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INVICTUS: A Phase 3, *IN*ter*V*ential, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Ripretinib as ≥4th Line Therapy *I*n Patients with Advan*C*ed Gastrointestinal Stromal *TU*mor*S* (GIST) Who Have Received Treatment with Prior Anticancer Therapies (NCT03353753)

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Acknowledgements

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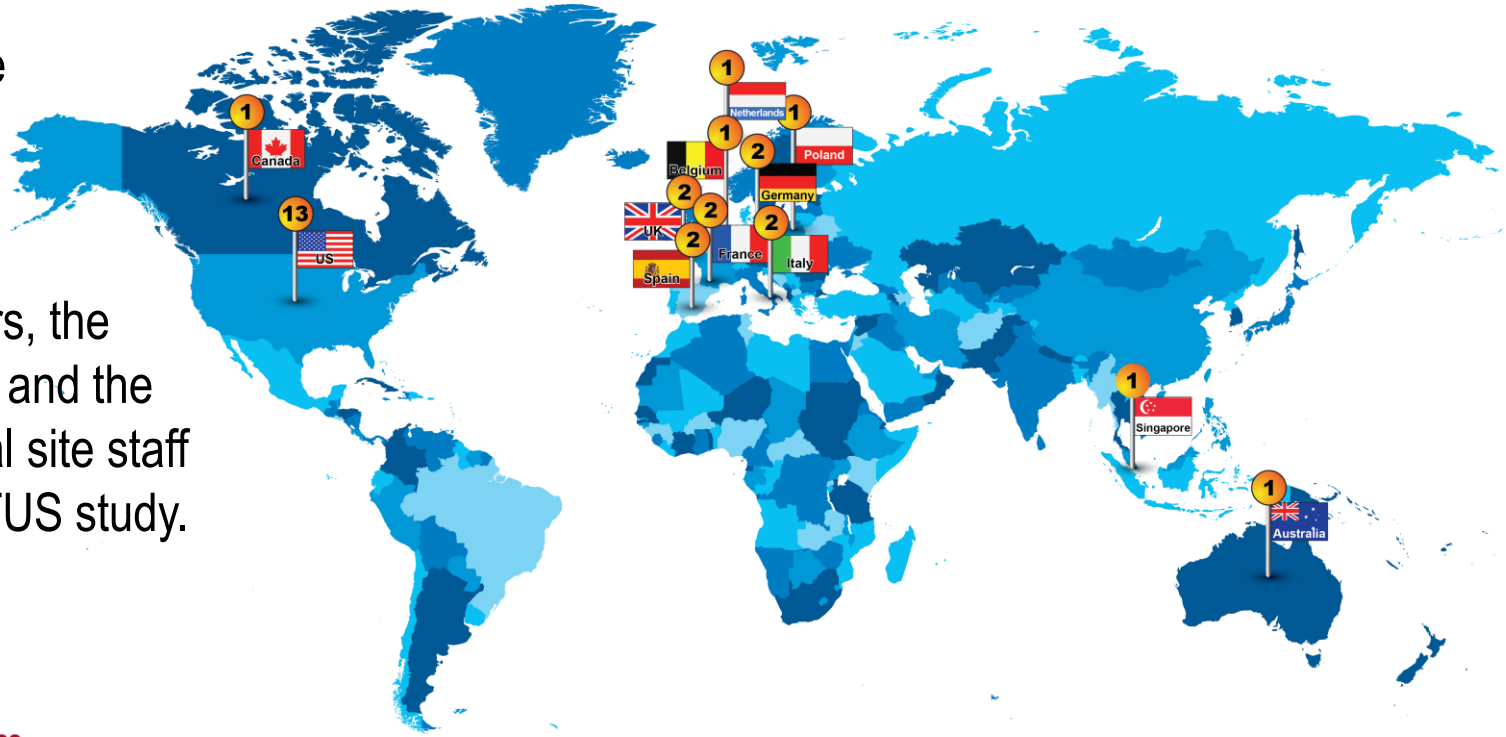

Each flag corresponds to the participating country and the number of participating centers within that country.

Disclosures

Margaret von Mehren: advisory/consultancy role with Deciphera Pharmaceuticals, LLC, Blueprint Medicines™ Corporation, and Exelixis, Inc.; travel accommodations from Deciphera Pharmaceuticals, LLC and the National Comprehensive Cancer Network®; institutional supportive research funding from ASCO, Deciphera Pharmaceuticals, LLC, Blueprint Medicines™ Corporation, AROG Pharmaceuticals, Inc., Novartis, Gradalis®, Inc., and Genmab.

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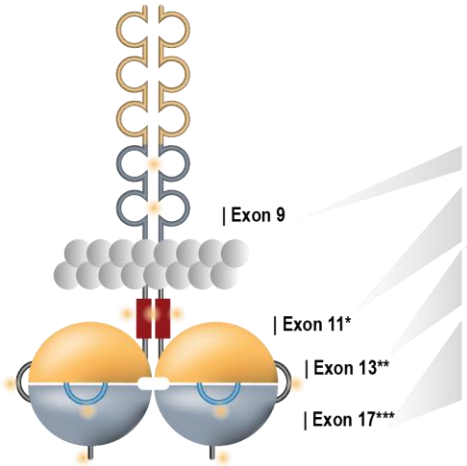
KIT Mutations Drive ~80% of GIST

- GIST is a rare sarcoma accounting for 1% to 2% of GI malignancies[1]
- Primary mutations in KIT or PDGFRA occur in >85% of patients with GIST[2]
- Mutations lead to activation of the kinase[3]



Domain	Gene	1° Mutation Frequency	2° Mutation Frequency
D5	*KIT*	10%	
JM	*KIT* *PDGFRA*	67* 1	
TK1 (ATP-binding pocket)	*KIT* *PDGFRA*	1 1	56**
Activation loop	*KIT* *PDGFRA D842* *PDGFRA*	1 5 1	41*** 3

*Exon 11 mutations of the JM domain result in loss of function of the KIT inhibitory switch[4]

**Mutations in the TK1 region of KIT reflect mutations in the ATP-binding pocket ("switch pocket region")[4,5]

***Mutations in the activation loop of KIT reflect mutations in the KIT activating switch region[4]

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1. Parab TM, et al. *J Gastrointest Oncol*. 2019;10:144-154. **2.** Hsueh YS, et al. *PLOS One*.2013;e65762. **3**. Smith BD, et al. *Cancer Cell*. 2019;35:738-751
4. Bai Y, et al. *Leukemia*.2013;27:278-285. **5**. Oppelt PJ, et al. *J Gastrointest Oncol*. 2017;8:466-473.

GIST Current Treatment Landscape

No approved 4th line therapies are available

	Line of Therapy			
	1st line	**2nd line**	**3rd line**	**4th line**
Current approved therapy	Imatinib	Sunitinib	Regorafenib	No approved therapy
Median PFS	Imatinib 400 mg: 20.4 mo[1a] Imatinib 800 mg: 24.0 mo[1a] *P*=0.18	Sunitinib: 5.6 mo[2b] Placebo: 1.4 mo[2b] *P*<0.0001	Regorafenib: 4.8 mo[3] Placebo: 0.9 mo[3] *P*<0.0001	
Overall response rate (CR + PR)	Imatinib 400 mg: 51.0%[1] Imatinib 800 mg: 56.7%[1] *P*=0.08	Sunitinib: 6.8%[2] Placebo: 0% *P*=0.006	Regorafenib: 4.5%[4] Placebo: 1.5% *P*=NR	
Median OS	Imatinib 400 mg: 46.8 mo[1a] Imatinib 800 mg: 46.8 mo[1a] *P*=0.31	Sunitinib: 17.0 mo[5b] Placebo: 14.9 mo[5b] *P*=0.161	Regorafenib: 17.4 mo[3] Placebo: 17.4 mo[3] *P*=0.5716	

[a] PFS / OS converted from years to months. [b] PFS converted from weeks to months.
NR, not reported.

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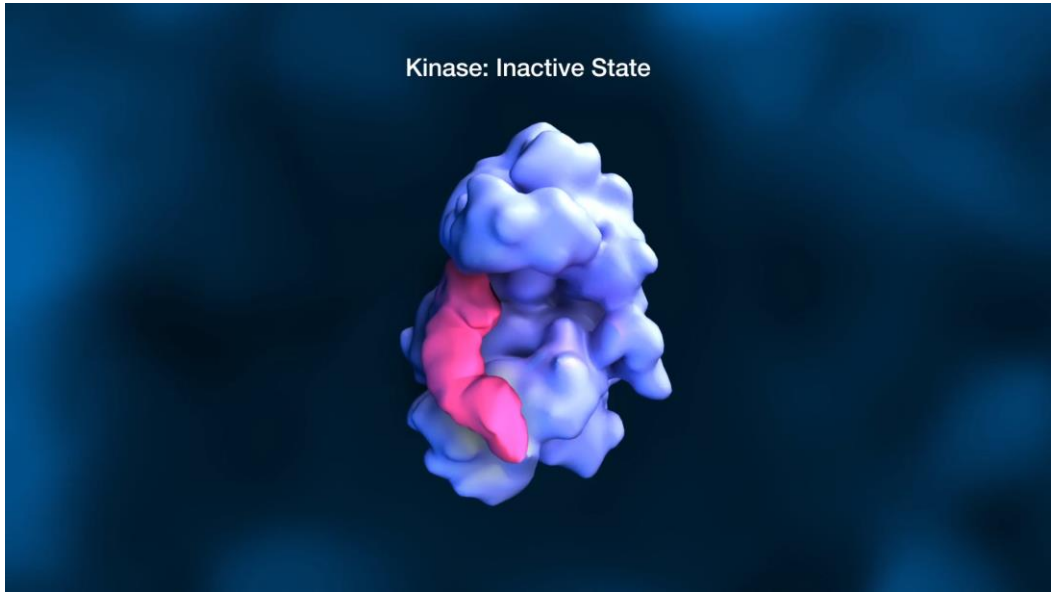
1. Casali PG, et al. *J Clin Oncol*. 2017;35:1713-1720. **2.** Sutent [package insert]. New York, NY: Pfizer Labs; 2017. **3.** Stivarga [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2017. **4.** Demetri GD, et al. *Lancet*. 2013;381:295-302. **5.** Garrett CR, et al. Poster presented at: Connective Tissue Oncology Society: November 13-15, 2008; London, UK. Abstract 35049.

Ripretinib Mechanism of Action



- Ripretinib is a novel tyrosine kinase **switch control** inhibitor engineered to broadly inhibit KIT and PDGFRA mutated kinases by using a unique **dual mechanism of action** that regulates the kinase switch pocket and activation loop

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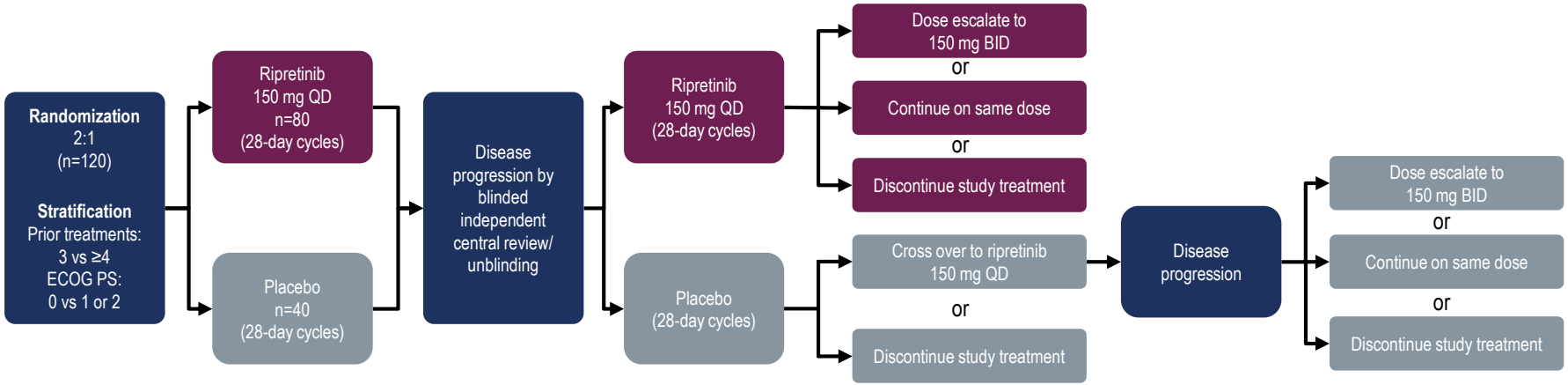
Smith BD, et al. *Cancer Cell*. 2019;35:738-751.

INVICTUS: Randomized Phase 3 Study Design

Evaluated ripretinib as ≥4th line therapy in patients with advanced GIST



Primary endpoint

PFS

(per modified RECIST based on **B**linded **I**ndependent **C**entral **R**eview [BICR])

Select Secondary endpoints

- **Objective response rate (ORR)** assessed by BICR (Key endpoint)
- **Overall survival (OS)**

Data cutoff
May 31, 2019

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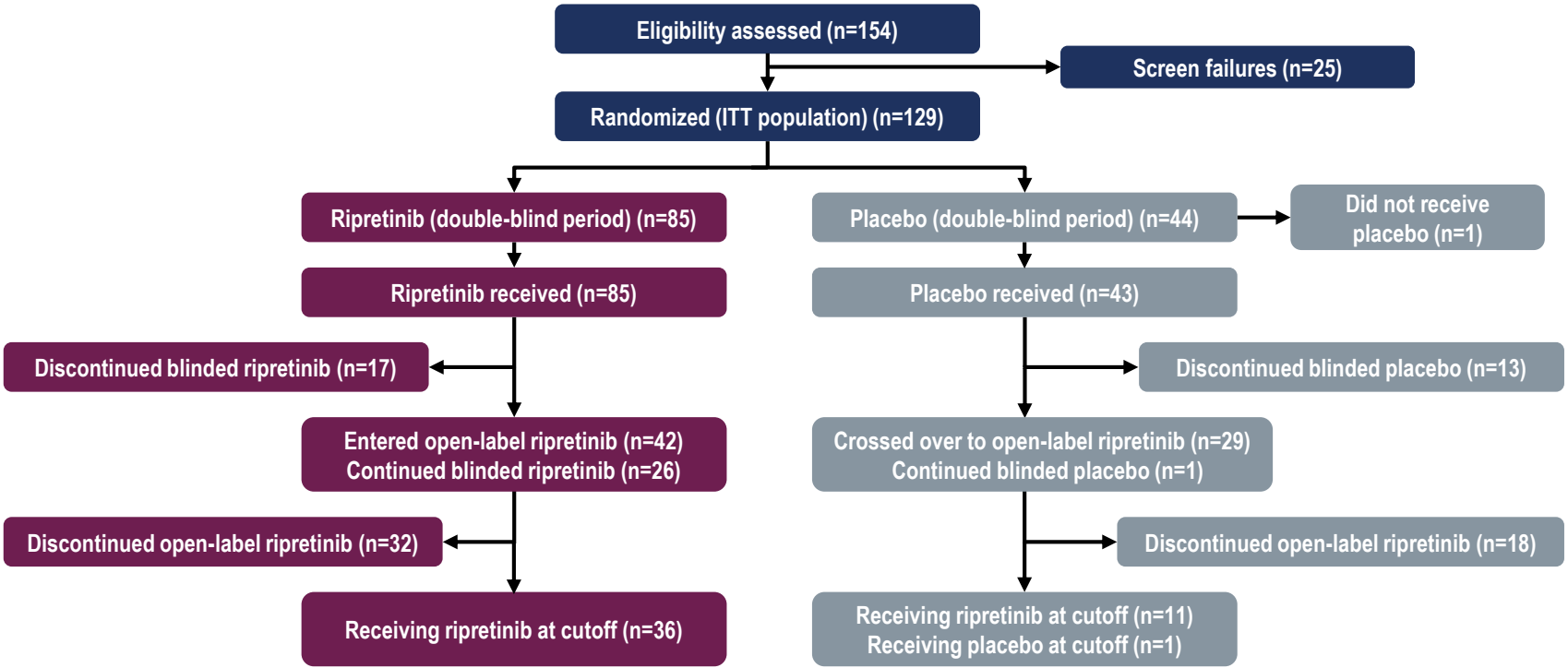
Patient Disposition

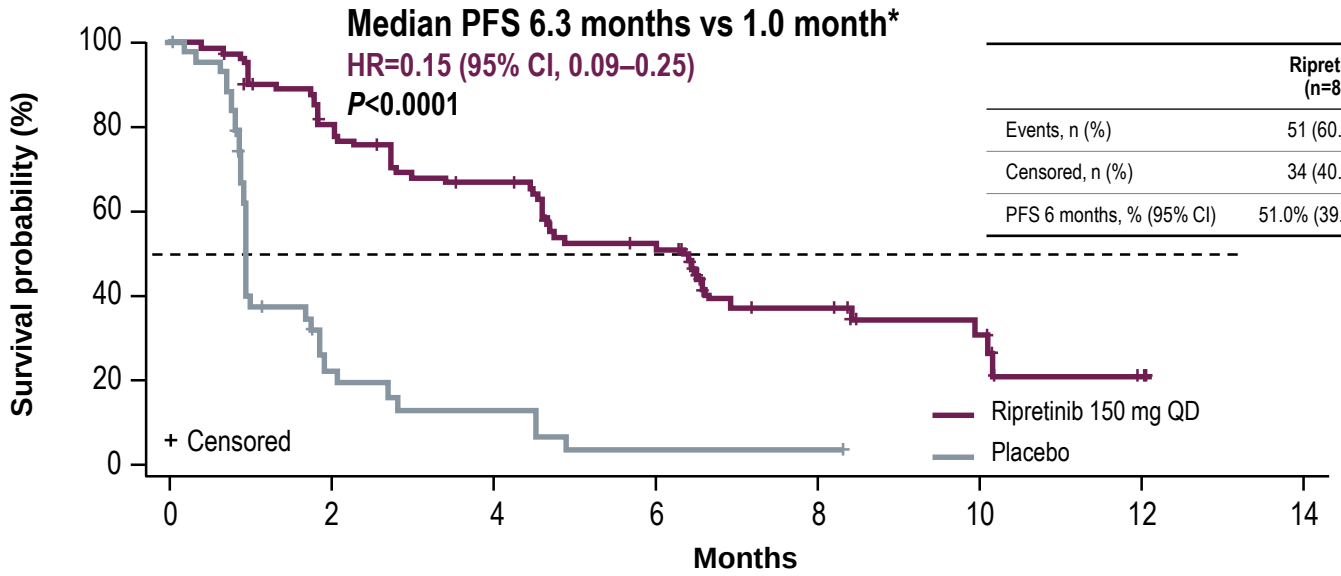


Baseline Characteristics

	Ripretinib (n=85)	Placebo (n=44)	Total (n=129)
Age (years) Median (min, max)	59 (29, 82)	65 (33, 83)	60 (29, 83)
18–64 years	57 (67%)	22 (50%)	79 (61%)
65–74 years	20 (24%)	12 (27%)	32 (25%)
≥ 75 years	8 (9%)	10 (23%)	18 (14%)
Gender			
Male (%)	47 (55%)	26 (59%)	73 (57%)
Race			
White (%)	64 (75%)	33 (75%)	97 (75%)
Region			
US (%)	40 (47%)	20 (46%)	60 (47%)
ECOG PS (%)			
ECOG PS 0	37 (44%)	17 (39%)	54 (42%)
ECOG PS 1/2	48 (56%)	27 (61%)	75 (58%)
Number of prior therapies (%)			
3	54 (64%)	27 (61%)	81 (63%)
≥4 (range, 4-7)	31 (36%)	17 (39%)	48 (37%)
Primary mutation (central testing of tumor tissue) n (%)			
KIT exon 9	14 (17%)	6 (14%)	20 (16%)
KIT exon 11	47 (55%)	28 (64%)	75 (58%)
Other KIT	2 (2%)	2 (5%)	4 (3%)
PDGFRA	3 (4%)	0	3 (2%)
KIT/PDGFRA wild type	7 (8%)	3 (7%)	10 (8%)
Not available / not done*	12 (14%)	5 (11%)	17 (13%)

*Not available=tumor tissue analyzed for baseline mutations but analysis failed; Not done=biopsy completed per protocol but sample not received for analysis.

85% Risk Reduction of Disease Progression or Death With Ripretinib Compared With Placebo



	Ripretinib (n=85)	Placebo (n=44)
Events, n (%)	51 (60.0%)	37 (84.1%)
Censored, n (%)	34 (40.0%)	7 (15.9%)
PFS 6 months, % (95% CI)	51.0% (39.4–61.4)	3.2% (0.2–13.8)

Number of patients at risk:

Ripretinib 150 mg QD	85	64	52	37	18	8	1	0
Placebo	44	7	4	1	1	0		

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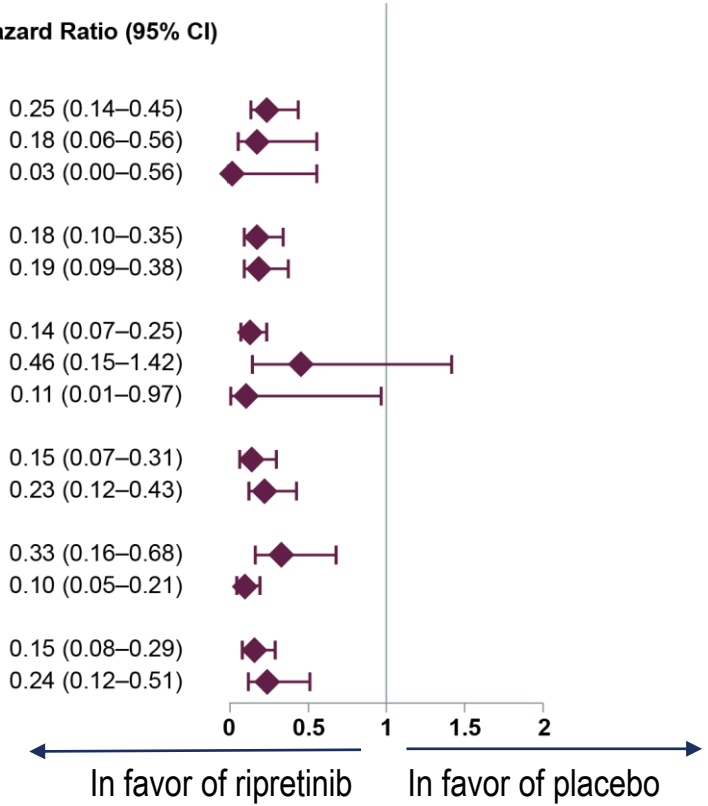
*Double-blind period.

Ripretinib Showed PFS Benefit in All Assessed Patient Subgroups

Subgroup	Ripretinib 150 mg QD (n)	Placebo (n)	Hazard Ratio (95% CI)
Age			
18–64 years	57	22	0.25 (0.14–0.45)
65–74 years	20	12	0.18 (0.06–0.56)
≥ 75 years	8	10	0.03 (0.00–0.56)
Gender			
Male	47	26	0.18 (0.10–0.35)
Female	38	18	0.19 (0.09–0.38)
Race			
White	64	33	0.14 (0.07–0.25)
Non-white	13	7	0.46 (0.15–1.42)
Not reported	8	4	0.11 (0.01–0.97)
Region			
US	40	20	0.15 (0.07–0.31)
Non-US	45	24	0.23 (0.12–0.43)
Screening ECOG PS			
0	38	19	0.33 (0.16–0.68)
1 or 2	47	25	0.10 (0.05–0.21)
Number of prior therapies			
3	54	27	0.15 (0.08–0.29)
≥ 4	31	17	0.24 (0.12–0.51)



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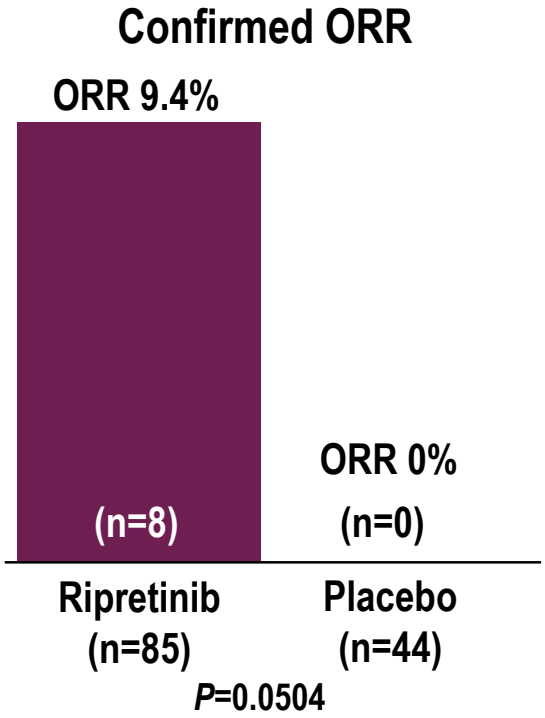
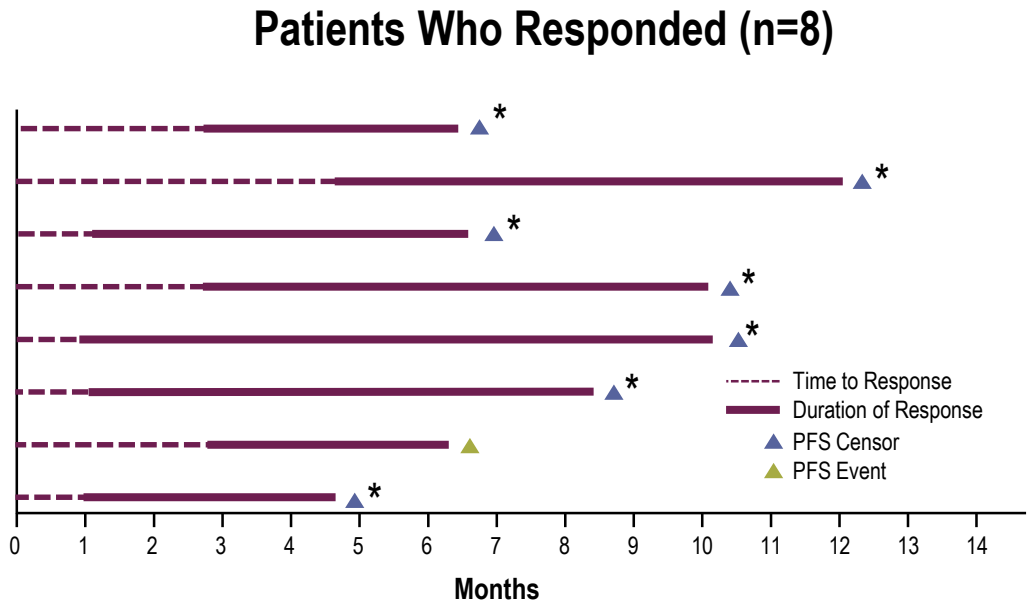
Durable Response With Ripretinib





- Median duration of response has not been reached yet
- *7 of 8 ripretinib responders are still responding as of data cutoff
- All responders had partial responses

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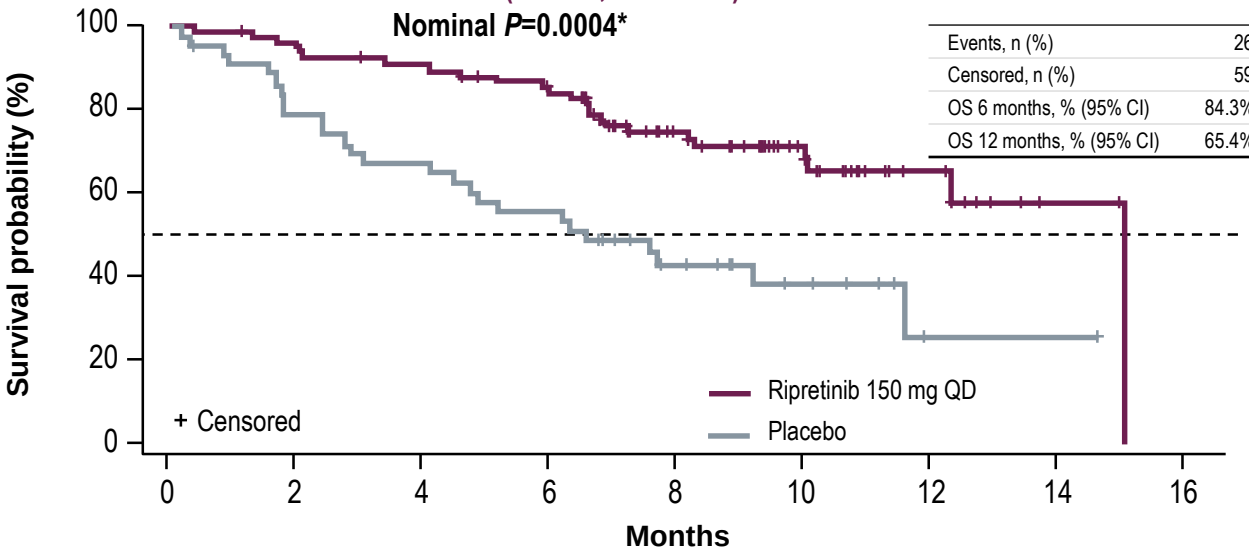
OS Benefit: 64% Risk Reduction of Death Compared With Placebo

Median OS 15.1 vs 6.6 months
HR=0.36 (95% CI, 0.20–0.62)
Nominal *P*=0.0004*



	Ripretinib (n=85)	Placebo (n=44)
Events, n (%)	26 (30.6%)	26 (59.1%)
Censored, n (%)	59 (69.4%)	18 (40.9%)
OS 6 months, % (95% CI)	84.3% (74.5–90.6)	55.9% (39.9–69.2)
OS 12 months, % (95% CI)	65.4% (51.6–76.1)	25.9% (7.2–49.9)

Number of patients at risk:

Ripretinib 150 mg QD	85	81	76	67	42	24	10	2	0
Placebo	44	34	29	24	14	8	1	1	0

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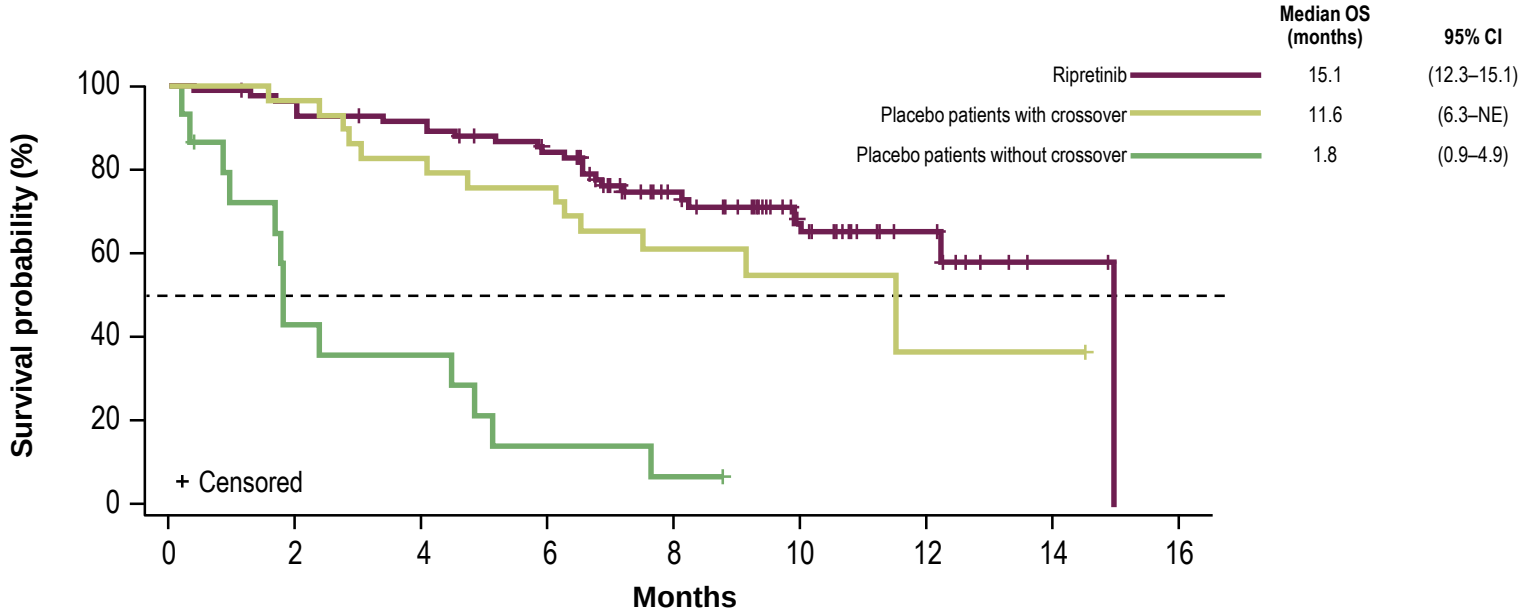
*Due to hierarchal testing procedures of the end points, the OS end point could not be formally tested because the ORR was not statistically significant.

Crossover Provided OS Benefit



Number of patients at risk:

Ripretinib	85	81	76	67	42	24	10	2	0
Placebo patients with crossover	29	28	24	22	13	8	1	1	0
Placebo patients without crossover	15	6	5	2	1	0			

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NE, not estimable.

TEAEs in >10% of Patients

Preferred Term	Ripretinib any grade (n=85)	Placebo any grade (n=43)*
Any TEAE or grade 3/4 TEAE**	**84 (98.8%)**	**42 (97.7%)**
Alopecia	44 (51.8%)	2 (4.7%)
Fatigue	36 (42.4%)	10 (23.3%)
Nausea	33 (38.8%)	5 (11.6%)
Abdominal pain	31 (36.5%)	13 (30.2%)
Constipation	29 (34.1%)	8 (18.6%)
Myalgia	27 (31.8%)	5 (11.6%)
Diarrhea	24 (28.2%)	6 (14%)
Decreased appetite	23 (27.1%)	9 (20.9%)
Palmar-plantar erythrodysesthesia syndrome	18 (21.2%)	0
Vomiting	18 (21.2%)	3 (7%)
Headache	16 (18.8%)	2 (4.7%)
Weight decreased	16 (18.8%)	5 (11.6%)

Preferred Term	Ripretinib any grade (n=85)	Placebo any grade (n=43)*
Arthralgia	15 (17.6%)	2 (4.7%)
Blood bilirubin increased	14 (16.5%)	0 (0%)
Edema peripheral	14 (16.5%)	3 (7%)
Muscle spasms	13 (15.3%)	2 (4.7%)
Anemia	12 (14.1%)	8 (18.6%)
Hypertension	12 (14.1%)	2 (4.7%)
Asthenia	11 (12.9%)	6 (14%)
Dry skin	11 (12.9%)	3 (7%)
Dyspnea	11 (12.9%)	0
Hypophosphatemia	9 (10.6%)	0
Lipase increased	9 (10.6%)	0
Pruritus	9 (10.6%)	2 (4.7%)
Stomatitis	9 (10.6%)	0

*44 patients were randomized to placebo, but 1 did not receive treatment.
**Regardless of causality

TEAEs in >10% of Patients
Grade 3/4 TEAEs

Preferred Term	Ripretinib any grade (n=85)	Ripretinib grade 3/4 (n=85)†	Placebo any grade (n=43)*	Placebo grade 3/4 (n=43)*†
Any TEAE or grade 3/4 TEAE**	84 (98.8%)	**42 (49.4%)**	42 (97.7%)	**19 (44.2%)**
Alopecia	44 (51.8%)	0	2 (4.7%)	0
Fatigue	36 (42.4%)	3 (3.5%)	10 (23.3%)	1 (2.3%)
Nausea	33 (38.8%)	3 (3.5%)	5 (11.6%)	0
Abdominal pain	31 (36.5%)	6 (7.1%)	13 (30.2%)	2 (4.7%)
Constipation	29 (34.1%)	1 (1.2%)	8 (18.6%)	0
Myalgia	27 (31.8%)	1 (1.2%)	5 (11.6%)	0
Diarrhea	24 (28.2%)	1 (1.2%)	6 (14%)	1 (2.3%)
Decreased appetite	23 (27.1%)	1 (1.2%)	9 (20.9%)	1 (2.3%)
Palmar-plantar erythrodysesthesia syndrome	18 (21.2%)	0	0	0
Vomiting	18 (21.2%)	3 (3.5%)	3 (7%)	0
Headache	16 (18.8%)	0	2 (4.7%)	0
Weight decreased	16 (18.8%)	0	5 (11.6%)	0

Preferred Term	Ripretinib any grade (n=85)	Ripretinib grade 3/4 (n=85)†	Placebo any grade (n=43)*	Placebo grade 3/4 (n=43)*†
Arthralgia	15 (17.6%)	0	2 (4.7%)	0
Blood bilirubin increased	14 (16.5%)	1 (1.2%)	0 (0%)	0
Edema peripheral	14 (16.5%)	1 (1.2%)	3 (7%)	0
Muscle spasms	13 (15.3%)	0	2 (4.7%)	0
Anemia	12 (14.1%)	8 (9.4%)	8 (18.6%)	6 (14%)
Hypertension	12 (14.1%)	6 (7.1%)	2 (4.7%)	0
Asthenia	11 (12.9%)	1 (1.2%)	6 (14%)	2 (4.7%)
Dry skin	11 (12.9%)	0	3 (7%)	0
Dyspnea	11 (12.9%)	0	0	0
Hypophosphatemia	9 (10.6%)	4 (4.7%)	0	0
Lipase increased	9 (10.6%)	4 (4.7%)	0	0
Pruritus	9 (10.6%)	0	2 (4.7%)	0
Stomatitis	9 (10.6%)	0	0	0

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*44 patients were randomized to placebo, but 1 did not receive treatment.
**Regardless of causality

†Corresponding grade 3/4 TEAEs to TEAEs in >10% of patients receiving ripretinib.

TEAE Leading to Dose Modification

Categories n (%)	Ripretinib (n=85)	Placebo (n=43)*
Any TEAE leading to dose reduction	6 (7.1%)	1 (2.3%)
Any TEAE leading to dose interruption	20 (23.5%)	9 (20.9%)
Any TEAE leading to treatment discontinuation	7 (8.2%)	5 (11.6%)
Any TEAE leading to death**	5 (5.9%)	10 (23.3%)

*44 patients were randomized to placebo, but one did not receive treatment.
**One patient in each arm considered possibly related to blinded study drug

INVICTUS: Conclusions

- **Median PFS** was significantly improved with ripretinib compared with placebo (6.3 vs 1.0 months; HR=0.15 [95% CI, 0.09–0.25])
  - **Risk of progression or death reduced by 85%** compared with placebo
- **Median OS** with ripretinib was 15.1 months vs 6.6 months in the placebo arm (HR=0.36 [95% CI, 0.20–0.63])
  - **Risk of death reduced by 64%** compared with placebo
- Ripretinib was associated with a **favorable tolerability profile**
- Ripretinib represents a **potential new standard of care** with broad activity in ≥4th line GIST, a patient population with advanced refractory disease and no other approved options

Enrollment is ongoing in **intrigue**, a Phase 3, interventional, randomized, multicenter, open-label study of ripretinib vs sunitinib in patients with advanced GIST after treatment with imatinib (NCT03673501)