THE NOVEL KIT INHIBITOR IDRX-42 SHOWS PROMISING ACTIVITY IN 2ND AND LATER-LINE GASTROINTESTINAL STROMAL TUMORS: RESULTS FROM A PHASE 1 STUDY (STRATEGIST 1)

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2024 ANNUAL MEETING

1. Dana-Farber Cancer Institute – Sarcoma Center, Boston, Massachusetts, USA; 2. Oregon Health & Science University (OHSU), Portland, OR, USA; 3. University of Miami – Sylvester Comprehensive Cancer Center, Miami, Florida, USA; 4. Hospital Universitari Vall d'Hebron - Vall d'Hebron Institut d'Oncologia (VHIO), Barcelona, Spain; 5. Universitaetsklinikum Essen - Westdeutsches Tumorzentrum (WTZ) (West German Cancer Center), Essen, North Rhine-Westphalia, Germany; 6. Fox Chance Cancer Center, Philadelphia, Pennsylvania, USA; 7. MD Anderson Cancer Center, Houston, Texas, USA; 8. Helios Klinikum Berlin-Buch, Berlin, Germany; 9. IDRx, Plymouth, Massachusetts, USA; 10. University Hospitals Leuven, Department of General Medical Oncology, Leuven Cancer Institute, KU Leuven, Leuven, Belgium

IDRX-42: a KIT TKI designed to address unmet need in GIST

- *KIT* mutations drive most GIST, with resistance to 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]
  - Response rates with 2nd line sunitinib, 3rd line regorafenib, and 4th line ripretinib are approximately 18%, 5%, and 9%, respectively [2,3,4]
- IDRX-42 is an investigational KIT TKI which has shown:
  - Superior *in vivo* activity vs standard TKIs in xenograft mouse models with exon 9, 11, 13 and 17 mutations[5,6]
  - Selectivity over off-target kinases, sparing VEGFR-2 and FLT3[5]

FLT3, fms-like tyrosine kinase 3; TKI, tyrosine kinase inhibitor; VEGFR-2, vascular endothelial growth factor receptor 2; Sources: 1. Kelly CM et al. J Hematol Oncol. 2021;14(1):2; 2. Bauer et al. J Clin Oncol. 2022;40(34):3918-3928; 3. Demetri et al. Lancet. 2013;381(9863):295-302; 4. Blay et al. Lancet Oncol. 2020 (7):923-934.; 5. Blum A et al. J Med Chem. 2023;66:(4):2386-2395; 6. De Sutter L et al. Clin Cancer Res. 2023;29(15):2859-2868

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STRATEGIST 1: 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

Key Endpoints

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

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

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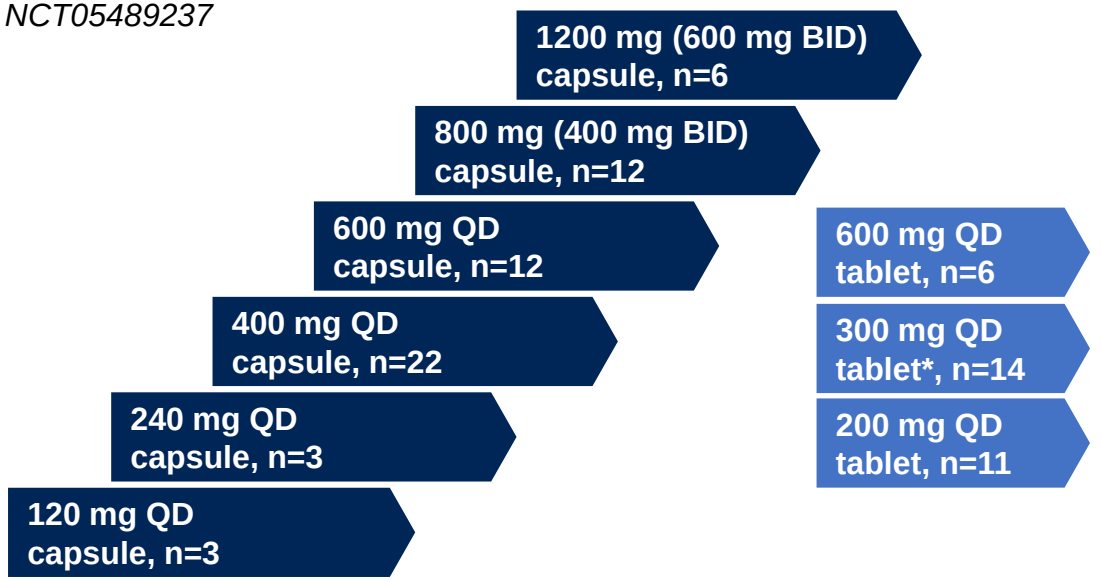

**Based on similar steady-state plasma exposure, data from 300 mg tablet dose and 400 mg capsule dose are analyzed together in this presentation*

Phase 1b Cohorts
at RP1bD(s)‡

- 1st Line
- 2nd Line
- ≥3rd Line with approved TKIs
- ≥3rd Line with investigational TKIs‡‡

- **As of 30 September 2024, 89 patients were enrolled in the Phase 1 portion at doses of 120 mg – 1200 mg, and are the focus of this update**
- Phase 1b was initiated in May 2024 at a Recommended Phase 1b Dose (RP1bD) of 300 mg QD (tablet)

§ Per NCI CTCAE version 5.0; †According to modified Response Evaluation in Solid Tumors (mRECIST) v1.1 (Demetri et al. Lancet. 2013;381(9863):295-302); †† Dose escalation performed with IDRX-42 capsules, administered in 28-day cycles. Additionally, 3 cohorts enrolled with IDRX-42 tablets at 200 mg QD, 300 mg QD and 600 mg QD. Enrollment beyond 3+3 included backfill and dose confirmation patients; ‡ RP1bD: Recommended Phase 1b dose; 1-2 dose levels from the Phase 1 portion may be evaluated in Phase 1b; ‡‡ Prior bezuclastinib, NB003, or THE-630; BID, twice daily; DLT, dose limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PK, pharmacokinetics; PDGFRA, platelet-derived growth factor receptor alpha; QD, once daily; RP1bD(s), TKIs, tyrosine kinase inhibitor

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STRATEGIST 1: Patient and tumor characteristics

	All Patients N=89
Median age, years	59 (32-78)
Male, n (%)	57 (64)
Median time since diagnosis of unresectable/metastatic GIST, years	4.5
Median lines of prior systemic therapy (range) †	4 (1-8)
Prior therapy: 1 / 2 / ≥3 lines, n (%)	15 (17) / 10 (11) / 64 (72)
≥3 lines without ripretinib, n (%)	25 (28)
KIT* mutation status §, n (%)** ***By local assessment or central baseline ctDNA analysis	
Any *KIT* mutation	89 (100)
Any Exon 9	25 (28)
Any Exon 11	63 (71)

As of 30 September 2024, 63% of patients (56/89) remain on IDRX-42††, with a median duration of treatment of 6.6 mo (range: 0.2-26)

† Imatinib administered in both the (neo)adjuvant setting and then first-line advanced setting is counted as 1 prior line; § 7/89 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 had a mutation in exon 13 alone and 2 patients had a mutation in exon 17 alone) and 6/89 patients had a mutation reported in both exons 9 and 11; †† 28 patients discontinued for radiographic PD, 2 for clinical PD, 2 for adverse events, 1 for death (pneumonia, not related); ctDNA, circulating tumor deoxyribonucleic acid; PD, Data cutoff date: 30 September 2024

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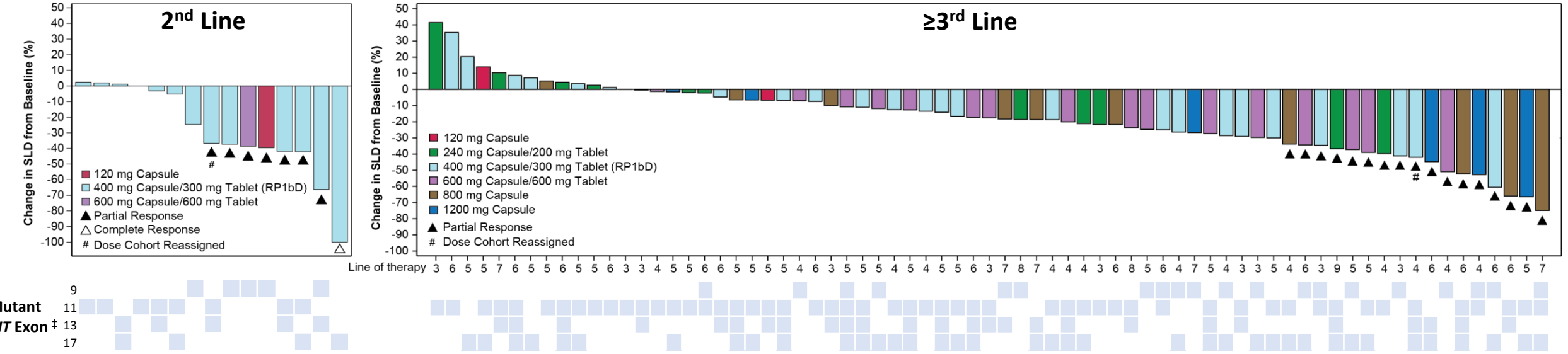
STRATEGIST 1: Promising anti-tumor activity in 2nd and later-line GIST

Objective Response Rate (ORR)†, n/N (%)	2nd Line	3rd Line	≥4th Line No Prior Ripretinib	All Patients
All Doses	8/15 (53)	2/10 (20)	9/25 (36)	25/87 (29) ††
400 mg capsule/300 mg tablet (RP1bD)#	6/13 (46)	2/4 (50)	2/10 (20)	10/38 (26)

Best Change in Tumor Target Lesions per mRECIST



† In the efficacy evaluable population, defined as all patients with at least one postbaseline disease assessment or prior clinical progression or death. Disease assessments according to mRECIST (modified RECIST v1.1; Demetri et al. Lancet. 2013;381(9863):295-302) performed at baseline, 4 weeks, 8 weeks and every 8 weeks thereafter; †† Responses (n=25) includes 1 confirmed CR, 22 confirmed PR, and 2 PRs awaiting confirmation; # One patient each in the 600 and 800 mg cohorts had dose reduction to 400 mg early in Cycle 1 (Day 2 and 14, respectively) and are analyzed as effectively treated at 400 mg; ‡ As detected by local assessment or central baseline ctDNA analysis; Based on similar steady-state plasma exposures, data from the following dose/formulation pairs are analyzed together in this presentation: 200 mg tablet/240 mg capsule, 300 mg tablet/400 mg capsule, and 600 mg tablet/600 mg capsule; QD, once daily; RP1bD, Recommended Phase 1b Dose;; SLD, Sum Lesion Diameter; Data cutoff date: 30 September 2024

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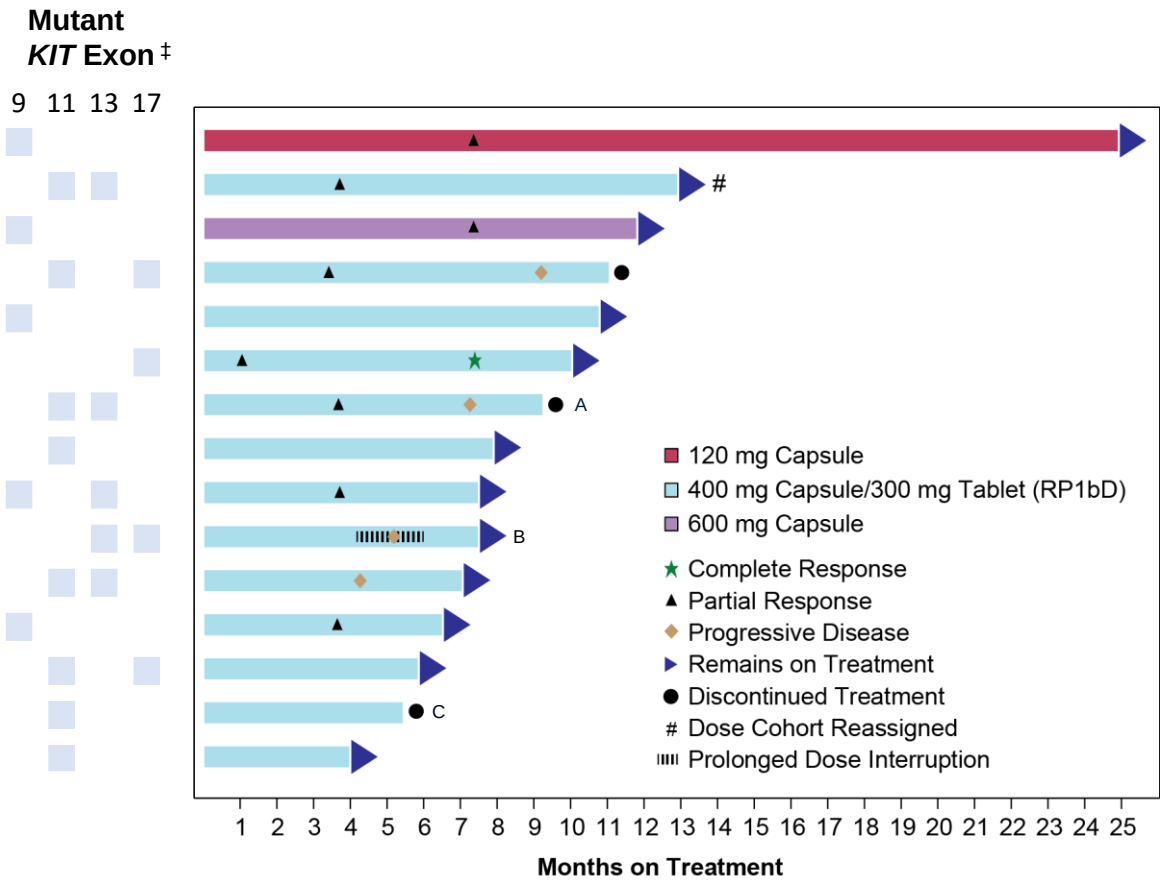
STRATEGIST 1: Duration of treatment and response in 2nd line patients



- Median duration of treatment: 8.7 months (range: 4.8-25.8)
- PFS (95% CI) at 6 months: 85% (51%-96%)
- Median PFS not estimable

‡ As detected by local assessment or central baseline ctDNA analysis; # One patient in the 800 mg dose cohort had dose reduction to 400 mg early in Cycle 1 (Day 14) and is analyzed as effectively treated at 400 mg; A Patient with *KIT* T670I mutation (exon 14) initially detected in ctDNA on C1D15. In preclinical studies, IDRX-42 had lower potency against T670I-containing variants compared to resistance mutations in exons 13 and 17; B Patient had PD after 30 days of dose interruption due to management of small bowel obstruction; C Patient with T670I mutation based on local assessment at baseline. This patient had a solitary hepatic lesion present at study entry which was subsequently completely resected on Study Day 88, with efficacy information censored thereafter in the analysis; PFS, progression-free survival (Kaplan-Meier estimate); PR, partial response; RP1bD, Recommended Phase 1b Dose; Data cutoff date: 30 September 2024

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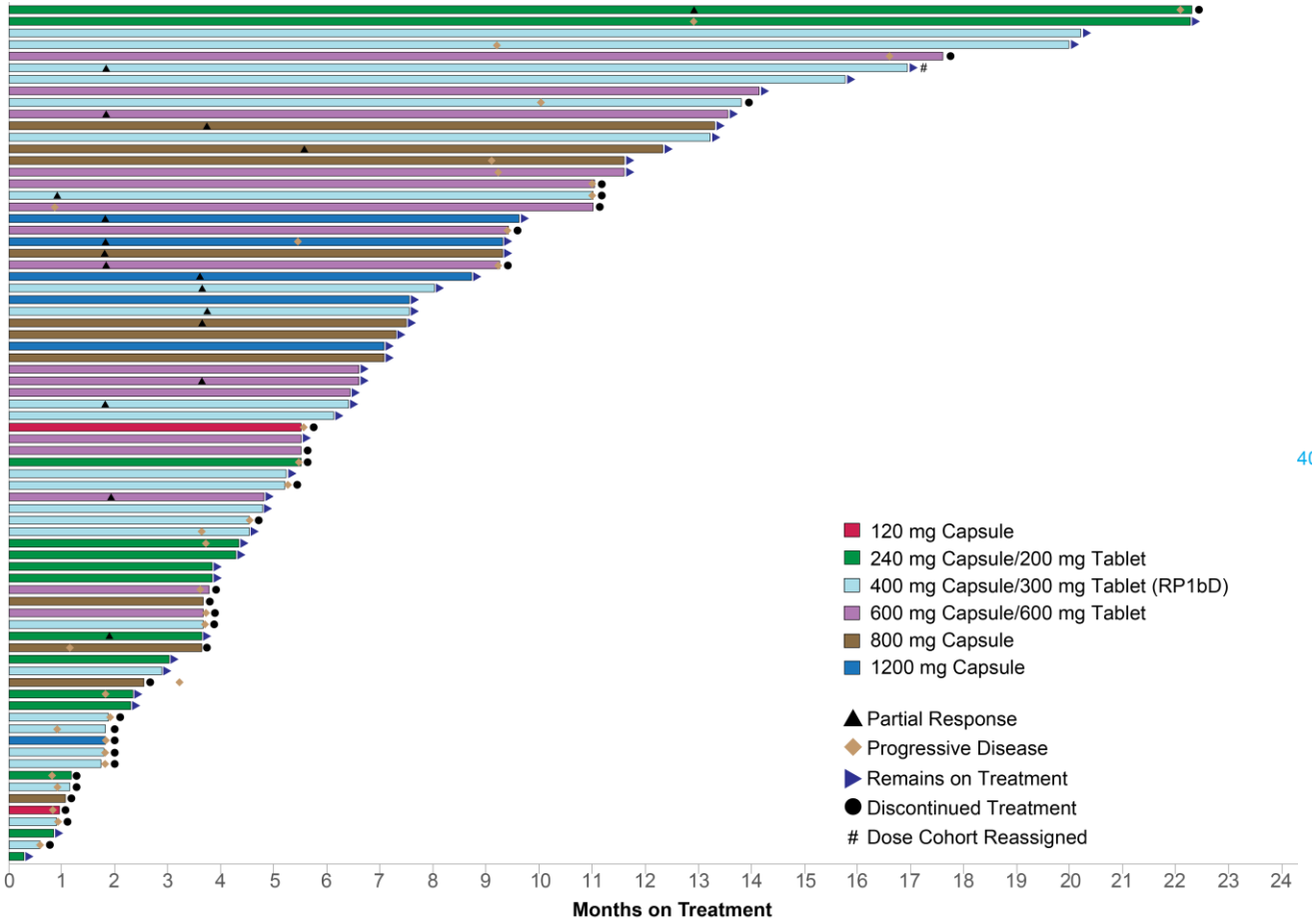
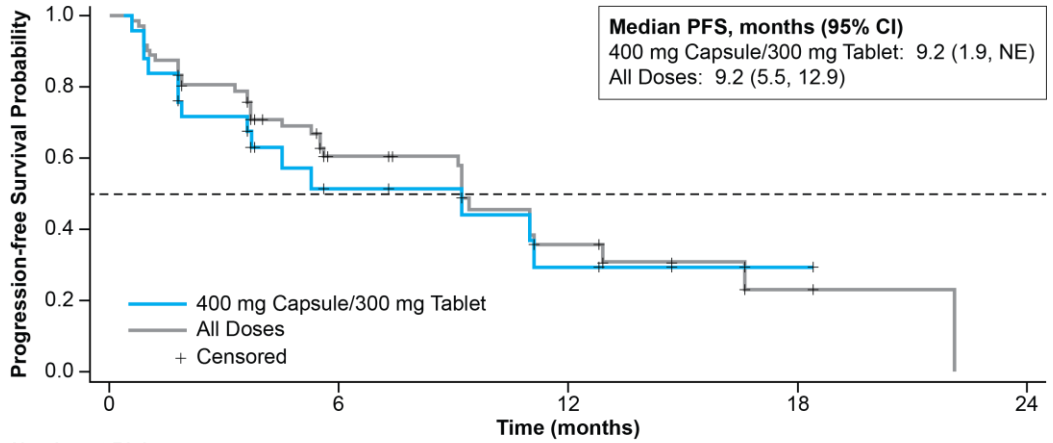
STRATEGIST 1: Durable clinical activity in heavily pretreated patients

Duration of Treatment and Response ≥3rd Line Patients



Progression-Free Survival, ≥3rd Line Patients



Number at Risk

400 mg Capsule/ 300 mg Tablet	25	8	4	1	0
All Doses	72	23	9	2	0

Progression-Free Survival (PFS)

	3rd Line		≥4th Line No Prior Ripretinib	
	N	Median PFS, months (95%CI)	N	Median PFS, months (95%CI)
All Doses	10	12.9 (0.8, NE)	25	9.2 (3.7, NE)
400 mg capsule/ 300 mg tablet (RP1bD)#	4	NE (1.9, NE)	10	11.0 (0.6, NE)

One patient in the 600 mg cohort had dose reduction to 400 mg early in Cycle 1 (Day 2) and is analyzed as effectively treated at 400 mg; NE, not estimable; PFS, progression-free survival (Kaplan-Meier estimate); RP1bD, Recommended Phase 1b Dose; Data cutoff date: 30 September 2024

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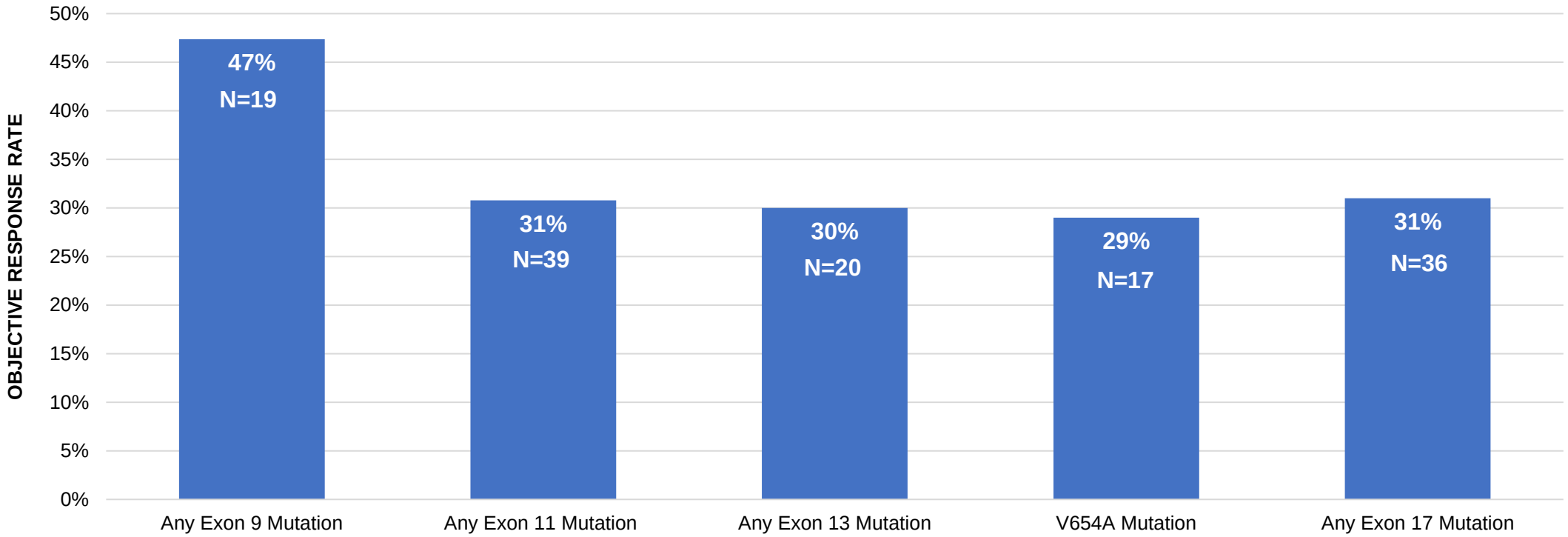
STRATEGIST 1: Responses observed across *KIT* mutation subsets

ORR† by *KIT* Mutation According to Baseline Central ctDNA Analysis



† Confirmed responses and responses awaiting confirmation in the efficacy evaluable population (all lines of therapy) according to mRECIST (modified RECIST v1.1; Demetri et al. Lancet. 2013;381(9863):295-302); ctDNA, circulating tumor DNA;; ORR, objective response rate; Data cutoff date: 30 September 2024

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STRATEGIST 1: IDRX-42 Favorable safety and tolerability profile

- Recommended Phase 1b Dose (RP1bD) yielded fewer dose reductions and Grade 3-4 TRAE (compared to higher doses)
- Mean relative dose intensity >90% at RP1bD for all completed cycles

Treatment-Related AEs (TRAE) and Dose Modifications

	400 mg capsule/300 mg tablet (RP1bD) N=36[#]			All Patients N=89		
	Highest CTCAE Grade[†]					
	1	2	3-4[††]	1	2	3-4[††]
Any TRAE, n (%)	16 (44)	16 (44)	3 (8)[§]	27 (30)	34 (38)	21 (24)
TRAE in ≥15% Patients Overall						
Diarrhea	20 (56)	3 (8)		43 (48)	14 (16)	3 (3)
Nausea	17 (47)	4 (11)		37 (42)	9 (10)	3 (3)
Dysgeusia	12 (33)	2 (6)		24 (27)	6 (7)	
Fatigue	7 (19)	4 (11)		17 (19)	10 (11)	2 (2)
Decreased appetite	5 (14)			19 (21)	8 (9)	1 (1)
Vomiting	10 (28)	2 (6)		19 (21)	5 (6)	3 (3)
Anemia	2 (6)	5 (14)		7 (8)	11 (12)	6 (7)
Gastroesophageal reflux disease	7 (19)	3 (8)		15 (17)	5 (6)	
Periorbital edema	5 (14)			16 (18)		
Peripheral edema	2 (6)	1 (3)		13 (15)	2 (2)	
Neutrophil count decreased	2 (6)	4 (11)		3 (3)	7 (8)	4 (5)
Dose Modifications						
TRAE leading to dose reduction[‡], n (%)	3 (8)			15 (17)		
TRAE leading to dose interruption, n (%)	6 (17)			21 (24)		
TRAE leading to discontinuation, n (%)	0			2 (2)		

[#] All patients who initiated treatment at either 400 mg capsules or 300 mg tablets; [†] AEs graded according to NCI CTCAE v5.0; [††] No Grade 5 TRAE were reported; [§] Grade 3 TRAEs reported: esophagitis, lymphocyte count decreased, leukopenia; [‡] From starting dose; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; RP1bD, Recommended Phase 1b Dose; TRAE, treatment-related adverse event; Data cutoff date: 30 September 2024

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STRATEGIST 1: Conclusions

- IDRX-42 has demonstrated:
  - Promising responses in previously-treated GIST
    - 2nd line ORR = 53%
    - ≥3rd line ORR = 24%
    - Responses across important *KIT* activating and resistance mutation subsets
  - Durable clinical activity: 9.2 months median PFS in ≥3rd line patients overall
    - Longer median PFS estimated for 3rd line patients overall (12.9 months) and ≥4th line patients without prior ripretinib, at the recommended Phase 1b dose (11.0 months)
  - A favorable safety profile, with manageable AEs
- Phase 1b is ongoing in 1st, 2nd and later-line GIST
  - 1st line cohort remains open to accrual
- A randomized Phase 3 study comparing IDRX-42 to sunitinib in 2nd line GIST is planned

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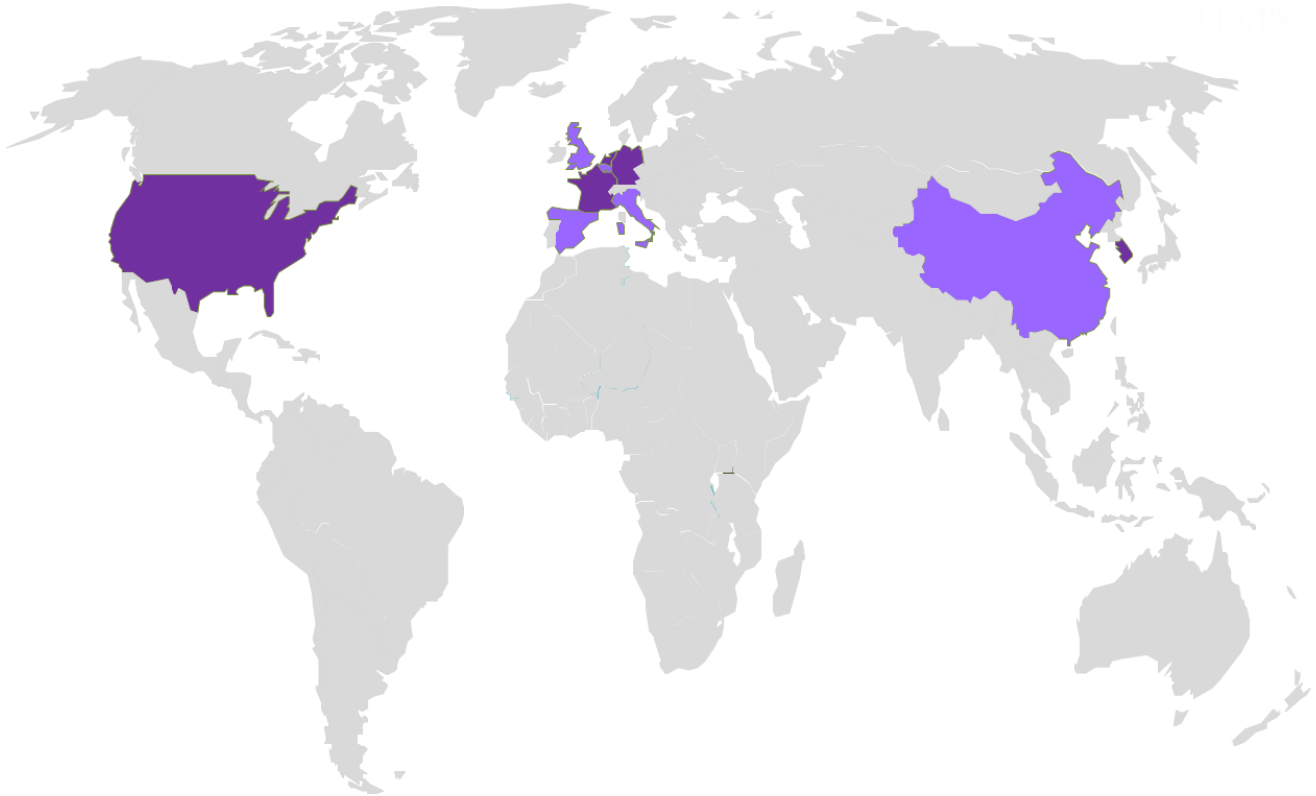
StrateGIST 1 Countries:

- USA
- Belgium
- France
- Germany
- Spain
- Italy
- Netherlands
- United Kingdom
- Korea
- China



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