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Phase Ia study to evaluate GDC-6036 monotherapy in patients with colorectal cancer (CRC) with *KRAS G12C* mutation

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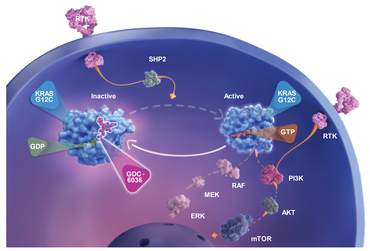
BACKGROUND

- The oncogenic *KRAS G12C* mutation is one of the most prevalent *KRAS* mutations in cancer, present in ~12% non-small cell lung cancer (NSCLC), ~4% CRC, and up to 4% of other cancers
- GDC-6036 is an oral, highly potent and selective KRAS G12C inhibitor that irreversibly locks the protein in an inactive state to turn off its oncogenic signaling
- GDC-6036 is more potent and selective *in vitro* than sotorasib and adagrasib[1]
- Single-agent GDC-6036 data in NSCLC presented at the 2022 World Conference on Lung Cancer[2]

Figure 1. GDC-6036 is a potent, selective, covalent inhibitor of KRAS G12C.



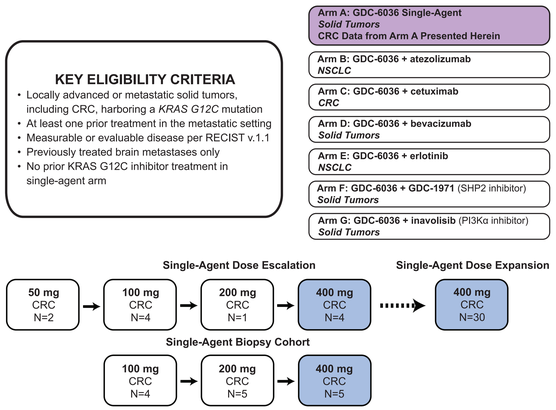
OBJECTIVES

- To characterize the safety (NCI-CTCAE v.5), preliminary antitumor activity (RECIST v1.1), pharmacokinetics and exploratory biomarkers of GDC-6036 as a single agent or in combination therapy in patients with locally advanced or metastatic solid tumors with *KRAS G12C* mutation

METHODS

- Ongoing Phase I dose-escalation/expansion study (ClinicalTrials.gov: **NCT04449874**)
- **GDC-6036 50-400 mg administered orally once a day** in 21-day cycles until intolerable toxicity or disease progression
- Serial circulating tumor DNA (ctDNA) levels were assessed at Cycle 1 Day 1 (pre-GDC-6036 dose), Cycle 1 Day 15 (C1D15) and Cycle 3 Day 1 (C3D1) using the PredicineBEACON MRD assay

Figure 2. Study design.



RESULTS

DISPOSITION AND BASELINE DEMOGRAPHICS - CRC

- Data reported as of 10 June 2022 on 55 patients with CRC, enrolled and treated with single-agent GDC-6036 (n, 50 mg: 2; 100 mg: 8; 200 mg: 6; 400 mg: 39) (Table 1)
- Twenty-nine (53%) patients discontinued study treatment: 22 due to RECIST progression, 3 due to clinical progression, 3 due to adverse events (all unrelated to GDC-6036), and 1 due to other reasons

Table 1. Patient demographics and disease characteristics.

	CRC Patients (N=55)
Age, median (range), years	62 (34-81)
Sex, female	33 (60%)
ECOG: 0 / 1 (N=53)	23 (43%) / 30 (57%)
Median (range) number of prior therapies in a metastatic setting	3 (1-7)
Prior oxaliplatin therapy Prior irinotecan therapy Prior bevacizumab therapy	54 (98%) 45 (82%) 34 (62%)
Time on treatment, median (range), months	4.47 (0.2-10.3)

SAFETY - ALL SOLID TUMORS

- In CRC patients, the most frequent GDC-6036-related adverse events (AEs) in ≥10 patients were nausea, diarrhea, vomiting, and fatigue; the only treatment-related Grade ≥3 AEs were diarrhea (3 patients, 5.5%; all Grade 3) and neutropenia (1 patient, 1.8%; Grade 3) (Table 2). AEs were manageable with supportive measures
- Eight (14.5%) CRC patients required a dose modification (interruption [5 patients] or reduction [3 patients]; no withdrawals) for GDC-6036-related AEs (Table 3). AEs that resulted in GDC-6036 dose reduction were diarrhea, gastrointestinal stoma complication, and nausea (1 patient each)

Table 2. Treatment-related AEs in ≥10 patients overall (among all solid tumors and corresponding in CRC) and corresponding Grade 3-4 AEs.

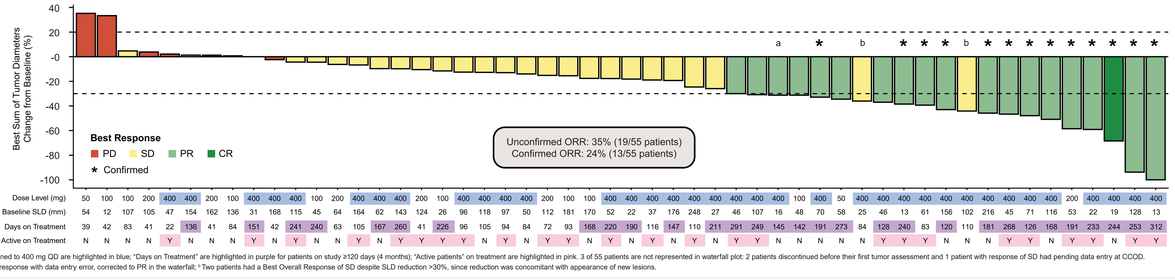
	CRC Patients (N=55)		All Patients (N=136)	
	Related AEs	Grade 3-4	Related AEs	Grade 3-4
Patients with at least one AE	53 (96%)	4 (7%)	124 (91%)	14 (10%)
Nausea	42 (76%)	0	99 (73%)	0
Diarrhea	37 (67%)	3 (5.5%)	83 (61%)	5 (4%)
Vomiting	29 (53%)	0	72 (53%)	0
Fatigue	10 (18%)	0	27 (20%)	1 (1%)
Decreased appetite	6 (11%)	0	17 (12.5%)	0
ALT increased	1 (2%)	0	12 (9%)	4 (3%)
AST increased	3 (5.5%)	0	12 (9%)	3 (2%)
Dyspepsia	6 (11%)	0	12 (9%)	0
Lipase increased	0	0	10 (7%)	1 (1%)

No treatment-related Grade 5 events were reported.

Table 3. Dose modifications due to treatment-related AEs.

	CRC Patients (N=55)	All Patients (N=136)
Patients with AEs resulting in GDC-6036 modification (interruption/reduction/withdrawal)	8 (14.5%)	33 (24%)
Patients with AEs resulting in GDC-6036 reduction	3 (5.5%)	18 (13%)
Patients with AEs resulting GDC-6036 withdrawal	0	3 (2%)

Figure 3. Best percentage changes in sum of tumor diameters.



Patients assigned to 400 mg QD are highlighted in blue; "Days on Treatment" are highlighted in purple for patients on study ≥120 days (4 months); "Active patients" on treatment are highlighted in pink. 3 of 55 patients are not represented in waterfall plot: 2 patients discontinued before their first tumor assessment and 1 patient with response of SD had pending data entry at CCOD.
[a] Best overall response with data entry error, corrected to PR in the waterfall; [b] Two patients had a Best Overall Response of SD despite SLD reduction >30%, since reduction was concomitant with appearance of new lesions.

Figure 4. Percentage changes in sum of tumor diameters over time (N=55).

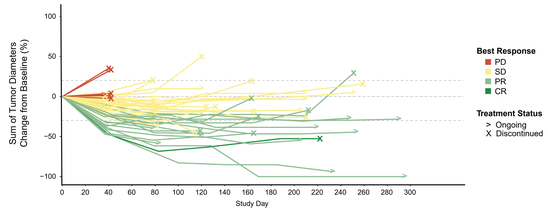
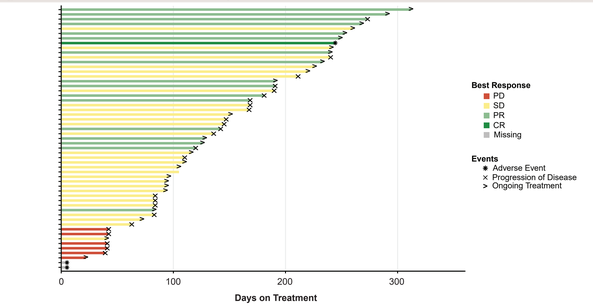


Figure 5. Time on treatment, best response, and reason for treatment discontinuation (N=55).



PRELIMINARY ANTI-TUMOR ACTIVITY - CRC

- At 400 mg, unconfirmed overall response rate (ORR) was **41%** (16/39 patients) and confirmed ORR was **31%** (12/39 patients)

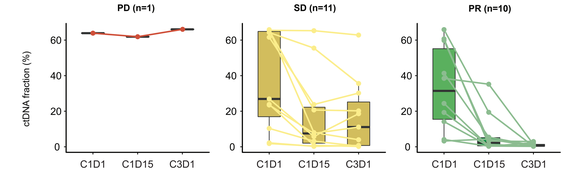
PHARMACOKINETICS - ALL SOLID TUMORS

- Following a single dose (50-400 mg) of GDC-6036, mean $t_{1/2}$ ranged from **13 to 17 hours**, compatible with QD dosing
- The majority of patients treated at the expansion dose (400 mg QD) of GDC-6036 are predicted to achieve exposures corresponding to maximal covalent target engagement from nonclinical studies

EXPLORATORY BIOMARKERS - CRC

- After 2 weeks of GDC-6036 treatment, ctDNA fraction was reduced in patients with PR, and a subset of patients with SD
- After 6 weeks of GDC-6036 treatment, low ctDNA fraction (< 3%) observed among patients with PR

Figure 6. ctDNA dynamics in association with tumor response.



CONCLUSIONS

- **Single-agent GDC-6036 demonstrated an acceptable safety profile with manageable, tolerable, and reversible adverse events across tumor types, including CRC**
- **As a single agent, GDC-6036 has encouraging anti-tumor activity in patients with previously treated *KRAS G12C*-positive CRC**
- **GDC-6036 PK profile is compatible with once-daily dosing**
- **Reductions in ctDNA fractions on treatment were associated with tumor response in CRC**

- GDC-6036 in combination with other anti-cancer therapies, including cetuximab and SHP2 inhibitor GDC-1971, is under investigation in CRC
- ESMO 2022 mini-oral presentation on 12 September 2022, Patel et al. Monotherapy GDC-6036 in Solid Tumors, except NSCLC and CRC
- A **Phase II/III study** is recruiting advanced/metastatic previously treated NSCLC patients for treatment with GDC-6036 vs. docetaxel (**BFAST**; NCT03178552)

www.clinicaltrials.gov/ct2/show/NCT03178552

REFERENCES

1. Purkey H, et al. Discovery of GDC-6036, a clinical stage treatment for KRAS G12C-positive cancers. American Association for Cancer Research Annual Meeting, New Orleans, Lousiana; April 8-13, 2022.
2. Sacher A, et al. Phase Ia study to evaluate GDC-6036 monotherapy in patients with non-small cell lung cancer (NSCLC) with KRAS G12C mutation. 2022 World Conference on Lung Cancer, Vienna, Austria; August 6-9, 2022.

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