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KRYSTAL-1: Pooled Phase 1/2 Efficacy and Safety Data of Adagrasib (MRTX849) in Combination with Cetuximab in Patients with Metastatic Colorectal Cancer (CRC) Harboring a KRAS^{G12C} Mutation

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Disclosure Information

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Background

- $KRAS^{G12C}$ mutations occur in 3–4% of CRC cases and are associated with a poor prognosis[1,2]
- Adagrasib is an irreversible inhibitor of $KRAS^{G12C}$ with favorable properties, including a long half-life (23 hours), dose-dependent PK, and CNS penetration[3]
- In patients with previously treated $KRAS^{G12C}$-mutated metastatic CRC, adagrasib monotherapy produced an ORR of 19% and median PFS of 5.6 months[4]
- Dual $KRAS^{G12C}$/EGFR blockade with adagrasib and cetuximab, an EGFR inhibitor, has demonstrated promising clinical activity in a Phase 1 sub-study of the KRYSTAL-1 study[4]
- Adagrasib in combination with cetuximab or panitumumab is recommended for patients with previously treated $KRAS^{G12C}$-mutated CRC by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[5,6,a]

[a]Adagrasib may be considered as a single agent if a patient is unable to tolerate an EGFR inhibitor due to toxicity
NCCN, National Comprehensive Cancer Network

KRYSTAL-1 (849-001) Phase 1 and Phase 2 CRC Cohorts: Study Design

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Key eligibility criteria

- Unresectable or metastatic KRAS^{G12C}-mutated[a] CRC
- Previous therapy:
  - Phase 1 and 2: No available treatment with curative intent or patient refuses/is ineligible for SOC
  - Phase 2: Previous treatment with fluoropyrimidine, irinotecan, oxaliplatin, and a VEGF/VEGFR inhibitor
- ECOG PS 0–1

Phase 1	Phase 2
Adagrasib 600 mg BID[b] + cetuximab[c] n=32	Adagrasib 600 mg BID[b] + cetuximab[d] n=62

Key study objectives[e]

- Primary endpoints:
  - Phase 1: Safety
  - Phase 2: ORR (BICR per RECIST v1.1)
- Secondary endpoints:
  - Phase 1/2: DOR, PFS, OS
  - Phase 2: Safety

N=94

- Preliminary data from Phase 1 sub-study demonstrated promising clinical activity and manageable safety (median follow-up: 17.5 months)[4]
- Here, we report data from Phase 1 and Phase 2 cohorts of the KRYSTAL-1 study of heavily pre-treated patients with KRAS^{G12C}-mutated CRC treated with adagrasib plus cetuximab (data cutoff: June 30, 2023; median follow-up: 11.9 months)

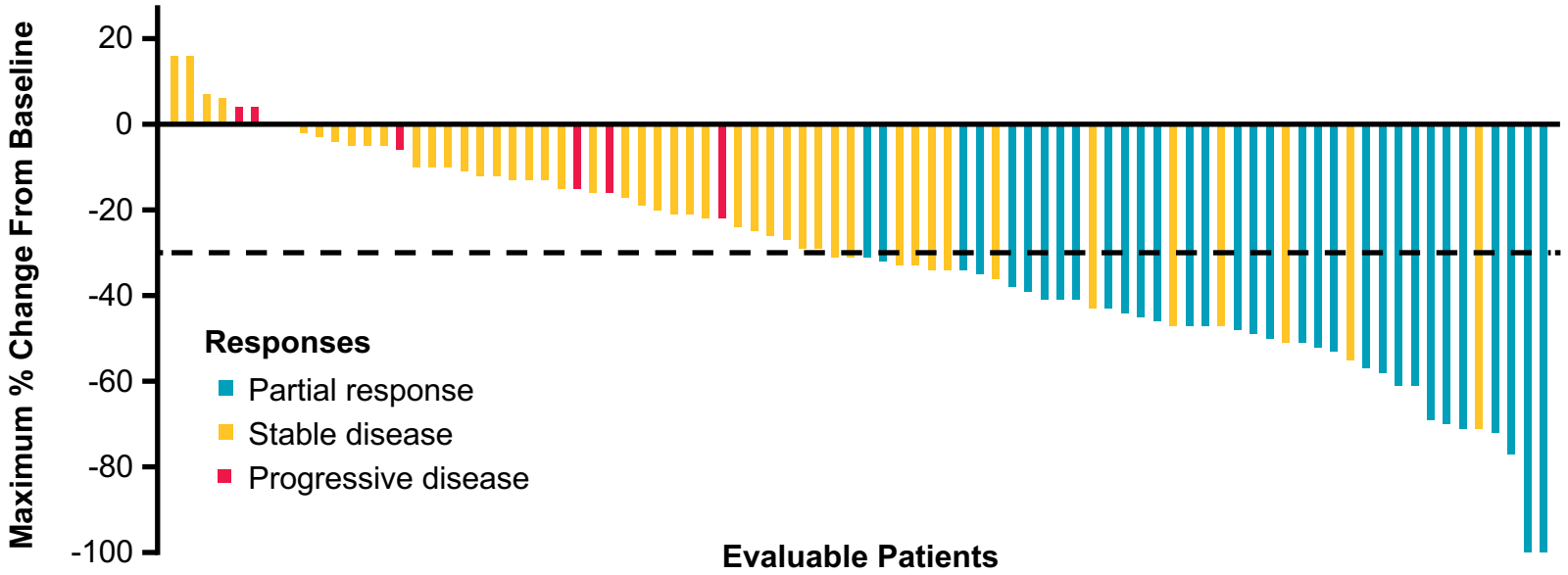
[a]KRAS^{G12C} mutation detected in tumor tissue (Phase 1 and 2) and/or ctDNA (Phase 1). [b]Capsule (fasted) or tablet. In Phase 1, all patients started on capsules and five transitioned to tablets. In Phase 2, 26 patients started on capsules and then transitioned to tablets; 36 patients started on tablets. [c]Cetuximab dosing, 400 mg/m^2 followed by 250 mg/m^2 QW or 500 mg/m^2 Q2W. [d]Cetuximab dosing, 500 mg/m^2 Q2W. [e]Efficacy and safety endpoints were analyzed in the full analysis set
ClinicalTrials.gov. NCT03785249

Demographics and Baseline Characteristics

	Adagrasib + Cetuximab CRC Cohort (N=94)
Median age (range), years	57 (24–75)
Female, n (%)	50 (53.2)
Race, n (%) White / Black or African American / Asian / Other	 67 (71.3) / 13 (13.8) / 5 (5.3) / 9 (9.6)[a]
Ethnicity, n (%) Hispanic or Latino / Not Hispanic or Latino / Missing	 16 (17.0) / 75 (79.8) / 3 (3.2)
ECOG PS, n (%) 0 / 1	 48 (51.1) / 46 (48.9)
Prior lines of systemic therapy Median (range) 1 / 2 / 3 / 4+, n (%)	 3 (1–9) 8 (8.5) / 34 (36.2) / 29 (30.9) / 23 (24.5)
Prior systemic treatments, n (%)[b] Fluoropyrimidine / Oxaliplatin / Anti-VEGF monoclonal antibody / Irinotecan / Trifluridine and tipiracil / Regorafenib / Anti-PD-1 or anti-PD-L1 / Anti-EGFR monoclonal antibody	 94 (100) / 93 (98.9) / 90 (95.7) / 89 (94.7) / 11 (11.7) / 8 (8.5) / 8 (8.5) / 3 (3.2)
Metastatic disease per BICR, n (%) Lung / Liver / Bone / Adrenal / Brain	 67 (71.3) / 60 (63.8) / 13 (13.8) / 2 (2.1) / 1 (1.1)
Concurrent molecular alterations, n/m (%)[c] EGFR amplification / NTRK fusion / TP53 mutation / PIK3CA mutation	 2/81 (2.5) / 1/80 (1.3) / 59/80 (73.8) / 14/80 (17.5)

[a]Includes one American Indian or Alaska native patient, one Puerto Rican patient, and seven with race unknown. [b]Patients may be counted towards more than one regimen. One (1.1%) patient had received a prior KRAS^{G12C} inhibitor. Eighty-four patients (89.4%) received fluoropyrimidine, oxaliplatin, irinotecan, and anti-VEGF monoclonal antibody. [c]No BRAF V600E (0/90), MSI-H/dMMR (0/73), or HER2 (ERBB2; 0/81) alterations were reported. n = number of patients with the molecular alteration; m = number of patients with definitive test result
Data as of June 30, 2023

Best Tumor Change From Baseline



- Confirmed objective responses were observed in 32/94 patients (34.0%)[a]
- Disease control was observed in 80/94 patients (85.1%)

[a]ORR for the Phase 1 portion (n=32) was 43.8%; ORR for the Phase 2 portion (n=62) was 29.0%
All results are based on BICR. Waterfall plot excludes eight patients without any post-baseline scans
Data as of June 30, 2023 (median follow-up 11.9 months)

Duration of Treatment in Patients With Tumor Response

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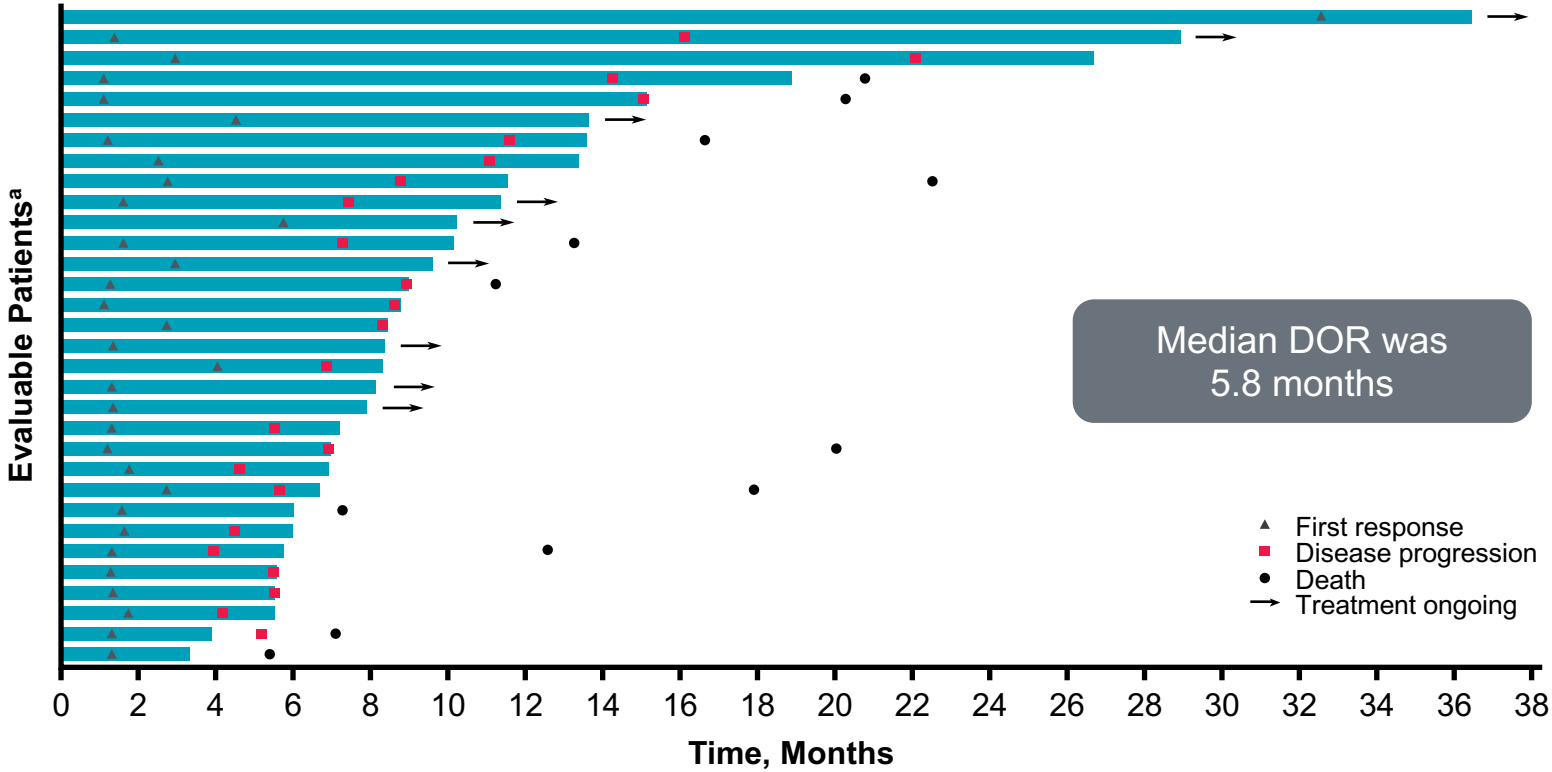
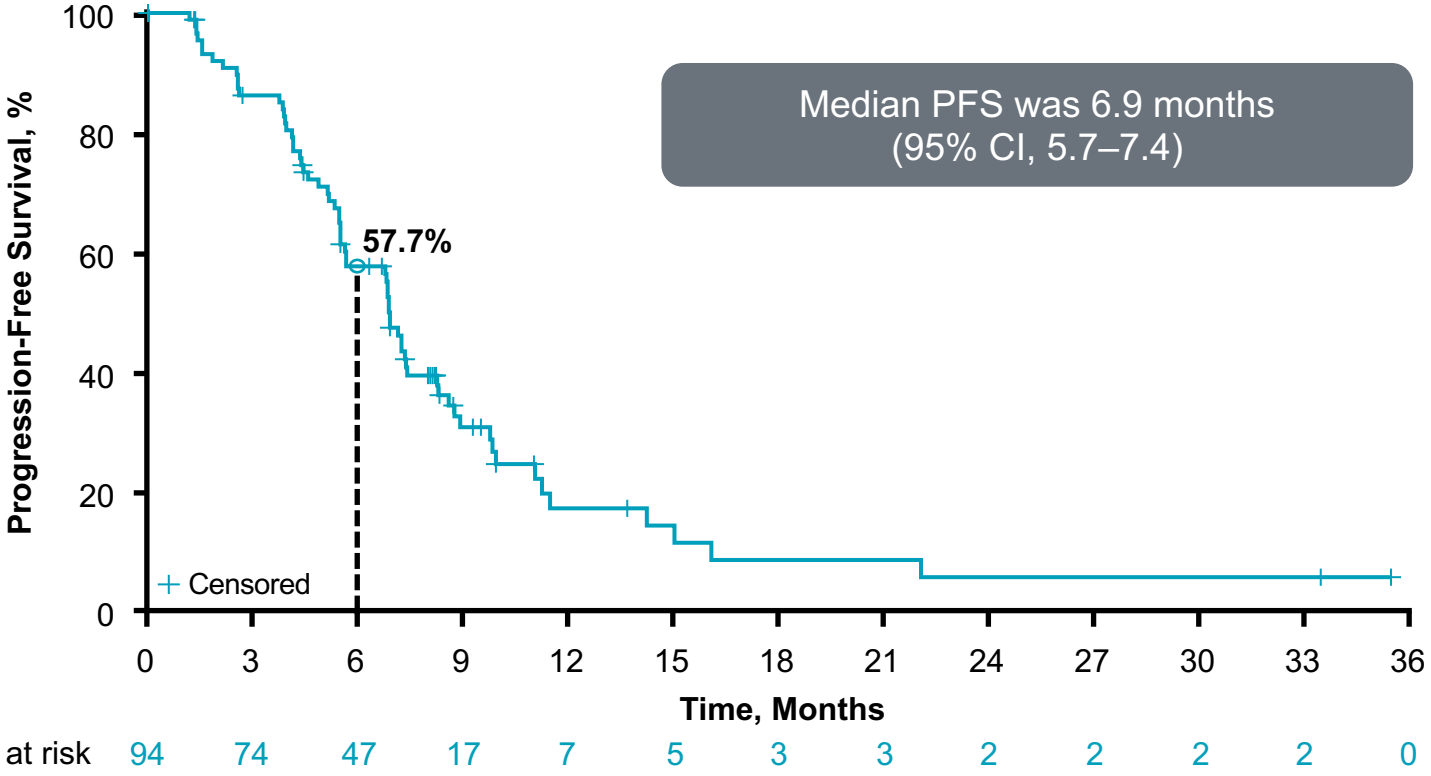


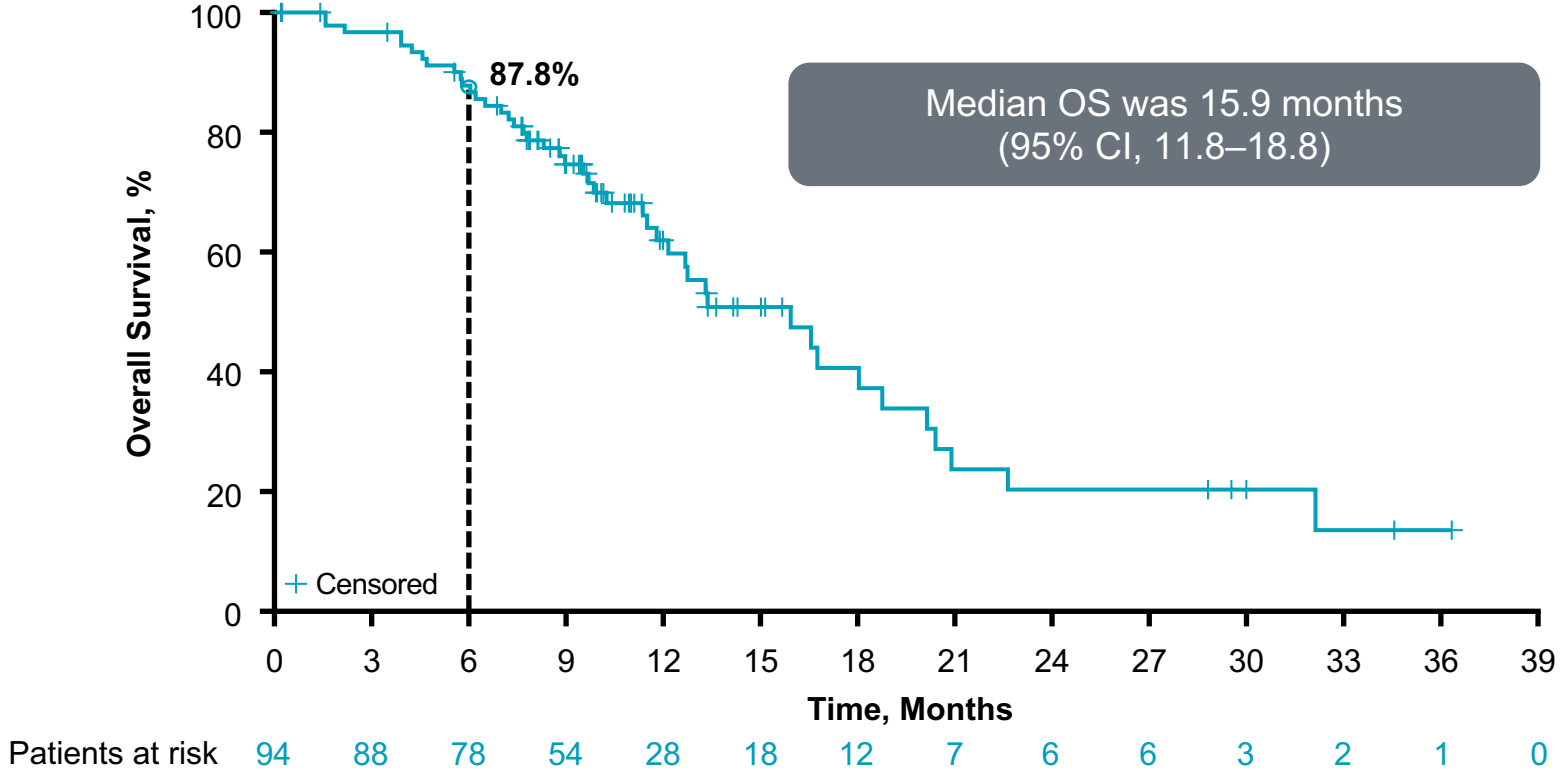
[a]Only patients with objective tumor responses are displayed (n=32)
All results are based on BICR
Data as of June 30, 2023 (median follow-up 11.9 months)

Progression-Free Survival



All results are based on BICR
Data as of June 30, 2023 (median follow-up 11.9 months)

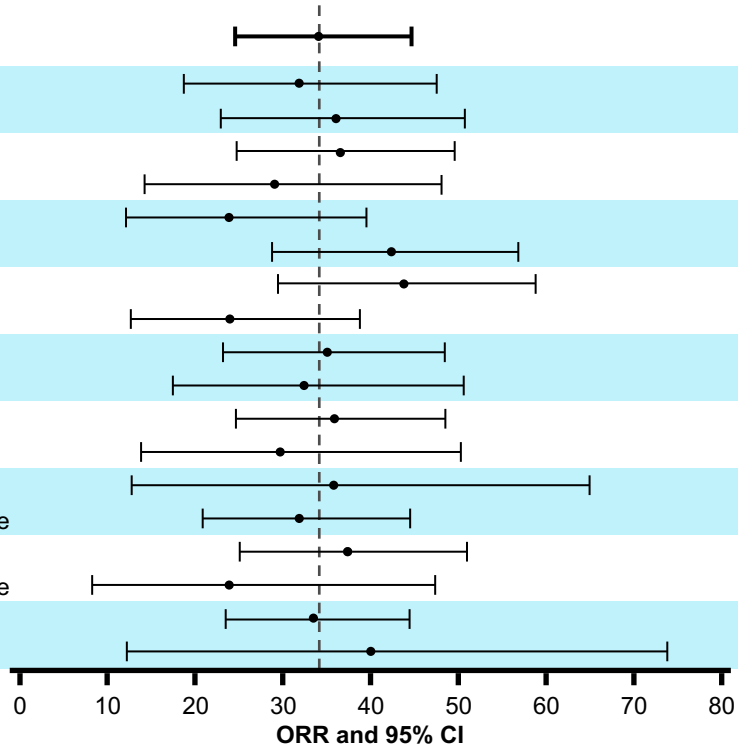
Overall Survival



Data as of June 30, 2023 (median follow-up 11.9 months)

Subgroup Analysis of Tumor Response

Subgroup		ORR, % (95% CI)		N
Overall		34.0	(24.6–44.5)	94
Sex	Male	31.8	(18.6–47.6)	44
	Female	36.0	(22.9–50.8)	50
Age, years	<65	36.5	(24.7–49.6)	63
	≥65	29.0	(14.2–48.0)	31
Number of prior systemic therapies	≤2	23.8	(12.1–39.5)	42
	>2	42.3	(28.7–56.8)	52
Baseline ECOG PS	0	43.8	(29.5–58.8)	48
	1	23.9	(12.6–38.8)	46
Liver metastases at baseline	Yes	35.0	(23.1–48.4)	60
	No	32.4	(17.4–50.5)	34
Lung metastases at baseline	Yes	35.8	(24.5–48.5)	67
	No	29.6	(13.8–50.2)	27
PIK3CA mutation status	Positive	35.7	(12.8–64.9)	14
	Negative	31.8	(20.9–44.4)	66
TP53 mutation status	Positive	37.3	(25.0–50.9)	59
	Negative	23.8	(8.2–47.2)	21
Prior fluoropyrimidine, oxaliplatin, irinotecan, and anti-VEGF monoclonal antibody	Yes	33.3	(23.4–44.5)	84
	No	40.0	(12.2–73.8)	10



All results are based on BICR
Data as of June 30, 2023 (median follow-up 11.9 months)

$KRAS^{G12C}$ ctDNA Concordance and Response

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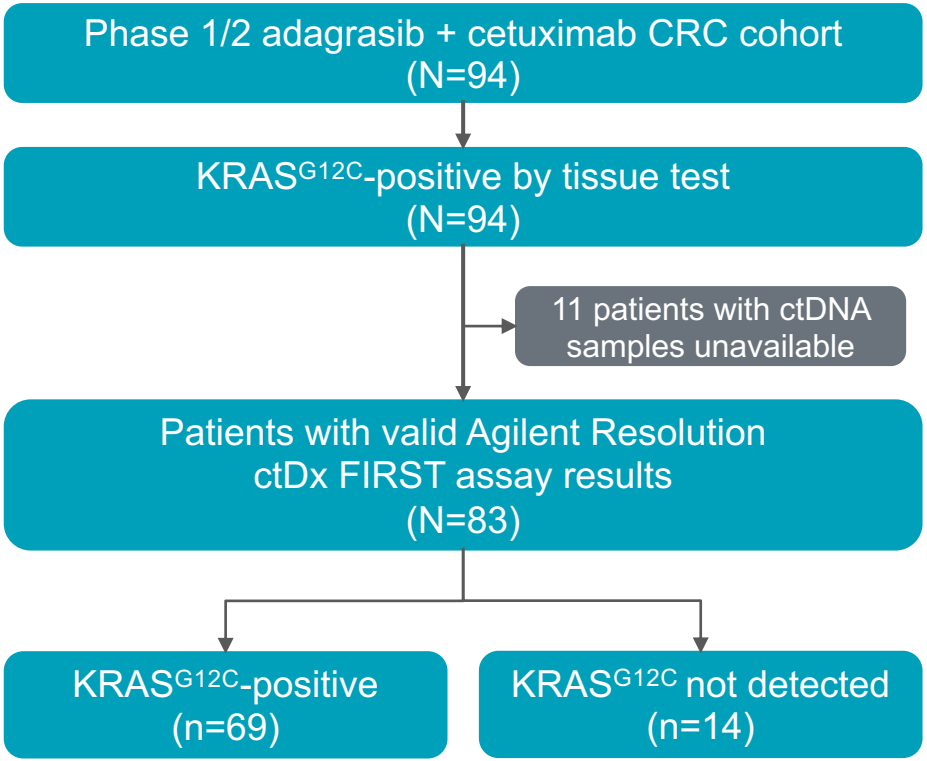

The concordance of $KRAS^{G12C}$-positive status at baseline for patients with paired tissue and plasma samples was 83% (69/83)

Tumor Response in Patients with Paired Tissue and Plasma Samples

	$KRAS^{G12C}$ detected in ctDNA n=69	$KRAS^{G12C}$ not detected in ctDNA n=14	All patients N=83
ORR, % (n/N)	39% (27/69)[a]	14% (2/14)[b]	35% (29/83)

[a]3 patients were not evaluable. [b]4 patients were not evaluable. All results are based on BICR

Treatment-Related Adverse Events

TRAEs, n (%)	Adagrasib + Cetuximab CRC Cohort (N=94)				
	Any grade[a]	Grade 1	Grade 2	Grade 3	Grade 4
Any TRAEs	94 (100)	8 (8.5)	60 (63.8)	22 (23.4)	4 (4.3)[b]
Most frequent TRAEs[c]					
Nausea	57 (60.6)	35 (37.2)	20 (21.3)	2 (2.1)	0
Vomiting	48 (51.1)	30 (31.9)	18 (19.1)	0	0
Diarrhea	46 (48.9)	31 (33.0)	14 (14.9)	1 (1.1)	0
Dermatitis acneiform	45 (47.9)	28 (29.8)	15 (16.0)	2 (2.1)	0
Fatigue	40 (42.6)	23 (24.5)	16 (17.0)	1 (1.1)	0
Dry skin	32 (34.0)	24 (25.5)	8 (8.5)	0	0
Hypomagnesemia	27 (28.7)	17 (18.1)	7 (7.4)	2 (2.1)	1 (1.1)
Headache	25 (26.6)	14 (14.9)	8 (8.5)	3 (3.2)	0
Rash	21 (22.3)	11 (11.7)	8 (8.5)	2 (2.1)	0

- TRAEs led to dose reductions of adagrasib in 28 (29.8%) patients and cetuximab in six (6.4%) patients
- Dose interruptions of adagrasib were required in 34 (36.2%) patients and cetuximab in 33 (35.1%) patients
- TRAEs led to discontinuation of cetuximab in eight (8.5%) patients[d]; no TRAEs led to discontinuation of adagrasib

[a]No Grade 5 events occurred. [b]Other Grade 4 TRAEs were cetuximab-related infusion-related reaction, neutrophil count decrease, and hyperkalemia (n=1 each). [c]Any grade TRAEs occurring in ≥20% of patients. [d]TRAEs that resulted in discontinuation of cetuximab were: cetuximab-related infusion-related reaction (n=4), malaise (n=1), alanine aminotransferase increase (n=1), dermatitis acneiform (n=1), and flushing (n=1). 6 of these patients continued adagrasib as a single agent

Data as of June 30, 2023 (median follow-up 11.9 months)

Conclusions

- Current late-line SOC regimens for metastatic CRC (trifluridine-tipiracil plus bevacizumab, regorafenib, or fruquintinib) produce an ORR of 1–6%, median PFS of 1.9–5.6 months, and median OS of 6.4–10.8 months,[7–9] which warrant the need for more effective options
- Adagrasib plus cetuximab demonstrated clinically meaningful activity (ORR 34%, median PFS 6.9 months, median OS 15.9 months) in previously treated patients with $KRAS^{G12C}$-mutated metastatic CRC
- The safety profile for adagrasib plus cetuximab was tolerable and consistent with previous reports,[4] and with the known safety profile of each drug individually
- These data support adagrasib plus cetuximab as a potential new SOC for patients with previously treated metastatic $KRAS^{G12C}$-mutated CRC

Cancer Discovery Simultaneous Publication

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RESEARCH ARTICLE

Efficacy and Safety of Adagrasib Plus Cetuximab in Patients With *KRAS*^{G12C}-Mutated Metastatic Colorectal Cancer

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KRYSTAL-10 (849-010) Phase 3: Study Design

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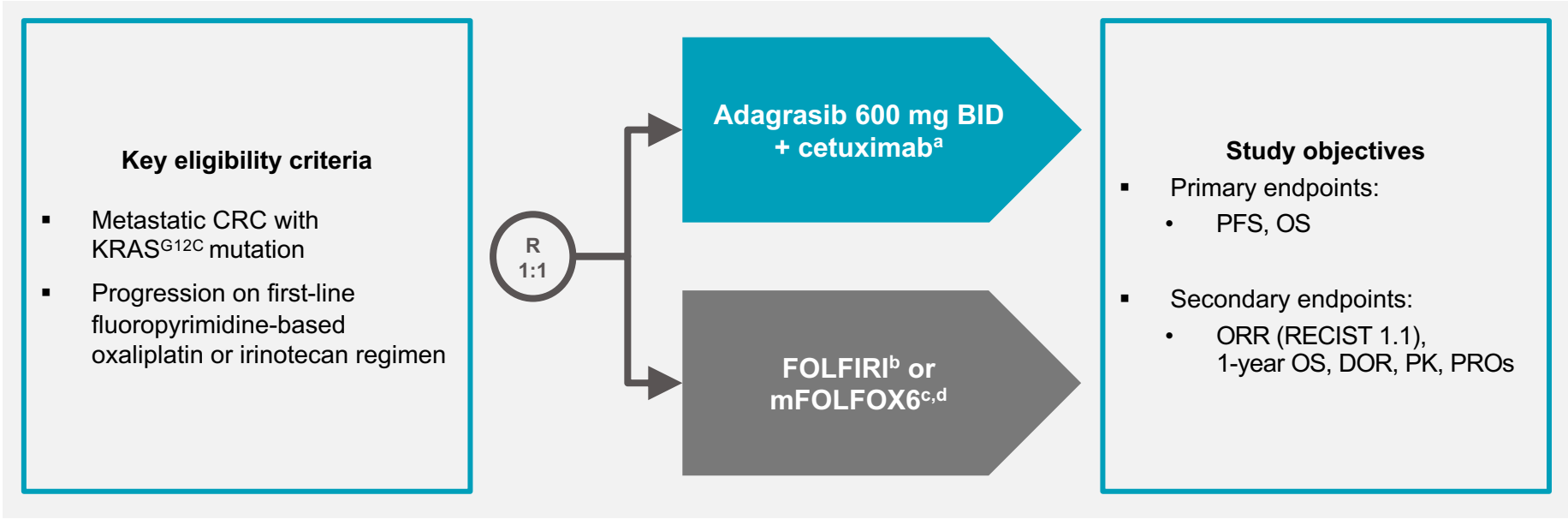

KRYSTAL-10 is a global, Phase 3, randomized, open-label trial of second-line adagrasib + cetuximab versus chemotherapy in metastatic CRC with KRAS^{G12C} mutation

[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 2,400 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 2,400 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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KRYSTAL-1 Phase 1 and Phase 2 Enrolling Investigators

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