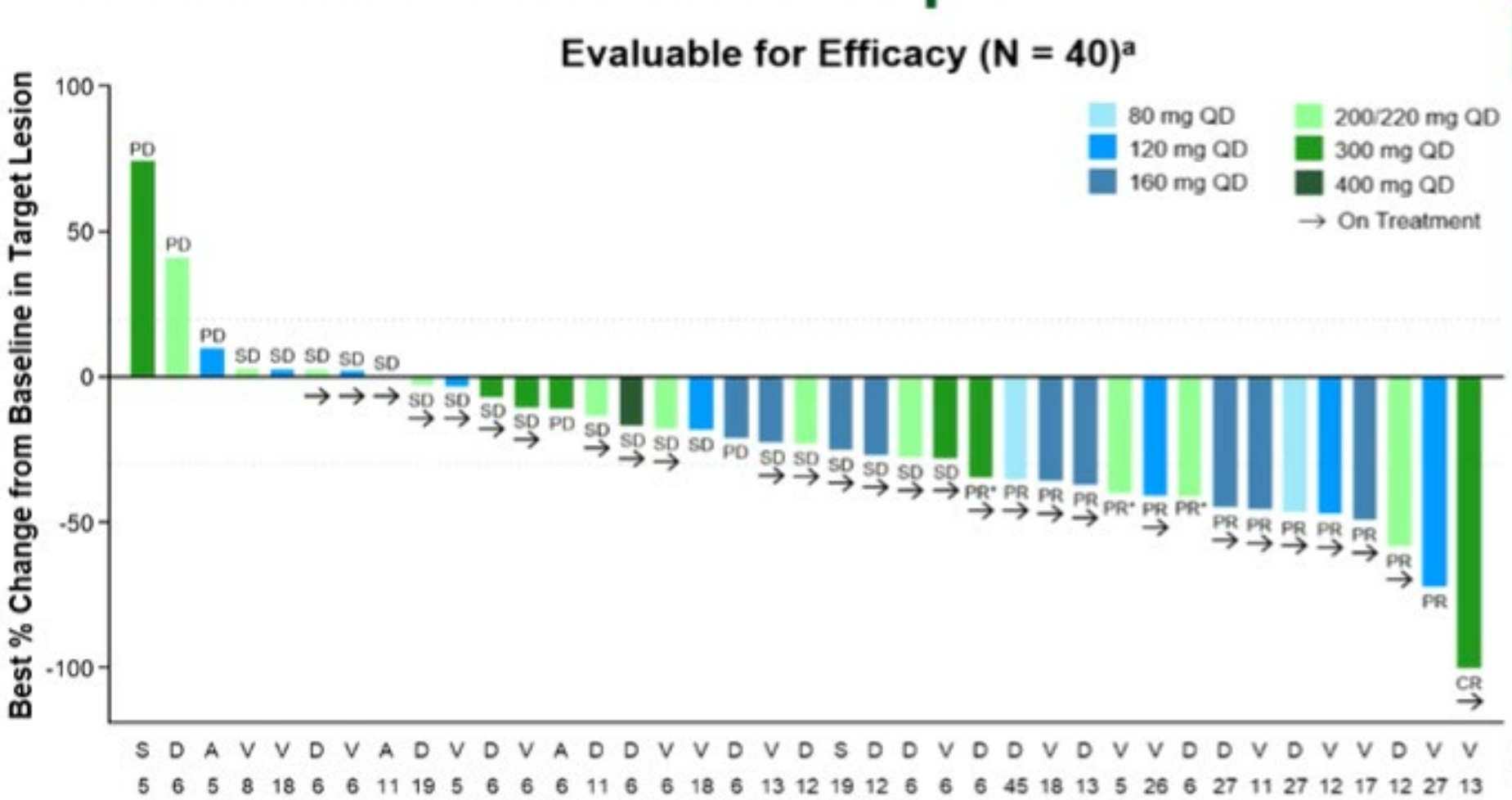
Patients with NSCLC and PDAC Treated at ≥80 mg QD (N = 111)					
Maximum severity of treatment-related AEs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**
TRAEs occurring in ≥10% of patients, n (%)					
Rash[a]	58 (52)	25 (23)	7 (6)	0	90 (81)
Nausea	40 (36)	11 (10)	0	0	51 (46)
Diarrhea	28 (25)	14 (13)	1 (1)	0	43 (39)
Vomiting	30 (27)	7 (6)	0	0	37 (33)
Stomatitis	13 (12)	9 (8)	2 (2)	0	24 (22)
Fatigue	11 (10)	6 (5)	0	0	17 (15)
Other select TRAEs, n (%)					
ALT elevation	8 (7)	1 (1)	0	0	9 (8)
AST elevation	8 (7)	0	0	0	8 (7)
Electrocardiogram QT prolonged	1 (1)	0	0	0	1 (1)
TRAEs leading to dose reduction[b], n (%)	0	10 (9)	5 (5)[c]	0	15 (14)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	1 (1)[d]	1 (1)

- Median time on treatment was 2.1 months (range: 0.2–10.9).
- No fatal TRAEs were observed.

[a]Includes preferred terms of dermatitis acneiform, rash maculopapular, rash, rash pustular, erythema, rash erythematous; multiple types of rash may have occurred in the same patient; [b]The most common reason for dose reduction was rash; [c]Grade 3 TRAEs leading to reduction were rash (n = 4), including one patient with a dose reduction due to rash and decreased appetite, and stomatitis (n = 1); [d]One Grade 4 TRAE occurred in a patient with PDAC at the 80 mg dose level who had a large intestine perforation at the site of an invasive tumor that reduced in size while on treatment.
ALT, alanine transaminase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

Data Extracted 12 Oct 2023.

KRAS^{G12X} NSCLC: Best Response



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
CR	1 (3)
PR	14 (35)
SD	19 (48)
PD	5 (13)
NE[b]	1 (3)
ORR, n (%)	15 (38)
Confirmed, n	12
DCR (CR+PR+SD), n (%)	34 (85)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]One subject withdrew from study without post-baseline scans.

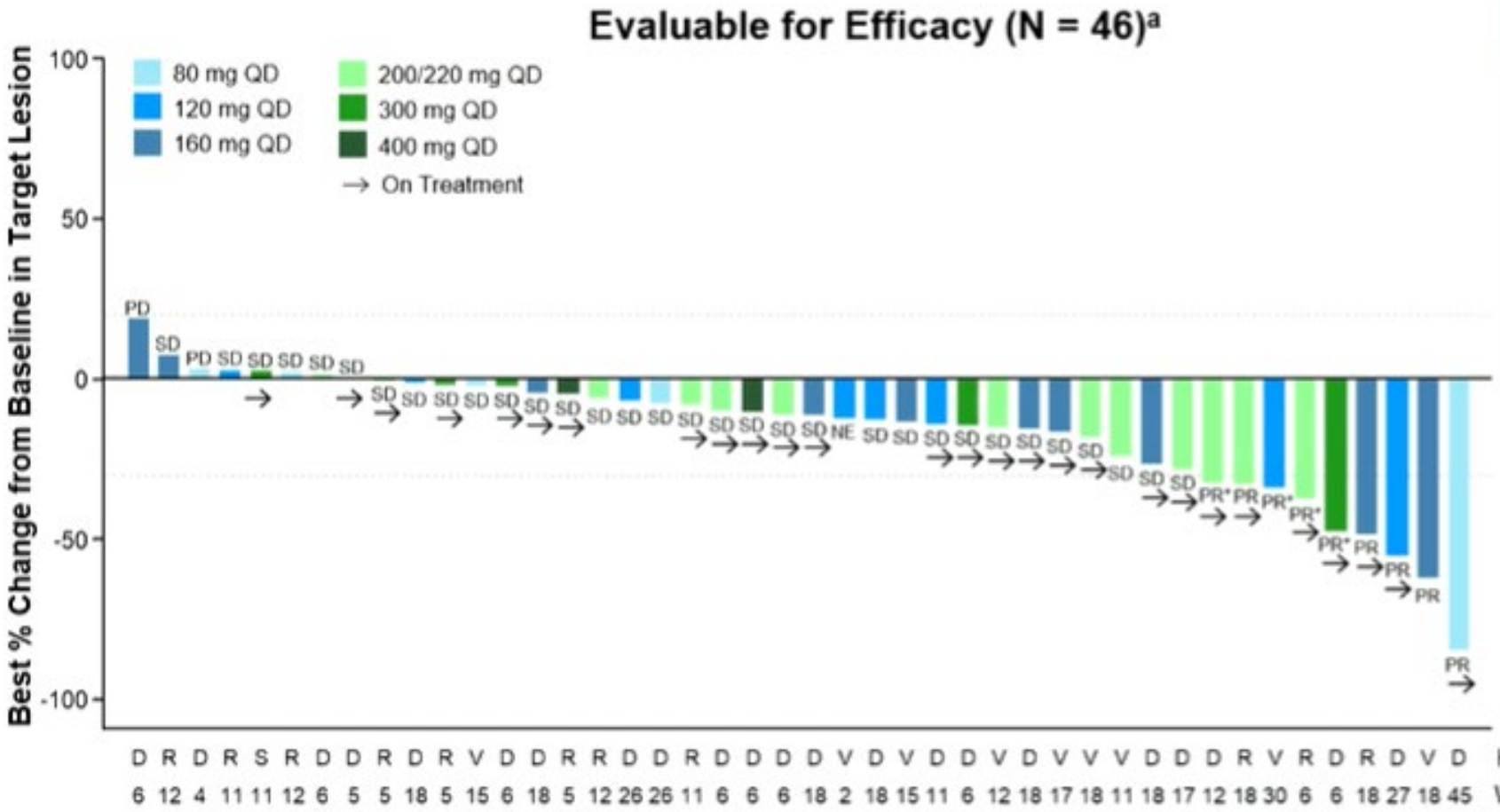
CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

MADRID 2023 ESMO congress

Kathryn C. Arbour, MD

Data Extracted 12 Oct 2023.

KRAS^{G12X} PDAC: Best Response



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
PR	9 (20)
SD	31 (67)
PD	3 (7)
NE[b]	3 (7)
ORR, n (%)	9 (20)
Confirmed, n	5
DCR (CR+PR+SD), n (%)	40 (87)

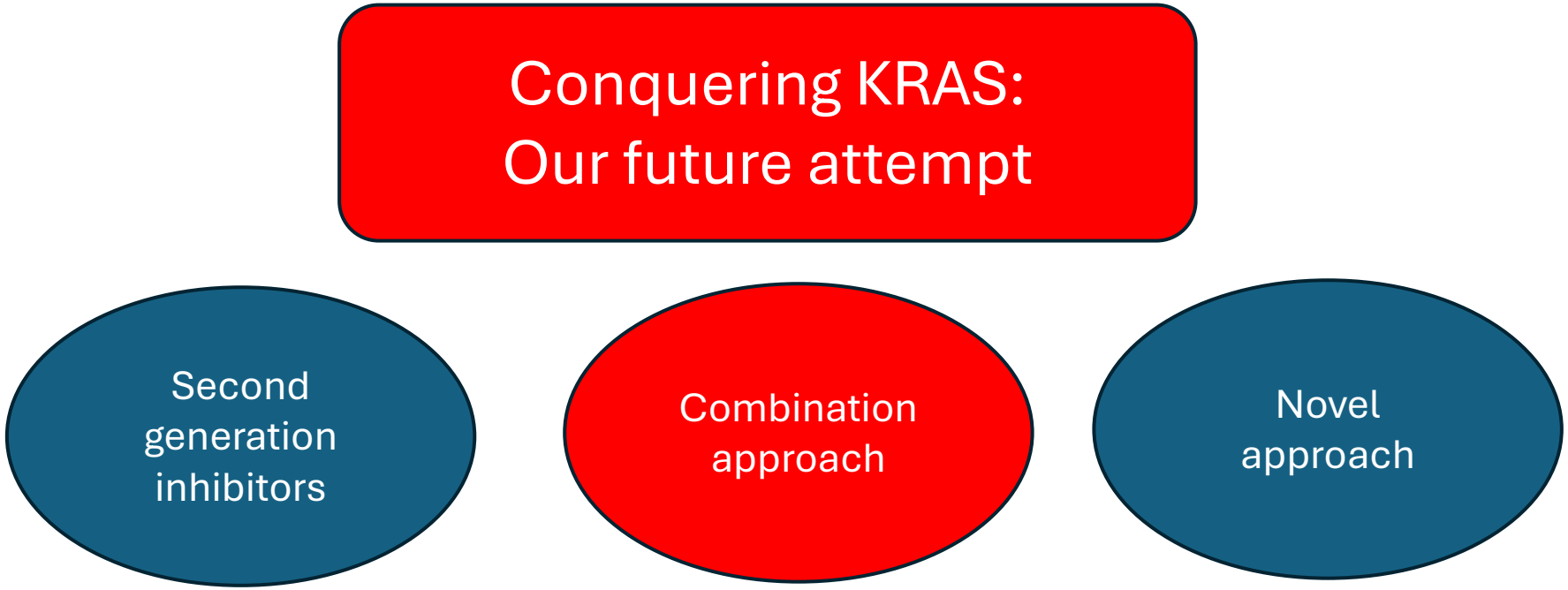
*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

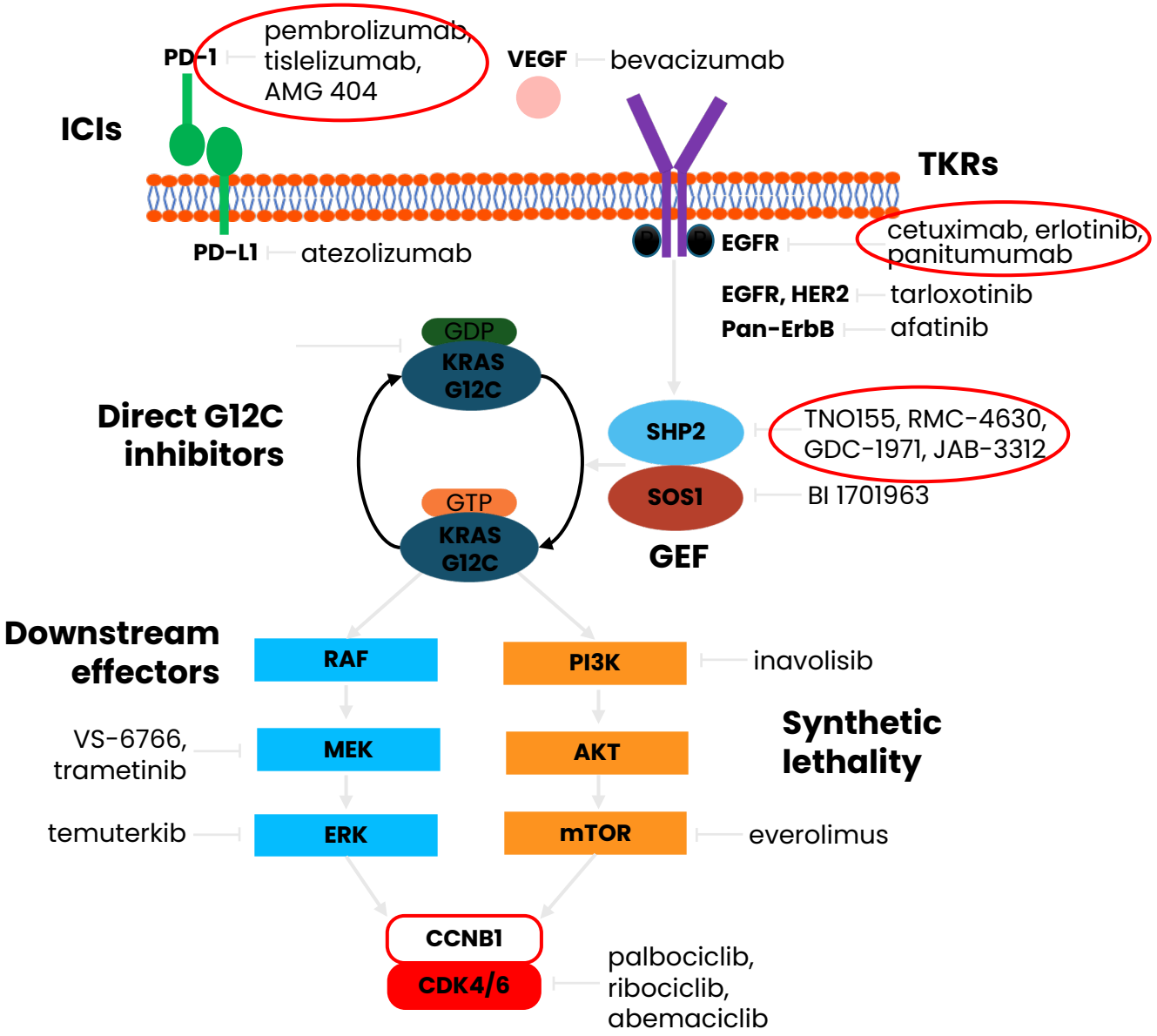
[b]Two patients died prior to first post-baseline scan; 1 patient had scan after 11 days of treatment and subsequently died due to PD.

Data Extracted 12 Oct 2023.

Conquering KRAS mutations

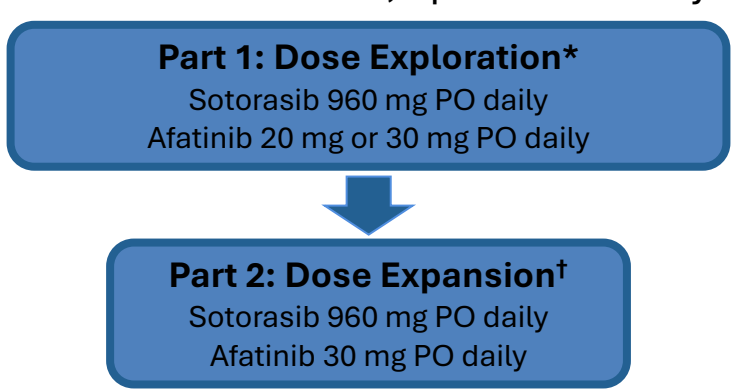


Multiple potential partners



Sotorasib + afatinib

- Phase 1b multicenter, open label study



Total of 33 patients enrolled

NSCLC (n = 10)
Sotorasib 960 mg/afatinib 20 mg PO daily
4 patients with prior $KRAS^{G12C}$ inhibitor (sotorasib)

NSCLC (n = 23)
Sotorasib 960 mg/afatinib 30 mg PO daily
1 patient with prior $KRAS^{G12C}$ inhibitor (sotorasib)

Key eligibility criteria

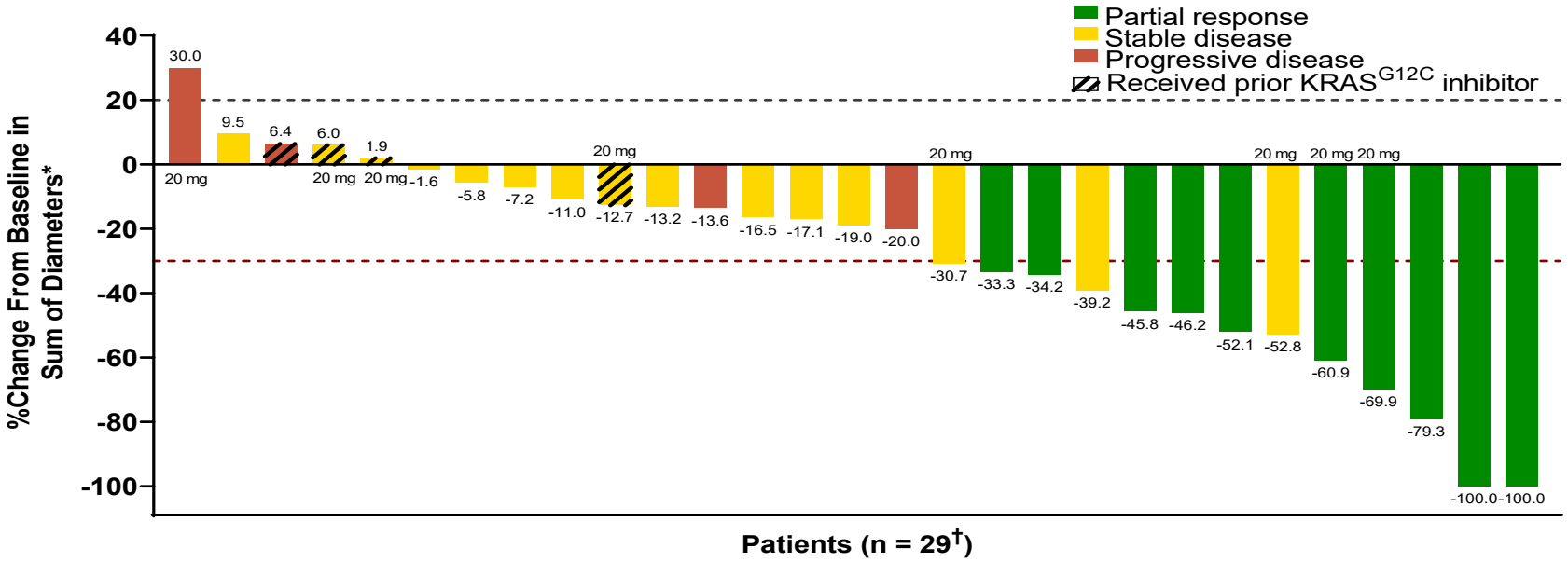
- Locally advanced or metastatic NSCLC with *KRAS* p.G12C mutation as assessed by molecular testing
- ≥ 1 prior treatment for advanced disease; prior anti-PD1/PD-L1 and/or platinum-based chemotherapy and targeted therapy (if applicable) was required

Primary endpoints

- Dose-limiting toxicities
- Adverse events

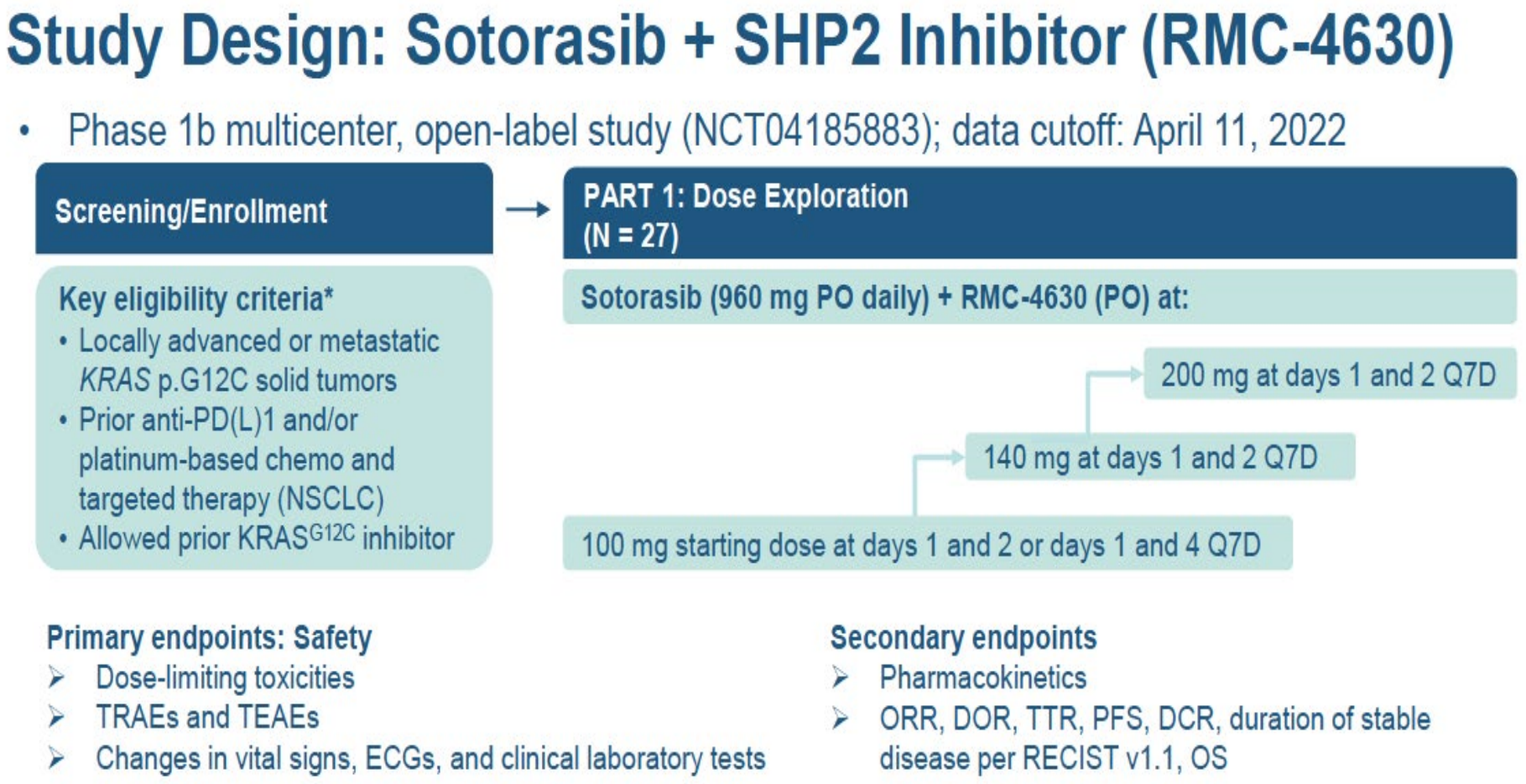
Gandara et al AACR-NIH-EORTC 2021

Efficacy



Response assessed by investigator	Sotorasib 960 mg + Afatinib 20 mg (n = 10)*	Sotorasib 960 mg + Afatinib 30 mg (n = 23)†	Sotorasib 960 mg PO QD + Afatinib 20 mg or 30 mg QD Combined Cohorts (N = 33)
ORR,‡ % (95% CI)	20.0 (2.5, 55.6)	34.8 (16.4, 57.3)	30.3 (15.6, 48.7)
Best overall response, n (%)			
Partial response, confirmed	2 (20.0)	8 (34.8)	10 (30.3)
Stable disease	5 (50.0)	10 (43.5)	15 (45.5)

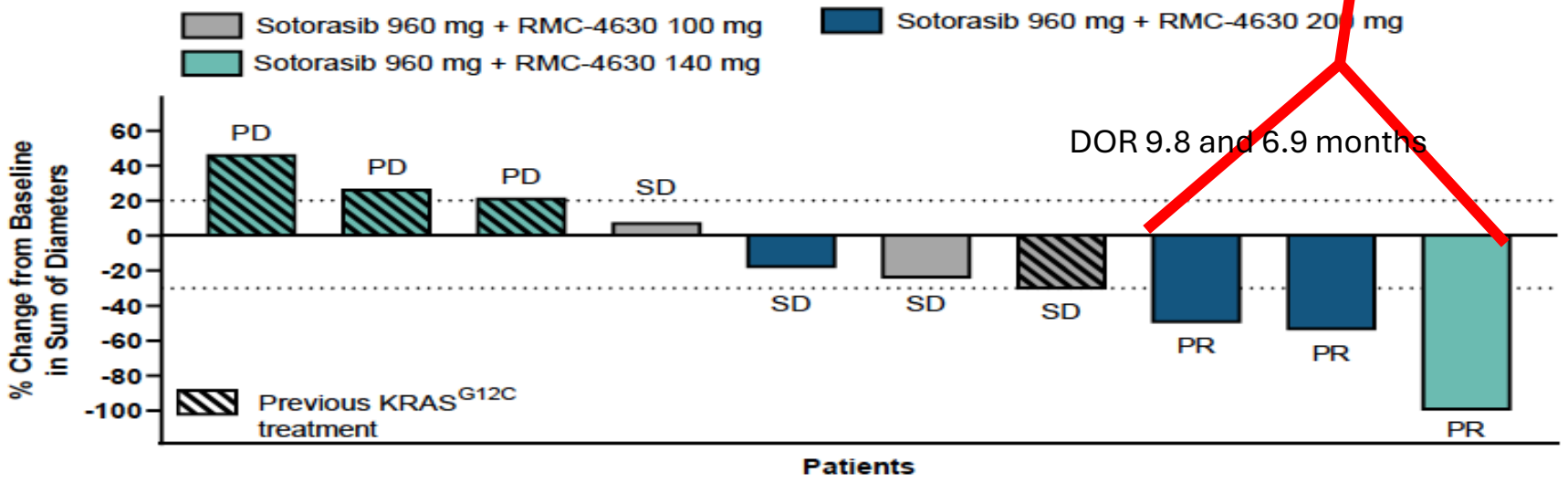
Sotorasib + RMC-4630



Falchook et al WCLC 2022

Efficacy

Response assessed by investigator	NSCLC	
	All enrolled (N = 11)	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)

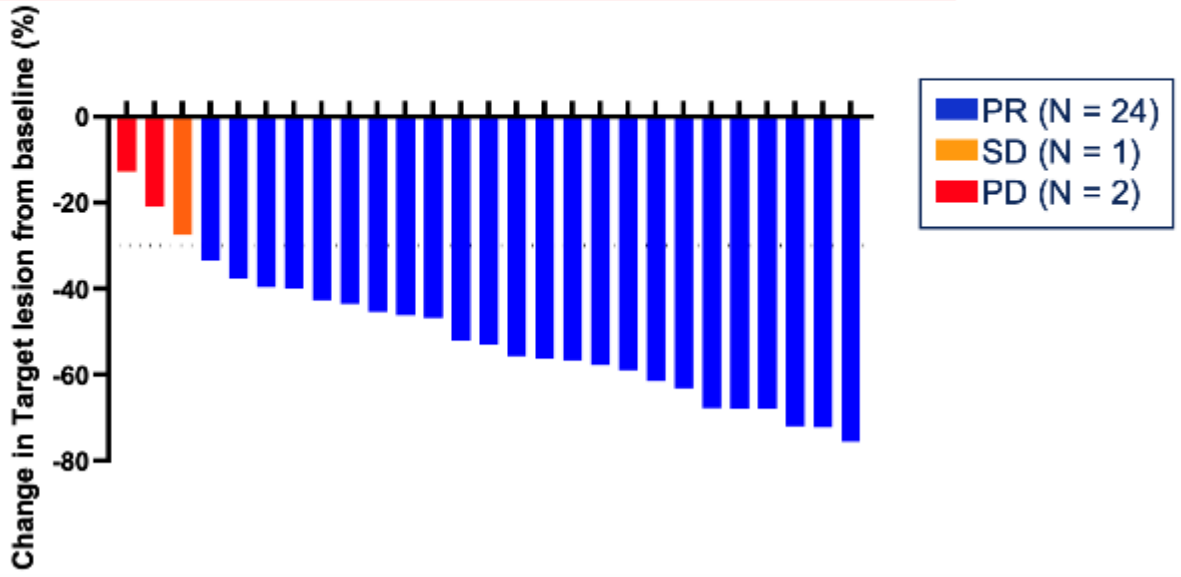


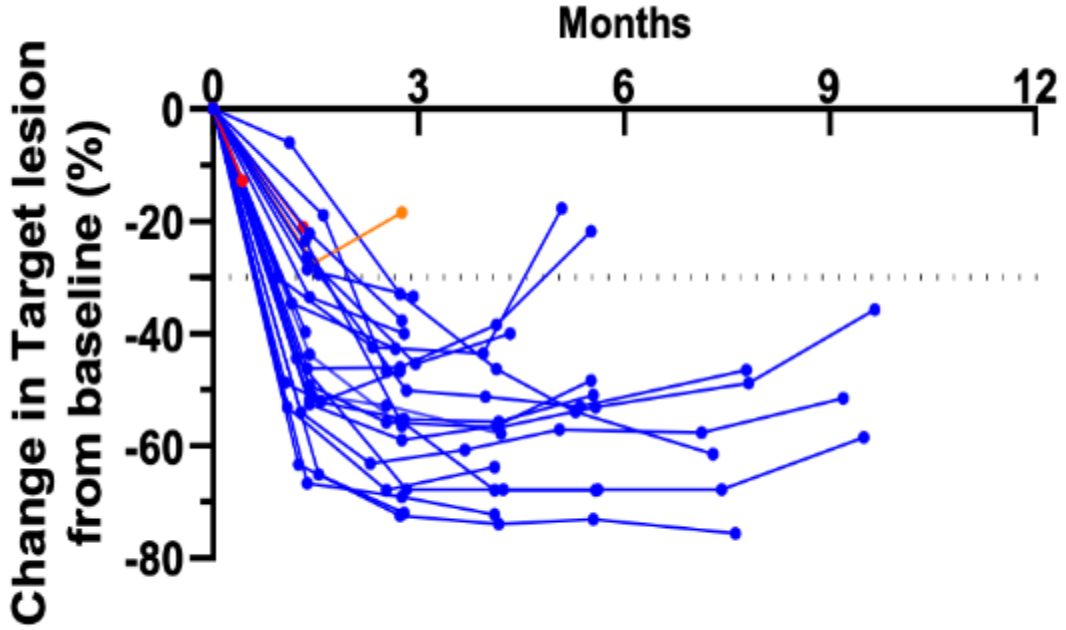
*One patient with PD was not included in tumor response due to data entry error.

SCARLET (WJOG14821L, Phase II): Sotorasib + carboplatin-pemetrexed among patients with advanced NSQ *KRAS* G12C-mutated NSCLC

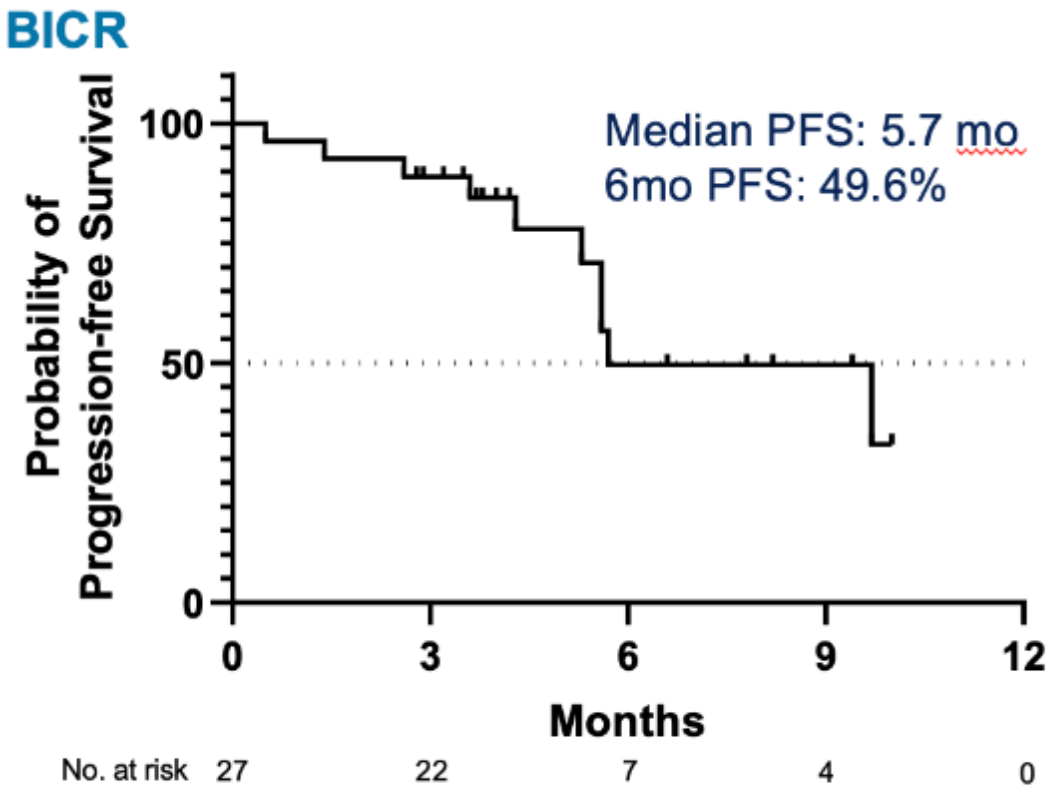
Primary endpoint: ORR by BICR

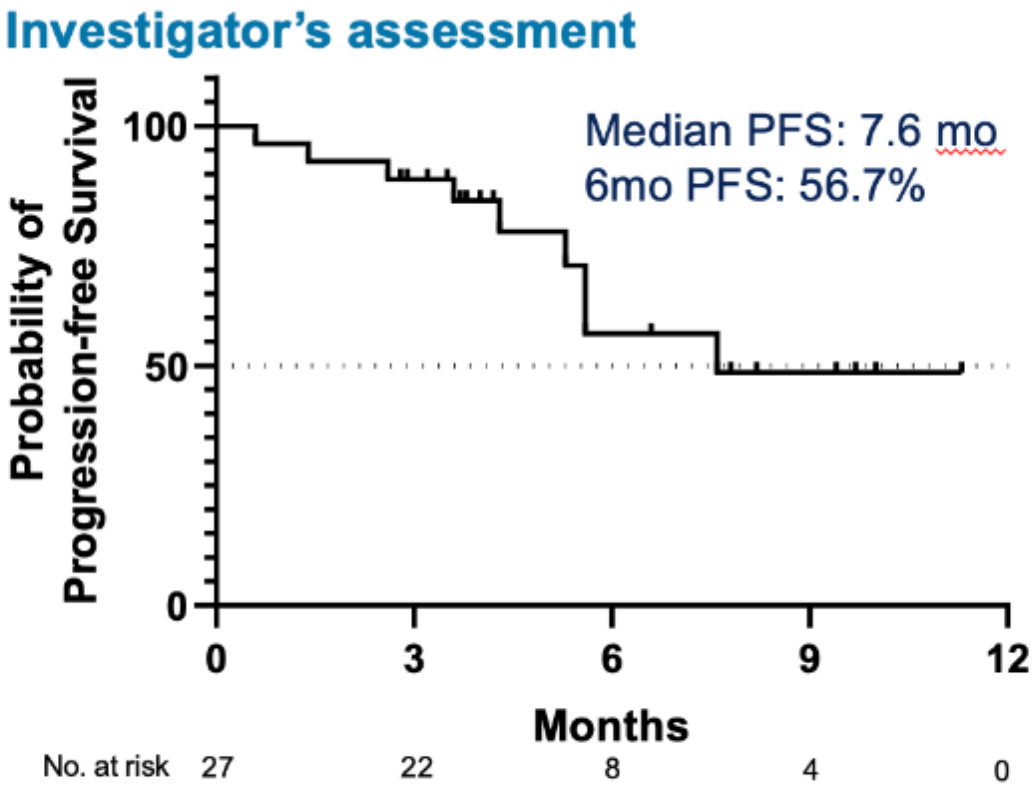
ORR 88.9% (80%CI 76.9-95.8%, 95%CI 70.8-97.6%)





SCARLET (WJOG14821L, Phase II): Sotorasib + carboplatin-pemetrexed among patients with advanced NSQ *KRAS* G12C-mutated NSCLC





Median follow-up: 4.1 months (range, 0.6-11.3)
Data cut-off; Oct 4, 2022

KRYSTAL-7 (849-007) Phase 2 Cohorts

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with $KRAS^{G12C}$ mutation[a]
- No prior systemic therapy for locally advanced/ metastatic disease[b]
- Stable brain metastases allowed
- Known PD-L1 TPS score[c]

Cohorts 1a and 2[c]
Adagrasib 400 mg BID + Pembrolizumab
N=148

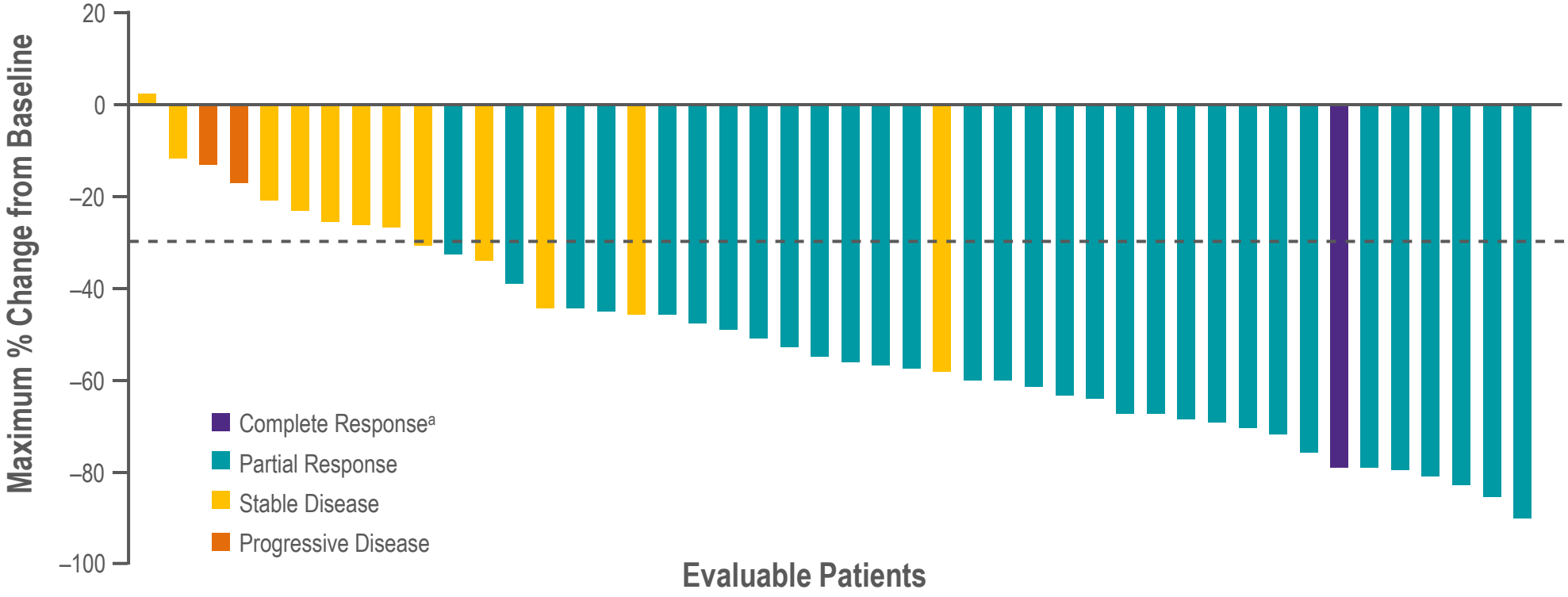
Key Study Objectives

- Primary endpoint: ORR (RECIST v1.1 per investigator assessment)
- Secondary endpoints: DOR and PFS (per investigator assessment), OS, safety, PK

- We report safety in all treated patients (N=148) and efficacy in patients with PD-L1 TPS ≥50% (n=51[d]) from the KRYSTAL-7 study evaluating adagrasib[e] + pembrolizumab (200 mg IV Q3W) in treatment-naïve patients with NSCLC harboring a $KRAS^{G12C}$ mutation
- Median follow-up for all treated patients, 8.7 months; PD-L1 TPS ≥50%, 10.1 months

- [a]$KRAS^{G12C}$ mutation detected in tumor tissue and/or ctDNA by sponsor-approved local laboratory testing. [b]Prior systemic therapy or chemoradiation in the (neo)adjuvant setting were allowed if >1 year prior to the first dose of study treatment, and no TRAE of grade ≥2 while on (neo)adjuvant CPI (exceptions for clinically stable vitiligo and psoriasis regardless of grade, and hyper- or hypothyroidism that was adequately controlled). [c]Cohort 1a enrolled patients with PD-L1 TPS <1%; Cohort 2 enrolled patients with PD-L1 TPS ≥1%. Molecular testing for PD-L1 TPS was performed locally or centrally, with a sponsor-approved laboratory test (PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 28-8 pharmDx or Ventana PD-L1 [SP142] assay). An additional cohort (1b) is enrolling patients with PD-L1 TPS <1% to receive adagrasib monotherapy, 600 mg BID. [d]Three patients excluded due to protocol deviations, including one each of atrial fibrillation, stroke within 6 months of enrollment, and presence of $KRAS^{G13C}$ mutation. [e]KRYSTAL-7 was initiated using the capsule (fasted) form of adagrasib but switched to the tablet (fed or fasted) form during study conduct

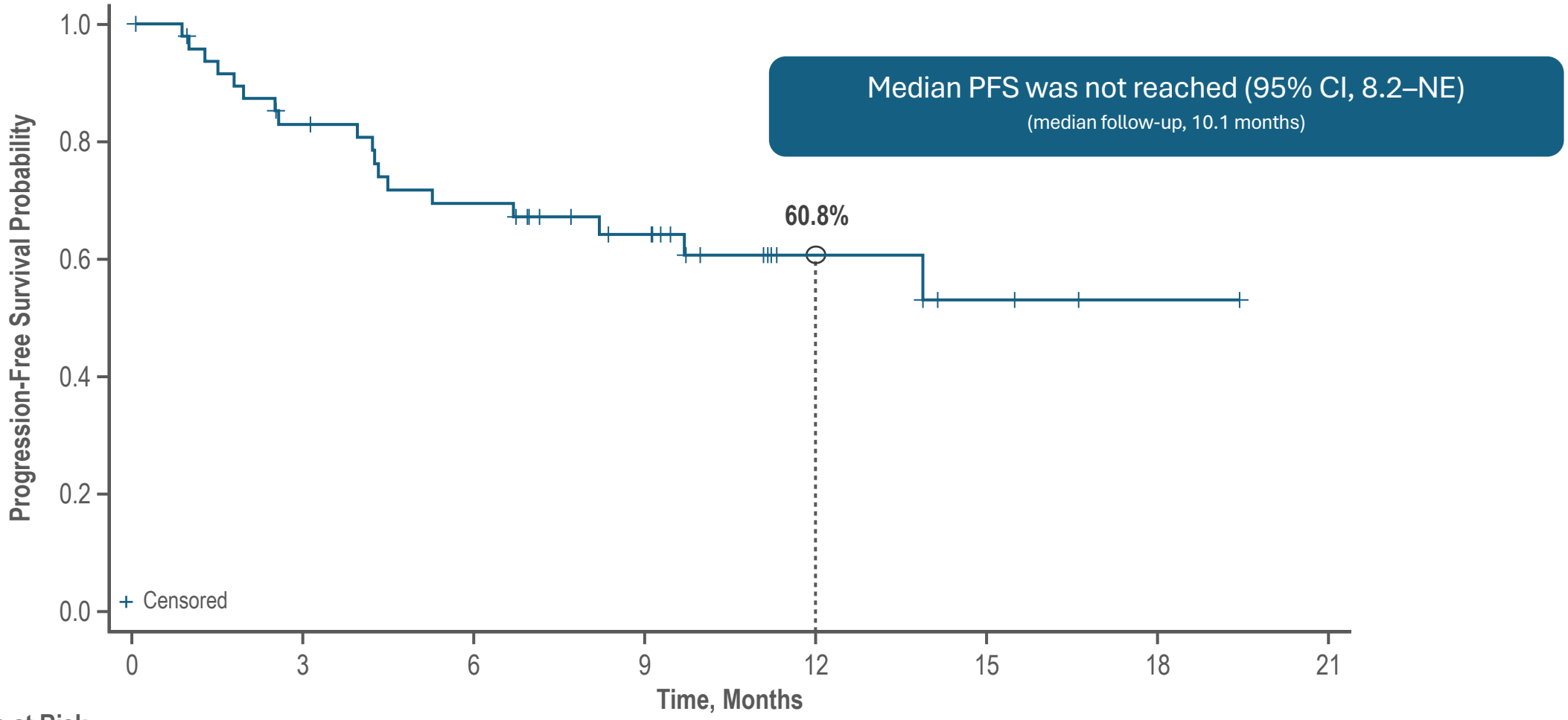
ORR and Best Tumor Change from Baseline in Patients With PD-L1 TPS ≥50%



- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity[b], ORR was 70% (14/20; 95% CI, 46–88)

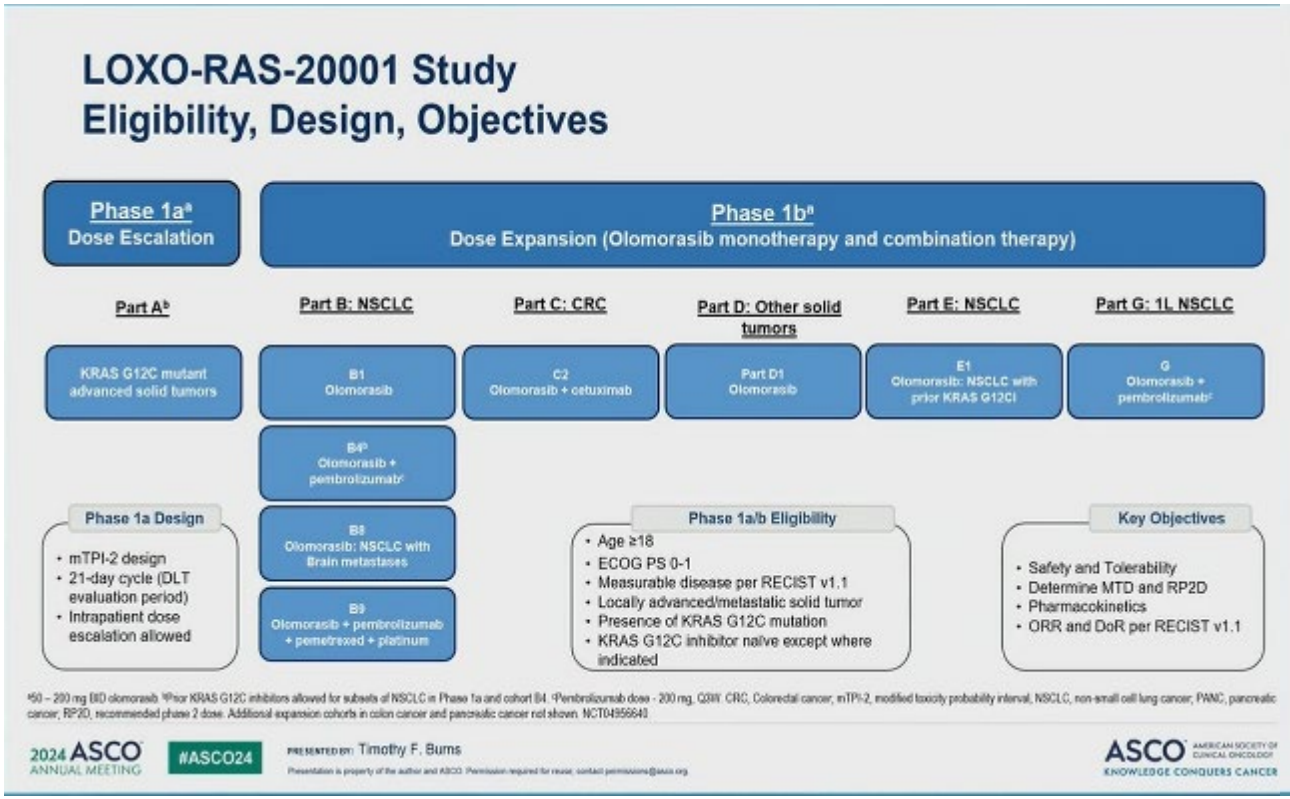
- Response per investigator assessment (n=51; modified full analysis set). Waterfall plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days). [a]One patient had CR without –100% change from baseline due to lymph node as target lesion. [b]Includes AST increase, ALT increase, mixed liver injury and liver function test increase; no grade 4 hepatotoxicity was observed in patients with PD-L1 TPS ≥50%
- Data as of 19 June 2023. Median follow-up 10.1 months

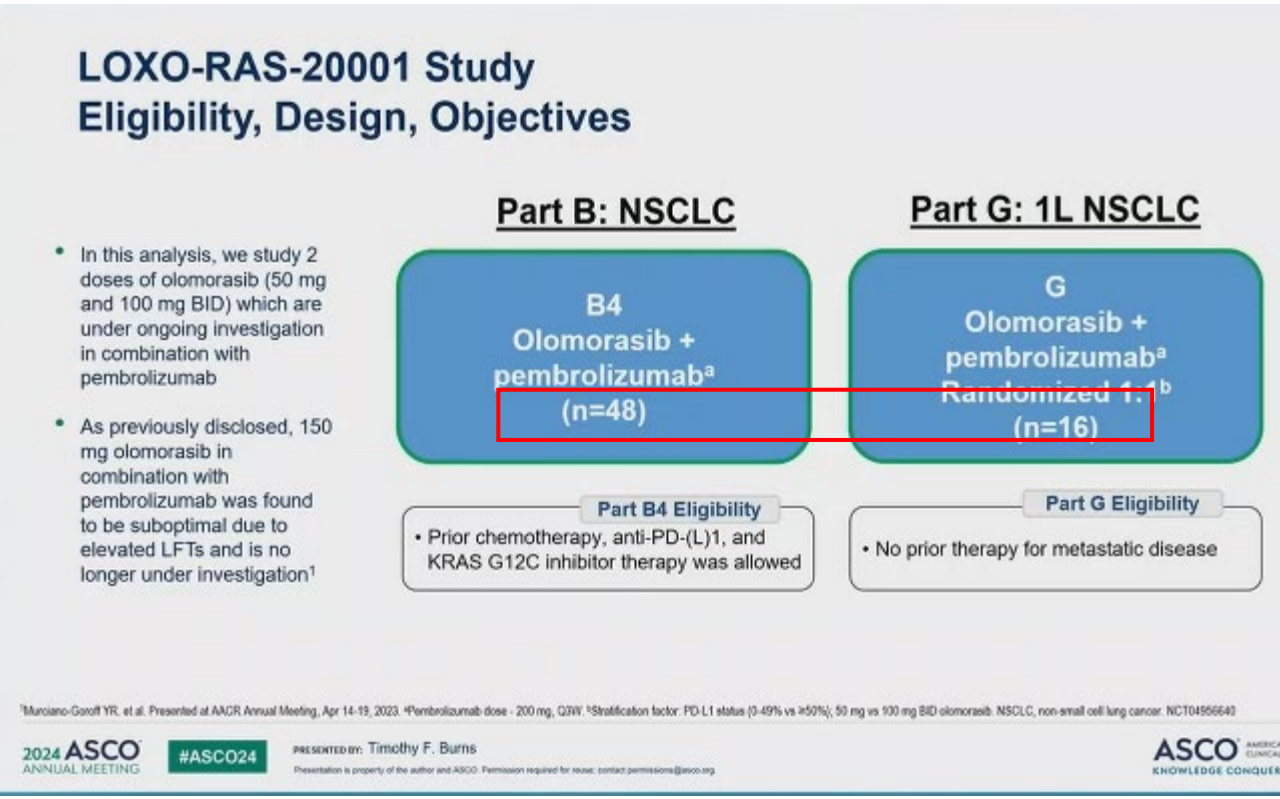
Progression-Free Survival in Patients With PD-L1 TPS ≥50%



- Response per investigator assessment (n=51; modified full analysis set)
- Data as of 19 June 2023. Median follow-up 10.1 months

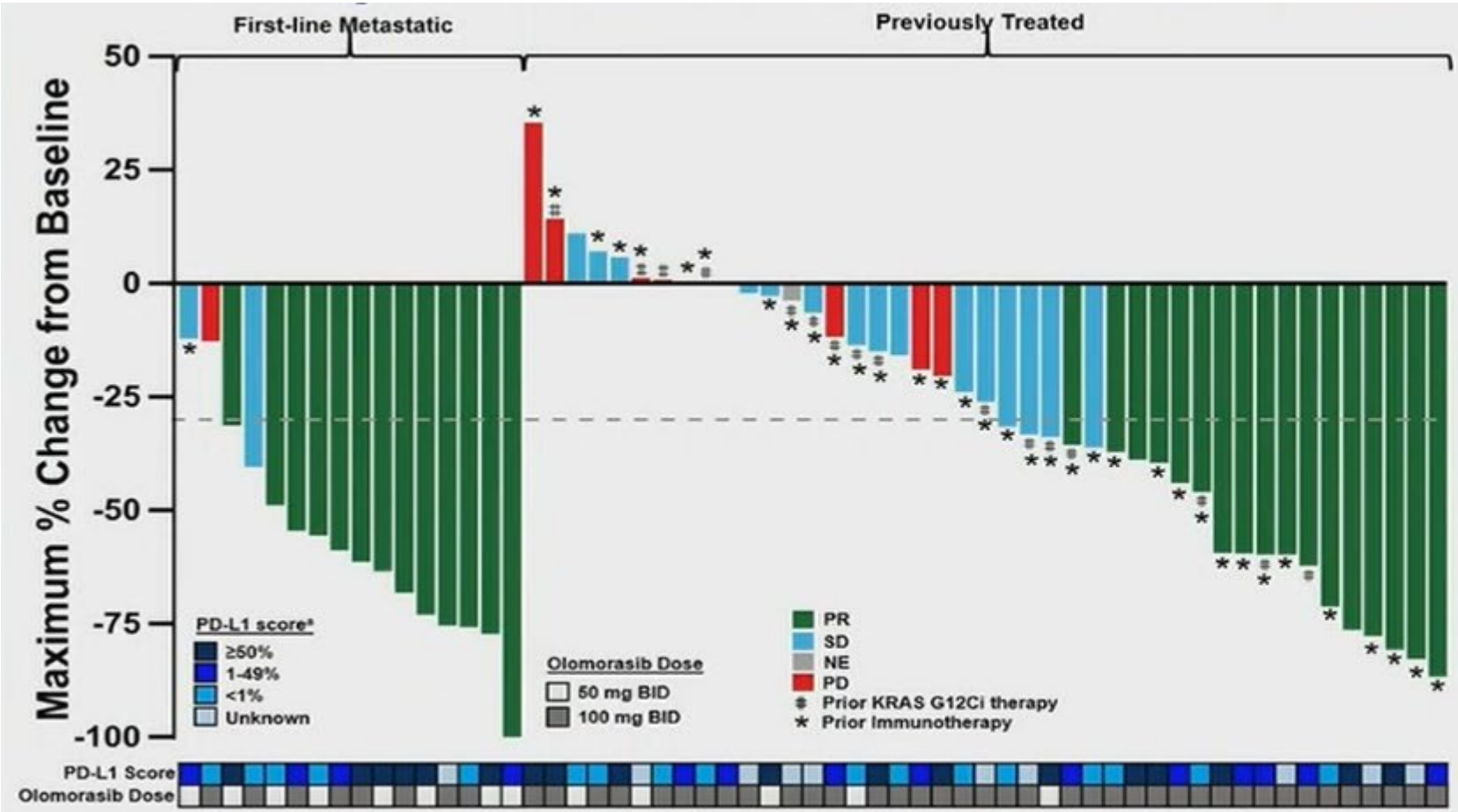
Olomorasib + pembrolizumab among patients with *KRAS* G12C-mutant advanced NSCLC





Olomorasib also known as LY3537982.
Burn, et al. ASCO 2024. Abstract 8510.

Response rate: First line vs previously treated



Efficacy Evaluable Patients[b]	First-line Metastatic (N=17)	Previously Treated (N=43)
Objective Response Rate[c], % (n/N)	77% (13/17)	40% (17/43)
Best overall response		
CR, n (%)	-	-
PR, n (%)	13 (77)	17 (40)
SD, n (%)	2 (12)	18 (42)
PD, n (%)	1 (6)	7 (16)
NE, n (%)	1 (6)	1 (2)
DCR, % (n/N)	88% (15/17)	81% (35/43)

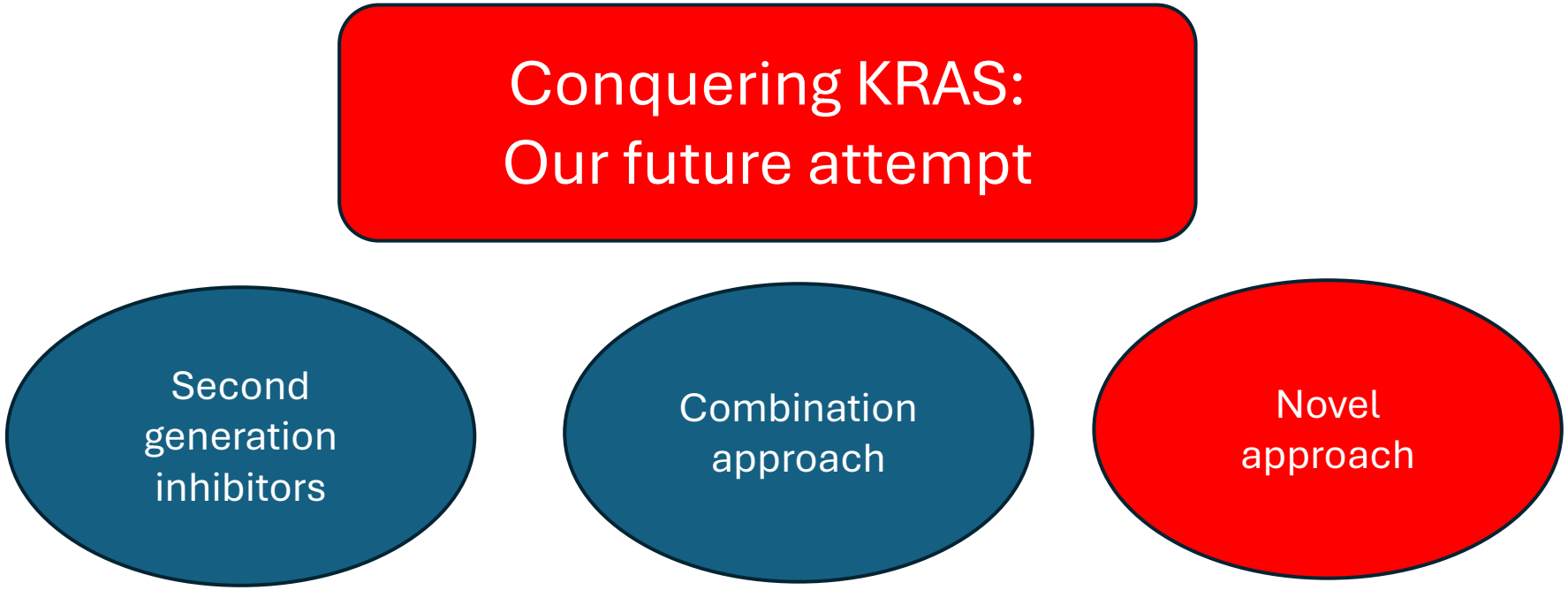
- 81% (35/43) of previously treated patients had received prior immunotherapy
- Median time to response was 1.4 months; median duration of response was NE

Burn, et al. ASCO 2024. Abstract 8510.

What is the optimal first line approach for *KRAS* G12C

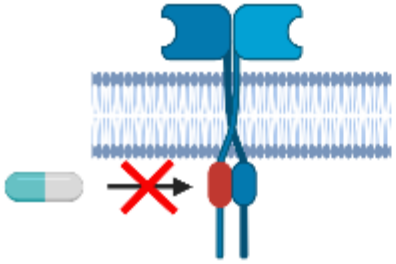
- Chemo + sotorasib (Codebreak 202): Targeting PD-L1<1%
- Pembrolizumab + adagrasib (KRYSTAL 2): Targeting PD-L1>50%
- Pembrolizumab + olomorasib (SUNRAY-01): Targeting PD-L1>50%
- Pembrolizumab + chemo +olomorsasib (SUNRAY-01): Targeting all PD-L1
- Cetuzimab + Fulzerasib: ????
- Single agent second generation???

Conquering KRAS mutations



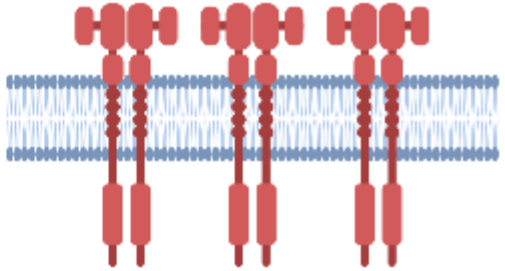
Mechanisms of Acquired Resistance to Kinase Inhibitors in Lung Cancer

Mutations in the drug target



Impact drug binding

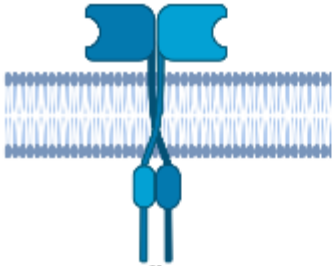
Bypass Signaling

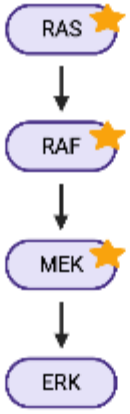


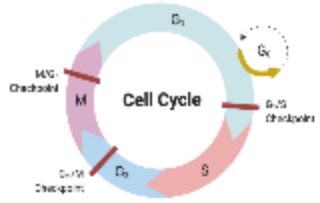
Oncogene Amplification

Oncogene Rearrangement

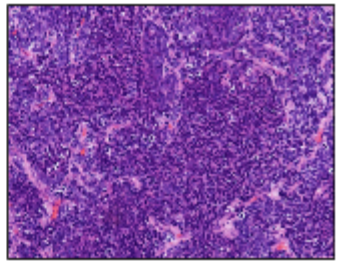
Mutations in Downstream Effectors





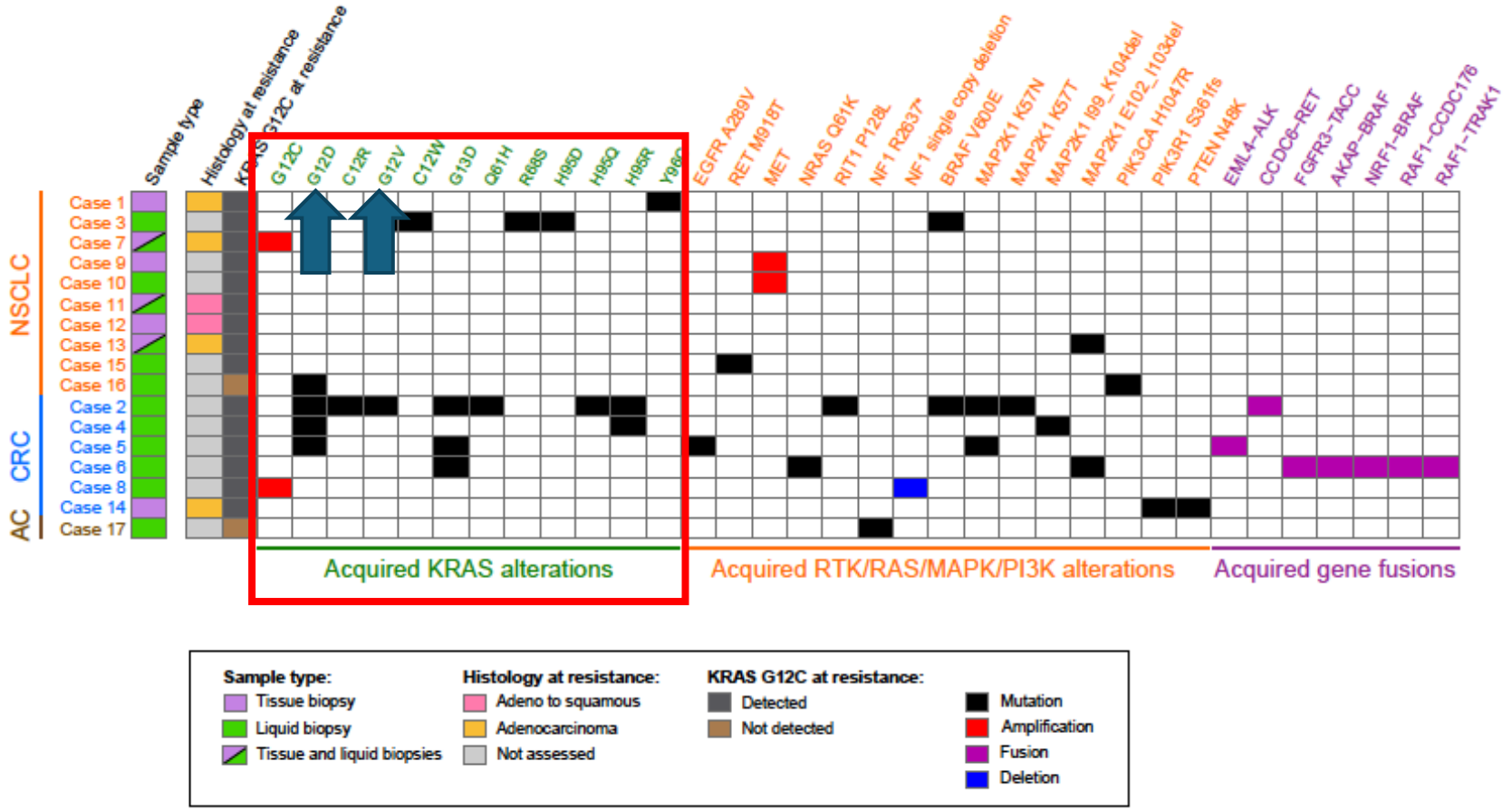


State Transformation



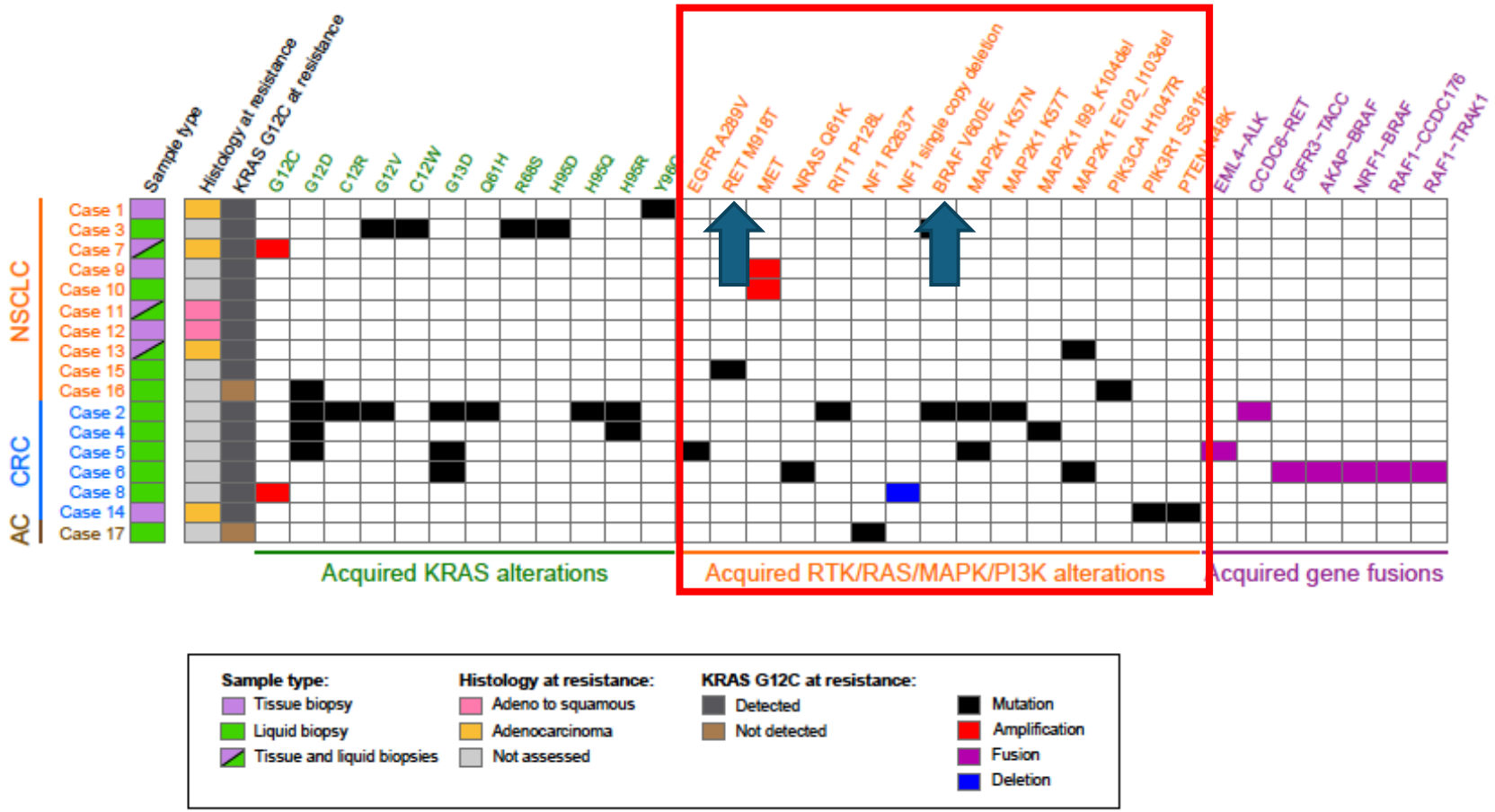
Small Cell Lung cancer
Squamous Cell lung cancer

Comparison of resistance mechanisms in NSCLC and CRC



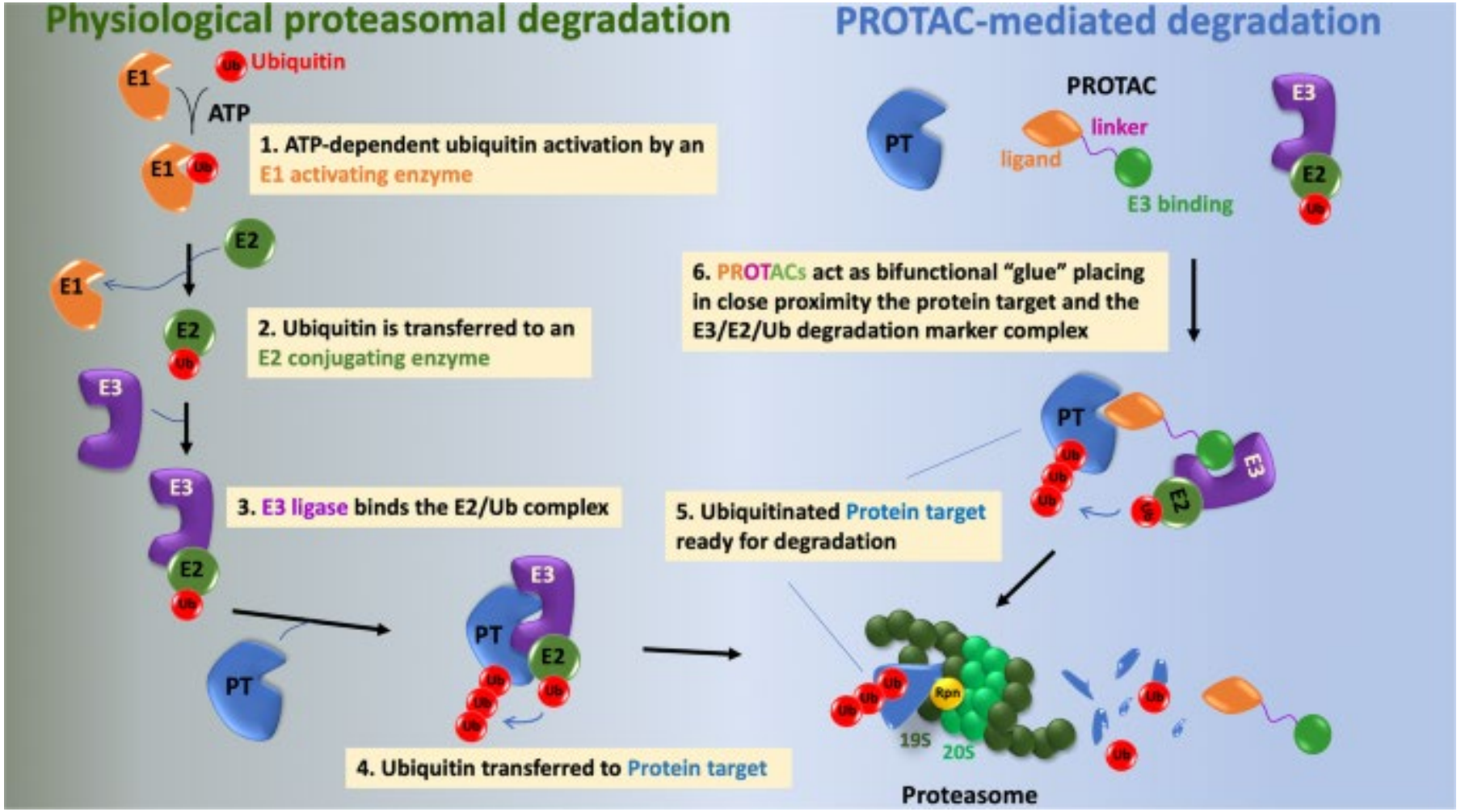
Awad et al. NEJM 2021

Comparison of resistance mechanisms in NSCLC and CRC



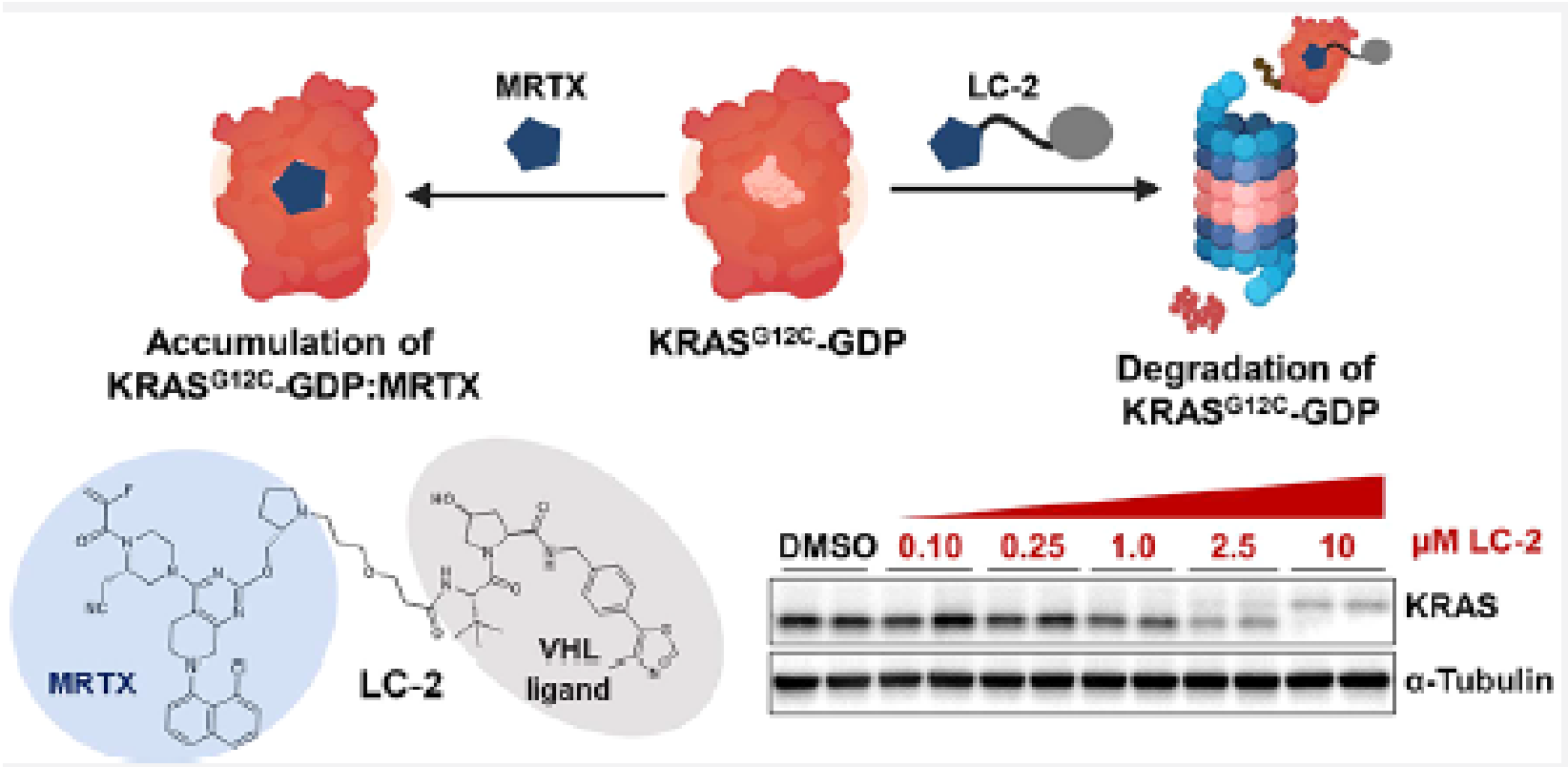
Awad et al. NEJM 2021

PROTAC: PROteolysis-TArgeting Chimeras



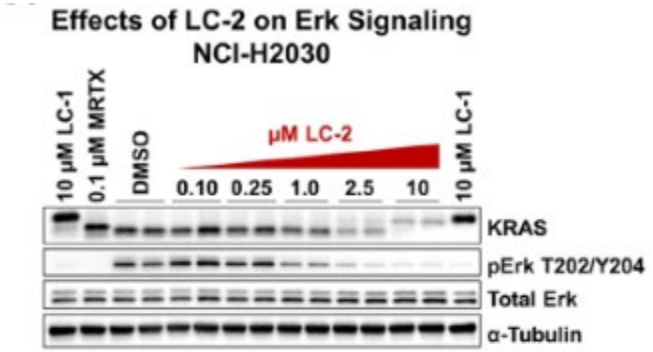
Ocana et al JECCR 2020

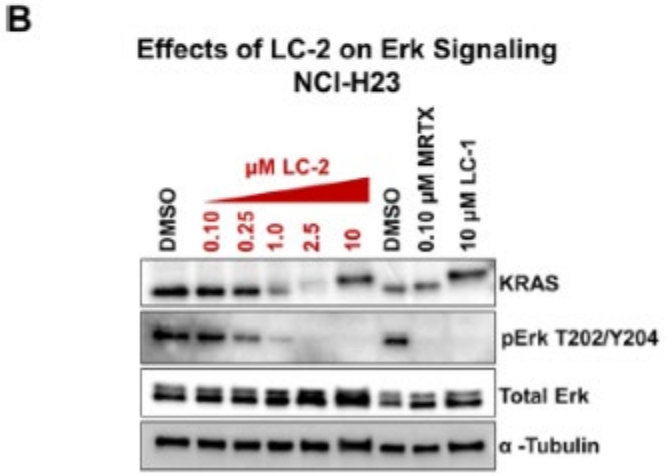
LC-2 is the first PROTAC KRAS G12C degrader

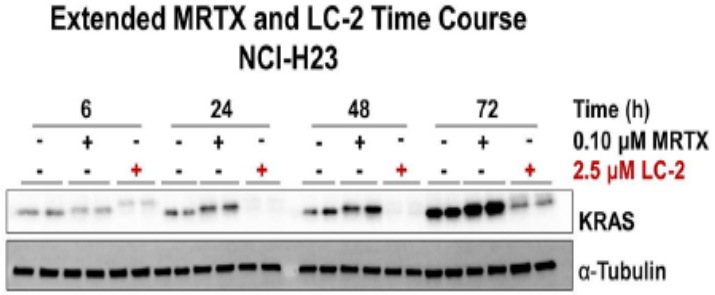


Bond et al ACS Central Sci 2020

Pre-clinical data with KRAS-ERG inhibition

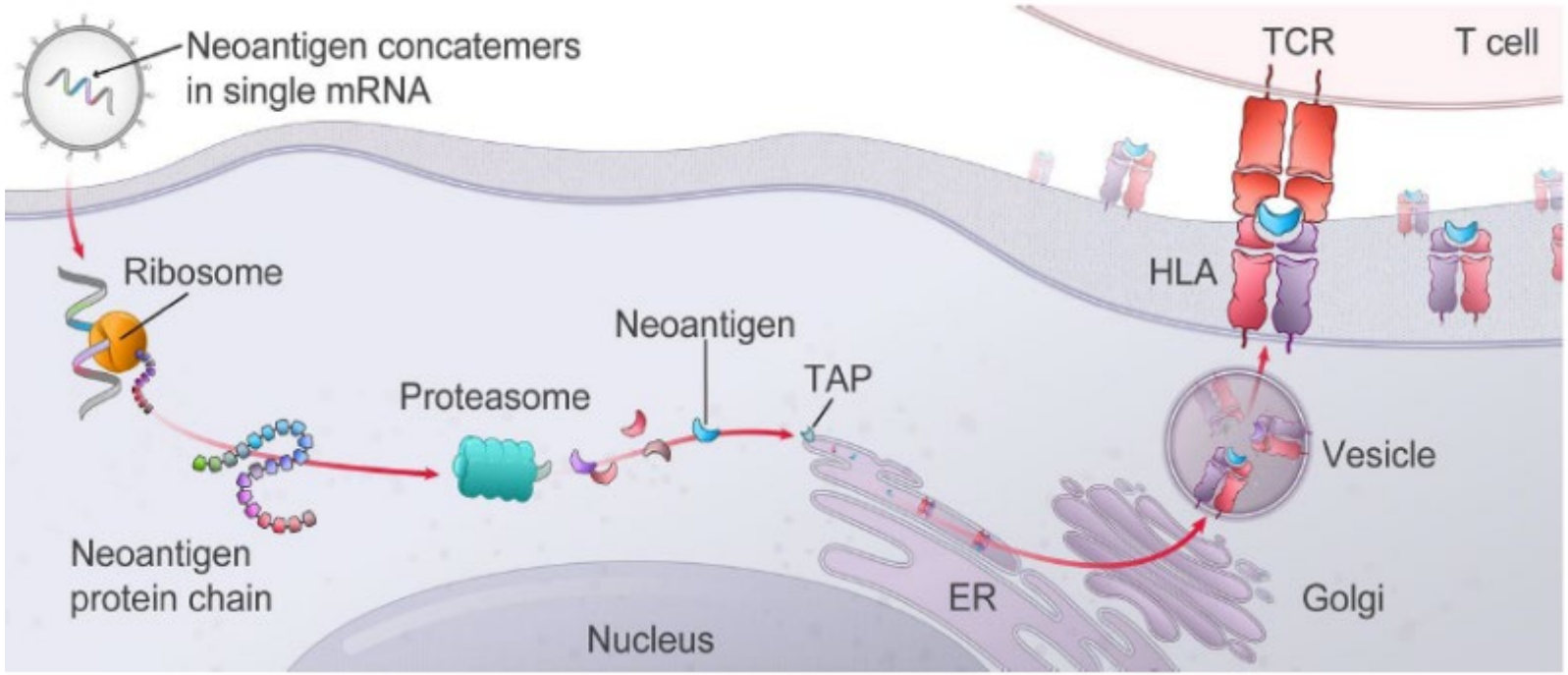




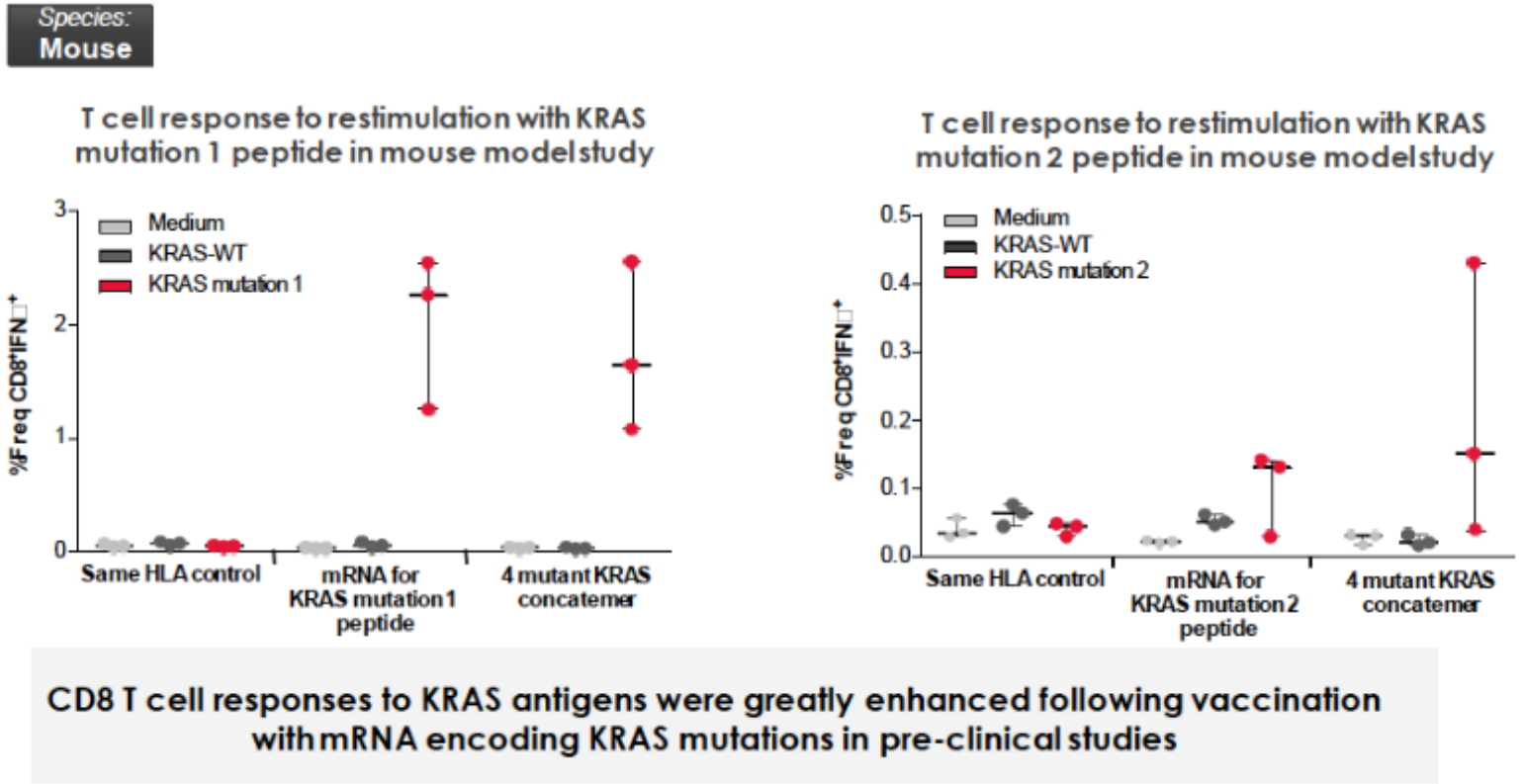


Bond et al ACS Central Sci 2020

mRNA 5671 against KRAS G12D, G12V, G13D and G12C



CD8 T cell response to mRNA 5671



CD8 T cell responses to KRAS antigens were greatly enhanced following vaccination with mRNA encoding KRAS mutations in pre-clinical studies

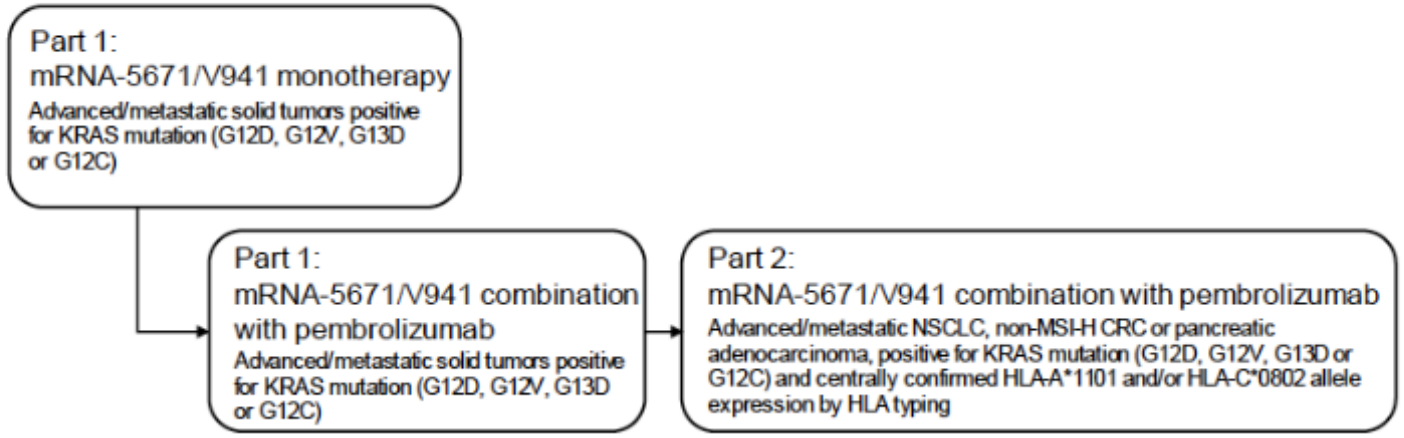
Moderna: data in file

Ongoing phase I study

Study Overview

- A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma

- Selecting for HLA subtypes (HLA-A*1101 and/or HLA-C*0802) most likely to respond



Summary

- Knowing KRAS mutations
  - KRAS is a driver oncogene
  - Oscillate between GDP and GTP state with GTP inducing downstream signaling pathways
  - KRAS G12C inhibitor binds to GDP and prevents GTP from being active
- Conquering KRAS mutations: First attempts
  - CodeBreak 200 on sotorasib: RR. %, med PFS 5.6 months
  - Krystal 12 (adagrasib vs docetaxel): RR 32%, med PFS 5.5 months
- Conquering KRAS mutations: Future attempts
  - Second generation drugs: Divarasib, D3S001, RMC 6236
  - Combination: multiple first lines studies with immunotherapy
  - Novel idea: PROTAC, vaccine

Can you conquer this?