

Avapritinib is Highly Active and Well-tolerated in Patients With Advanced GIST Driven by a Diverse Variety of Oncogenic Mutations in KIT and PDGFRA

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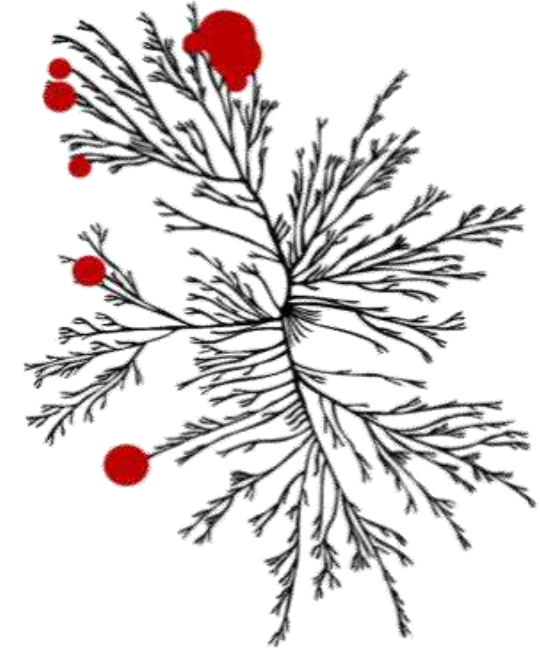
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Disclosures

- Avapritinib is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)
- Data are preliminary and based on a cutoff date of October 15, 2018
- Dr. Michael Heinrich is an investigator for Blueprint Medicines' ongoing Phase 1 study in unresectable gastrointestinal stromal tumors
- Dr. Michael Heinrich has the following disclosures:
 - Consultant: Blueprint Medicines, Novartis, Molecular MD, Deciphera
 - Research funding: Blueprint Medicines, Deciphera
 - Stock or stock options: Molecular MD
 - Patents: 4 patents on diagnosis and treatment of PDGFR α -mutant GIST, 1 patent on imatinib treatment of GIST

Avapritinib: a highly selective and potent KIT/PDGFR α inhibitor for GIST

GIST mutation(s)		Medical need by mutation	Avapritinib biochemical IC ₅₀ ¹
KIT Exon 11 deletion	JM domain	1L imatinib is effective 2L sunitinib/3L regorafenib have low ORR/short PFS	0.6 nM
KIT Exon 11 V560G			1 nM
KIT Exon 11/13	ATP binding site	Approved 2L/3L agents have low ORR/short PFS	11 nM
KIT Exon 11/14			28 nM
KIT Exon 11/17	Activation loop	No highly effective therapy in any line	0.1 nM
PDGFR α D842V			0.24 nM



Ongoing clinical trials

Avapritinib kinome selectivity

NAVIGATOR
GIST

Phase 1 advanced GIST

VOYAGER
GIST

Phase 3 trial of avapritinib vs. regorafenib in 3L and 4L GIST

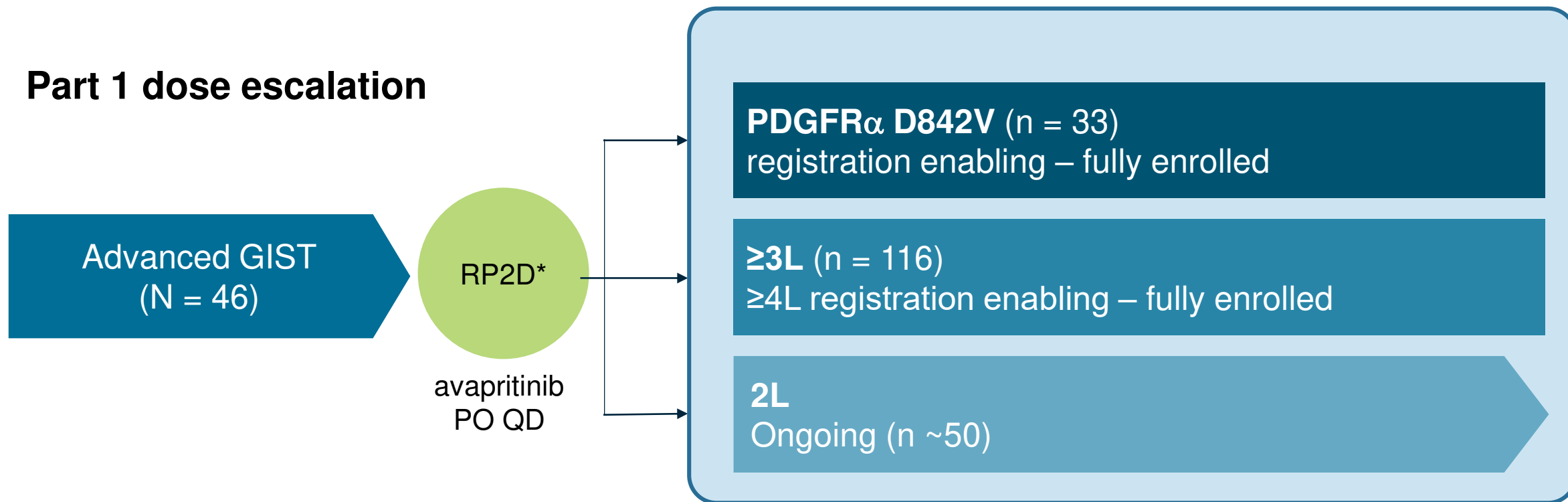
KIT, KIT proto-oncogene receptor tyrosine kinase; PDGFR α , platelet-derived growth factor alpha; IC₅₀, concentration causing 50% inhibition; L, line; JM, juxtamembrane; ORR, objective response rate; PFS, progression-free survival.

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¹Evans E, et al. Sci Transl Med. 2017;9(414). pii: eaao1690.

NAVIGATOR Phase 1 study design

Part 1 dose escalation



KEY OBJECTIVES

- Determine MTD/RP2D, safety, PK and clinical activity by line of therapy and mutational status
- ORR/DOR per central radiology assessment (mRECIST 1.1) for planned NDA and MAA regulatory filings

RP2D, recommended Phase 2 dose; PO, orally; QD, once daily; MTD, maximum tolerated dose; PK, pharmacokinetics; DOR, duration of response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NDA, New Drug Application; MAA, Marketing Authorization Application.

*MTD 400 mg; RP2D 300 mg.

Demography and baseline characteristics

Parameter	All patients (N = 231)	
Age (years), median (range)	62 (25, 90)	
GIST mutational subtype, % (n)		
KIT	72% (167)	
PDGFR α D842V	24% (56)	
PDGFR α non-D842V	4% (8)	
Metastatic disease, % (n)	89% (205)	
Largest target lesion size, % (n)		
\leq 5 cm	34% (79)	
>5– \leq 10 cm	40% (93)	
>10 cm	20% (47)	
Pending	5% (12)	
No. prior kinase inhibitors, % (n)	<u>PDGFRα</u>	<u>KIT</u>
Median (range)	1 (0-6)	4 (1-11)
0	17% (11)	0
1	37% (24)	19% (31)
2	19% (12)	8% (14)
3	11% (7)	20% (34)
4	8% (5)	23% (38)
\geq 5	8% (5)	30% (50)

Efficacy populations

PDGFR α D842V

\geq 4L

3L/4L regorafenib-naïve*

2L

*Similar to Phase 3 trial population (VOYAGER).

Data are preliminary and based on a cutoff date of October 15, 2018.

Adverse events ≥20%

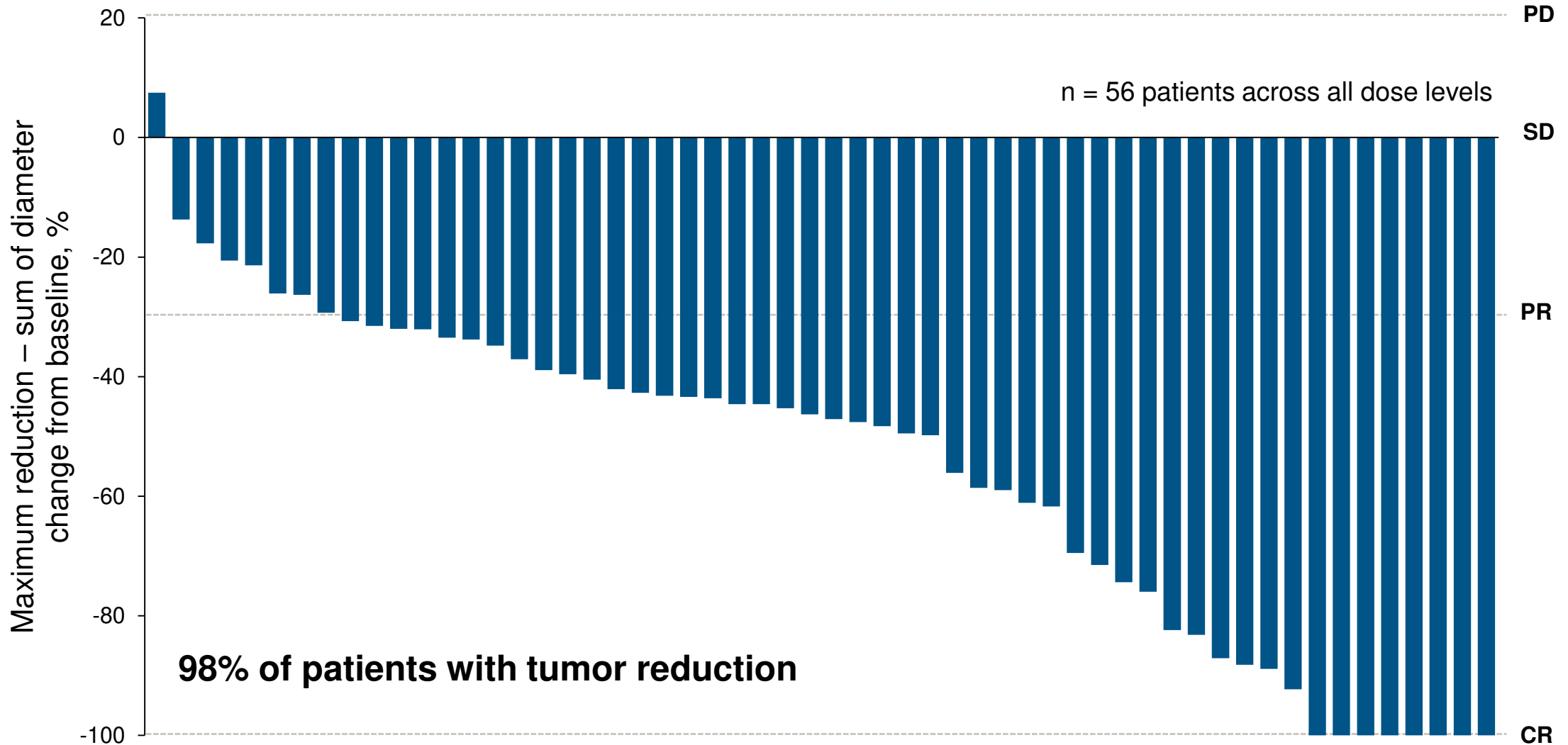
Safety population; all doses (N = 231)					
AE, % (n)	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	61% (142)	46% (106)	13% (30)	3% (6)	0
Fatigue	55% (127)	21% (48)	28% (64)	6% (15)	0
Anemia	46% (107)	5% (11)	15% (35)	25% (58)	1% (3)
Periorbital edema	40% (93)	34% (79)	6% (13)	<1% (1)	0
Diarrhea	39% (90)	22% (50)	13% (30)	4% (10)	0
Vomiting	38% (88)	30% (69)	6% (14)	2% (5)	0
Decreased appetite	35% (82)	23% (54)	9% (20)	3% (8)	0
Peripheral edema	33% (77)	23% (53)	10% (22)	<1% (2)	0
Increased lacrimation	31% (72)	28% (64)	3% (8)	0	0
Memory impairment*	26% (60)	19% (45)	6% (15)	0	0
Constipation	23% (53)	14% (32)	8% (18)	<1% (2)	<1% (1)
Face edema	23% (53)	19% (43)	4% (9)	<1% (1)	0
Hair color changes	21% (49)	20% (46)	<1% (2)	<1% (1)	0
Dizziness	20% (47)	16% (38)	3% (8)	<1% (1)	0

- Most AEs are grade 1 or 2
- No treatment-related grade 5 AEs
- 8.7% (20) of patients discontinued due to related AEs
- Grade 3-4 treatment-related AEs ≥2%: anemia, fatigue, hypophosphatemia, increased bilirubin, decreased white blood count/neutropenia, and diarrhea

AE, adverse event.

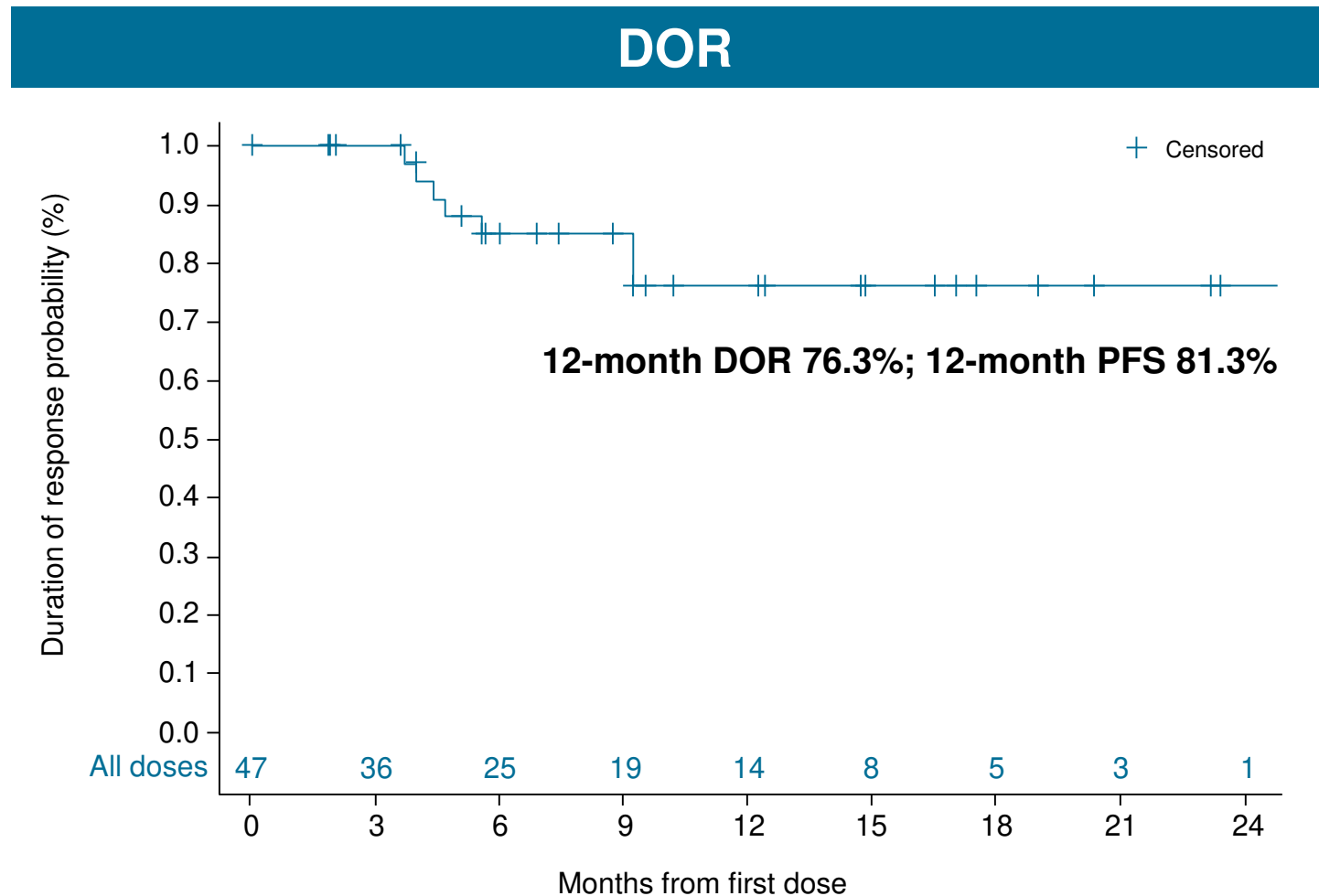
*The most commonly reported cognitive AE

Best response by central radiology in PDGFR α D842V GIST



ORR and DOR by central radiology in PDGFR α D842V GIST

Best response* n = 56	mRECIST 1.1 % (n) [95% CI]
ORR	84% (47) [71.7-92.47]
CR/PR*	9% (5)/75% (42)
SD	16% (9)
CBR [†]	96% (54) [87.7-99.6]

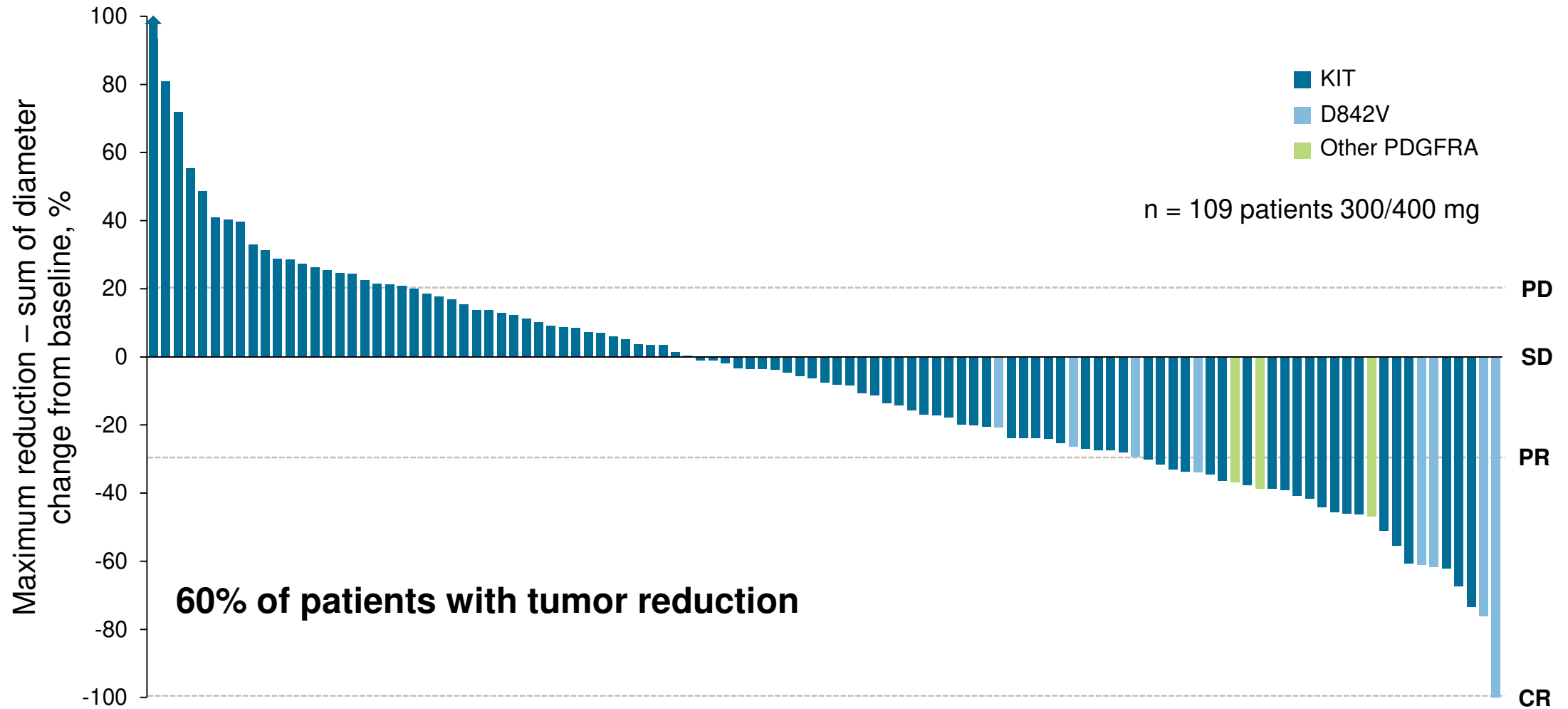


CI, confidence interval; CBR, clinical benefit rate.

*4 PR pending confirmation. Patients who have had ≥ 1 post-baseline radiographic assessment. Response evaluable includes all doses.

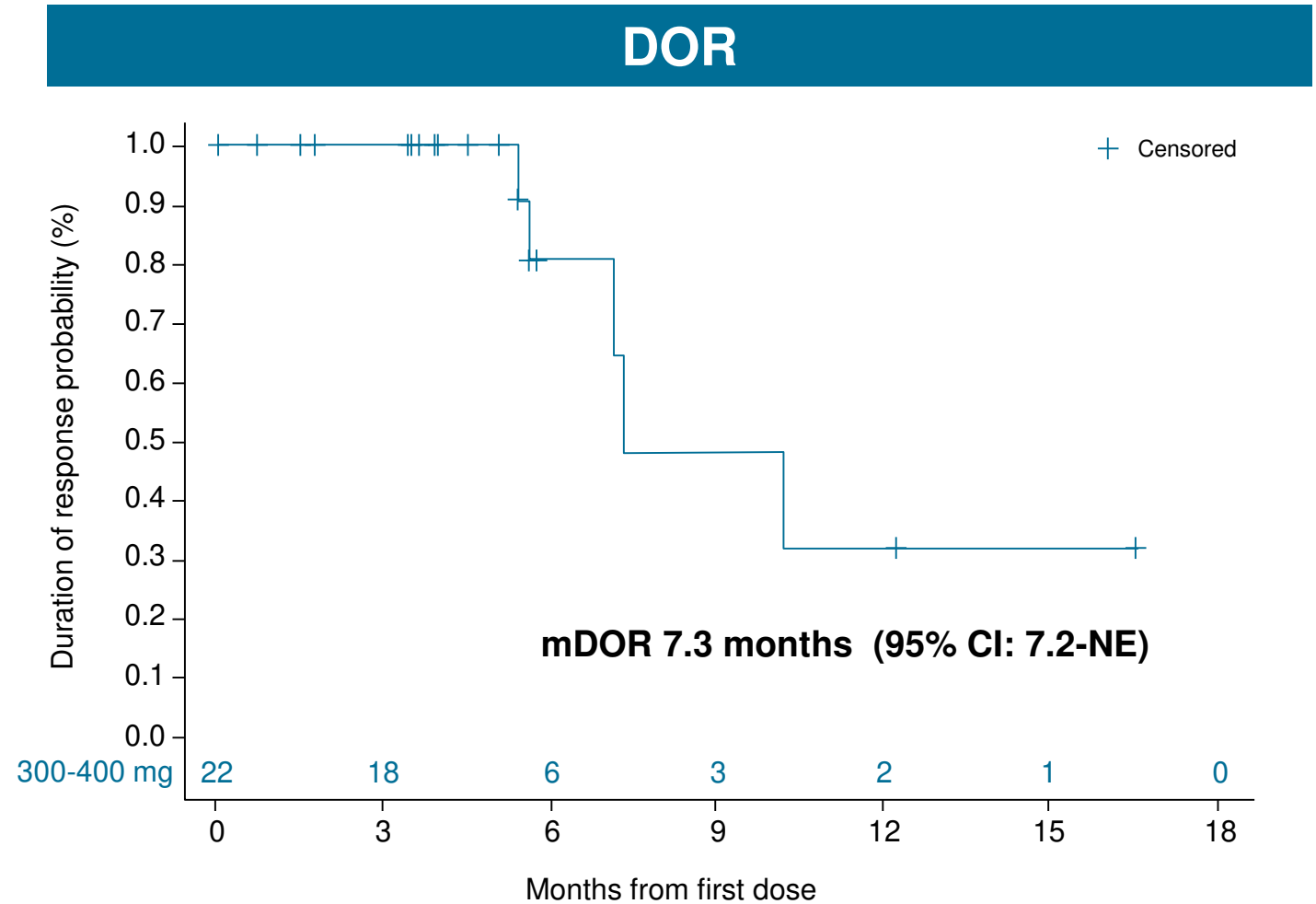
[†] PR + SD lasting ≥ 4 months.

Best response by central radiology in $\geq 4L$ GIST



ORR and DOR by central radiology $\geq 4L$ GIST

Best response* n = 109	mRECIST 1.1 % (n) [95% CI]
ORR	20% (22) [13.1-29.0]
CR/PR*	1% (1)/19% (21)
SD	46% (50)
CBR [†]	40% (44) [31.1-50.2]

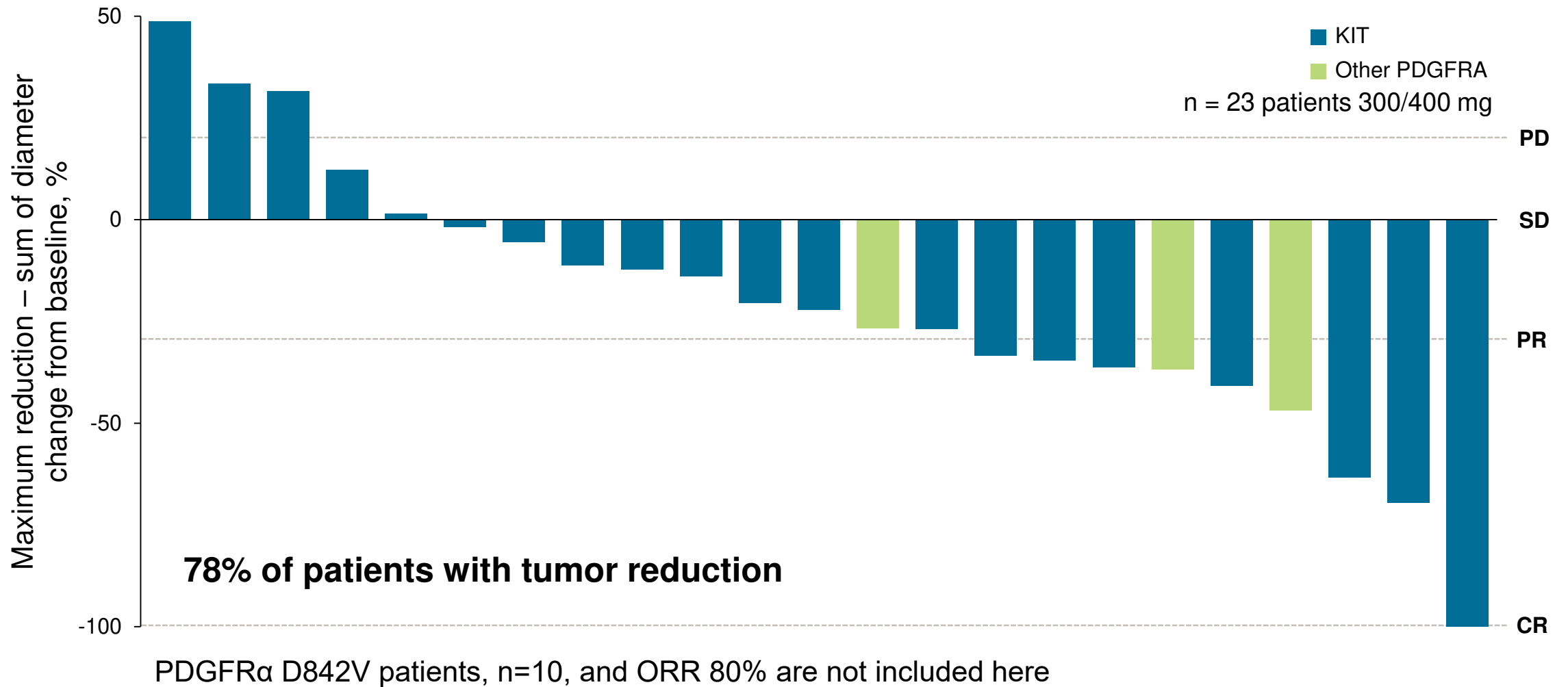


mDOR, median duration of response; NE, not estimatable

*1 PR pending confirmation. Patients who have had ≥ 1 post-baseline radiographic assessment. Response evaluable includes 300 mg and 400 mg.

[†]PR + SD lasting ≥ 4 months

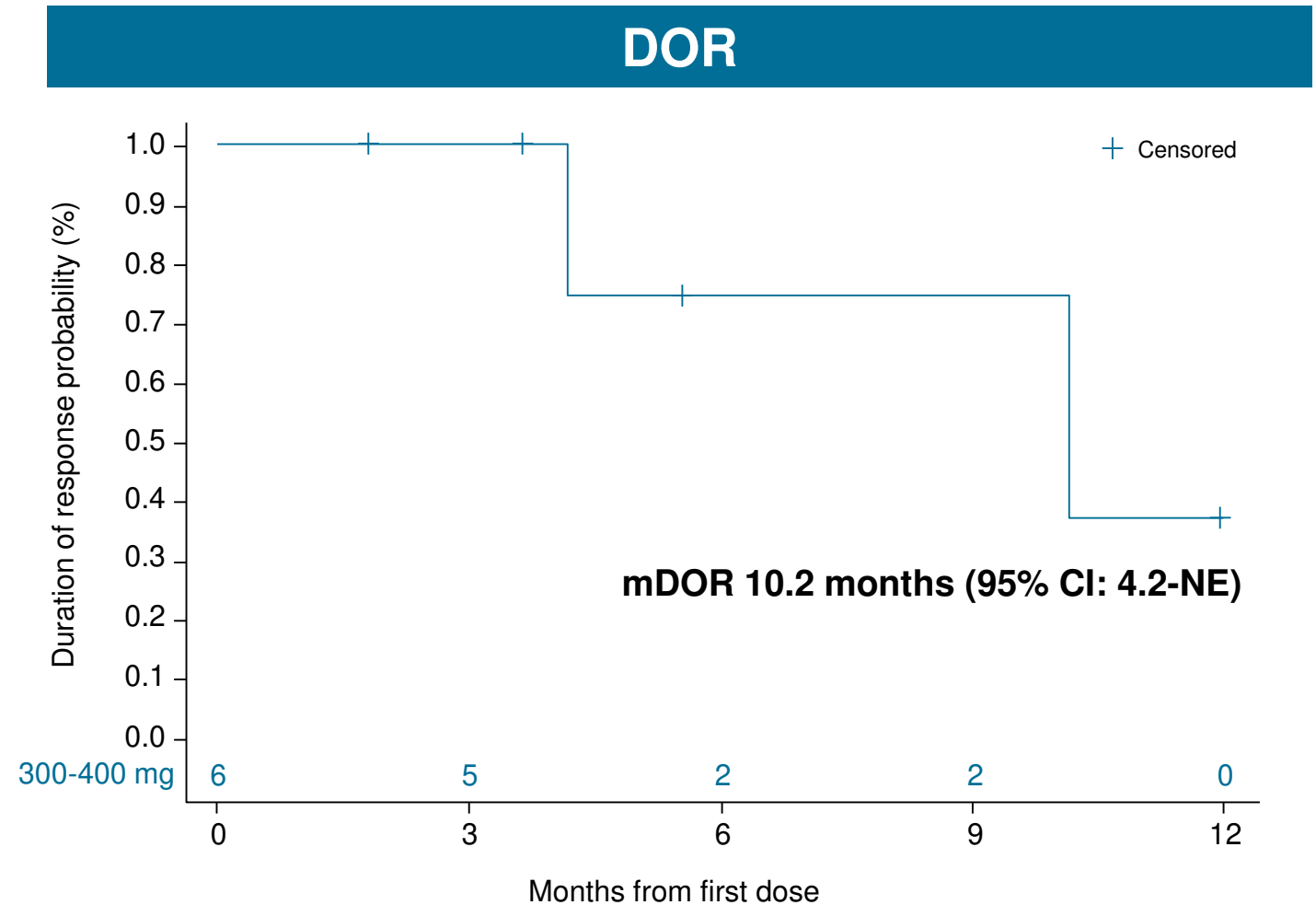
Best response by central radiology in 3L/4L regorafenib-naïve GIST*



*Similar to Phase 3 trial population (VOYAGER), except that PDGFRα D842V patients (ORR 80%) are not included here.

ORR and DOR by central radiology in 3L/4L regorafenib-naïve GIST

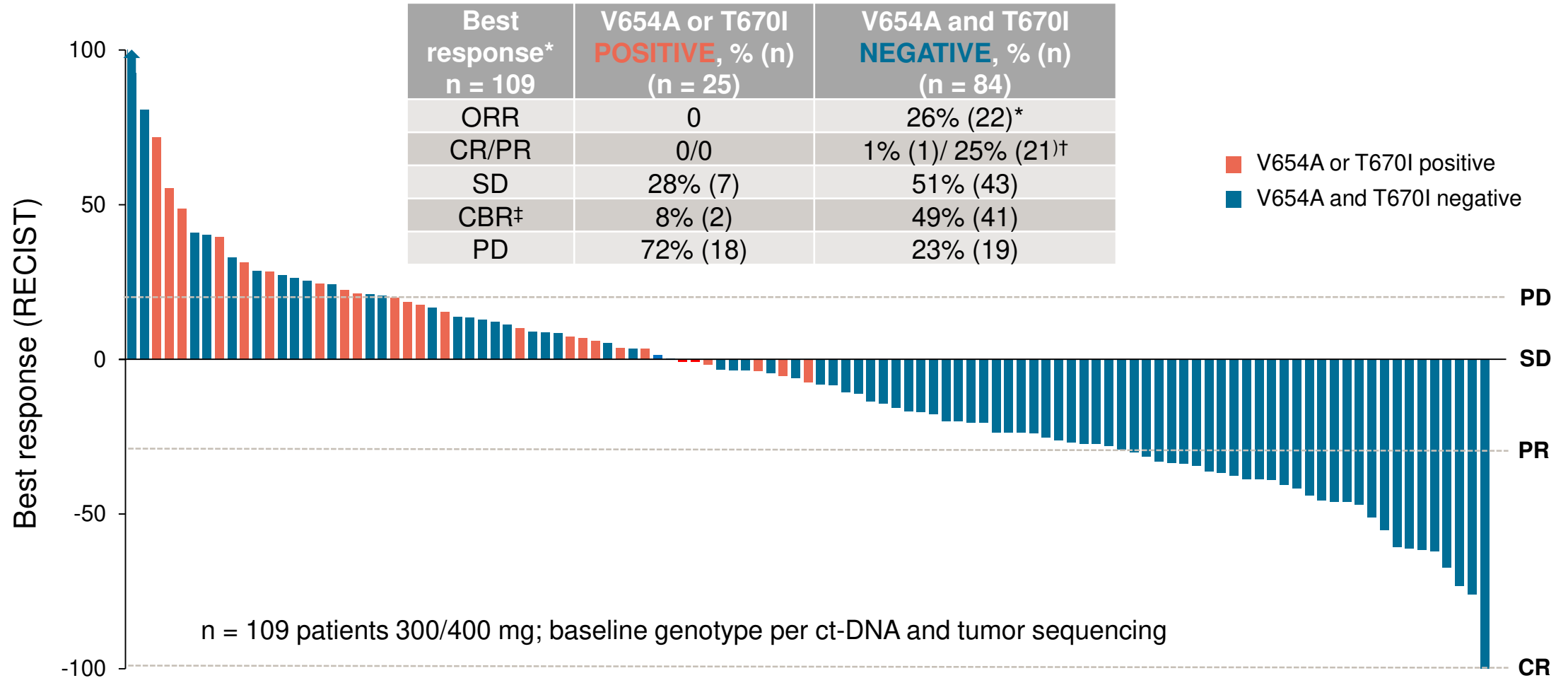
Non-D842V patients best response* n = 23	mRECIST 1.1 % (n) [95% CI]
ORR	26% (6) [10.0-48.4]
CR/PR	0% (0)/26% (6)
SD	57% (13)
CBR†	70% (16) [47.1-86.8]



*All responses are confirmed. Patients who have had ≥ 1 post-baseline radiographic assessment. Response evaluable includes 300 mg and 400 mg.

†PR + SD lasting ≥ 4 months

Best response by mutational profile in $\geq 4L$ GIST



ct-DNA, circulating tumor DNA.

*Patients who have had ≥ 1 post-baseline radiographic assessment. Response evaluable includes 300 mg and 400 mg.

† Includes 1 unconfirmed PR.

‡PR + SD lasting ≥ 4 months

Avapritinib has important clinical activity in advanced GIST

	PDGFR α D842V n = 56	\geq 4L all patients n = 109	3L/4L regorafenib- naïve non-D842V n = 23	2L non-D842V n = 20
ORR (central radiology), % (n) [95% CI]	84% (47) [72-92]	20% (22) [13.1-29.0]	26% (6) [10.2-48.4]	25% (5) [9-49]
mDOR (central radiology), months [95% CI]	NE [NE, NE]	7.3 [7.2-NE]	10.2 [4.2-NE]	NR
CBR (central radiology), % (n) [95% CI]	96% (54) [88-100]	40% (44) [31.1-50.2]	70% (16) [47.1-86.8]	NR
mPFS (central radiology), months [95% CI]	NE [NE, NE]	3.7 [3.5-5.6]	8.6 [5.6-14.7]	NR
mPFS (investigator), months [95% CI]	22.8 [20.8-28.4]	5.5 [3.8-6.8]	10.2 [5.7-NE]	NR
Benchmarks	PDGFRα D842V Approved agents: ORR ~0% mPFS ~3 mo mOS ~15 mo	4L imatinib re-treatment: ORR ~0% PFS 1.8 mo	3L regorafenib: ORR ~5% PFS 4.8 mo	2L sunitinib: ORR ~7% PFS 6 mo

NR, not reported; mPFS, median progression-free survival; mOS, median overall survival.

— ORR is not an endpoint for 2L but is early signal readout.

Avapritinib has the potential to change GIST treatment paradigms

- Phase 1 NAVIGATOR study demonstrates favorable tolerability and encouraging clinical activity across lines of therapy
 - Most AEs were grade 1 or 2, with manageable on-target toxicity
 - Important efficacy in PDGFR α D842V GIST and refractory, ≥ 4 L GIST supports regulatory filing
 - Encouraging activity in 3L/4L regorafenib-naïve GIST indicates the potential for a favorable outcome in the ongoing randomized Phase 3 VOYAGER study
 - Mutational profiling analyses and promising 2L data provide strong rationale for genotype-selected 2L study

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