Targeting KRAS G12C In Colorectal Cancer

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Disclosures

- Consultant for Amgen, Taiho Oncology, Bayer, Pfizer, PsiOxus Therapeutics, GlaxoSmithKline, Roche/Genentech, Mirati Therapeutics and AstraZeneca
- Speakers Bureau for Guardant360

I will be discussing the off-label drugs: Adagrasib, Sotorasib, Cetuximab and Panitumumab

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

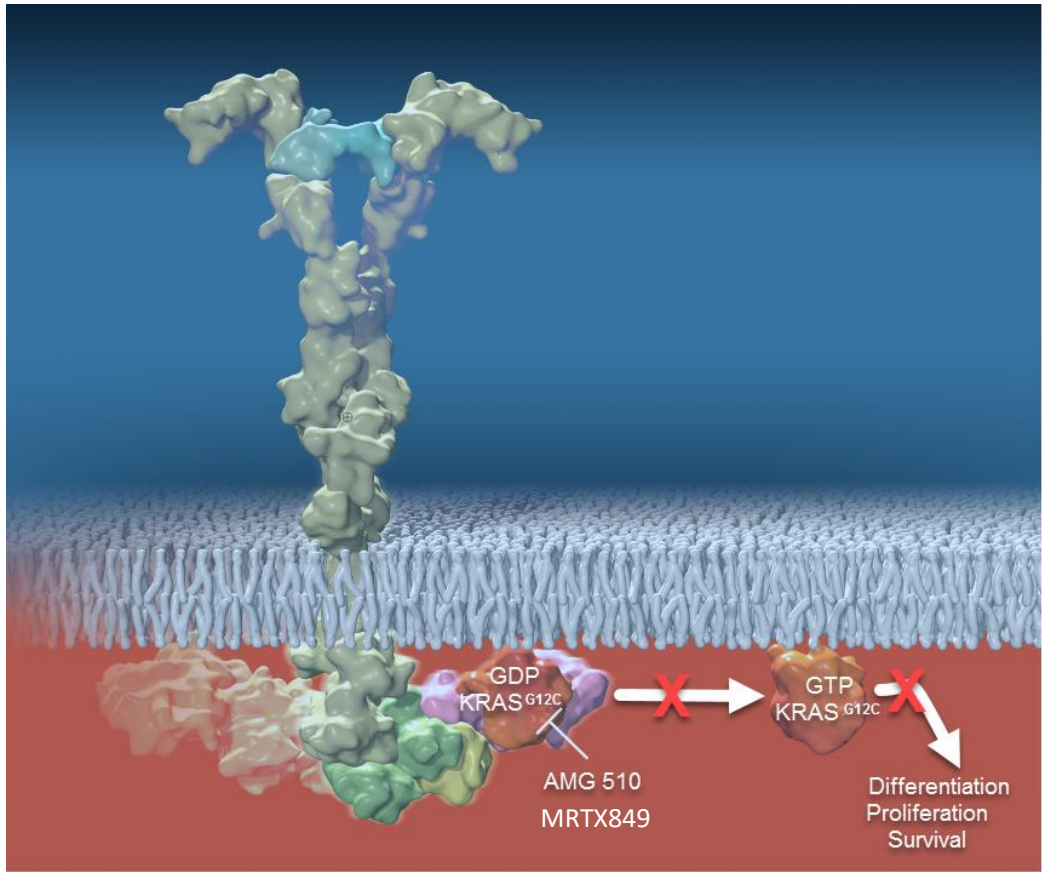
EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Targeting KRAS^{G12C} with Small Molecule Inhibitors

- KRAS is a GTP-binding protein that links receptor tyrosine kinase activation to intracellular signaling [1,2]
- Mutation of KRAS favors the GTP-bound active state and constitutive activation of downstream effects (differentiation, proliferation, survival)[3]
- *KRAS^{G12C}* mutation is found in approximately 13% of lung cancer[4], 3% of colorectal (CRC)[5] and appendix cancer, and 1-3% of other solid tumors[6]
- Small molecules, such as sotorasib and adagrasib, have been developed to specifically and irreversibly inhibit KRAS^{G12C} by locking it in an inactive GDP-bound state
- KRAS^{G12C} is the only KRAS that can be effectively targeted with a small molecule, thanks to lysine substitution that creates a "groove" in RAS protein that amenable to binding and blockade.



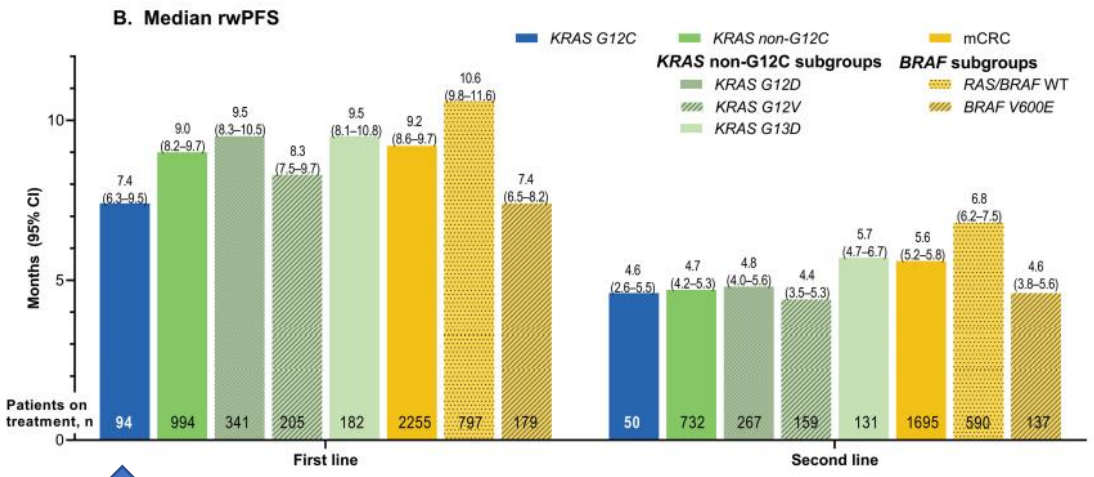
GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma viral oncogene homolog;
KRAS^{G12C}, KRAS protein with a G12C mutation at the protein level.

1. Prior IA, et al. *Cancer Res.* 2012;72:2457-2467.
2. Ostrem JM, et al. *Nat Rev Drug Discov*. 2016;15:771-785.
3. Ryan MB, et al. *Nat Rev Clin Oncol.* 2018;15:709-720.
4. Biernacka A, et al. *Cancer Genet.* 2016;209:195-198.
5. Neumann J, et al. *Pathol Res Pract.* 2009;205:858-862
6. Zhou L et al. *Med Oncol.* 2016;33:32.

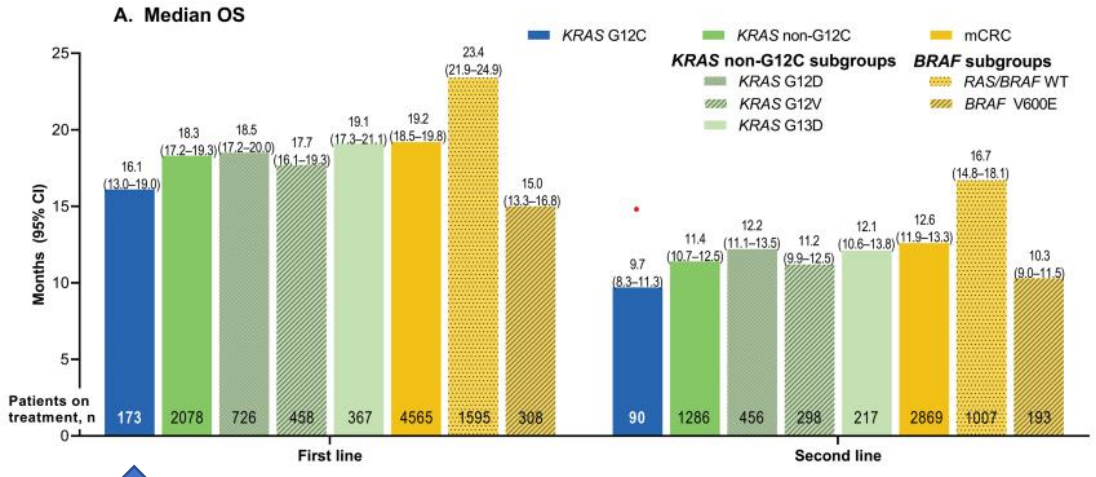
$KRAS^{G12C}$ Is Associated with Poor Outcome in MCRC in Real World Setting

- Overall, 6477 patients with genomically profile mCRC (Flatiron-FMI data base) were included: 238 (3.7%) had KRAS p.G12C (KRAS G12C cohort), 2947 (45.5%) had KRAS mutations other than p.G12C (KRAS non-G12C cohort) mutations.

KRASG12C had the shortest *RAS* 1st line PFS = 7.4 months



KRASG12C had the shortest *RAS OS* = 16.1 months

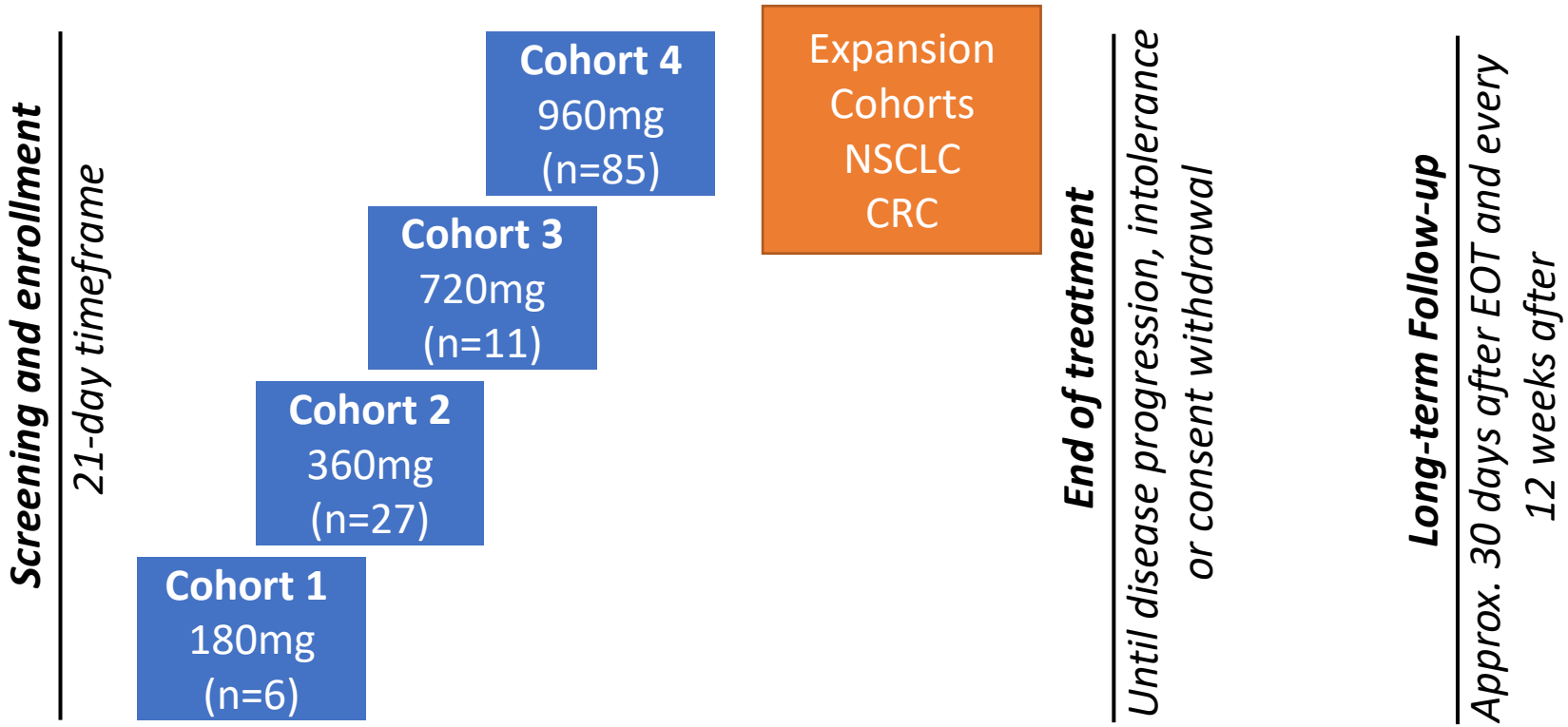


Despite its low frequency, KRAS G12C represents an unmet need in MCRC

Fakih, M. The Oncologist, 2022, 27, 663–674

CodeBreaK100: Sotorasib in Patients With Previously Treated Cancers With *KRAS* p.G12C Mutation

Adult pts with locally advanced or metastatic *KRAS* p.G12C mutant solid tumors, ECOG PS ≤ 2 who could not tolerate, or previously received appropriate therapy for tumor type and stage, with no active brain metastases or severe cardiac history



- Multicenter, open-label, phase 1, first in human dose escalation study
- Primary endpoint: Safety and tolerability including the incidence of AEs and DLTs
- Secondary endpoints: PK, best response, ORR, DOR, PFS, duration of stable disease

Hong and Fakih, NEJM. 2020;383:1207.

CodeBreaK100: Colorectal Cancer Patient Cohort

- Multicenter, open-label, first-in-human phase I/II trial (data cutoff: June 1, 2020)

Adult patients with locally advanced/metastatic *KRAS* p.G12C mutant solid tumors and PD on prior SoC therapy specific to tumor/disease stage; no active brain metastases (N = 129*)

CRC Escalation cohort (n = 42)†
Sotorasib (mg) PO QD‡
180 (n = 3), 360 (n = 10), 720 (n = 4), 960 (n =25)

Evaluable for tumor response as of the data cutoff

*Includes NSCLC (n = 59), CRC (n = 42), pancreatic cancer (n=12), appendiceal cancer (n = 4), unknown primary cancer (n=2), endometrial cancer (n = 2), and n=1 in each of the following: ampullary cancer, small bowel cancer, sinonasal cancer, esophageal cancer, bile duct cancer, SCLC, gastric cancer, and melanoma. †2-4 patients enrolled in each cohort to evaluate safety, with additional enrollment at any dose deemed safe. Intrapatient dose escalation permitted. Radiographic scans Q6W on treatment, 30 days after end of treatment, then Q12W.

- Median follow-up: 12.8 months (range: 9.0- 20.9)
- At current data cutoff: 3 patients remain on treatment, 37 discontinued due to progression/death, and 2 discontinued per request of patient

Hong and Fakih. NEJM. 2020;383:1207.

CodeBreaK100: PFS and OS in CRC Cohort

Survival	All dose levels (n = 42)	960 mg Dose (n = 25)
Median PFS, mos (95% CI) †	4.0 (2.8, 5.5) [1]	4.2 (2.8, NE) [2]
PFS Range (Min, Max) †	(0.0+, 11.1+) [1]	(1.2, 5.7*) [2]
KM PFS estimate, % (95% CI) [2]		
▪ At 3 mos	58.5 (41.9, 71.9)	59.7 (38.1, 76.0)
▪ At 6 mos	20.6 (7.3, 38.7)	NE (NE, NE)
Median OS, mos (95% CI) [2]	10.1 (7.7, NE)	NE (NE, NE)
OS Range, (Min, Max) [2]	(1.3*, 11.4*)	(2.3, 8.0*)
KM OS estimate, % (95% CI) [2]		
▪ At 3 mos	92.7 (79.0, 97.6)	96.0 (74.8, 99.4)
▪ At 6 mos	76.4 (57.7, 87.7)	82.9 (53.3, 94.6)

*Censored value. † Data collected from two different time points (January and June 2020) consistent with respective citation.

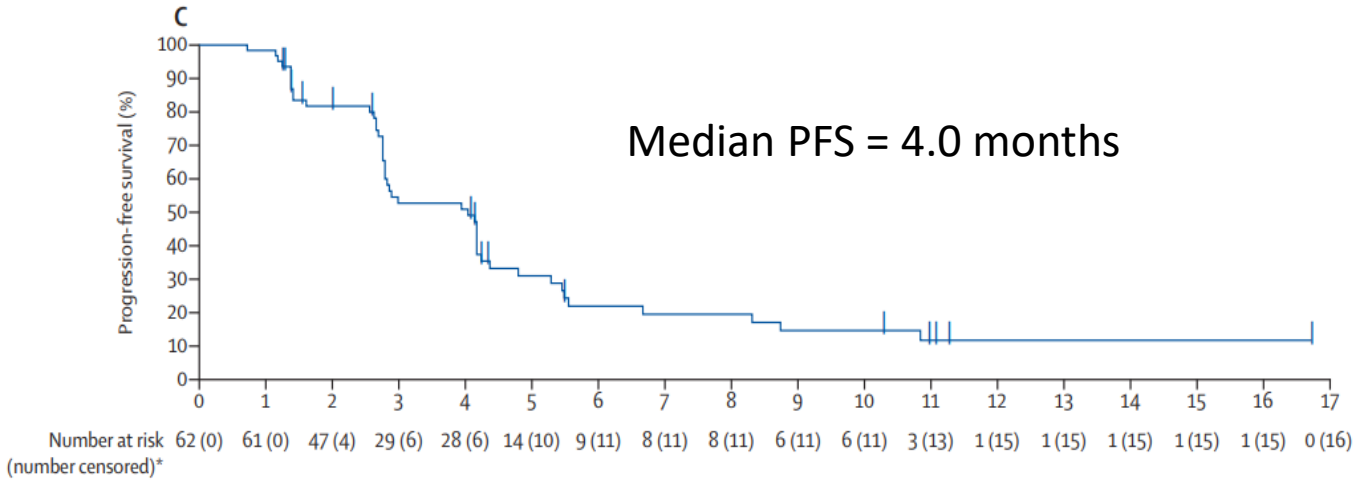
1. Hong and Fakih. NEJM. 2020;383:1207. 2. Hong. ASCO 2020. Abstr 3511.

CodeBreaK100: Phase II CRC Multicenter Trial

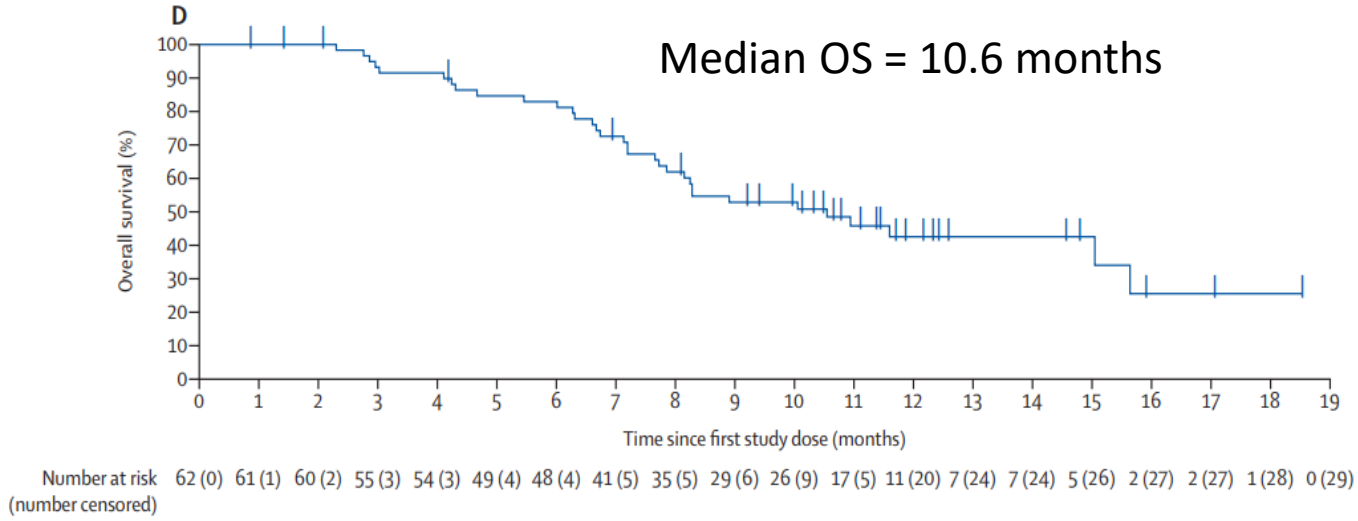
- KRAS G12C
- ECOG 0-1
- Measurable disease
- PD following fluoropyrimidine, oxaliplatin, irinotecan

62 pts treated with sotorasib 960 mg per day

	Patients (n=62)
Objective response, n (%; 95% CI)*	6 (9·7%; 3·6–19·9)
Disease control, n (%; 95% CI)†	51 (82·3%; 70·5–90·8)
Best response, n (%)	
Complete response	0
Partial response	6 (10%)
Stable disease	45 (73%)
Progressive disease	11 (18%)
Median time to response, months (IQR)‡	2·0 (1·4–2·8)
Median duration of response, months (IQR)‡	4·2 (2·9–8·5)



Median PFS = 4.0 months

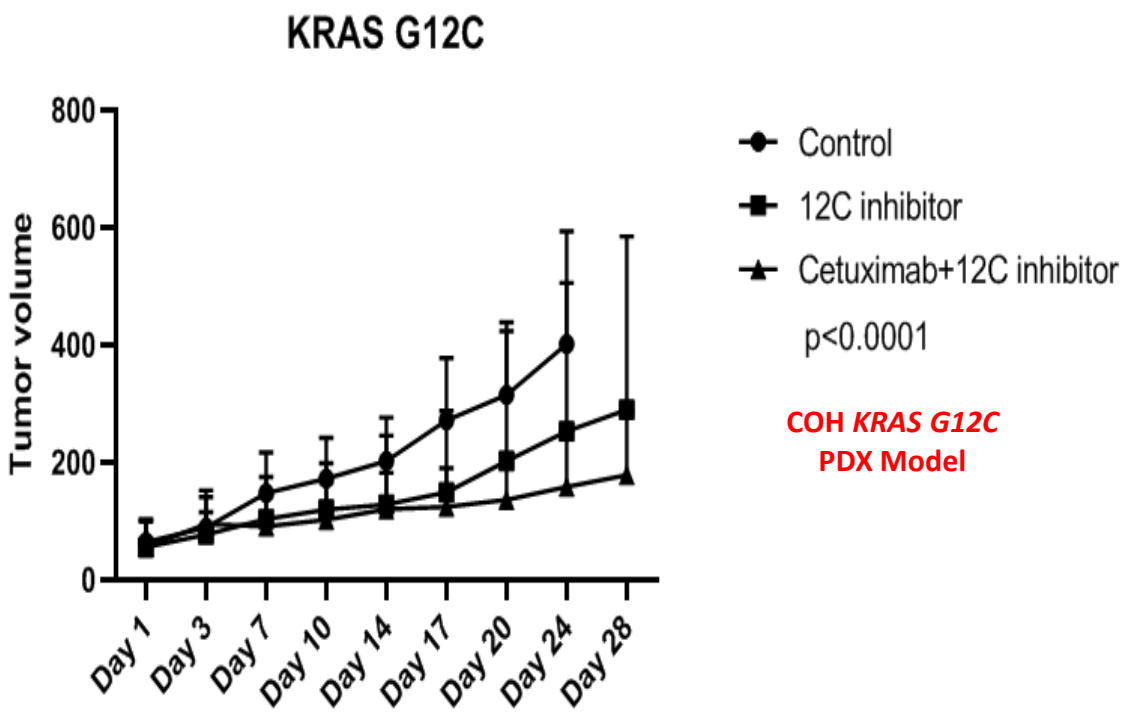


Median OS = 10.6 months

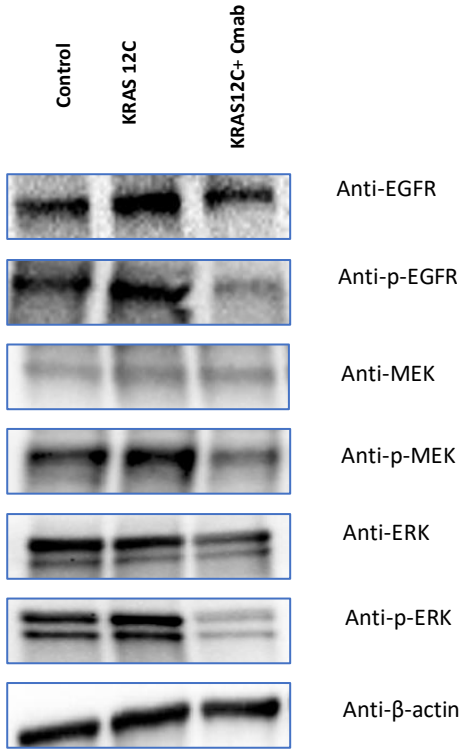
Fakih, M. Lancet Oncol 2022; 23: 115–24

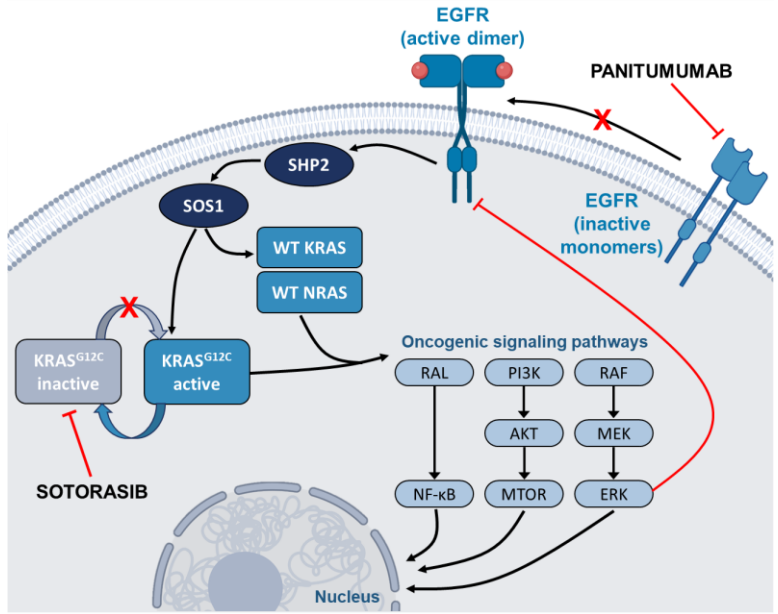
KRAS G12C Inhibition Results in Feedback EGFR Phosphorylation

KRAS G12C inhibitor-**ARS-1620**



COH *KRAS G12C*
PDX Model





Targeting EGFR with anti-EGFR antibodies may overcome *KRAS G12* small molecule inhibitors

CodeBreaK 101 Subprotocol H Study Design

Phase 1b, multicentre study*:
Sotorasib + panitumumab in chemorefractory *KRAS G12C*-mutated mCRC

Screening/enrolment

Key eligibility criteria (Part 2 Cohort A)

- *KRAS G12C*-mutated mCRC, identified through molecular testing
- $KRAS^{G12C}$ inhibitor-naive
- ≥1 prior treatment for advanced disease†
- Progressed on or after fluoropyrimidine, oxaliplatin, irinotecan, and an anti-angiogenic agent

Part 1: Cohort A dose exploration‡

Sotorasib PO daily

+

Panitumumab 6 mg/kg IV Q2W

Part 2: Cohort A dose expansion (N=40)

Sotorasib: 960 mg PO daily

+

Panitumumab: 6 mg/kg IV Q2W

Treatment until disease progression, withdrawal of consent, or end of study

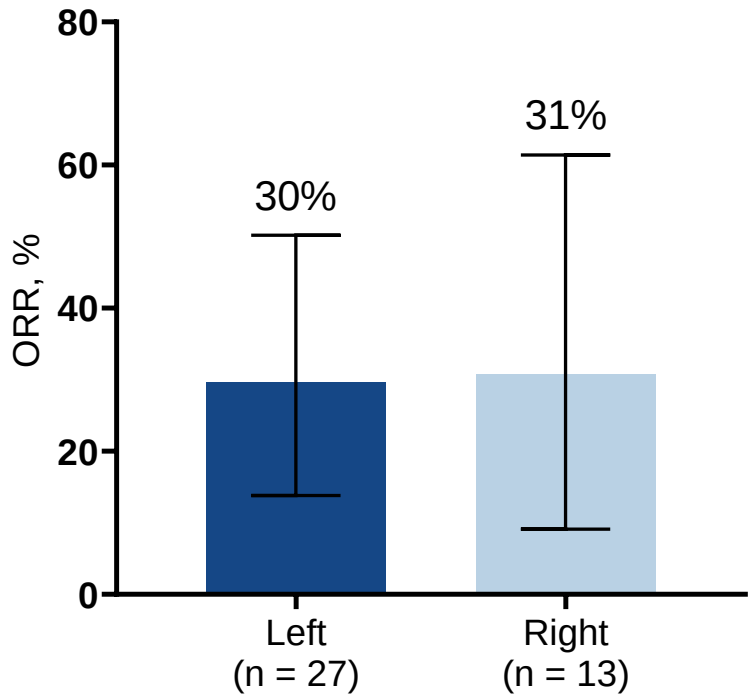
Primary endpoint: Safety/tolerability
Secondary endpoints: Anti-tumour efficacy (ORR, DCR, DOR, TTR, PFS per RECIST v1.1, and OS) **and PK**

Efficacy

Response by investigator assessment	N = 40 n (%)
ORR confirmed (95% CI)	**12 (30)** (16.6, 46.5)
Complete response	0
Partial response	12 (30)
Stable disease*	25 (63)
Progressive disease	3 (8)
DCR (95% CI)	**37 (93)** (79.6, 98.4)

Data cutoff: June 24, 2022.
*Minimum requirement for stable disease was 5 weeks.
DCR, disease control rate; mCRC, metastatic colorectal cancer; ORR, objective response rate.

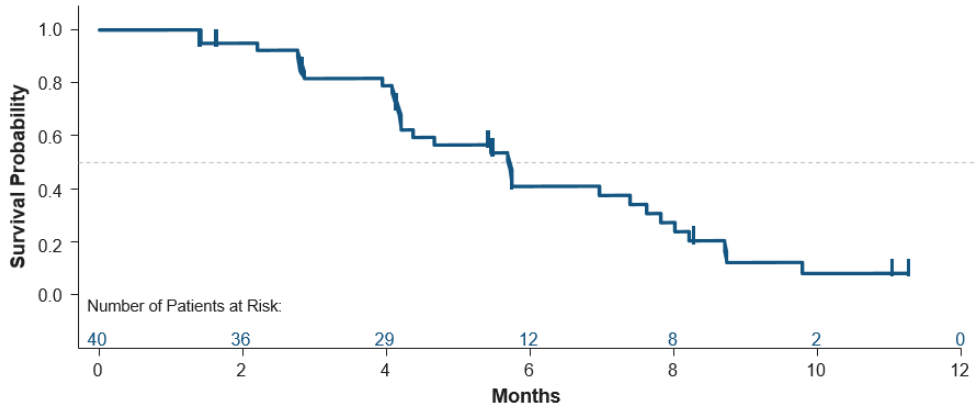
ORR subgroup analysis by primary tumour location



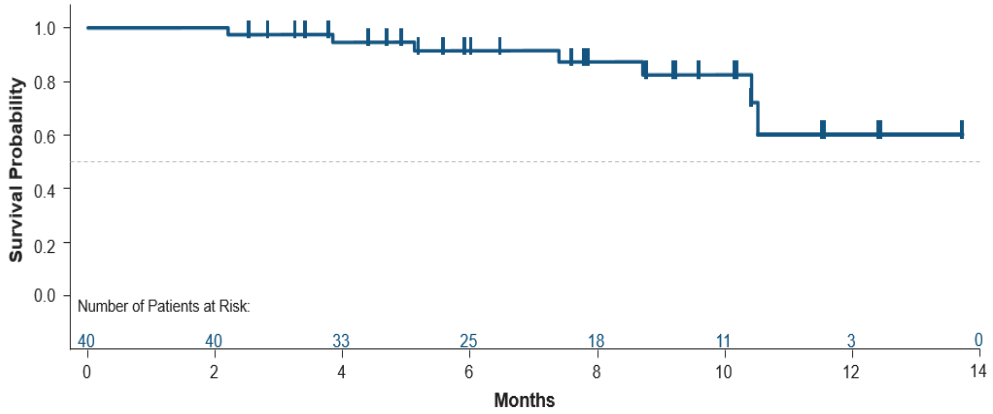
- **30% confirmed response rate for sotorasib + panitumumab in patients with chemorefractory mCRC, with disease control rate of 93%**
- **No obvious differences in response based on tumour location**

Yasutoshi Kuboki, ESMO 2022

PFS and OS to Sotorasib and Panitumumab in Chemotherapy Resistant *KRAS G12C* MCRC



Kaplan-Meier estimate of PFS	N = 40
Median PFS, months (95% CI)	5.7 (4.2, 7.6)
Left primary tumour	5.8 (4.2, 7.8)
Right primary tumour	5.5 (3.9, 8.2)
PFS rate, % (95% CI)	
At 3 months	81.7 (65.4, 90.9)
At 6 months	41.1 (24.7, 56.7)
At 9 months	12.3 (3.4, 27.2)



Kaplan-Meier estimate of OS	N = 40
Median OS, months (95% CI)	NE (10.4, NE)
Left primary tumour	NE (10.4, NE)
Right primary tumour	NE (8.7, NE)
OS rate, % (95% CI)	
At 3 months	97.5 (83.6, 99.6)
At 6 months	91.5 (75.7, 97.2)
At 9 months	82.5 (61.8, 92.6)

Yasutoshi Kuboki, ESMO 2022

Study Design

CodeBreaK 300: Phase 3 Multicentre, Randomized, Active-controlled Study of Sotorasib + Panitumumab in KRAS G12C-mutated mCRC

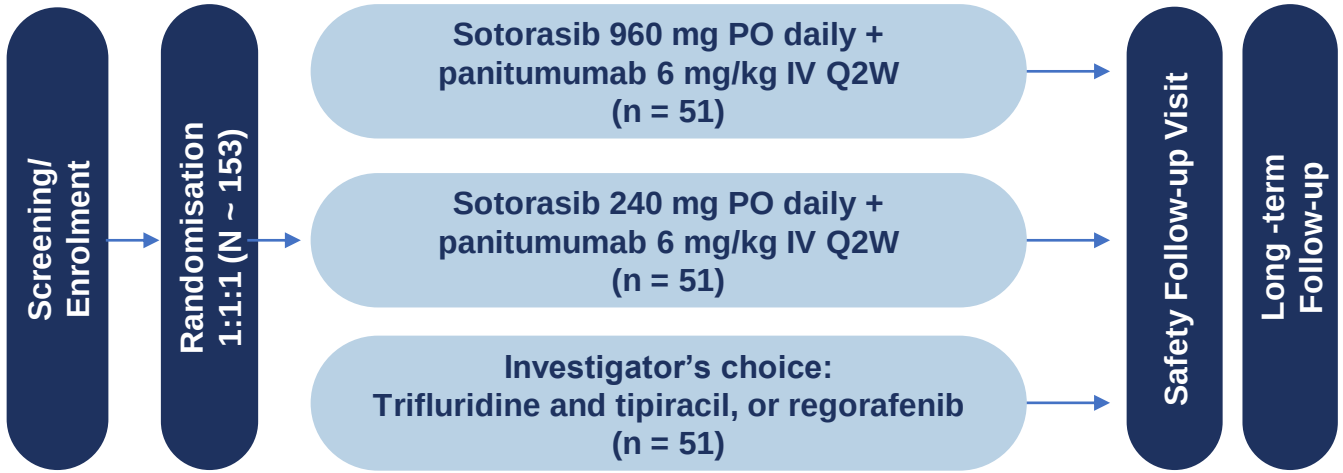
Key inclusion criteria:

- ≥ 18 years of age
- KRAS G12C-mutated mCRC, identified through central molecular testing of tumour biopsy
- ≥ 1 prior line of therapy for mCRC; progressed on or after fluoropyrimidine, irinotecan, and oxaliplatin*
- ECOG ≤ 2
- Measurable disease per RECIST 1.1

Key exclusion criteria:

- Radiation therapy within 2 weeks, antitumour therapy within 4 weeks of study
- Prior $KRAS^{G12C}$ inhibitor
- Prior treatment with trifluridine and tipiracil and/or with regorafenib, where the investigator's choice would be these agents

Stratified by: **prior anti-angiogenic therapy** (yes/no), **time from diagnosis of mCRC** (≥ 18 mo/< 18 mo), **ECOG status** (0 or 1/2)



Treat until disease progression, start of another anticancer treatment, or withdrawal of consent

Primary endpoint:

- **PFS per BICR** (measured by CT/MRI and assessed by RECIST v1.1)

Secondary endpoints:

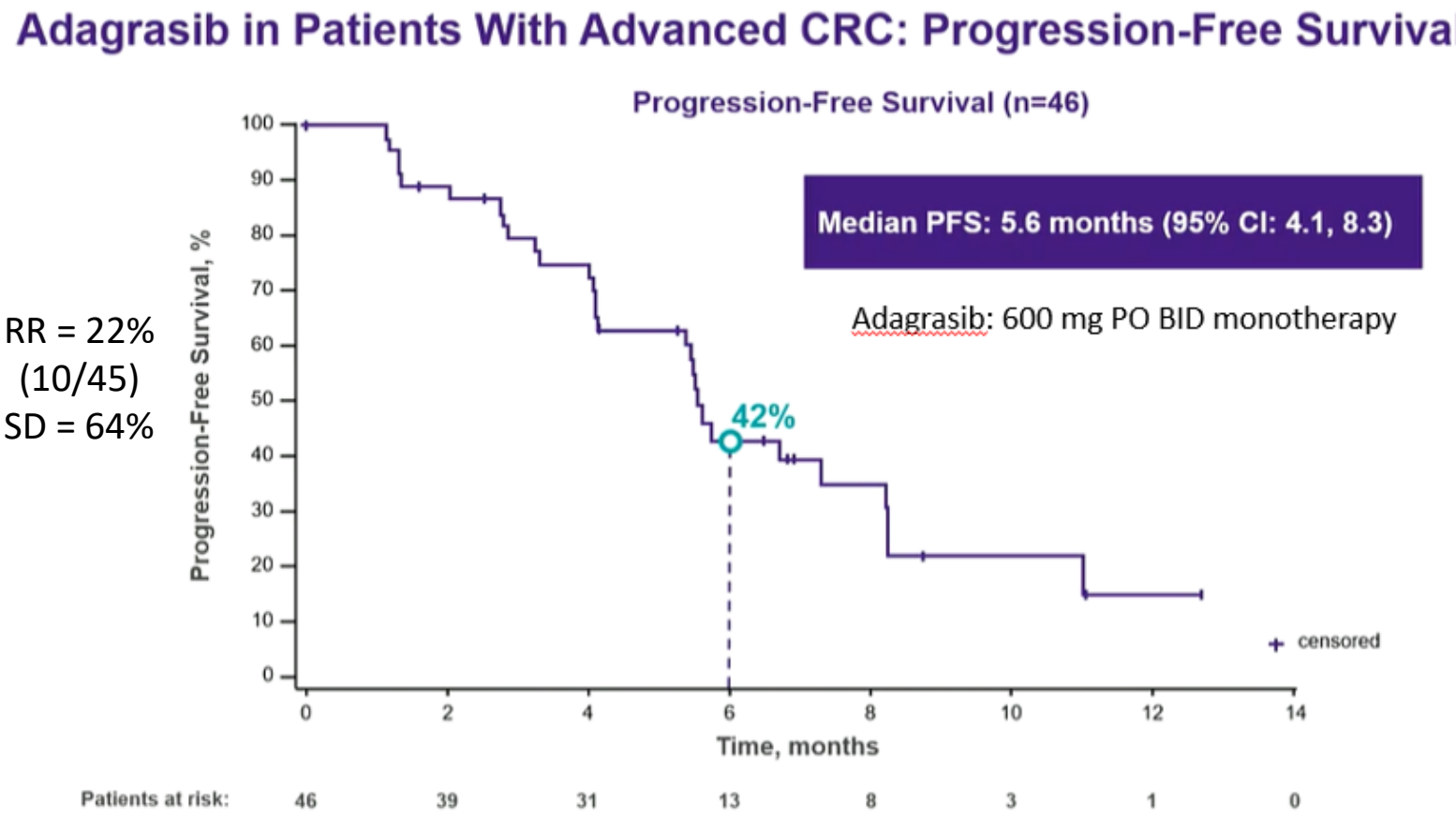
- OS, ORR, DOR, DCR, TTR
- Safety/tolerability
- PROs, QoL
- PK

*Patients deemed by the investigator not to be candidates for fluoropyrimidine, irinotecan, or oxaliplatin may still be eligible if ≥1 prior line of therapy was received for metastatic disease and trifluridine and tipiracil and/or regorafenib were deemed appropriate next line of therapy. †After the safety follow-up visit, followed up for survival and documentation of anti-cancer treatment until death, withdrawal of consent, or end of study, whichever occurs first; patients who discontinue treatment for reasons other than progressive disease will have long-term follow-up imaging for disease status until disease progress is documented, a non-study cancer treatment is initiated, withdrawal of consent, or end of study.

BICR, blinded independent central review; CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; IV, intravenous; *KRAS,* Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; OS, overall survival; ORR, objective response rate; PFS, progression free survival; PO, orally; PRO, patient reported outcome; PK, pharmacokinetics, Q2W, every 2 weeks; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumours; TTR, time to response.

Adagrasib (KRYSTAL-1) as monotherapy or in combination with cetuximab in pts with CRC with a $KRAS^{G12C}$ mutation

RR = 22%
(10/45)
SD = 64%



Combination Therapy:

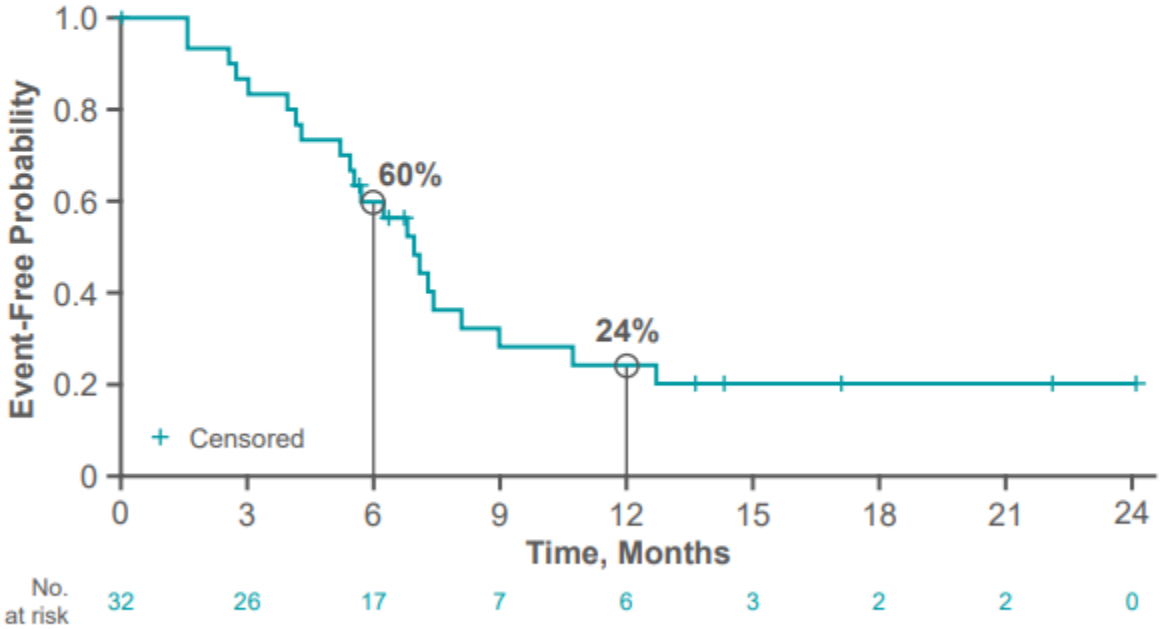
Adagrasib + Cetuximab
(n = 28)

RR = 43% (12/28)
SD = 57%
DCR = 100%

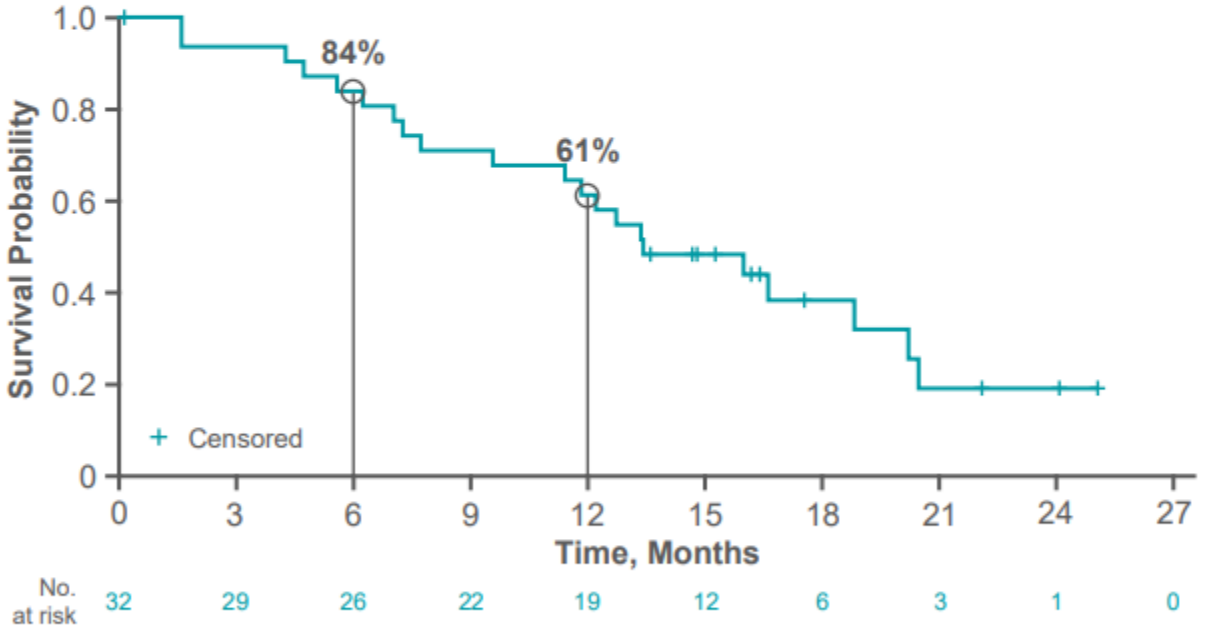
Weiss J, et al. ESMO 2021. Abs LBA6

Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Progression-Free Survival and Overall Survival

Progression-Free Survival



Overall Survival

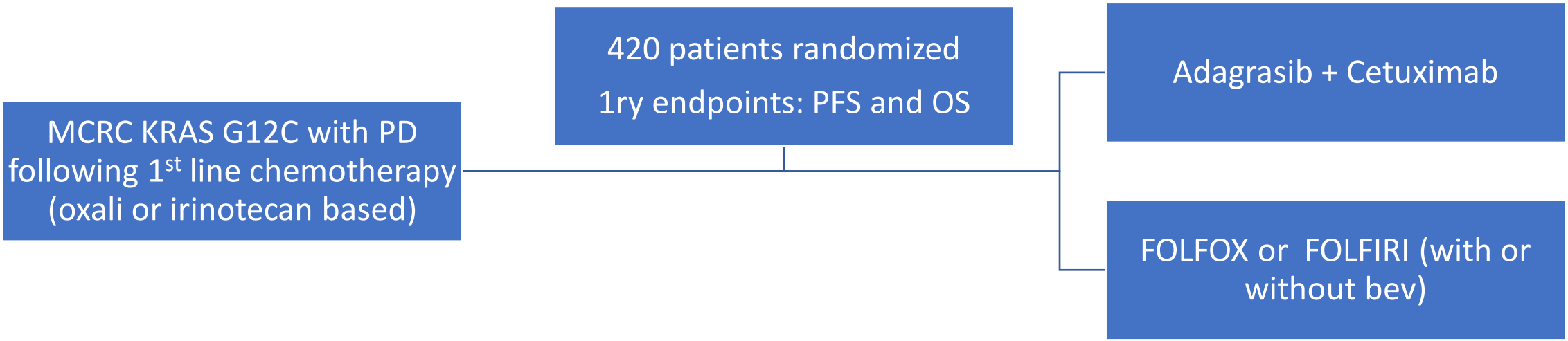


Median PFS was 6.9 months (95% CI, 5.4–8.1)

Median OS was 13.4 months (95% CI, 9.5–20.1)

- Klempner et al, ESMO 2022

KRYSTAL-10:A Randomized Phase 3 Study of MRTX849 in Combination With Cetuximab Versus Chemotherapy in Patients With Advanced Colorectal Cancer With KRAS G12C Mutation With Disease Progression On or After Standard First-Line Therapy



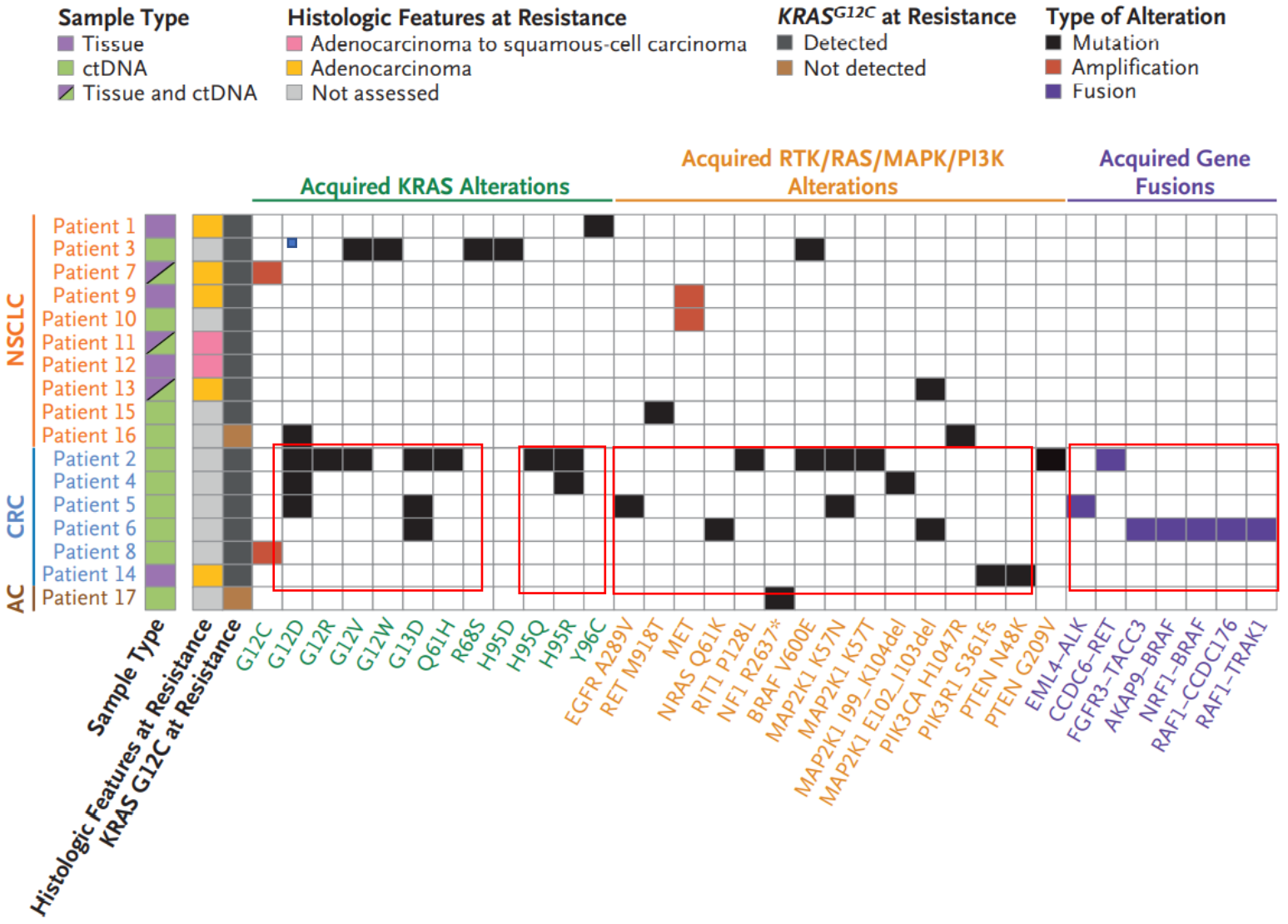
NCT04793958

Potential Mechanisms of Resistance in KRAS^{G12C} CRC

Adagrasib monotherapy study with ctDNA assays at time of resistance (6 patients with colorectal cancer)

Colorectal Cancer

- **5/6 developed RAS mutations**
- **2 of the 5 had KRAS G12C binding domain alterations along with other RAS mutations**
- **5/6 acquired RTK/MAPK/PI3KCA alteration**
- **3/6 pts with fusion**



CodeBreaK 100 Study – CRC

Screening/ Enrollment

Pooled Phase 1/2: oral sotorasib 960 mg daily
N = 91 CRC

Patients with progressive disease
n = 61

Patients with paired plasma samples (baseline and at progression)
n = 45

Key eligibility criteria

- Locally advanced or metastatic *KRAS* p.G12C-mutated solid tumours, including CRC
- 1+ prior systemic therapy, or ineligible/ intolerant[a]
- Stable brain metastases allowed

Primary Endpoint

ORR assessed by RECIST 1.1 by central review

Exploratory Endpoint

Acquired genomic alterations at disease progression[b]

Methodology[c]
74-gene Guardant 360 ctDNA test

- With baseline tissue sample (n = 32; 71%)

Data cut-off: 29 November 2021

Note: detection of genomic alterations is not adjusted for tumour volume or shedding.

[a]For CRC, ≥ 2 prior systemic regimens including fluoropyrimidine, oxaliplatin, and irinotecan-based regimens; [b]Absent at baseline in plasma and tissue, but present at disease progression, with putative emergent ctDNA alterations cross-referenced to baseline tissue genetic alterations where available and, if found, excluded from further analysis; [c]0/45 patients with CRC had no detectable ctDNA at any time point (non-shedders).
CRC, colorectal cancer; ctDNA, circulating tumour DNA; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours.

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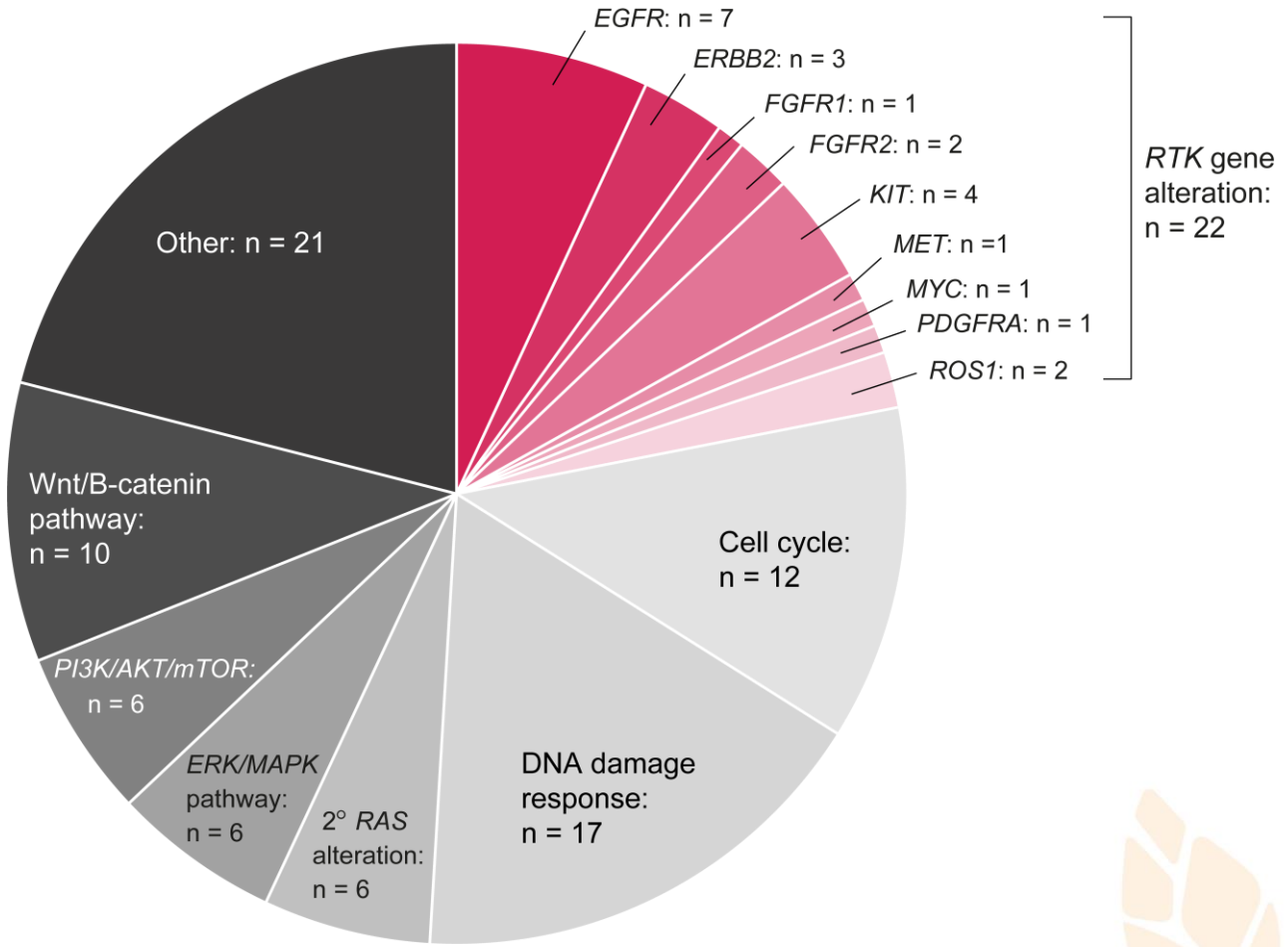
Acquired Genomic Alterations Were Heterogeneous

In total, 100 acquired alterations were detected in 32 patients with colorectal cancer

13 pts no alterations



Cell cycle: *CCND1*, n = 2; *CCND2*, n = 2; *CCNE1*, n = 2; *CDK12*, n = 2; *CDKN2A*, n = 2; *RB1*, n = 2.
DNA damage response: *BRCA2*, n = 8; *ATM*, n = 5; *BRCA1*, n = 2; *DDR2*, n = 1; *MLH1*, n = 1.
Secondary *RAS* alterations: *KRAS* copy number variant amplification, n = 4; *KRAS* R68T single-nucleotide variant, n = 1; *KRAS* Y96H single-nucleotide variant, n = 1.
***EGFR* alterations:** R1068* single-nucleotide variant, n = 1; copy number variant amplification, n = 6.
***ERBB2* alterations:** single-nucleotide variants (F258V, Q429H, S963C), n = 3.
***ERK/MAPK* pathway:** *RHOA*, n = 2; *BRAF*, n = 2; *ARAF*, n = 1; *MAPK1*, n = 1.
***FGFR2* alterations:** L761R single nucleotide variant, n=1; copy number variant amplification, n = 1.
***MET* alterations:** C800_Q807 deletion-insertion, n = 1.
***PI3K/AKT/mTOR*:** *PIK3CA*, n = 5; *STK11*, n = 1.
***ROS1* alterations:** single nucleotide variant (Q1708H, L1968V), n = 2.
Wnt/B-catenin pathway: *APC*, n = 7; *SMAD4*, n = 2; *CTNNB1*, n = 1.
Other: *AR*, n = 8; *ARID1A*, n = 6; *TP53*, n = 4; *ESR1*, n = 1; *GNAS*, n = 1; *HNF1A*, n = 1.

*Termination or stop codon.

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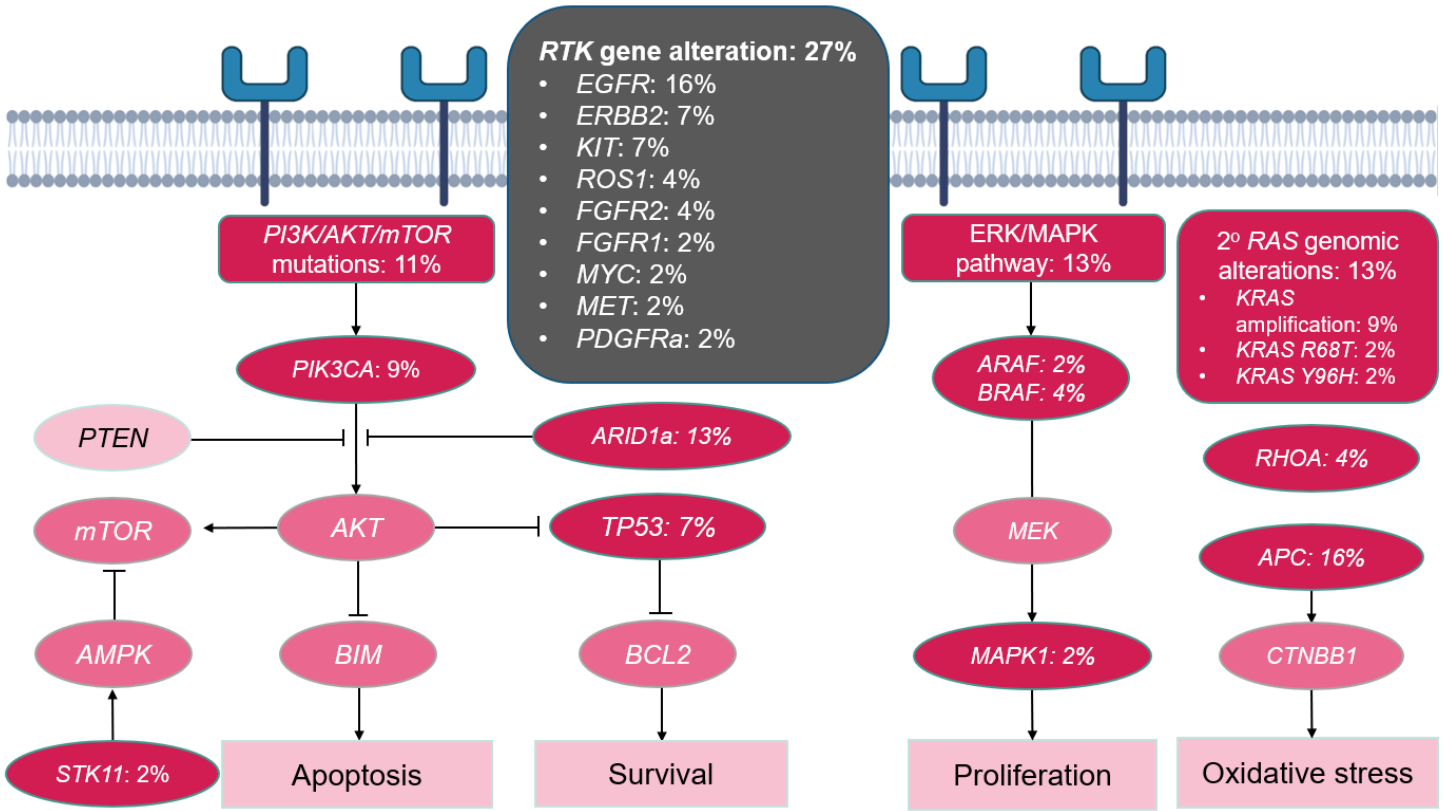
Putative Acquired Resistance Mechanisms After Sotorasib[a]



OncoKB[1]

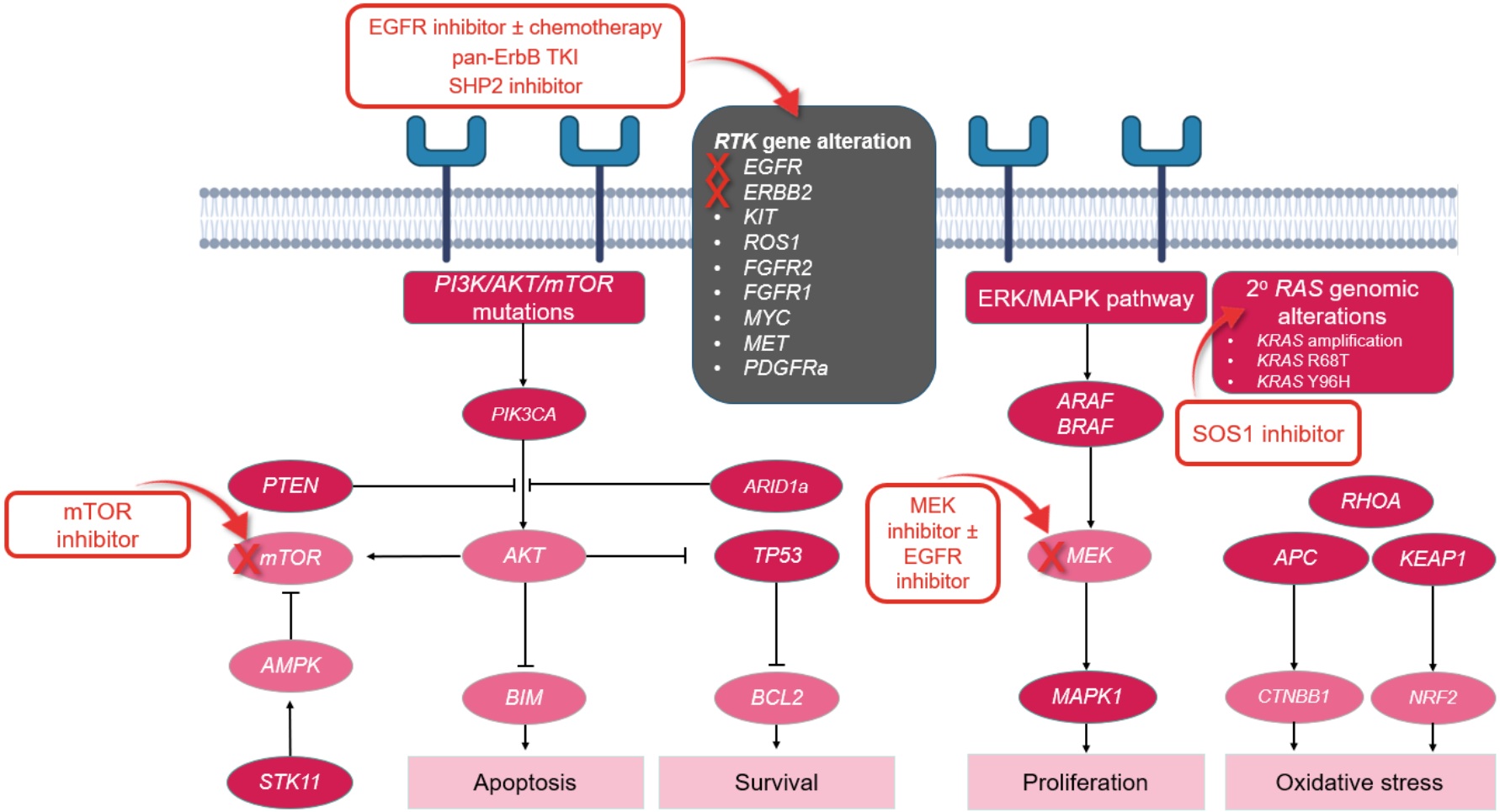
- **16/100 alterations were potentially targetable[b]**
- **Higher incidence of secondary *RAS* variants in CRC versus NSCLC**

***RTK* gene alterations were the most prevalent acquired genomic alteration in patients with CRC (12/45; 27%)**

1. Chakravarty D, et al. *JCO Precis Oncol*. 2017, doi:10.1200/PO.17.00011.
[a]Mutation rate presented based on 45 evaluable patients with CRC; [b]Actionability levels defined in full at https://www.oncokb.org/levels. Actionable variants: Level 1; *BRCA1* E352* (n = 1), *BRCA2* S196R (n = 1), *CDK12* G909* (n = 1), *PIK3CA* E542K (n = 2). Level 2; *PIK3CA* R38C (n = 1). Level 4; *ARID1A* Q1402* (n = 1), *ARID1A* R1721* (n = 1), *ARID1A* single nucleotide variant (n = 1), *CDKN2A* truncating mutation (n = 1), *EGFR* copy number variant (n = 6); *Termination or stop codon.

CRC, colorectal cancer; NSCLC, non-small cell lung cancer.

Acquired Resistance Mechanisms May Inform Potential Sotorasib Combination Therapies (CodeBreaK 101)



TKI, tyrosine kinase inhibitor.

Hans Prenan, GI ESMO 2022

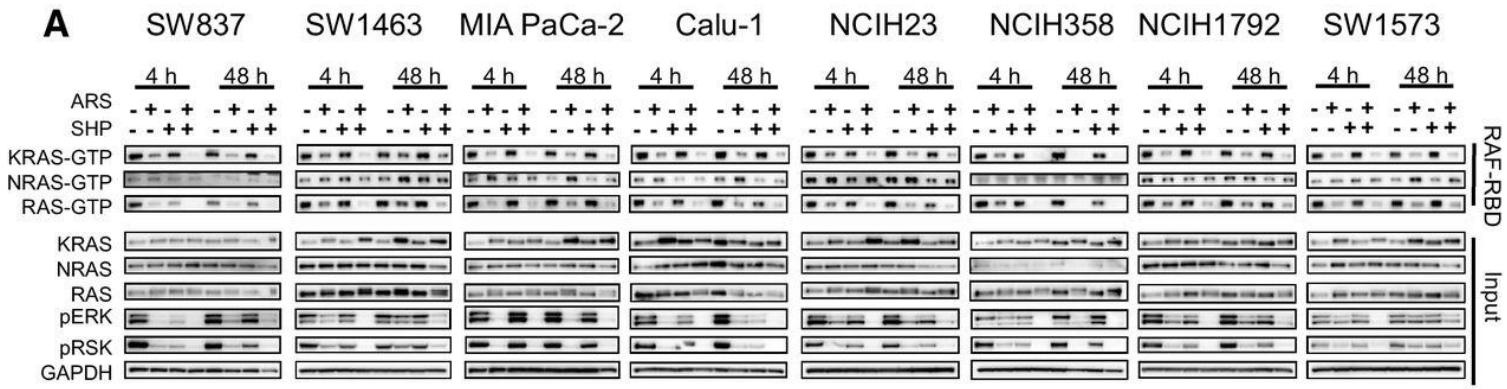
KRAS G12C Inhibitors + MEKi (Sotorasib + Trametinib)

- 41 patients were treated (18 NSCLC, 18 CRC, 5 others)
- For CRC exploration (1 mg trametinib + 960 mg sotorasib)cohort (n=3). 1 PR and 2 SD
- For the 2 mg trametinib+960 mg sotorasib cohort (n=15), 4 pts with prior sotorasib had SD; 1 PR, 7 SD and 3 PD was reported in the 11 naïve pts
- In NSCLC pts (N=18) treated with 2 mg trametinib/960 mg sotorasib QD, of pts with prior KRASG12C inhibitor, 2-SD and 1-PD were reported; of naïve pts, 3-confirmed PR, 10-SD, 1-PD, and 1-non evaluable

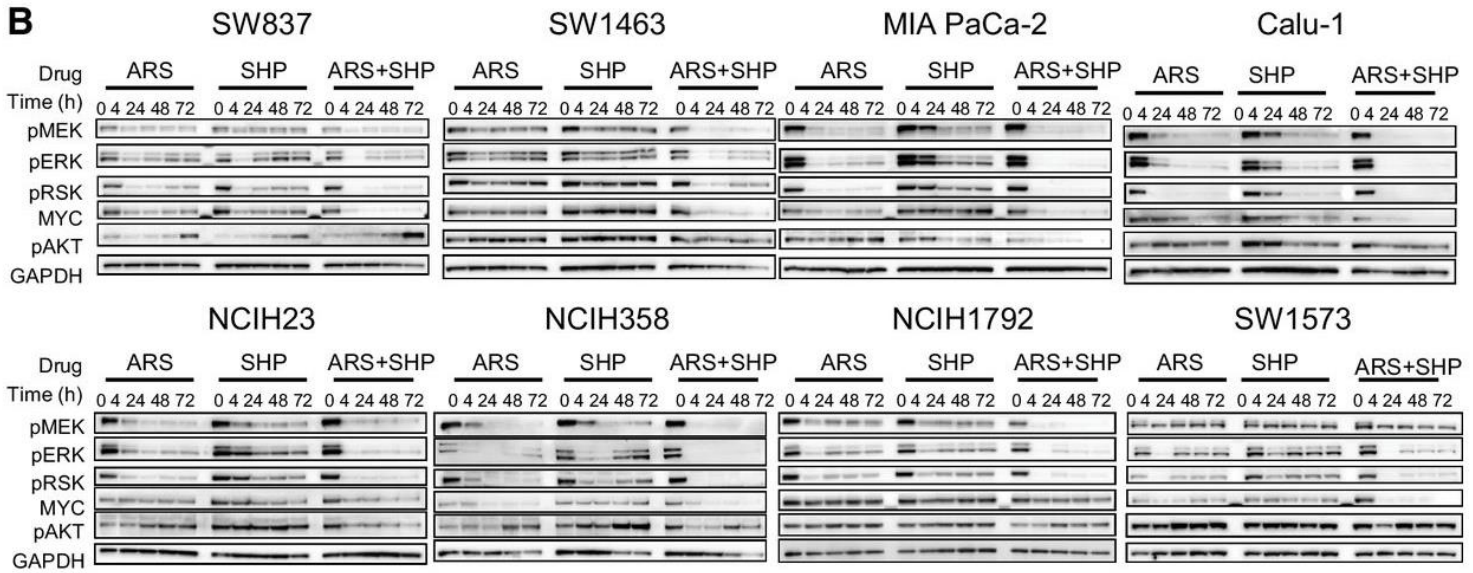
Abstract P05-01: A phase 1b study evaluating the safety and efficacy of sotorasib, a KRASG12C inhibitor, in combination with trametinib, a MEK inhibitor, in KRAS p.G12C-Mutated Solid Tumors. Mol Cancer Ther 1 December 2021; 20 (12_Supplement): P05–01. https://doi.org/10.1158/1535-7163.TARG-21-P05-01

SHP2 inhibitor+KRAS^{G12C} inhibitor in preclinical setting

More complete suppression of KRAS-GTP and total RAS-GTP with combination therapy

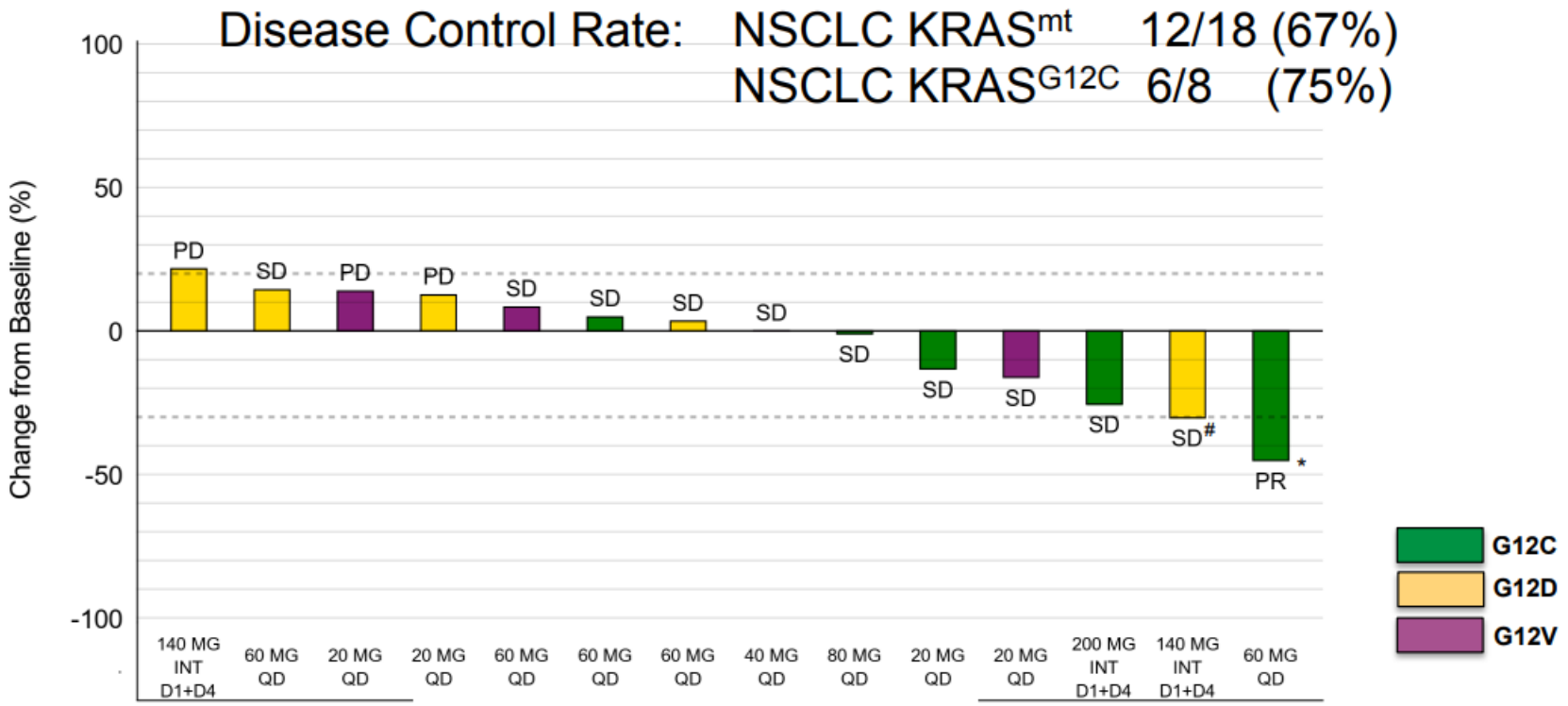


More complete suppression of MAPK pathway with combination therapy



Vertical Pathway Inhibition Overcomes Adaptive Feedback Resistance to KRASG12C Inhibition. Clin Cancer Res 1 April 2020; 26 (7): 1633–1643

SHP2 Inhibitor RMC-4630 in KRAS-mt NSCLC-Phase 1 trial

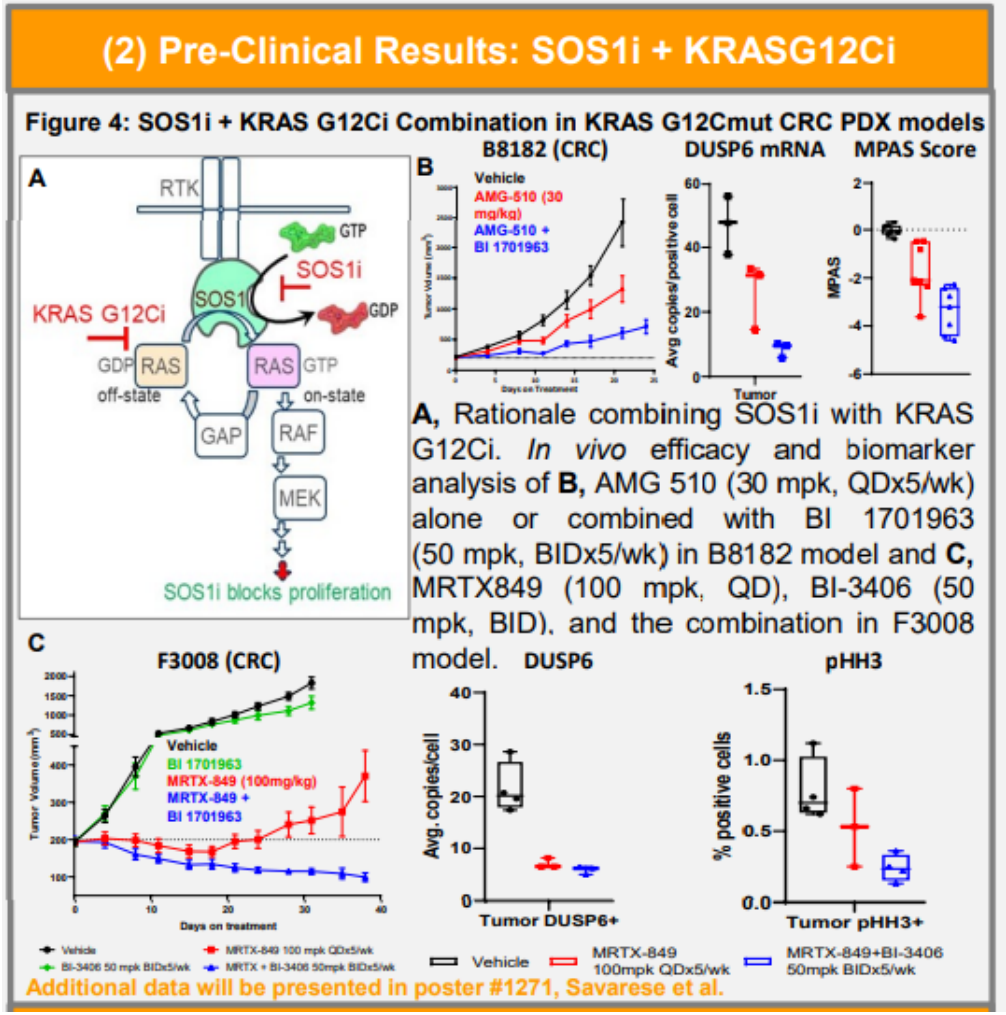


RMC-4630 is being investigated with sotorasib in KRAS G12C mutated tumors

A12 The SHP2 Inhibitor RMC-4630 in Patients with KRAS-Mutant Non-Small Cell Lung Cancer: Preliminary Evaluation of a First-in-Man Phase 1 Clinical Trial Ou, S.I. et al. Journal of Thoracic Oncology, Volume 15, Issue 2, S15 - S16

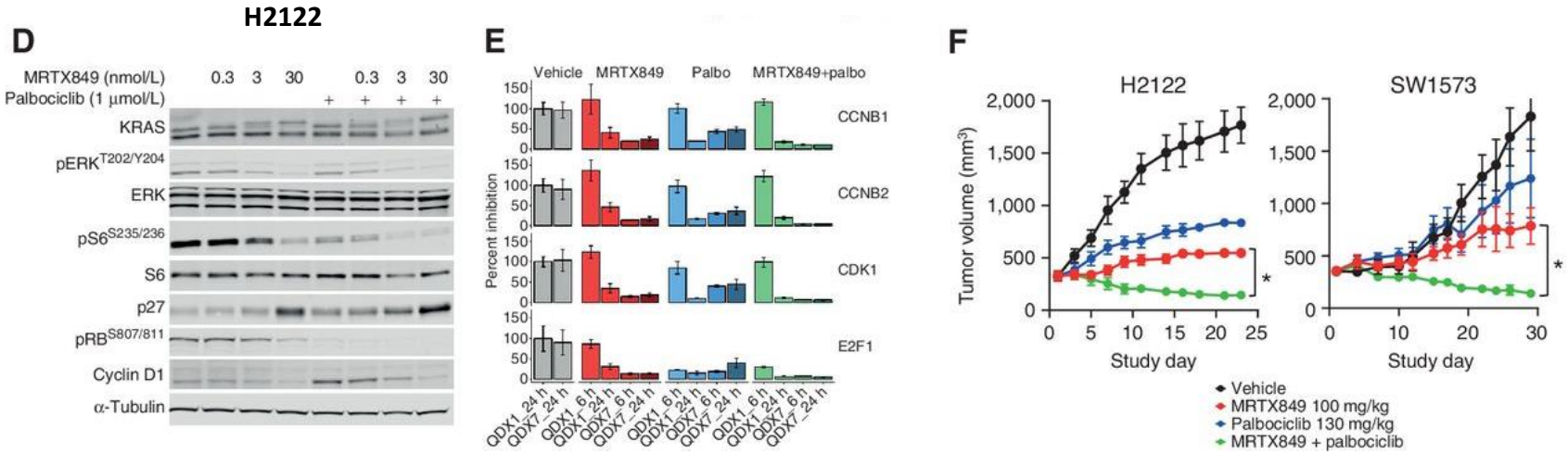
SOS1 inhibitor

- SOS1 inhibitor (BI 1701963, BI-3406): small molecules bind to the catalytic domain of SOS1, prevent the formation of the KRAS–SOS1 complex, thereby block reloading of KRAS with GTP
- SOS1 inhibitors exhibit activity on a broad spectrum of KRAS alleles, including all major G12D/V/C and G13D.
- Combination of SOS1::KRASi and KRASG12Ci led to a synergistic anti-proliferative effect in vitro and enhanced MAPK pathway modulation
- SOS1::KRASi+KRASG12Ci combination in CDX and PDX models demonstrated enhanced efficacy in combination compared to both mono-therapies
- Clinical trials evaluating the combination of BI1701963 with Adagrasib in NSCLC and CRC harboring KRASG12C mutation are ongoing



Vertical pathway inhibition with a SOS1::KRAS inhibitor enhances the efficacy of KRAS G12C inhibitors, delays feedback resistance and demonstrates durable response Savarese, F. et al. European Journal of Cancer, Volume 138, S22
Abstract CT210: Trial in Process: Phase 1 studies of BI 1701963, a SOS1::KRAS Inhibitor, in combination with MEK inhibitors, irreversible KRASG12C inhibitors or irinotecan.. Cancer Res 1 July 2021; 81 (13_Supplement): CT210

CDK4/6 inhibitor+Adagrasib in preclinical setting



D. Combination of adagrasib and Palbociclib showed near complete inhibition of pERK, pS6 and pRB
E. RNAseq data showed combination of adagrasib and palbociclib significantly inhibited E2F1 and selected E2F family target genes
F. This combination also induced tumor regression in tumor xenograft models that was significant compared with either single-agent control

Combinations of sotorasib + CDK4/6i and adagrasib + CDK4/6i are under investigation

The KRASG12C Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients. Cancer Discov 1 January 2020; 10 (1): 54–71

Conclusions

- Sotorasib and adagrasib monotherapy have modest clinical benefits in refractory KRAS G12C metastatic colorectal cancer
- The addition of an anti-EGFR to sotorasib or adagrasib increases downstaging and results in a more clinically meaningful progression free survival
- Resistance to KRAS G12C inhibitors is the rule and the mechanisms of resistance appear to be heterogenous and include: *RAS* mutations, MAPK pathway activation, fusions, and RTK activation
- Ongoing studies are investigating the relevance of co-inhibiting SOS, SHP2, CDK4/6, MEK, among others to potentiate RAS inhibitions and/or overcome resistance to KRASG12C inhibitors