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KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients With Colorectal Cancer (CRC) and Other Solid Tumors Harboring a KRAS^{G12C} Mutation

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Disclosures

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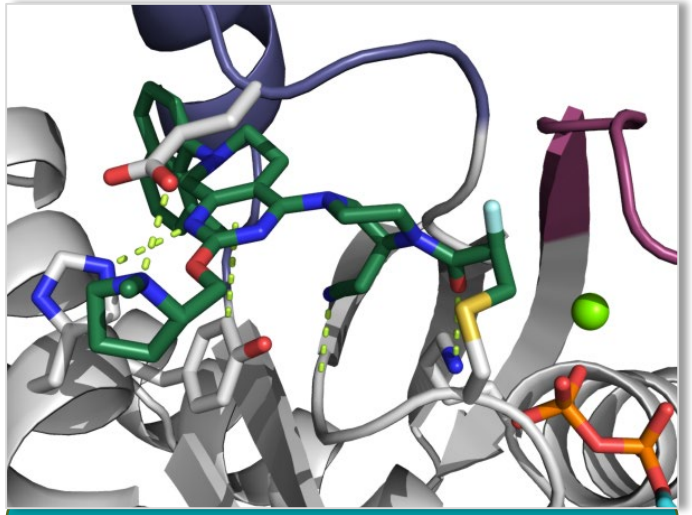
Adagrasib (MRTX849) Is a Differentiated and Selective Inhibitor of KRAS^{G12C}

- KRAS^{G12C} mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinoma), 3-4% of CRC, and 1-2% of several other cancers[1-3]
- The KRAS protein cycles between GTP-On and GDP-Off states and has a protein resynthesis half-life of ~24 h[4,5]
- Adagrasib is a covalent inhibitor of KRAS^{G12C} that irreversibly and selectively binds KRAS^{G12C} in its inactive, GDP-bound state[6]
- Adagrasib was optimized for desired properties of a KRAS^{G12C} inhibitor:
  - Potent covalent inhibitor of KRAS^{G12C} (cellular IC_{50}: ~5 nM)
  - High selectivity (>1000X) for the mutant KRAS^{G12C} protein vs wild-type KRAS
  - Favorable PK properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution



Adagrasib Crystal Structure

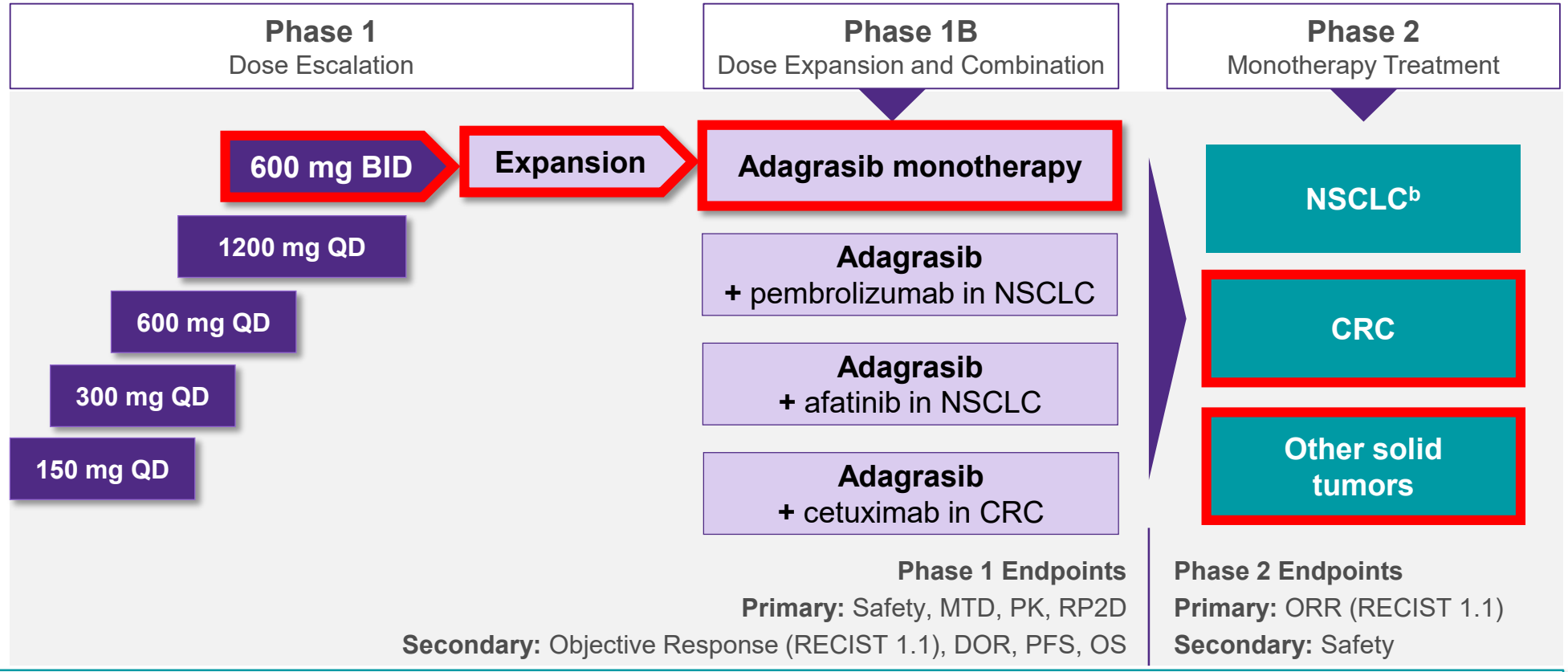
Hypothesis: Maintaining continuous exposure of adagrasib above a target threshold enables inhibition of KRAS-dependent signaling for the complete dose interval and maximizes depth and duration of antitumor activity

1. Zehir A, Benayed R, Shah RH, et al. *Nat Med*. 2017;23(6):703–713. 2. Schirripa M, Nappo F, Cremolini C, et al. *Clin Colorectal Cancer*. 2020;S1533-0028(20)30067-0. 3. NIH TCGA: The Cancer Genome Atlas. 4. Bos JL, Rehmann H, Wittinghofer A. *Cell*. 2007;129: 865-877. 5. Shukla S, Allam US, Ahsan A, et al. *Neoplasia*. 2014;16(2):115-128; 6. Hallin J, Engstrom LD, Hargis L, et al. *Cancer Discov*. 2020;10(1): 54-71.

KRYSTAL-1 (849-001) Study Design

Key Eligibility Criteria
Up to n=391

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



- Previously reported data from Phase 1 demonstrated clinical activity with adagrasib (MRTX849) in patients with pretreated KRAS^{G12C} CRC and NSCLC
- 600 mg BID was chosen as the RP2D
- Here we report data for 31 patients, evaluating adagrasib 600 mg BID in patients with previously treated CRC (n=24)[c] or other solid tumors (n=7); median follow-up, 4.3 mo for patients with CRC and not calculated for patients with other solid tumors
- Data as of 30 August 2020

[a]For Phase 2 NSCLC cohorts, patients must have received prior treatment with platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. [b]CRC/other solid tumor cohort eligibility based on tissue or plasma test; KRAS^{G12C} testing for entry was performed locally or centrally using a sponsor preapproved test. [c]CRC=Phase 1/1b (n=2) and Phase 2 (n=22); ClinicalTrials.gov. NCT03785249.

Patient Demographics and Baseline Characteristics

	CRC (Pooled), 600 mg BID (n=24)	"Other" Cohort, 600 mg BID (n=7)
Median age, y (range)	59 (37-79)	64 (25-80)
Female, n (%)	12 (50%)	2 (29%)
Race, n (%)		
White	18 (75%)	5 (71%)
Black	4 (17%)	0 (0%)
Asian	2 (8%)	1 (14%)
Other	0 (0%)	1 (14%)
ECOG PS, n (%)		
0	9 (38%)	0 (0%)
1	15 (63%)	7 (100%)
Tumor type, n (%)		
CRC	24 (100%)	
Pancreatic ductal adenocarcinoma		2 (29%)
Cholangiocarcinoma		1 (14%)
Endometrial cancer		1 (14%)
Ovarian cancer		1 (14%)
Appendiceal cancer		2 (29%)
Prior lines of anticancer therapy, median (range)	4 (1-9)	2 (1-5)

Data as of 30 August 2020. Pooled includes Phase 1/1b (n=2) and Phase 2 (n=22) 600 mg BID.

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Incidence of Treatment-Related Adverse Events

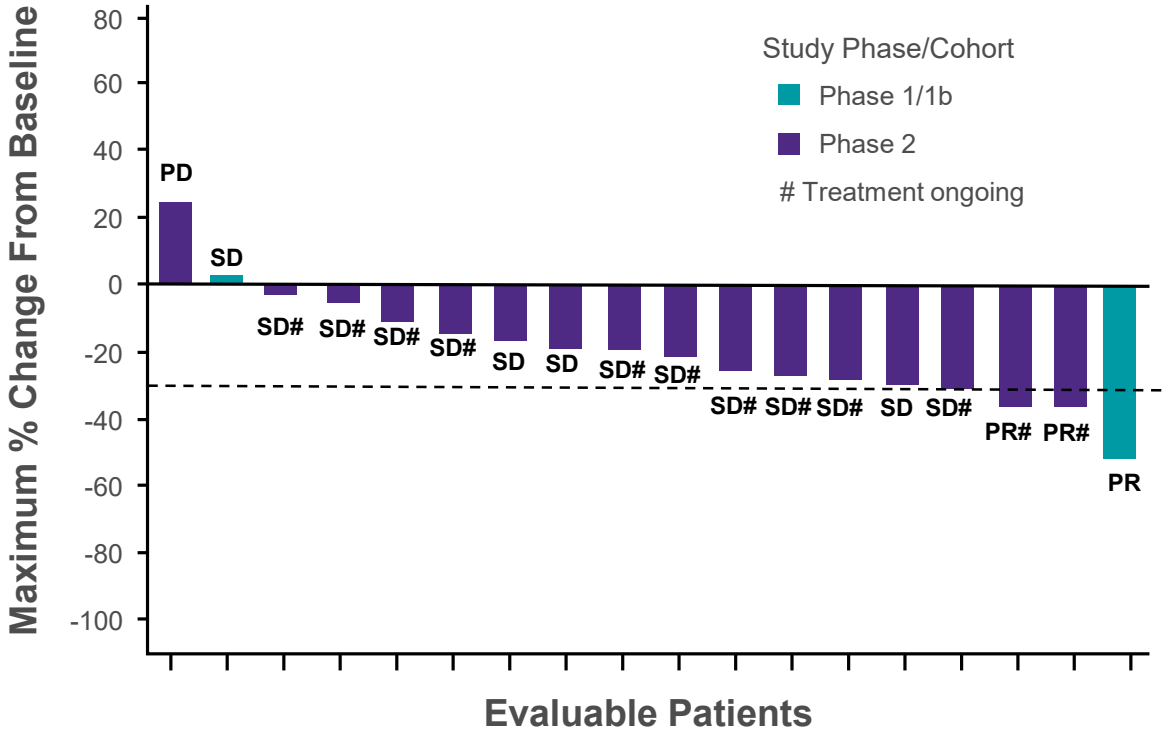
	All Cohorts Pooled, 600 mg BID[a] (n=110)		
TRAEs[b,c], %	**Any Grade**	**Grades 3-4**	**Grade 5**
Any TRAEs	85%	30%	2%
Most frequent TRAEs[a,d], %			
Nausea	54%	2%	0%
Diarrhea	51%	0%	0%
Vomiting	35%	2%	0%
Fatigue	32%	6%	0%
Increased ALT	20%	5%	0%
Increased AST	17%	5%	0%
Increased blood creatinine	15%	0%	0%
Decreased appetite	15%	0%	0%
QT prolongation	14%	3%	0%
Anemia	13%	2%	0%

- Grade 5 TRAEs included pneumonitis in a patient with recurrent pneumonitis (n=1) and cardiac failure (n=1)
- 7.3% of TRAEs led to discontinuation

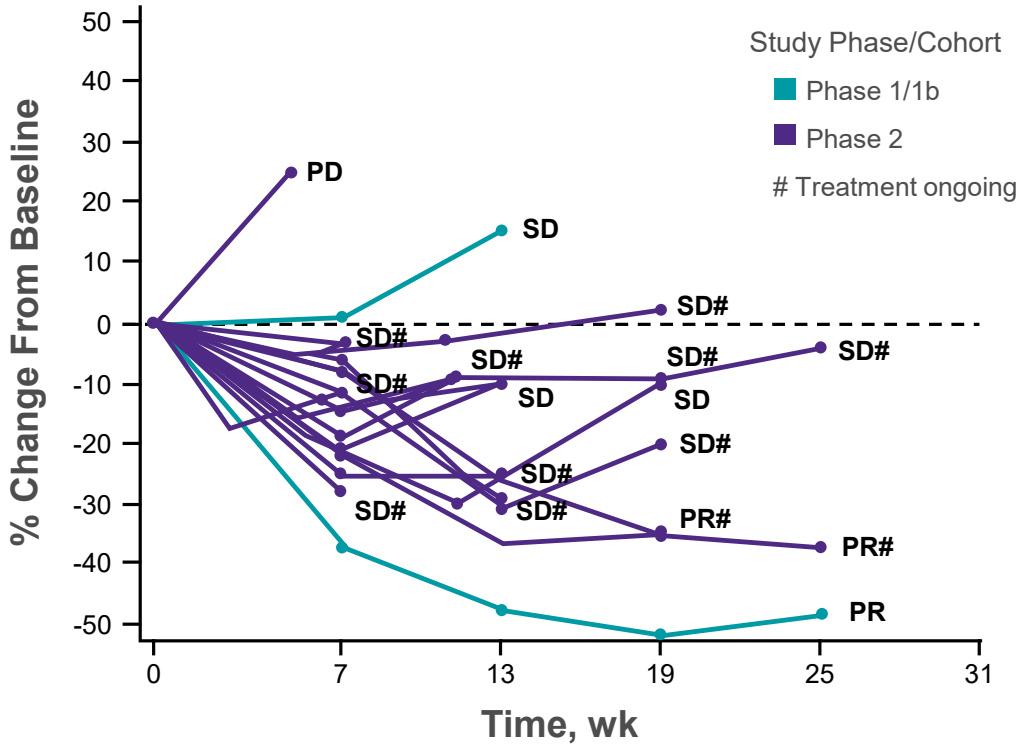
[a]Includes patients pooled from Phase 1/1b and Phase 2 NSCLC (n=79), and CRC and Phase 2 other tumor cohorts (n=31). [b]Includes events reported between first dose and 30 August 2020. [c]The most common treatment-related SAEs (2 patients each) reported were diarrhea (grade 1, grade 2) and hyponatremia (both grade 3). [d]Occurred in ≥10%. Data as of 30 August 2020.

Adagrasib in Patients With CRC: Best Overall Response and Disease Control Rate

Best Tumor Change from Baseline[a]



Change in Sum of Target Lesion Over Time[a]



- Confirmed ORR 17% (3/18) of patients; SD 78% (14/18)
- Disease control observed in 94% (17/18) of patients

[a]All results based on investigator assessments.
Data as of 30 August 2020. Pooled includes Phase 1/1b and Phase 2 600 mg BID.

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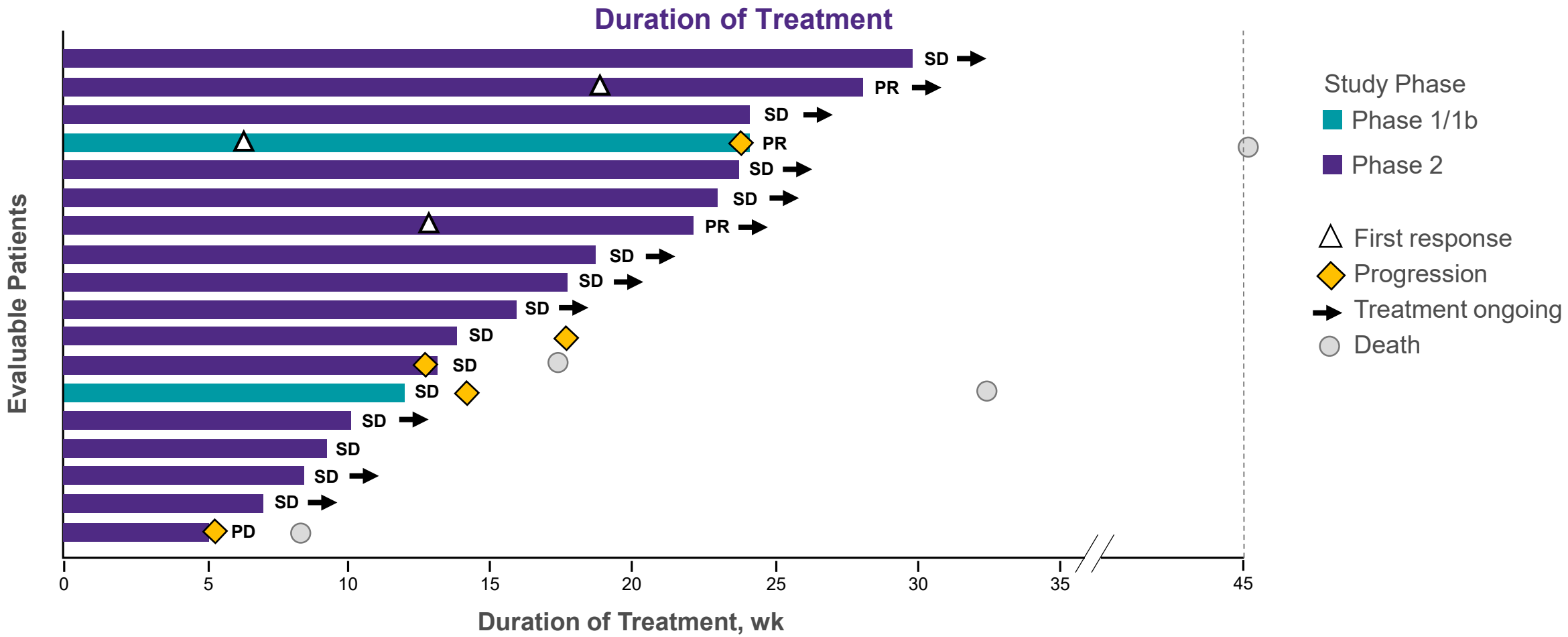
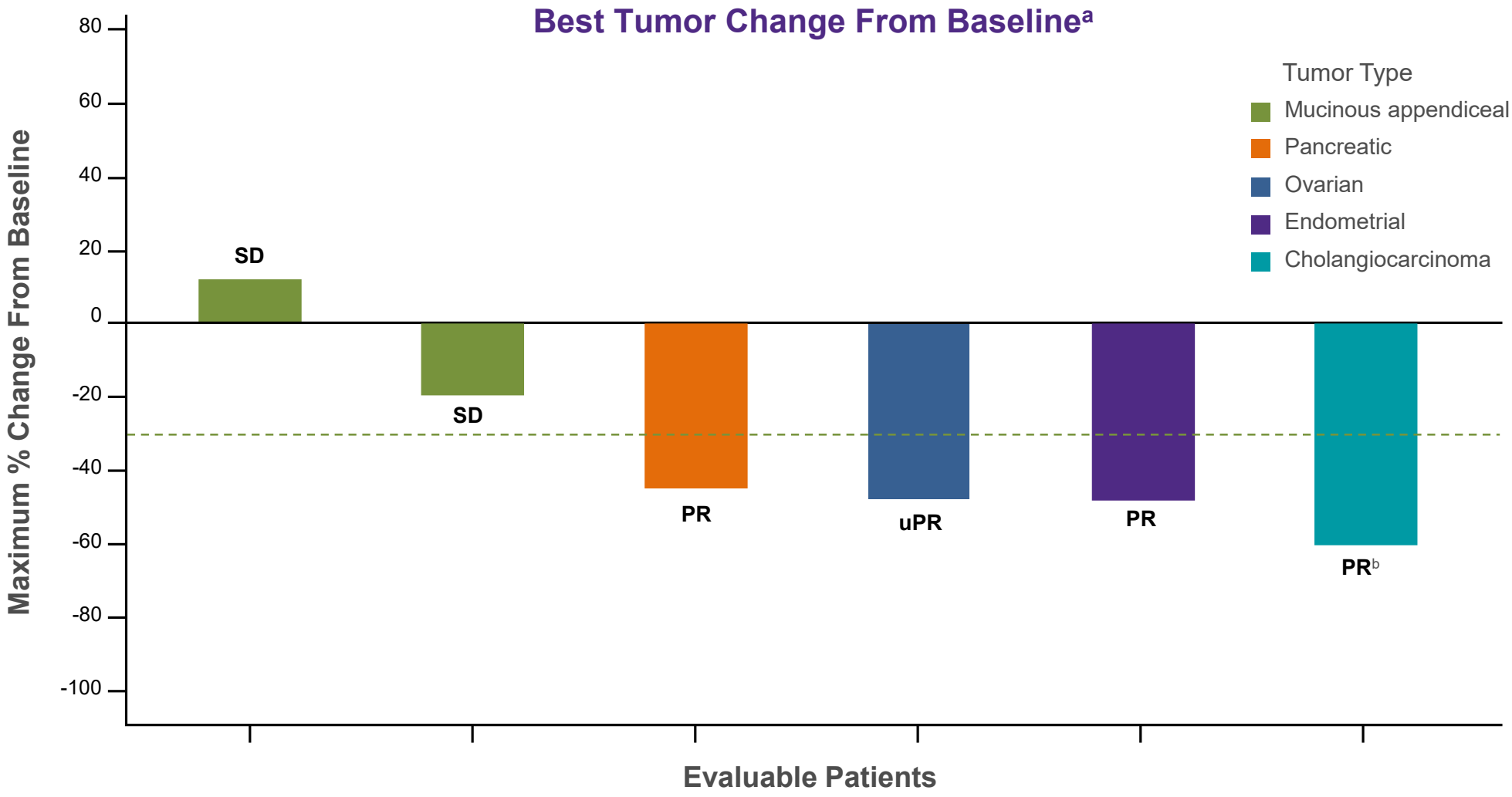
Adagrasib in Patients With Advanced CRC: Duration of Treatment



- Median time to response 12.9 wk
- At time of analysis, 67% (12/18) of patients remain on treatment
- 55% (10/18) of patients have been on treatment for ≥4 mo

Data as of 30 August 2020. Pooled includes Phase 1/1b and Phase 2 600 mg BID.

Adagrasib in Patients With Other Advanced Solid Tumors: Best Overall Response



[a]All results based on investigator assessments. [b]At the time of the 30 August 2020 data cut off, the cholangiocarcinoma patient had unconfirmed PR; the response was subsequently confirmed by scans that were performed after the 30 August 2020 data cut off.
Data as of 30 August 2020. All patients treated at 600 mg BID.

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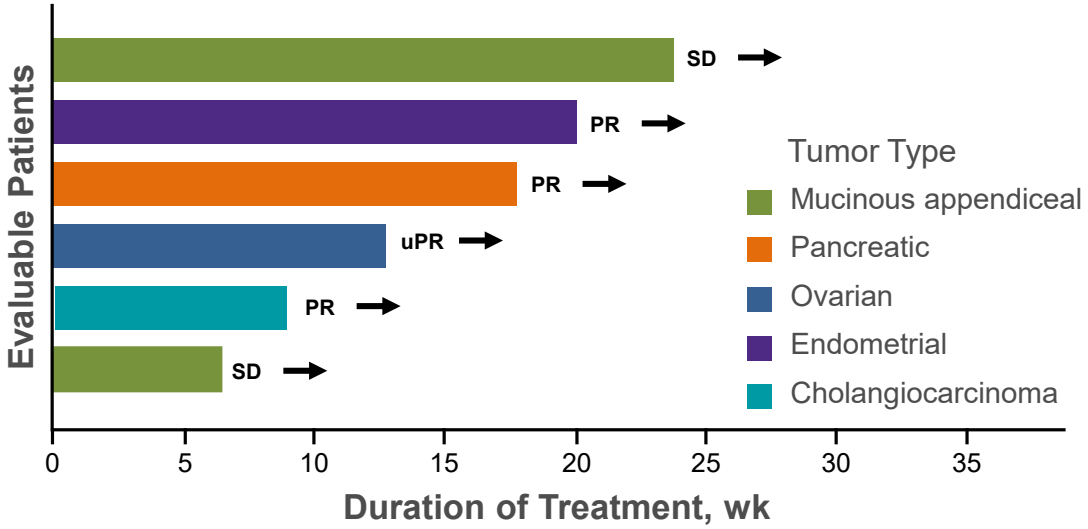
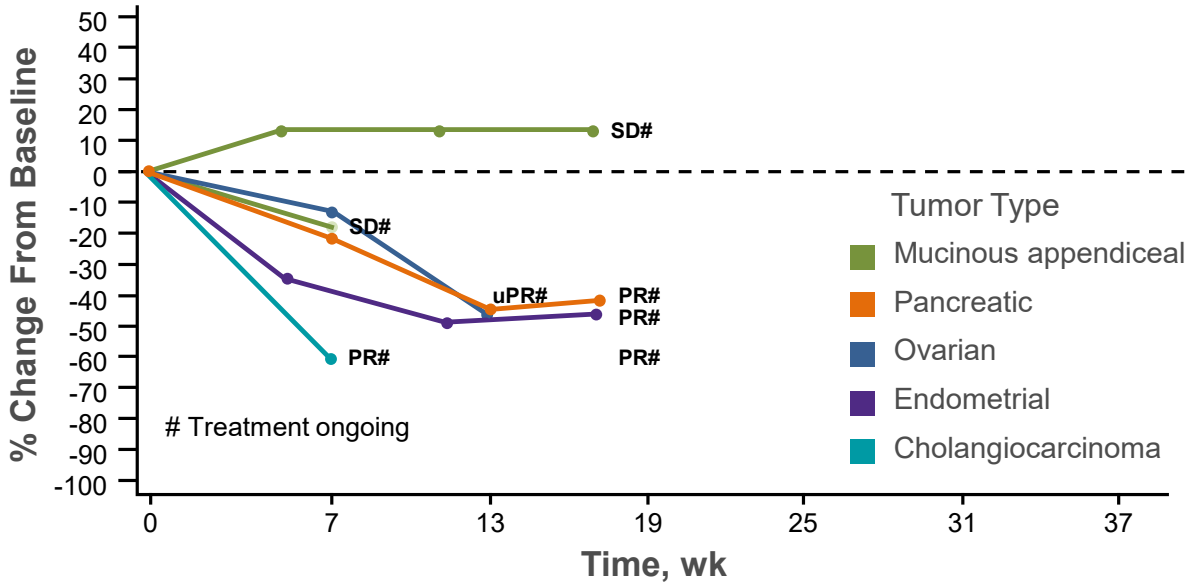
Adagrasib in Patients With Other Advanced Solid Tumors: Duration of Treatment

Duration of Treatment



Change in Sum of Target Lesion Over Time



- All patients remain on treatment

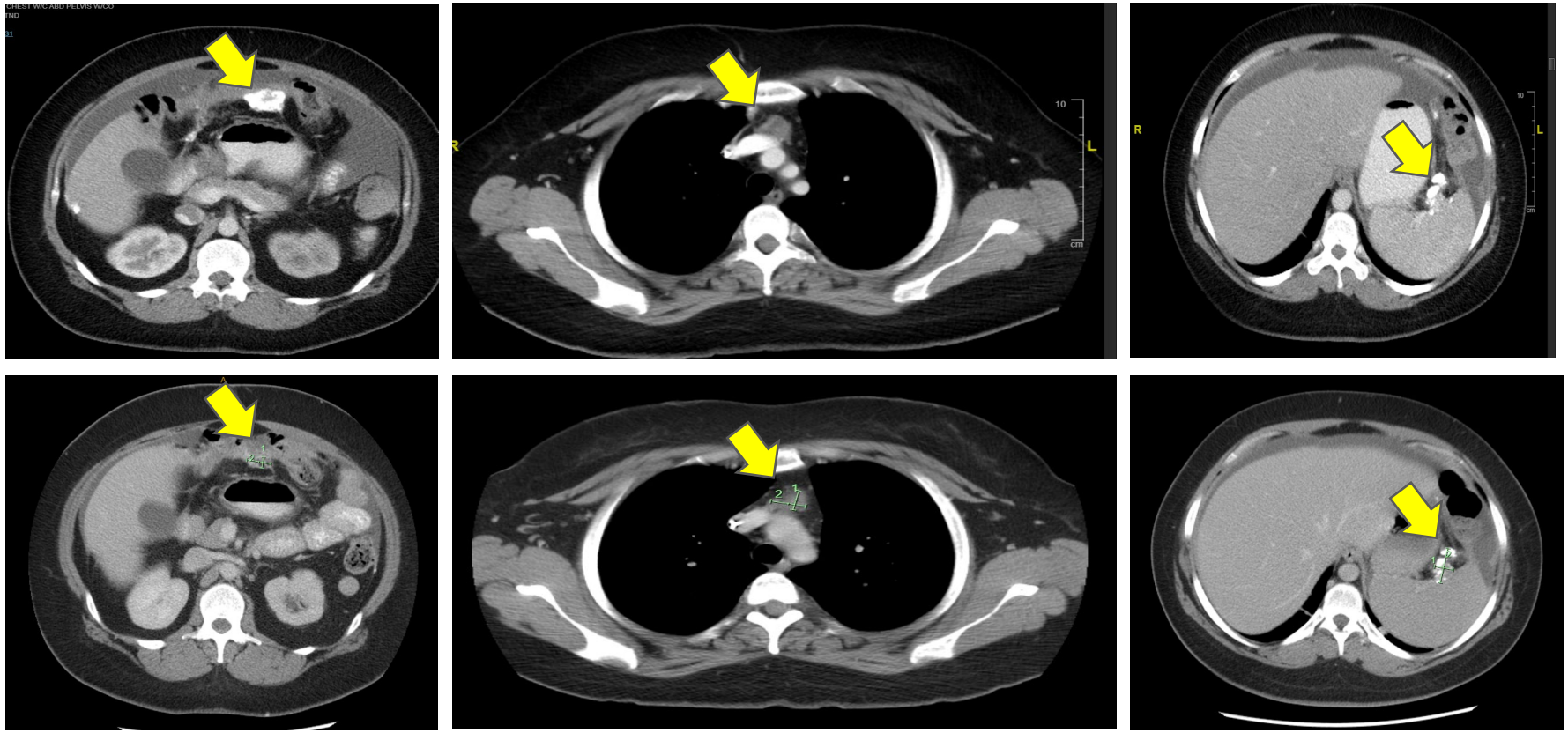
Data as of 30 August 2020. All patients treated at 600 mg BID.

Patient Case: Ovarian Cancer

Baseline

Adagrasib 600 mg BID

Scan 2, uPR (-46%) August 2020

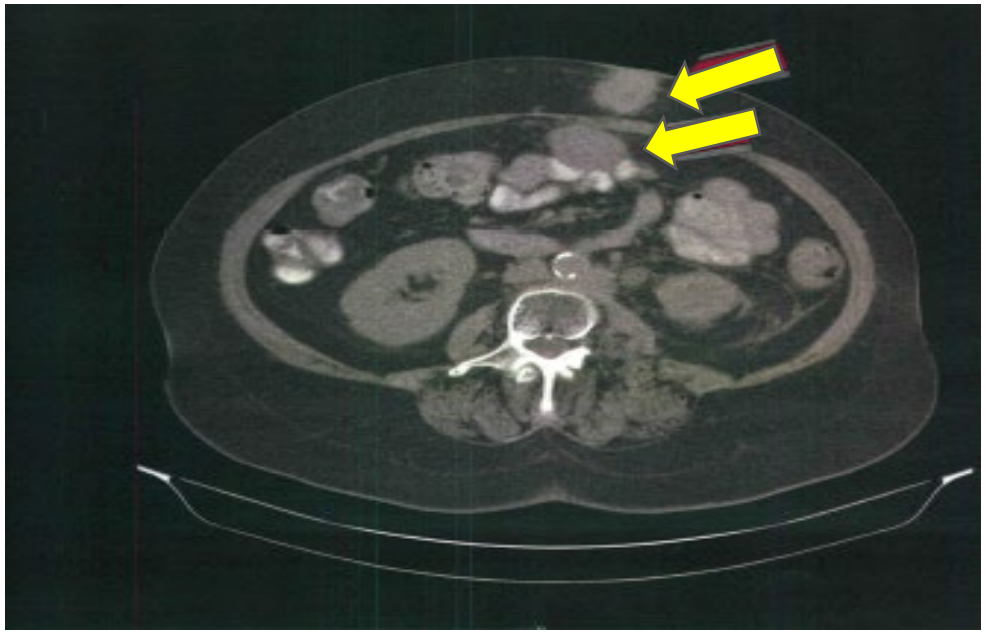


- **25-year-old female**
- **Ovarian cancer diagnosed June 2019**
- **Treatment history**
  - TAH/BSO, July 2019
  - Adjuvant carboplatin/docetaxel/bevacizumab, August-December 2019
  - Letrozole, January-May 2020
- **TRAEs:** Grade 1 peripheral edema
- **Currently on cycle 6**

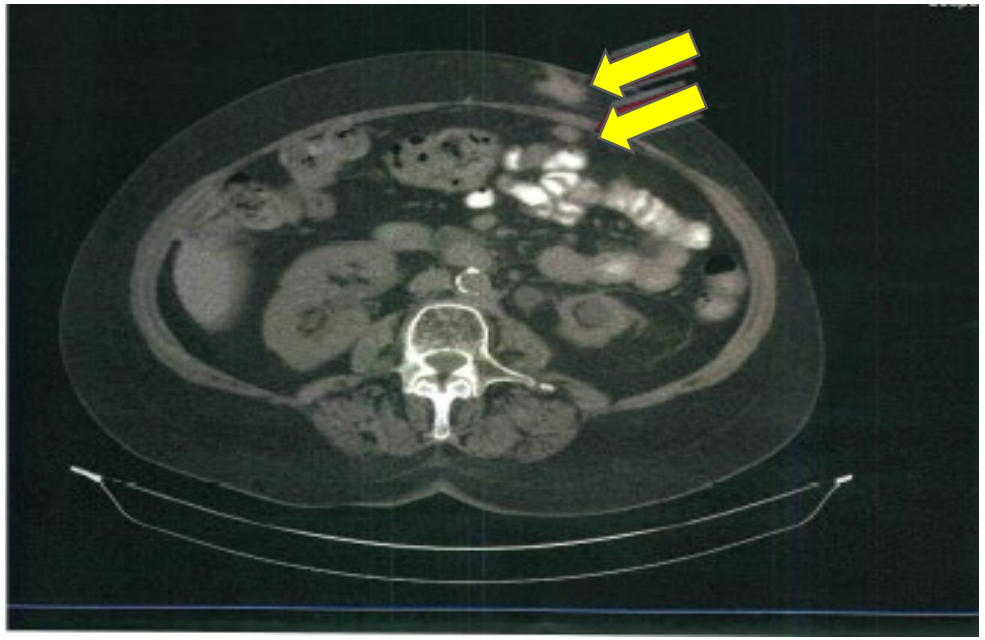
Data as of 25 September 2020.

Patient Case: Endometrial Cancer

Baseline
17 March 2020



Adagrasib 600 mg BID, End of Cycle 6
PR (-46%)



- **63-year-old female**
- **Endometrial cancer diagnosed June 2016**
- **Treatment history**
  - TAH/BSO June 2016
  - Carboplatin/paclitaxel, October 2016-June 2017
  - Local radiation, April-June 2017
  - Investigational agent (tinostamustine), March-October 2019
  - Pelvic radiation, March 2020

- **Molecular analysis by expanded NGS panel**
  - KRAS^{G12C}, PTEN^{R130Q}, PTEN^{T319fs}
  - MSS (microsatellite stable) and p53 WT

- **TRAEs**
  - Grade 1 vomiting

- **Currently in cycle 8**

Data as of 25 September 2020.

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Conclusions

- Adagrasib is a KRAS^{G12C}-selective covalent inhibitor with a long half-life, and extensive predicted target coverage throughout the dosing interval
- Adagrasib is well tolerated
- Adagrasib provides durable benefit to patients with CRC harboring KRAS^{G12C} mutations
  - Durable responses were observed
  - Broad disease control rate was observed
- Adagrasib demonstrated clinical activity in various KRAS^{G12C}-mutated solid tumors, including pancreatic, ovarian, and endometrial cancers, and cholangiocarcinoma
- Enrollment in the CRC and other solid tumor monotherapy Phase 2 cohorts is ongoing
- Evaluation of adagrasib in combination with cetuximab (CRC) at full dose of each agent is ongoing[a]; a Phase 3 trial of adagrasib in combination with cetuximab is planned

Durable responses observed in NSCLC (n=23/51; 45%); See Jänne PA et al., abstract LBA-03.

[a]ClinicalTrials.gov. NCT03785249

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Abbreviations

ALT = alanine aminotransferase

AST = aspartate aminotransferase

BID = twice daily

CRC = colorectal cancer

DCR = disease control rate

DOR = duration of response

ECOG = Eastern Cooperative Oncology Group

MTD = maximum tolerated dose

nM = nanomolar

NSCLC = non–small-cell lung cancer

ORR = objective response rate

OS = overall survival

PD = progressive disease

PFS = progression-free survival

PK = pharmacokinetics

PR = partial response

PS = performance status

QD = once daily

RP2D = recommended Phase 2 dose

SAE = serious adverse event

SD = stable disease

TAH/BSO = total abdominal hysterectomy with bilateral salpingo-oophorectomy

TRAE = treatment-related adverse event

uPR = unconfirmed partial response