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KRYSTAL-1: Updated Efficacy and Safety of Adagrasib (MRTX849) With or Without Cetuximab in Patients With Advanced Colorectal Cancer (CRC) Harboring a KRAS^{G12C} Mutation

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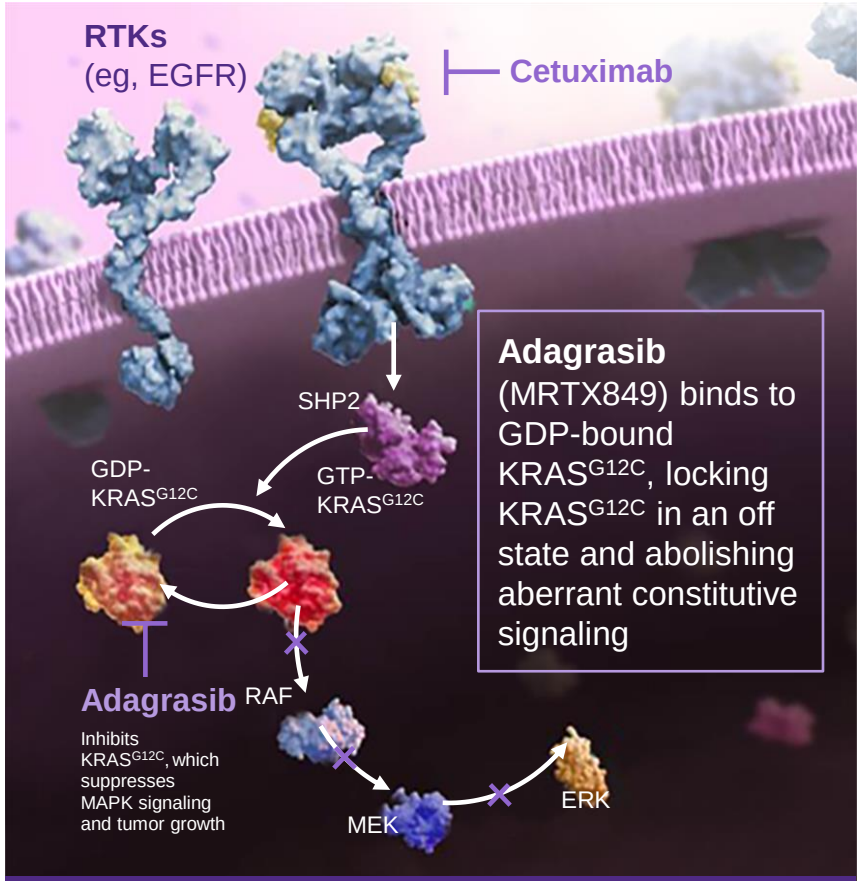
Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

- KRAS^{G12C} mutations act as oncogenic drivers, occur in ~3–4% of CRC, and are a negative predictor of cetuximab efficacy[1–4]
- KRAS^{G12C} mutations are associated with poor prognosis compared with other KRAS mutations in patients with CRC,[5] and late-line treatment options are limited[6]
- Adagrasib exhibits desired properties of a KRAS^{G12C} inhibitor, including a long half-life (23 hours), dose-dependent PK and CNS penetration[7,8]
- Combining adagrasib with cetuximab may enhance inhibition of KRAS-dependent signaling or overcome adaptive feedback[9]
- Clinical activity with adagrasib has been shown in patients across 9 KRAS^{G12C}-mutated solid tumor types[8,10–12]



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

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

Key Eligibility Criteria

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

Phase 1b
CRC Combination

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

Phase 2
CRC Monotherapy

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

Study Objectives

Phase 1b

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

Phase 2

- Primary endpoint: ORR (RECIST 1.1)[d]
- Secondary endpoints: safety, DOR, PFS, OS

- Previously reported data demonstrated clinical activity of adagrasib monotherapy and adagrasib + cetuximab in patients with previously treated KRAS^{G12C}-mutated CRC[10,e]
- Here we report updated data for adagrasib 600 mg BID as monotherapy (Phase 2; median follow-up: 20.1 months) and in combination with cetuximab (Phase 1b; median follow-up: 17.5 months) in patients with previously treated KRAS^{G12C}-mutated CRC

[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. [d]Response was analysed in the clinically evaluable population with local radiology review. [e]Previous data were reported for 46 patients (n=2 in Phase 1/1b and n=44 in Phase 2) receiving adagrasib monotherapy (median follow-up: 8.9 months) and 32 patients receiving adagrasib + cetuximab (median follow-up: 7 months)[10]

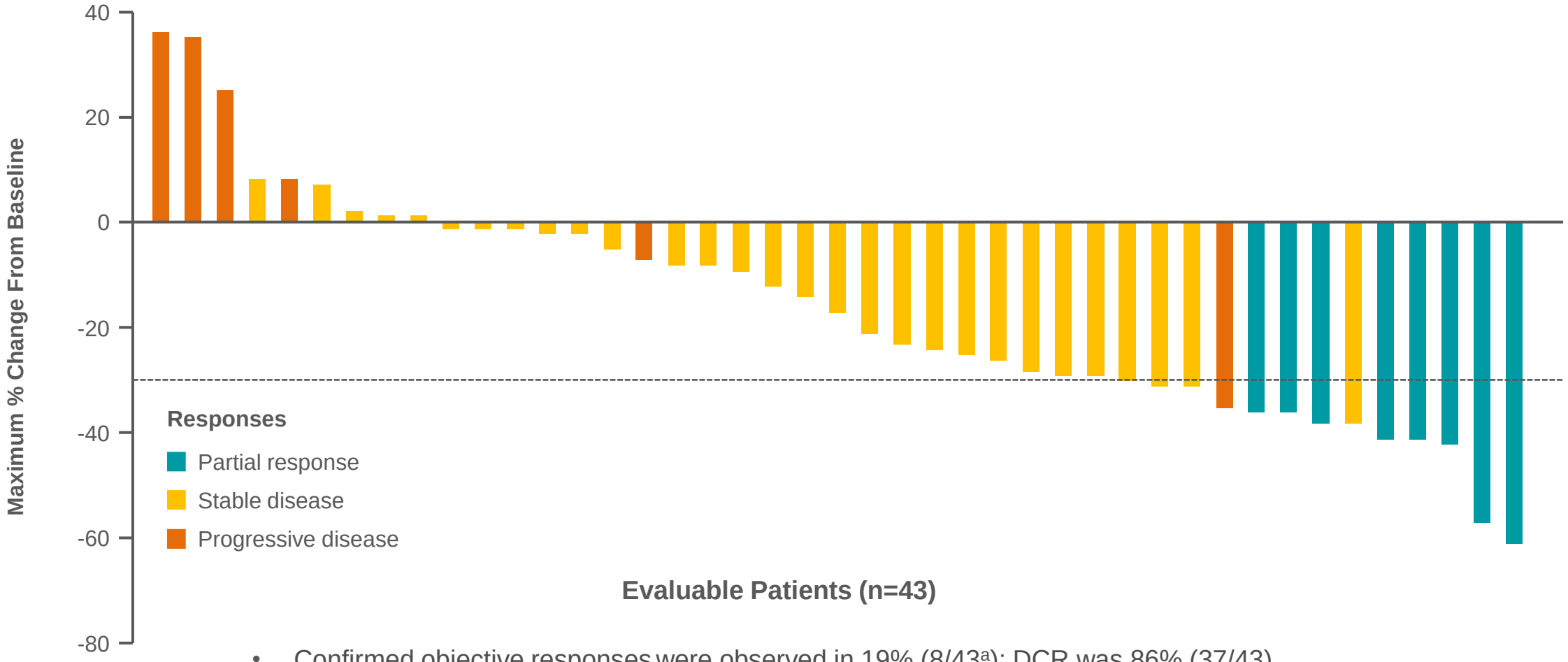
ClinicalTrials.gov. NCT03785249

Demographics and Baseline Characteristics

	Adagrasib Monotherapy (n=44)	Adagrasib + Cetuximab (n=32)
Median age, y (range)	59 (29–79)	60 (41–74)
Female, n (%)	22 (50%)	17 (53%)
Race, n (%)		
White	33 (75%)	26 (81%)
Black	6 (14%)	4 (13%)
Asian	3 (7%)	2 (6%)
Other	2 (5%)	0 (0%)
ECOG PS, n (%)		
0	23 (52%)	14 (44%)
1	21 (48%)	18 (56%)
Prior lines of systemic anticancer therapy, median (range)	3 (1–9)	3 (1–8)
Prior lines of systemic anticancer therapy, %		
1 / 2 / 3 / ≥4	18% / 21% / 25% / 36%	9% / 25% / 34% / 31%
Prior systemic anticancer therapy, %		
Fluoropyrimidine / oxaliplatin / irinotecan	100% / 98% / 80%	100% / 100% / 88%
Anti-VEGF	82%	88%
Anti-EGFR biological therapy	2%	0%
Regorafenib and/or trifluridine/tipiracil	23%	19%

Data as of June 16, 2022 (median follow-up adagrasib monotherapy, 20.1 months; adagrasib + cetuximab, 17.5 months)

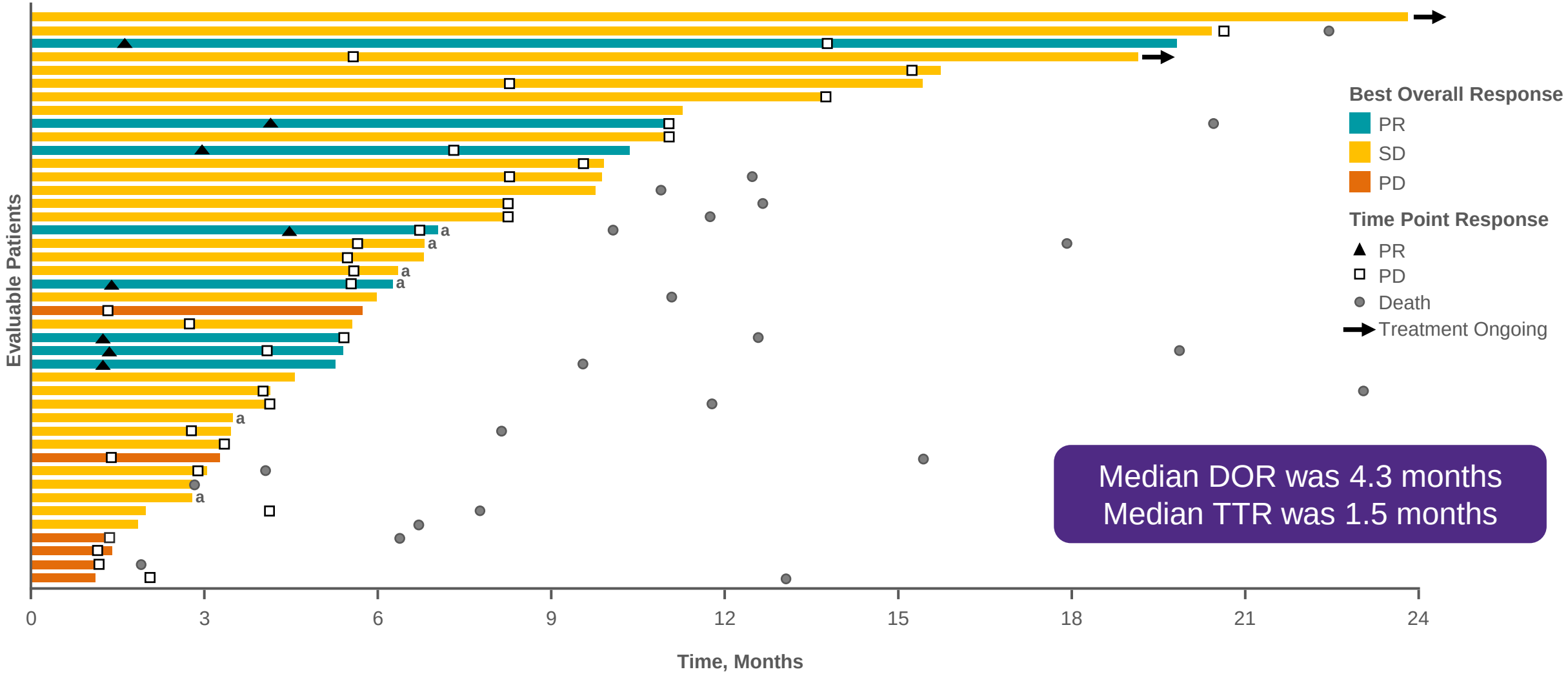
Adagrasib Monotherapy in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Best Tumor Change From Baseline



- Confirmed objective responses were observed in 19% (8/43[a]); DCR was 86% (37/43)
- Tumor shrinkage of any magnitude occurred in 79% of patients

[a]Response per investigator assessment (n=43; one patient withdrew consent prior to the first scan)
Data as of June 16, 2022 (median follow-up, 20.1 months)

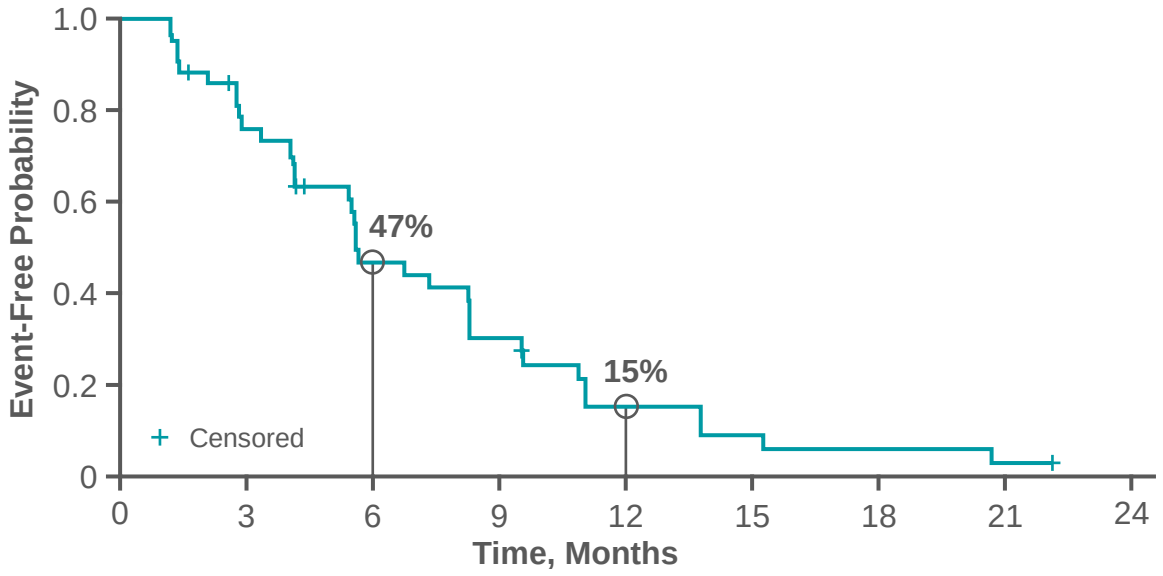
Adagrasib Monotherapy in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Duration of Treatment



[a]Patients who crossed over to receive adagrasib + cetuximab; data are summarized prior to crossover
Response outcomes per investigator assessment
Data as of June 16, 2022 (median follow-up, 20.1 months)

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

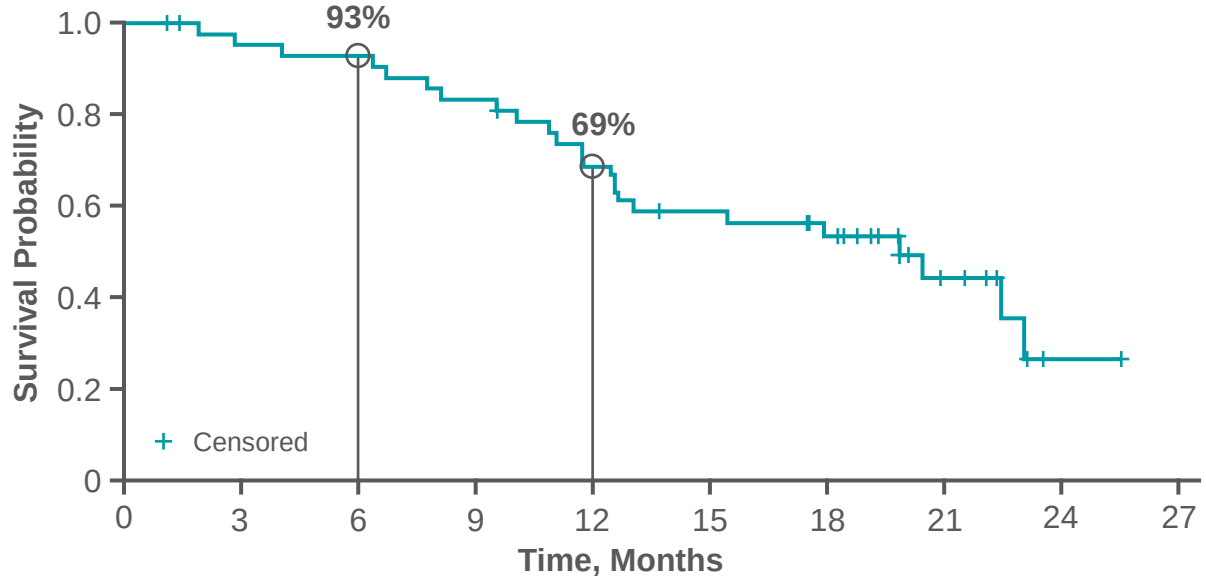
Progression-Free Survival



No. at risk	44	30	17	11	5	3	2	1	0

Median PFS was 5.6 months (95% CI, 4.1–8.3)

Overall Survival



No. at risk	44	40	39	35	28	23	19	8	1	1

Median OS was 19.8 months (95% CI, 12.5–23.0)

PFS per investigator assessment (n=44)
Data as of June 16, 2022 (median follow-up, 20.1 months)

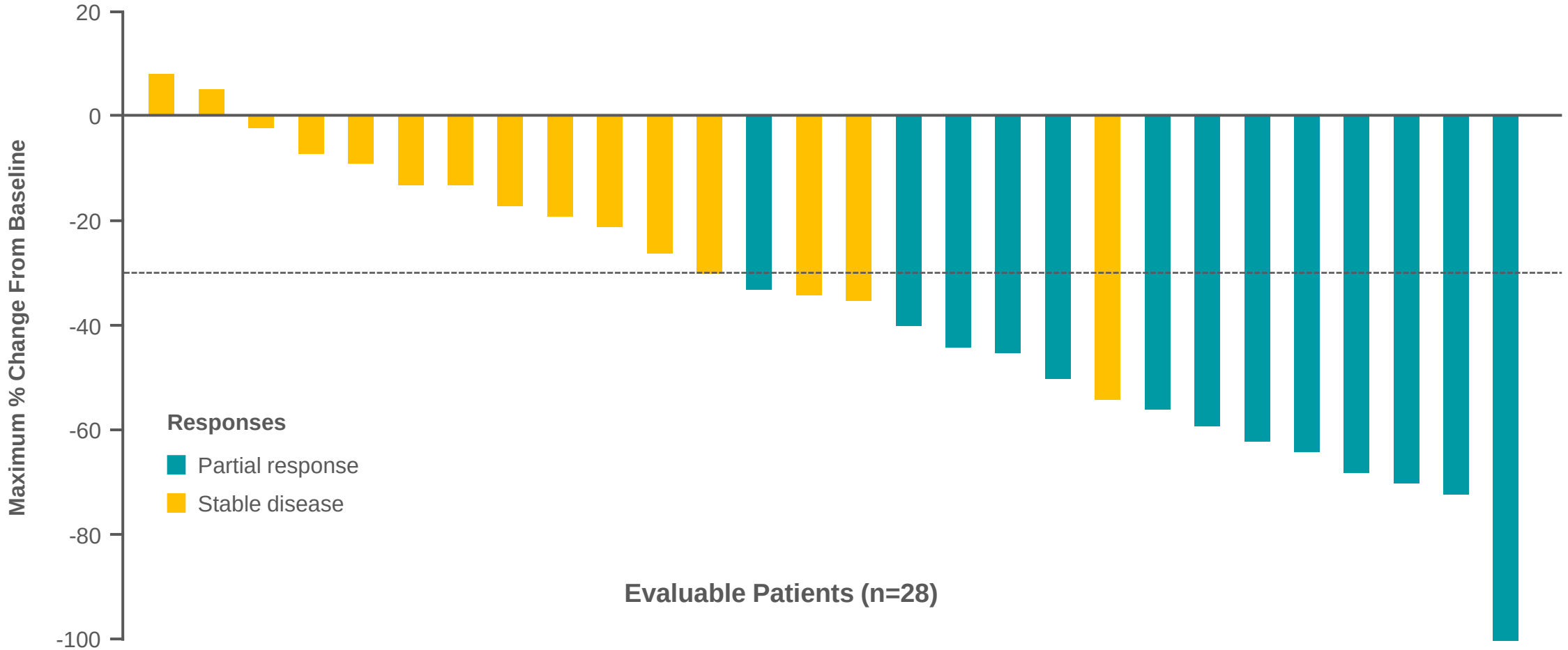
Adagrasib Monotherapy in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Treatment-Related Adverse Events

Most Frequent TRAEs	Adagrasib Monotherapy (n=44)			
TRAEs, %	**Any grade**	**Grade 1**	**Grade 2**	**Grade 3**
Any TRAEs[a]	93%	23%	36%	30%
Most frequent TRAEs[b], %				
Diarrhea	66%	36%	23%	7%
Nausea	57%	34%	23%	0
Fatigue	46%	25%	16%	5%
Vomiting	46%	27%	18%	0
Decreased appetite	18%	9%	9%	0
Anemia	16%	5%	2%	9%
QT prolongation	16%	5%	7%	5%
Peripheral edema	16%	14%	2%	0

- 2 Grade 4 TRAEs (pericardial effusion, n=1; decreased neutrophil count, n=1); no Grade 5 TRAEs
- No TRAEs that led to discontinuation
- TRAEs led to adagrasib dose reduction in 39% (17/44) and to adagrasib interruption in 46% (20/44)

[a]By maximum grade. [b]Occurring in >15% of patients (any grade)
Data as of June 16, 2022 (median follow-up, 20.1 months)

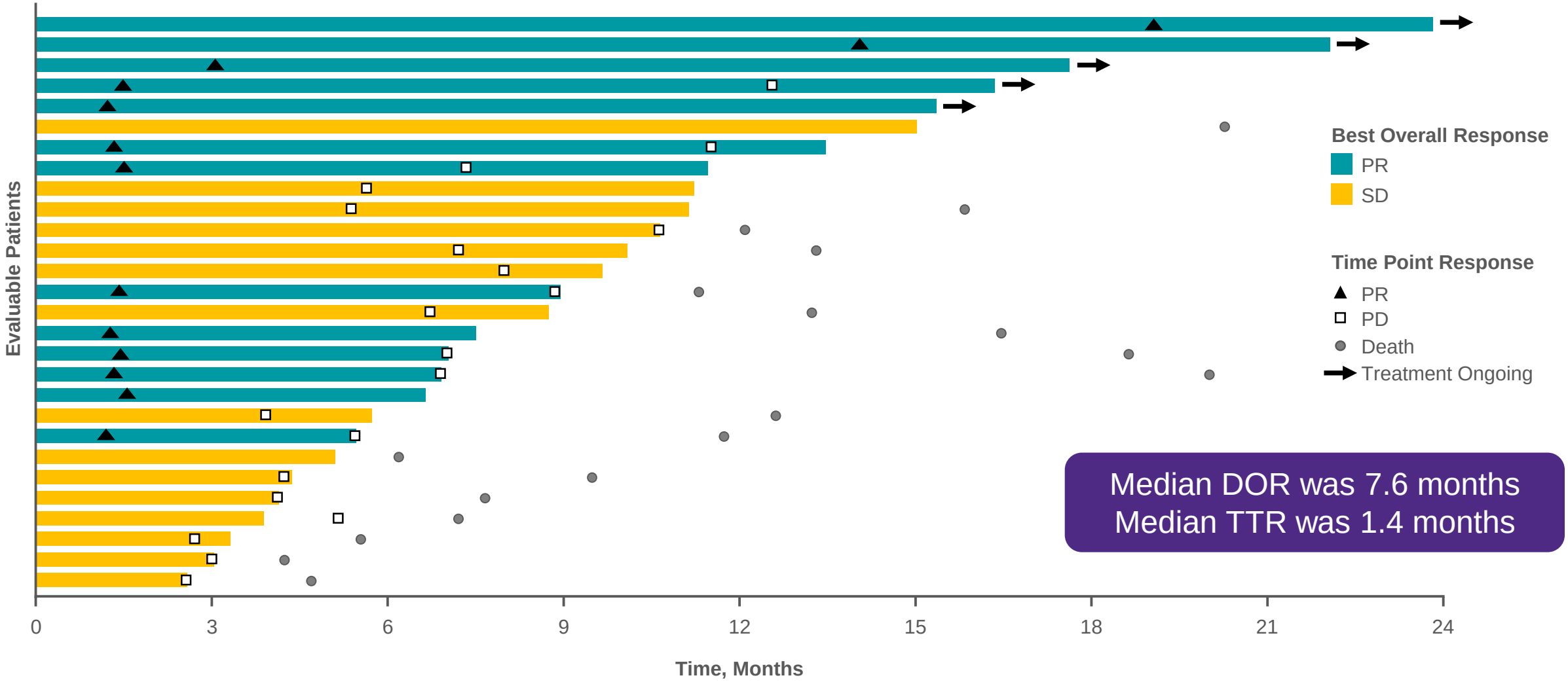
Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Best Tumor Change From Baseline



- Confirmed objective responses were observed in 46% (13/28[a]); DCR was 100% (28/28)
- Tumor shrinkage of any magnitude occurred in 93% of patients

[a]Response per investigator assessment (n=28; four patients are not included due to no post-baseline assessment of target lesions)
Data as of June 16, 2022 (median follow-up, 17.5 months)

Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Duration of Treatment

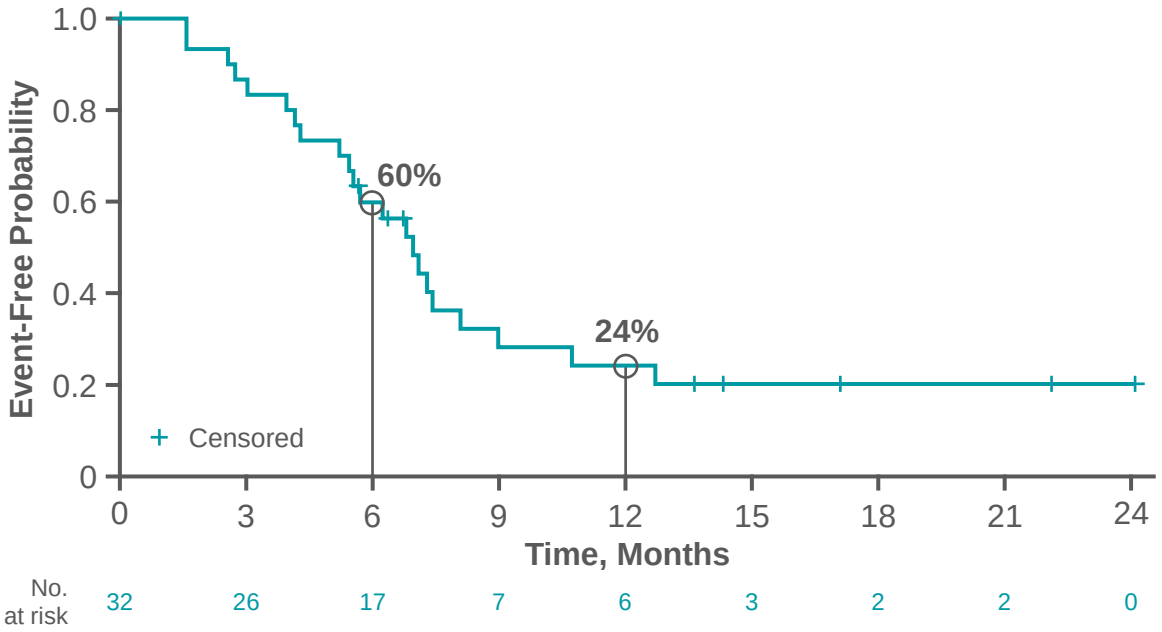


Median DOR was 7.6 months
Median TTR was 1.4 months

Response outcomes per investigator assessment (n=28; four patients are not included due to no post-baseline assessment of target lesions)
Data as of June 16, 2022 (median follow-up, 17.5 months)

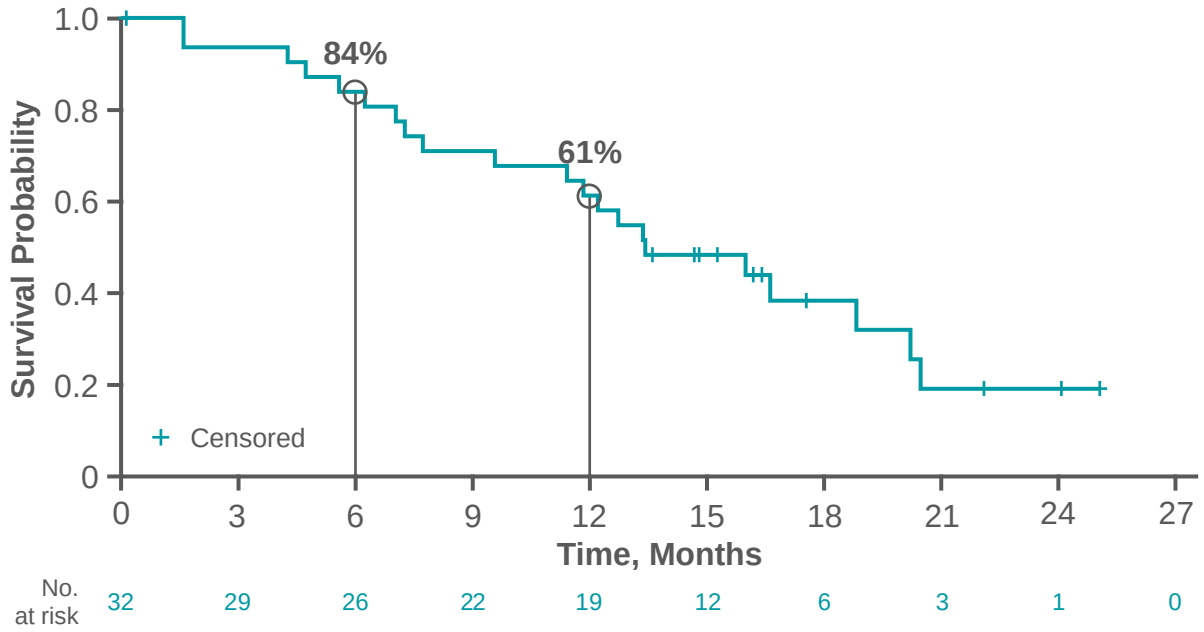
Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Progression-Free Survival and Overall Survival

Progression-Free Survival



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

Overall Survival



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

PFS per investigator assessment (n=32)
Data as of June 16, 2022 (median follow-up, 17.5 months)

Adagrasib + Cetuximab in Previously Treated Patients with KRAS^{G12C}-Mutated CRC: Treatment-Related Adverse Events

Most Frequent TRAEs	Adagrasib + Cetuximab (n=32)			
TRAEs, %	**Any grade**	**Grade 1**	**Grade 2**	**Grade 3**
Any TRAEs[a]	100%	16%	69%	9%
Most frequent TRAEs[b], %				
Nausea	63%	41%	22%	0
Diarrhea	56%	34%	19%	3%
Vomiting	53%	41%	13%	0
Dermatitis acneiform	47%	34%	9%	3%
Fatigue	47%	25%	22%	0
Dry skin	41%	34%	6%	0
Headache	31%	22%	9%	0
Dizziness	25%	13%	13%	0
Rash maculopapular	25%	22%	3%	0
Stomatitis	22%	16%	3%	3%

- 2 Grade 4 TRAEs (cetuximab-related infusion-related reaction, n=1; hyperkalemia, n=1); no Grade 5 TRAEs
- 16% (5/32) of TRAEs led to discontinuation of cetuximab[c]. No TRAEs led to discontinuation of adagrasib
- TRAEs led to adagrasib dose reduction in 31% (10/32) and to adagrasib interruption in 44% (14/32)

[a]By maximum grade. [b]Occurring in >20% of patients (any grade). [c]TRAEs leading to cetuximab discontinuation were treatment-related cetuximab-related infusion-related reaction (n=3), malaise (n=1) and vascular flushing (n=1)

Data as of June 16, 2022 (median follow-up, 17.5 months)

Conclusions

- KRAS^{G12C} mutations are associated with poor prognosis in metastatic CRC, and late-line treatment options for these patients are limited
- Adagrasib ± cetuximab demonstrated encouraging clinical activity in heavily pretreated patients with metastatic CRC harboring a KRAS^{G12C} mutation
  - Adagrasib + cetuximab resulted in a numerically higher response rate and longer mPFS than adagrasib monotherapy (combination: ORR 46%; DCR 100%; mPFS 6.9 months)
- Adagrasib ± cetuximab is tolerable and has a manageable safety profile
- Adagrasib + cetuximab is being evaluated in patients with KRAS^{G12C}-mutated mCRC in the 2L setting in KRYSTAL-10 (Phase 3, NCT04793958) and late-line setting in KRYSTAL-1 (potentially registration-enabling phase 2 cohort, NCT03785249)

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

Key Eligibility Criteria

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

N=420

R 1:1

Adagrasib 600 mg BID + Cetuximab[a]

FOLFIRI[b] or mFOLFOX6[c,d]

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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Abbreviations

5-FU, 5-fluorouracil
1L, first line
2L, second line
BID, twice daily
CI, confidence interval
CNS, central nervous system
CR, complete response
CRC, colorectal cancer
ctDNA, circulating tumor DNA
DCR, disease control rate
DOR, duration of response
ECOG, Eastern Cooperative Oncology Group
EGFR, epidermal growth factor receptor
ERK, extracellular signal–regulated kinase
FOLFIRI, folinic acid (leucovorin), fluorouracil, irinotecan
FOLFOX6, folinic acid (leucovorin), fluorouracil, oxaliplatin
GDP, guanosine diphosphate
GTP, guanosine triphosphate
IV, intravenous
KRAS, Kirsten rat sarcoma virus
LV, leucovorin
MAPK, mitogen-activated protein kinase
MEK, mitogen-activated protein kinase kinase
mCRC, metastatic colorectal cancer
mPFS, median progression-free survival
ORR, objective response rate
OS, overall survival
PD, progressive disease
PFS, progression-free survival
PK, pharmacokinetics
PR, partial response
PROs, patient-reported outcomes
PS, performance status
QW, every week
Q2W, every 2 weeks
R, randomized
RECIST, Response Evaluation Criteria in Solid Tumors
RP2D, recommended Phase 2 dose
SD, stable disease
SHP2, Src homology phosphatase 2
TRAE, treatment-related adverse event
TTR, time to response
VEGF, vascular endothelial growth factor
VEGFR, vascular endothelial growth factor receptor