Phase 1 Study of IDRX-42 in Patients With Advanced Gastrointestinal Stromal Tumors Resistant to Prior Systemic Therapy: Early Results

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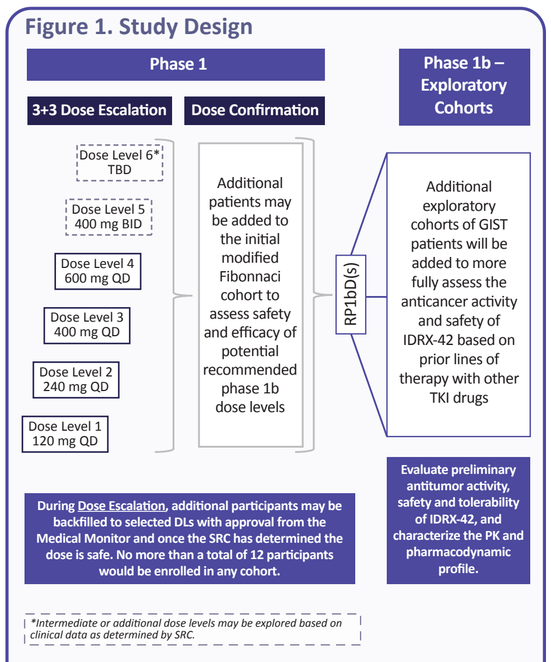
BACKGROUND

- Gastrointestinal stromal tumors (GIST) are the most common subtype of soft tissue sarcoma.[1,2]
- Most cases arise from gain of function mutations in either the KIT or platelet-derived growth factor receptor alpha (*PDGFRA*) receptor tyrosine kinases, driving the malignancy through constitutive activation of aberrant signaling.[1,2]
- IDRX-42 is a potent, highly selective, oral inhibitor of multiple mutated variants of the *KIT* tyrosine kinase (including exons 9, 11, 13, and 17) to target disease-specific primary oncogenic drivers and clinically relevant resistance mutations of *KIT*.[3]
- In preclinical studies, IDRX-42 demonstrated superior antitumor activity compared to imatinib, the current first-line of therapy, in GIST human xenograft models expressing mutations in *KIT* exons 9 and 11.
- In xenograft models expressing secondary resistance mutations in *KIT* exon 13 or 17, IDRX-42 treatment resulted in potent and dose-dependent antitumor activity superior to the second-line standard of care agent, sunitinib.[4]
- We now present preliminary results of the ongoing phase 1 first-in-human study evaluating IDRX-42 in patients with metastatic and/or surgically unresectable GIST after failure of imatinib and other approved drugs.

METHODS

- This open-label, phase 1/1b study (NCT05489237) evaluates the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of orally administered IDRX-42 in adult patients

Figure 1. Study Design



DLs, dose levels; PK, pharmacokinetics; QD, once daily; RP1bD (s), recommended Phase 1b dose(s); SRC, safety review committee; TBD, to be determined; TKI, tyrosine kinase inhibitor

KEY INCLUSION CRITERIA

- Men or women ≥ 18 years of age
- Histologically or cytologically confirmed metastatic and/or surgically unresectable GIST
- Failure to control GIST based on prior treatment as follows:
  a) Phase 1 Dose Escalation patients: documented progression on at least imatinib
  b) Phase 1b Exploratory Cohorts will be expanded based on cohort-defined lines of prior TKI therapy
- Documented pathogenic mutation in *KIT* or any *PDGFRA* mutation (other than *PDGFRA* exon 18)
- At least 1 measurable GIST lesion by mRECIST v1.1
- ECOG performance status of 0 or 1

ECOG, Eastern Cooperative Oncology Group; *PDGFRA*, platelet-derived growth factor receptor alpha; mRECIST v1.1, Modified Response Evaluation Criteria in Solid Tumors version 1.1.

ENDPOINTS

Phase 1 – Dose Escalation

Primary
- Determine the maximum tolerated dose (MTD) and/or recommended Phase 1b dose and schedule (RP1bD[s]) of IDRX-42 in participants with metastatic and/or surgically unresectable GIST
- Incidence and severity of AEs and DLTs

Secondary
- Change from baseline in laboratory results
- PK parameters of IDRX-42
- Objective response rate[a]
- Duration of response[a]
- Progression-free survival[a]
- Time to response[a]

Exploratory
- Pharmacodynamic markers
- Relationship between cancer alterations and antitumor response

Phase 1b – Cohort-Defined

Primary
- Safety and efficacy (objective response rate)

Secondary
- Duration of response[a]
- Progression-free survival[a]
- Clinical benefit rate[a]
- Time to response[a]
- Pharmacokinetic parameters of IDRX-42
- Overall survival

Exploratory
- Pharmacodynamic markers
- Relationship between cancer alterations and antitumor response

[a]Per mRECIST v1.1 by investigator assessment In Phase 1 and by Independent Review in Phase 1b; DLT, dose limiting toxicity; PK, pharamacokinetics; AE, adverse events

RESULTS

Study Accrual and On-study Continuation to Date

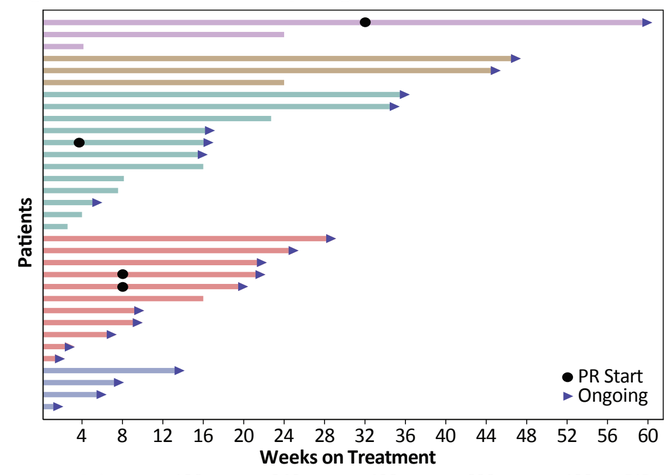
- As of October 5 2023, 33 patients (all *KIT*-mutated GIST patients) received treatment with IDRX-42 in the ongoing dose escalation portion of the study with median duration on treatment of 16 weeks and continuing (**Table 1, Figure 2**)
- 23 pts (70%) remain on study: 10 patients discontinued due to disease progression; no discontinuation for toxicity has occurred
- Median age was 60 years, median number of lines of prior therapy was 4, 70% of patients had any *KIT* exon 11 mutation, and 33% of patients had any *KIT* exon 9 mutation (**Table 1**)
- Four dose levels (120, 240, 400 and 600 mg QD) have been cleared per protocol, and accrual to the 800 mg (400 mg BID) cohort is ongoing (**Figure 2**)

Table 1: Pre-Study Baseline Characteristics

	120 mg QD N = 3	240 mg QD N = 3	400 mg QD N = 12	600 mg QD N = 11	800 mg [400 BID] N = 4	Total N = 33
Female sex, n (%)	1 (33)	1 (33)	7 (58)	3 (27)	2 (50)	14 (42)
Median age, years	70	60	56.5	63	59	60
Median time since GIST diagnosis, years	8	12	7	9	6	8
Median time since metastatic/ unresectable GIST, years	4	3	5	4	5	5
Median lines of prior therapy, n	4	3	4	4	5	4
Median duration on treatment to date, weeks	24	45	16	16	7	16
Discontinued from study, n (%)	2 (67)	1 (33)	6 (50)	1 (9)	0 (0)	10 (30)
Baseline Mutational Data: n(%)[a]						
KIT Exon 11 mutation	2 (67)	3 (100)[b]	10 (83)	5 (46)	3 (75)	23 (70)
Exon 11 + 13	1 (33)	0 (0)	2 (17)	1 (9)	1 (25)	5 (15)
Exon 11 + 17	1 (33)	1 (33)	2 (17)	0 (0)	0 (0)	4 (12)
Exon 11 + 13 + 17	0 (0)	1 (33)	2 (17)	2 (18)	0 (0)	5 (15)
Exon 11 + 13 + 17+[c]	0 (0)	0 (0)	1 (8)	2 (18)	0 (0)	3 (9)
Exon 11 only	0 (0)	1 (33)	2 (17)	0 (0)	2 (50)	5 (15)
KIT Exon 9 mutation	1 (33)	0 (0)	3 (25)	6 (55)	1 (25)	11 (33)
Exon 9 only	1 (33)	0 (0)	1 (8)	5 (46)	1 (25)	8 (24)

[a]Detected in tumor or ctDNA; [b]1 patient had both an exon 9 and exon 11 mutation;
[c]Includes other exons in addition to 11, 13, 17

Figure 2: IDRX-42-001 Study Progress



Early Antitumor Results

- Twenty-eight of 33 patients are currently evaluable for objective response
- Although the MTD has not been reached, clinical benefit rate (partial response [PR] or durable stable disease ≥ 16 weeks) across the initial doses studied to date is 67.9% (19 of 28 evaluable patients) (**Table 2**)
- Four patients have demonstrated confirmed partial responses per modified RECIST (**Table 3, Figure 3**)
  – One confirmed partial response at the 120 mg dose level, and one confirmed partial response at the 400 mg dose level
  – Two confirmed partial responses at the 600 mg dose level
- Tumor shrinkage and confirmed partial responses were observed across all mutational variants of *KIT*, including both primary and secondary resistance mutations (exons 9, 11, 13, and 17) (**Figure 3, Figure 4**)
- Analysis of ctDNA show notable reductions in all identified mutant exons of *KIT* (**Figure 5**)
- All patients who had exploratory ^{18}FDG-PET imaging at baseline and on IDRX-42 showed PET responses

Table 2: Clinical Benefit Rate

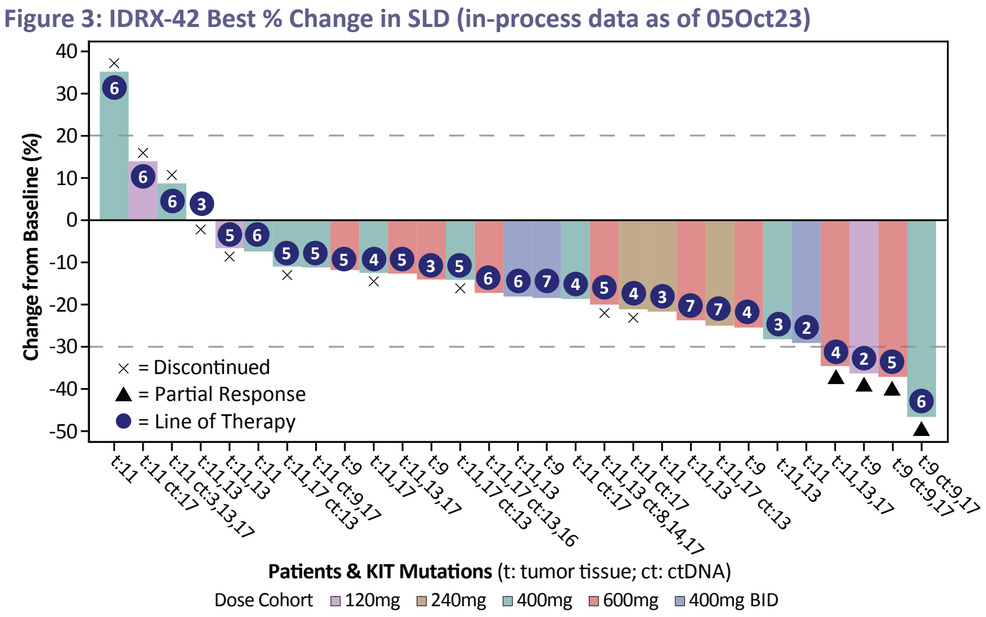
CBR = PR or Durable SD ≥16 weeks			
Dose Level	**N**	**CB**	**CBR**
120mg	3	2	66.7%
240mg	3	3	100.0%
400mg	11	7	63.6%
600mg	8	6	75.0%
800mg	3	1	33.3%
All	28	19	67.9%

Table 3: Best Overall Response

All Dose Levels (N=28)	
BOR	**n (%)**
PR, Confirmed	4 (14.3)
SD	15 (53.6)
PD	5 (17.9)
NE*	4 (14.3)

Efficacy evaluable patients have had at least 1 dose of study drug and have at least 1 post-baseline tumor assessment or have clinical progression or death before the first post baseline tumor assessment
*4 patients are not yet evaluable per mRECIST for best overall response. All 4 of these recently-accrued patients have an initial scan of stable disease at 4 weeks but have not been on study long enough to receive their second scan at 8 weeks to determine best overall response. These 4 patients are also counted in the CBR analysis but have not yet had sufficient time on study for CBR determination (<16 weeks).
Note: Denominator for BOR and CBR analyses are N=28. There is 1 additional patient who has had an initial efficacy assessment but had not yet completed the overall response criteria information in the database at the time of this datacut

Figure 3: IDRX-42 Best % Change in SLD (in-process data as of 05Oct23)



SLD, sum of the longest diameter of the target lesions per mRECIST

Figure 4: Evolution of mRECIST Target Lesions [% Change in SLD] (in-process data as of 05Oct23)

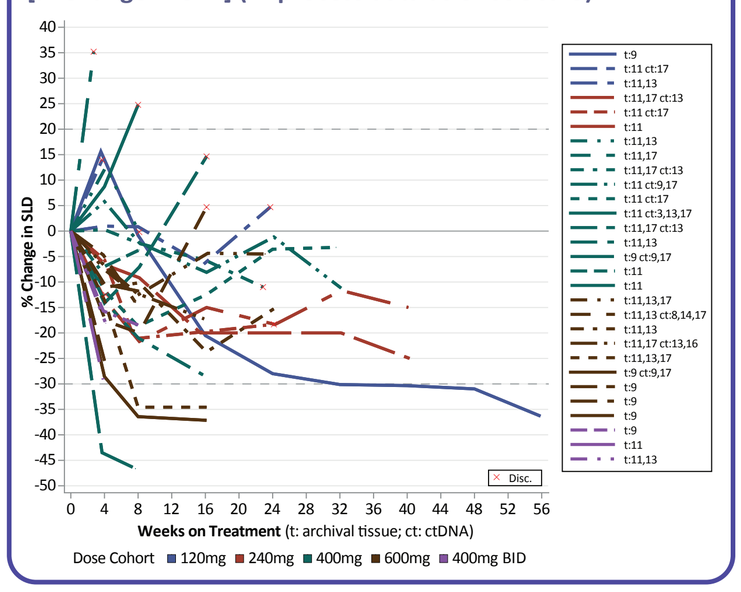
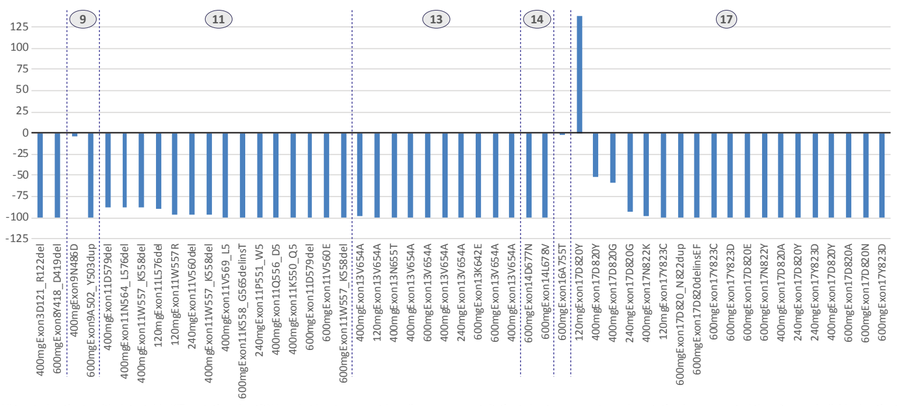


Figure 5: ctDNA Change in MUTANT ALLELE FRACTION from Baseline Across All Mutated Exons in *KIT* Identified

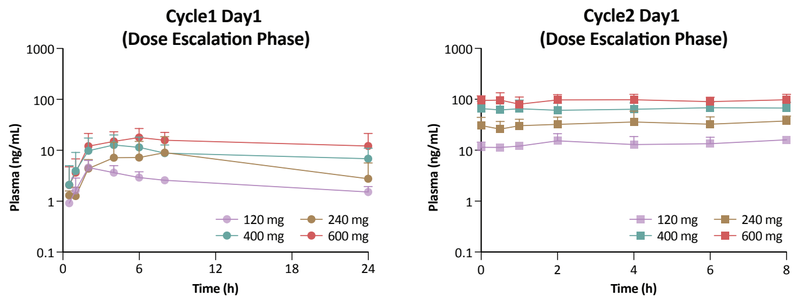


All treated patients with detectable KIT mutations in ctDNA and at least one post-baseline assessment. Patients best response to each mutation is represented therefore an individual patient may be represented more than once.
Not detectable mutation burdens were set to 0%.

Pharmacokinetics

- IDRX-42 demonstrated a dose-dependent increase in exposure with a long half-life (~125 hours) and a 5-8 fold accumulation at steady state

Figure 6: Mean plasma IDRX-42 concentration versus time profiles following an oral administration of IDRX-42 to patients with GIST at C1D1 and C2D1



*IDRX-42 was administered once daily on a 4-week cycle, with Cycle 2 beginning on day 29 (Cycle 2 day1) from the initiation of treatment

Safety

- The most common (>25%) treatment-related AEs were diarrhea (70%), nausea (52%), and vomiting (27%) (**Table 4**). Most AEs were grade 1 in severity. The most common (>5%) ≥ Grade 3 treatment-related AE was diarrhea (**Table 5**).
- No patients discontinued treatment due to adverse events

Table 4: Treatment-Related AEs (Any Grade) by MedDRA Preferred Term (≥ 10%)

n (%)	120 mg QD N = 3	240 mg QD N = 3	400 mg QD N = 12	600 mg QD N = 11	800 mg [400 mg BID] N = 4	Total N = 33
Any drug-related AE	3 (100)	2 (67)	10 (83)	10 (91)	4 (100)	29 (88)
Diarrhea	1 (33)	2 (67)	8 (67)	9 (82)	3 (75)	23 (70)
Nausea	1 (33)	0	6 (50)	7 (64)	3 (75)	17 (52)
Vomiting	0	0	4 (33)	3 (27)	2 (50)	9 (27)
Decreased appetite	1 (33)	0	0	5 (46)	2 (50)	8 (24)
Fatigue	1 (33)	0	1 (8)	5 (46)	1 (25)	8 (24)
Dysgeusia	1 (33)	0	2 (17)	2 (18)	0	5 (15)
Abdominal Pain	0	1 (33)	0	3 (27)	0	4 (12)
Anemia	0	0	2 (17)	2 (18)	0	4 (12)
Gastroesophageal reflux disease	0	0	2 (17)	1 (9)	1 (25)	4 (12)
Oedema peripheral	0	0	1 (8)	3 (27)	0	4 (12)

AEs assessed using CTCAE v5.0

Table 5: Treatment-Related ≥ Grade 3 AEs by MedDRA Preferred Term

n (%)	120 mg QD N = 3	240 mg QD N = 3	400 mg QD N = 12	600 mg QD N = 11	800 mg [400 mg BID] N = 4	Total N = 33
Any drug-related ≥ Grade 3 AE	0	0	1 (8)	3 (27)	2 (50)	6 (18)
Diarrhea	0	0	0	1 (9)	1 (25)	2 (6)
Anemia	0	0	0	1 (9)	0	1 (3)
Decreased appetite	0	0	0	0	1 (25)	1 (3)
Dyspepsia	0	0	1 (8)	0	0	1 (3)
Lymphocyte count decreased	0	0	0	1 (9)	0	1 (3)
Nausea	0	0	0	0	1 (25)	1 (3)
Syncope	0	0	0	1 (9)	0	1 (3)
Vomiting	0	0	0	0	1 (25)	1 (3)

AEs assessed using CTCAE v5.0

- 600 mg QD patient: Grade 3 syncope was considered a DLT. Patient chose to proceed with a dose reduction and was rechallenged at a dose of 400 mg QD and remains on treatment for more than 5 months as of the data cut off. The patient reported he experienced similar toxicities when taking sunitinib in the past.
- 800 mg (400 mg BID) patient: Grade 3 vomiting was considered a DLT. Patient chose to proceed with a dose reduction and was rechallenged at a dose of 400 mg QD and remains on treatment for more than 2 months as of the data cut off.
- All AEs are Grade 3 in severity. There were no Grade 4 or Grade 5 treatment-related adverse events

CONCLUSIONS

- IDRX-42 demonstrated promising antitumor activity and a favorable safety profile in a heavily pre-treated group of patients with advanced/metastatic GIST after failure of imatinib and other approved drugs
- IDRX-42 has a broad inhibitory profile across all mutational variants of KIT treated including both primary driver and resistance mutations (exons 9, 11, 13 and 17) with the potential for best in class activity
- Phase 1b will evaluate IDRX-42 in patients after failure of first-line imatinib as well as after failure of later lines of TKI therapy
- Based on the excellent tolerability and documented antitumor activity of IDRX-42, use of IDRX-42 in earlier lines of therapy will be investigated in the future

REFERENCES

1. Søreide K, et al. *Cancer Epidemiol*. 2016;40:39-46.
2. Kelly CM, et al. *J Hematol Oncol*. 2021;14(1):2.
3. Blum A, et al. *J Med Chem*. 2023;66:(4):2386-2395.
4. De Sutter L, et al. *Clin Cancer Res*. 2023;29(15):2859-2868.