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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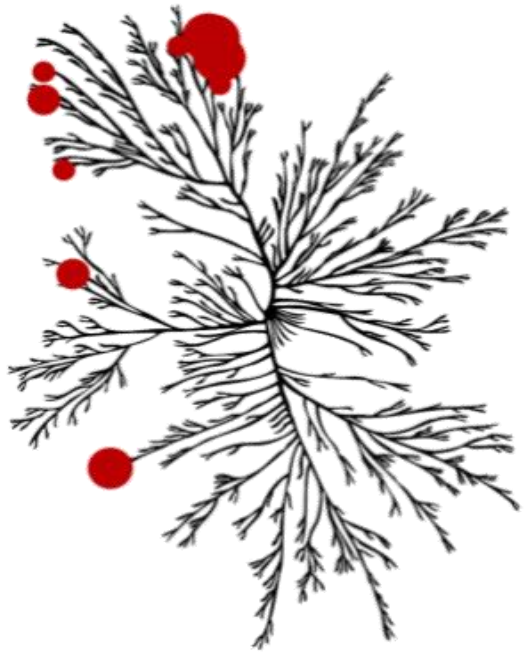
Disclosures

- 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 PDGFRα-mutant GIST, 1 patent on imatinib treatment of GIST

Avapritinib: a highly selective and potent KIT/PDGFRA 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		0.1 nM
PDGFRα D842V		No highly effective therapy in any line	0.24 nM



Avapritinib kinome selectivity

Ongoing clinical trials

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; PDGFRA, platelet-derived growth factor alpha; IC_{50}, concentration causing 50% inhibition; L, line; JM, juxtamembrane; ORR, objective response rate; PFS, progression-free survival.

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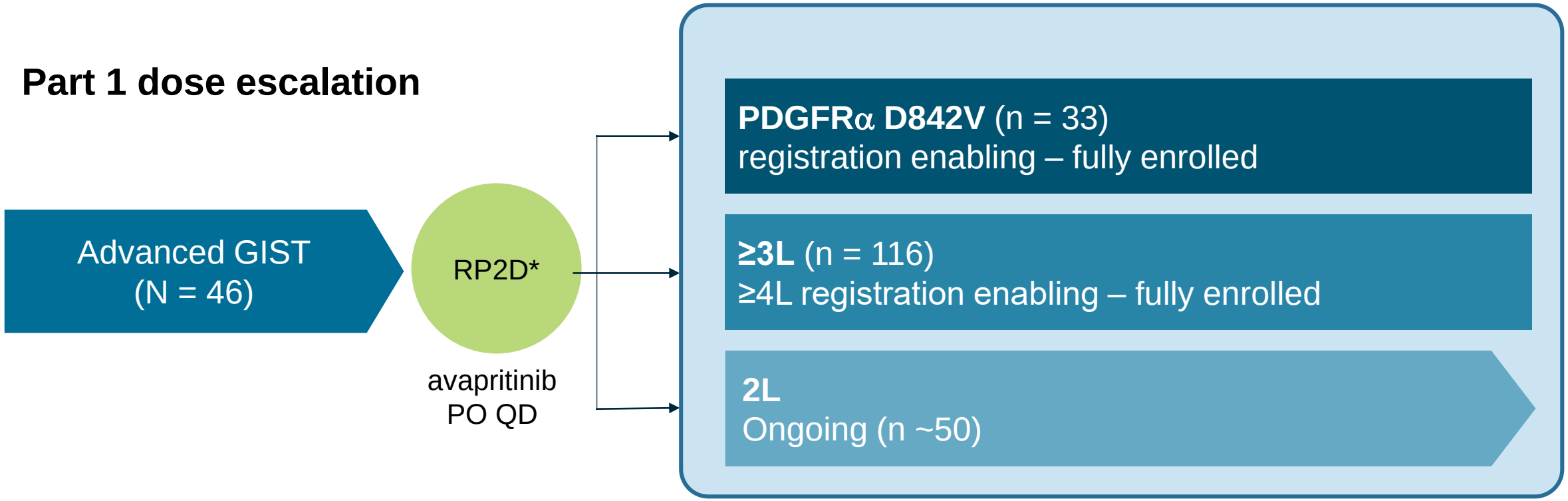
[1]Evans E, et al. Sci Transl Med. 2017;9(414). pii: eaao1690.

NAVIGATOR Phase 1 study design



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 PDGFRα D842V PDGFRα non-D842V	 72% (167) 24% (56) 4% (8)	
Metastatic disease, % (n)	89% (205)	
Largest target lesion size, % (n) ≤5 cm >5–≤10 cm >10 cm Pending	 34% (79) 40% (93) 20% (47) 5% (12)	
No. prior kinase inhibitors, % (n) Median (range) 0 1 2 3 4 ≥5	<u>PDGFRα</u> 1 (0-6) 17% (11) 37% (24) 19% (12) 11% (7) 8% (5) 8% (5)	<u>KIT</u> 4 (1-11) 0 19% (31) 8% (14) 20% (34) 23% (38) 30% (50)

Efficacy populations

PDGFRα D842V

≥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.

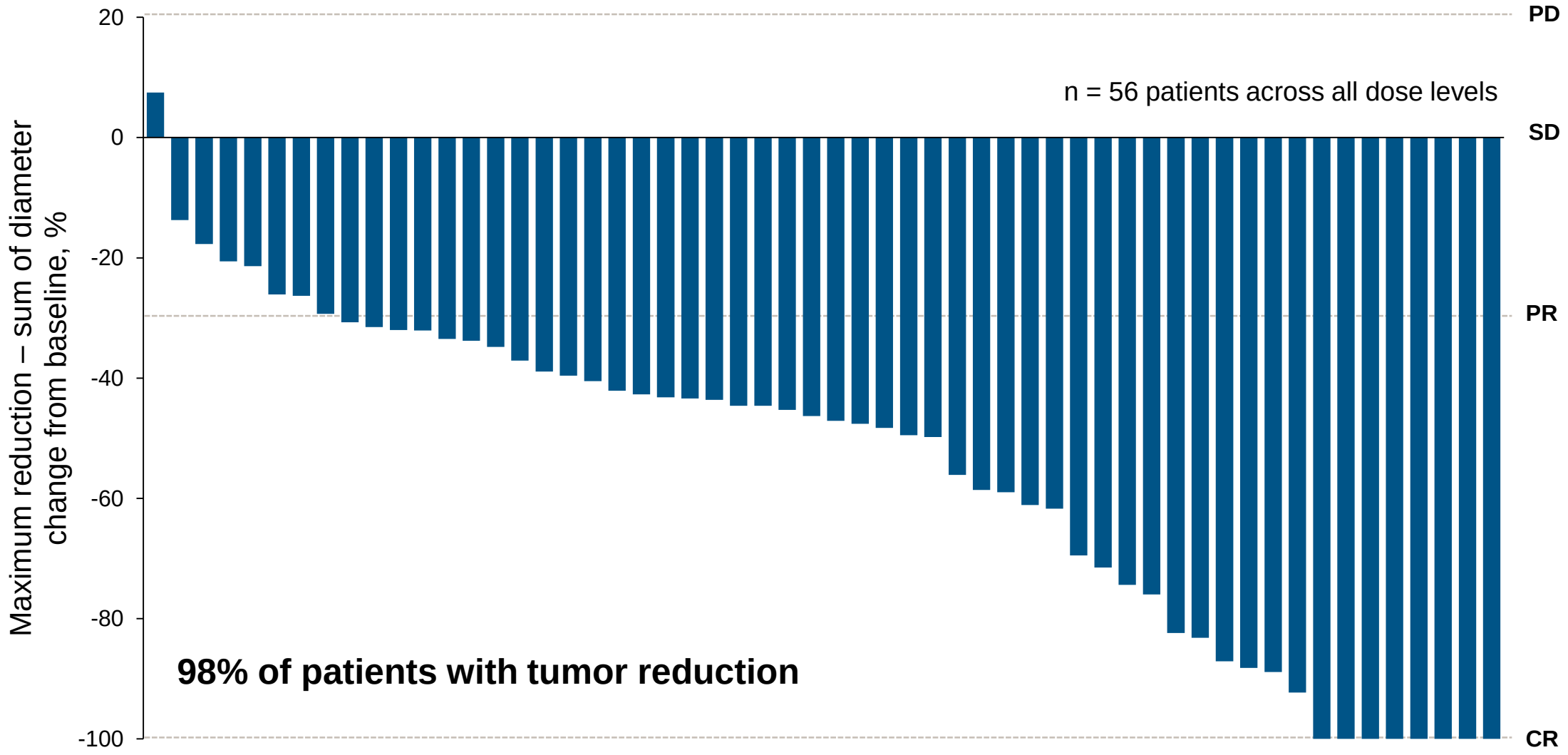
Adverse events ≥20%

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

AE, adverse event.
*The most commonly reported cognitive AE

- 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

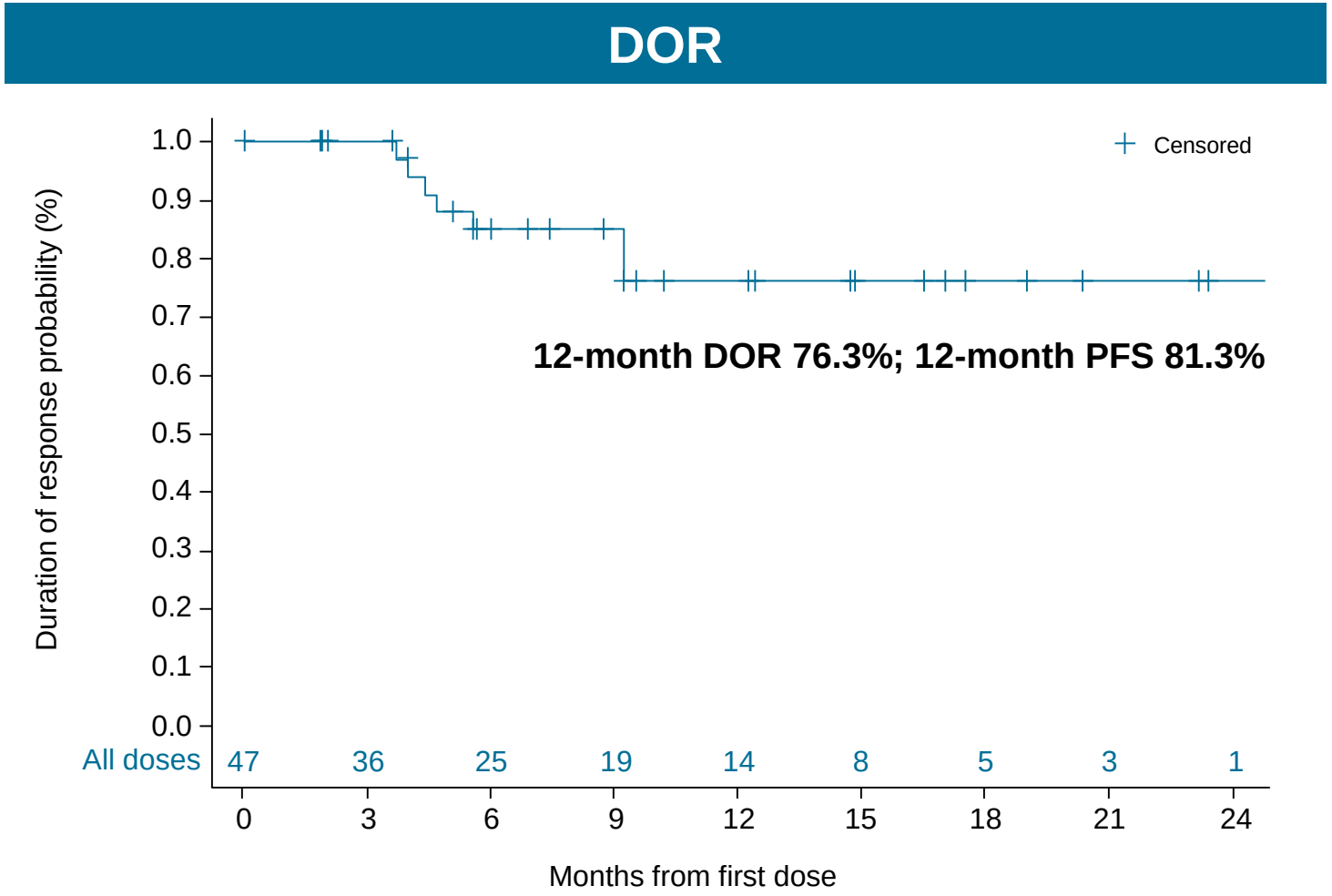
Best response by central radiology in PDGFRα D842V GIST



PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

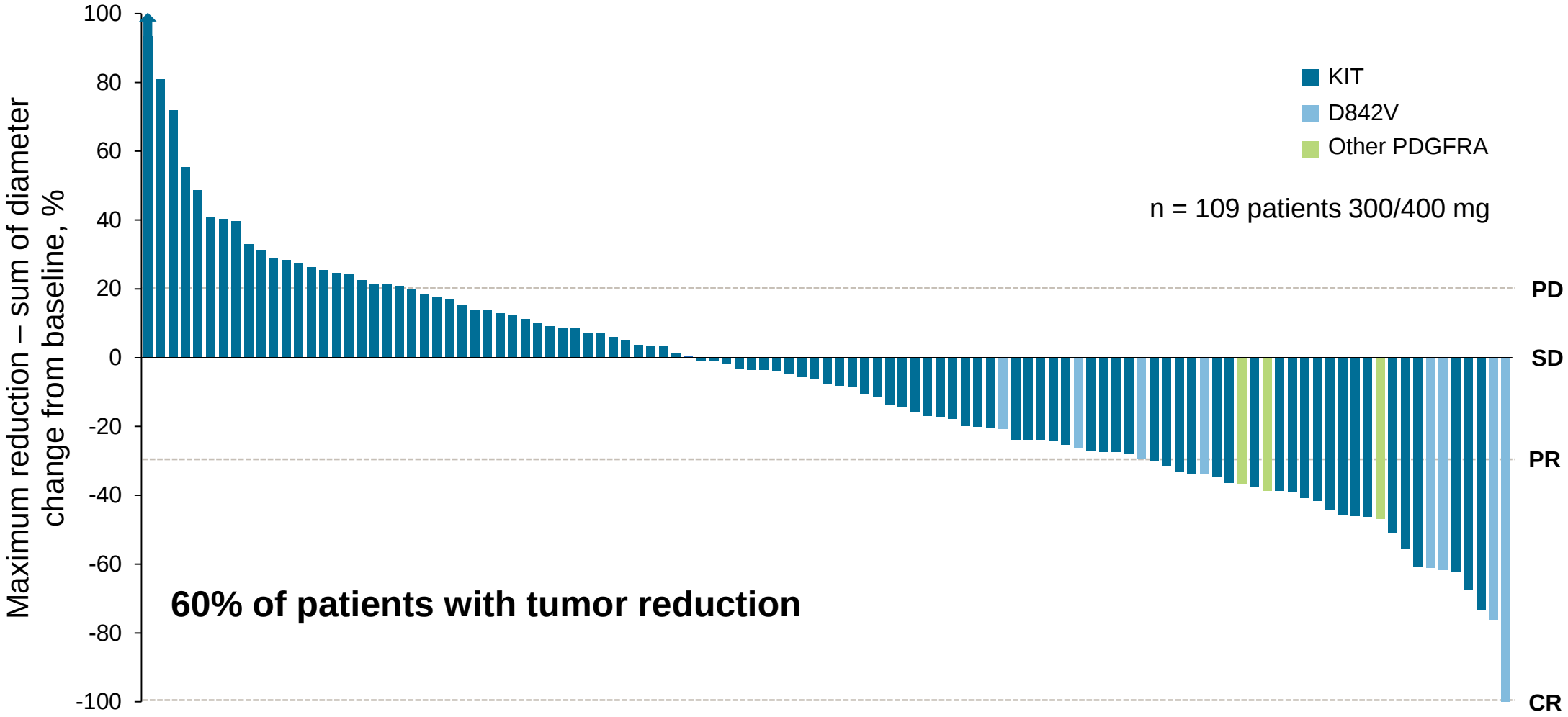
ORR and DOR by central radiology in PDGFRα D842V GIST

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]



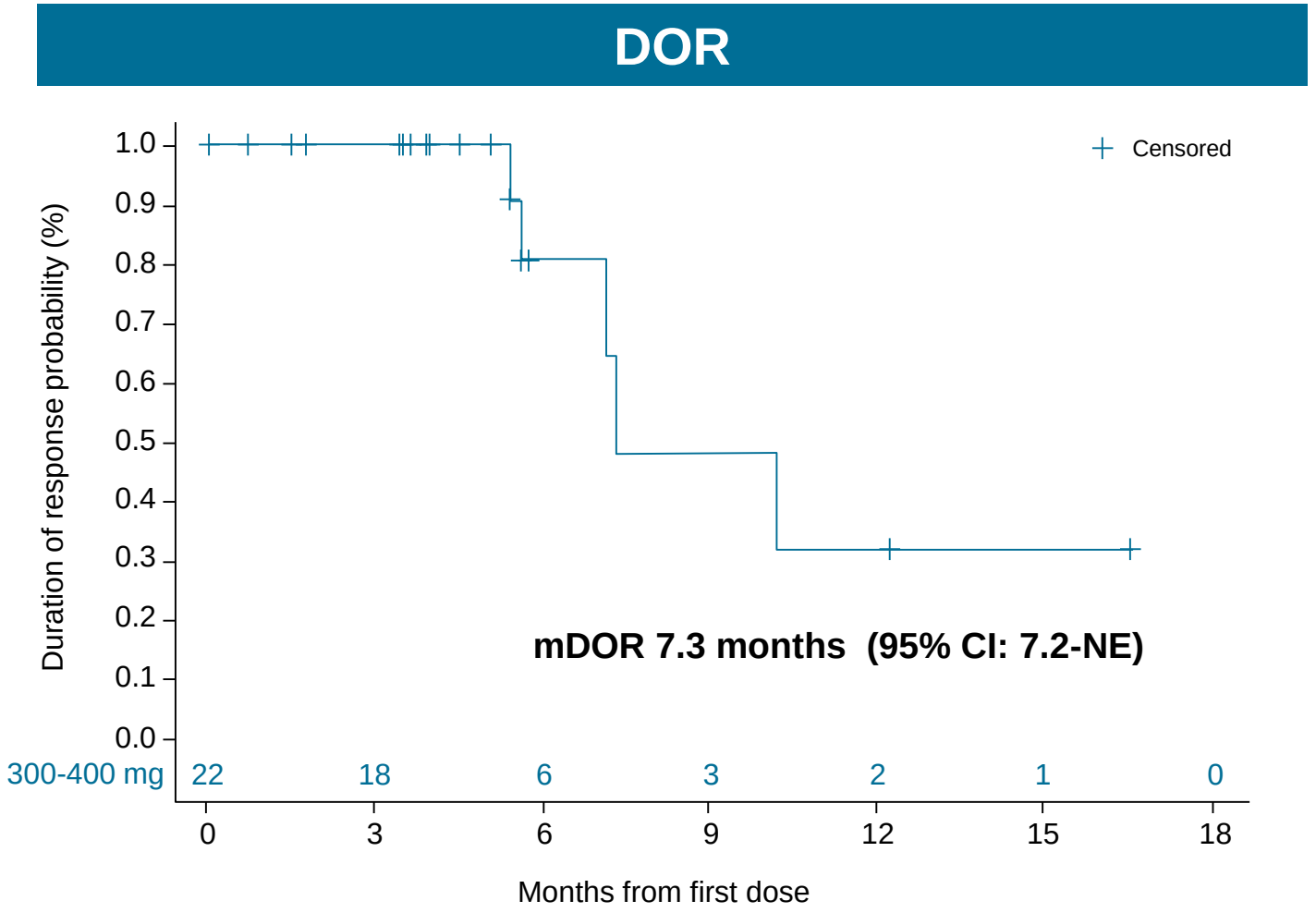
CI, confidence interval; CBR, clinical benefit rate.
*4 PR pending confirmation. Patients who have had ≥1 post-baseline radiographic assessment. Response evaluable includes all doses.
† PR + SD lasting ≥4 months.

Best response by central radiology in ≥4L GIST



ORR and DOR by central radiology ≥4L GIST

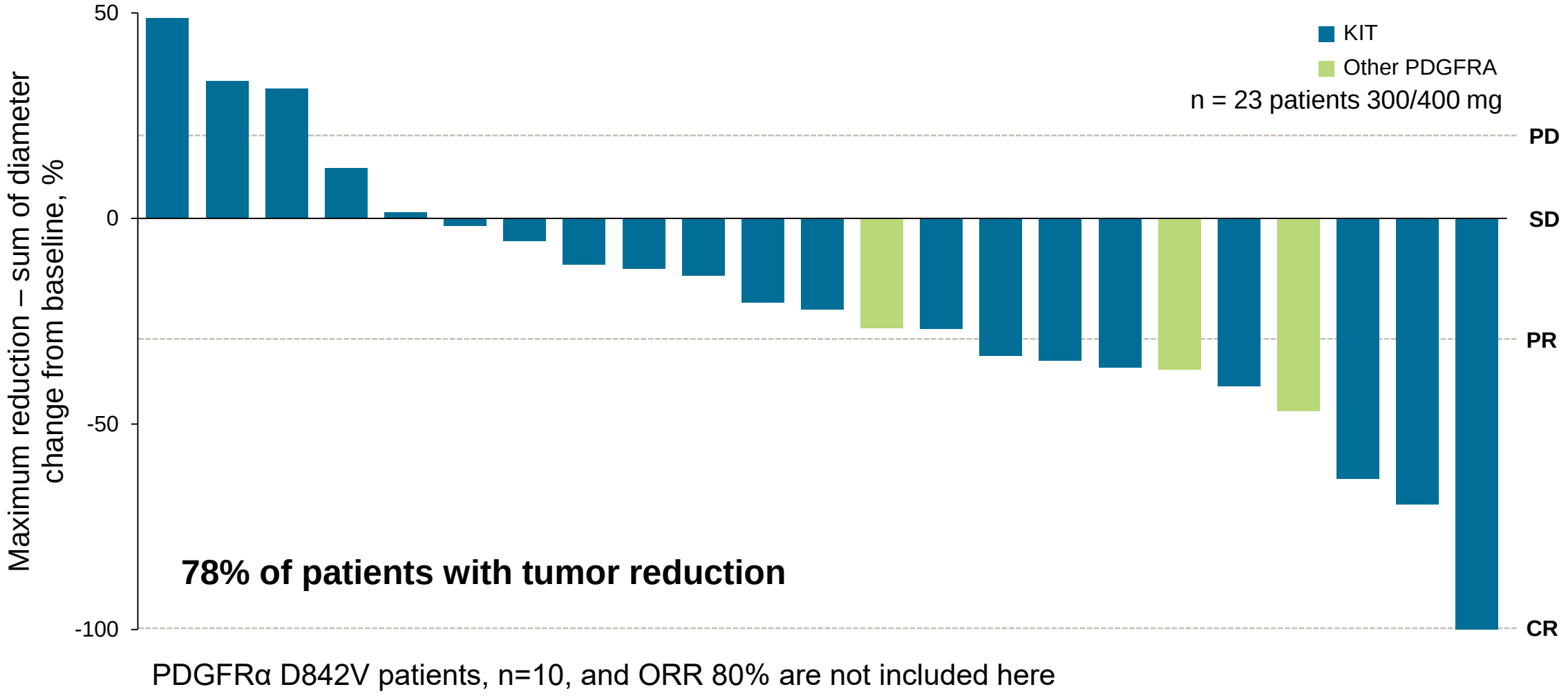
Best response* n = 109	mRECIST 1.1 % (n) [95% CI]
ORR	20% (22) [13.1-29.0]
CR/PR*	1% (1)/19% (21)
SD	46% (50)
CBR†	40% (44) [31.1-50.2]



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

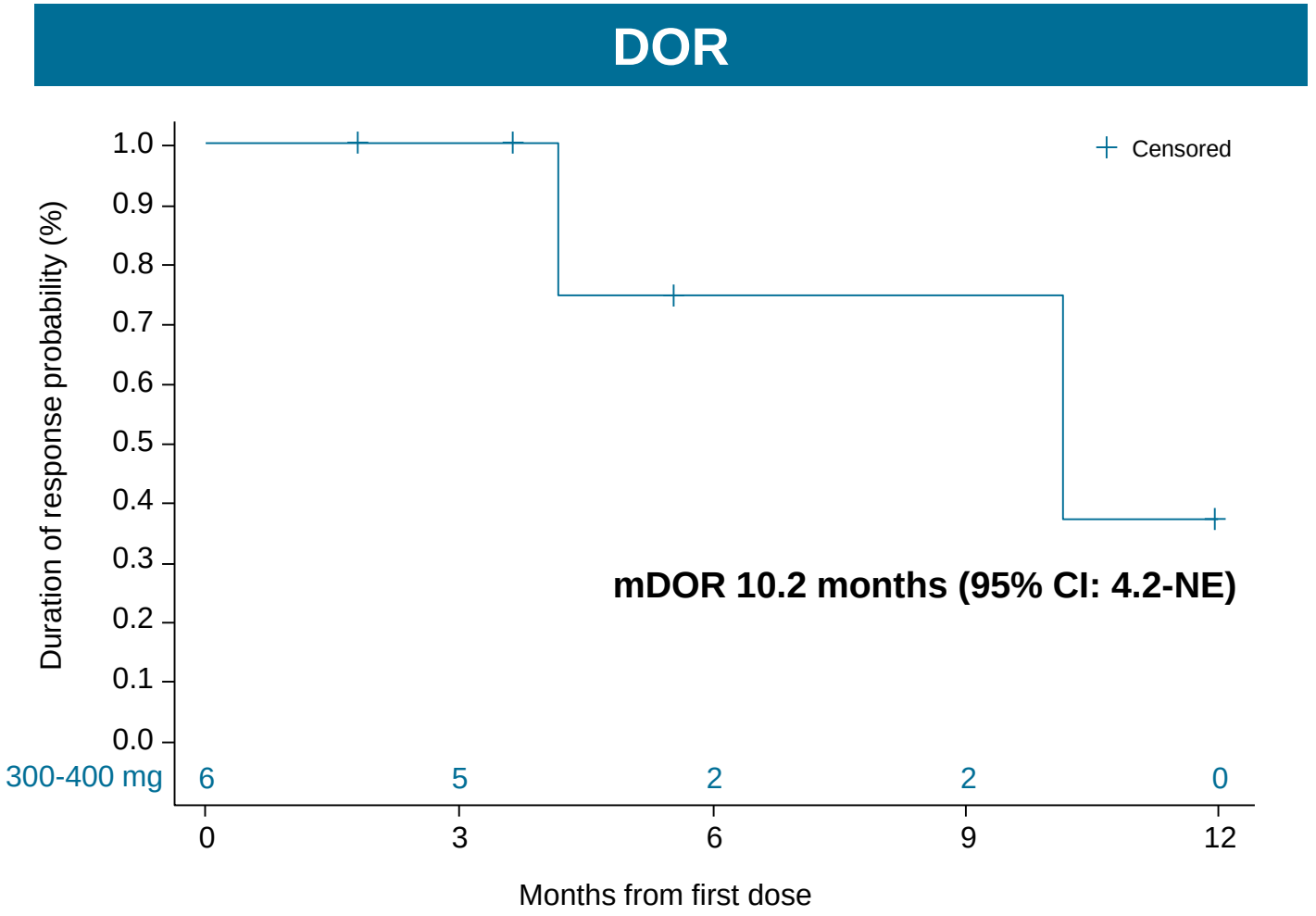
Best response by central radiology in 3L/4L regorafenib-naïve GIST*



*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

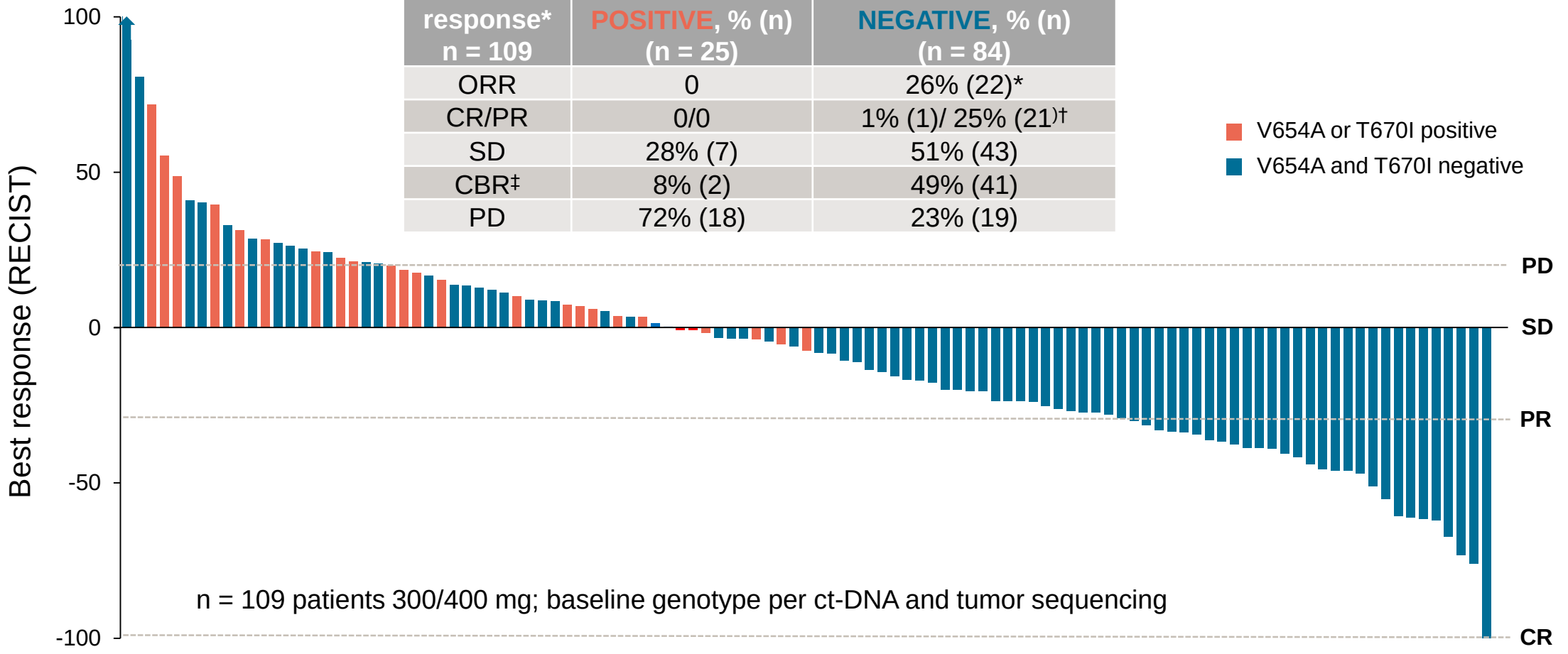
Non-D842V patients best response* n = 23	mRECIST 1.1 % (n) [95% CI]
ORR	26% (6) [10.0-48.4]
CR/PR	0% (0)/26% (6)
SD	57% (13)
CBR†	70% (16) [47.1-86.8]



*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 ≥4L GIST

Best response* n = 109	V654A or T670I POSITIVE, % (n) (n = 25)	V654A and T670I NEGATIVE, % (n) (n = 84)
ORR	0	26% (22)*
CR/PR	0/0	1% (1)/ 25% (21)†
SD	28% (7)	51% (43)
CBR‡	8% (2)	49% (41)
PD	72% (18)	23% (19)



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

	PDGFRα D842V n = 56	≥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 PDGFRα D842V GIST and refractory, ≥4L 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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