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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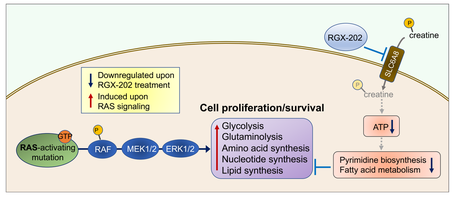
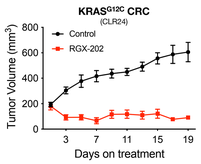
Background

- 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 rational 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]

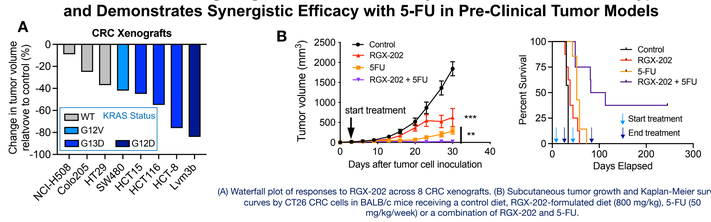
KRAS Mutant Tumors are Sensitive to the Effects of SLC6a8 Inhibition by RGX-202





Subcutaneous tumor growth by CLR24 PDX fragments implanted in athymic nude mice receiving a control or RGX-202-supplemented diet (~800 mg/kg).

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) Waterfall plot of responses to RGX-202 across 8 CRC xenografts. (B) 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.

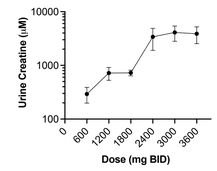
*Bevacizumab IV 5 mg/kg followed by irinotecan 180 mg/m2 IV concurrently with folinic acid 400 mg/m^2 IV, followed by 5-FU 2400 mg/m^2 IV over 46 hours, on Days 1 and 15 of each 28-day cycle.

Patient Demographics

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

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

AE/Cohort	ALL		RGX-202 2400 mg BID + FOLFIRI + Bevacizumab (Escalation)		RGX-202 3000 mg BID + FOLFIRI + Bevacizumab (Escalation + Expansion)	
Number of Subjects	19		4		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
- In conclusion, the overall safety profile of RGX-202 in combination with FOLFIRI/BEV supports the further development of the combination in 2L CRC

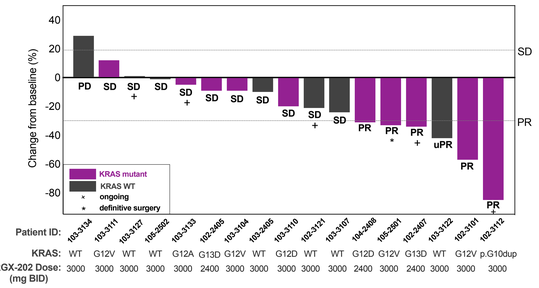
Preliminary Efficacy (Dose Escalation and Expansion Stages)

Efficacy Summary

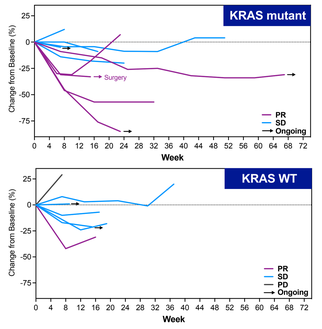
Clinical Response	KRAS status	
	KRAS mutant	KRAS WT
Total evaluable*	10	7
PR (confirmed)	5 (50%)	0 (0%)
PR (unconfirmed)	0 (0%)	1 (14%)
SD	5 (50%)	5 (71%)
PD	0 (0%)	1 (14%)

*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.

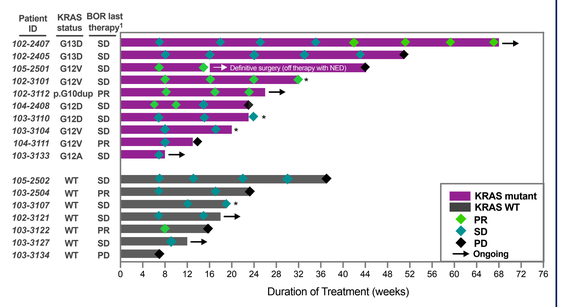
Best Response by RECIST 1.1 in all Evaluable Patients (n=17)



Percent Change from Baseline in Target Lesions by RECIST 1.1

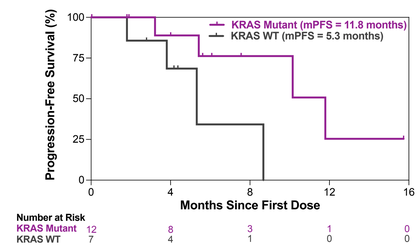


Duration of Treatment in all Evaluable Patients (n=17)



1BOR= 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

- 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)

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 patients harboring RAS mutant CRC**

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).
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