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KRYSTAL-1: Adagrasib (MRTX849) as Monotherapy or in Combination With Cetuximab in Patients With Colorectal Cancer Harboring a KRAS^{G12C} Mutation

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Disclosures

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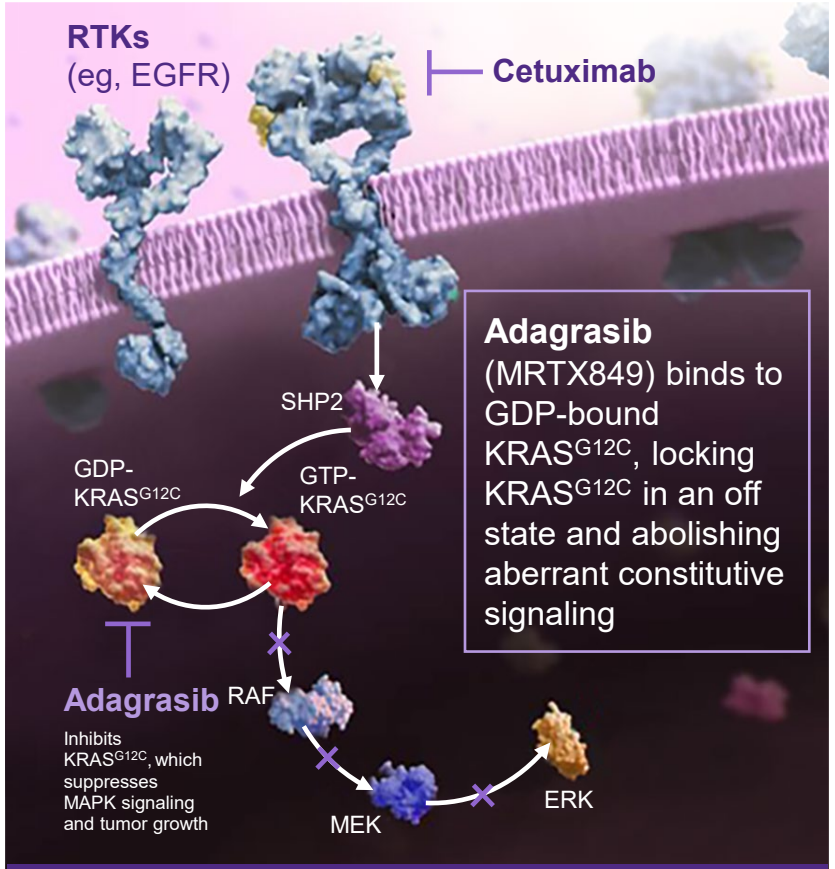
Adagrasib (MRTX849) Is a Differentiated, Selective Inhibitor of KRAS^{G12C}

- KRAS^{G12C} mutations occur in approximately 3%-4% of CRC, act as oncogenic drivers, and are a negative predictor of cetuximab efficacy[1-4]
- The KRAS protein cycles between GTP-on and GDP-off states and has a protein resynthesis half-life of ~24 hours[5,6]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, irreversibly and selectively binds KRAS^{G12C} in its inactive, GDP-bound state and was optimized for desired properties, including[7]:
  - Long half-life of ~24 hours, dose-dependent PK, and brain penetration
- Maintaining continuous adagrasib exposure above a target threshold enables inhibition of KRAS-dependent signaling for the complete dosing interval and maximizes antitumor activity
- Combining adagrasib with cetuximab, an EGFR inhibitor, may enhance inhibition of KRAS-dependent signaling or overcome adaptive feedback to improve outcomes[8]



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

KRYSTAL-1 (849-001) Study Design

Key Eligibility Criteria (Up to n=565)

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

Phase 1
Dose Escalation

- 600 mg BID n=2 (CRC) → Expansion
- 1200 mg QD
- 600 mg QD
- 300 mg QD[b]
- 150 mg QD[b]

Phase 1 Endpoints
Primary: Safety, MTD, PK, RP2D
Secondary: Objective response (RECIST 1.1), DOR, PFS, OS

Phase 2 Endpoints
Primary: ORR (RECIST 1.1)
Secondary: Safety

Phase 1b
Dose Expansion and Combination

- **Adagrasib** monotherapy in solid tumors
- **Adagrasib** brain metastases in solid tumors
- **Adagrasib** NSCLC treatment-naive[c]
- **Adagrasib** NSCLC prior KRAS^{G12C} inhibitor
- **Adagrasib** + pembro in NSCLC[d]
- **Adagrasib +** afatinib in NSCLC
- **Adagrasib** + cetuximab in CRC[e,f,g] n=32

Phase 2
Monotherapy Treatment

- **NSCLC**[h,i]
- **CRC**[i,j] n=44
- **Other Solid Tumors**[i]
- **NSCLC KRAS^{G12C} and STK11 Treatment-Naive**[c,i]

- Previously reported data demonstrated the clinical activity of adagrasib in patients with pretreated CRC with a KRAS^{G12C} mutation[9]
- Here we report preliminary data for adagrasib 600 mg BID as monotherapy (n=2 in Phase 1/1b and n=44 in Phase 2; median follow-up: 8.9 months) and in combination with cetuximab (n=32; median follow-up: 7 months) in patients with pretreated CRC with a KRAS^{G12C} mutation
- Data as of 25 May 2021 (monotherapy), 9 July 2021 (cetuximab combination)

[a]Tissue test and/or ctDNA allowed for Phase 1/1b eligibility. [b]Patients subsequently dose escalated up to 600 mg BID. [c]Patients must have declined 1L systemic therapy. [d]Subjects receiving prior treatment with a KRAS^{G12C} inhibitor not eligible. [e]Subjects receiving prior treatment with a KRAS^{G12C} inhibitor eligible for the Phase 1b adagrasib + cetuximab cohort. [f]Patients who received cetuximab who experienced clinical benefit had the option to continue on adagrasib alone. [g]Cetuximab was administered IV at a dose of 400 mg/m^2 followed by 250 mg/m^2 QW, or 500 mg/m^2 Q2W (Phase 1b). [h]Trial is registrational. [i]KRAS^{G12C} mutation detected in tumor tissue and/or blood. [j]Patients who have stable disease compared to baseline measurements at week 13 or later during treatment with single agent adagrasib are eligible to cross over to adagrasib + cetuximab combination cohort. ClinicalTrials.gov. NCT03785249.

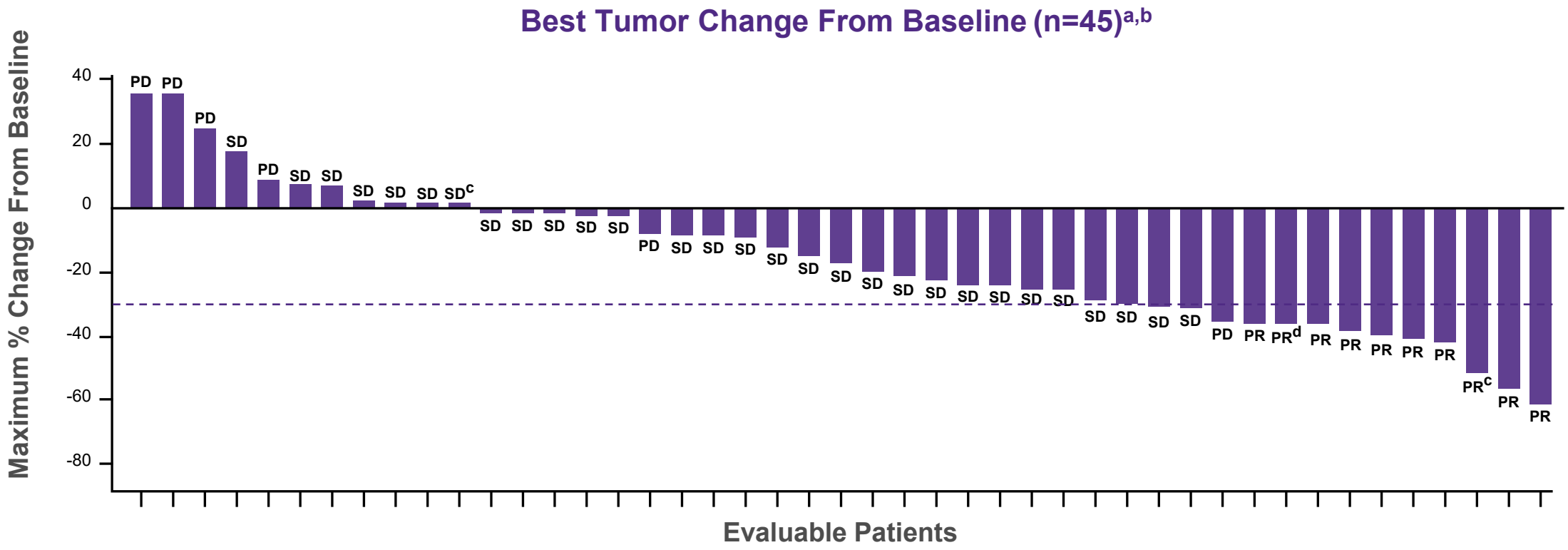
Demographics and Baseline Characteristics

	Adagrasib Monotherapy[a] (n=46)	Adagrasib + Cetuximab[b] (n=32)
Median age, y (range)	58 (29-79)	60 (41-74)
Female, n (%)	23 (50%)	17 (53%)
Race, n (%)		
White	35 (76%)	26 (81%)
Black	6 (13%)	4 (13%)
Asian	3 (7%)	2 (6%)
Other	2 (4%)	0 (0%)
ECOG PS, n (%)		
0	23 (50%)	14 (44%)
1	23 (50%)	18 (56%)
Prior lines of systemic anticancer therapy, median (range)	3 (1-10)	3 (1-8)
Prior lines of systemic anticancer therapy, %		
1/2/3/≥4	20%/26%/20%/35%	9%/25%/34%/31%
Prior systemic anticancer therapy, %		
Fluoropyrimidine/oxaliplatin/irinotecan	100%/98%/80%	100%/100%/88%
Anti-VEGF	83%	84%
Anti-EGFR biological therapy	2%	0%
Regorafenib and/or trifluridine/tipiracil	22%	19%
Molecular status, n (%)[c]		
BRAF V600E	0/44 (0%)	0/30 (0%)
MSI-H or dMMR	1/35 (3%)	0/19 (0%)
EGFR amplification	1/35 (3%)	1/28 (4%)
TP53	23/34 (68%)	18/26 (69%)
PIK3CA	5/36 (14%)	3/26 (12%)

[a]Adagrasib monotherapy was administered at a dose of 600 mg BID. [b]Adagrasib was administered at a dose of 600 mg BID. Cetuximab was administered IV at a dose of 400 mg/m^2 followed by 250 mg/m^2 QW, or 500 mg/m^2 Q2W (Phase 1b). [c]Molecular status includes patients with conclusively evaluable test results.

Data as of 25 May 2021 for monotherapy (median follow-up: 8.9 months). Data as of 9 July 2021 for the cetuximab combination (median follow-up: 7 months).

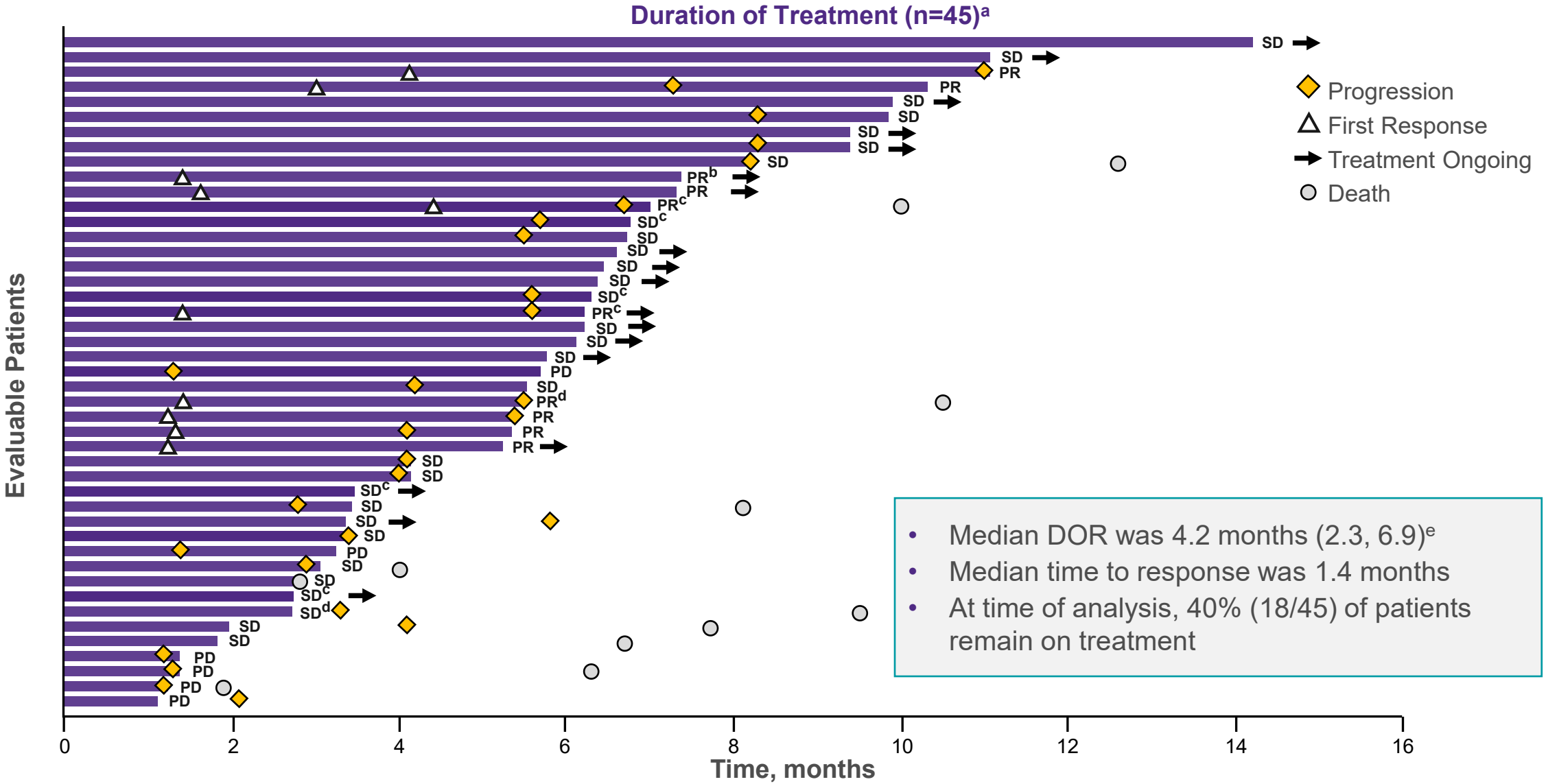
Adagrasib in Patients With Advanced CRC: Best Overall Response



- Response rate was 22% (10/45), including 1 unconfirmed PR
- SD was observed in 64% (29/45) of patients
- Clinical benefit (DCR) was observed in 87% (39/45) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

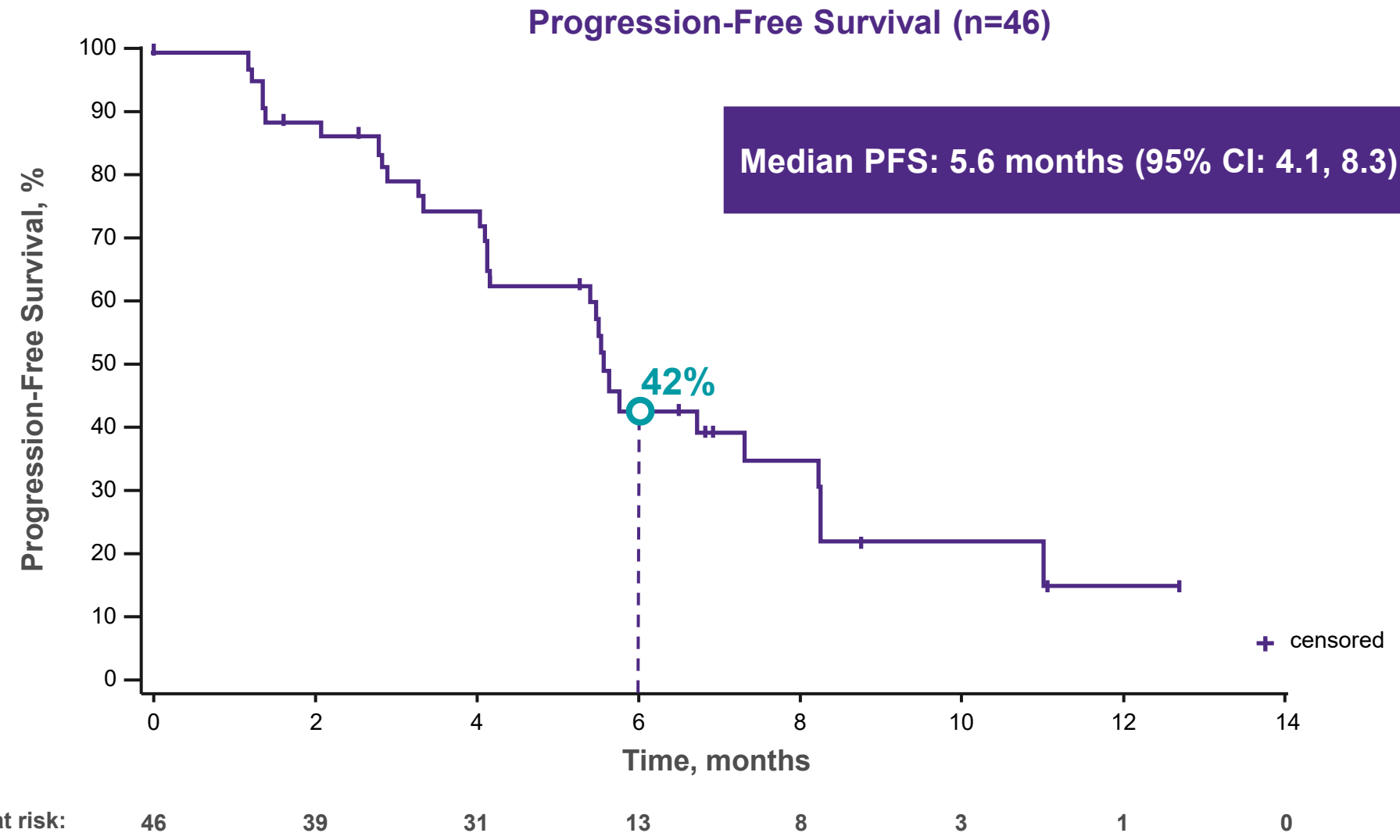
[a]All results are based on investigator assessments. [b]Evaluable population (n=45) excludes 1 patient who withdrew consent prior to the first scan. [c]Phase 1/1b. [d]At the time of the 25 May 2021 data cutoff, the patient had uPR. [e]Molecular status (BRAF V600E mutation, MSI-H or dMMR, EGFR amplification, TP53 mutation, PIK3CA mutation) includes patients with conclusively evaluable test results.
Data as of 25 May 2021 for monotherapy (median follow-up: 8.9 months).

Adagrasib in Patients With Advanced CRC: Duration of Treatment



[a]All results are based on investigator assessments. [b]At the time of the 25 May 2021 data cutoff, the patient had uPR. [c]Patients who crossed over to receive adagrasib + cetuximab. [d]Phase 1/1b. [e]Median duration of response is based on 9 confirmed responses.
Data as of 25 May 2021 for monotherapy (median follow-up: 8.9 months).

Adagrasib in Patients With Advanced CRC: Progression-Free Survival



Data as of 25 May 2021 for monotherapy (median follow-up: 8.9 months).

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Adagrasib in Patients With Advanced CRC: Treatment-Related Adverse Events

Most Frequent TRAEs	Adagrasib Monotherapy[a] (n=46)	
TRAEs,[b,c] %	**Any Grade**	**Grades 3-4**
Any TRAEs	91%	30%
Most frequent TRAEs, %		
Diarrhea	63%	7%
Nausea	57%	0%
Fatigue	46%	4%
Vomiting	46%	0%
Decreased appetite	15%	0%
Peripheral edema	15%	0%
AST increase	13%	4%
QT prolongation	13%	2%
ALT increase	11%	4%
Anemia	11%	2%

- No Grade 5 TRAEs
- No TRAEs that led to discontinuation

[a]Adagrasib monotherapy was administered at a dose of 600 mg BID. [b]Includes events reported between the first dose and 25 May 2021. [c]Occurred in ≥10% of patients.
Data as of 25 May 2021 for monotherapy (median follow-up: 8.9 months).

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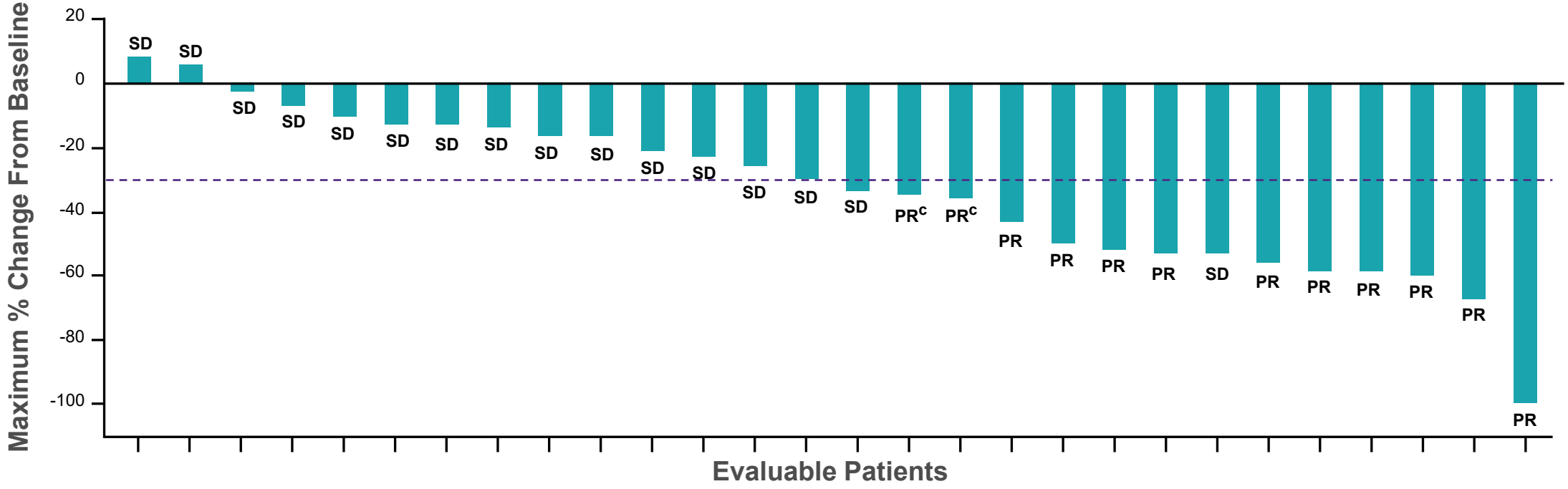
Adagrasib + Cetuximab in Patients With Advanced CRC: Best Overall Response

Best Tumor Change From Baseline (n=28)[a,b]

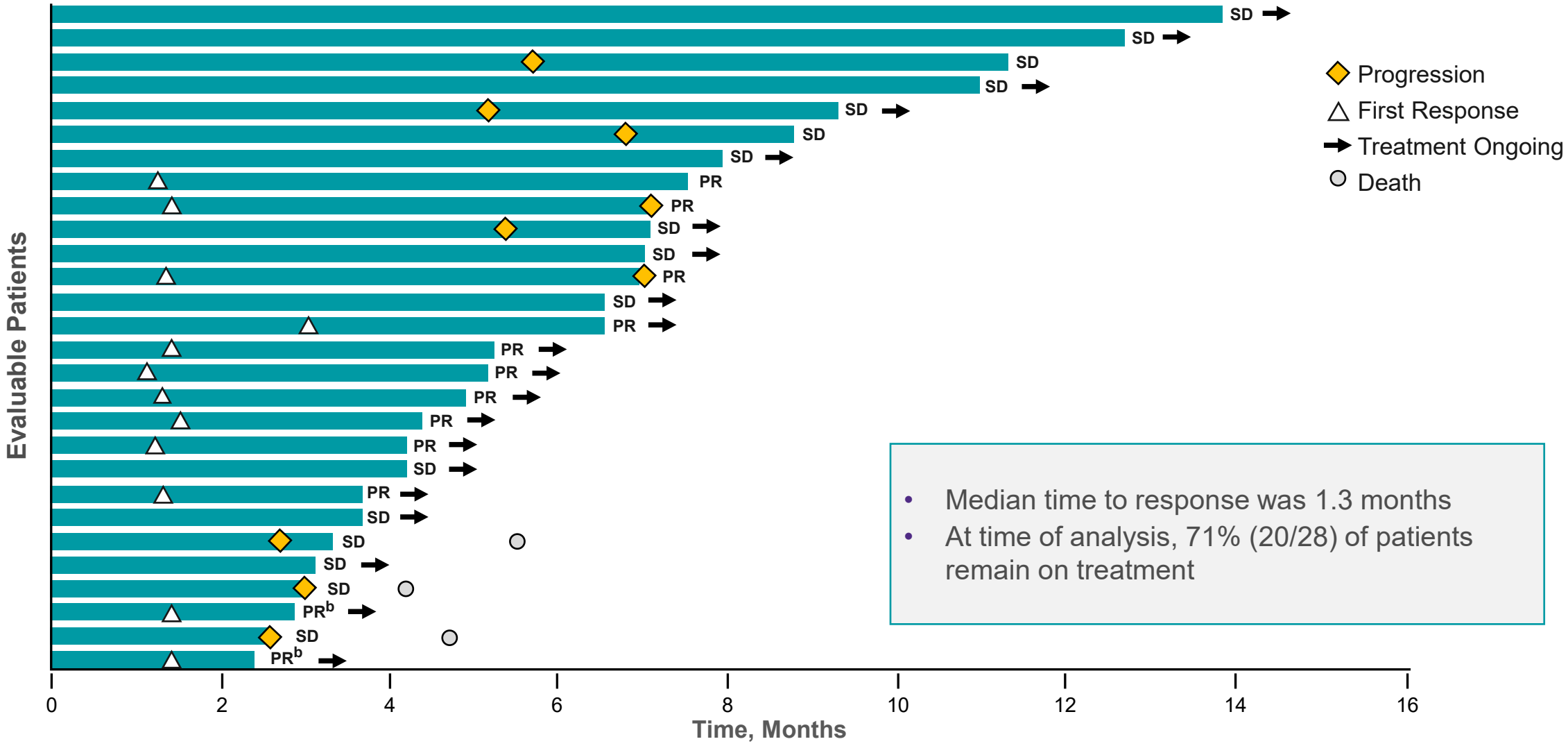


- Response rate was 43% (12/28), including 2 unconfirmed PRs
- SD was observed in 57% (16/28) of patients
- Clinical benefit (DCR) was observed in 100% (28/28) of patients
- No apparent association between response rate and molecular status was shown in an exploratory analysis[e]

[a]All results are based on investigator assessments. [b] Evaluable population (n=28) excludes 4 patients who withdrew consent prior to the first scan. [c]At the time of the 9 July 2021 data cutoff, 2 patients had uPRs.
[e]Molecular status (BRAF V600E mutation, MSI-H or dMMR, EGFR amplification, TP53 mutation, PIK3CA mutation) includes patients with conclusively evaluable test results.
Data as of 9 July 2021 (median follow-up: 7 months).

Adagrasib + Cetuximab in Patients With Advanced CRC: Duration of Treatment

Duration of Treatment (n=28)[a]



- Median time to response was 1.3 months
- At time of analysis, 71% (20/28) of patients remain on treatment

[a]All results are based on investigator assessments. [b]At the time of the 9 July 2021 data cutoff, 2 patients had uPRs.
Data as of 9 July 2021 (median follow-up: 7 months).

Adagrasib + Cetuximab in Patients With Advanced CRC: Treatment-Related Adverse Events

Most Frequent TRAEs	Adagrasib + Cetuximab[c] (n=32)	
TRAEs,[a,b] %	**Any Grade**	**Grades 3-4**
Any TRAEs	100%	16%
Most frequent TRAEs, %		
Nausea	63%	0%
Diarrhea	56%	3%
Vomiting	50%	0%
Fatigue	47%	0%
Dermatitis acneiform	44%	3%
Dry skin	38%	0%
Headache	28%	0%
Rash maculopapular	22%	0%
Dyspepsia	19%	0%
Infusion-related reaction	19%	3%
Peripheral edema	19%	0%
Rash	19%	0%
Stomatitis	19%	3%
Decreased appetite	16%	0%
Dizziness	16%	0%
QT prolongation	16%	3%
ALT increase	13%	0%
Dyspnea	13%	0%
Hypomagnesemia	13%	0%

- No Grade 5 TRAEs
- 6% (n=2) of TRAEs led to discontinuation of treatment[d]

[a]Includes events reported between the first dose and 9 July 2021. [b]Occurred in ≥10% of patients. [c]Adagrasib was administered at a dose of 600 mg BID + cetuximab was administered IV at a dose of 400 mg/m^2 followed by 250 mg/m^2 QW, or 500 mg/m^2 Q2W. [d]TRAEs leading to discontinuation were grade 2 treatment-related malaise and grade 2 cetuximab-related infusion-related reaction.
Data as of 9 July 2021 (median follow-up: 7 months).

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Summary

- Adagrasib is a KRAS^{G12C}-selective covalent inhibitor with a long half-life that enables exposure above a target threshold throughout the dosing interval
- Adagrasib monotherapy demonstrated promising clinical activity (response rate 22%) and broad disease control (DCR 87%) in heavily pretreated patients with CRC harboring a KRAS^{G12C} mutation
- Adagrasib + cetuximab showed encouraging clinical activity (response rate 43%; DCR 100%) in heavily pretreated patients with CRC harboring a KRAS^{G12C} mutation
- Adagrasib is tolerable and has a manageable safety profile, both as monotherapy and combined with cetuximab
- Adagrasib + cetuximab is being evaluated in the 2L setting in KRYSTAL-10, a Phase 3 trial (NCT04793958) in patients with KRAS^{G12C}-mutant mCRC

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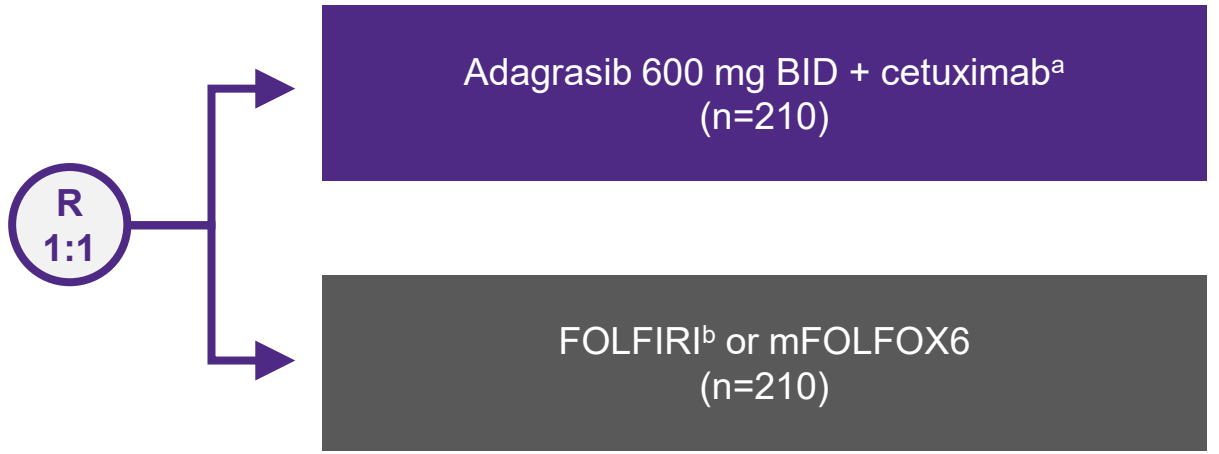
KRYSTAL-10 (849-010): Phase 3 Randomized, Open-Label Trial of 2L Adagrasib + Cetuximab vs Chemotherapy in mCRC With KRAS^{G12C} Mutation

Key Eligibility Criteria

- Histologically confirmed diagnosis of advanced or metastatic CRC
- Confirmed KRAS^{G12C} mutation in tumor tissue
- Progression on 1L fluoropyrimidine-based regimen containing oxaliplatin or irinotecan



Anti-VEGF/VEGFR allowed per investigator discretion in comparator arm

Outcome Measures

Primary: PFS, OS

Secondary: 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).
ClinicalTrials.gov NCT04793958.

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Abbreviations

5-FU, fluorouracil
1L, first line
2L, second line
ALT, alanine aminotransferase
AST, aspartate aminotransferase
BID, twice daily
CRC, colorectal cancer
CDx, cell line derived xenograft
CI, confidence interval
DCR, disease control rate
dMMR, deficient mismatch repair
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
IV, intravenous
LV, leucovorin
MAPK, mitogen-activated protein kinase
MEK, mitogen-activated protein kinase kinase
mCRC, metastatic colorectal cancer
MSI-H, microsatellite instability high
MTD, maximum tolerated dose
mFOLFOX6, modified FOLFOX6 (folinic acid [leucovorin], fluorouracil, oxaliplatin)
NSCLC, non–small-cell lung cancer
ORR, objective response rate
OS, overall survival
PD, progressive disease
PDX, patient-derived xenograft
PFS, progression-free survival
PK, pharmacokinetics
PR, partial response
PROs, patient-reported outcomes
PS, performance status
QD, once daily
QW, every week
Q2W, every 2 weeks
R, randomized
RAF, rapidly accelerating sarcoma
RECIST, Response Evaluation Criteria in Solid Tumors
RP2D, recommended Phase 2 dose
SD, stable disease
SHP2, Src homology phosphatase 2
STK11, serine/threonine kinase 11
TRAE, treatment-related adverse event
uPR, unconfirmed partial response
VEGF, vascular endothelial growth factor
VEGFR, vascular endothelial growth factor receptor