2024 ASCO ANNUAL MEETING

Abstract #: 11501

StrateGIST 1: a first-in-human (FIH), phase 1 study of IDRX-42 in patients with metastatic gastrointestinal stromal tumors resistant to prior treatment with tyrosine kinase inhibitors (TKIs)

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IDRX-42: a highly selective and potent inhibitor of activating and resistance mutations in *KIT*

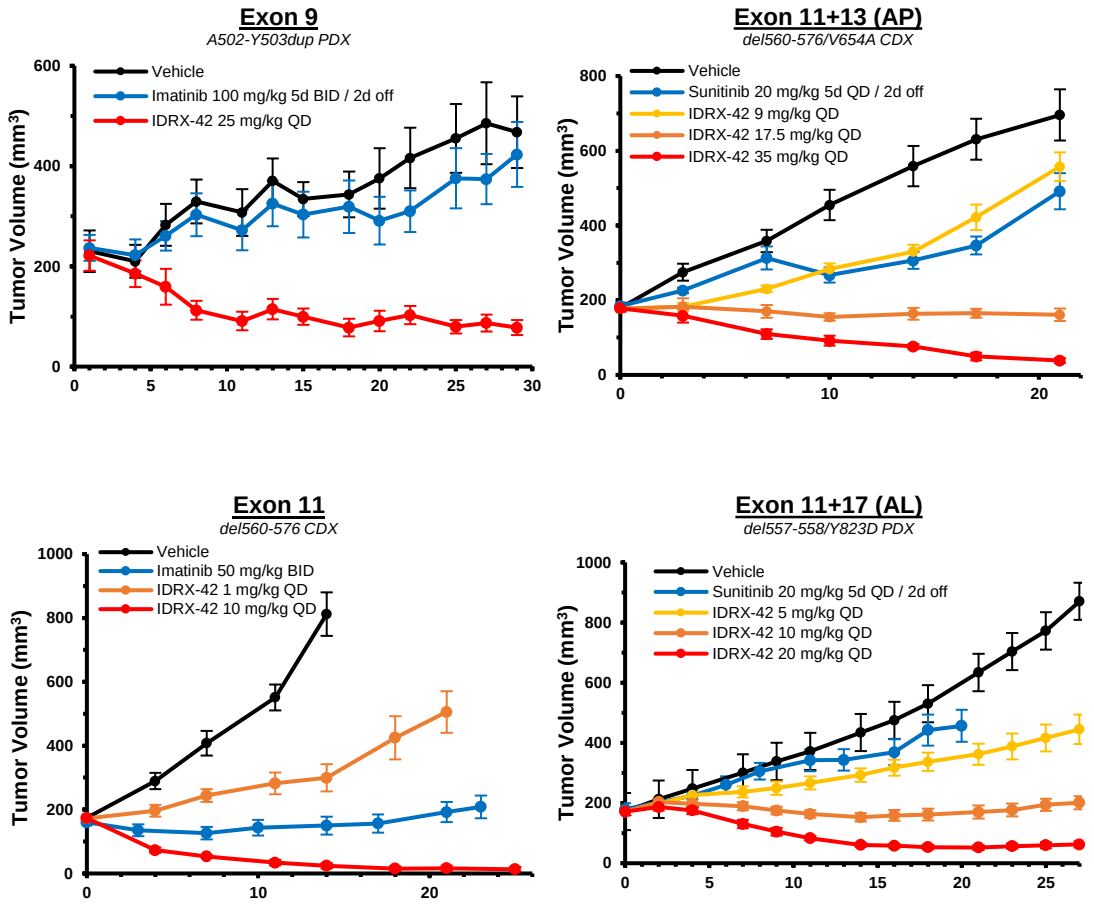
- IDRX-42 is being evaluated in a Phase 1/1b study in patients with advanced gastrointestinal stromal tumor (GIST)
- In the dose escalation portion of the study, IDRX-42 demonstrates:
  - Very promising clinical activity in patients following resistance to prior TKIs
  - Evidence of activity across relevant *KIT* mutations
  - A favorable safety profile
- Further evaluation in advanced GIST is warranted, including in early lines of therapy and patients with *KIT* exon 9 mutations

GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor

IDRX-42 and GIST

- *KIT* mutations drive most GIST, with resistance to standard TKIs due to diverse secondary mutations in the ATP-binding pocket and activation loop
- No approved TKI inhibits the full spectrum of these mutations[1]
- IDRX-42 has superior *in vivo* activity vs standard TKIs in preclinical models with exon 9, 11, 13 or 17 mutations, while sparing off-target kinases, e.g. VEGFR-2, FLT3[2,3]

IDRX-42 Activity in *KIT* Mutant Xenograft Mouse Models



3. De Sutter L et al. Clin Cancer Res. 2023;29(15):2859-2868; data on file

AP, ATP-binding pocket; AL. activation loop; CDX, cell-derived xenograft; FLT3, fms-like tyrosine kinase 3; PDX, patient-derived xenograft; TKI, tyrosine kinase inhibitor; VEGFR-2, vascular endothelial growth factor receptor 2

1. Kelly CM et al. *J Hematol Oncol*. 2021;14(1):2; 2. Blum A et al. *J Med Chem*. 2023;66:(4):2386-2395

Study design

Key Eligibility Criteria

- Metastatic and/or unresectable GIST
- Pathogenic mutations in *KIT* or non-exon 18 *PDGFRA*
- Progression on imatinib (phase 1)
- ECOG PS 0-1

Endpoints

- Safety/tolerability
- PK
- Anti-tumor activity (investigator-assessed)†

Phase 1 Dose Escalation (3+3 Design) ††

NCT05489237

First patient enrolled: 09 August 2022

- **1200 mg (600 mg BID) capsules, n=6**
- **800 mg (400 mg BID) capsules, n=12**
- **600 mg QD tablets, n=5**
- **600 mg QD capsules, n=12**
- **400 mg QD capsules, n=22**
- **300 mg QD tablets, n=10**
- **240 mg QD capsules, n=3**
- **120 mg QD capsules, n=3**

tablets provide 1.35x exposure by dose vs capsules

Enrollment beyond 3+3 at doses between 400 mg and 800 mg (backfill and dose confirmation)

Phase 1b Cohorts

at RP1bD(s)‡

1st Line
Treatment naïve

2nd Line
Progression on imatinib

≥3rd Line with approved TKIs
Progression on at least imatinib and sunitinib

≥3rd Line with investigational TKIs
prior bezuclastinib, NB003, or THE-630 (in addition to approved TKIs)

- As of 28 April 2024, 73 patients (all with *KIT*-mutant GIST) were enrolled in the Phase 1 portion, with doses up to 1200 mg clearing DLT evaluation, MTD not reached
- Phase 1b has recently been initiated with a dose of 300 mg QD tablets

†According to modified Response Evaluation in Solid Tumors (mRECIST) version 1.1; ††Dose escalation performed with IDRX-42 capsules, administered in 28-day cycles. Additionally, 2 cohorts enrolled at exposure equivalent doses of IDRX-42 tablets at 300 mg QD (equivalent to 400 mg capsule) and 600 mg QD (equivalent to 800 mg capsules); ‡1-2 dose levels from the Phase 1 portion may be evaluated in Phase 1b; BID, twice daily; DLT, dose limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MTD, maximum tolerated dose; PK, pharmacokinetics; PDGFRA, platelet-derived growth factor receptor alpha; QD, once daily; RP1bD(s), Recommend Phase 1b Dose(s); TKIs, tyrosine kinase inhibitor

Patient and tumor characteristics

	All Patients, N=73
Median age, years	59
Male, n (%)	47 (64)
Median time since diagnosis of unresectable/metastatic GIST, years	4.3
Median lines of prior systemic therapy (range) †	4 (1-8)
Prior therapy: 1 / 2 / ≥3 lines, n (%)	14 (19) / 8 (11) / 51 (70)
KIT mutation status (locally-assessed and/or by central ctDNA analysis), n (%)	
Any *KIT* mutation	73 (100)††
Any Exon 11 mutation	49 (67)
Exon 11 only	10 (14)
Exon 11 + 13 only	12 (16)
Exon 11 + 17 only	12 (16)
Exon 11 + 13 + 17 (+/- other exons)	9 (12)
Any Exon 9 mutation	21 (29)

†Imatinib administered in both the (neo)adjuvant setting and then first-line advanced setting is counted as 1 prior line; †† 6/73 patients did not have a mutation reported in either exon 9 or 11 (2 patients each had a mutation in exon 8 and exon 13+17 and 1 patient each had a mutation in exon 13 alone and exon 17 alone) and 3/73 patients had a mutation reported in both exons 9 and 11; ctDNA, circulating tumor deoxyribonucleic acid; PD, progressive disease; Data cutoff date: 28 April 2024

IDRX-42 exhibits a favorable safety profile

- GI TRAE most commonly Grade 1
- Low rate of dose modifications due to TRAE at 400 mg (n=32)[#]
  - 6% reductions, 9% interruptions
- DLTs in 3 patients:

600 mg QD: single event of syncope (Grade 3) on Day 1 – reduced to 400 mg QD, currently on treatment > 11 months (confirmed PR)

400 mg BID: vomiting (Grade 3) – reduced to 400 mg QD, currently on treatment >8 months (confirmed PR)

600 mg BID: Drug interrupted for >7 days (in Cycle 1) due to nausea/diarrhea/vomiting – reduced to 400 mg BID, currently on treatment >3 months

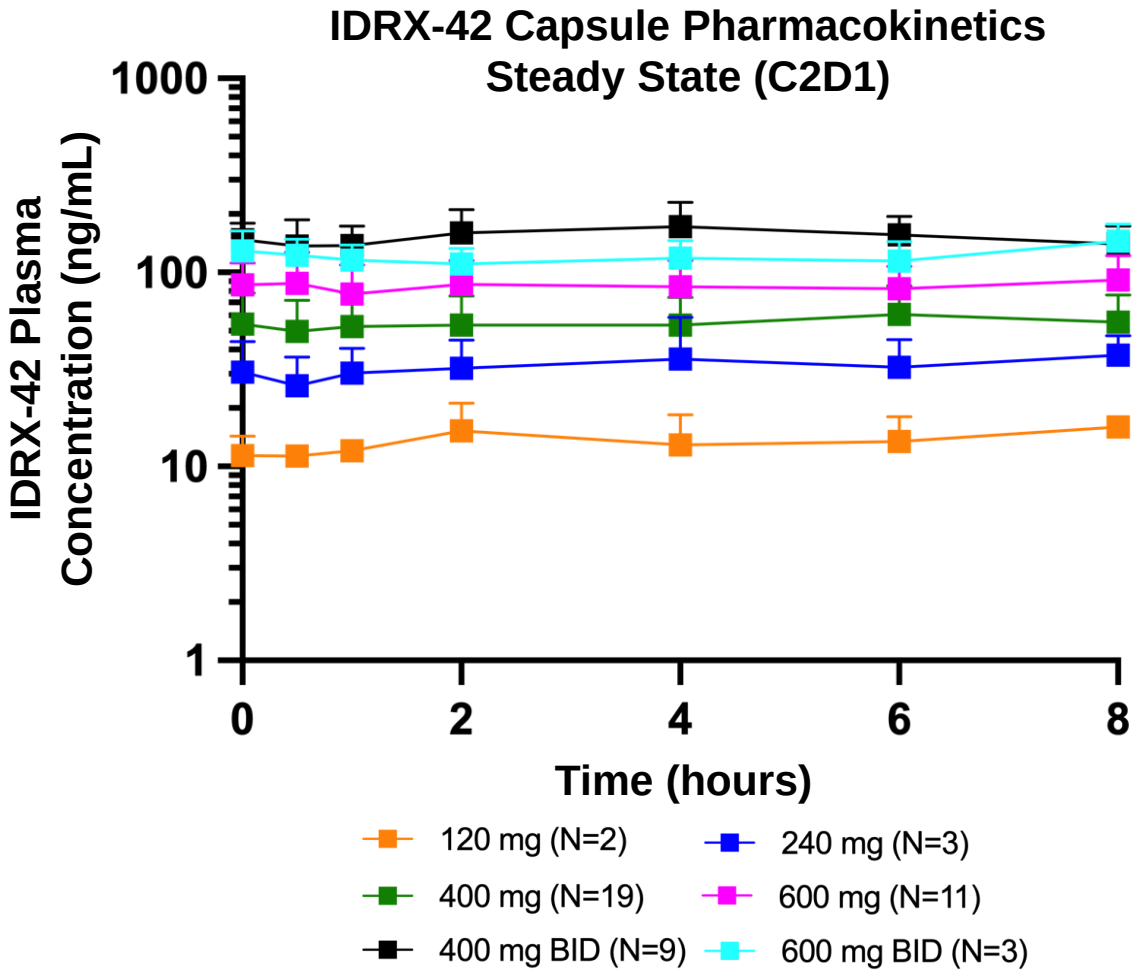
Treatment-related AEs (TRAE) occurring in ≥15% of patients, N=73

	Highest CTCAE Grade[†]		
	Grade 1	**Grade 2**	**Grade 3-4[††]**
Any TRAE, n (%)	25 (34)	26 (36)	14 (19)
Diarrhea	37 (51)	10 (14)	3 (4)
Nausea	31 (42)	9 (12)	2 (3)
Decreased appetite	16 (22)	7 (10)	1 (1)
Fatigue	11 (15)	8 (11)	2 (3)
Vomiting	14 (19)	6 (8)	1 (1)
Dysgeusia	16 (22)	2 (3)	
Anemia	4 (5)	6 (8)	3 (4)
Gastroesophageal reflux disease	8 (11)	4 (5)	
Periorbital edema	11 (15)*		
Peripheral edema	9 (12)	2 (3)	
TRAE leading to dose reduction[‡] / interruption, n (%)			11 (15) / 15 (21)
TRAE leading to treatment discontinuation, n (%)			2 (3)

[†]AEs graded according to CTCAE v5.0; [††]No Grade 5 TRAE were reported; [‡] From starting dose; *One additional patient had periorbital edema reported without CTCAE grade at time of data cutoff; [#]Includes 10 patients at equivalent 300 mg tablet dose; AE, adverse event; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose limiting toxicity; GI, gastrointestinal; MTD, maximum tolerated dose; PR, partial response; QD, once daily; TRAE, treatment-related adverse event; Data cutoff date: 28 April 2024

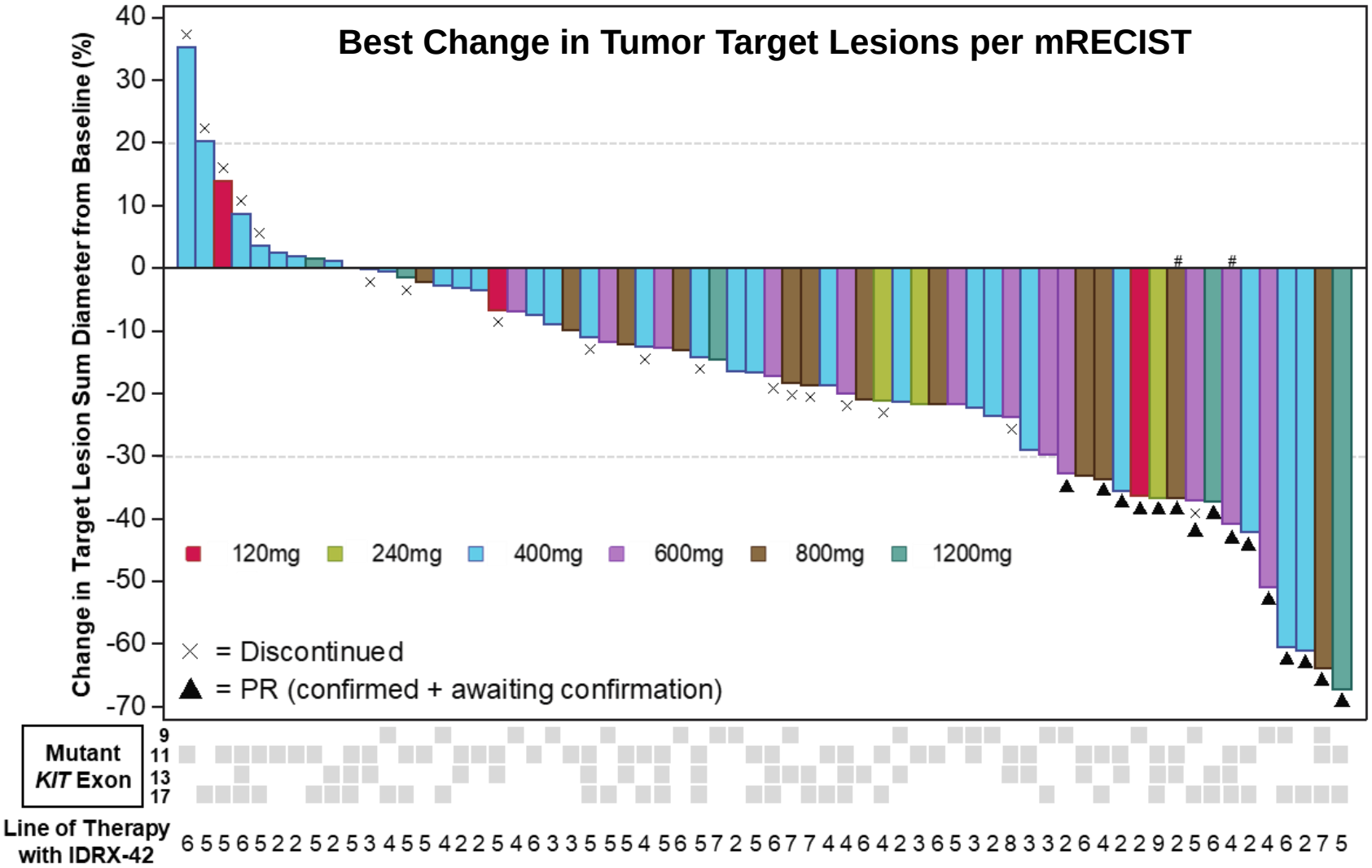
IDRX-42 shows a dose-linear PK profile

- 5-8x exposure accumulation from single dose to steady state
- Half-life: ~160-220 hours
  - BID administration at ≥800 mg daily dose to ease capsule burden
- Dose-dependent increase in exposure from 120 to 800 mg/day
- Tablets are utilized in Phase 1b (1.35x plasma exposure by dose vs capsules†)



†In a separate bioavailability study in healthy volunteers; AUC, area under the curve; BID, twice daily; C2D1, Cycle 2 Day 1; PK, pharmacokinetics; Data cutoff date: 19 April 2024

Promising anti-tumor activity in heavily pretreated GIST patients

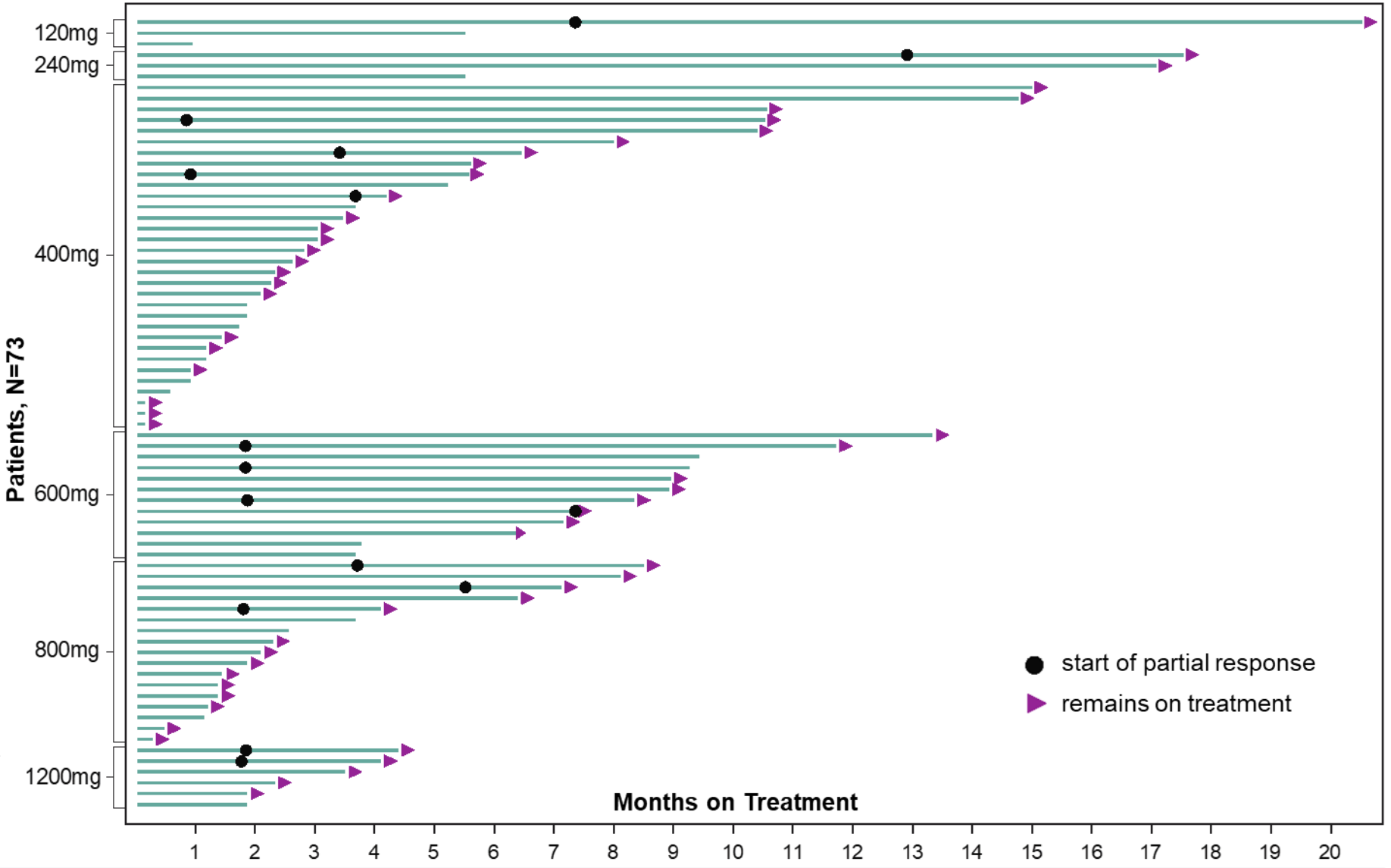


mRECIST Response Evaluable for Efficacy†	All Patients N=66	2nd Line Patients N=14
Median follow-up, months	5.6	3.0
Partial Response, n (%) *confirmed + awaiting confirmation*	15 (23) ††	6 (43) ‡
Median time to response, months	2.6	3.7

†Defined as all patients with at least 1 postbaseline disease assessment or prior clinical progression or death. Disease assessments performed at baseline, 4 weeks, 8 weeks and every 8 weeks thereafter; ††Includes 3 PRs awaiting confirmation; ‡Includes 2 PRs awaiting confirmation. Of 2nd line patients with opportunity for ≥16 weeks follow up, 6/7 achieved a PR; #One patient with PR each in the 600 and 800 mg cohorts had dose reduction to 400 mg early in Cycle 1 (Day 2 and 14, respectively); 400 mg and 800 mg capsule equivalent dose levels include patients treated with 300 mg QD tablets and 600 mg QD tablets, respectively; mRECIST, modified RECIST; PR, partial response; QD, once daily; Data cutoff date: 28 April 2024

IDRX-42 duration of treatment and response

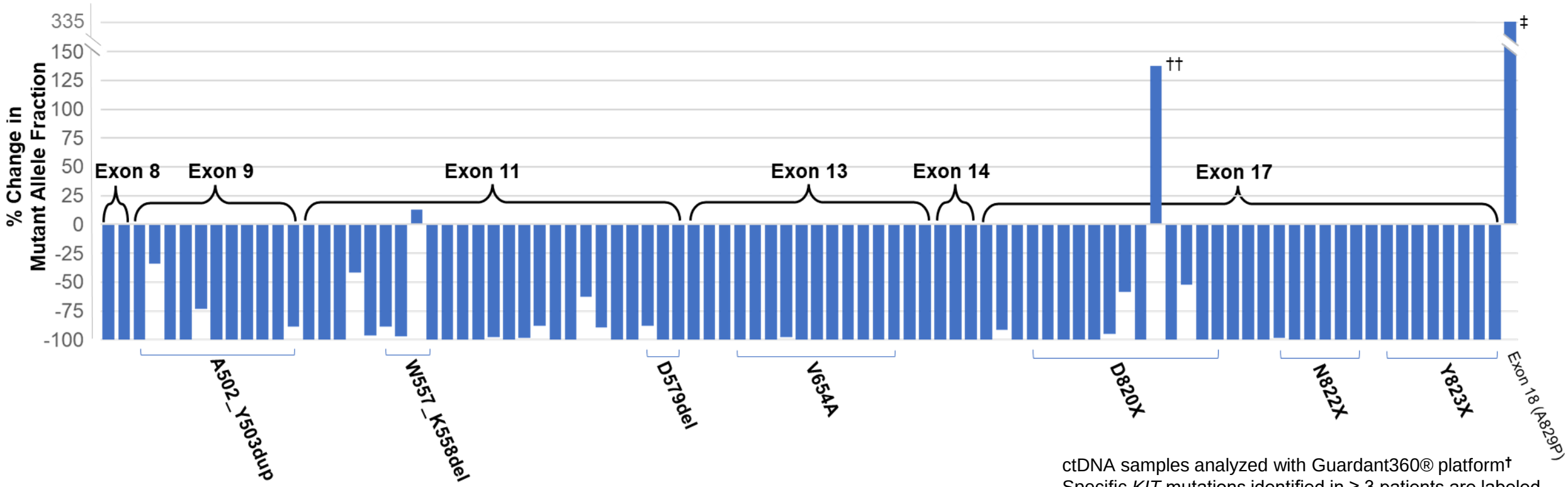
- 74% of patients remain on treatment†
- 16 weeks median duration of treatment
- 70% (33/47) Clinical Benefit Rate in patients with adequate follow up††



†16 patients discontinued for PD, 2 for adverse events, 1 for death (pneumonia, not related); ††Clinical Benefit Rate (SD for ≥16 weeks or confirmed PR) evaluable population excludes patients who are ongoing without a 16-week assessment and have not yet had PD or a confirmed PR; PD, progressive disease; PR, partial response; SD, stable disease; Data cutoff date: 28 April 2024

Reductions in ctDNA observed across *KIT* mutations

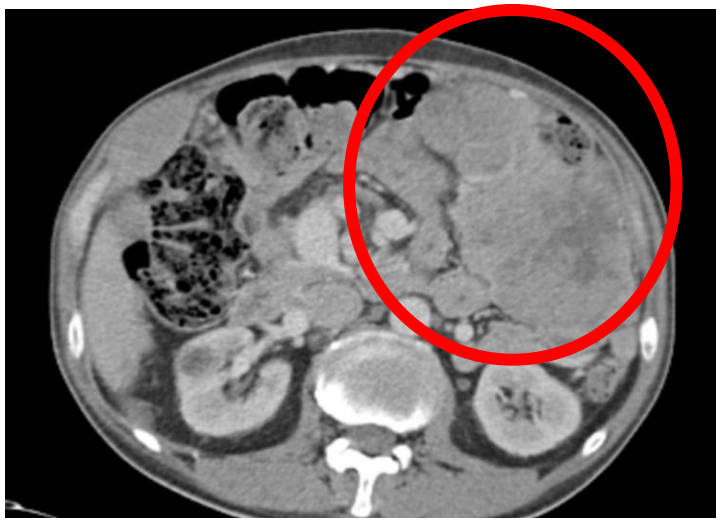
Best Change in Mutant Allele Fraction by *KIT* Mutation



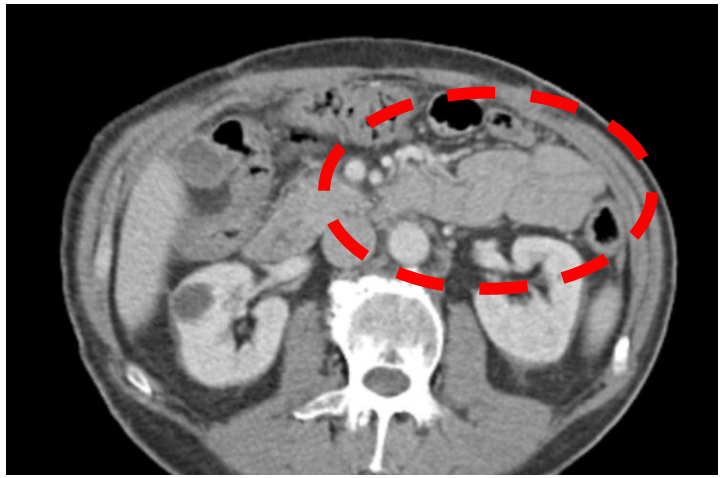
ctDNA samples analyzed with Guardant360® platform†
Specific *KIT* mutations identified in ≥ 3 patients are labeled

†Samples obtained at C1D1, C1D15, C2D1, C3D1, then every 6 cycles, at End-of-Treatment and 30-day Follow-Up after last dose. 41/53 baseline samples (as of 15 April 2024) had ≥1 KIT mutation detected. Of these, 37 had a postbaseline sample and are included in this analysis. Best response for each baseline mutation is represented, and individual patients may be represented more than once. Postbaseline, for mutations below the lower limit of quantitation, mutant allele frequency value was set to 0%. 3 *KIT* mutations of unknown significance were also detected in exons 3, 4, and 16, respectively, with all showing a 100% decrease in mutant allele fraction; ††120 mg patient with increase in exon 17 D820X mutation had disease progression at 4 weeks; ‡400 mg patient with increase in Exon 18 A829P mutation had stable disease for >8 months (ongoing); ctDNA, circulating tumor deoxyribonucleic acid; CXDX, Cycle X Day X

Radiographic response in *KIT* exon 9 and 17 mutant GIST (6th Line)

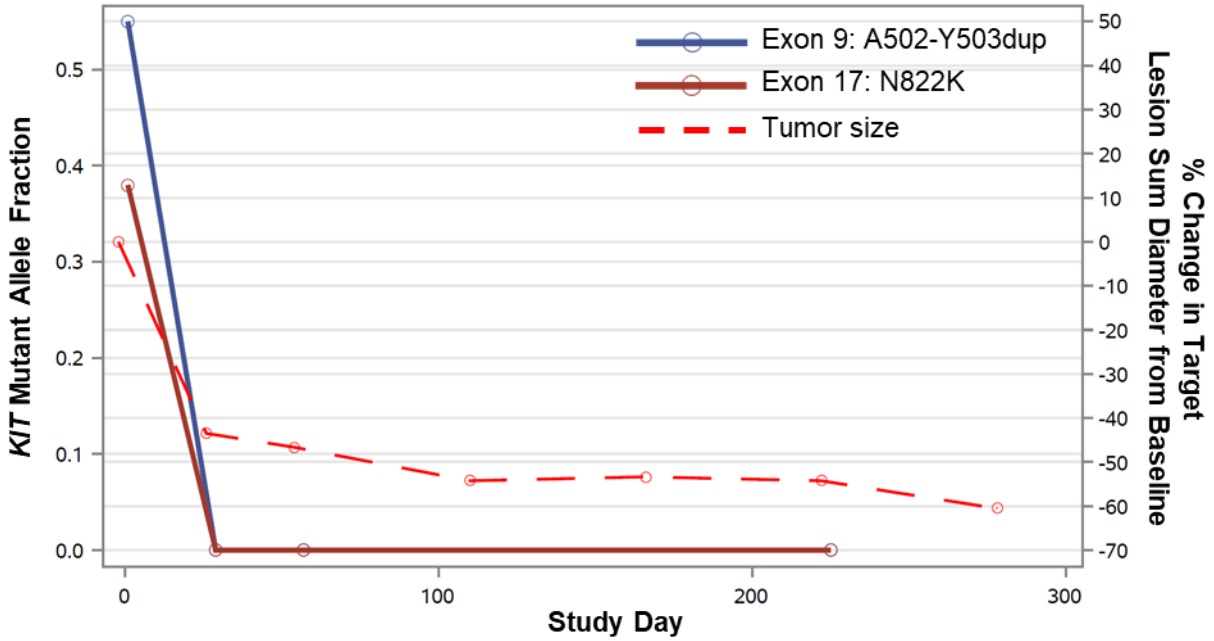


Baseline



Study Day 54

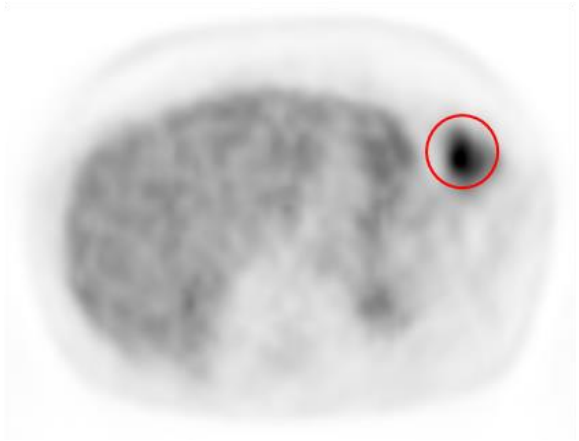
- 60 year old male (400 mg QD)
- Prior imatinib, sunitinib, regorafenib, cabozantinib, and regorafenib rechallenge
- No known response to prior therapy
- PR by mRECIST at 4 weeks
- Currently on treatment >10 months



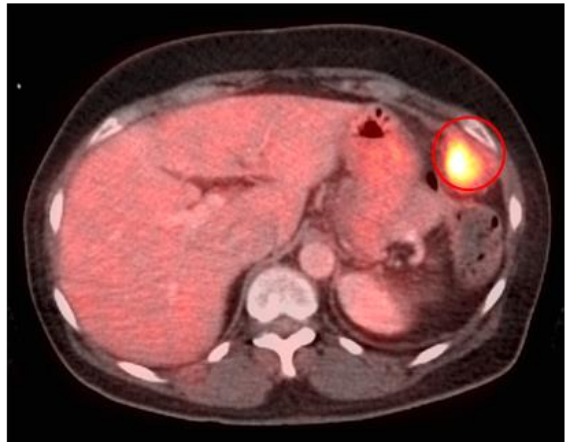
Radiographic images provided by César Serrano, Vall d'Hebron Institut d'Oncologia (VHIO)

mRECIST; modified RECIST; PR, partial response; QD, once daily; Data cutoff date: 28 April 2024

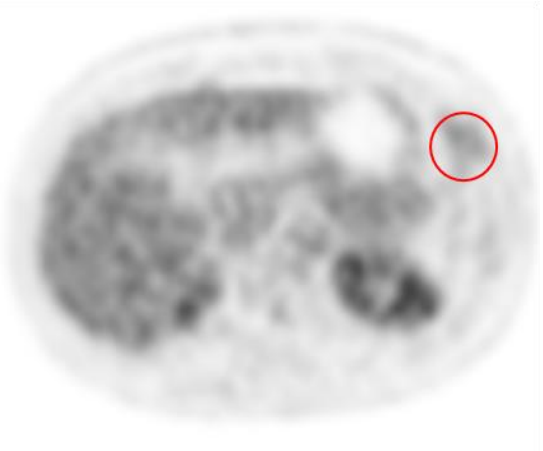
FDG-PET response in *KIT* exon 11 and 13 mutant GIST (2nd Line)



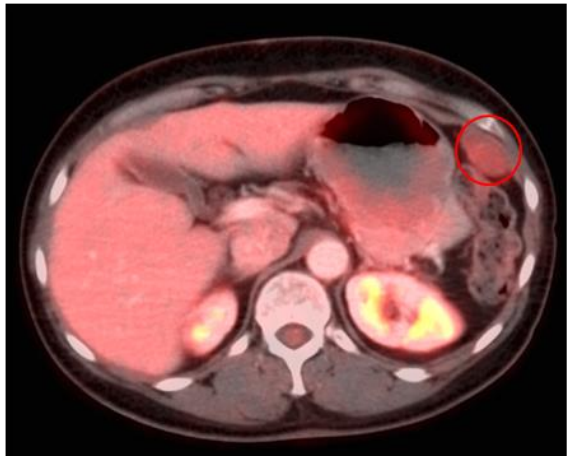
Baseline



Metabolic tumor volume: 51.1 mL SUV_{peak}:6.3
SUV_{max}: 7.4

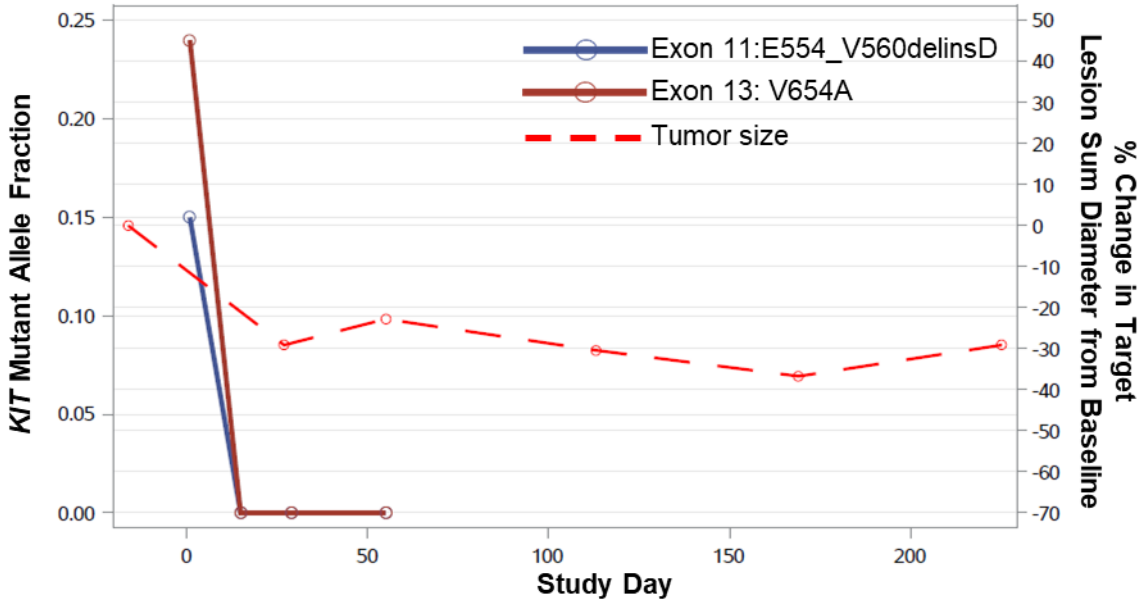


Study Day 27



Metabolic tumor volume: 0 mL SUV_{peak}: 2.7*
SUV_{max}: 3.1*

- 59 year old female (400 mg BID)
- Progression on prior imatinib only
- Dose reduced to 400 mg QD due to vomiting in Cycle 1
- PR by mRECIST at 16 weeks
- Currently on treatment >8 months



Radiographic images provided by Patrick Schöffski, Leuven Cancer Institute, with technical support of Sander Jentjens, University Hospitals in Leuven

*Below liver uptake; BID, twice daily; FDG-PET, fluorodeoxyglucose positron emission tomography; mRECIST, modified RECIST; PR, partial response; QD once daily; SUV, standardized uptake value; Data cutoff date: 28 April 2024

Conclusions

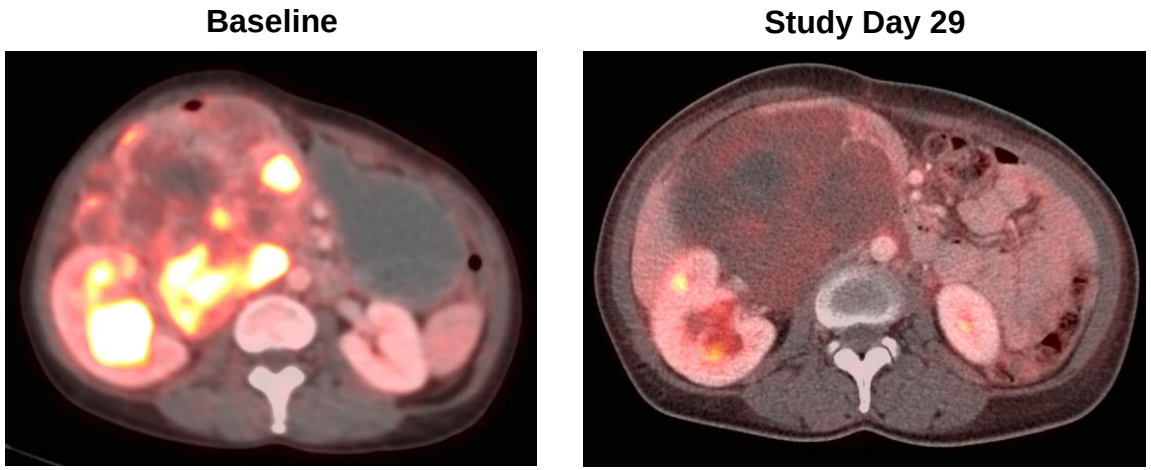
- In this Phase 1 study in patients with advanced GIST, IDRX-42 demonstrates:
  - Very promising clinical activity following resistance to prior TKIs
  - Evidence of activity in patients with activating mutations in *KIT* exons 9 and 11, as well as resistance mutations in exons 13 and 17
  - A favorable safety profile with manageable AEs, and linear PK
- Phase 1b has been initiated with a dose of 300 mg QD tablets (equivalent to 400 mg QD capsules)
- Clinical data support further evaluation of IDRX-42 in advanced GIST, including in early lines of therapy and patients with difficult-to-treat *KIT* exon 9 mutations

AE, adverse event; GIST, gastrointestinal stromal tumor; PK, pharmacokinetics; QD, once daily; TKI, tyrosine kinase inhibitor

Acknowledgments

The authors would like to acknowledge the scientists at Merck KGaA, who led the discovery and preclinical development of IDRX-42

The authors would like to thank the patients who are participating in this study, their families and caregivers, as well as the investigators and study teams at all StrateGIST 1 clinical sites



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