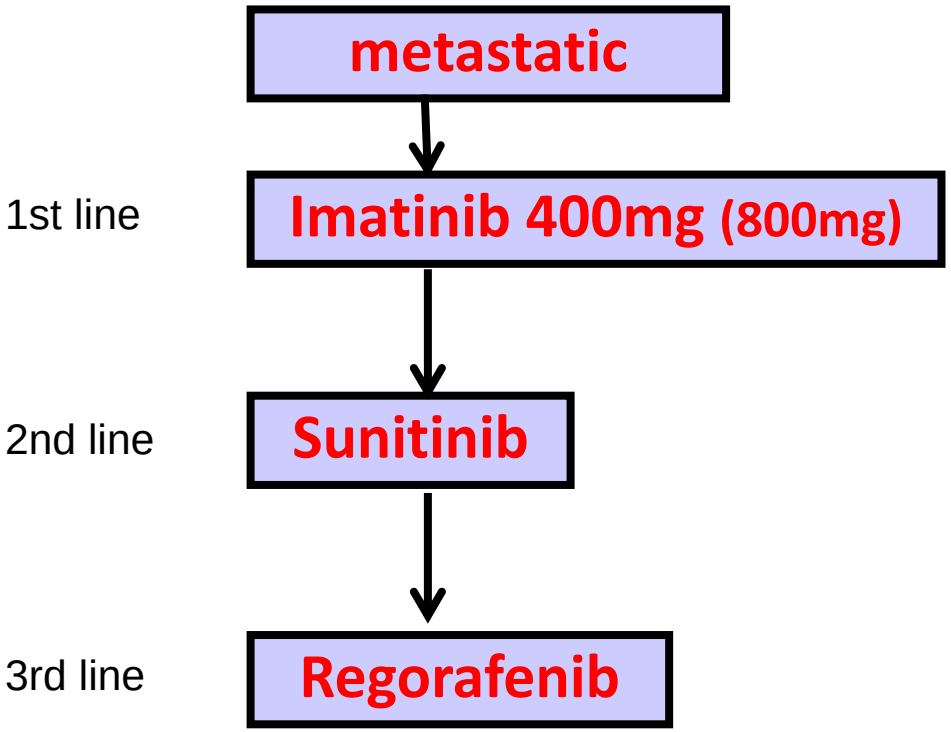
SPAEN 2020

GIST
Current and upcoming trials

wtz westdeutsches tumorzentrum

Universitätsklinikum Essen

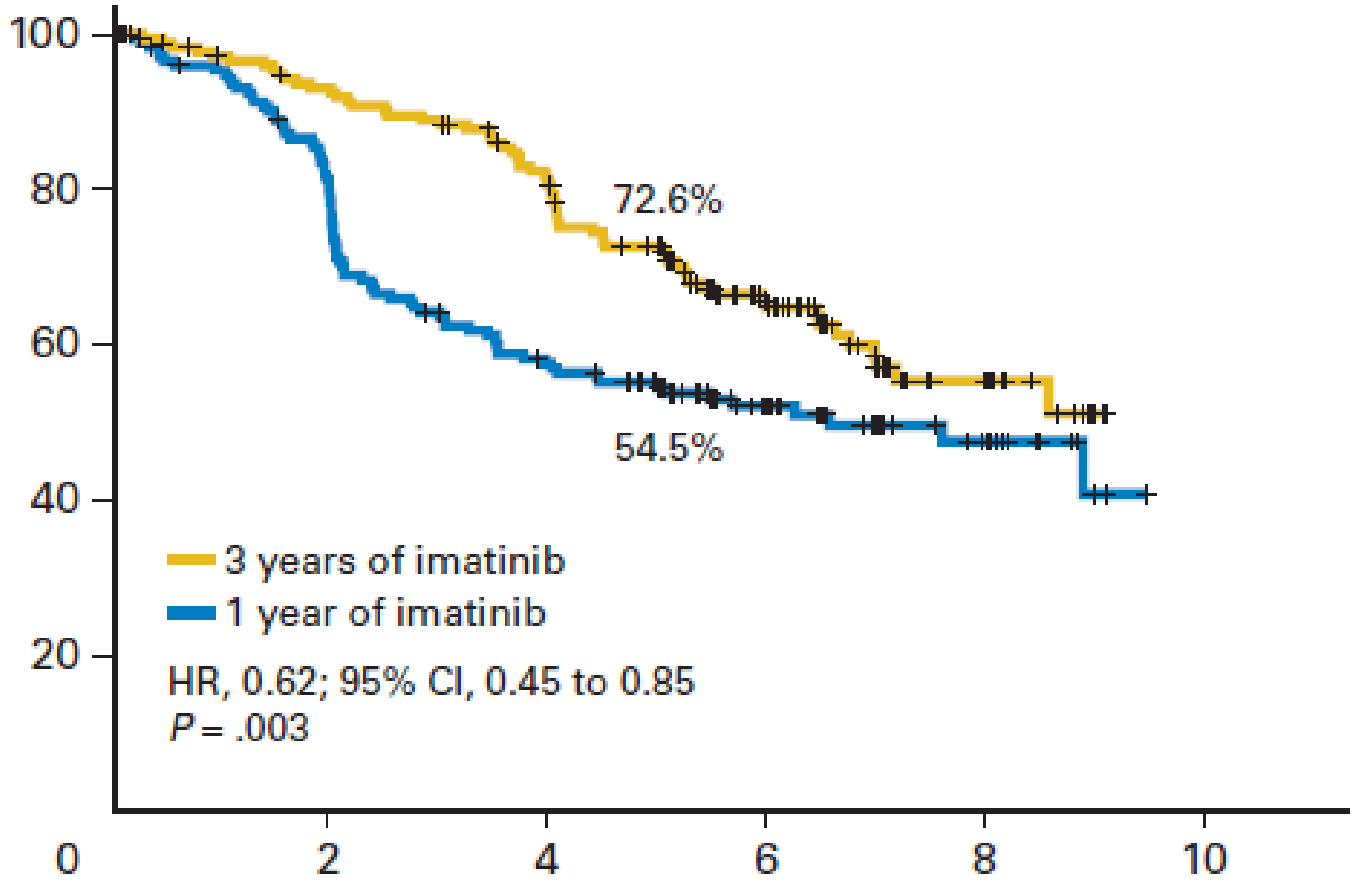
Trials: 2020



localized

SSG XXII:
Imatinib 3 vs 5 years
(HR-Patienten)

ADJUVANT TREATMENT = SAFETY TREATMENT



Approaching cure

Localized (high risk) GIST

Review Article

Cancer July 1, 2019

Tailored Management of Primary Gastrointestinal Stromal Tumors

Mark S. Etherington, MD; and Ronald P. DeMatteo, MD, FACS

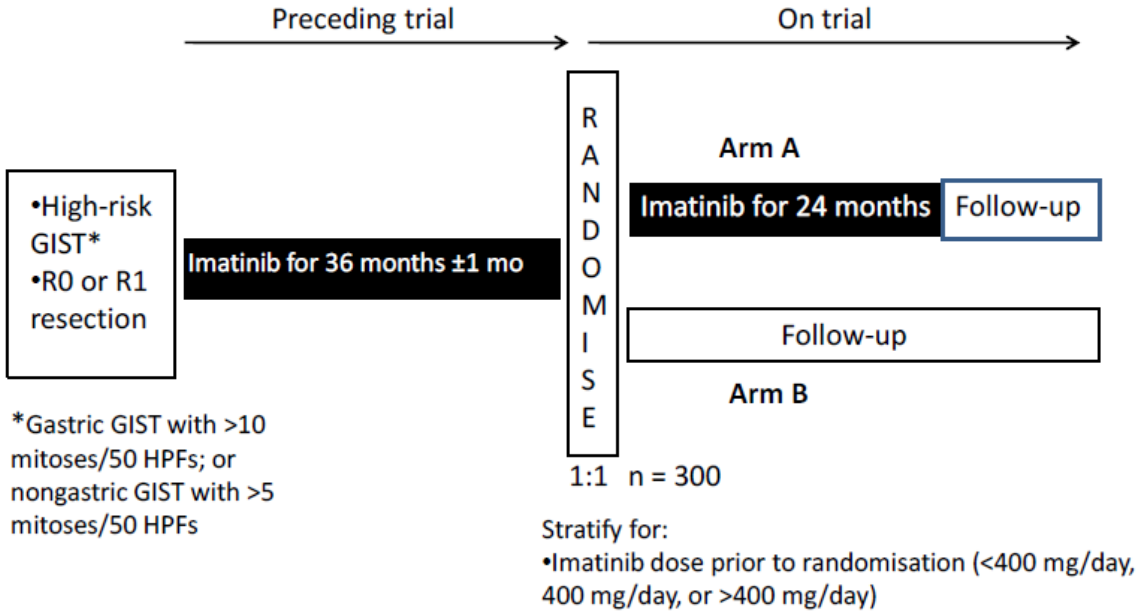
TABLE 1. Summary of Adjuvant Imatinib Trials in Primary Gastrointestinal Stromal Tumors

Trial	Phase	Entry Criteria	Treatment Dose/ Duration	Relevant Findings
ACOSOG Z9001 (DeMatteo 2013[56])	3	Tumor ≥3 cm	400 mg daily for 1 y vs placebo	1-y RFS, 98% vs 83%; no difference in OS
SSG XVIII (Joensuu 2012,[57] Joensuu 2016[58])	3	High-risk tumor	400 mg daily for 1 y vs 3 y	3-y RFS, 73% vs 55%; 3-y OS 92% vs 85%; 3-y DSS, 95% vs 89%[a]
EORTC 62024 (Casali 2017[59])	3	Intermediate-risk and high-risk tumor	400 mg daily for 2 y vs no treatment	5-y IFFS, 87% vs 84%[a]; 3-y RFS, 84% vs 66%; 5-y RFS, 69% vs 63%
PERSIST-5 (Raut 2018[31])	1	Intermediate-risk or high-risk tumor	400 mg daily for 5 y	5-y, RFS 90%; 5-y, OS 95%; 50% in treatment arm discontinued imatinib

1 year | 2 years | 3 years | 5 years | Life-long

Approaching cure

SSG XXII – is 5 better than 3?

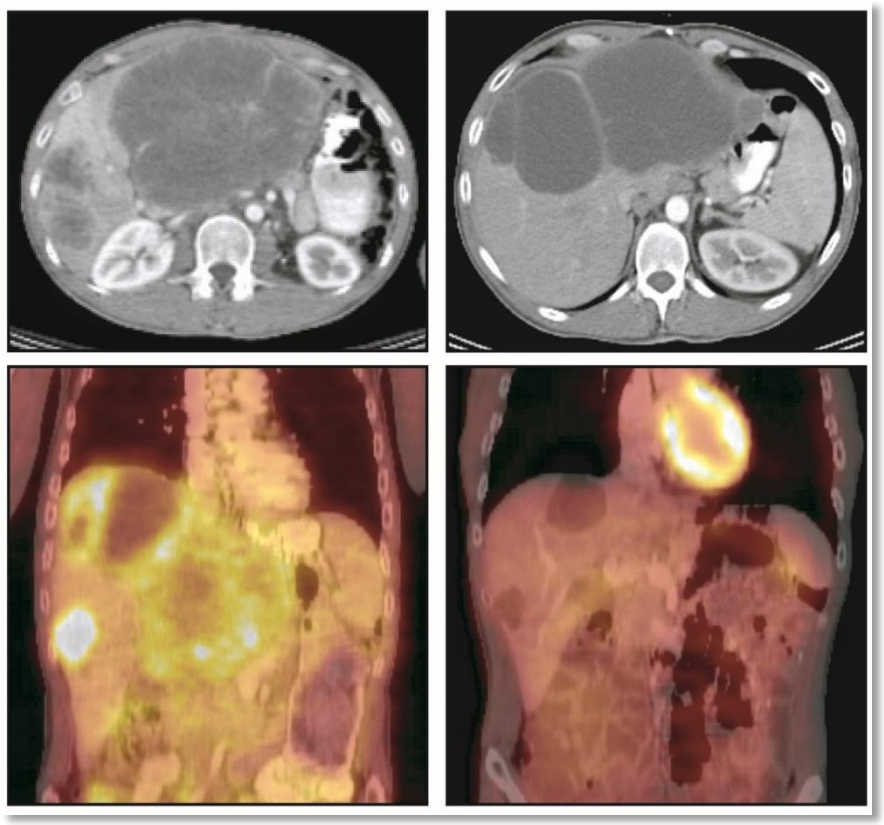


n=300
1:1 Randomization

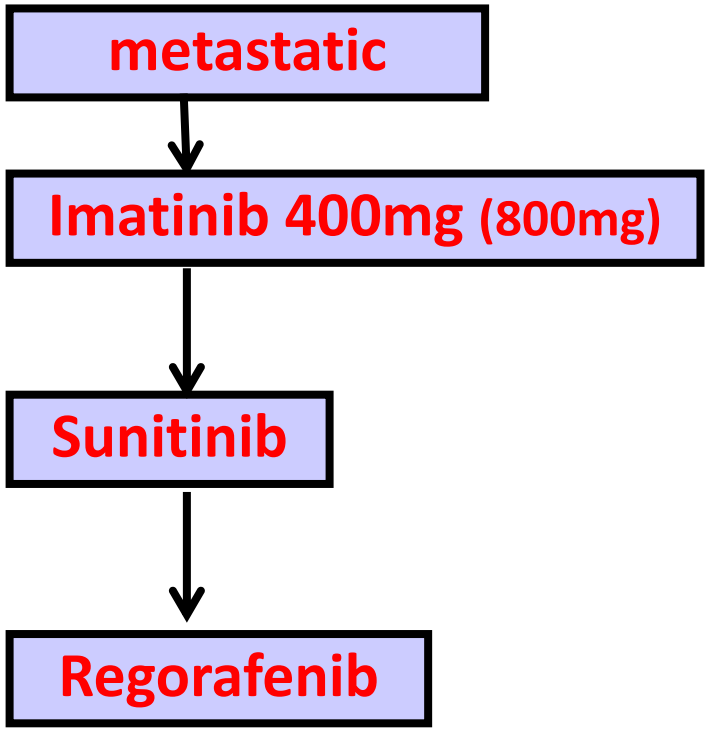
- ≤35months of adjuvant IM, ≤ 9mo neoadjvuant IM
- Preceding doses of ≥ 200mg and ≤ 800mg
- Exon 9 mutant GIST may receive 800mg

PLEASE INFORM PATIENTS

Update for patients with metastatic disease



Trials: 2020 in Europe



1st line

2nd line

3rd line

4th line

>4th line

localized

SSG XXII:
Imatinib 3 vs 5 years
(HR-Patienten)

Intrigue: Ripretinib vs Placebo (Phase III)

Navigator: Avapritinib (Phase II)

COMPASS?

CABO GIST TRIAL (Phase II)

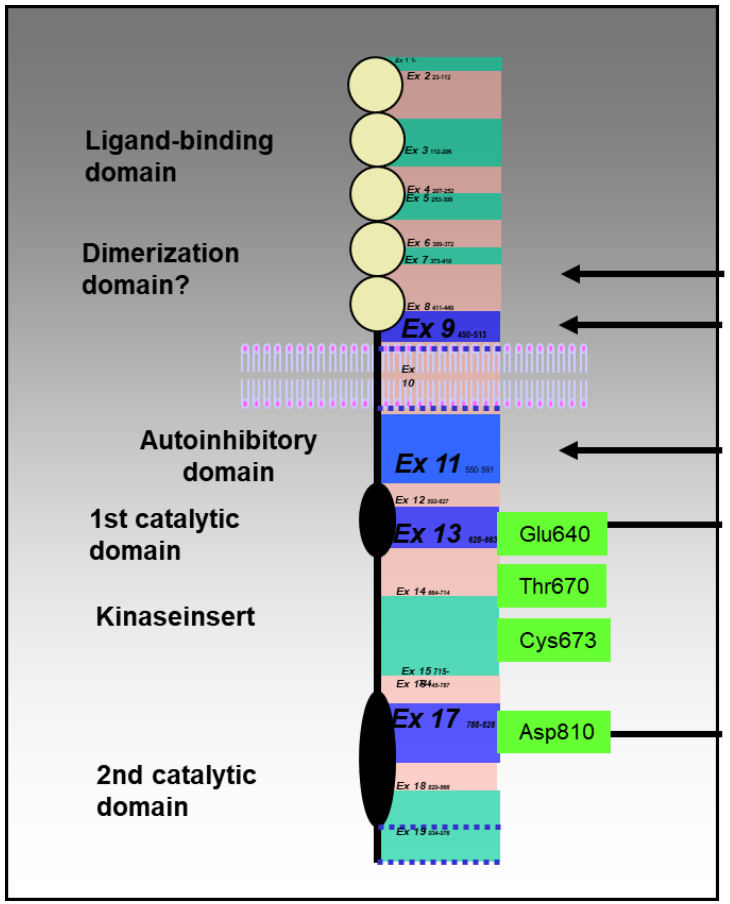
Voyager-Studie: Avapritinib vs Regorafenib (Phase III)

Invictus-Studie: Ripretinib vs Placebo (Phase III)

Avapritinib Compassionate Use Programm

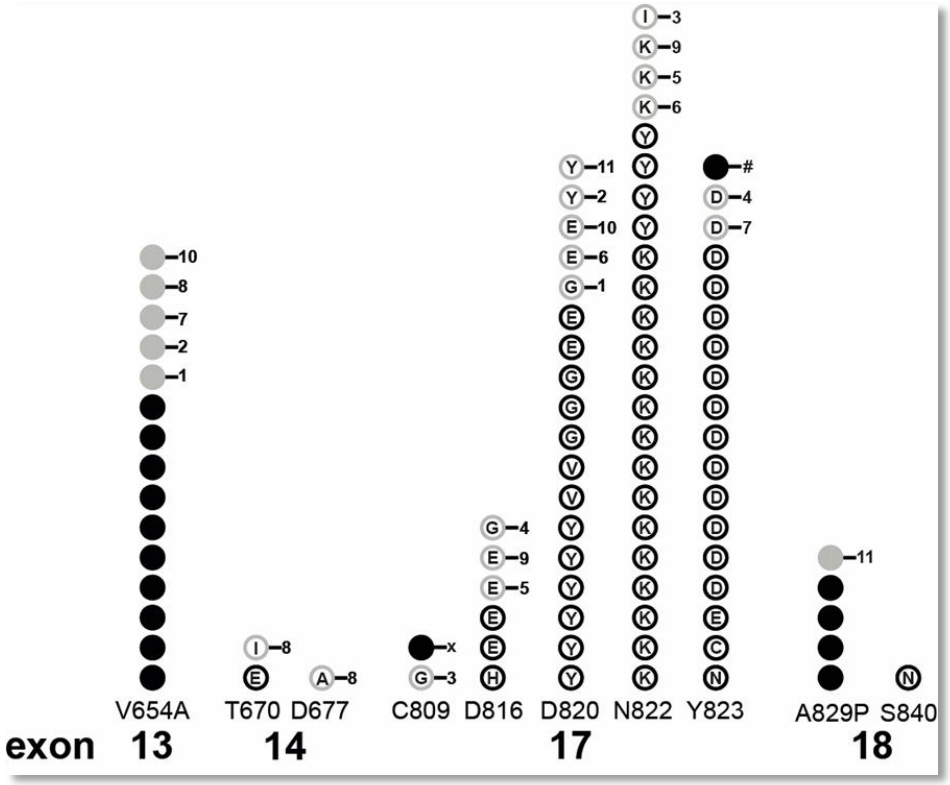
Ripretinib Compassionate Use Programm

Why do GIST become resistant to Imatinib and other drugs?



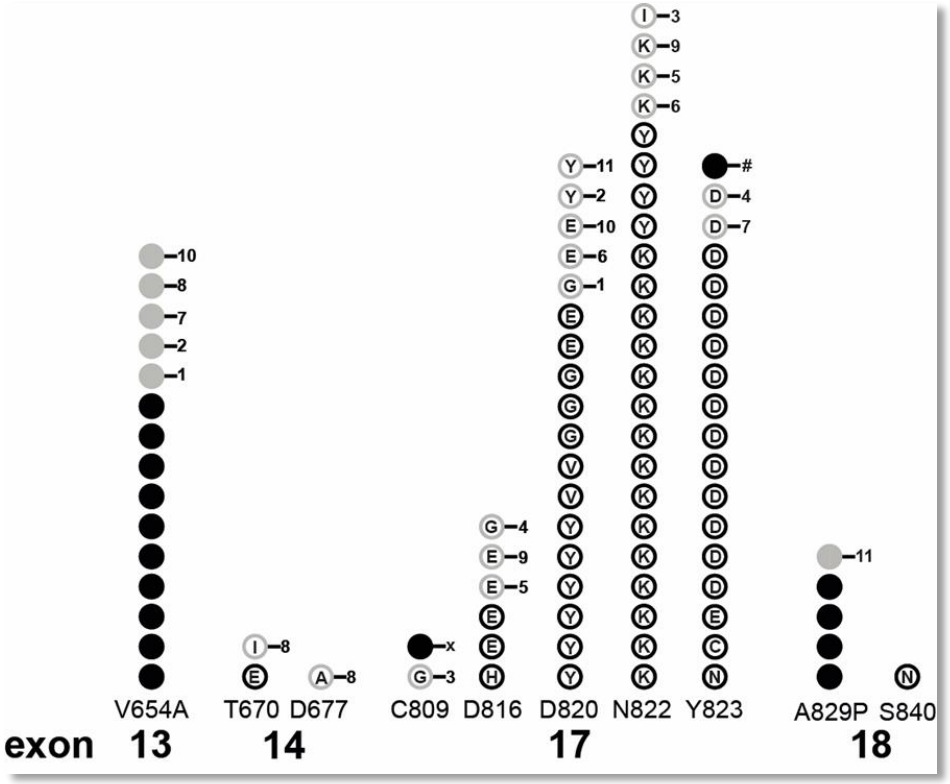
	KIT	PDGFRA
	1 case	
	9.1 %	
	59.6 %	2.5% (Ex12)
	1.9 %	0.5% (Ex14)
	0.8 %	6.9% (Ex18)

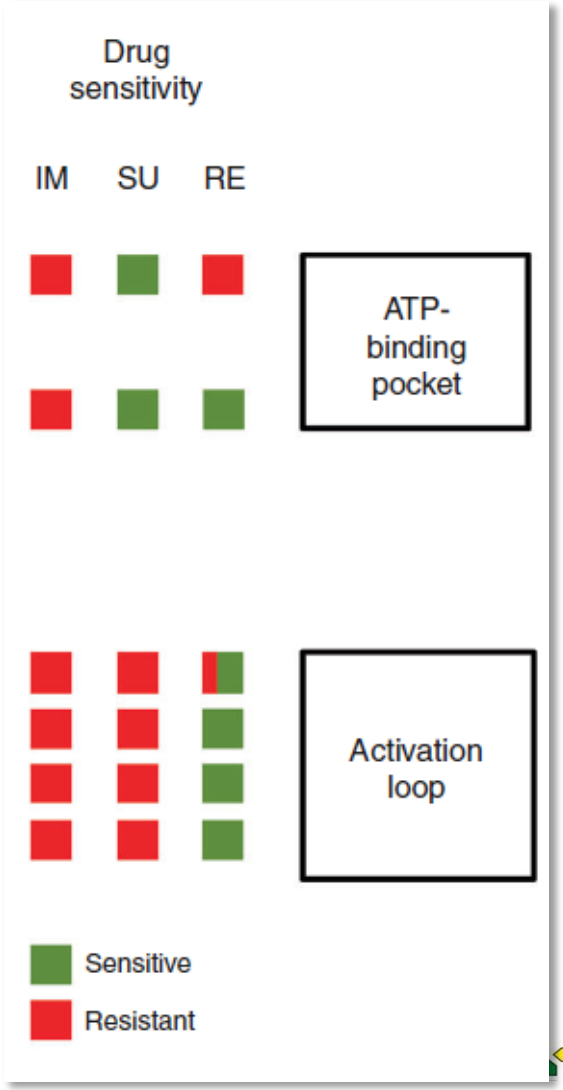
N= Activation-Loop-Mutationen



Heinrich MC, *ASCO* 2010: educational session
Hornick,J.L. et al. HumPathol 2007,38(5),679–687
Mühlenberg, Mol Cancer Ther. 2019 Jul 15 epub ahead

Why do GIST become resistant to Imatinib and other drugs?





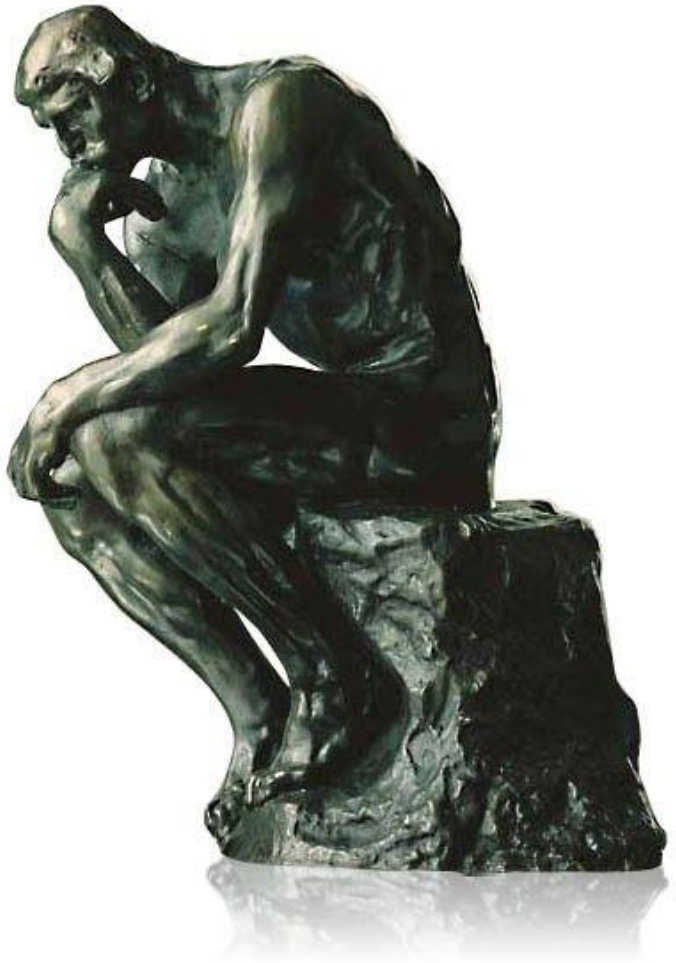
Mühlenberg, Mol Cancer Ther. 2019 Jul 15 epub ahead

Serrano, British Journal of Cancervolume 120, pages612–620 (2019)

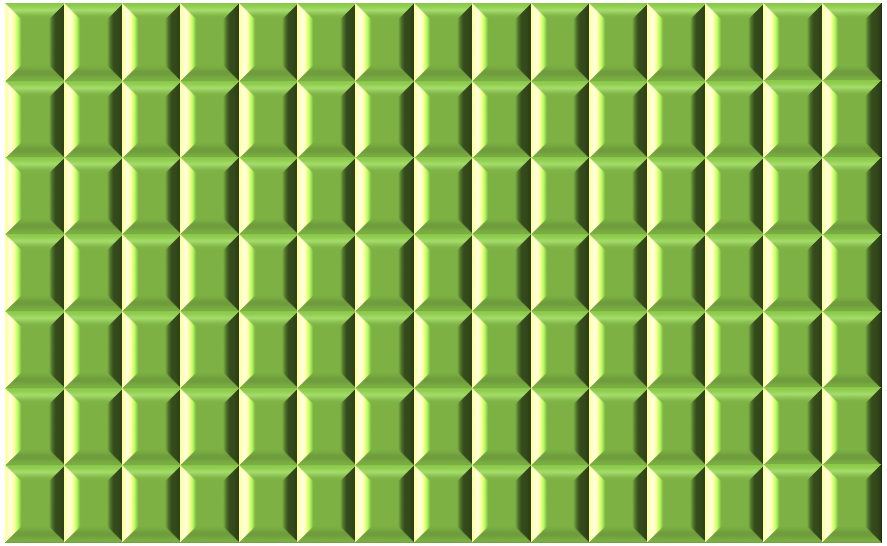
Why is there resistance?

Can we prevent resistance in the first place?

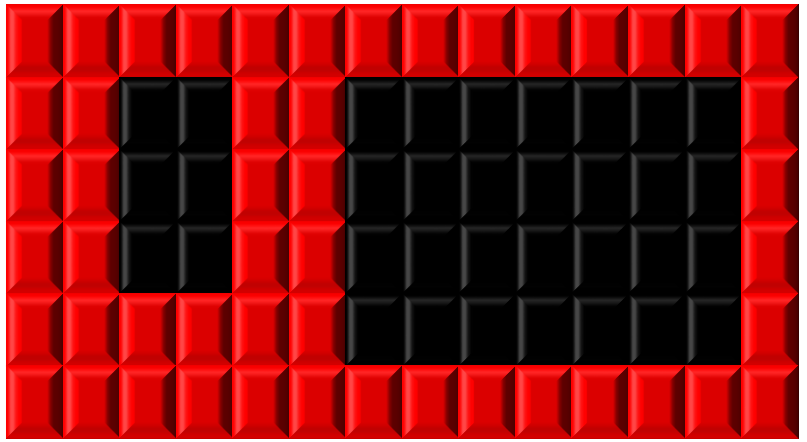
When does resistance develop?



Development of resistance to imatinib – concepts



Baseline



Response to imatinib

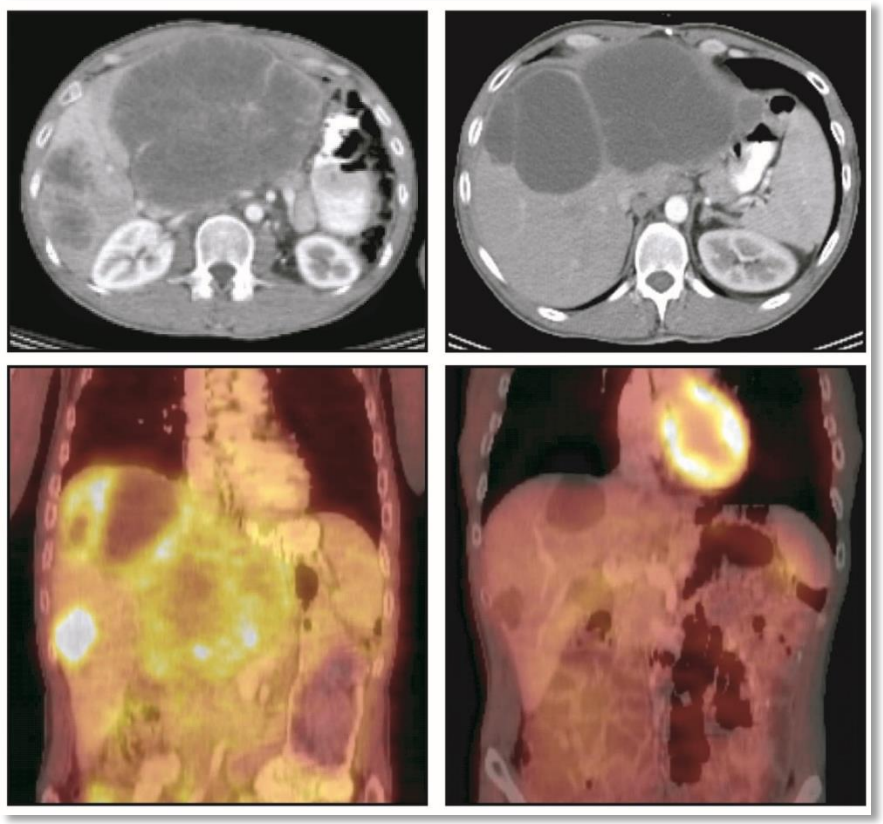
= growing

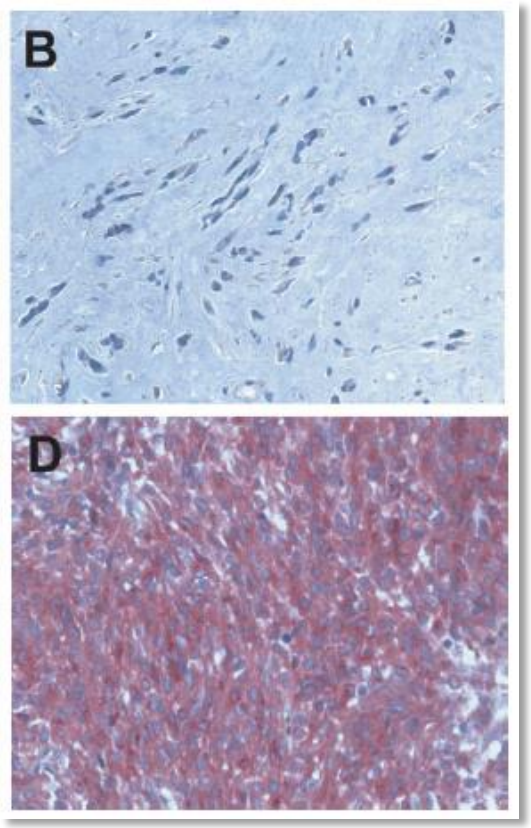
= not growing

= dead

Preventing resistance in GIST

Clinical evidence for sequence of events?





Bauer et al, Int J Cancer 2005;117:316–25

Preventing resistance in GIST

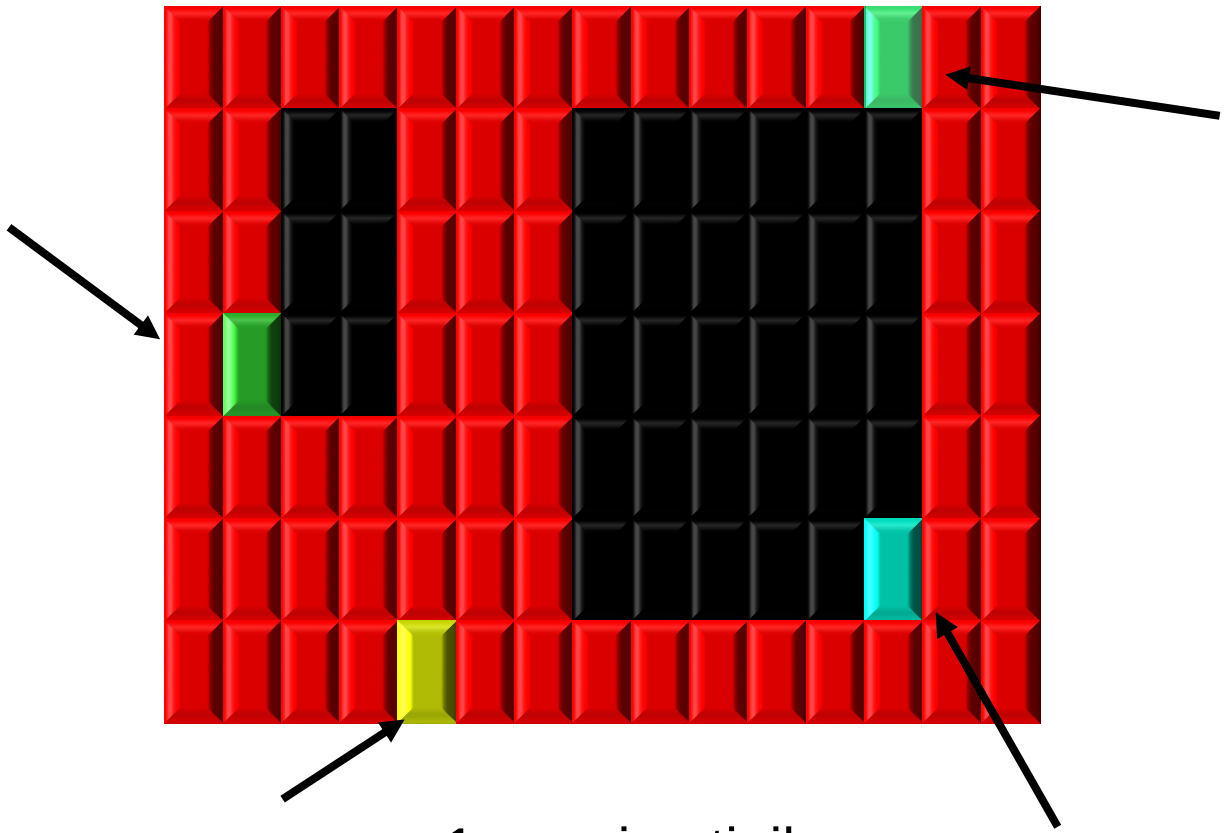
Clinical evidence for pre-existing resistance?

Setting	Advanced disease—clinical trial				Population based						Population based, exhaustive	
Author	Debiec-Rychter *et al* (2006)		Heinrich *et al* (2008)		Braconi *et al* (2008)		Braggio *et al* (2008)		Du *et al* (2008)		Current series	
Number of patients included	946		746		104		81		141		131	
Number analysed for mutations	377		378		94		55		141		106	
Mutations	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Kit	315	84	314	83	81	86	40	73	108	77	71	67
Exon 9	58	15	31	8	11	12	2	4	8	6	10	9
Exon 11	248	66	275	73	69	73	38	69	99	70	56	53
Exon 13	6	2	3	1	0	0	0	0	1	1	4	4
Exon17	3	1	4	1	1	1	0	0	0	0	1	1
PDGFRA	10	3	6	2	13	14	4	7	8	6	17	16
Exon 12	1	0	0	0	3	3	3	5	0	0	2	2
Exon 18	9	2	6	2	10	11	1	2	8	6	15	15
Wild type	52	14	58	15	10	11	11	20	25	18	18	17

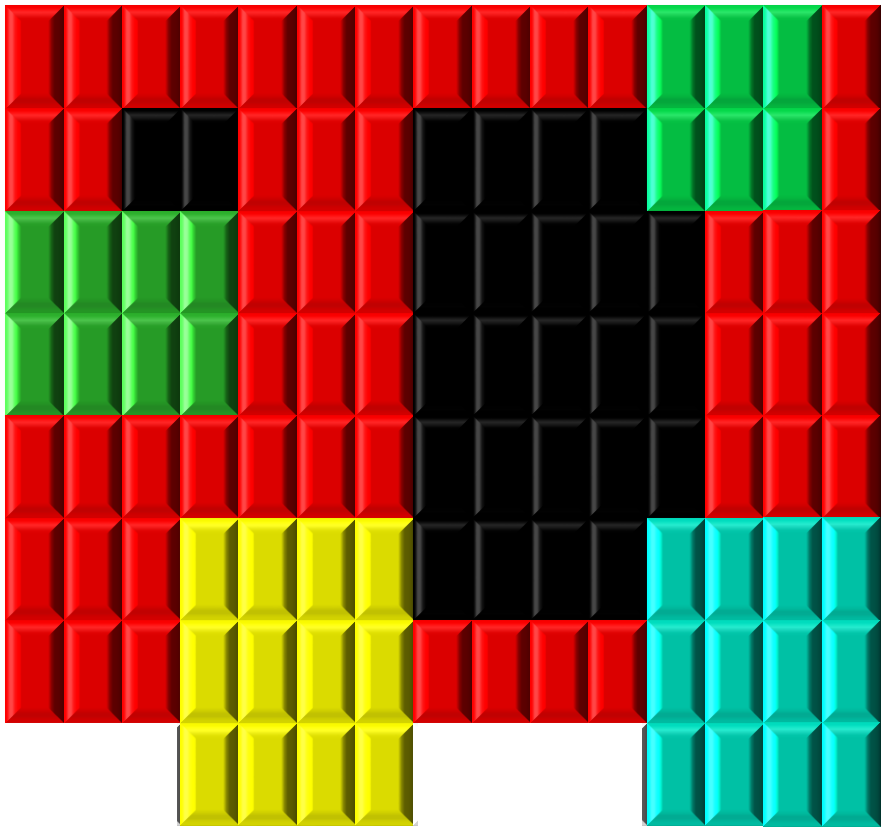
Clinical routine testing does not show pre-existing secondary mutations (at all…)

Cassier et al, 2010 BJC

Development of resistance to imatinib – concepts



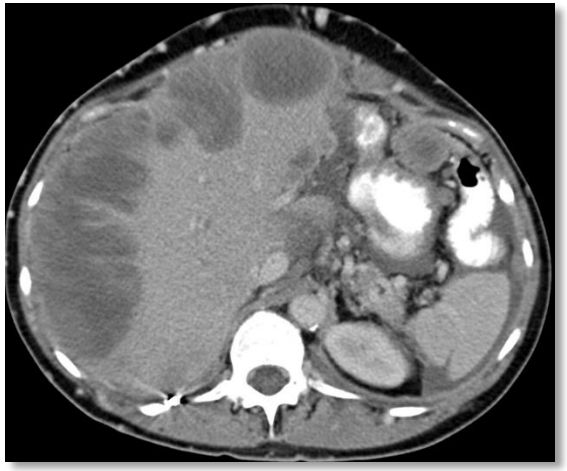
1 year imatinib

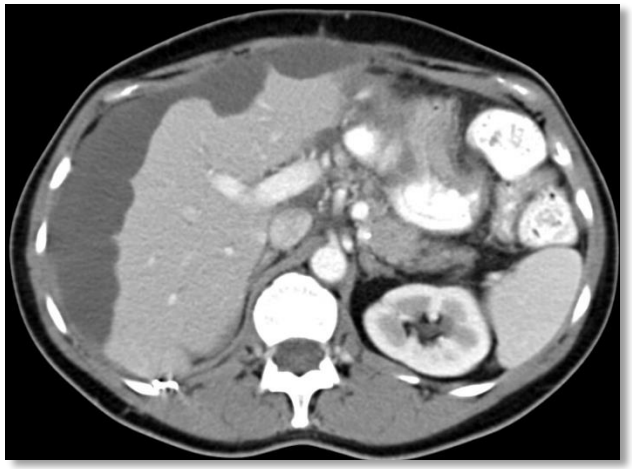


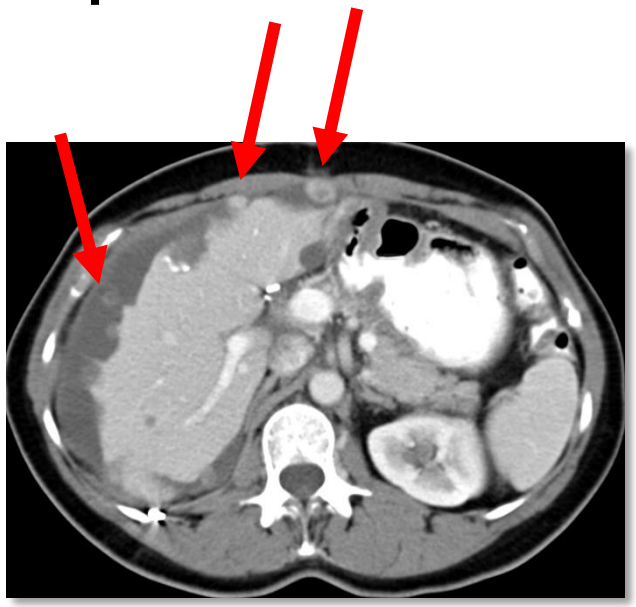
Secondary progression

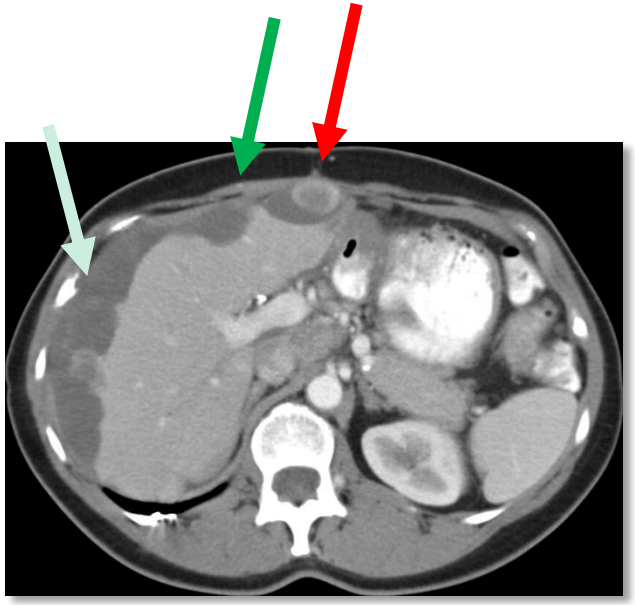
Proliferation is a pre-requisite: Pre-existing clones? Low-level proliferation?

Development of resistance to imatinib – concepts







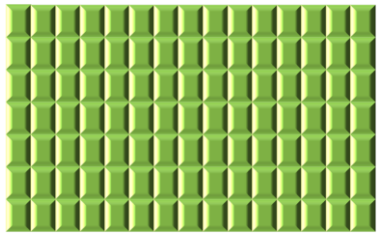


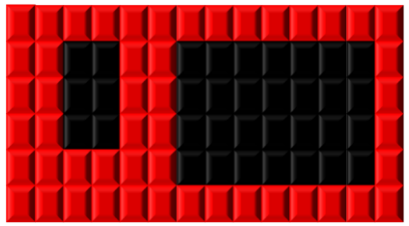
Baseline

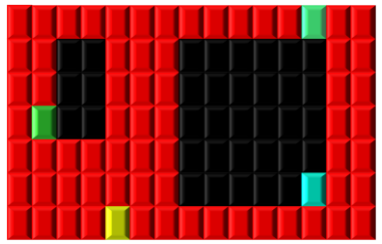
Response to IM

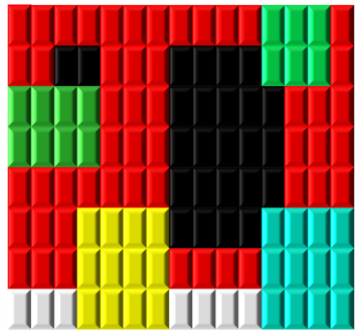
18 months - SU

21 months



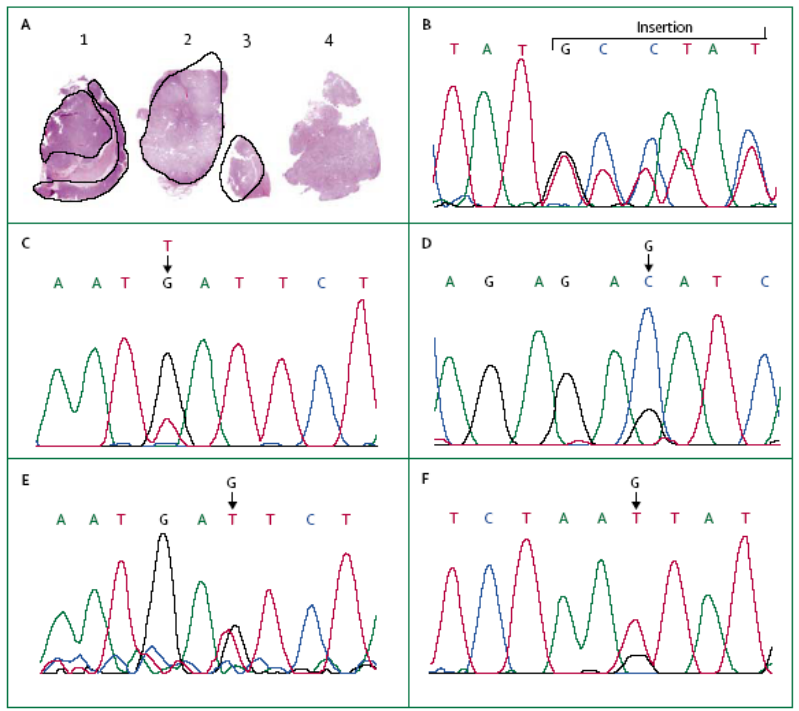






Mechanisms of imatinib resistance

Genomic heterogeneity



D820Y

D820E

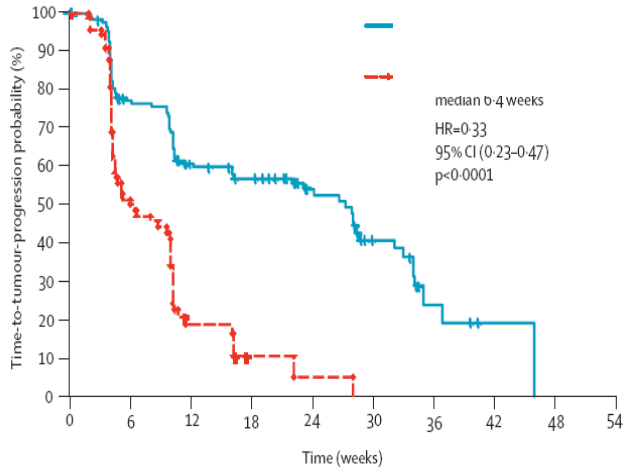
insertion Exon 9

D816E

N822K

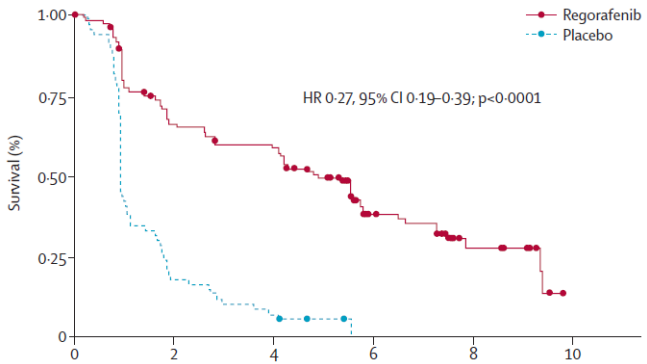
„genomic heterogeneity“

Sunitinib



Median PFS: 6.2 vs 1.2 mo

Regorafenib



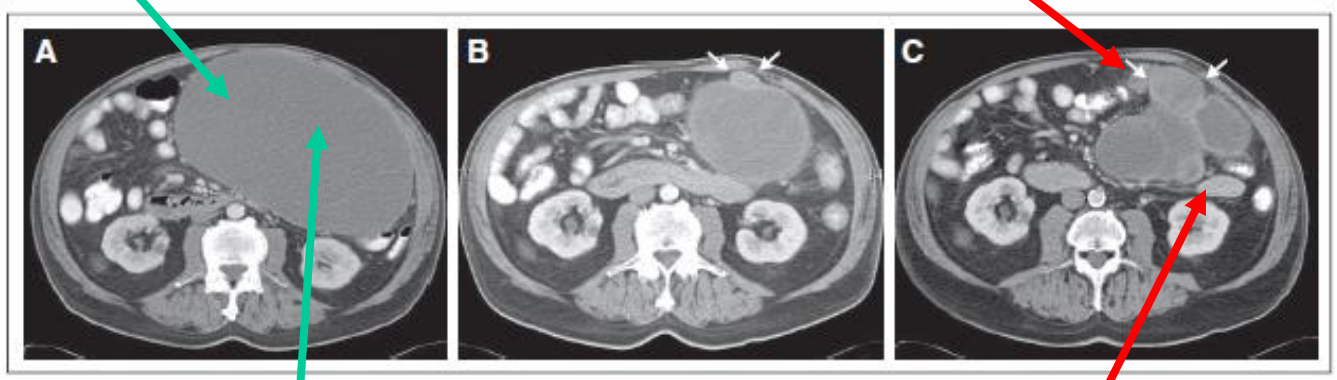
Median PFS: 4.8 vs 0.9 mo

Wardelmann et al, Lancet Oncol 2005; 6: 249–51;Demetri et al, Lancet 2006; 368: 1329–38; Lancet 2013 381(9863):295-302

Is it getting more complex? Why is this going to be important?

hzg KIT ex 11: E554_V559del

KRAS G12R



hzg PTEN C124S missense mut

KIT T670I

Patient	Gene	AA-change	AF [%]	KIT/PDGFRA mutation
1	AKT3	F27I	13	PDGFRA – D842V + V658A
2	BRAF	V600E	60	WT
3	BRAF	V600E	32	WT
4	KRAS	G13D	36	KIT – e11 + N822K
5	PIK3CA	H1065Y	33	KIT – e11 + N822K
6	PIK3CA	H1047R	21	KIT – e11
7	PIK3CA	H1047R	81	KIT – e11
8*	NF1	M1981V	5	KIT – e11 + Y823E
9*	NF1	I719fs	32	KIT – e11 + D820Y + A829P
10	PTEN	I122S	78	KIT – e11
11	TSC1	E479del	46	PDGFRA – D842V
12	TSC2	A1719T	58	PDGFRA – D842V

Serrano et al J Clin Oncol. 2015 Aug 1;33(22):e93-6

Mühlenberg, Mol Cancer Ther. 2019 Jul 15 epub ahead

Now what is new then?

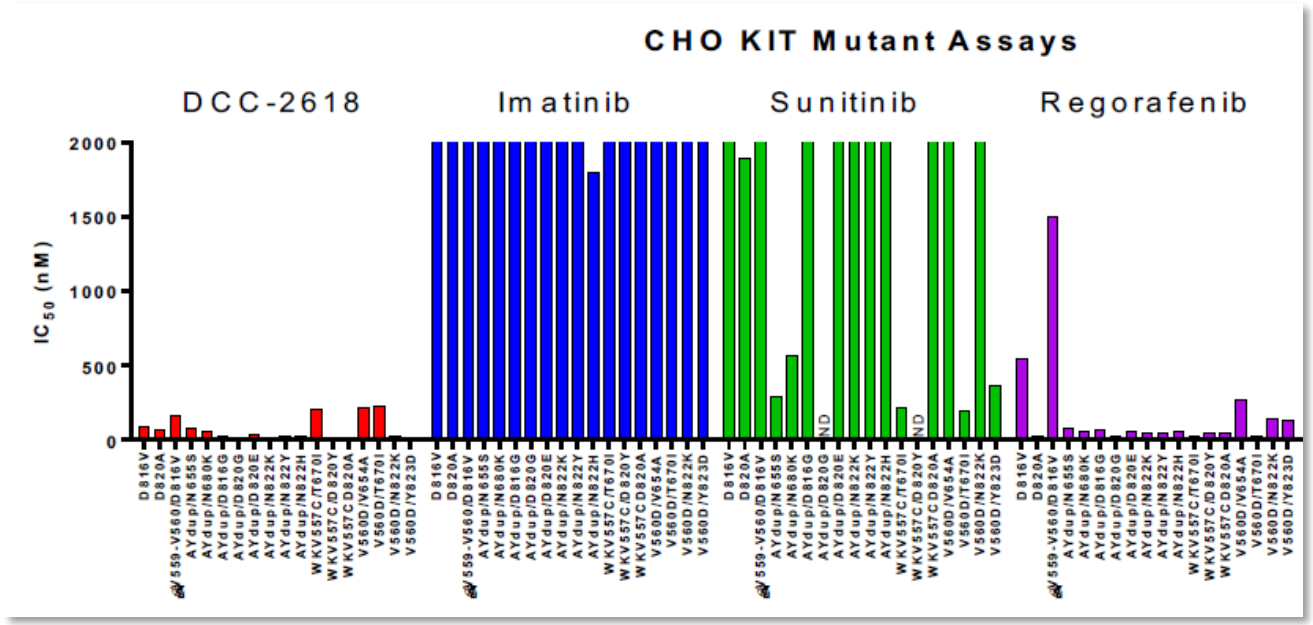
Approaching cure

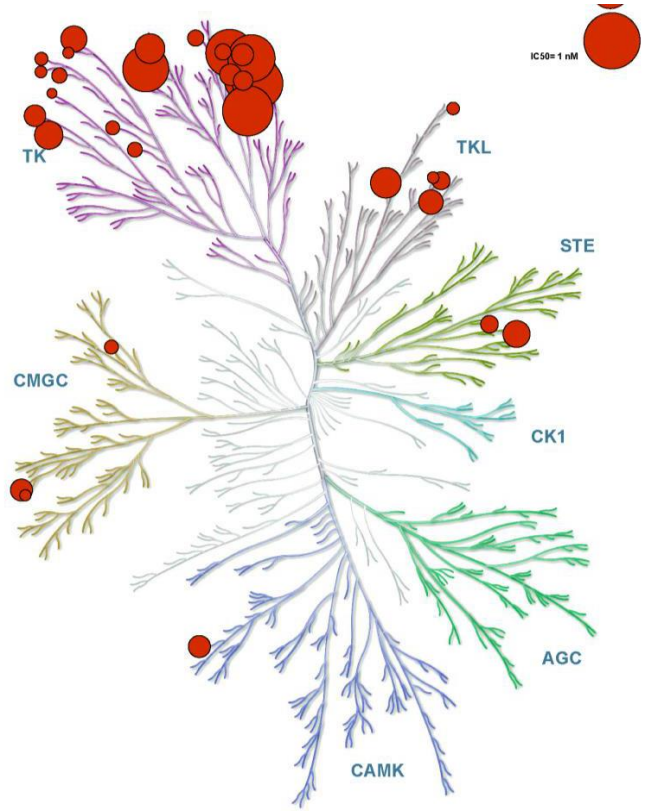
Current randomized trials

Study name	Study drug	Planned size; Randomization	Eligibility	Study number
INVICTUS	DCC2618 vs Placebo	120; 2:1	≥4th line GIST	NCT03353753
INTRIGUE	DCC2618 vs Sunitinib	358; 1:1	2nd line GIST	NCT03673501
VOYAGER	AVAPRITINIB vs Regorafenib	460; 1:1	3nd and 4th line GIST	NCT03465722
CRENOGIST	CRENOLANIB vs Placebo	120; 2:1	D842V Mutated PDGFRA Gene	NCT02847429

Approaching cure? Novel KIT/PDGFRA inhibitors

Ripretinib (DCC-2618)





Ongoing clinical trials

Ripretinib kinome selectivity

INVICTUS
≥4th line

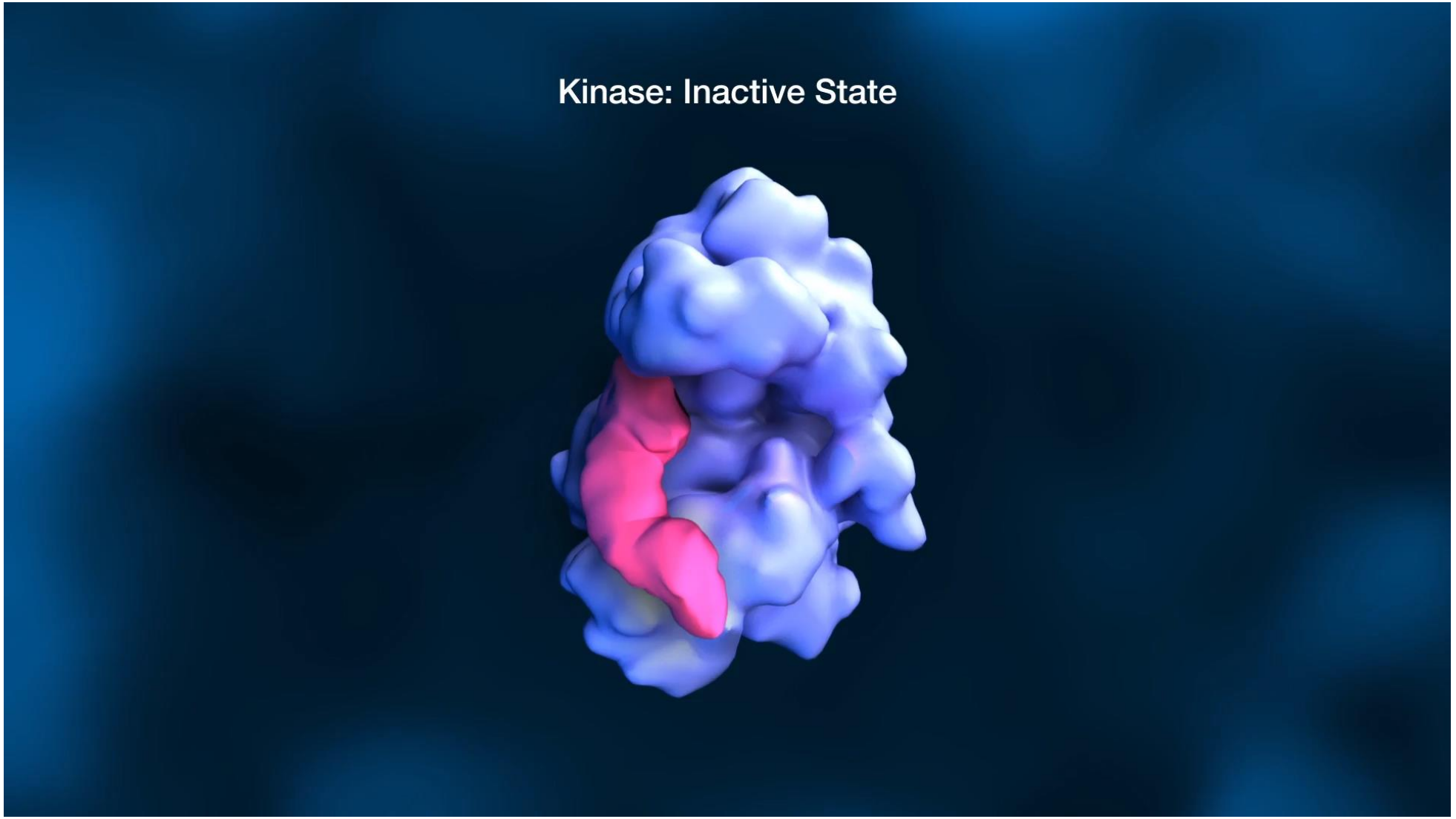
INTRIGUE
2nd-line

Janku et al, European Journal of Cancer 2016, Vol. 69, S1 pS4

INVICTUS:
A Phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib (DCC-2618) in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753)

Jean-Yves Blay, Steven Attia, Sebastian Bauer, Ping Chi, Gina D'Amato, Suzanne George, Hans Gelderblom, Michael C. Heinrich, Robin L. Jones, Peter Reichardt, Patrick Schoffski, Cesar Serrano, John Zalcberg, Julie Meade, Kelvin Shi, Rodrigo Ruiz-Soto, Margaret von Mehren

Ripretinib Mechanism of Action



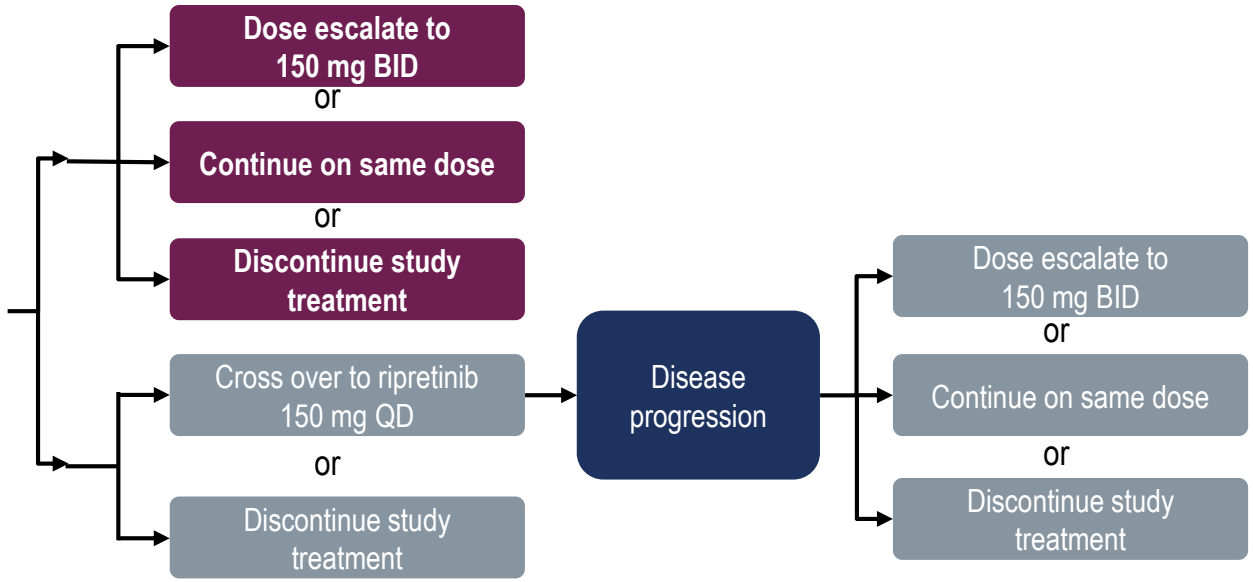
Smith BD, et al. *Cancer Cell*. 2019;35:738-751.

INVICTUS: Randomized Phase 3 Study Design

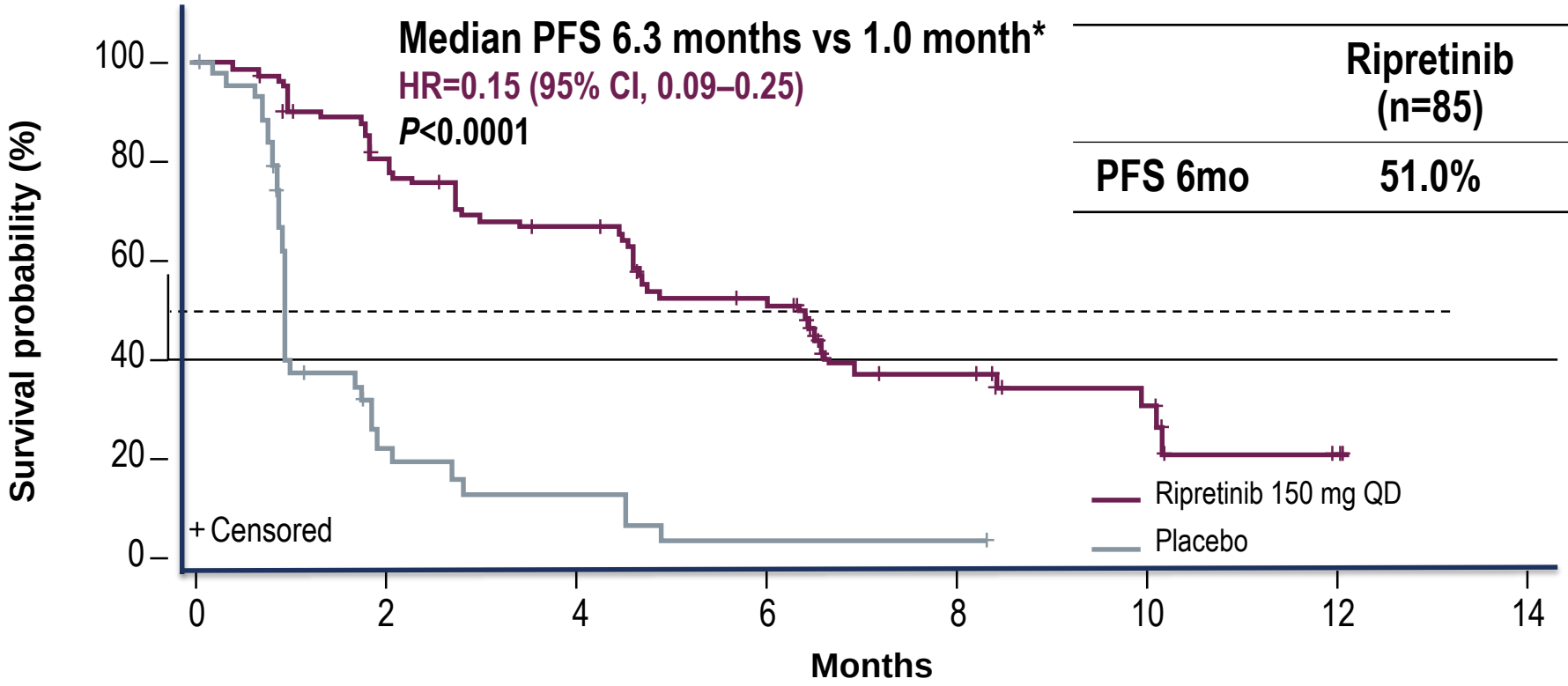
Evaluated ripretinib as ≥4th line therapy in patients with advanced GIST

Ripretinib received (n=85)

Placebo received (n=43)



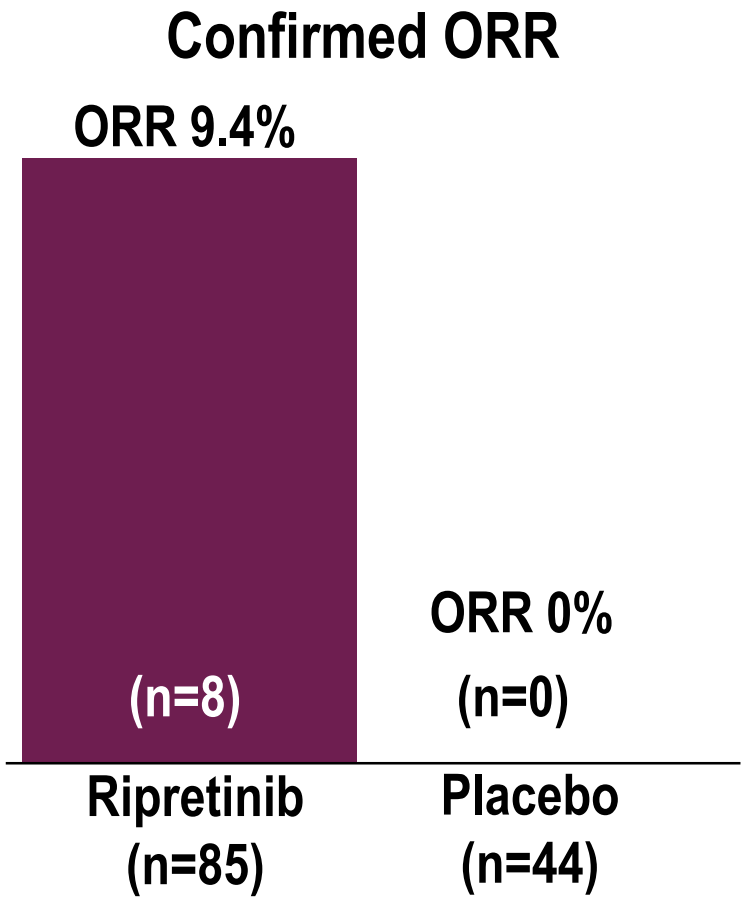
Results of ripretinib vs placebo (progression)



	Ripretinib (n=85)	Placebo (n=44)
PFS 6mo	51.0%	3.2%

*Double-blind period.

Not so many responses – but long lasting



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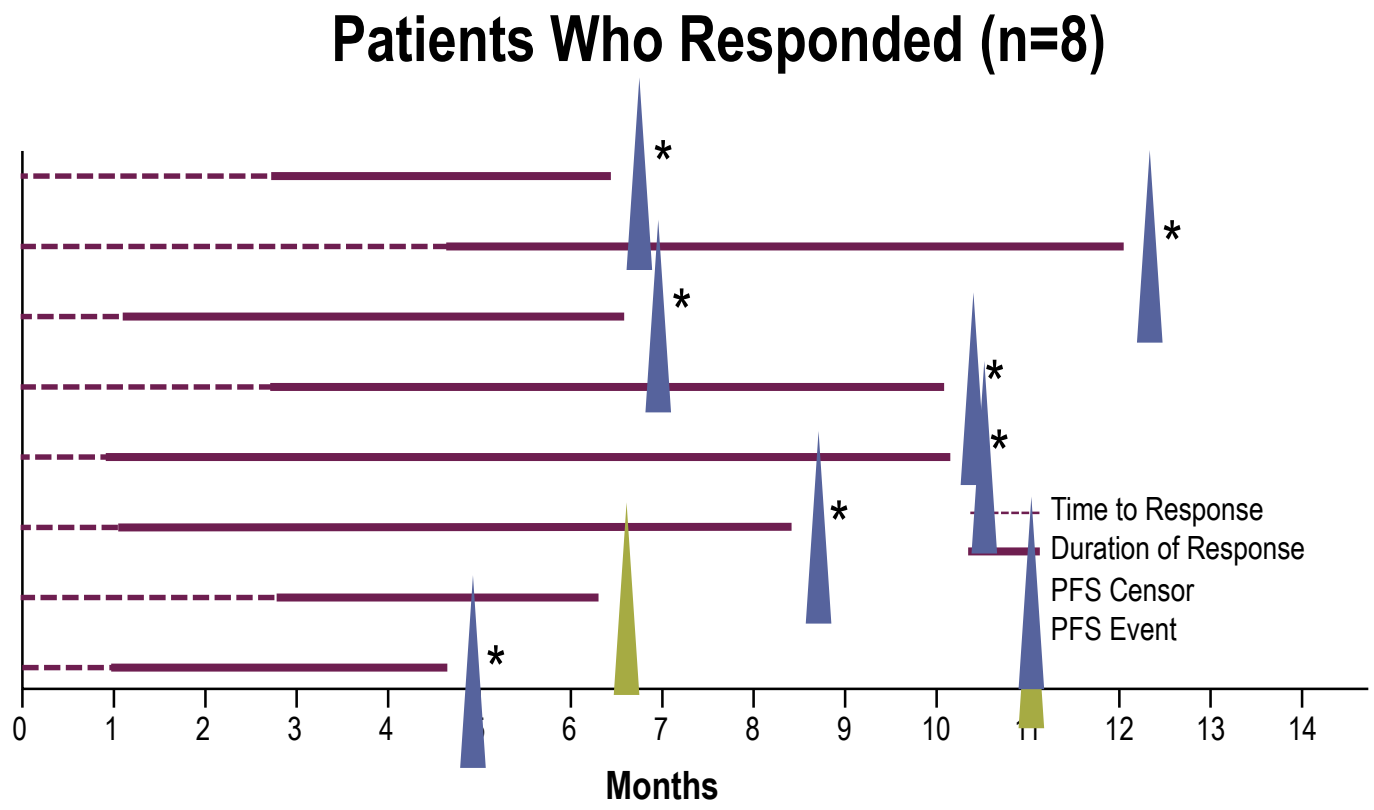
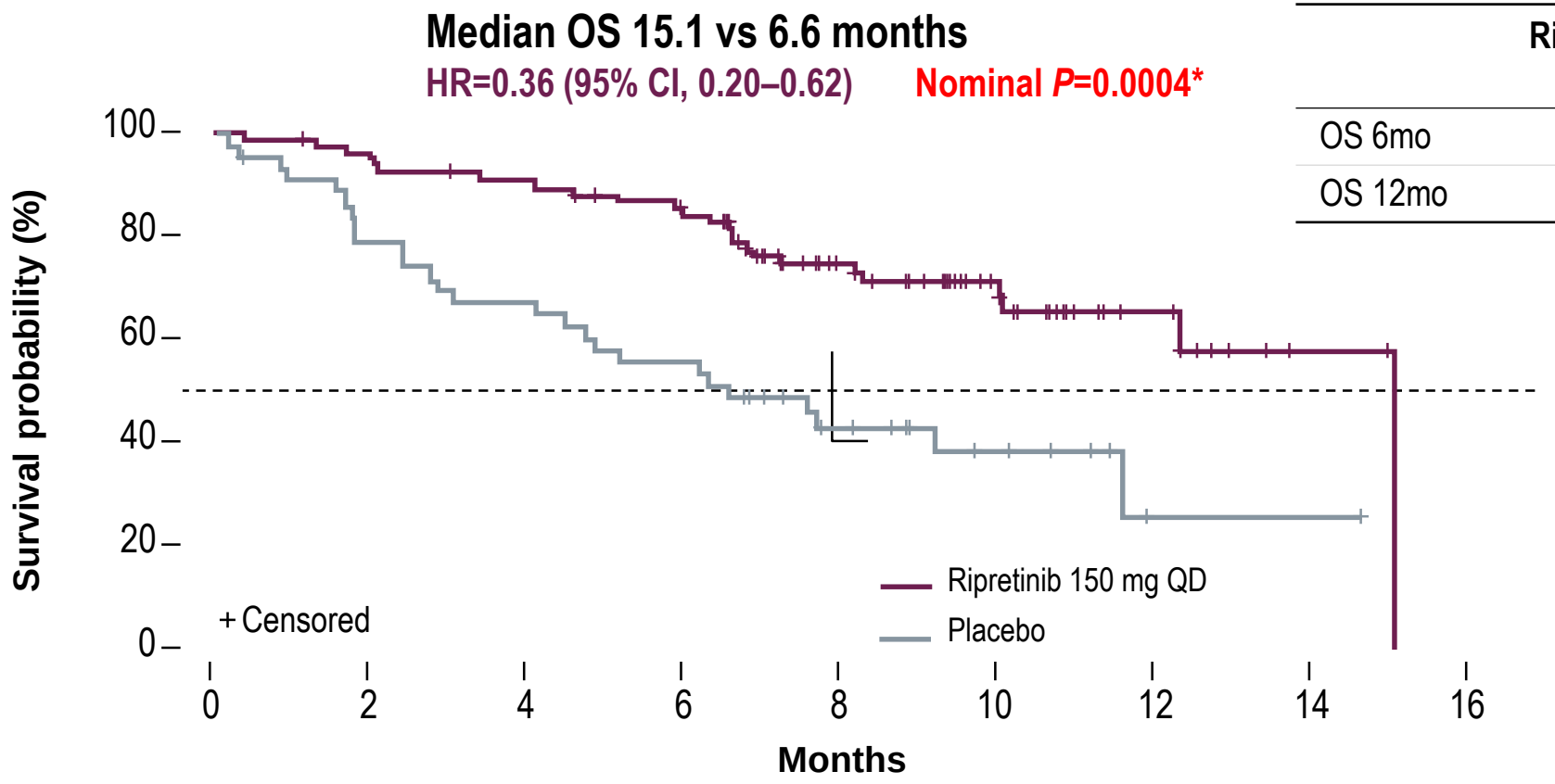


- Median duration of response has not been reached yet
- *7 of 8 ripretinib responders are still responding as of data cutoff
- All responders had partial responses

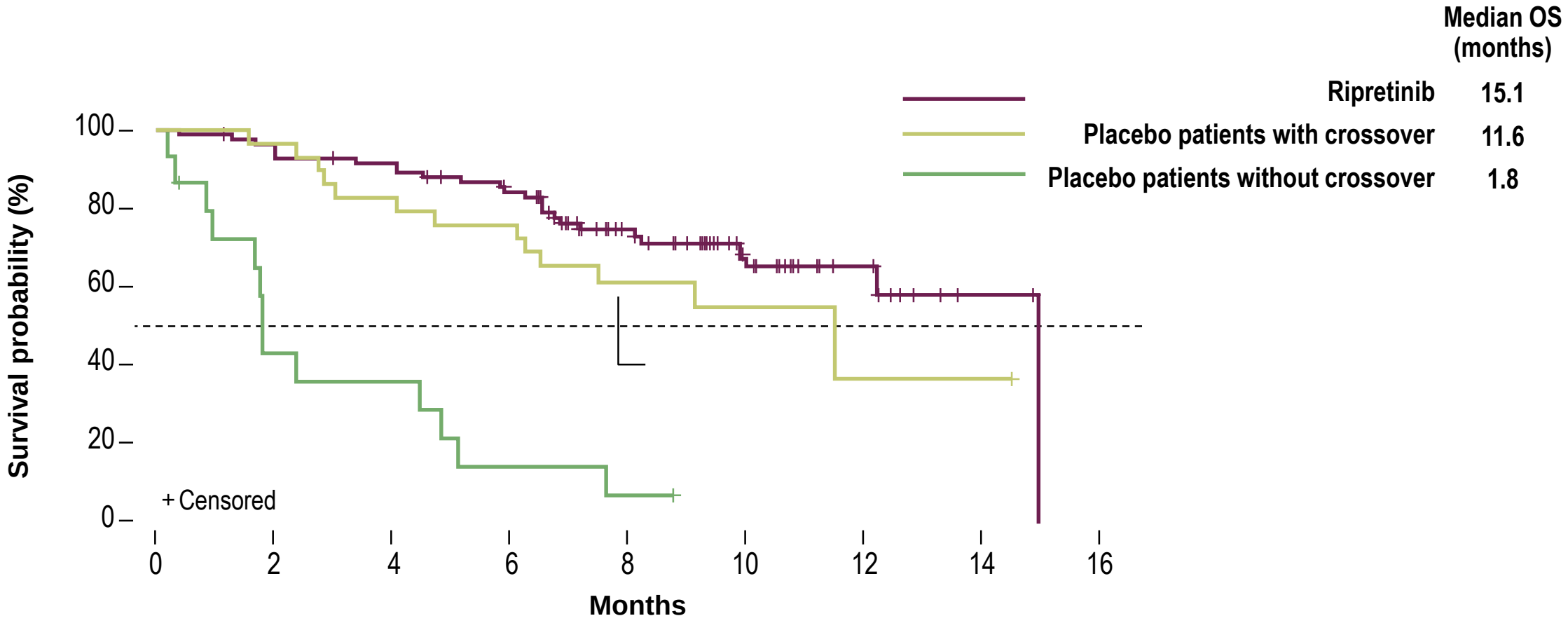
Results on survival



	Ripretinib (n=85)	Placebo (n=44)
OS 6mo	84.3%	55.9%
OS 12mo	65.4%	25.9%

*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 saved those patients that crossed over



What does this mean for future trials?

What are side effects?

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 relatedness

Severe side effects?

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

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

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

Do side effects lead to dose reduction/interruption?

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

Ripretinib – what is next?

- **Approval in 2020 Q3? Europe?**
- **Compassionate use**

- **INTRIGUE trial - SUPPORT the trial : Ripretinib vs Sunitinib**

Challenge: **No crossover**

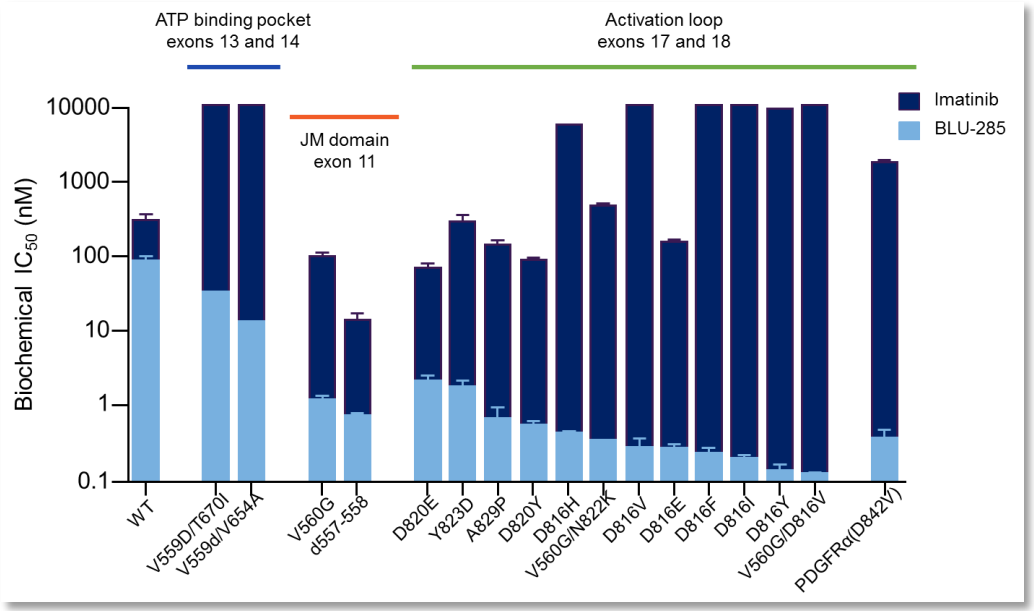
Sunitinib not worth the long travel

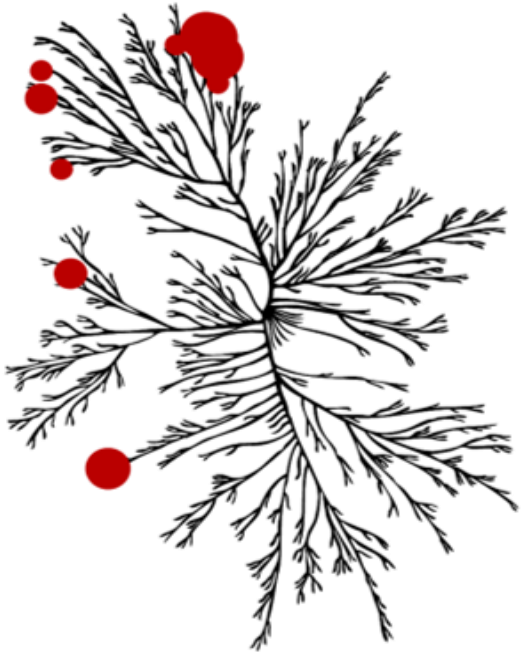
Patients help patients by supporting trials

Drop-out in trials may delay access

Approaching cure? Novel KIT/PDGFRA inhibitors

Avapritinib (BLU-285)





Ongoing clinical trials

Avapritinib kinome selectivity

NAVIGATOR GIST

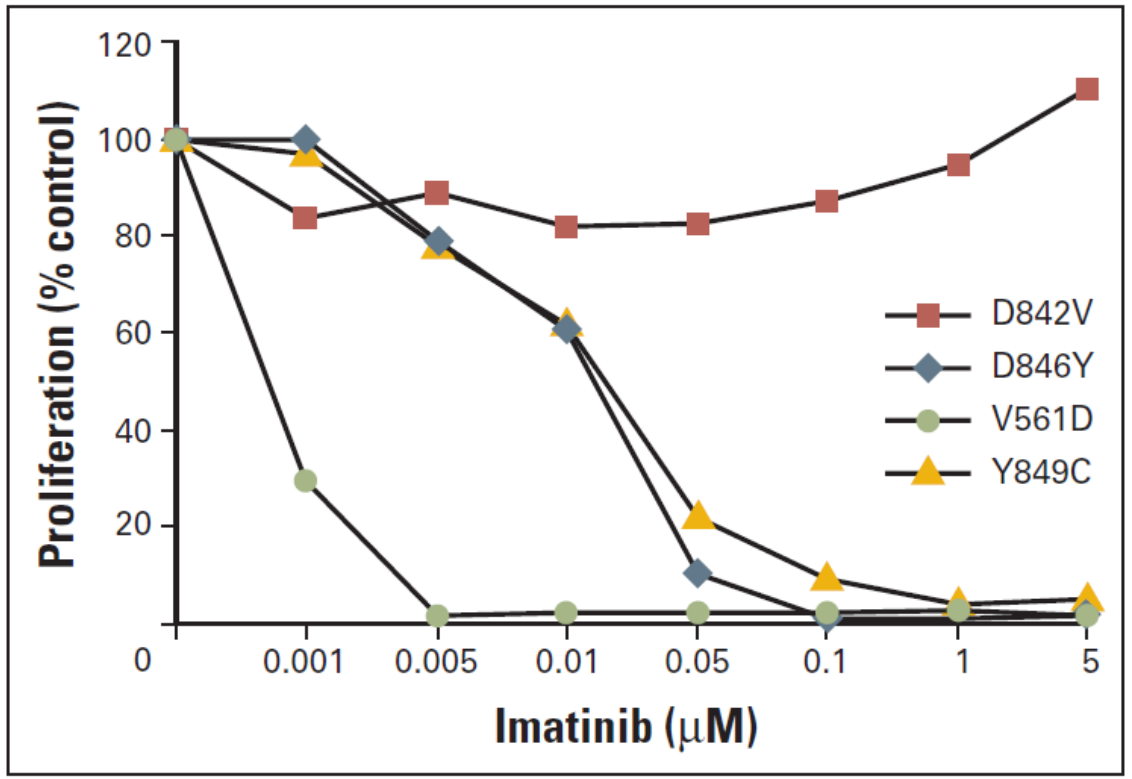
Phase 1 advanced GIST

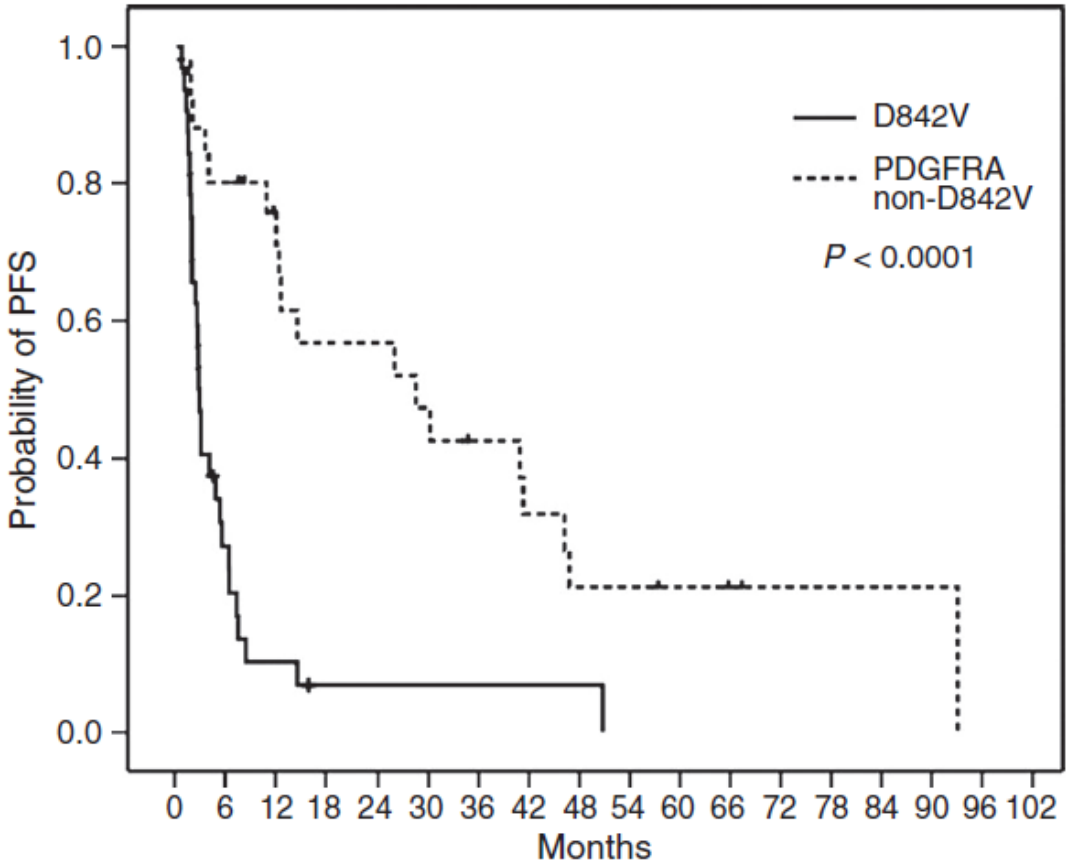
VOYAGER GIST

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

Approaching cure? Novel KIT/PDGFRA inhibitors

PDGFRA D842V – the former untreatable





- Absolute IM-resistance

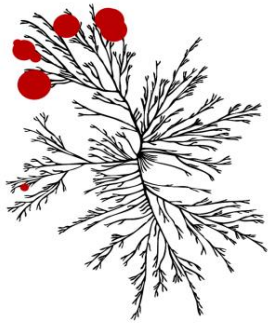
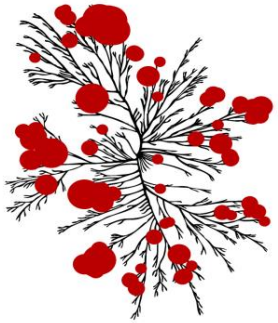
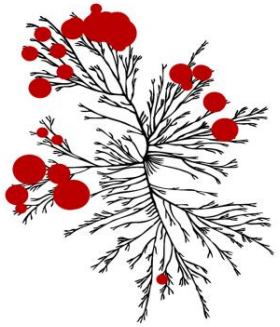
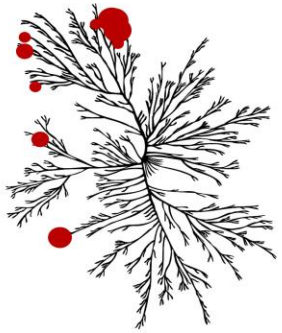
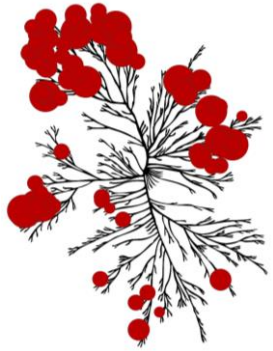
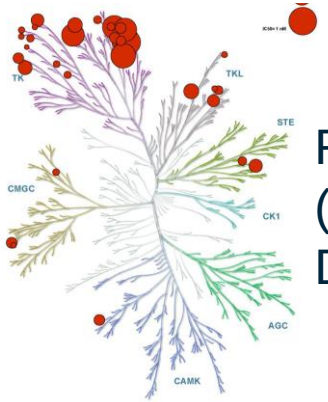
Dismal prognosis

Clinical Response to Avapritinib by RECIST and Choi Criteria in ≥4th Line and PDGFRA Exon 18 Gastrointestinal Stromal Tumors (GIST)

Michael Heinrich, Robin L. Jones, Margaret von Mehren, Sebastian Bauer, Yoon-Koo Kang, Patrick Schöffski, Ferry Eskens, Olivier Mir, Philippe Cassier, Cesar Serrano, William D. Tap, Jonathan Trent, Piotr Rutkowski, Shreyaskumar Patel, Sant P. Chawla, Eyal Meiri, Teresa Zhou, Maria Roche, Suzanne George

Connective Tissue Oncology Society 2019 Annual Meeting
Tokyo, Japan • November 15, 2019

Avapritinib is a selective KIT/PDGFRA inhibitor

	Selective therapies	Multi-targeted kinase therapies	
Approved for GIST	 Imatinib	 Sunitinib	 Regorafenib
Investigational for GIST	 Avapritinib	 Ripretinib (according to Blueprint)	 Ripretinib (according to Deciphera)

Kinome illustrations reproduced courtesy of Cell Signaling Technology, Inc. (CTSI) (www.cellsignal.com). Blueprint Medicines is not responsible for the content of the CTSI site. The trademarks appearing in this presentation are the property of their respective owners. From Erica K. Evans, et al. A precision therapy against cancers driven by *KIT*/*PDGFRA* mutations. *Science Translational Medicine* 2017;9(414):eaao1690. Reprinted with permission from AAAS.

Avapritinib starting dose 300/400 mg QD: ≥4th line (4L+) and PDGFRA exon 18 mutated GIST

Safety population
N=204
Avapritinib 300/400 mg orally once daily

Key eligibility:
- Advanced GIST following at least 2 prior lines of TKI therapy
- Mutation in *KIT* or *PDGFRA*[b]

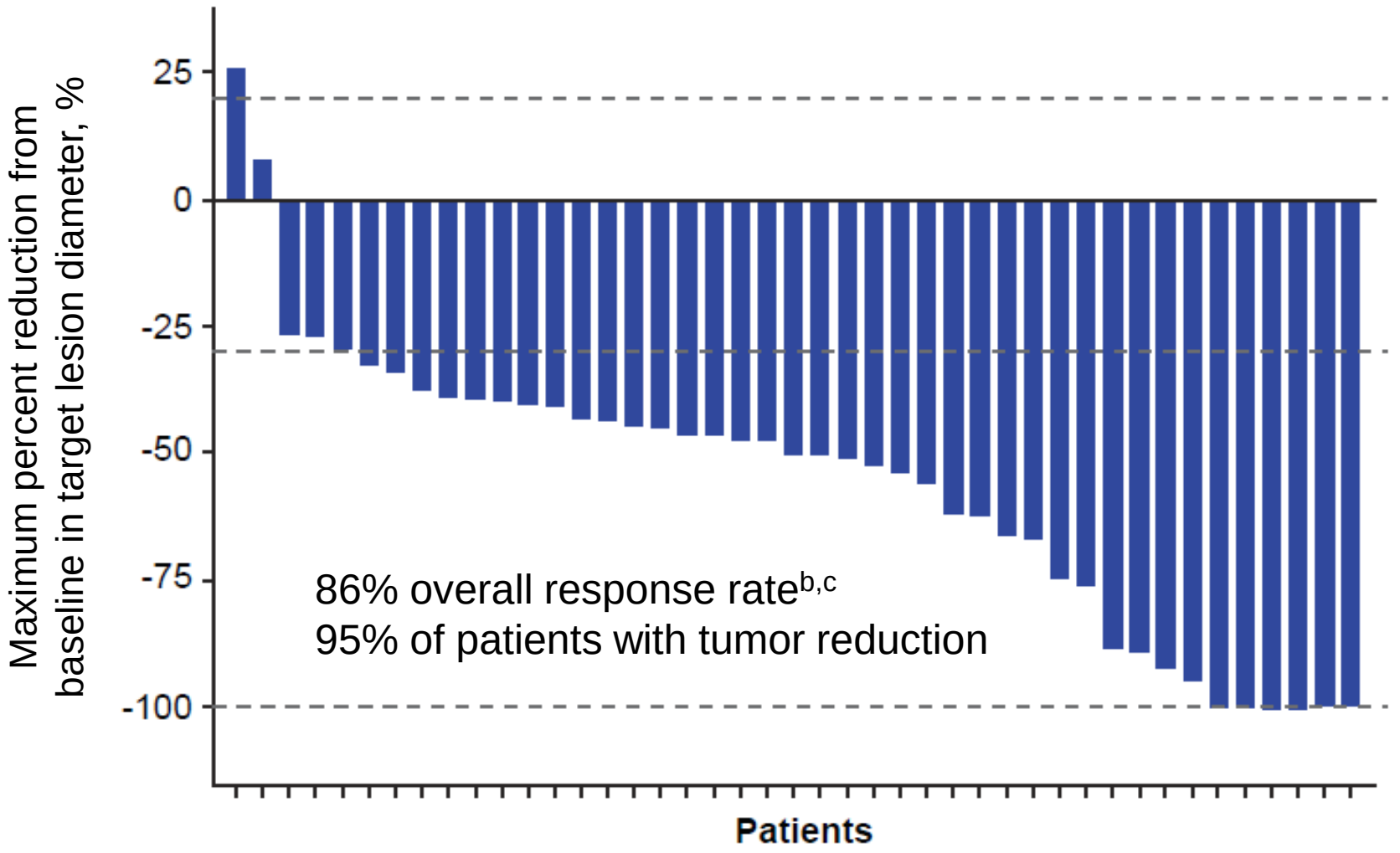
Pivotal analyses
Populations with no approved therapy

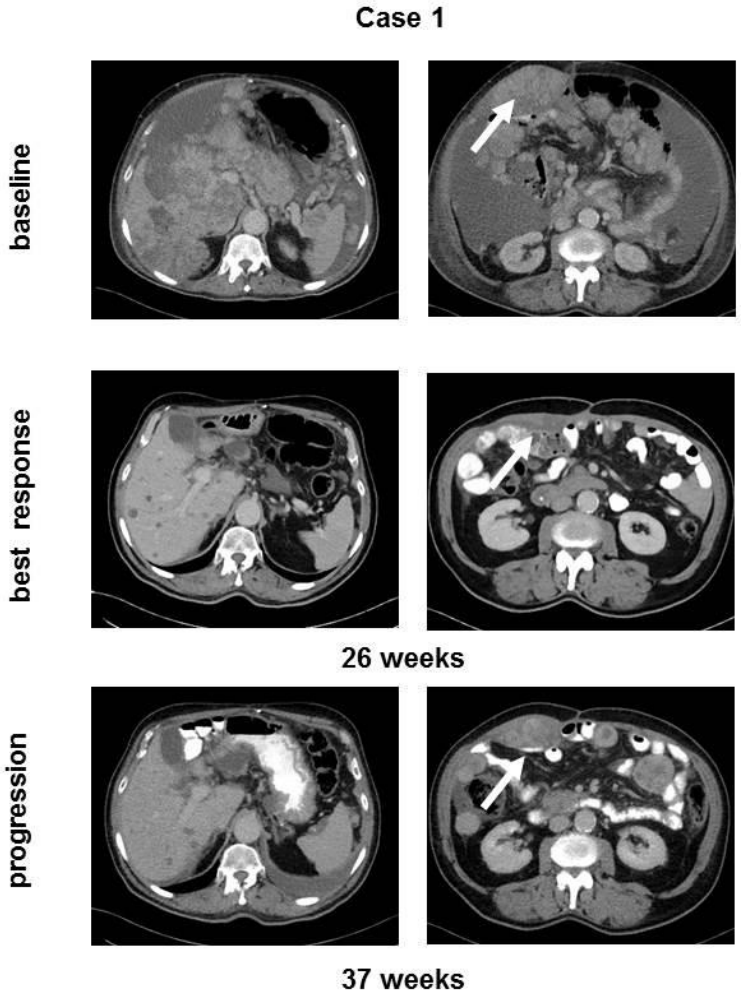
PDGFRA Exon 18 GIST	4L+ GIST[a]
n=43	n=121
Response evaluable n=43	Response evaluable n=111

Avapritinib once daily at the RP2D of 300 mg or MTD of 400 mg

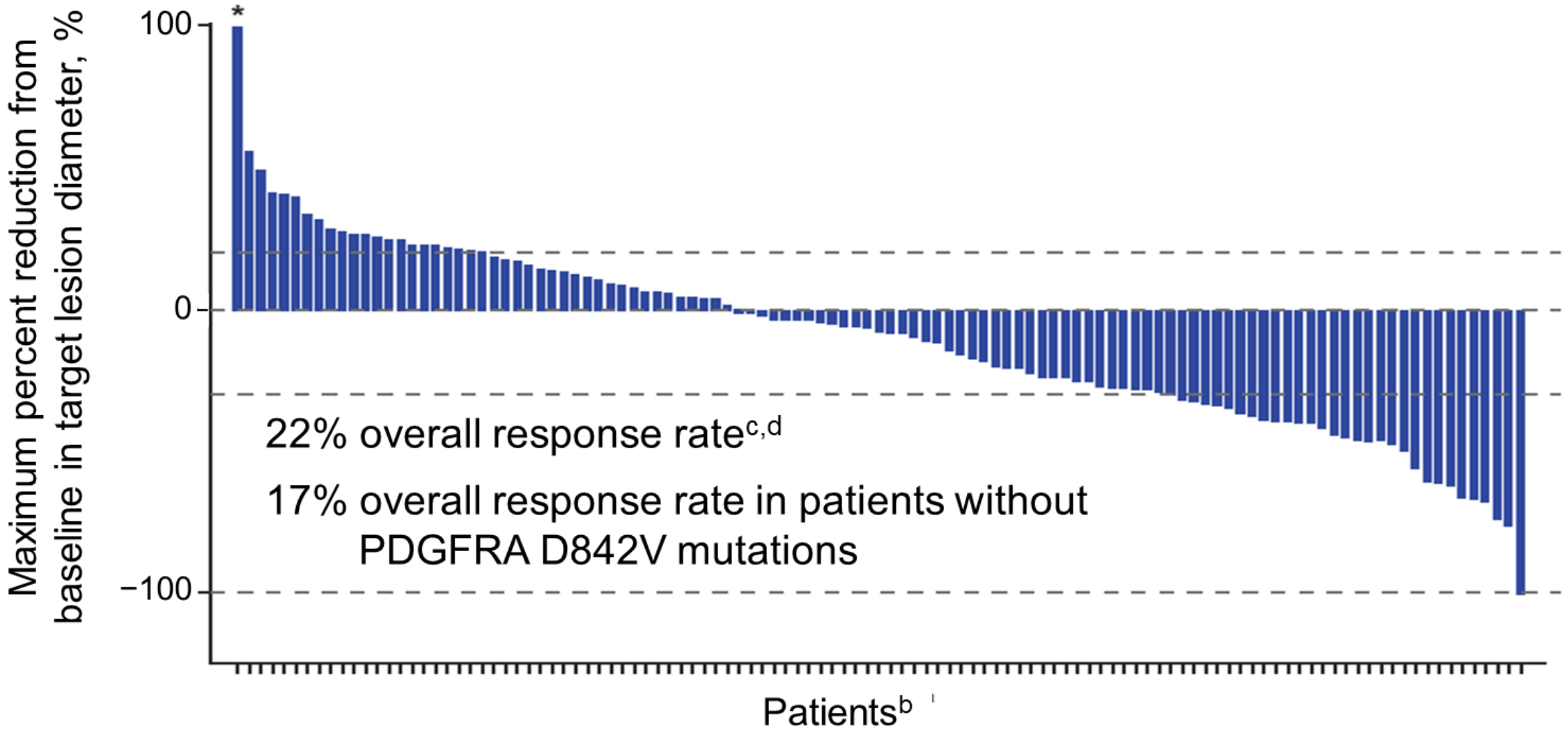
Key objectives: Overall response rate, duration of response, and safety

Avapritinib in PDGFRA exon 18 GIST (300-400mg) – almost everyone benefits..





4L+ treatment – avapritinib starting dose 300/400 mg QD (central radiology)



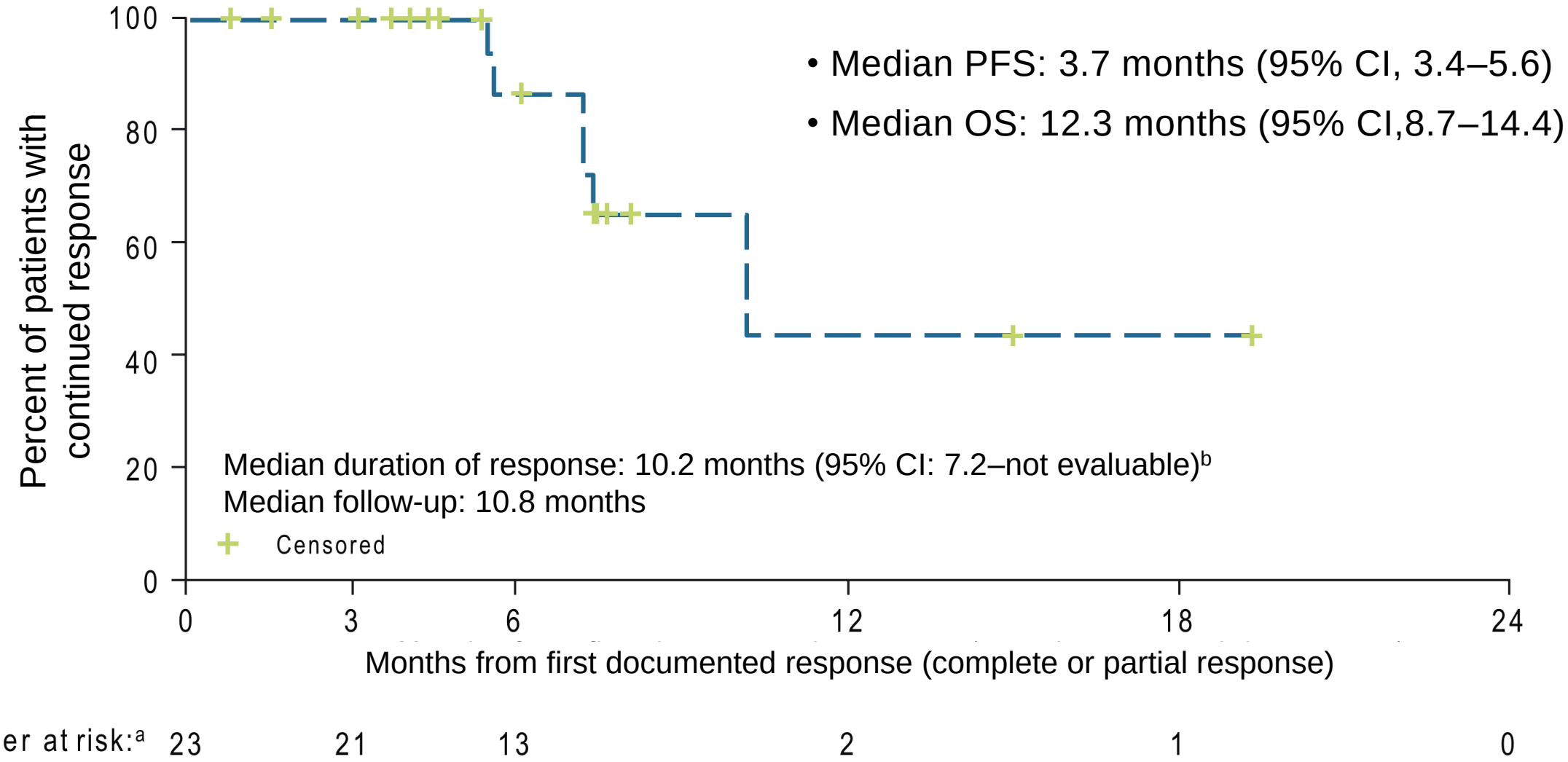
Most common AEs occurring in ≥20% of the safety population
Avapritinib starting dose 300/400 mg QD

n (%)	Safety Population (N=204)			
	All AEs		Treatment-related AEs	
	All Grades[b]	Grade ≥3[c]	All Grades[b]	Grade ≥3[c]
Nausea	131 (64)	5 (3)	121 (59)	-
Fatigue	113 (55)	15 (7)	96 (47)	13 (6)
Anemia	102 (50)	58 (28)	74 (36)	33 (16)
Cognitive effects[a]	84 (41)	8 (4)	84 (41)	8 (4)
Periorbital edema	83 (41)	-	82 (40)	-
Vomiting	78 (38)	4 (2)	65 (32)	-
Decreased appetite	77 (38)	6 (3)	58 (28)	-
Diarrhea	76 (37)	10 (5)	65 (32)	6 (3)
Increased lacrimation	67 (33)	-	62 (30)	-
Peripheral edema	63 (31)	-	55 (27)	-
Face edema	50 (25)	-	49 (24)	-
Constipation	46 (23)	-	-	-
Dizziness	45 (22)	-	-	-
Hair color changes	43 (21)	-	42 (21)	-
Blood bilirubin increased	43 (21)	9 (4)	-	8 (4)
Abdominal pain	41 (20)	11 (5)	-	-

[a]Cognitive effects include pooled terms of:
memory impairment (29%)
cognitive disorder (11%)
confusional state (7%)
encephalopathy (1%).

What is that?

Duration of response
4L+ treatment – avapritinib starting dose 300/400 mg QD



[a]Patients with a confirmed response. [b]Duration of response is unchanged without the inclusion of patients with PDGFRA D842V mutations.
CI, confidence interval; OS, overall survival; PFS, progression-free survival; QD, once daily.

Avapritinib

- Approval for PDGFRA Exon 18 mutant GIST (USA): Ayvakit ®

- What is the randomized activity in KIT-mutant GISTS?
- What are the results of VOYAGER: AVAPRITINIB vs Regorafenib
- How well can we manage unusual toxicity?

Novel KIT/PDGFRA inhibitors

Ongoing Phase II trials

Drug name	Population	Line of treatment	Phase	ClinicalTrials.gov identifier
Avapritinib	KIT/PDGFRA-mutated	3rd/4th regorafenib-naïve	III	NCT03465722
Ripretinib	KIT/PDGFRA-mutated	2nd line	III	NCT03673501
Masitinib	KIT-positive (immunohistochemistry) imatinib-resistant/progressive	⩾2nd line	III	NCT01694277
Crenolanib	PDGFRA D842V-mutated	any	III	NCT02847429
Ponatinib	KIT/PDGFRA-mutated	2nd line (cohort A); after all approved lines (cohort B)	II	NCT03171389
Cabozantinib	KIT/PDGFRA-mutated	3rd line	II	NCT02216578
Regorafenib	KIT/PDGFRA wildtype GIST	1st line	II	NCT02638766
Temozolamide	SDH-mutant/deficient GIST	any	II	NCT03556384
Nivolumab ± ipilimumab	Imatinib-resistant/progressive	⩾2nd line	II	NCT02880020
Epadocast + Pembrolizumab	Imatinib-resistant/progressive	2nd to 5th line	II	NCT03291054

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EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Activity and safety of cabozantinib in patients with gastrointestinal stromal tumor (GIST) after failure of imatinib and sunitinib. Final clinical and early molecular data from EORTC Phase 2 trial 1317 "CaboGIST"

P. Schöffski, O. Mir, B. Kasper, Z. Papai, J.-Y. Blay, A. Italiano, C. Benson, K. Kopeckova, N. Ali, P. Dileo, A. Le Cesne, F. Menge, S. Cousin, C. Charon-Barra, S. Marreaud, S. Litiere, A. Nzokirantevye, I. Vanden Bempt, H. Gelderblom, A. Wozniak

EORTC Soft Tissue and Bone Sarcoma Group (STBSG)

Connective Tissue Oncology Society Annual Meeting (Tokyo), November 15, 2019

Cabozantinib

- Multi-targeted tyrosine kinase inhibitor (TKI) inhibiting KIT, MET, AXL and VEGFR2
- Antitumor activity in multiple solid tumors
- Approved for treatment of advanced renal cell carcinoma, hepatocellular carcinoma and medullary thyroid cancer

Grade 1-4 treatment-related clinical adverse events occurring in >10% of pts

	(n=50)			
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade ≥1 n (%)
All AE	7 (14.0)	7 (14.0)	34 (68.0)	48 (96)
Diarrhea	14 (28)	11 (22)	13 (26)	38 (76)
Palmar-plantar erythrodysesthesia	13 (26)	13 (26)	4 (8)	30 (60)
Fatigue	11 (22)	14 (28)		25 (50)
Hypertension		3 (6)	18 (36)	21 (42)
Weight loss	10 (20)	10 (20)		20 (40)
Mucositis oral	10 (20)	5 (10)		15 (30)
Anorexia	7 (14)	4 (8)	1 (2)	12 (24)
Abdominal pain	6 (12)	5 (10)		11 (22)
Hypothyroidism	6 (12)	3 (6)	1 (2)	10 (20)
Hoarseness	9 (18)			9 (18)
Dysgeusia	8 (16)			8 (16)
Other cutaneous AE	7 (14)	1 (2)		8 (16)
Nausea	2 (4)	4 (8)		6 (12)
Myalgia	3 (6)	3 (6)		6 (12)

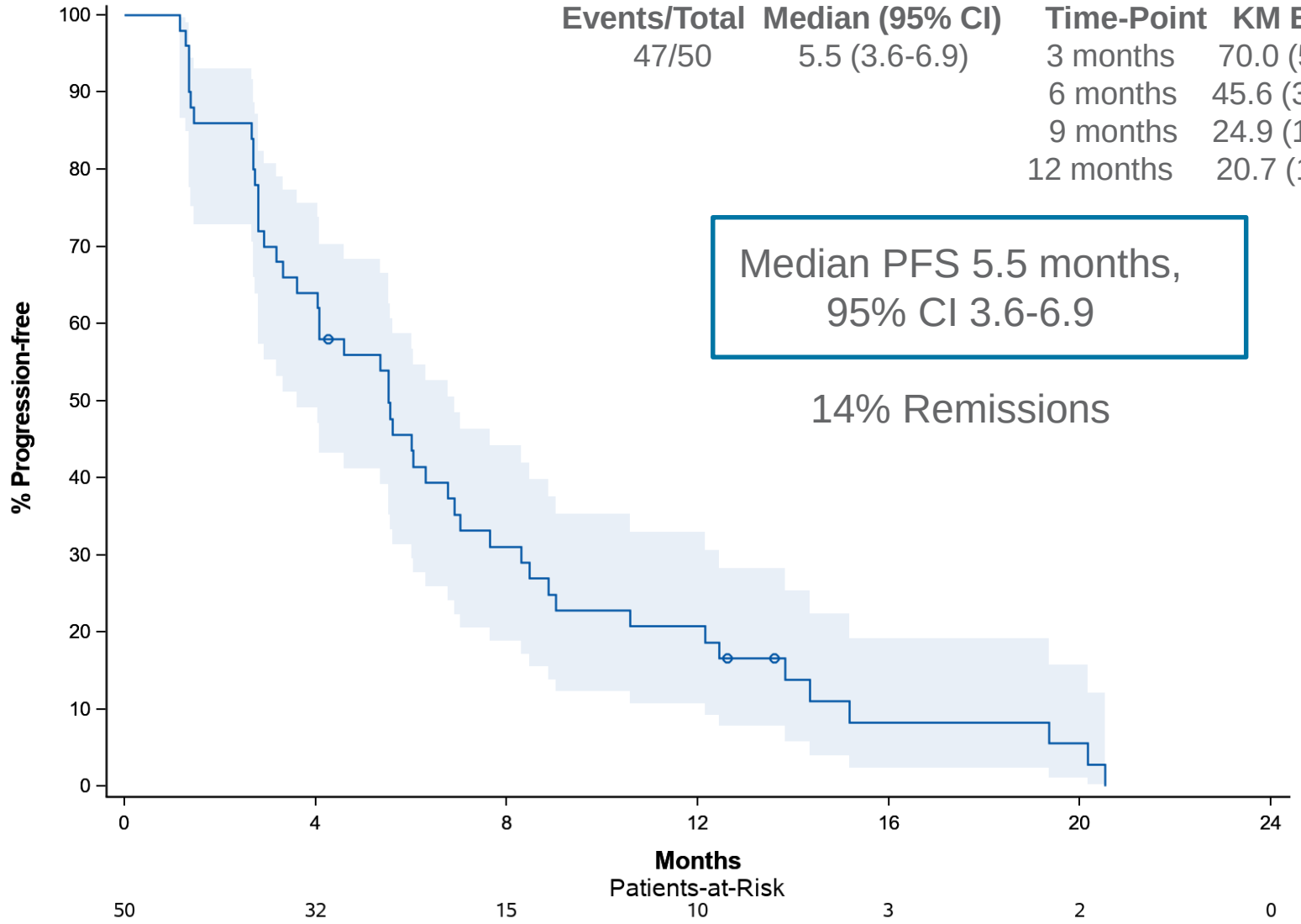
Progression-free survival (PFS) (Kaplan-Meier estimate)

Events/Total	Median (95% CI)
47/50	5.5 (3.6-6.9)

Time-Point	KM Est (95% CI)
3 months	70.0 (55.3-80.7%)
6 months	45.6 (31.4-58.7%)
9 months	24.9 (13.8-37.5%)
12 months	20.7 (10.7-33.0%)

Median PFS 5.5 months,
95% CI 3.6-6.9

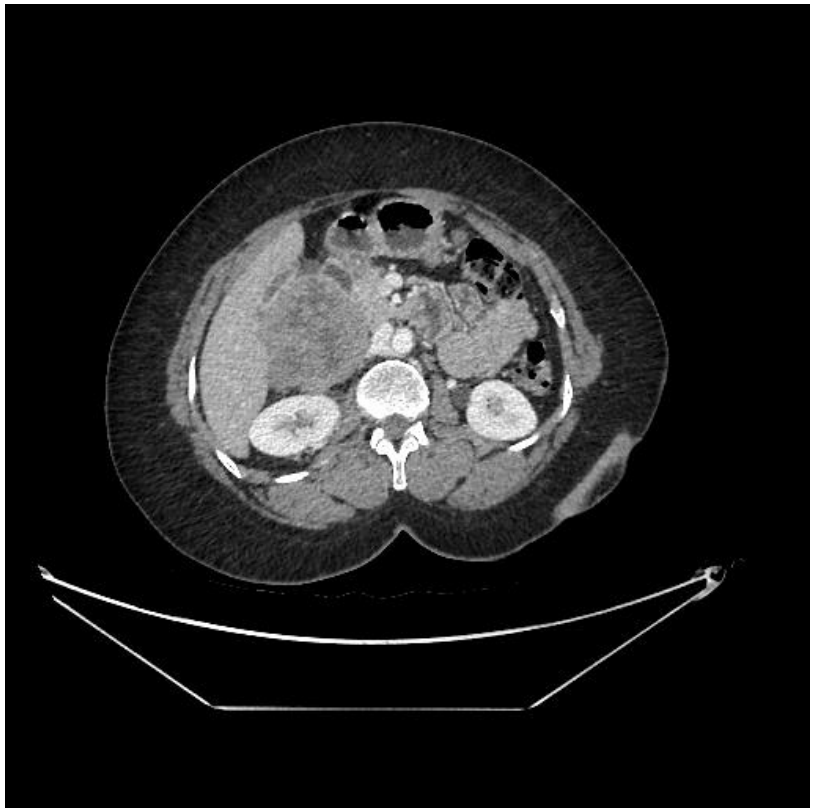
14% Remissions



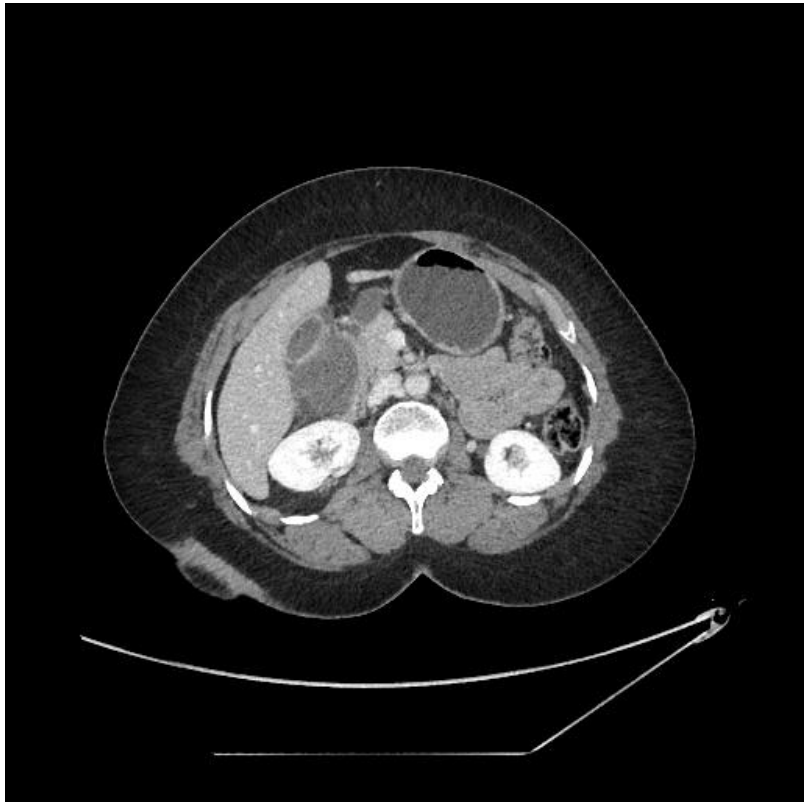
Shadow represents 95%CI

Response to cabozantinib: shrinkage of metastasis and typical density changes

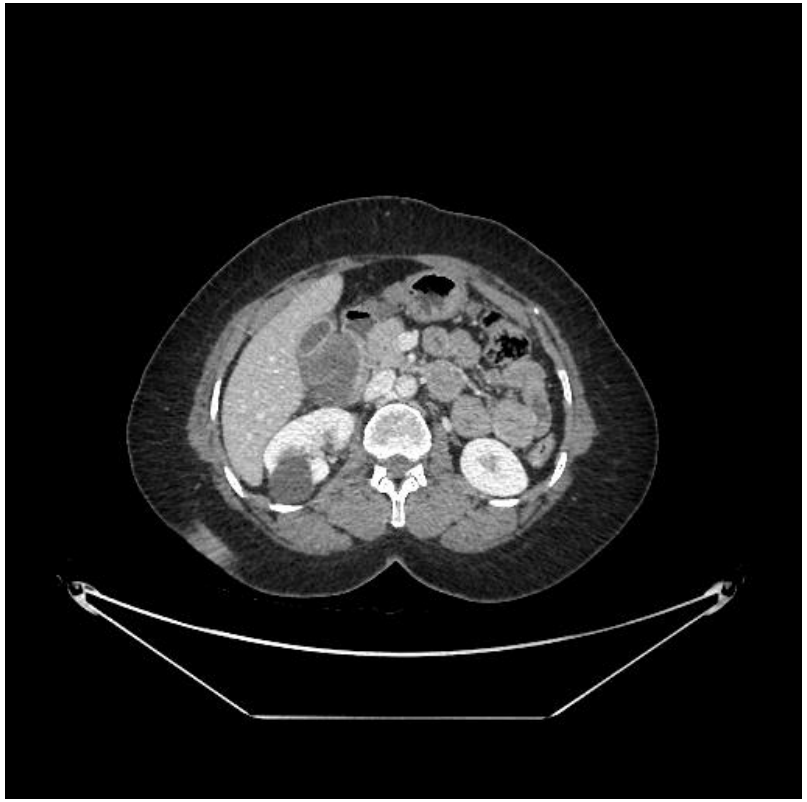
03-2018



04-2018



05-2018



- Patient 30, gastric GIST, peritoneal metastasis, genotype unknown. Cabozantinib 60 mg 03-2018 – 05-2019

Conclusions

- ✓ Cabozantinib has activity in GIST
- ✓ Activity due to KIT and additional inhibitory functions?
- ✓ Will there be a randomized trial?

Approaching cure? Novel KIT/PDGFRA inhibitors

Response rates in imatinib-resistant GIST

Drug name	Line of treatment	ORR	Ref	
Sunitinib	2	7%	Demetri and colleagues[61]	6.2 mo
Regorafenib	3	5%	Demetri and colleagues[64]	4.8 mo
Ripretinib	2	18%	George and colleagues[74]	9.6 mo
Ripretinib	3	24%	George and colleagues[74]	
Ripretinib	⩾4	9%	George and colleagues[74]	6.0 mo
Avapritinib	3/4 regorafenib-naïve	26%	Heinrich and colleagues[75]	8.6 mo
Avapritinib	⩾4	20%	Heinrich and colleagues[75]	3.7 mo
Cabozantinib	3	7%	Schöffski	5.5mo

ORR, overall response rate.

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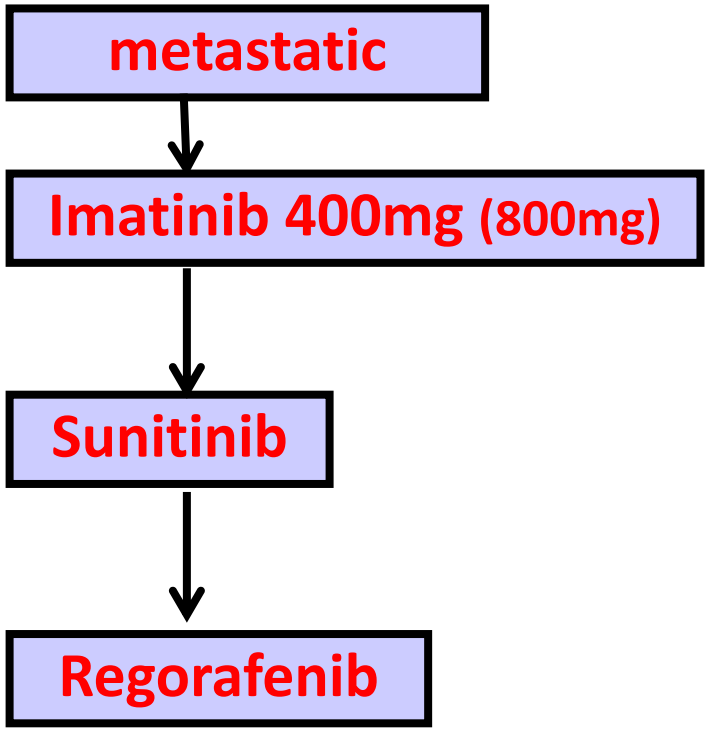
Summary for KIT / PDGFRA-mutant GIST

- Ripretinib (INVICTUS TRIAL) defines a new standard in 4/4+-line (approval pending)
- Avapritinib (NAVIGATOR) defines a new standard in PDGFRA exon 18 mutant GIST
- Cabozantinib with some promising evidence in 3rd-line (randomized comparison coming?)
- Clinical trials: INTRIGUE (2nd-line) is recruiting! Please inform people about the trial!
- CRENOGIST-Trial in D842V-mutant GIST in select centers
- Compassionate use avapritinib active, ripretinib
- WHAT WILL BE NEW COMBINATIONS? WHAT WILL BE THE NEW REASONS FOR RESISTANCE?

Trials: KIT/PDGFRA in 2020



1st line

2nd line

3rd line

4th line

>4th line

localized

PDGFRA D842V: CRENOGIST

SSG XXII:
Imatinib 3 vs 5 years
(HR-Patienten)

Intrigue: Ripretinib vs Placebo (Phase III)

Navigator: Avapritinib (Phase II)

COMPASS?

CABO GIST TRIAL (Phase II)

Voyager-Studie: Avapritinib vs Regorafenib (Phase III)

Invictus-Studie: Ripretinib vs Placebo (Phase III)

Avapritinib Compassionate Use Programm

Ripretinib Compassionate Use Programm