Phase 1b study of RGX-202-01, a first-in-class oral inhibitor of the SLC6a8/CKB pathway, in combination with FOLFIRI and bevacizumab (BEV) in second-line advanced colorectal cancer (CRC)

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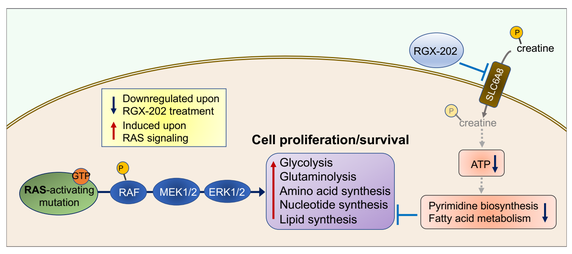
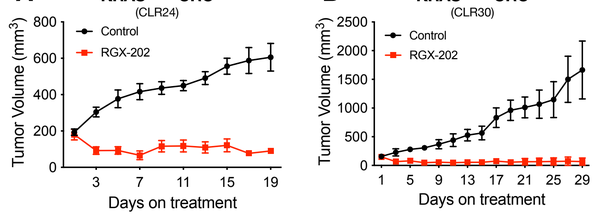
BACKGROUND

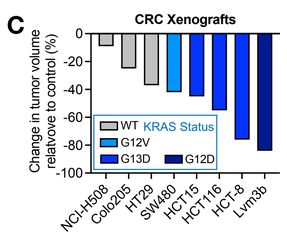
- Colorectal Cancer (CRC) is the fourth most frequent cancer diagnosis and the second leading cause of cancer death in the United States[1]
- Approximately 40-45% of patients with CRC harbor tumors that possess activating KRAS mutations[2]
- RGX-202-01 (for simplicity referred to herein as RGX-202) is a pharmaceutically optimized form of a new chemical entity SLC6a8 inhibitor that is suitable for clinical administration
- RGX-202 exerts its anti-tumor activity by competitively inhibiting the creatine transporter SLC6a8, which enables cells to generate ATP as well as other nucleotides by importing phospho-creatine (p-creatine). mCRC cells upregulate this pathway for survival under hypoxia[3]
- KRAS mutant tumors become dependent on several altered metabolic pathways downstream of active RAS signaling that are directly impacted by SLC6a8 inhibition, making them highly sensitive to RGX-202 treatment[4]
- In a completed Phase 1a monotherapy dose escalation study, RGX-202 demonstrated clinical activity in refractory patients with KRAS mutant CRC with a favorable safety profile resulting in predominantly low-grade GI toxicity with an absence of myelosuppression and dose-limiting toxicity[5]
- In addition to its single agent activity, RGX-202 also exhibits synergistic efficacy with 5-FU in pre-clinical animal models, providing rationale to combine RGX-202 with 5-FU containing regimens, such as FOLFIRI[6]
- FOLFIRI plus bevacizumab (FOLFIRI/BEV) is the most commonly used 2nd line regimen for metastatic CRC in the US, and its use is associated with an ORR of 5-15%, median PFS of 5-6 months and median OS of 12-18 months, providing a significant opportunity to meaningfully improve upon this regimen by the addition of RGX-202[7]

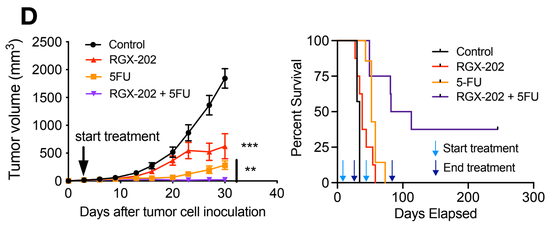
KRAS Mutant Tumors are Sensitive to the Effects of SLC6a8 Inhibition by RGX-202

RGX-202 Exhibits Single Agent Anti-Tumor Activity across KRAS Mutant Subtypes and Demonstrates Synergistic Efficacy with 5-FU in Pre-Clinical Tumor Models









(A, B) Subcutaneous tumor growth by CLR24 (A) or CLR30 (B) PDX fragments implanted in athymic nude mice receiving a control or RGX-202-supplemented diet (~800 mg/kg). (C) Waterfall plot of responses to RGX-202 across 8 CRC xenografts. (D) Subcutaneous tumor growth and Kaplan-Meier survival curves by CT26 CRC cells in BALB/c mice receiving a control diet, RGX-202-formulated diet (800 mg/kg), 5-FU (50 mg/kg/week) or a combination of RGX-202 and 5-FU.

Study Objectives, Key Inclusion/Exclusion Criteria and Design

Study Objectives

The objectives of the ongoing Phase 1b study are to evaluate safety, PK/PD, and efficacy of RGX-202 in combination with standard-of-care (SOC) FOLFIRI + BEV in second-line CRC

Key Inclusion and exclusion criteria for the RGX-202 + FOLFIRI + bevacizumab escalation and expansion cohorts:

- Advanced or Metastatic colorectal cancer
- Only 1 prior line of therapy for mCRC except for patients with MSI-H tumors who were allowed treatment with checkpoint inhibitors
- Demonstrated progression on oxaliplatin based 1st line regimen for mCRC
- Measurable disease by RECIST 1.1 criteria
- Adequate organ function ECOG 0 or 1
- CKB positivity by IHC for the expansion cohort

Phase 1b Dose Escalation + Expansion Study in 2L CRC

Dose Escalation Cohort 1
2400mg BID RGX-202 + FOLFIRI/BEV*
n = 4

Dose Escalation Cohort 2
3000mg BID RGX-202 + FOLFIRI/BEV*
n = 4

Expansion
3000mg BID RGX-202 + FOLFIRI/BEV*
n = 11 (still enrolling)

Data cut-off date for this presentation is April 28, 2022. Expansion stage is ongoing; open database.

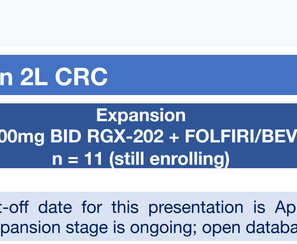
*Bevacizumab IV 5 mg/kg followed by irinotecan 180 mg/m^2 IV concurrently with folinic acid 400 mg/m^2 IV, followed by 5-FU 2400 mg/m^2 IV over 46 hours, on Days 1 and 15 of each 28-day cycle.

Patient Demographics

Total Enrolled, n	19
Dose escalation	8
Dose expansion	11
Median age, n [range]	60 [32-78]
Race, n (%)	
White	14 (74%)
African American	4 (21%)
Asian	1 (5%)
Sex, n (%)	
Male	13 (68%)
Female	6 (32%)
ECOG, n (%)	
0	9 (47%)
1	10 (53%)
KRAS Status, n (%)	
Mutant	12 (63%)
Wild Type (WT)	7 (37%)
≥2 metastatic organ sites, n (%)	18 (95%)
Prior therapies, n (%)	
Prior oxaliplatin and 5-Fluoropyrimidine	19 (100%)
Prior bevacizumab	14 (74%)

Pharmacodynamic Data Support the Phase 1b Expansion Dose

- RGX-202 pharmacodynamic effects are assessed by measuring urine creatine levels at steady state
- Composite data of the previously completed Phase 1a cohorts as well as the ongoing Phase 1b study, are shown on the right
- A dose dependent increase in absolute levels of urine creatine was evident at lower doses and plateaued at doses ≥ 2400 mg BID
- Data suggest robust and maximal pharmacodynamic effects of RGX-202 are achieved at doses ≥2400 mg BID



Urine creatine levels at steady-state on Cycle 1 Day 15 are plotted against RGX-202 BID doses. Shown are means +/- SEM.

Acknowledgements and References

References: [1]Siegel et al., *CA Cancer J. Clin.* 70, 7-30, (2020); [2]Jones *et al. Br. J. Cancer* 116, 923-929 (2017); [3]Loo et al. *Cell* 160, 393-406, (2015), [4]Mukhopadhyay et al.. *Nat Cancer* 2, 271-283, (2021); [5]Bendell et al., *J. of Clinical Oncology* 38(15) 2020; [6]Kurth et al. *Sci Adv* 7 (2021); [7]Bennouna, et al. *Lancet Oncol*.14, 29-37, (2013). **Acknowledgements:** We are grateful to all patients and their families, investigators, clinical and office staff. We thank Dr. Norihiro Yamaguchi for performing the PDX tumor studies and Ray Xie and Steve Wald for oversight of RGX-202-01 production.

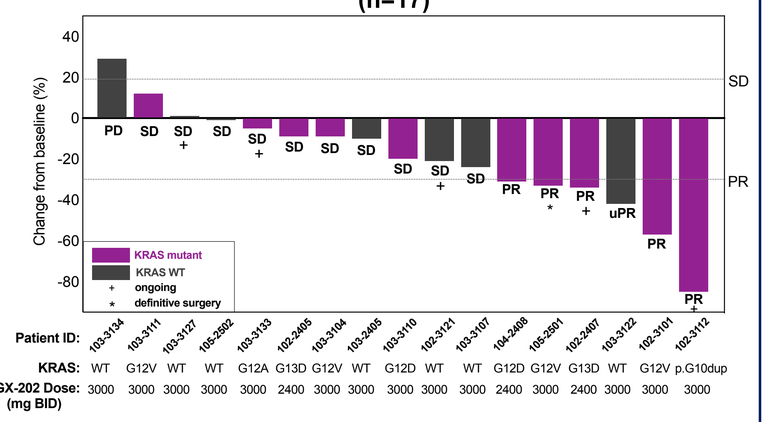
Preliminary Efficacy Dose Escalation and Expansion Stages

Efficacy Summary

Clinical Response	KRAS status	
	KRAS mutant	KRAS WT
Total evaluable*	10	7
PR (confirmed)	5 (50%)	0 (0%)
PR (unconfirmed)	0 (0%)	1 (14%)
SD	5 (50%)	5 (71%)
PD	0 (0%)	1 (14%)

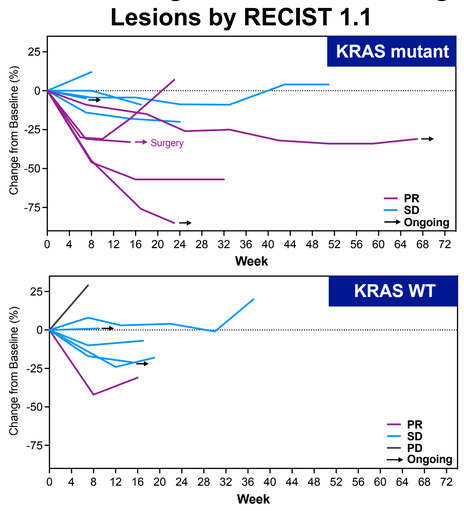
*Patients were evaluable for RECIST 1.1 response if they completed at least one cycle of treatment and had at least one follow-up scan for RECIST 1.1 assessment. Two KRAS mutant patients were not evaluable for response: 1 patient discontinued due to grade 2 allergic reaction, and 1 patient discontinued due to poor compliance.

Best Response by RECIST 1.1 in all Evaluable Patients (n=17)

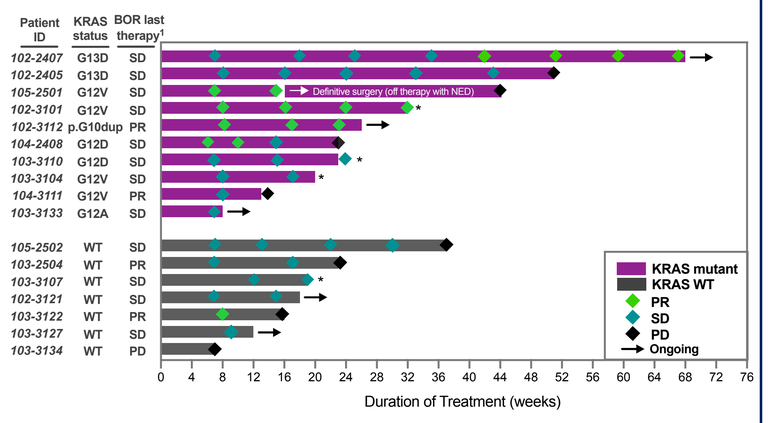


Patient ID:	103-3134	103-3111	103-3127	105-2502	103-3133	102-2405	103-3104	103-2405	103-3110	102-3121	103-3107	104-2408	105-2501	102-2407	103-3122	102-3101	102-3112
KRAS:	WT	G12V	WT	WT	G12A	G13D	G12V	WT	G12D	WT	WT	G12D	G12V	G13D	WT	G12V	p.G10dup
RGX-202 Dose: (mg BID)	3000	3000	3000	3000	3000	2400	3000	3000	3000	3000	3000	2400	3000	2400	3000	3000	3000

Percent Change from Baseline in Target Lesions by RECIST 1.1



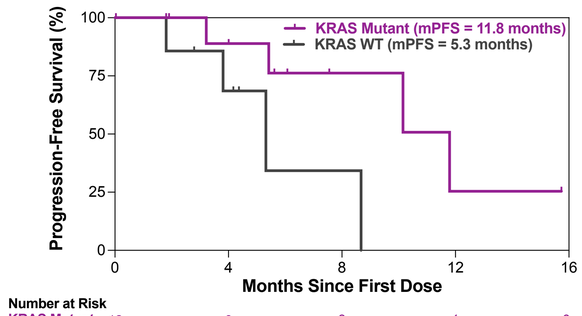
Duration of Treatment in all Evaluable Patients (n=17)



[1]BOR= Best overall response to last therapy. *Patients 102-3101 and 103-3110 withdrew consent due to treatment intolerability. Patients 103-3104 and 103-3107 withdrew from study and went to hospice.

Preliminary Progression-Free Survival (PFS)

PFS analysis includes all patients enrolled (n=19) as of the data cut-off date



Number at Risk					
KRAS Mutant	12	8	3	1	0
KRAS WT	7	4	1	0	0

- Patients with KRAS mutant tumors experienced durable clinical benefit with an ORR of 50% and a median PFS >11 months as of the data cut off date in this ongoing Phase 1b study
- Tumor regressions generally deepened over time in patients with KRAS mutant tumors with first radiographic evidence of PR appearing as late as 40 weeks after therapy initiation
- ORR and median PFS observed to date in patients with KRAS mutant tumors clearly exceed that expected with standard-of-care FOLFIRI/BEV alone in 2L CRC (~15% ORR, ~5-6 months mPFS)

Updates since April 28, 2022 (data cut off date) through June 10, 2022
- Two patients with KRAS mutant tumors had follow up imaging: patient 102-3112 remains in PR status and patient 102-2407 now has SD
- Two patients with KRAS WT tumors had follow up imaging: patient 102-3121 remains in SD status and patient 103-3127 maintained SD radiographically but was declared clinical PD as per the Investigator
- The ORR remains unchanged (50% in KRAS mutant group, 14% in the KRAS WT group)

Treatment-Emergent Adverse Events (TEAEs) / Safety Overview (Dose Escalation and Expansion Stages)

AE/Cohort	ALL		RGX-202 2400 mg BID + FOLFIRI + Bev (Escalation)		RGX-202 3000 mg BID + FOLFIRI + Bev (Escalation +Expansion)	
Number of subjects	19		4		4+11=15	
Grade	≤2	≥3	≤2	≥3	≤2	≥3
Nausea	11(58%)		3(75%)		8(53%)	
Diarrhoea	10 (53%)		3(75%)		7(47%)	
Neutropenia	6(32%)	2(11%)	2(50%)		4(27%)	2(13%)
Abdominal pain	5(26%)	2(11%)	2(50%)		3(20%)	2(13%)
Fatigue	5(26%)	2(11%)	1(25%)	1(25%)	4(27%)	1(7%)
Constipation	6 (32%)		3(75%)		3(20%)	
Vomiting	3(16%)	1(5%)	1(25%)		2(13%)	1(7%)
Hypertension	1(5%)	2(11%)	1(25%)	1(25%)		1(7%)
Rectal pain	1(5%)	2(11%)		1(25%)	1(7%)	1(7%)
Dehydration	2(11%)	1(5%)	1(25%)		1(7%)	1(7%)
Mucosal inflammation	3(16%)		1(25%)		2(13%)	
Intestinal obstruction		2(11%)				2(13%)
Anaemia	1(5%)	1(5%)	1(25%)			1(7%)
Hyponatraemia	1(5%)	1(5%)			1(7%)	1(7%)
Pulmonary embolism	1(5%)	1(5%)			1(7%)	1(7%)
Arthralgia	2(11%)		1(25%)		1(7%)	
Decreased appetite	2(11%)				2(13%)	
Face oedema	2(11%)		2(50%)			
Haemorrhoids	2(11%)		1(25%)		1(7%)	
Hyperglycaemia	2(11%)		1(25%)		1(7%)	
Muscular weakness	2(11%)				2(13%)	
Abdominal abscess		1(5%)				1(7%)
Aspartate aminotransferase increased		1(5%)				1(7%)
Back pain		1(5%)				1(7%)
Blood bilirubin increased		1(5%)				1(7%)
Colitis		1(5%)				1(7%)
Device related infection		1(5%)				1(7%)
Gastrointestinal fistula		1(5%)				1(7%)
Sepsis		1(5%)				1(7%)
Upper respiratory tract infection		1(5%)				1(7%)
Urinary tract infection		1(5%)				1(7%)
Urinary Tract Obstruction		1(5%)				1(7%)

Grade 1 or 2 TEAEs that occurred in ≥ 2 subjects are shown and all TEAEs ≥ Grade 3 are shown. For neutropenia, all abnormal lab values were classified as a TEAE and shown regardless of investigator assessment

- The Dose Escalation Phase did not reach an MTD and there were no DLTs at either the 2400mg BID or 3000mg BID dose
- There were 2 Grade 4 TEAEs at the 3000 mg BID Dose (sepsis and neutropenia). Sepsis TEAE was considered unrelated to study drug by investigator as it occurred off therapy and 12 days after PD. There were no Grade 5 TEAEs
- The incidence of GI and neutropenia TEAEs in the Dose Escalation/Expansion Stages are consistent with those reported for standard-of-care FOLFIRI/BEV 2L CRC regimens
- **Updates since April 28, 2022 (data cut off date) through June 10, 2022**
  - Two grade 3 TEAEs (neutropenia, pulmonary embolus) deemed unrelated to RGX-202
  - No grade 4 or 5 TEAEs reported

Conclusions/Next Steps

- **Promising efficacy signal (50% ORR, mPFS 11.8 months) observed in evaluable patients with KRAS mutant tumors receiving RGX-202 + FOLFIRI/BEV in 2L CRC in this ongoing Phase 1b study (clinicaltrials.gov RGX-202-01)**
- **RGX-202 demonstrated a favorable safety profile and ability to be combined with standard-of-care without DLTs**
- **As a first-in class SLC6a8 inhibitor that depletes intracellular ATP and nucleotide pools, RGX-202 represents a novel approach to target pan-RAS mutant CRC**
- **Given the favorable efficacy and safety, strong rationale exists to advance RGX-202 in combination with FOLFIRI/BEV into a randomized controlled trial for the 2L treatment of advanced/metastatic patients harboring RAS mutant CRC**