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Adagrasib With or Without Cetuximab in Patients With KRAS^{G12C}-Mutated Colorectal Cancer (CRC): Analysis of Tumor Biomarkers and Genomic Alterations

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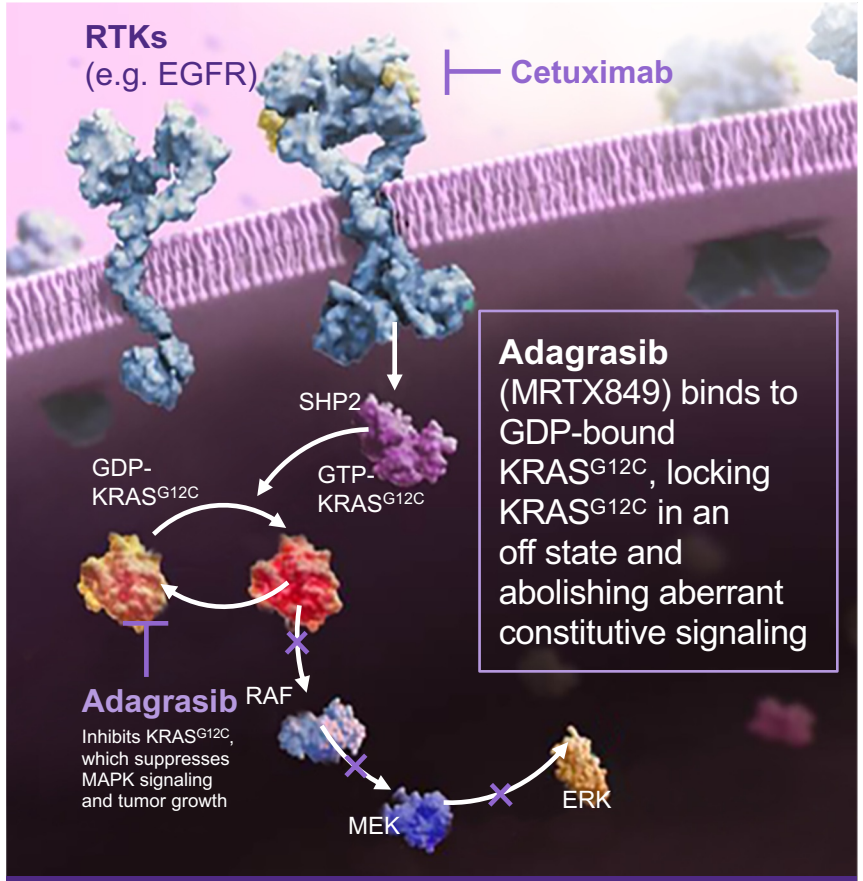
Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

- Adagrasib, a covalent KRAS^{G12C} inhibitor, was selected for favorable properties, including a long half-life (23 hours), dose-dependent PK, and CNS penetration[1–3]
- In Phase 1/2 cohorts of the KRYSTAL-1 study, adagrasib with or without cetuximab has shown promising clinical activity in heavily pretreated patients with KRAS^{G12C}-mutated CRC[4]
- Adagrasib has received:
  - FDA approval for patients with previously treated metastatic KRAS^{G12C}-mutated NSCLC[5]
  - BTD in combination with cetuximab in patients with previously treated advanced KRAS^{G12C}-mutated CRC[6]
  - NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommendation for use with cetuximab or panitumumab in patients with previously treated advanced KRAS^{G12C}-mutated CRC[7,8]
- Acquired resistance has been previously observed in CRC following KRAS^{G12C} inhibition with or without EGFR inhibition, and ctDNA analyses have been used to explore these resistance mechanisms[9,10]



EGFR signaling is implicated in feedback reactivation, providing rationale for a co-targeting strategy in KRAS-mutated CRC[11]

ctDNA, circulating tumor DNA; NCCN, National Comprehensive Cancer Network

KRYSTAL-1 (849-001) Phase 1b/2 CRC Cohorts Study Design

Key Eligibility Criteria[4]

- CRC with a KRAS^{G12C} mutation[a]
- Unresectable or metastatic disease
- No available treatment with curative intent or available standard of care

Phase 1b
CRC Combination[4]

Adagrasib 600 mg BID[b] + cetuximab[c] (N=32)

Phase 2
CRC Monotherapy[4]

Adagrasib 600 mg BID[b] (N=44)

Study Objectives[4]

Phase 1b

- Primary endpoints: safety, RP2D, PK
- Secondary endpoints: ORR (RECIST 1.1), DOR, PFS, OS

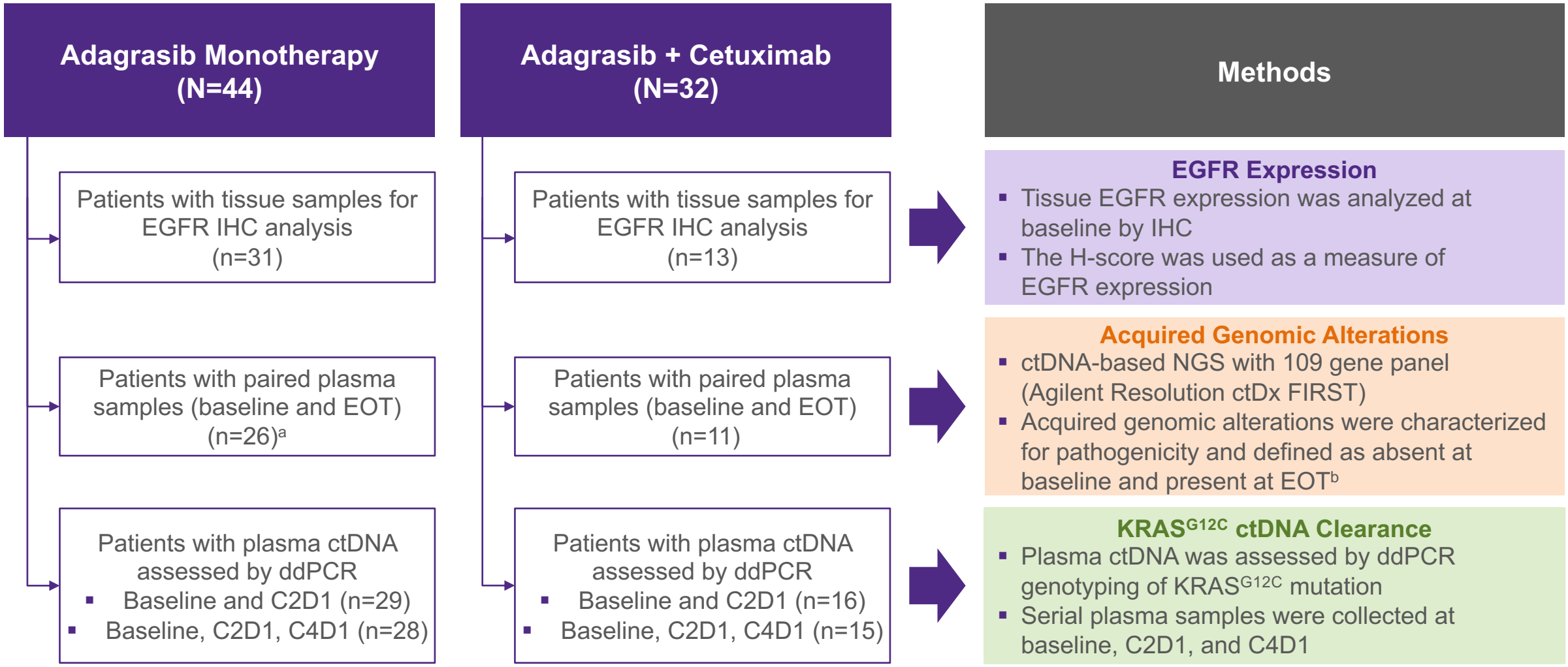
Phase 2

- Primary endpoint: ORR (RECIST 1.1)
- Secondary endpoints: safety, DOR, PFS, OS, 1-year survival

Here we report exploratory analyses of potential mechanisms of acquired resistance to adagrasib, as well as clinical response according to baseline tumor IHC-assessed EGFR expression and plasma ctDNA clearance

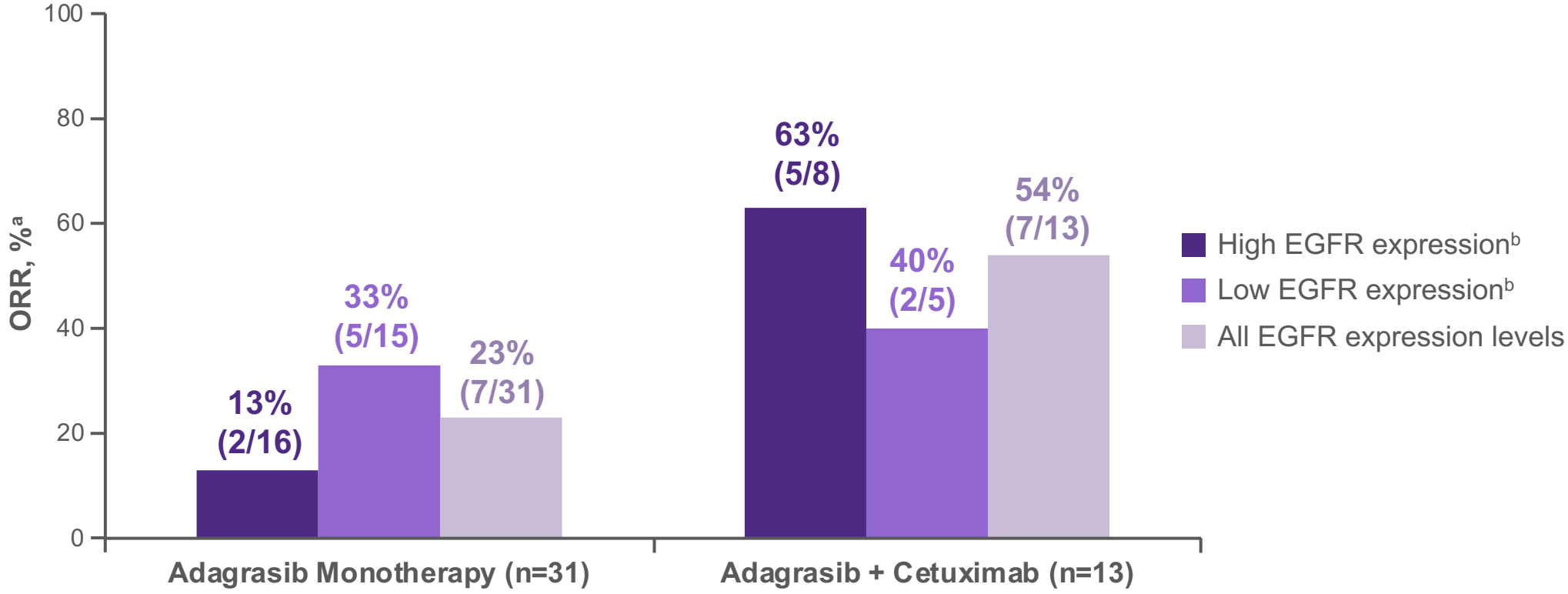
[a]KRAS^{G12C} mutation detected in tumor tissue and/or ctDNA per protocol; [b]Capsule, fasted; [c]Cetuximab dosing, 400 mg/m^2 followed by 250 mg/m^2 QW, or 500 mg/m^2 Q2W
IHC, immunohistochemistry
ClinicalTrials.gov. NCT03785249

Patients and Methods



[a]Including four patients who subsequently crossed over to adagrasib + cetuximab; [b]All clearly inactivating mutations (e.g. frameshift, nonsense, splice site) for known tumor suppressor genes were included. Well-established, annotated, clearly recurrent mutations were confirmed by COSMIC. Point mutations that are potential variants of unknown significance required evidence of recurrence in COSMIC (≥5 instances) plus structural impact assessment by SIFT and mutation assessor
C2D1, cycle 2 day 1; C4D1, cycle 4 day 1; ddPCR, droplet digital polymerase chain reaction; EOT, end of therapy; NGS, next-generation sequencing

Exploratory Analysis: ORR by EGFR Expression at Baseline in Patients With KRAS^{G12C}-Mutated CRC

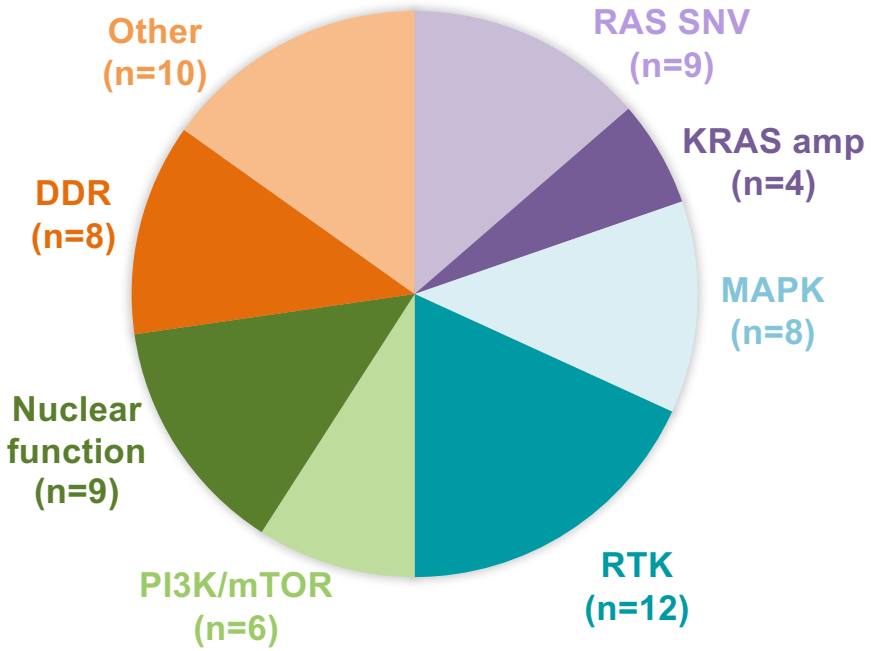


- Responses were observed regardless of EGFR expression (all PRs)
- In the monotherapy cohort, ORR was higher in patients with low EGFR expression compared with patients who had high EGFR expression
- ORR was higher in patients with high EGFR expression compared with those who had low EGFR expression in the combination cohort, although this sample size was very limited

[a]ORR assessed by BICR; [b]A median H-score of 60 was used as the cut-off for EGFR expression: H-score ≥60 was considered as high EGFR expression; H-score <60 was considered as low EGFR expression

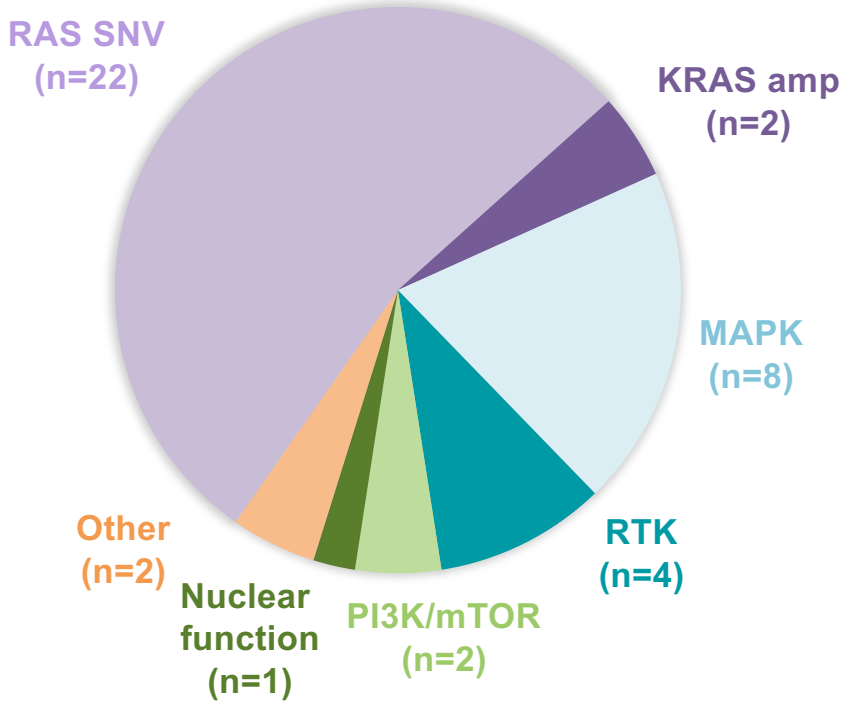
Exploratory Analysis: ctDNA Analysis of Acquired Genomic Alterations by Signaling Pathway in Patients With KRAS^{G12C}-Mutated CRC

Adagrasib Monotherapy[a]



- Acquired pathogenic genomic alterations were detected in 69% (18/26) of patients treated with adagrasib monotherapy
- A total of 66 pathogenic alterations were detected; 32% of these occurred in the RAS/MAPK pathway

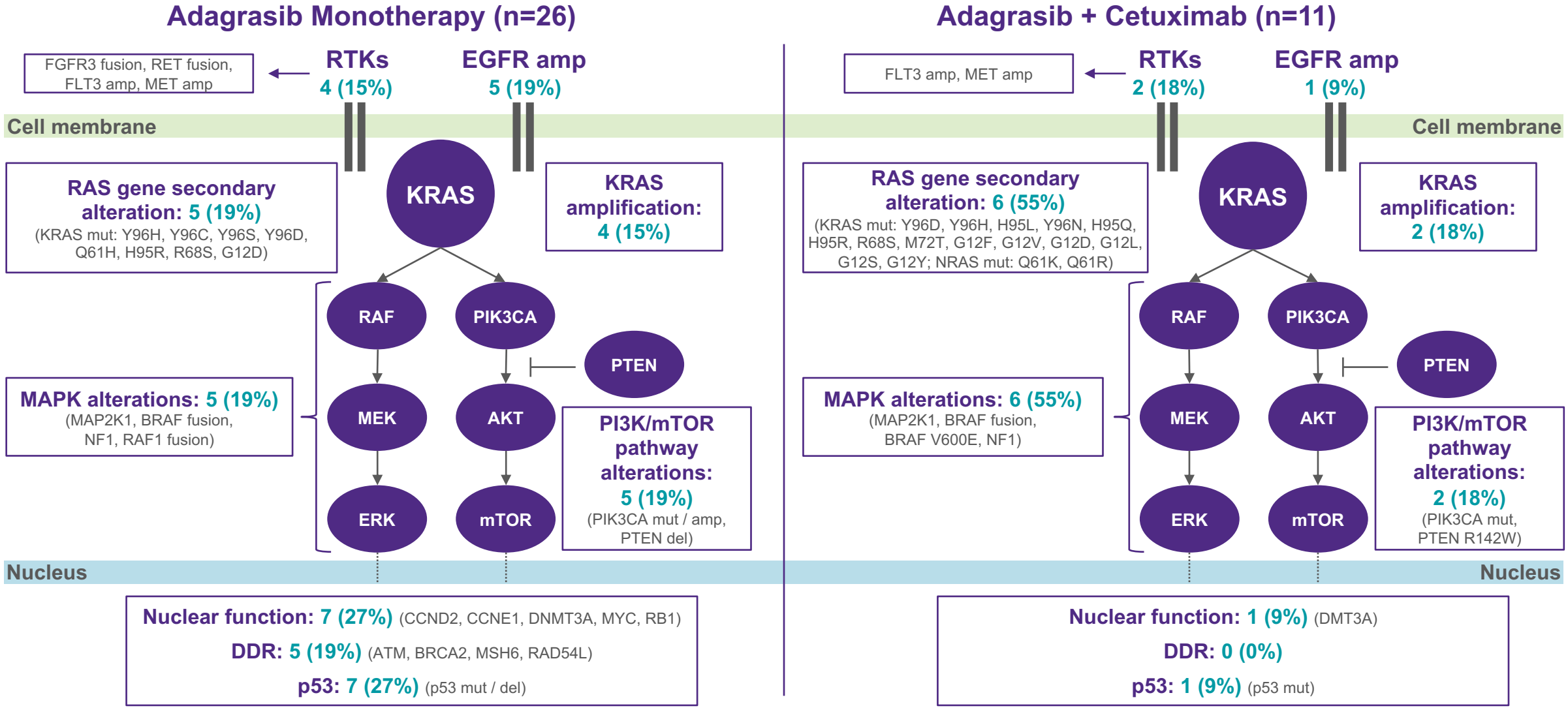
Adagrasib + Cetuximab[b]



- Acquired pathogenic genomic alterations were detected in 73% (8/11) of patients treated with adagrasib + cetuximab
- A total of 41 pathogenic alterations were detected; 78% of these occurred in the RAS/MAPK pathway

[a]Acquired genomic alterations with adagrasib monotherapy included RAS: KRAS; MAPK: BRAF, MAP2K1, NF1, RAF1; RTK: EGFR, FGFR3, FLT3, MET, RET; PI3K/mTOR: PIK3CA, PTEN; nuclear function: CCND2, CCNE1, DNMT3A, MYC, RB1; DDR: ATM, BRCA2, MSH6, RAD54L; other pathogenic: FBXW7, JAK2, TP53. [b]Acquired genomic alterations with adagrasib + cetuximab included RAS: KRAS, NRAS; MAPK: BRAF, MAP2K1, NF1; RTK: EGFR, MET, FLT3; PI3K/mTOR: PIK3CA, PTEN; nuclear function: DNMT3A; other pathogenic: FBXW7, TP53

Exploratory Analysis: Acquired RAS/MAPK Pathway Genomic Alterations Were More Common With Combination Than Monotherapy



Exploratory Analysis: ctDNA Analysis of Acquired Genomic Alterations in the RTK/MAPK/PI3K Pathway in Patients With KRAS^{G12C}-Mutated CRC

Adagrasib Monotherapy (n=18/26)[a]

Patient[a]	KRAS		RTK/RAS/MAPK/PI3K/p53											
	CNA	SNV	EGFR	FGFR3	BRAF	MAP2K1	MET	MYC	NF1	PIK3CA	PTEN	RAF1	RET	p53
1								Single Nucleotide Variant (SNV)						Single Nucleotide Variant (SNV)
2		Single Nucleotide Variant (SNV)												
3		Single Nucleotide Variant (SNV)												Single Nucleotide Variant (SNV)
4		Single Nucleotide Variant (SNV)												
5								Copy Number Alteration (CNA)						
6									Single Nucleotide Variant (SNV)	Single Nucleotide Variant (SNV)				
7	Copy Number Alteration (CNA)		Copy Number Alteration (CNA)											
8	Copy Number Alteration (CNA)								Single Nucleotide Variant (SNV)	Deletion				
9	Copy Number Alteration (CNA)	Single Nucleotide Variant (SNV)			Fusion		Copy Number Alteration (CNA)			Single Nucleotide Variant (SNV)				Single Nucleotide Variant (SNV)
10		Single Nucleotide Variant (SNV)				Single Nucleotide Variant (SNV)				Single Nucleotide Variant (SNV)				
11			Copy Number Alteration (CNA)											Deletion
12										Copy Number Alteration (CNA)	Deletion			Deletion
13			Copy Number Alteration (CNA)							Single Nucleotide Variant (SNV)				
14			Copy Number Alteration (CNA)											Deletion
15	Copy Number Alteration (CNA)		Copy Number Alteration (CNA)	Fusion	Fusion		Copy Number Alteration (CNA)					Fusion	Fusion	
16														Single Nucleotide Variant (SNV)

Adagrasib + Cetuximab (n=8/11)

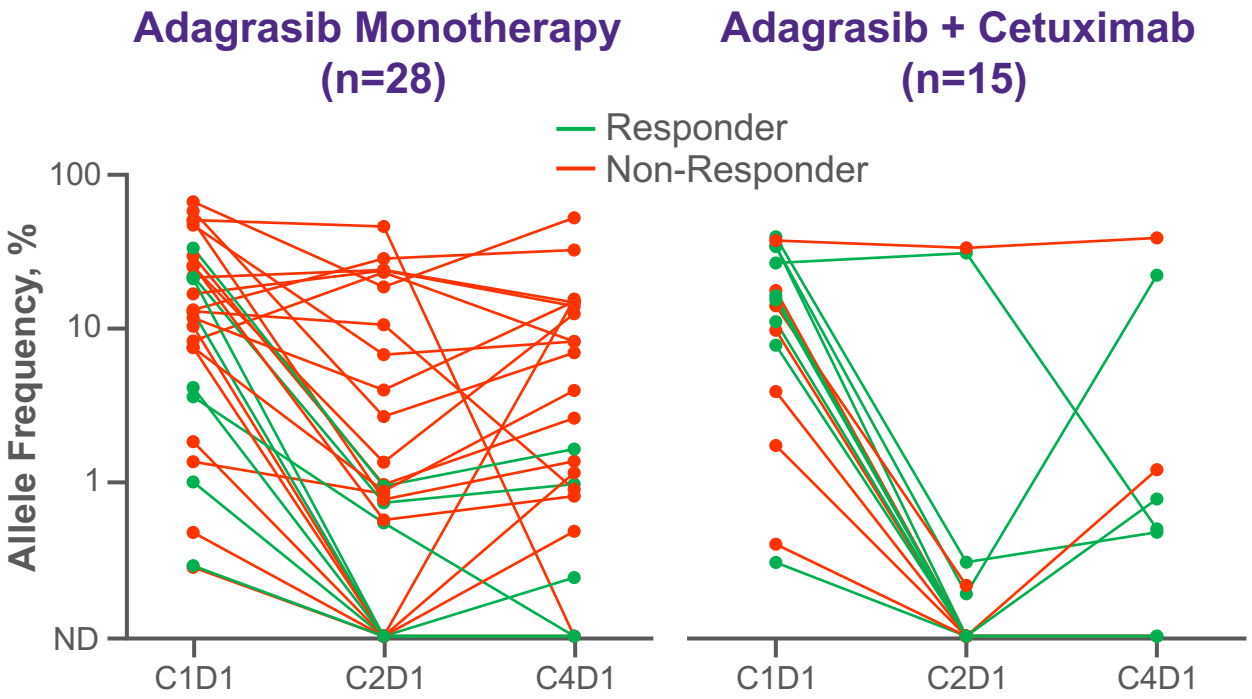
Patient	KRAS		RTK/RAS/MAPK/PI3K/p53							
	CNA	SNV	EGFR	NRAS	BRAF	MAP2K1	MET	NF1	PIK3CA	PTEN	p53
1	Copy Number Alteration (CNA)	Single Nucleotide Variant (SNV)			V600E		Copy Number Alteration (CNA)				
2		Single Nucleotide Variant (SNV)						Single Nucleotide Variant (SNV)			
3		Single Nucleotide Variant (SNV)		Single Nucleotide Variant (SNV)		Deletion			Single Nucleotide Variant (SNV)		
4		Single Nucleotide Variant (SNV)									
5		Single Nucleotide Variant (SNV)			Fusion						
6											Single Nucleotide Variant (SNV)
7					Fusion	Single Nucleotide Variant (SNV)					
8	Copy Number Alteration (CNA)	Single Nucleotide Variant (SNV)	Copy Number Alteration (CNA)			Single Nucleotide Variant (SNV)	Copy Number Alteration (CNA)			Single Nucleotide Variant (SNV)	

- Copy Number Alteration (CNA)
- Single Nucleotide Variant (SNV)
- Fusion
- Deletion

- Multiple diverse genomic alterations were observed in individual patients with KRAS^{G12C}-mutated CRC treated with adagrasib ± cetuximab

[a]Two patients did not have pathogenic alterations in the RTK/MAPK/PI3K pathway

Exploratory Analysis: ORR by MAFC at C4D1 in Patients With KRAS^{G12C}-Mutated CRC



ORR, n/N (%)[a]	Adagrasib Monotherapy (n=28)	Adagrasib + Cetuximab (n=15)
MAFC ≥90% by C4D1	7/15 (47)	8/12 (67)
MAFC <90% by C4D1	1/13 (8)	1/3 (33)
All patients analyzed for MAFC	8/28 (29)	9/15 (60)

- MAFC ≥90% by C4D1 was observed more commonly in patients treated with adagrasib + cetuximab (12/15; 80%) compared with those treated with adagrasib monotherapy (15/28; 54%)
- In patients with MAFC ≥90%, ORR was 47% in the monotherapy cohort and 67% in the combination cohort

[a]Radiographic responses assessed by BICR in MAFC-evaluable patients with plasma samples available at baseline, C2D1, and C4D1
MAFC, mutation allele frequency clearance

Conclusions

- Acknowledging the limitations of these retrospective exploratory analyses, including the small sample size and incomplete sample collection, initial data show that:
  - Partial responses were observed in patients regardless of EGFR expression
  - Diverse acquired genomic alterations were observed in patients treated with adagrasib monotherapy or in combination with cetuximab, in line with previous reports of acquired KRAS mutations and acquired RTK/RAS/MAPK/PI3K pathway alterations following KRAS^{G12C} inhibition with or without EGFR inhibition in CRC[9,10]
  - KRAS^{G12C} ctDNA clearance of ≥90% was associated with higher ORR
- Further analyses are required to confirm these findings in larger randomized trials

For more information contact
Mirati Medical Information at medinfo@mirati.com

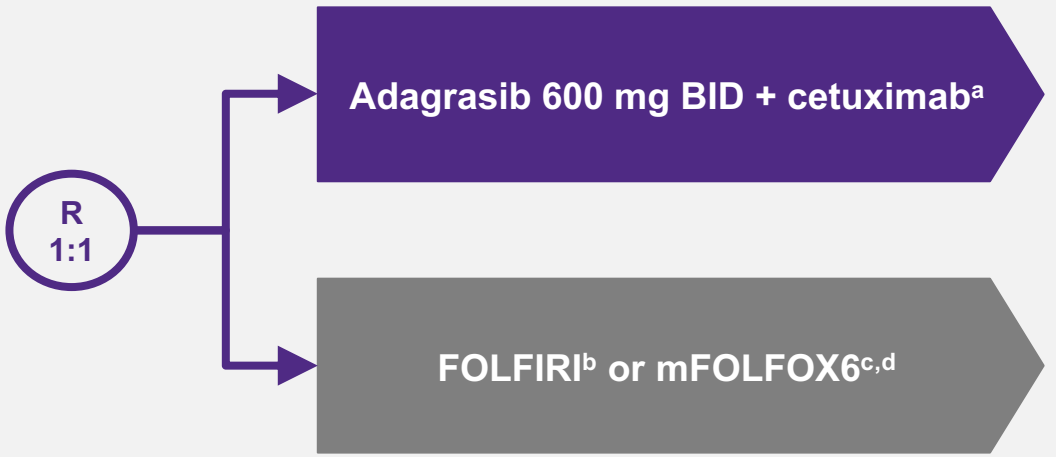
KRYSTAL-10 (849-010) Global, Phase 3, Randomized, Open-Label Trial of 2L Adagrasib + Cetuximab vs Chemotherapy in mCRC With KRAS^{G12C} Mutation

Phase 3

CRC Combination vs Chemotherapy[11,12]

Key Eligibility Criteria

- mCRC with KRAS^{G12C} mutation
- Progression on 1L fluoropyrimidine-based oxaliplatin or irinotecan regimen



Study Objectives

- Primary endpoints: PFS, OS
- Secondary endpoints: Safety, ORR (RECIST 1.1), 1-year OS, DOR, PK, PROs

[a]Dosing: cetuximab, 500 mg/m^2 Q2W; [b]FOLFIRI Q2W (irinotecan, 180 mg/m^2, 5-FU/LV with fluorouracil given as a 400 mg/m^2 IV bolus followed by a 2400 mg/m^2 dose given as a continuous infusion over 46–48 hours); [c]mFOLFOX6 Q2W (oxaliplatin, 85 mg/m^2, 5-FU/LV, with fluorouracil given as a 400 mg/m^2 IV bolus followed by a 2400 mg/m^2 dose given as continuous infusion over 46–48 hours); [d]A VEGF/VEGFR inhibitor may be given per investigator discretion
ClinicalTrials.gov NCT04793958

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