Phase 1 monotherapy dose escalation of RGX-202, a first-in-class oral inhibitor of the SLC6a8/CKB pathway, in patients with advanced gastrointestinal (GI) solid tumors

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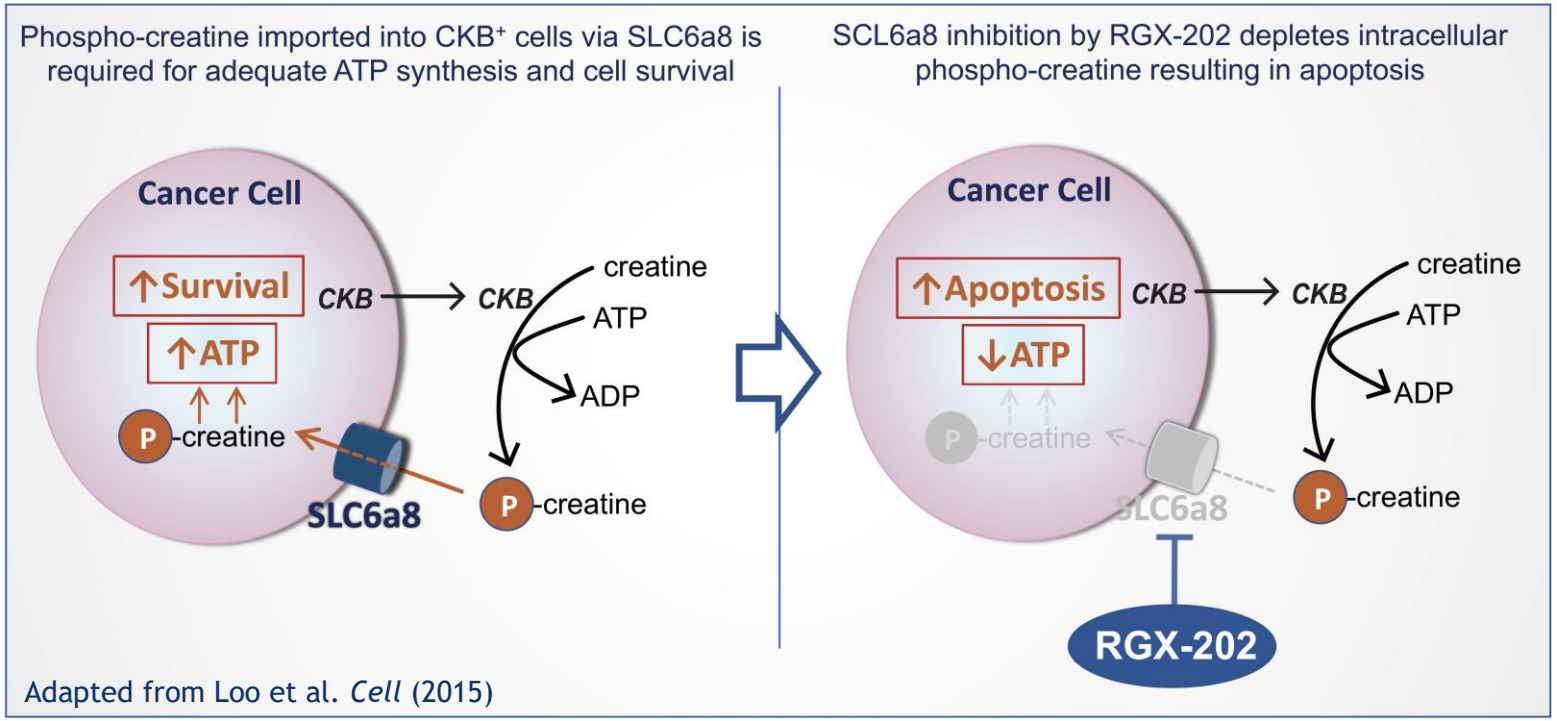
RGX-202 is a first-in-class oral inhibitor of the SLC6a8/CKB pathway

- Approximately 65% of colorectal cancer patients have Creatine Kinase-B (CKB) expressing tumors[1]
- CKB$^+$ cancer cells rely on phospho-creatine to generate ATP to support cell survival in the metastatic niche[2]
- Phospho-creatine is imported into CKB$^+$ cancer cells via the creatine transporter SLC6a8[2]
- RGX-202 is an oral small molecule inhibitor of SLC6a8 that induces cancer cell apoptosis[3]
- KRAS-driven metabolic demand confers susceptibility to RGX-202 in KRAS mutant CRC



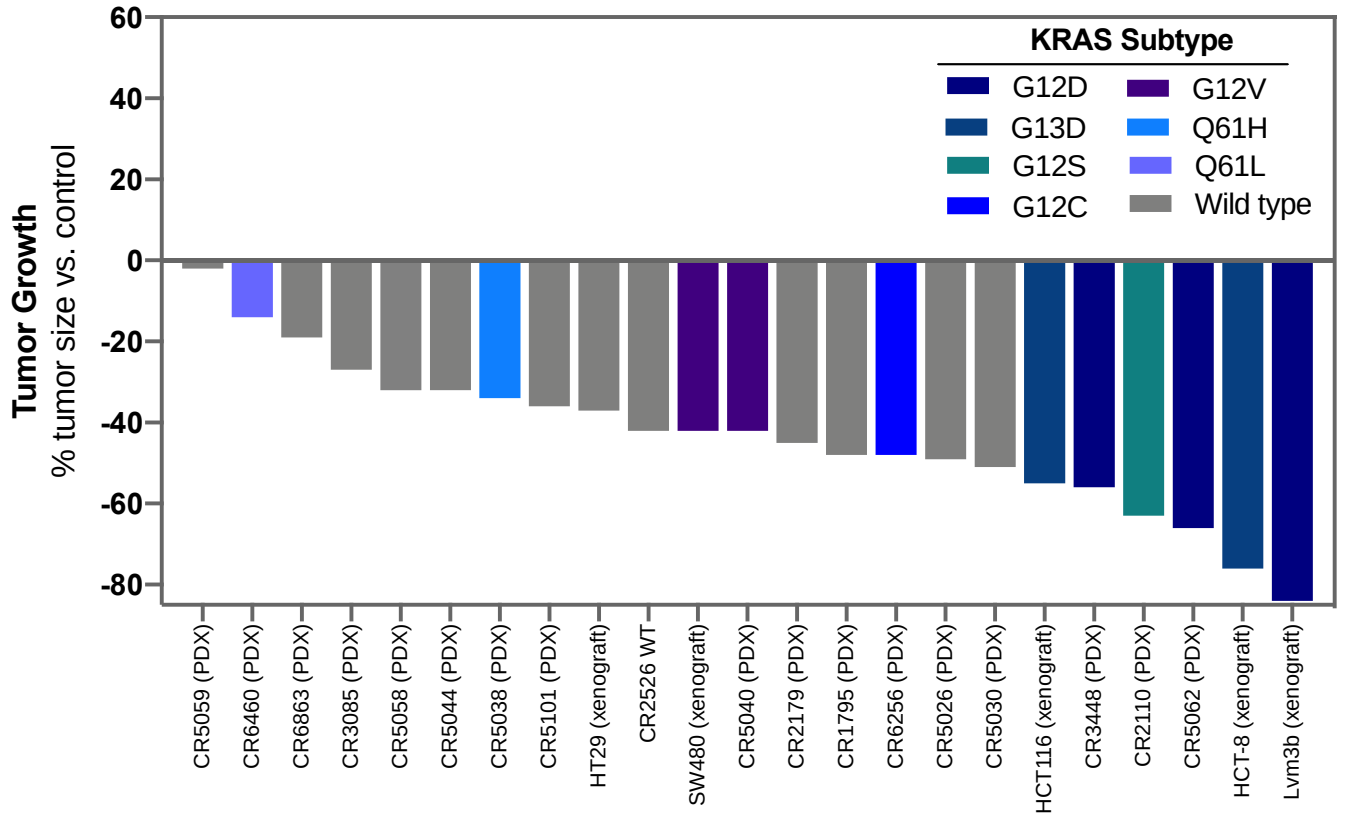
[1]RGENIX unpublished data
[2]Loo JM et al. *Cell*. 2015 Jan 29;160(3):393-406
[3]Kurth I et al. *AACR* 2018

RGX-202 has broad activity across KRAS subtypes in CKB^{+} CRC models

- RGX-202 has single agent activity in CKB^{+} human CRC xenograft, PDX, and murine syngeneic models[1]
- Activity is observed across KRAS subtypes (figure on right)
- RGX-202 enhances the activity of chemotherapy (5FU/irinotecan) in murine models[1]

[1]Kurth et al. *AACR* (2018)

RGX-202 *in vivo* activity in CKB^{+} human CRC xenografts and PDX models



Tumor growth measured versus control (negative values correspond to tumor growth inhibition). PDX experiments conducted by Crown Biosciences. CKB^{+} as defined by ≥5% CKB TPS (tumor IHC).

Study Design

- Standard 3 + 3 Dose Escalation
- Starting Dose was 600mg PO BID
- Tumor measurements and disease response assessments – RECIST 1.1
  - to be performed approximately every 8 weeks (q2cycles)
  - at week 24, may be done every 16 weeks thereafter
- DLT period of assessment through Cycle 1 completion (28 days)

Phase 1 Dose Escalation Objectives

- Primary safety objective; identify the maximum tolerated dose (MTD)
  - or the maximum tested dose without multiple dose-limiting toxicities (DLTs)
- Primary efficacy objective; estimate the antitumor activity by RECIST 1.1
- Secondary objectives; evaluate the pharmacokinetic (PK) profile and potential metabolites.
- Exploratory Objectives:
  - Evaluate the tumor expression of CKB and other creatine metabolism markers
  - Evaluate pharmacodynamic markers including creatine, creatinine, and guanidinoacetate (GAA),

Key Inclusion and Exclusion Criteria

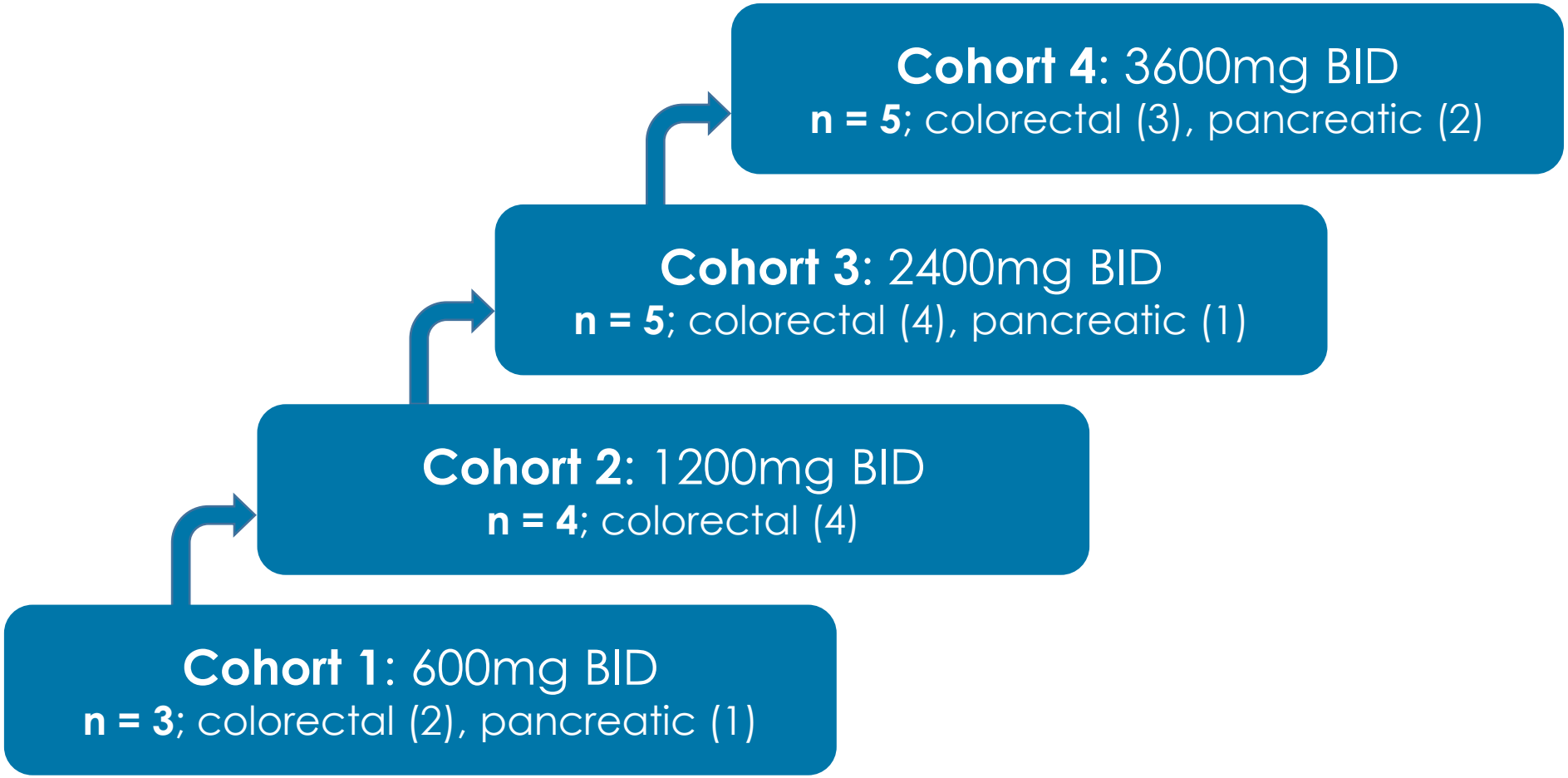
Inclusion Criteria

- Malignant gastrointestinal (GI) tumor of adenocarcinoma or poorly differentiated histology
- Resistant to or relapsed following available standard systemic therapy
- Metastatic or locally advanced and unresectable disease
- The patient is ≥18 years old.
- The patient has an ECOG PS of ≤1
- Patient selection was not performed based on CKB expression

Exclusion Criteria

- Persistent clinically significant toxicities (Grade ≥2) from previous anticancer therapy
- Prior Therapy
  - Treatment with chemotherapy, external-beam radiation, or other systemic anticancer therapy within 14 days prior to study therapy administration.
  - Treatment with an investigational systemic anticancer agent within 5 half-lives.

Overview of Dose Escalation and Enrollment by Cohort



Patient Demographics

Demographics Summary	
Total patients enrolled	17
Tumor types	colorectal (13), pancreatic (4)
Age range years, (median)	30-77 (56)
Male, n (%)	6 (35.3%)
Female, n (%)	11 (64.7%)
ECOG performance, n (%)	
0	5 (29.4%)
1	12 (70.6%)
Number of prior lines of therapy, n (%)	
2-3	5 (29.4%)
> 3	12 (70.6%)
Prior Therapies	
FOLFIRI	12 (70.6%)
FOLFOX	11 (64.7%)
FOLFIRINOX	4 (23.5%)
Bevacizumab	11 (64.7%)

Tumor Molecular Status	
RAS mutation n (%)	
Yes	10 (58.8%)
No (wildtype)	2 (11.8%)
Unknown	5 (29.4%)
BRAF mutation n (%)	
Yes	0 (0.0%)
No (wildtype)	7 (41.2%)
Unknown	10 (58.8%)
MSI-status n (%)	
MSI-H	0 (0.0%)
MSS or MSI-L	11 (64.7%)
Unknown	6 (35.3%)

Summary of RGX-202 Related Adverse Events (AEs)

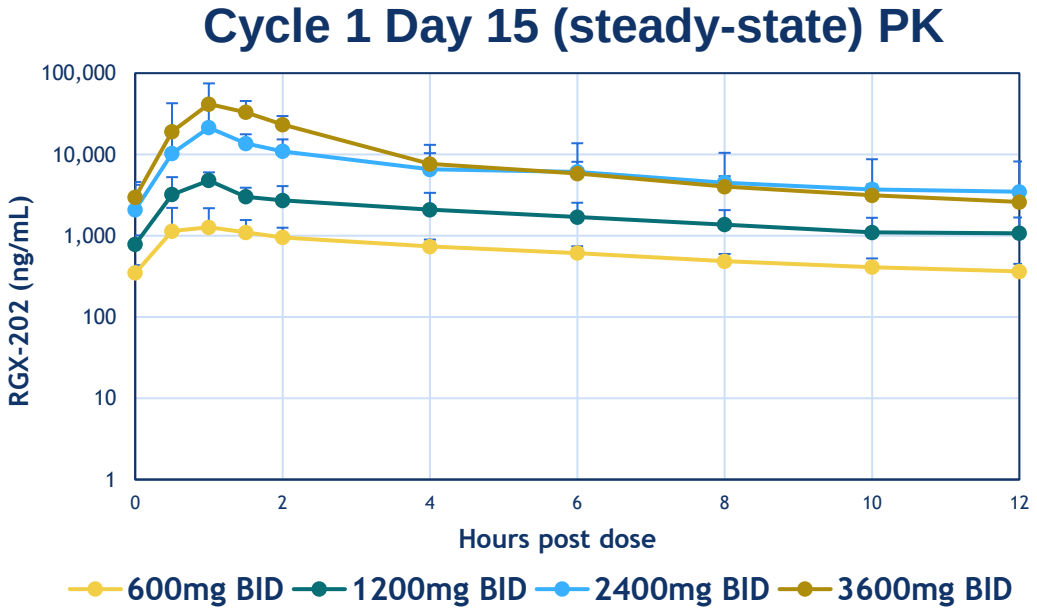
AE/Cohort	ALL		600 mg BID		1200 mg BID		2400 mg BID		3600 mg BID	
Number of patients	17		3		4		5		5	
Grade	≤2	3	≤2	3	≤2	3	≤2	3	≤2	3
Nausea	7 (41%)	1 (6%)				1 (25%)	2 (40%)		5 (100%)	
Vomiting	6 (35%)	1 (6%)			1 (25%)	1 (25%)	1 (20%)		4 (80%)	
Diarrhoea	5 (29%)		1 (33%)		1 (25%)		1 (20%)		2 (40%)	
Decreased appetite	4 (23%)				1 (25%)		1 (20%)		2 (40%)	
Fatigue	4 (23%)				1 (25%)				3 (60%)	
Blood alkaline phosphatase increased	2 (12%)								2 (40%)	
Muscle spasms	2 (12%)						1 (20%)		1 (20%)	
Weight decreased	2 (12%)						1 (20%)		1 (20%)	
Lymphocyte count decreased		1 (6%)								1 (20%)

- The majority (69.8%) of RGX-202 related AEs were Grade 1, with the most common being nausea and vomiting
- Grade 1-2 RGX-202 Related AEs are shown if they occurred in at least 2 patients (all Grade 3 AEs are shown)
- There were no RGX-202 related grade 4 or 5 AEs
- No DLTs were observed

RGX-202 was well tolerated and its monotherapy AE profile supports combinability with chemotherapy

RGX-202 Pharmacokinetics (PK)

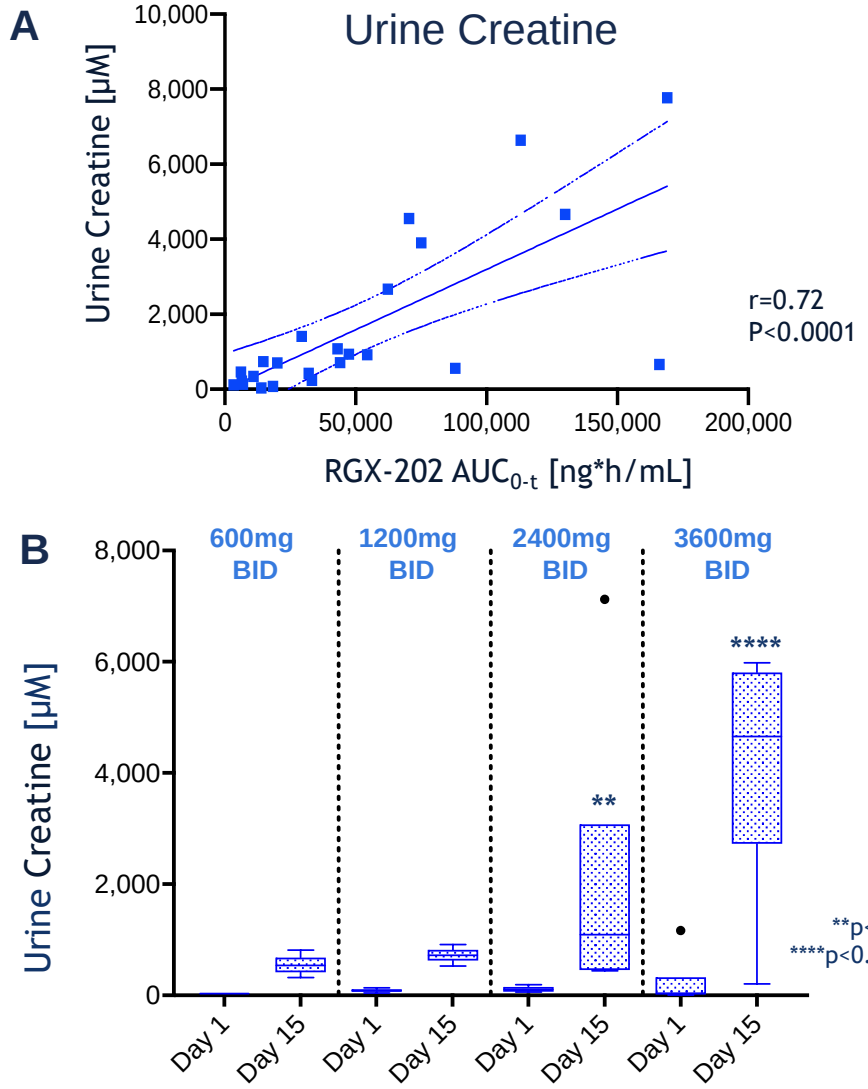
- A greater-than dose proportional increase in drug exposure was observed across dose cohorts
- $T_{1/2}$ range of 7-11 hours across dose cohorts
- Renal excretion is the major mode of RGX-202 elimination
- Projected efficacious exposure based on animal models is achieved at doses ≥ 2,400mg BID



Dose	Mean AUC_{0-t} (ng*h/mL)	Mean Estimated AUC_{0-24} (ng-hr/mL)	$T_{1/2}$ (h)	Mean Cmax (ng/mL)
600mg BID	7,850	15,700	11	1,400
1200mg BID	22,600	45,200	9	4,790
2400mg BID	82,400	164,800	8	26,800
3600mg BID	117,000	241,097	7	47,660

RGX-202 Pharmacodynamics (PD)

- Inhibition of the creatine transporter SLC6a8 by RGX-202 results in extracellular creatine accumulation, with subsequent renal excretion of excess creatine
- Therefore, an increase in urine creatine levels is a relevant pharmacodynamic marker of RGX-202 activity
- Urine creatine levels showed a statistically significant positive correlation with systemic exposure to RGX-202 as measured in the first cycle of treatment (fig. A)
- Increased urine creatine was observed across all dose cohorts and was significant in cohorts dosed with ≥ 2400mg BID (fig. B)

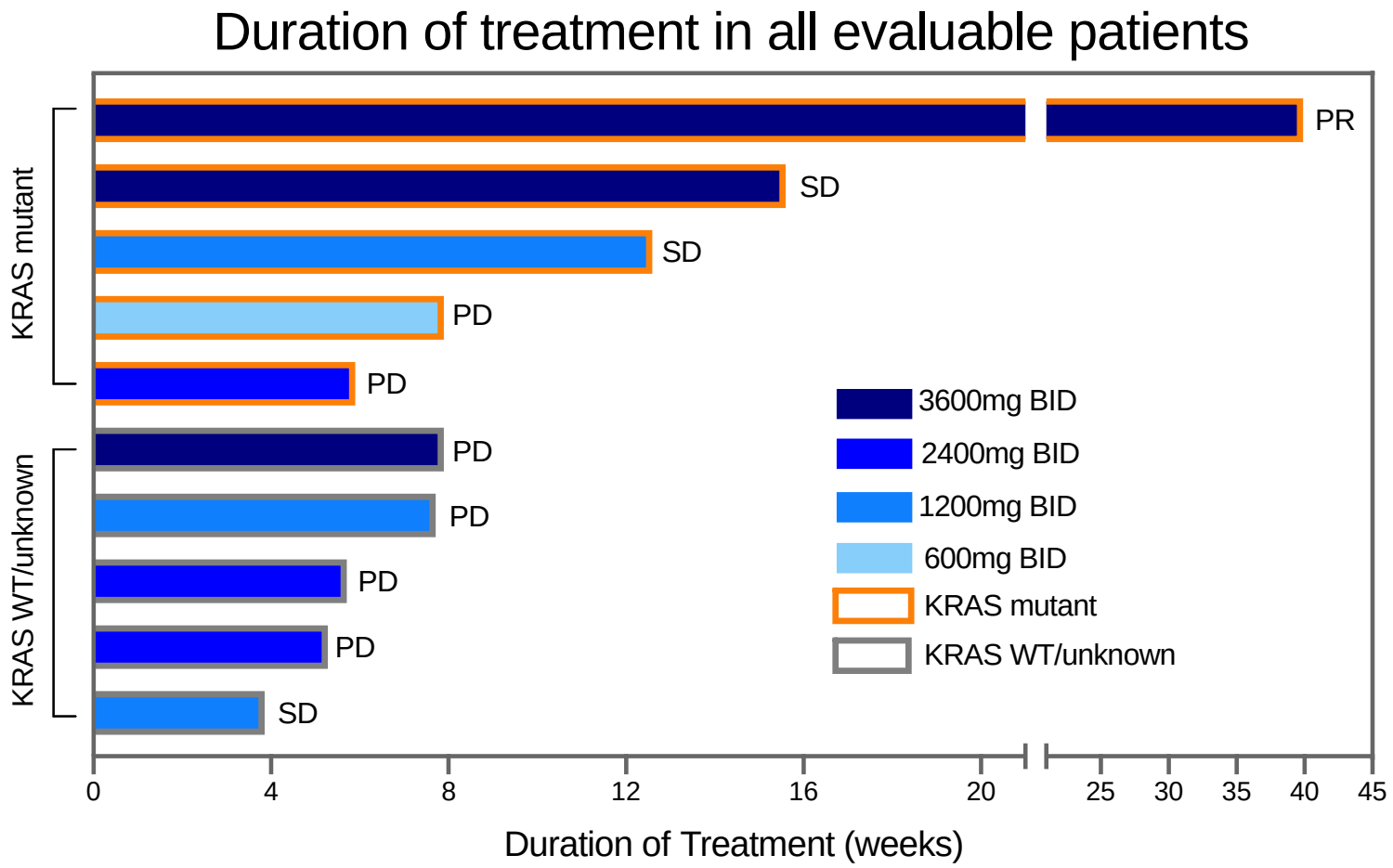


Efficacy

Summary		
Total patients evaluable for response*	**10**	colorectal (10); KRAS mutant (5), KRAS WT/unknown (5)
Best Response by RECIST 1.1		
Partial Response (PR)	**1 (10%)**	$KRAS^{G12V}$
Stable Disease (SD)	**3 (30%)**	$KRAS^{G13D}$ (2) $KRAS^{WT}$ (1)
Progressive Disease (PD)	**6 (60%)**	
Overall Response Rate (ORR)	**10%**	ORR 20% for KRAS mutant; ORR 0% for KRAS WT/unknown
Disease control Rate (DCR; PR+SD)	**40%**	DCR 60% for KRAS mutant; DCR 20% for KRAS WT/unknown

*Patients were evaluable for response if they had measurable disease, received at least one cycle of RGX-202 therapy, and had at least one follow up scan. Data cut-off 04/29/20 (open database).

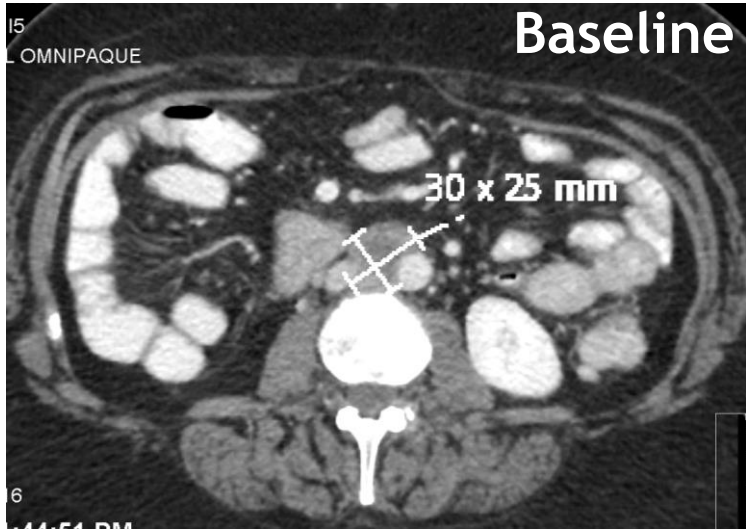
Clinical Activity Observed in KRAS mutant CRC Patients

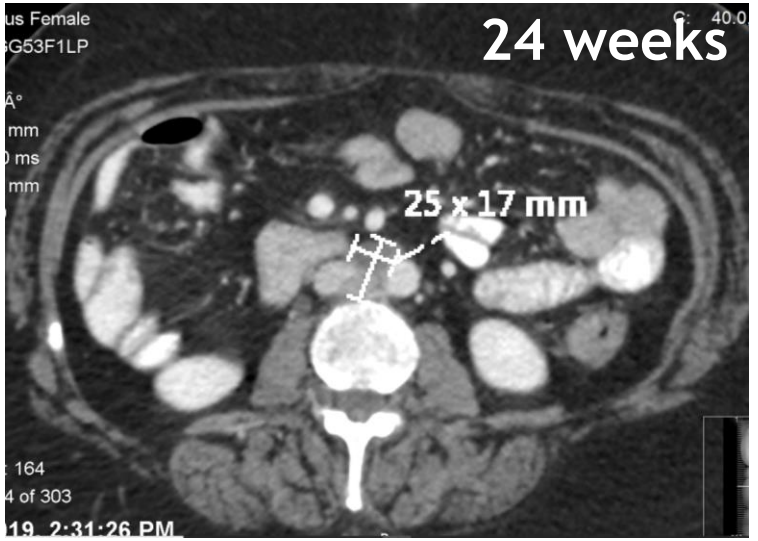


*Patients were evaluable for response if they had measurable disease, received at least one cycle of RGX-202 therapy, and had at least one follow up scan. Data cut-off 04/29/20 (open database).

Clinical Activity Observed in KRAS mutant CRC Patients (cont'd)

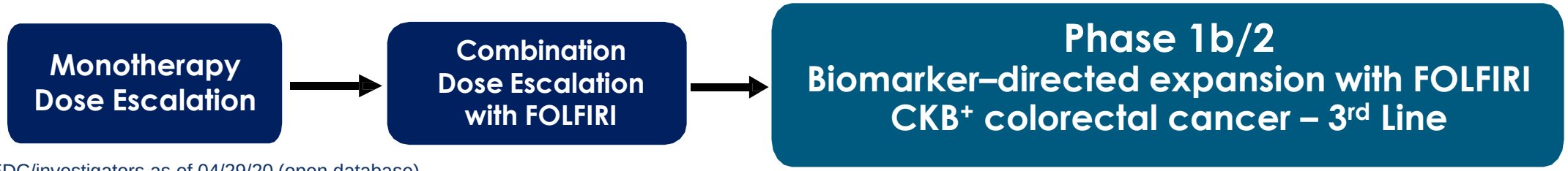
- **Confirmed PR observed in 55 year-old woman with *KRAS^{G12V}* mutant (MSS) colon cancer**
  - Patient had 6 prior lines of therapies including regimens containing 5-FU, oxaliplatin, irinotecan, bevacizumab, capecitabine, and atezolizumab
  - Scan at 16 weeks showed PR (confirmed PR at 24 weeks with 32% reduction in target lesion)
  - Week 32 scan with a 48% tumor regression, patient then had PD on Week 40 (end of cycle 10 scan)
  - Baseline and 24 week scan shown below with target lesion dimensions indicated by radiologist





Summary and Future Development

- **Monotherapy Dose Escalation**
  - Well tolerated agent that supports combinability with chemotherapy
  - Target PK and PD effects demonstrated at ≥ 2400 mg PO BID dose
  - Efficacy signal detected in KRAS mutant CRC in higher dose cohorts
- **Combination Dose Escalation with FOLFIRI ongoing**
  - Last cohort enrolling (1800, 2400, and 3000 mg PO BID of RGX-202 + standard dose FOLFIRI)
  - No DLTs observed to date
  - Prolonged Disease Control (≥ 16 weeks) observed in 4/5 (80%) of evaluable CRC patients treated to date*
- **Phase 1b/2 biomarker-directed expansion with FOLFIRI in CRC**
  - Phase 1b/2 expansion planned in 3rd line advanced CRC
  - Patient selection will be based on CKB biomarker positivity (≥ 5% TPS by tumor IHC)



*Data from EDC/investigators as of 04/29/20 (open database)

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