GISTs

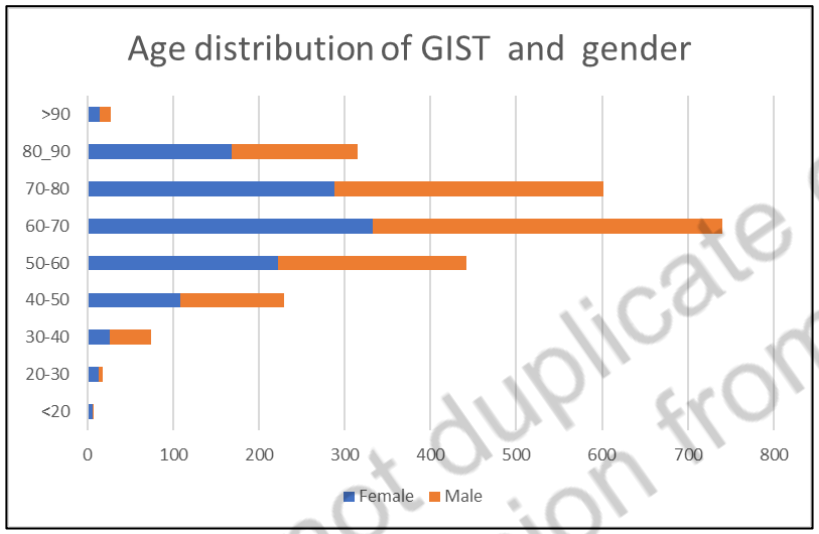
Jean-Yves Blay

Disclosures

(presenter orange, institution grey)

Company	Scientific advice	Research support	Symposia & oral communications
Abbvie	X	X	
Amgen	X	X	X
ARIAD	X	X	
AstraZeneca		X	X
Bayer	X	X	X
BMS	X	X	X
DDB	X	X	
EISAI	X	X	X
Genomic Health		X	X
Gilead		X	X
GSK		X	X
Innate-Pharma	X	X	
Jansen		X	X
LILLY		X	X
Merck Serono		X	X
MSD		X	X
Nanobiotix	X	X	
Novartis	X	X	X
Novex		X	X
Onxeo	X		
Pfizer		X	X
Pharmamar	X	X	
PRA		X	
Roche	X	X	X
Sanofi Aventis		X	X
Swedish Orphan		X	X
Takeda		X	
Toray	X	X	

Epidemiological characteristics GIST in the the nationwide NETSARC cohort



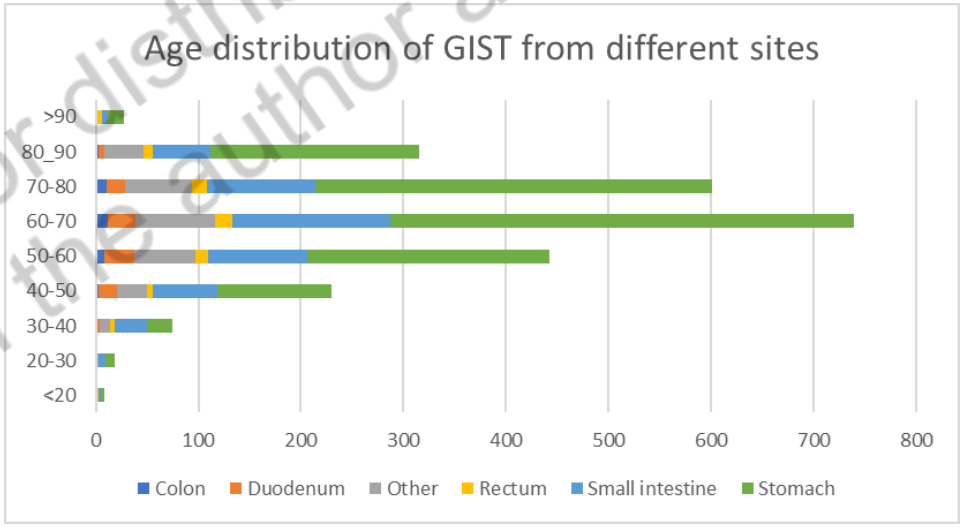
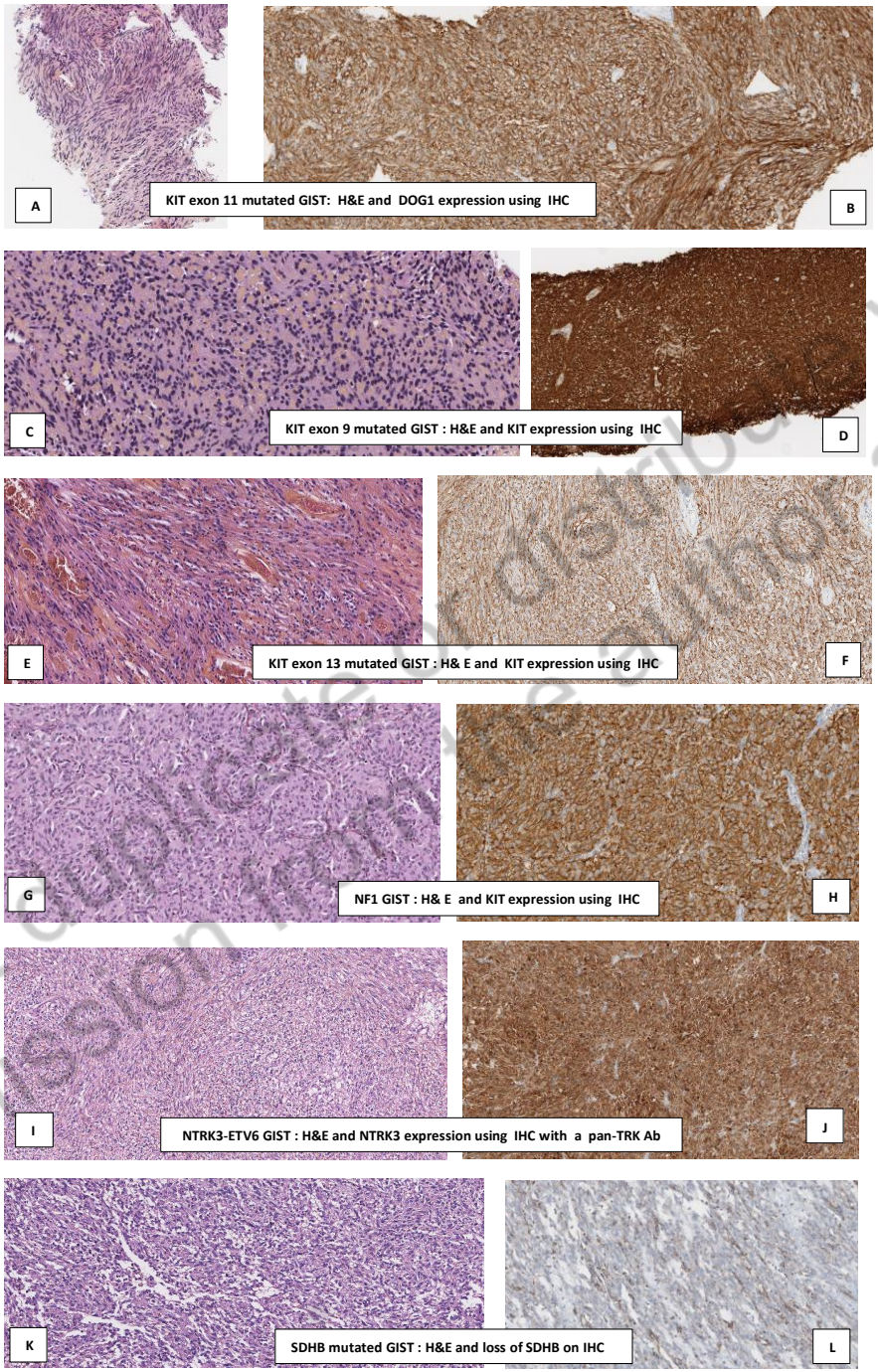
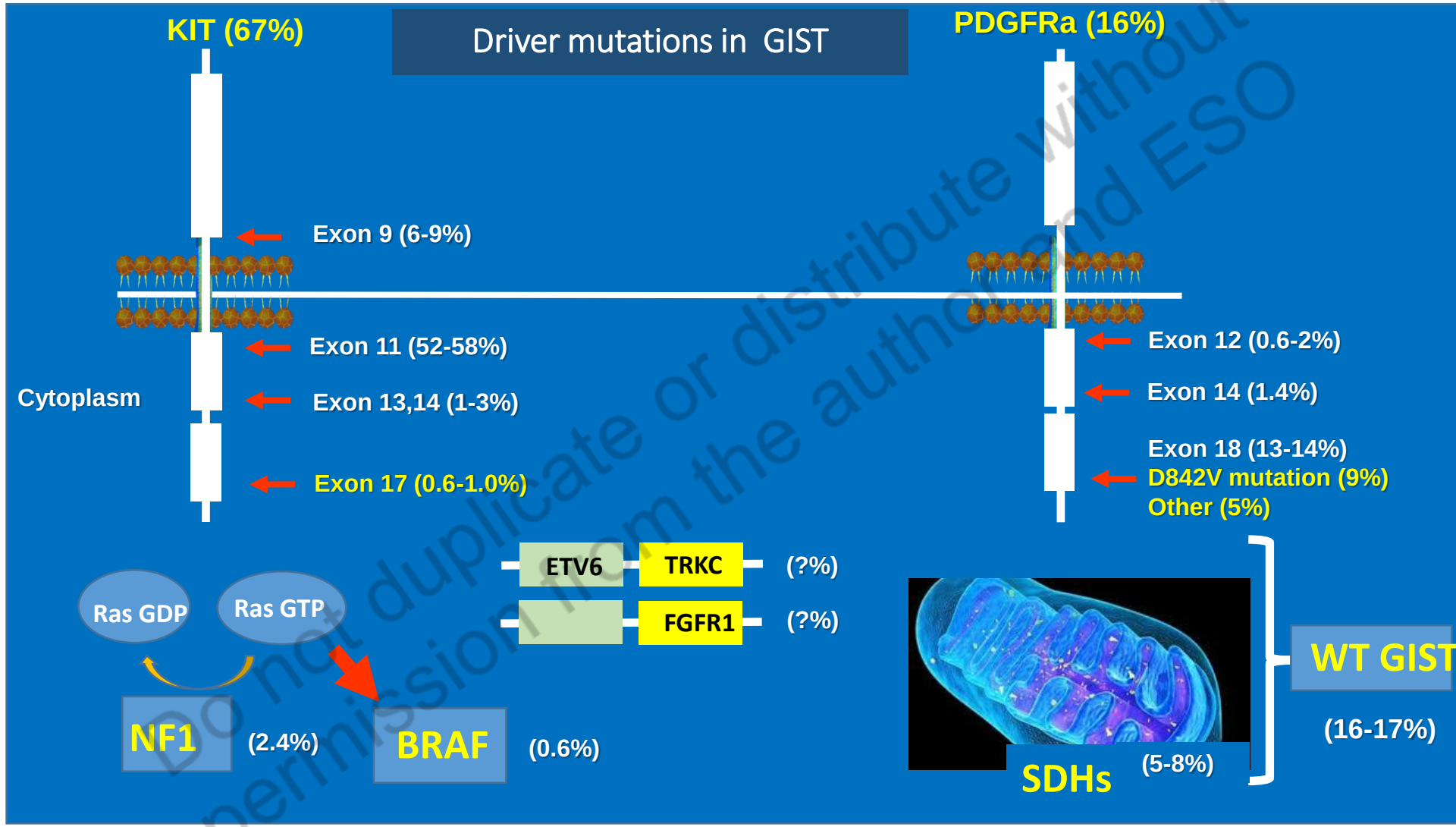


Figure 6 : Histology of different molecular subsets of GISTs



Driver mutations in GIST

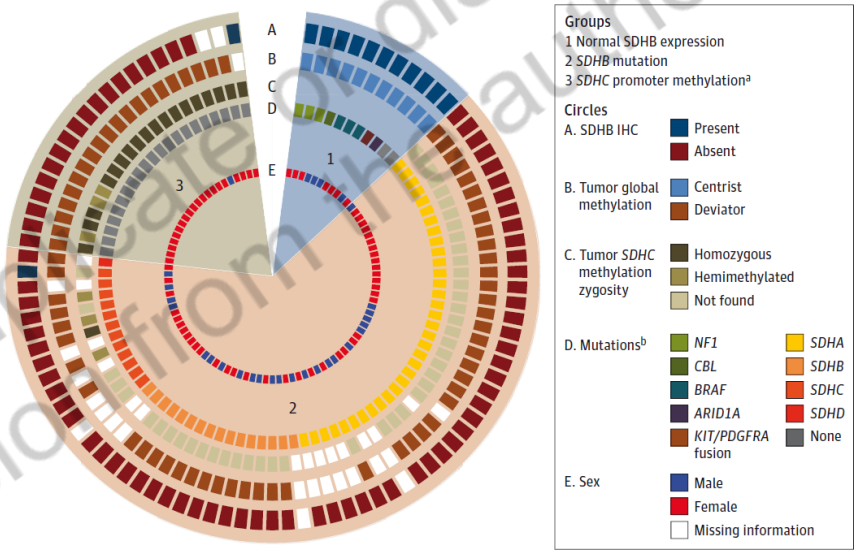


Molecular Subtypes of *KIT/PDGFRA* Wild-Type Gastrointestinal Stromal Tumors

A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic

Sosipatros A. Boikos, MD; Alberto S. Pappo, MD; J. Keith Killian, MD, PhD; Michael P. LaQuaglia, MD; Chris B. Weldon, MD; Suzanne George, MD; Jonathan C. Trent, MD, PhD; Margaret von Mehren, MD; Jennifer A. Wright, MD; Josh D. Schiffman, MD; Margarita Raygada, PhD; Karel Pacak, MD, PhD; Paul S. Meltzer, MD, PhD; Markku M. Miettinen, MD; Constantine Stratakis, MD, DSci; Katherine A. Janeway, MD; Lee J. Helman, MD

Figure. Immunohistochemical Analysis (IHC) and Genetic Characteristics of Tumors From 95 Patients With *KIT/PDGFRA* Wild-Type Gastrointestinal Stromal Tumors



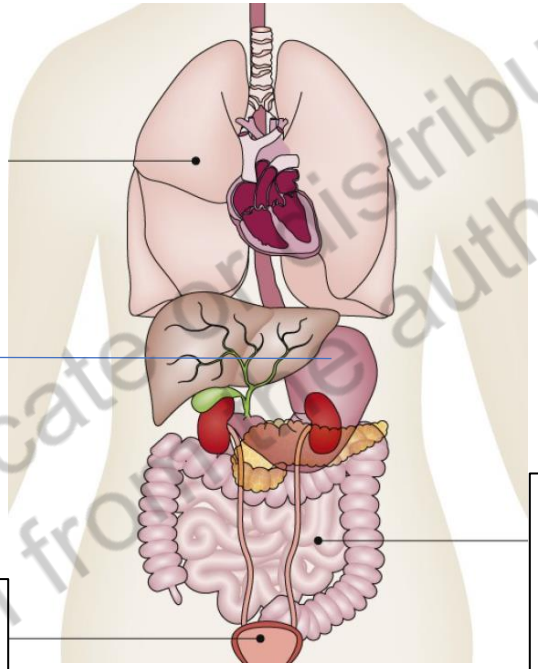
JAMA Oncol. 2016;2(7):922-928.

Molecular subtype	Percent of all GIST	
	Netherlands[1] (N=166)	France[2] (N=106)
KIT mutations	**67.50%**	**66.90%**
KIT exon 11 mutation	58.40%	52.80%
Codons 557-558 deletions	NR	31.20%
Other exon 11 mutations	NR	20.70%
KIT exon 9 mutation (AY duplication)	6.60%	9%
KIT with point mutations exon 13	1.20%	3.60%
KIT with point mutations exon 17	0.60%	1%
PDGFRA mutations	**16.20%**	**16%**
Exon 18	**13.50%**	**14.00%**
PDGFRA D842V mutation	NR	9%
PDGFRA exon 18 non D842V	NR	5%
Exon 12	0.60%	2%
Exon14	1.80%	NR
Wild type GIST	**16.30%**	**16.90%**
SDH deficient GIST	NR	NR
Mutation of SDHA,B,C orD genes	1.80%	NR
Epigenetic silencing of DH genes	NR	NR
NF1 mutation	2.40%	NR
BRAF mutation	0.60%	NR
ETV6- NTRK3	NR	NR

[1] 2 year period (2011-2012) in a population of 16.7 millions inhabitants (166 of 489 [33.4%] GIST had mutational testing ; total incidence of GIST **14.6/10^6/year**)

[2] 2 year period (2005-2006) in a population of 6.06 millions inhabitants (106 of 131 [74%]GIST had mutational testing ; total incidence of GIST **10.8/106/year**)

Distribution of mutations in the gastric, small bowel, and rectal GIST



Gastric GIST (60-65%)
- KIT exon 11 mutation : 54-60%
- KIT exon 9 mutation: <5%
- PDGFRA exon18: 15-18%
- Other mutations : 10-12%

Small bowel GIST (20-35%)
- KIT exon 11 mutation : 43-50%
- KIT exon 9 mutation : 20-25%
- PDGFRA mutation: 5-7%
- Other mutations : 8-10%

Rectal GIST (3-5%)
- KIT exon 11 mutation : 70-80%
- KIT exon 9 mutation :10-15%
- Other mutations : 5-10%

Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†

P. G. Casali[1], N. Abecassis[2], S. Bauer[3], R. Biagini[4], S. Bielack[5], S. Bonvalot[6], I. Boukovinas[7], J. V. M. G. Bovee[8], T. Brodowicz[9], J. M. Broto[10], A. Buonadonna[11], E. De Álava[10], A. P. Dei Tos[12], X. G. Del Muro[13], P. Dileo[14], M. Eriksson[15], A. Fedenko[16], V. Ferraresi[17], A. Ferrari[18], S. Ferrari[19], A. M. Frezza[1], S. Gasperoni[20], H. Gelderblom[21], T. Gil[22], G. Grignani[23], A. Gronchi[1], A. Hannu[24], B. Hassan[25], P. Hohenberger[26], R. Issels[27], H. Joensuu[28], R. L. Jones[29], I. Judson[30], P. Jutte[31], S. Kaal[32], B. Kasper[26], K. Kopeckova[33], D. A. Krákorová[34], A. Le Cesne[35], I. Lugowska[36], O. Merimsky[37], M. Montemurro[38], M. A. Pantaleo[39], R. Piana[40], P. Picci[19], S. Piperno-Neumann[6], A. L. Pousa[41], P. Reichardt[42], M. H. Robinson[43], P. Rutkovski[36], A. A. Safwat[44], P. Schöffski[45], S. Sleijfer[46], S. Stacchiotti[47], K. Sundby Hall[48], M. Unk[49], F. Van Coevorden[50], W. Van der Graaf[29], J. Whelan[51], E. Wardelmann[52], O. Zaikova[53] & J. Y. Blay[54], on behalf of the ESMO Guidelines Committee and EURACAN*

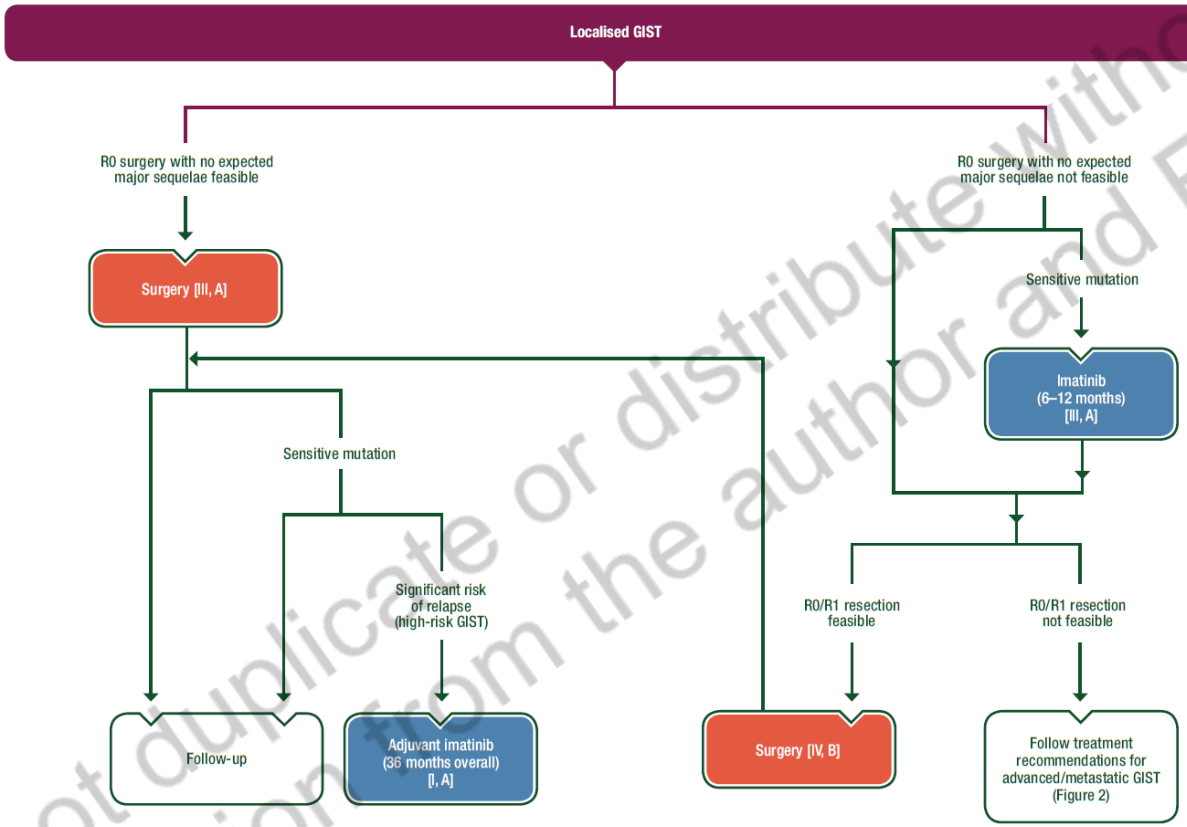


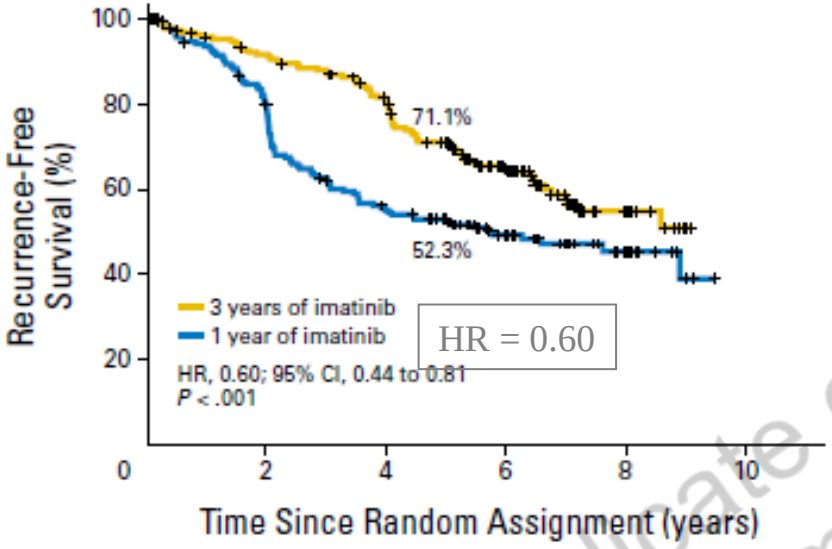
Figure 1. Management of local/locoregional GIST.
GIST, gastrointestinal stromal tumour; R0, no residual tumour; R1, microscopic residual tumour.

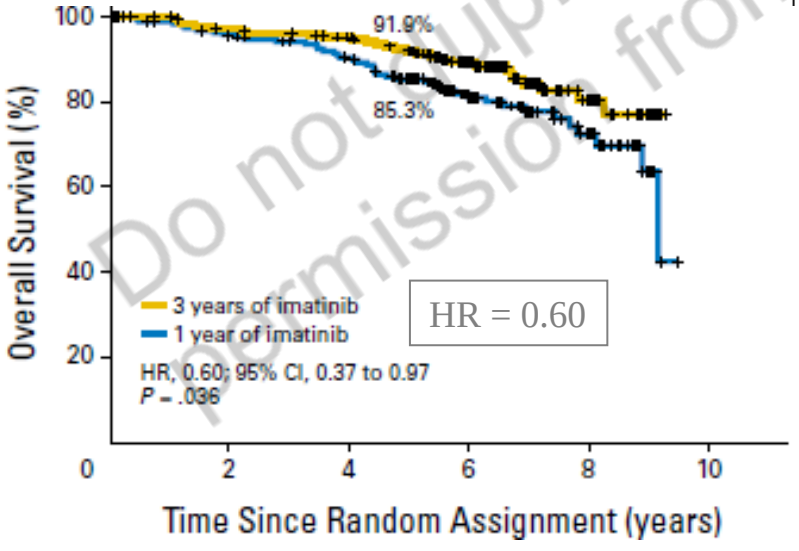
doi:10.1093/annonc/mdy095 | iv71

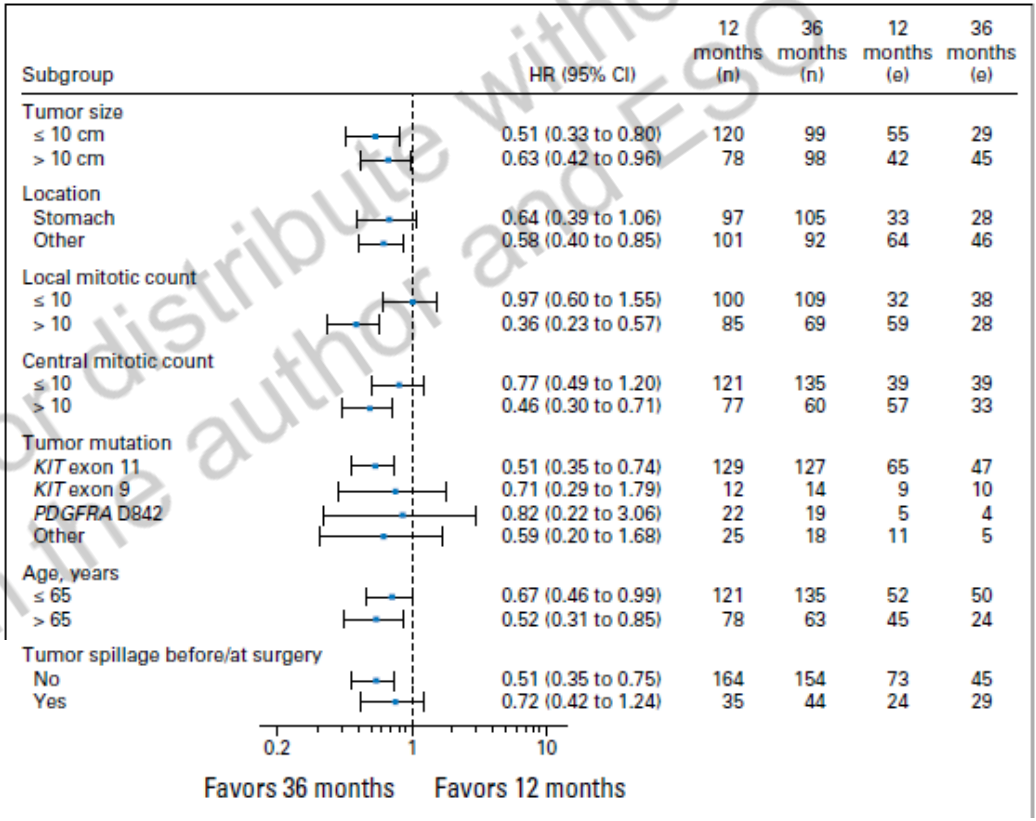
SSG-AIO: 1 vs 3 years adjuvant imatinib

Follow-up 7,5 years

Joensuu et al, *JCO*, 2016





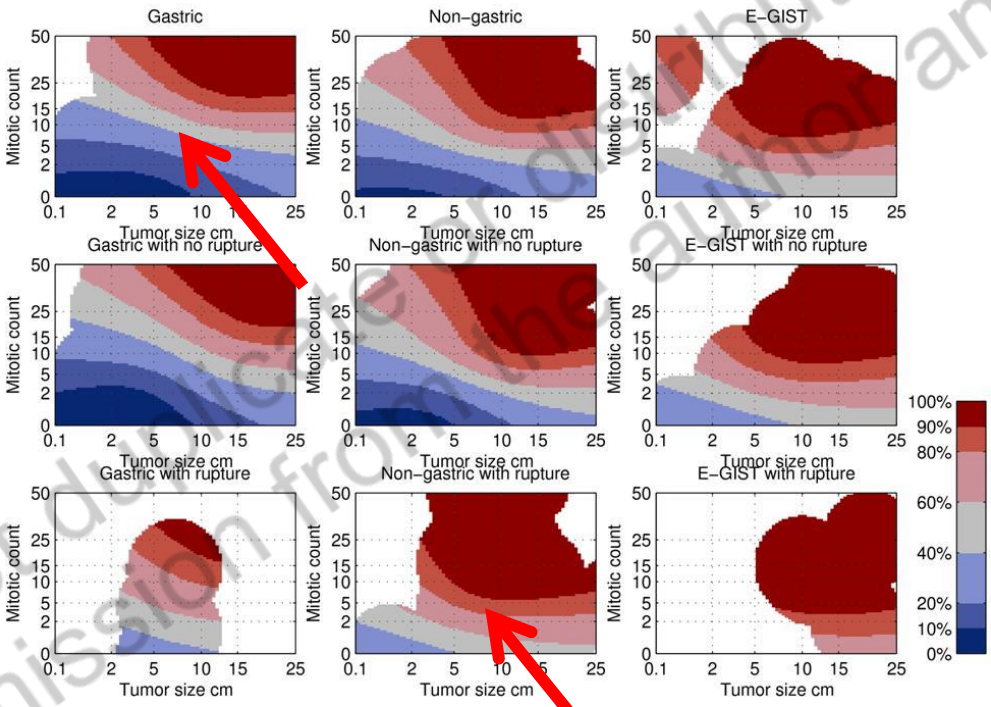


3 years of imatinib remains the standard of care

Risk stratification
(2006 AFIP criteria)

Tumor Parameters		% Patients with Disease Recurrence or Metastases			
Size	Mitotic Count	Stomach	Duodenum	Jejunum / Ileum	Rectum
≤ 2 cm	≤ 5 per 50 HPFs	0	0	0	0
> 2, ≤ 5 cm		1.9	8.3	4.3	8.5
> 5, ≤ 10 cm		3.6	} 34	24	} 57
> 10 cm		12		52	
≤ 2 cm	> 5 per 50 HPF	*	*	*	54
> 2, ≤ 5 cm		16	50	73	52
> 5, ≤ 10 cm		55	} 86	85	} 71
> 10 cm		86		90	

Risk of recurrence of GIST after surgery: An analysis of pooled population-based cohorts



Joensuu *et al. Lancet Oncol*. 2012; 13:265-74.

Ongoing trials: ImadGIST & SSG XXII

An open-label phase III study in high risk patient in CR after 3 years of adjuvant imatinib

Stratification:

1) Tumour rupture

2) Risk <80%

Gastrointestinal stromal tumours: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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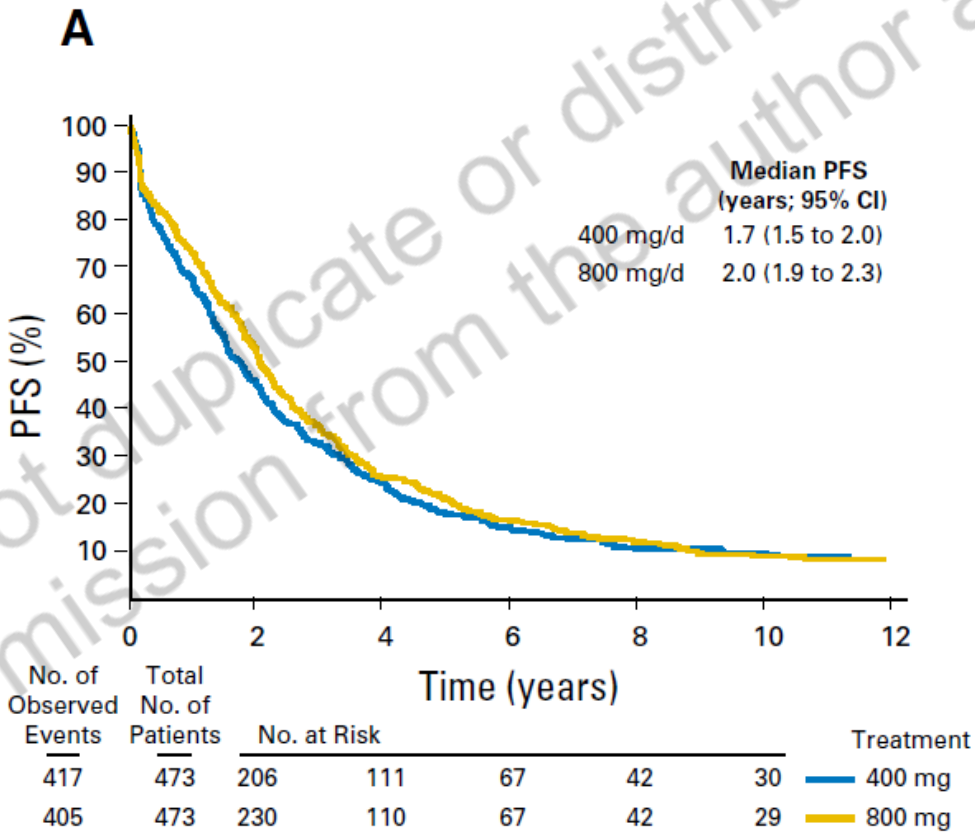
Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels

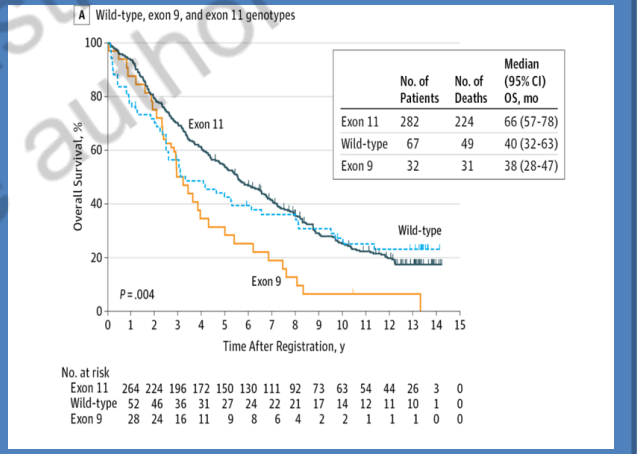
Paolo G. Casali, John Zalcberg, Axel Le Cesne, Peter Reichardt, Jean-Yves Blay, Lars H. Lindner, Ian R. Judson, Patrick Schöffski, Serge Leyvraz, Antoine Italiano, Viktor Grünwald, Antonio Lopez Pousa, Dusan Kotasek, Stefan Sleijfer, Jan M. Kerst, Piotr Rutkowski, Elena Fumagalli, Pancras Hogendoorn, Saskia Litière, Sandrine Marreaud, Winette van der Graaf, Alessandro Gronchi, and Jaap Verweij on behalf of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group



>10 molecular subtypes of GISTs

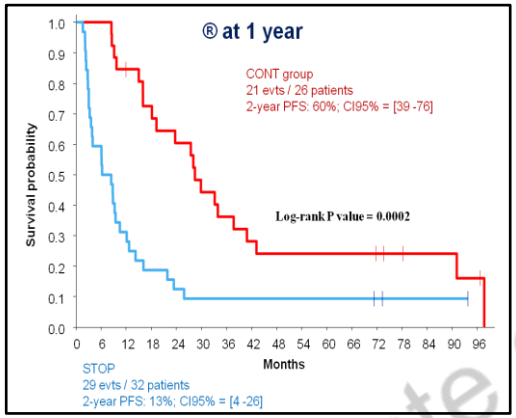
GIST

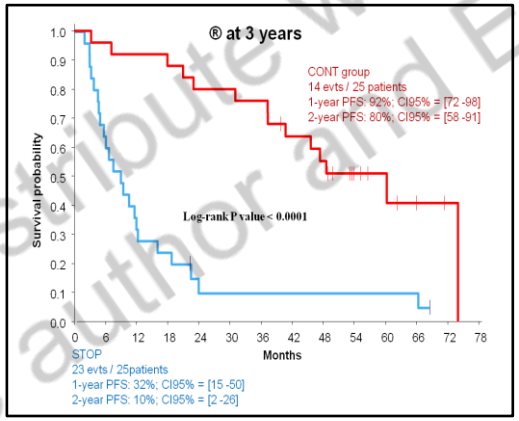
- *KIT* mutation (80%)
- *PDGFRA* mutation (10% in met, 25% in gastric primary)
- *SDH* mutation or deficiency (either *SDHA, SDHB, or SDHC*) (approx. 10%)
- *BRAF* or *NF1* mutations; *TRK* fusions (<2%)

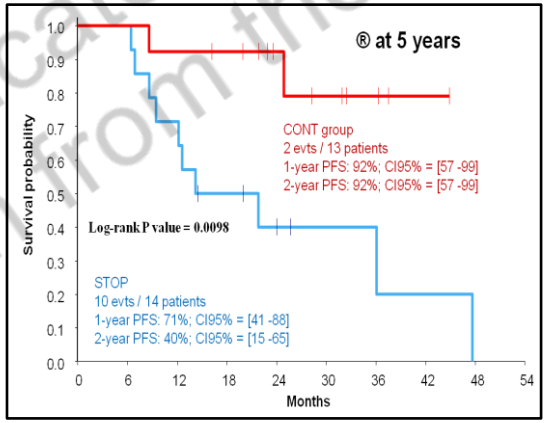


Corless CL, et al. *Nat Rev Cancer*. 2011;11(12):865-878.

Imatinib interruption in advanced GIST - PFS



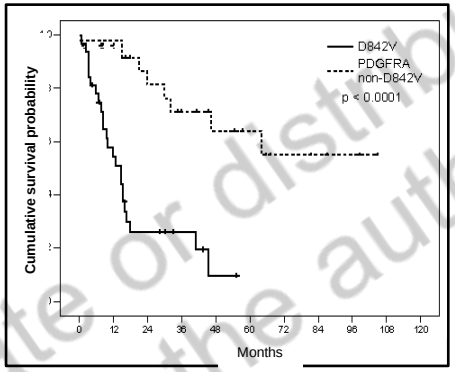


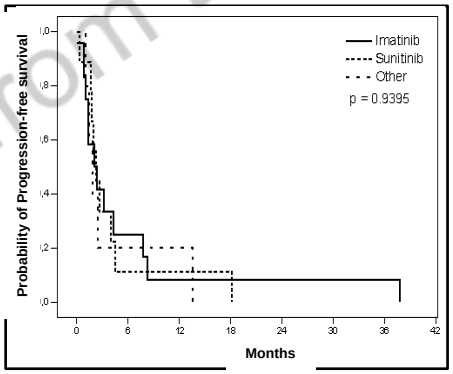


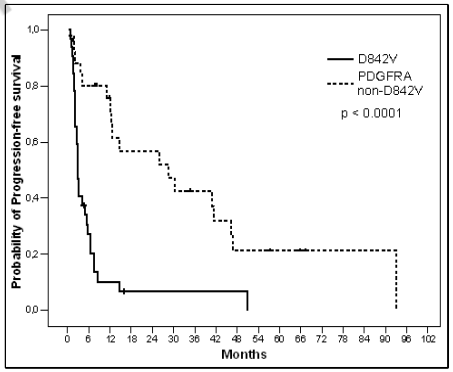
Blay *et al. J Clin Oncol.* 2007; 25:1107-13; Le Cesne *et al. Lancet Oncol.* 2010; 11: 942-49; Bertucci *et al. J Clin Oncol*. 2012: 30 [abstract 10095]

PDGFRA GIST
in the advanced phase

Characteristic	N	%
Total	**58**	**100**
Gender		
Male	34	58,6%
Female	24	41,4%
Primary tumor location		
Stomach	40	69,0%
Small bowel	7	12,1%
Peritoneum/Mesentery	2	3,4%
Rectum/Anus	1	1,7%
Other	4	6,9%
Unknown	4	6,9%
KIT/CD117 expression		
Positive	38	65,5%
Negative	7	12,1%
Unknown	13	22,4%
Type of mutation		
Exon 18 D842V substitution	32	55,2%
Other exon 18 mutation	17	29,3%
Exon 12 mutation	8	13,8%
Exon 4 mutation	1	1,7%
Metastatic sites		
Liver	36	62,1%
Peritoneum	33	56,9%
Liver & periotneum	15	25,9%
Other	15	25,9%
WHO PS		
0	28	48,3%
1	19	32,8%
2	2	3,4%
Unknown	9	15,5%

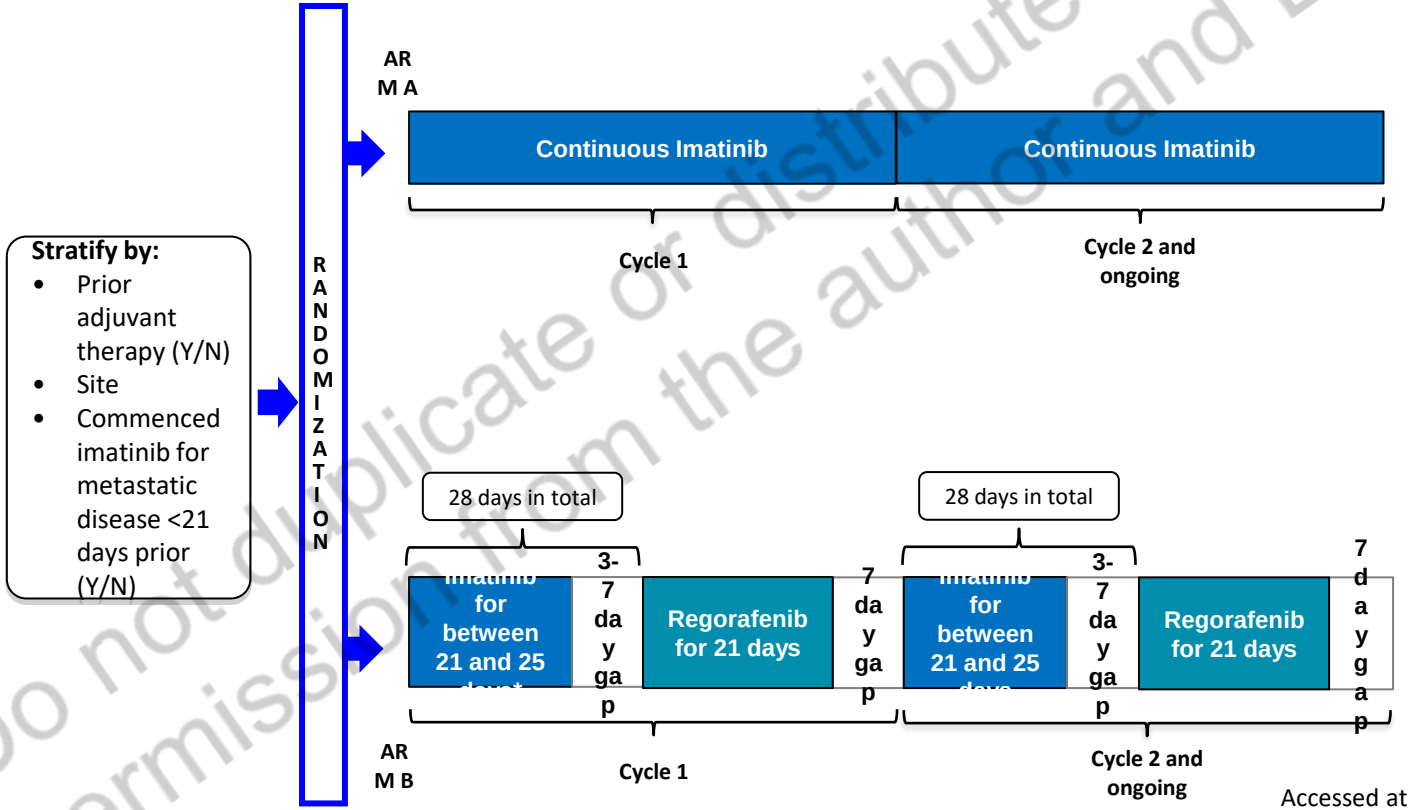






Study Schema: ALT-GIST

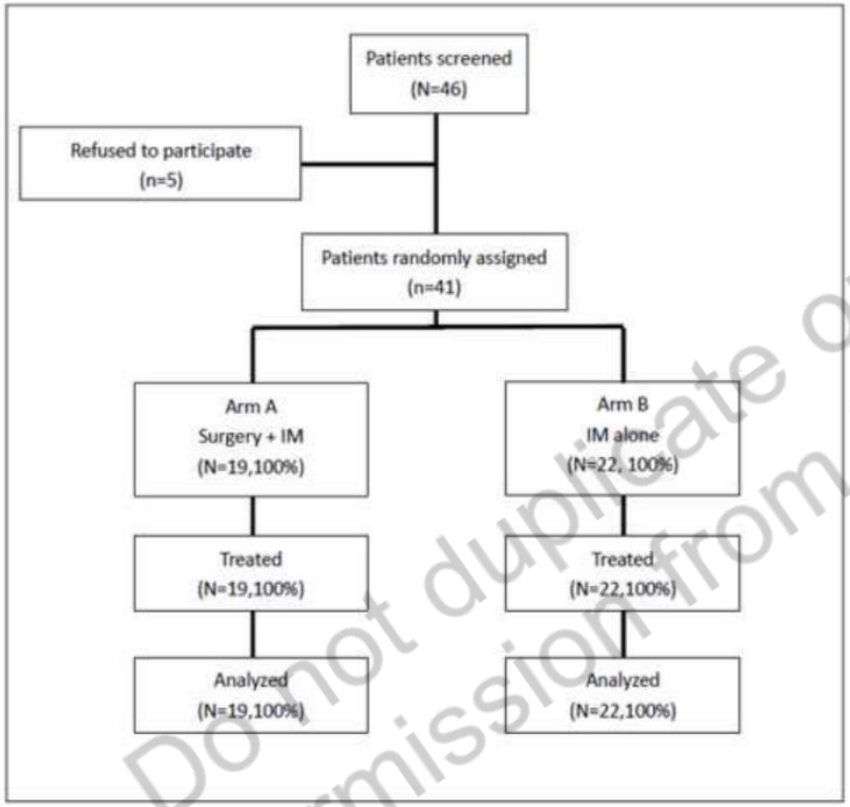
A randomized phase II trial of imatinib ALTernating with regorafenib compared with imatinib alone for the first-line treatment of advanced gastrointestinal stromal tumor (GIST)

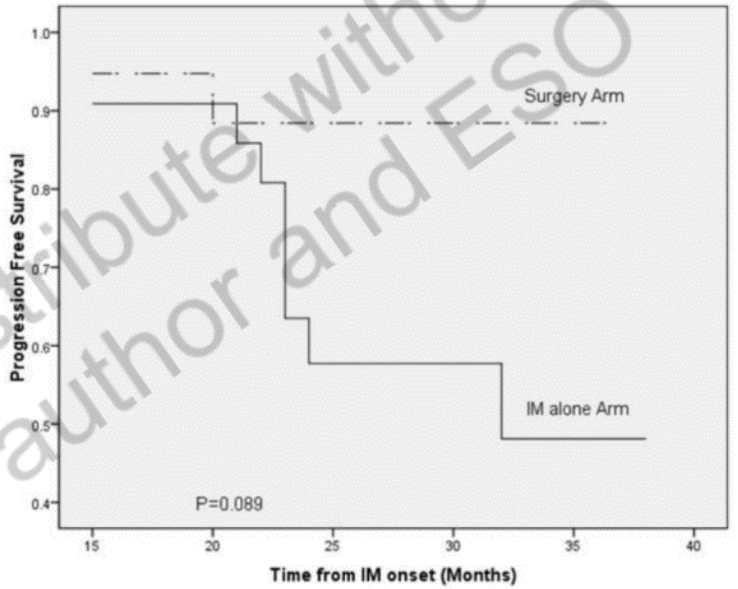


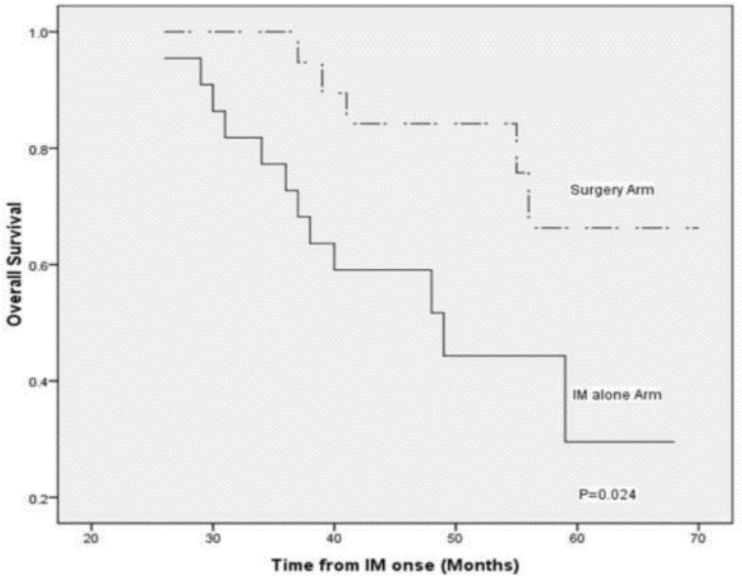
Accessed at https://clinicaltrials.gov/ct2/show/NCT02365441.

A randomized trial of surgery in metastatic GIST

Shi et al *Eur J Cancer 2014*







Sunitinib and regorafenib
Second and Third line agents

Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

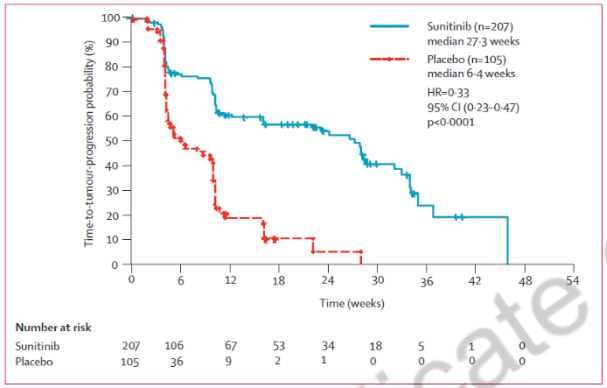
George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali

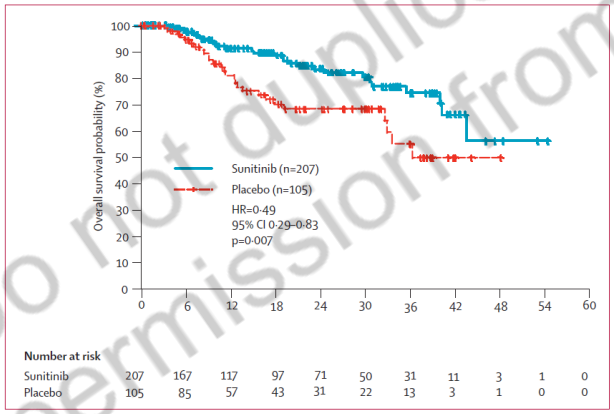
Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial

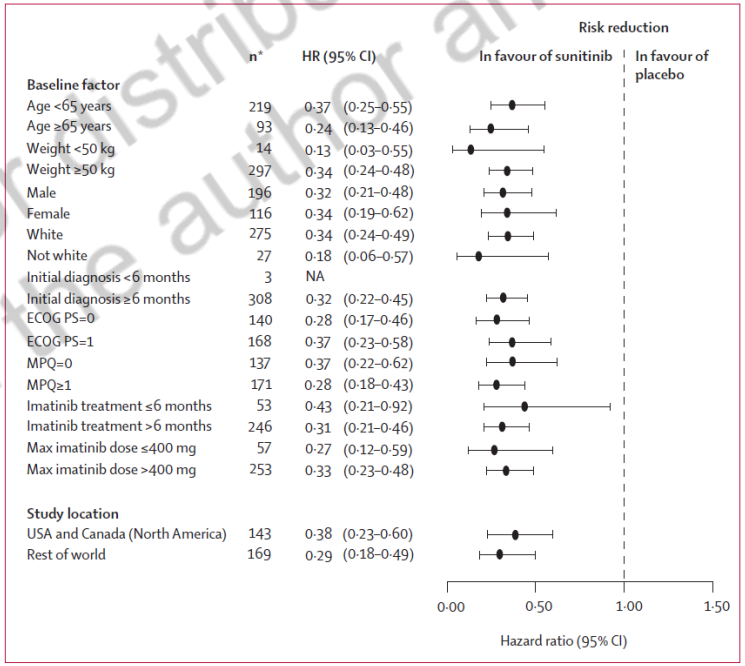
*George D Demetri, Peter Reichardt, Yoon-Koo Kang, Jean-Yves Blay, Piotr Rutkowski, Hans Gelderblom, Peter Hohenberger, Michael Leahy, Margaret von Mehren, Heikki Joensuu, Giuseppe Badalamenti, Martin Blackstein, Axel Le Cesne, Patrick Schöffski, Robert G Maki, Sebastian Bauer, Binh Bui Nguyen, Jianming Xu, Toshirou Nishida, John Chung, Christian Kappeler, Iris Kuss, Dirk Laurent, Paolo Casali, on behalf of all GRID study investigators**

Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

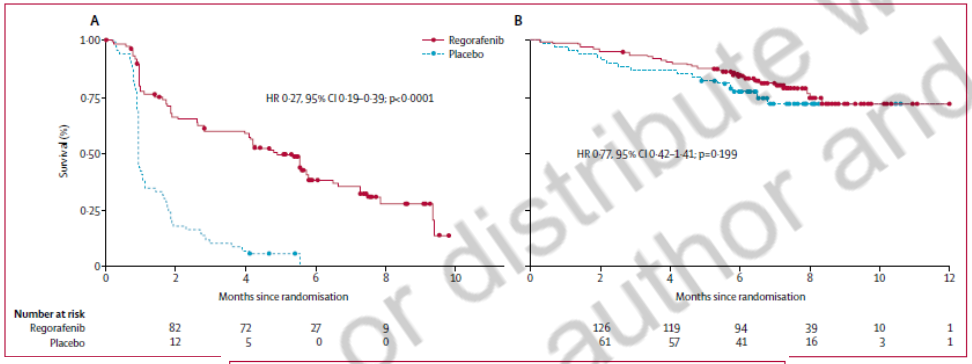
George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali

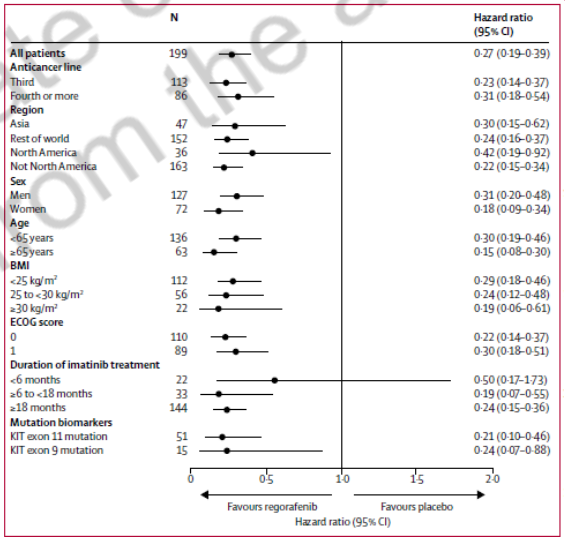




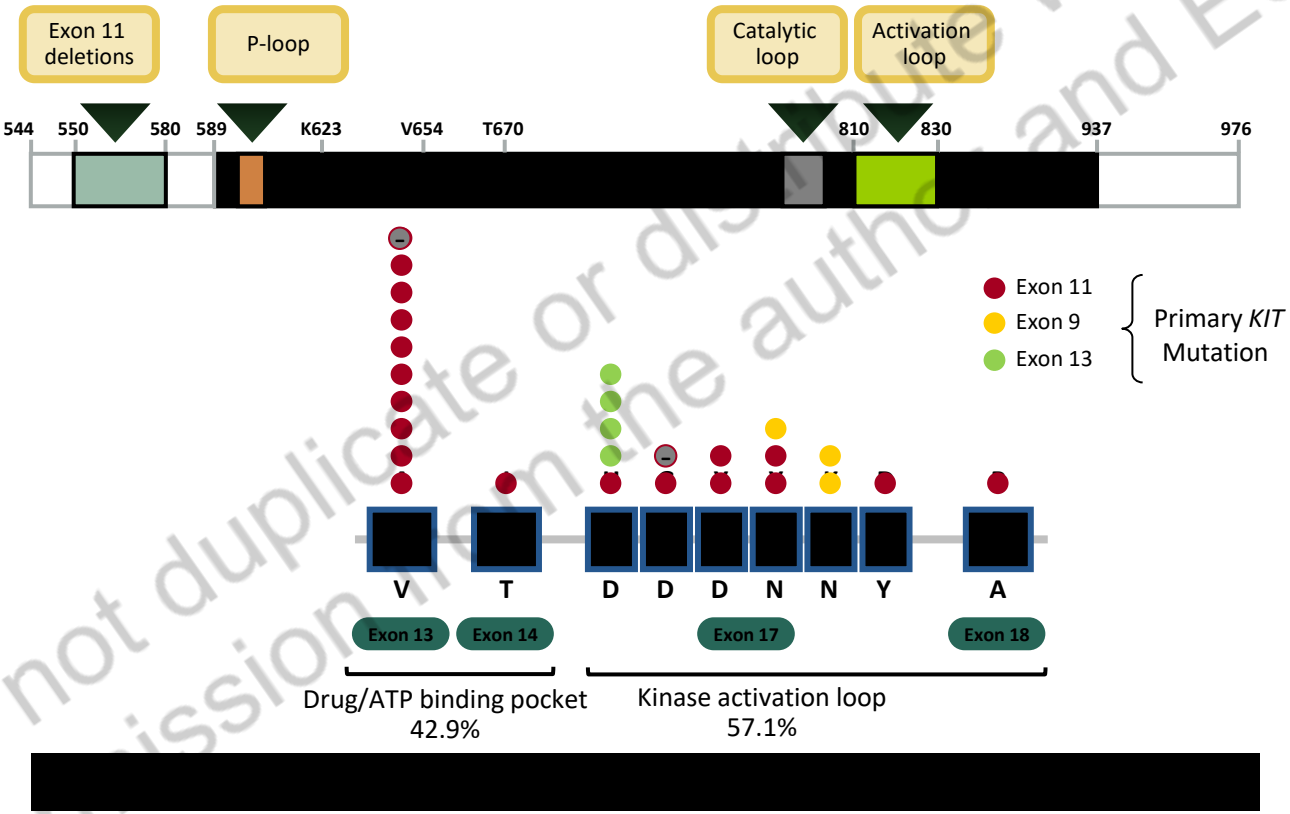


Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial





Secondary GIST Mutations in Patients Progressing on Imatinib or Sunitinib



DHPLC, denaturing high-pressure liquid chromatography.

Liegl B, et al. *J Pathol*. 2008;216(1):64-74; Wilhelm S. 2006; Patent #WO2007059154 A2, C'KIT Cytoplasmic Domain figure.

Five new drugs

- Ripretinib
- Avapritinib
- Cabozantinib
- Larotrectinib
- Entrectinib

Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial

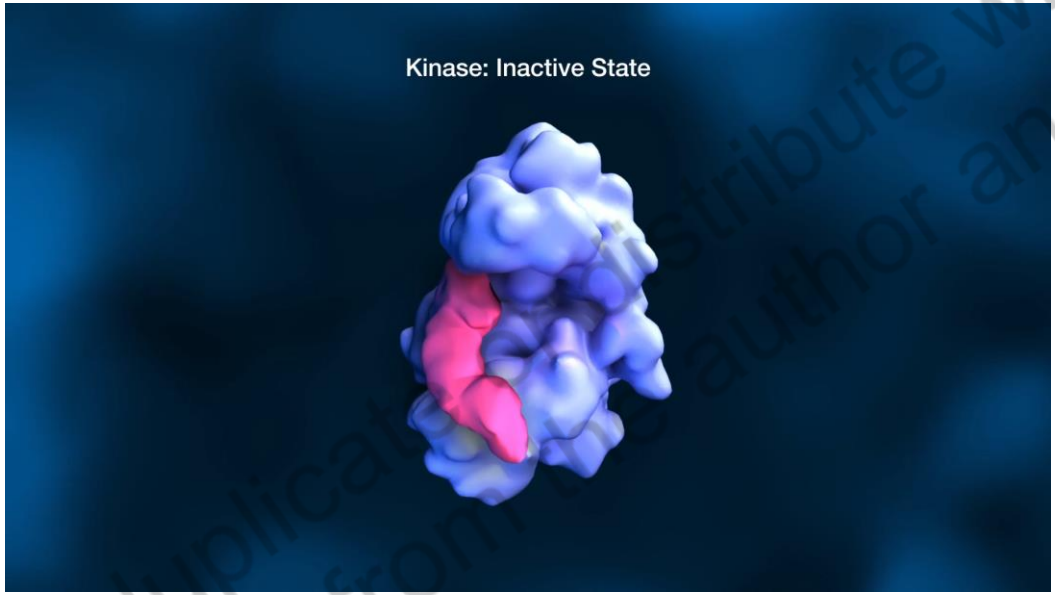
Jean-Yves Blay, César Serrano, Michael C Heinrich, John Zalcberg, Sebastian Bauer, Hans Gelderblom, Patrick Schöffski, Robin L Jones, Steven Attia, Gina D'Amato, Ping Chi, Peter Reichardt, Julie Meade, Kelvin Shi, Rodrigo Ruiz-Soto, Suzanne George, Margaret von Mehren

	Ripretinib group (n=85)	Placebo group (n=44)
Median age, years	59 (29–82)	65 (33–83)
18–64	57 (67%)	22 (50%)
65–74	20 (24%)	12 (27%)
≥75	8 (9%)	10 (23%)
Sex		
Male	47 (55%)	26 (59%)
Female	38 (45%)	18 (41%)
Race		
White	64 (75%)	33 (75%)
Non-white	13 (15%)	7 (16%)
Not reported	8 (9%)	4 (9%)
Region		
USA	40 (47%)	20 (46%)
Non-USA	45 (53%)	24 (55%)
Number of previous therapies		
3	54 (64%)	27 (61%)
4–7	31 (36%)	17 (39%)
ECOG performance status		
0	37 (44%)	17 (39%)
1 or 2	48 (56%)	27 (61%)
Primary tumour site		
Gastric	40 (47%)	18 (41%)
Jejunum or ileum	20 (24%)	8 (18%)
Mesenteric or omental	6 (7%)	6 (14%)
Other	7 (8%)	4 (9%)
Duodenum	2 (2%)	8 (18%)
Colon or rectum	9 (11%)	0
Unknown	1 (1%)	0
Sum of longest diameters of target lesions (mm), median (range)*	123 (28–495)	142 (17–412)
Primary mutation (central testing of tumour tissue)		
KIT exon 9	14 (17%)	6 (14%)
KIT exon 11	47 (55%)	28 (64%)
Other *KIT*	2 (2%)	2 (5%)
PDGFRA	3 (4%)	0
KIT and *PDGFRA* wild-type	7 (8%)	3 (7%)
Not available† or not done‡	12 (14%)	5 (11%)

Data are median (IQR), n (%), or median (range), and percentages might not add up to 100 due to rounding. ECOG=Eastern Cooperative Oncology Group. *KIT*=KIT proto-oncogene, receptor tyrosine kinase. *PDGFRA*=platelet-derived growth factor receptor α. *Independent assessment. †Tumour tissue analysed for baseline mutations but analysis failed. ‡Biopsy completed per protocol but sample not received for analysis.

Table 1: **Baseline patient characteristics**

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

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

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 Performance Status (%)			
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.

Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial

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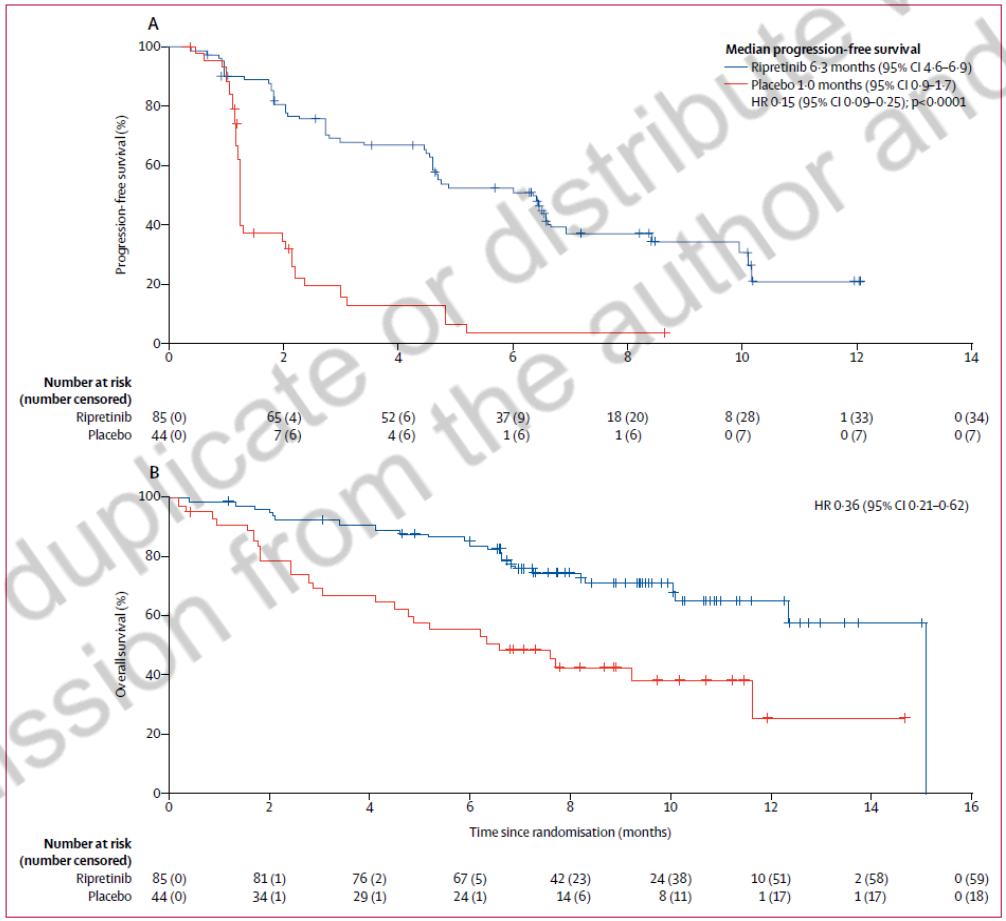

Figure 2: **Kaplan-Meier survival curves**
(A) Progression-free survival by blinded independent central review in patients receiving ripretinib or placebo in the double-blind part of the study. Crosses denote censoring events. (B) Overall survival in patients receiving ripretinib or placebo in the double-blind and open-label periods. Owing to the hierarchical testing procedures of the endpoints, overall survival endpoint could not be formally tested because the objective response rate was not statistically significant.

Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial

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	Ripretinib group (n=85)	Placebo group (n=44)	p value
Confirmed objective response	8 (9%; 4–18)	0 (0%; 0–8)	0·0504
Complete response	0 (0%; 0–4)	0 (0%; 0–8)	..
Partial response	8 (9%; 4–18)	0 (0%; 0–8)	..
Stable disease (6 weeks)	56 (66%; 55–76)	9 (20%; 10–35)	..
Stable disease (12 weeks)	40 (47%; 36–58)	2 (5%; 1–16)	..
Progressive disease	16 (19%; 11–29)	28 (64%; 48–78)	..
Not evaluable	4 (5%)	3 (7%)	..
No response assessment	1 (1%)	4 (9%)	..

Data are n (%; 95% CI) or n (%). *Assessed by blinded independent central review.

Table 2: **Objective response rate***

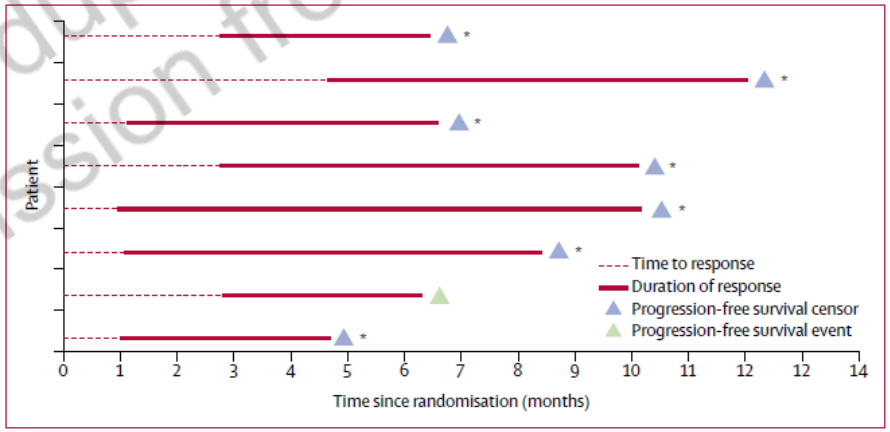


Figure 3: **Time to response and duration of response in the eight patients in the ripretinib group who responded**

Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial

	Ripretinib group (n=85)				Placebo group (n=43)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Alopecia	42 (49%)†	..	..	..	1 (2%)	..	..	..
Myalgia	23 (27%)	1 (1%)	..	..	4 (9%)	0	..	..
Nausea	21 (25%)	1 (1%)	..	..	1 (2%)	0	..	..
Fatigue	20 (24%)	2 (2%)	..	..	6 (14%)	1 (2%)	..	..
Palmar–plantar erythrodysesthesia syndrome	18 (21%)	0	..	..	0	0	..	..
Diarrhoea	17 (20%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Constipation	13 (15%)	0	0	0	3 (7%)	0	0	0
Decreased appetite	12 (14%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Weight loss	13 (15%)	0	..	..	3 (7%)	0	..	..
Blood bilirubin increased	12 (14%)	0	0	..	0	0	0	..
Arthralgia	10 (12%)	0	..	..	0	0	..	..
Muscle spasms	10 (12%)	0	..	..	2 (5%)	0	..	..
Hypertension	4 (5%)	3 (4%)	0	0	1 (2%)	0	0	0
Lipase increase	4 (5%)	4 (5%)	0	..	0	0	0	..
Pain in extremity	5 (6%)	1 (1%)	..	..	1 (2%)	0	..	..
Hypophosphataemia	3 (4%)	2 (2%)	0	0	0	0	0	0
Anaemia	2 (2%)	0	1 (1%)	0	1 (2%)	2 (5%)	1 (2%)	0
Blood triglycerides increase	1 (1%)	1 (1%)	0	0	0	0	0	0
Dermatosis	1 (1%)	1 (1%)	0	0	0	0	0	0
Dehydration	1 (1%)	0	0	0	0	1 (2%)	0	0
Gastroesophageal reflux disease	1 (1%)	1 (1%)	..	..	0	0	..	..
Hyperkalaemia	0	1 (1%)	0	0	0	1 (2%)	0	0
Hypokalaemia	0	1 (1%)	0	0	0	0	0	0
Anal abscess	0	1 (1%)	0	0	0	0	0	0
Ascites	0	1 (1%)	0	0	0	0	0	0
Cardiac failure	0	1 (1%)	0	0	0	0	0	0
Death, reason unknown	..	..	..	1 (1%)	..	..	..	0
Fecaloma	0	1 (1%)	0	0	0	0	0	0
Skin infection	0	1 (1%)	0	0	0	0	0	0
Syncope	..	1 (1%)	..	..	..	0	..	..
Upper gastrointestinal haemorrhage	0	1 (1%)	0	0	0	0	0	0
Acute kidney injury	0	0	0	0	0	1 (2%)	0	0
Pulmonary oedema	0	0	0	0	0	0	1 (2%)	0
Septic shock	..	..	0	0	..	..	0	1 (2%)

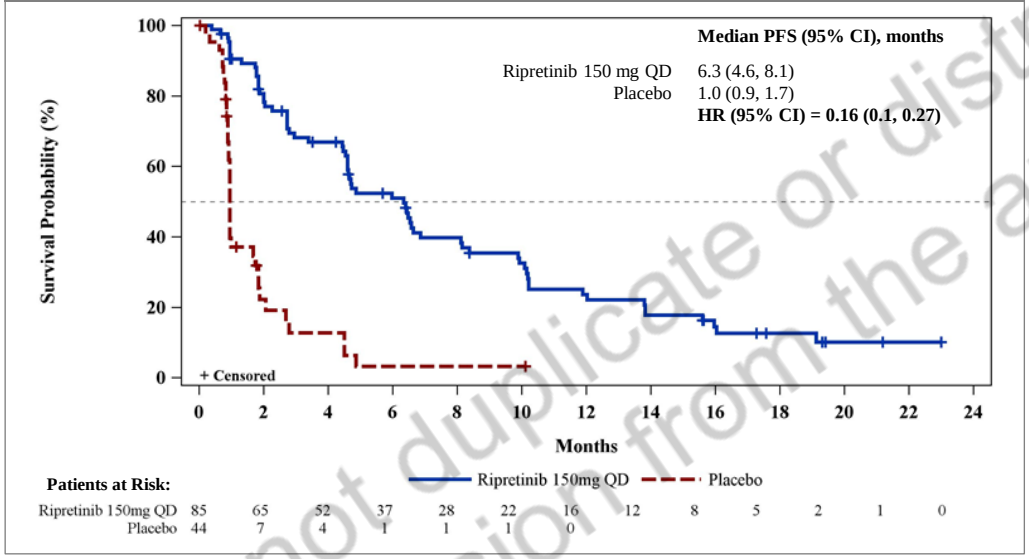
Data are n (%). Treatment-related treatment-emergent adverse events are listed that occurred in ≥10% of patients in either treatment group or were reported as grade 3, 4, or 5 in either treatment group are shown. .. indicates that no data were captured per adverse event grade ratings specified by Common Terminology Criteria for Adverse Events version 4.03. *44 patients were randomly assigned to receive placebo, but one patient did not receive treatment. †24 (63%) of 38 women who were given ripretinib had alopecia.

Table 3: **Treatment-related treatment-emergent adverse events**

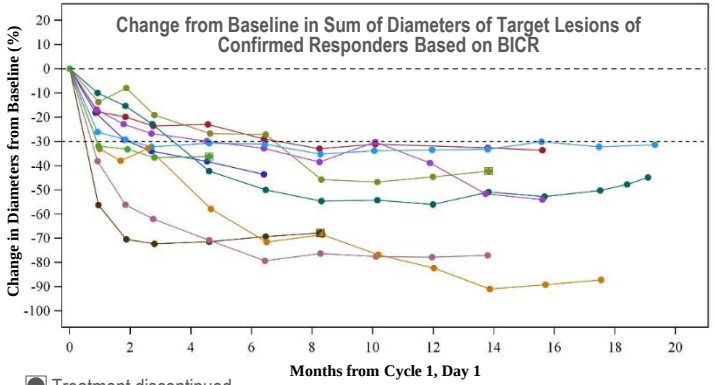
Progression Free Survival and Objective Response Rate*

ITT population

Kaplan-Meier Estimate of PFS



	Ripretinib (n = 85)	Placebo (n = 44)
Events, n (%)	66 (77.6%)	37 (84.1%)
Censored, n (%)	19 (22.4%)	7 (15.9%)
PFS 6 months, % (95% CI)	51.0% (39.4, 61.4)	3.2% (0.2, 13.8)
PFS 12 months, % (95% CI)	23.6% (14.6, 34.0)	NE (NE, NE)
PFS 18 months, % (95% CI)	12.6% (6.0, 21.9)	NE (NE, NE)
ORR, n (%) 95% CI	10 (11.8%) 5.8, 20.6	0 0.0, 8.0
DOR, months, median, (95% CI)	14.5 (3.7, NE)	NE (NE, NE)



The only patient remaining on placebo at the May 31, 2019 data cutoff crossed over to the ripretinib 150 mg QD treatment without BICR PD upon the study unblinding in Aug 2019. The PFS was censored on the last day before crossover.

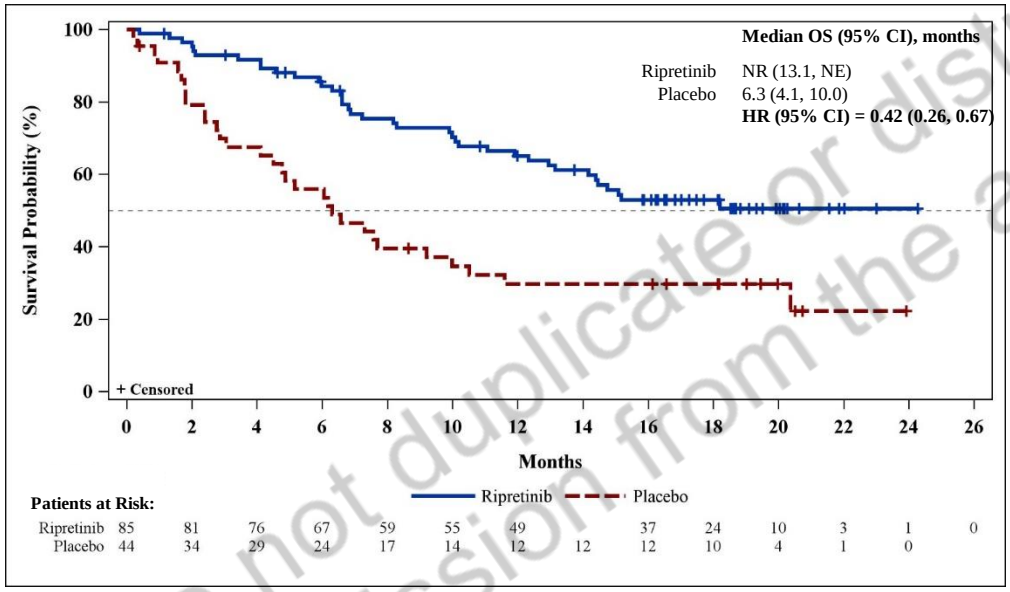
*Data from this study (including the primary endpoint) were initially evaluated at the 31 May 2019 data cutoff.

BICR, blinded independent central review; CI, confidence interval, DOR, duration of response; HR, hazard ratio; ITT, intent-to-treat (all randomized patients); NE, not estimable; ORR, objective response rate; PD, disease progression; PFS, progression-free survival; QD, once daily.

Overall Survival*

ITT population

Kaplan-Meier Estimate of OS



	Ripretinib (n = 85)	Placebo (n = 44)
Events, n (%)	38 (44.7%)	31 (70.5%)
Censored, n (%)	47 (55.3%)	13 (29.5%)
OS 6 months, % (95% CI)	84.3% (74.5, 90.6)	55.9% (39.9, 69.2)
OS 12 months, % (95% CI)	65.1% (53.6, 74.5)	29.7% (16.8, 43.7)
OS 18 months, % (95% CI)	53.0% (41.3, 63.3)	29.7% (16.8, 43.7)
OS 24 months, % (95% CI)	50.6% (38.5, 61.4)	NE (NE, NE)

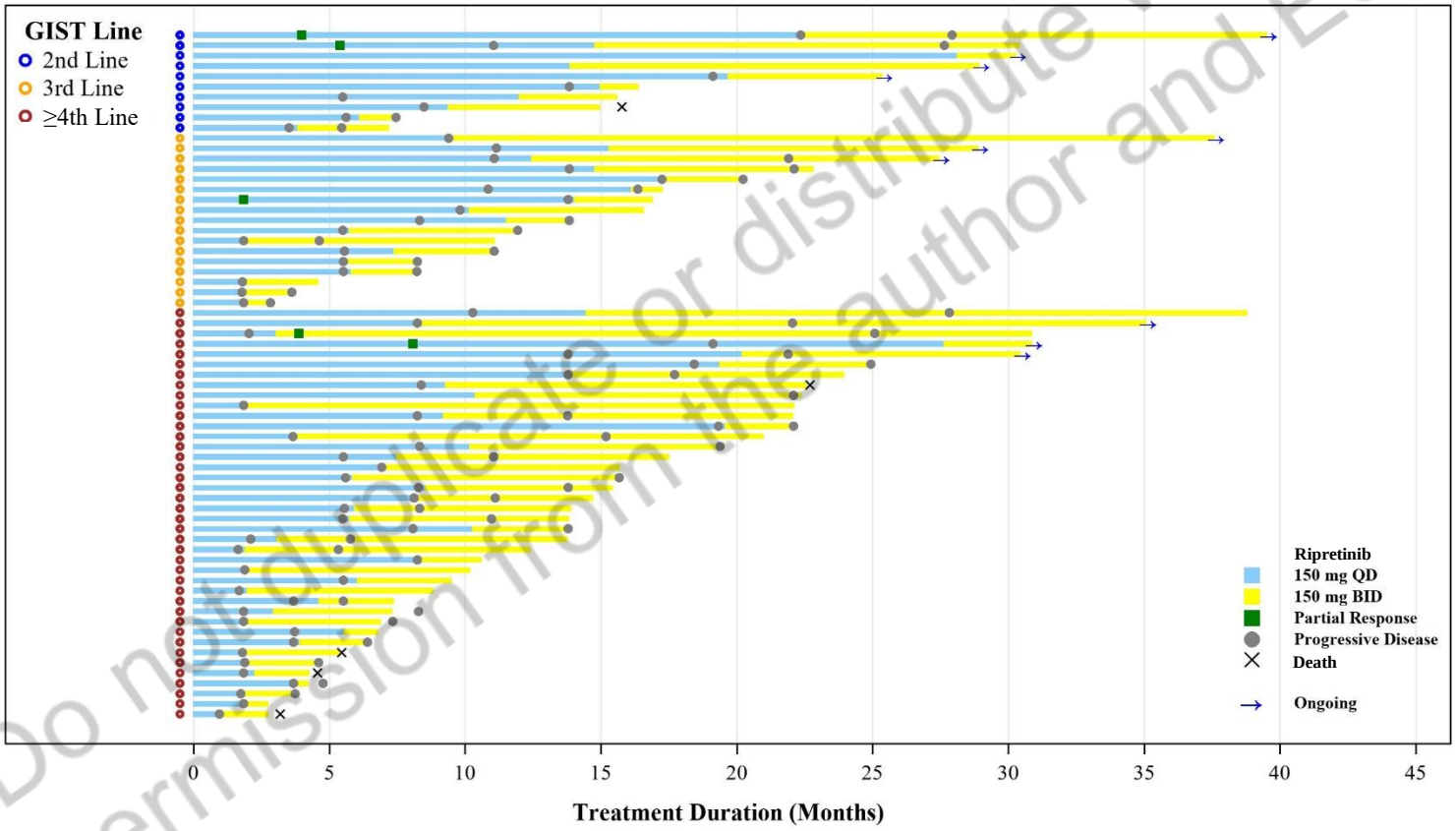
- With 9 months of additional follow-up after the primary analysis, the median OS for patients randomized to ripretinib has extended from 15.1 months to “not reached”

Overall survival data includes all time periods, including dose escalation to 150 mg BID. Placebo curve includes patients who crossed over to ripretinib treatment.

*Data from this study (including the primary endpoint) were initially evaluated at the 31 May 2019 data cutoff.
BID, twice daily; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat (all randomized patients); NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; QD, once daily.

Objective Responses and PFS Events

Patients with GIST who received ripretinib 150 mg QD and escalated to 150 mg BID



BID, twice daily; GIST, gastrointestinal stromal tumor; PFS, progression-free survival; QD, once daily.

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

Analysis of avapritinib starting dose 300/400 mg QD in ≥4th line (4L+) and PDGFRA exon 18 mutated GIST

NAVIGATOR (NCT02508532) is an open-label, dose escalation/dose expansion study of avapritinib

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

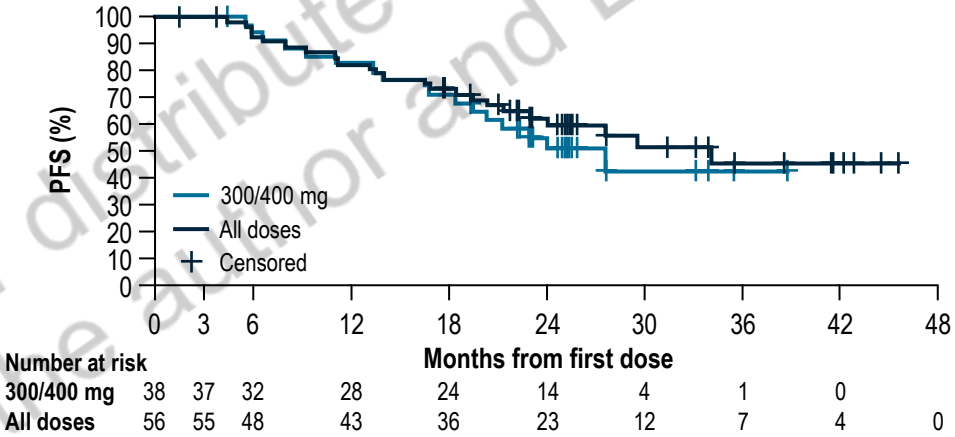
Avapritinib once daily at the RP2D of 300 mg or MTD of 400 mg

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

[a]Enrollment criteria specified that patients were required to have received only ≥2 prior lines of TKI therapy (ie, analysis population of 3L+), observed enrollment reflected a more heavily pretreated population (ie, 4L+). [b]Mutational analysis was performed locally and confirmed centrally. 3L, 3rd line; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

PDGFRA D842V-mutant GIST: ORR and PFS

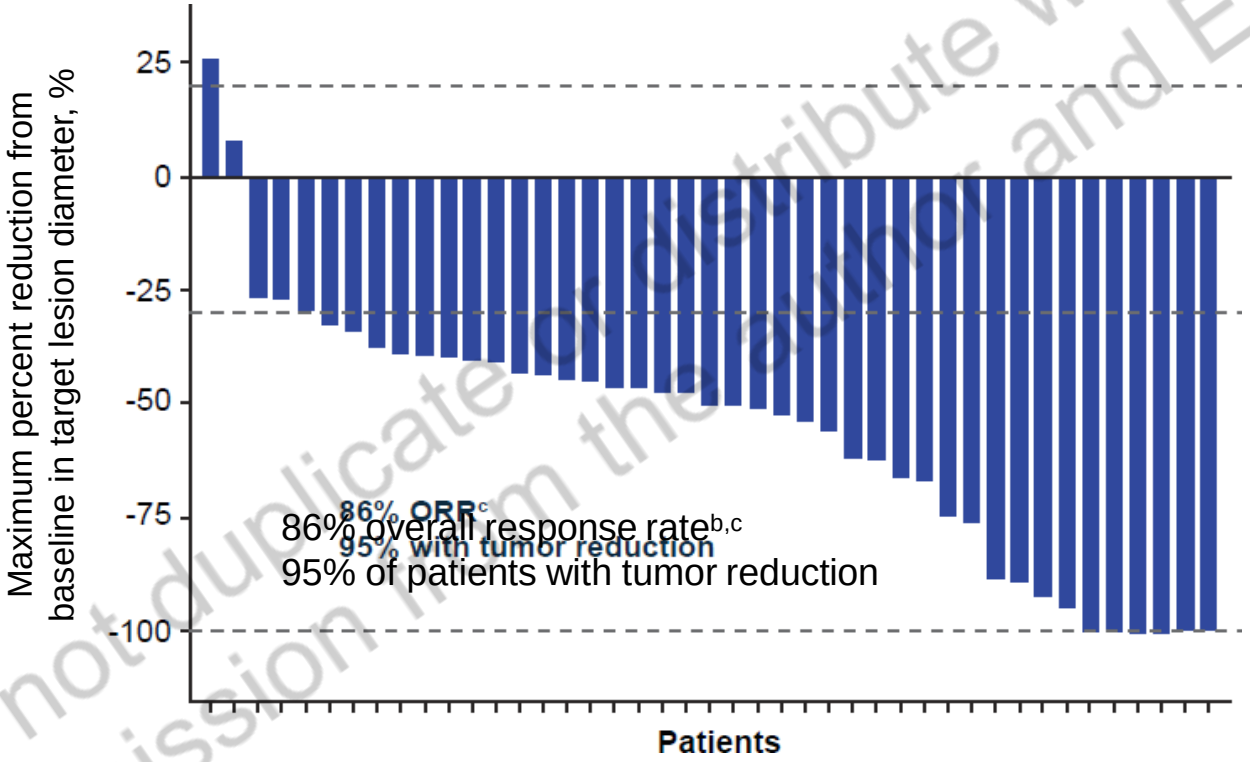
Response,[a] n (%)	Avapritinib starting dose				
	<300 mg (n=17)	300 mg (n=28)	400 mg (n=10)	300/400 mg (n=38)	All doses[b] (N=56)
ORR[c]	14 (82)	27 (96)	9 (90)	36 (95)	51 (91)
95% CI	57–96	82–100	56–100	82–99	80–97
CR	2 (12)	3 (11)	2 (20)	5 (13)	7 (13)
PR	12 (71)	24 (86)	7 (70)	31 (82)	44 (79)
SD	3 (18)	1 (4)	1 (10)	2 (5)	5 (9)



- Of the 5 TKI-naïve patients receiving avapritinib 300/400 mg, 2 achieved a CR and 3 achieved a PR
- Median DOR with avapritinib 300/400 mg was 22 months (95% CI, 14–NR), median PFS was 24 months (95% CI, 18–NR), and median OS was not reached
- At 36 months, estimated PFS and OS rates with avapritinib 300/400 mg were 34% and 71%, respectively

Enrollment as of a data cut-off March 9, 2020. Median follow-up for OS: 27.5 months. [a]mRECIST v1.1. [b]Includes n=1 patient with 600 mg starting daily dose. [c]CR or PR.
CI, confidence interval; CR, complete response; DOR, duration of response; mRECIST v.1., modified Response evaluation criteria in solid tumors version 1.1; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

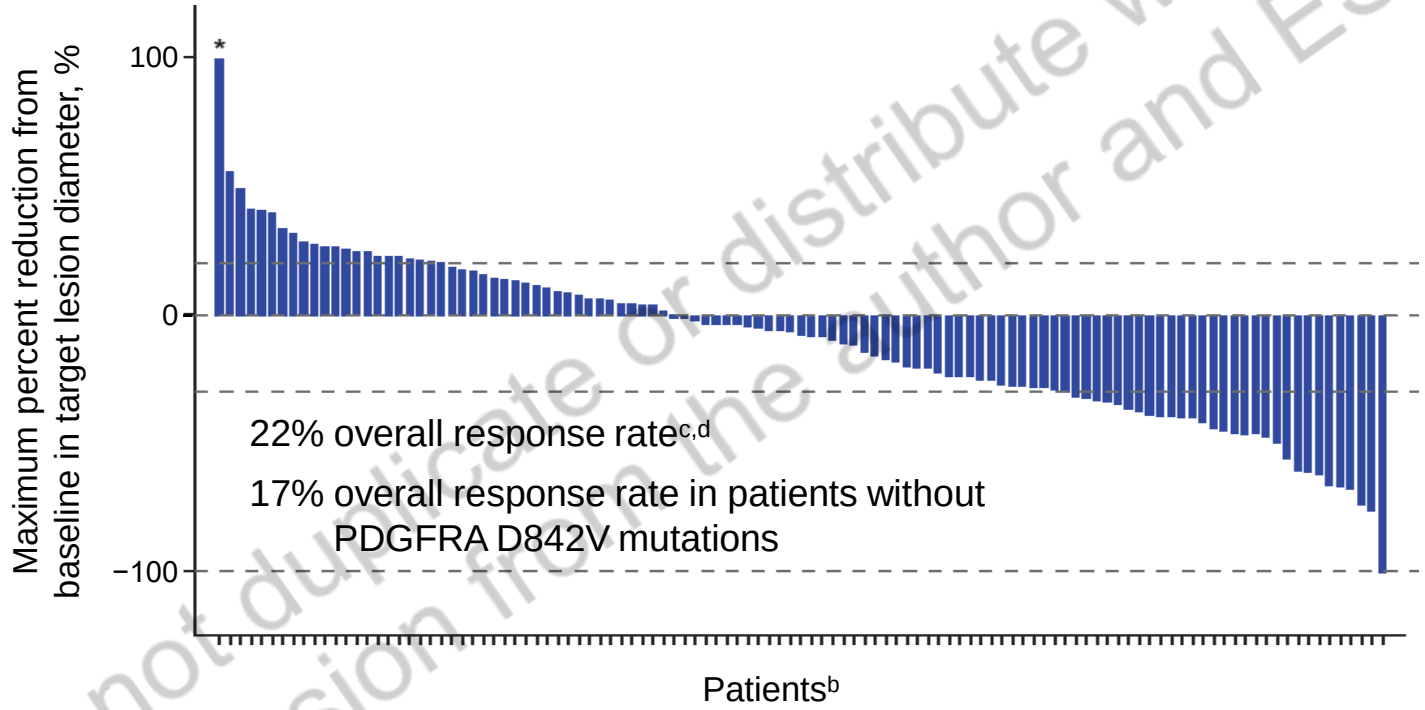
Antitumor activity in response-evaluable patients[a]
PDGFRA exon 18 GIST – avapritinib starting dose 300/400 mg QD (central radiology)



86% overall response rate[b,c]
95% of patients with tumor reduction

[a]Response-evaluable patients were comprised of patients who had ≥1 target lesion assessed at baseline by central radiology review and had ≥1 post-baseline disease assessment by central radiology. [b]Proportion of response-evaluable patients with a confirmed best response of complete response or partial response, confirmed by central radiology and assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST 1.1) in patients treated with avapritinib starting dose 300/400 mg QD. [c]1 partial response pending confirmation. QD, once daily.

Antitumor activity in response-evaluable patients[a]
4L+ treatment – avapritinib starting dose 300/400 mg QD (central radiology)



*One patient had an outlier value of >200% increase in target lesion diameter. [a]Response-evaluable patients were comprised of patients who had ≥1 target lesion assessed at baseline by central radiology review and had ≥1 post-baseline disease assessment by central radiology. [b]Two patients who had best response assessment are not included in the plot because they did not have measurable target lesions at baseline and thus, no percent change could be calculated. [c]1 partial response pending confirmation. [d]Includes 8 patients with PDGFRA D842V mutations; duration of response remains unchanged when these patients were removed from analysis. QD, once daily.

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

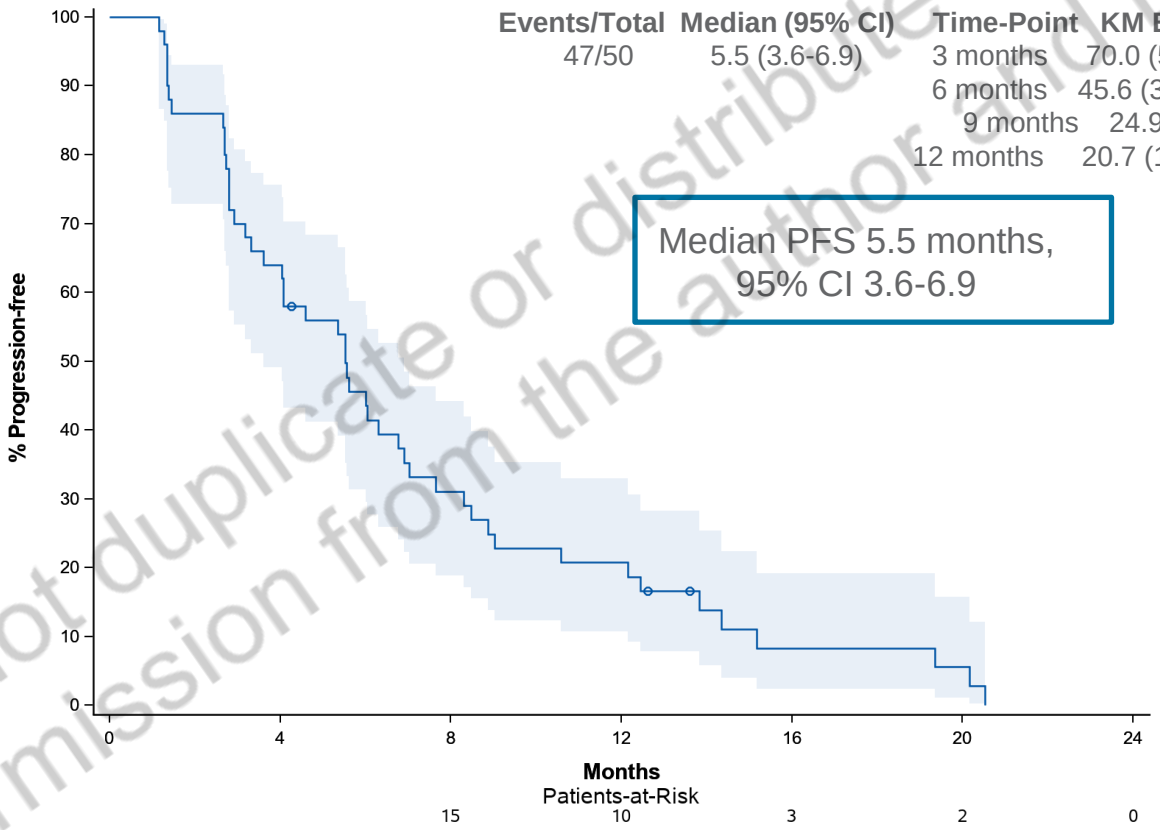
Genotype-specific activity and safety of cabozantinib in patients with gastrointestinal stromal tumor (GIST) after failure of imatinib and sunitinib. Early molecular data from EORTC Phase 2 trial 1317 "CaboGIST"

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
Abstract ID 3214982

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



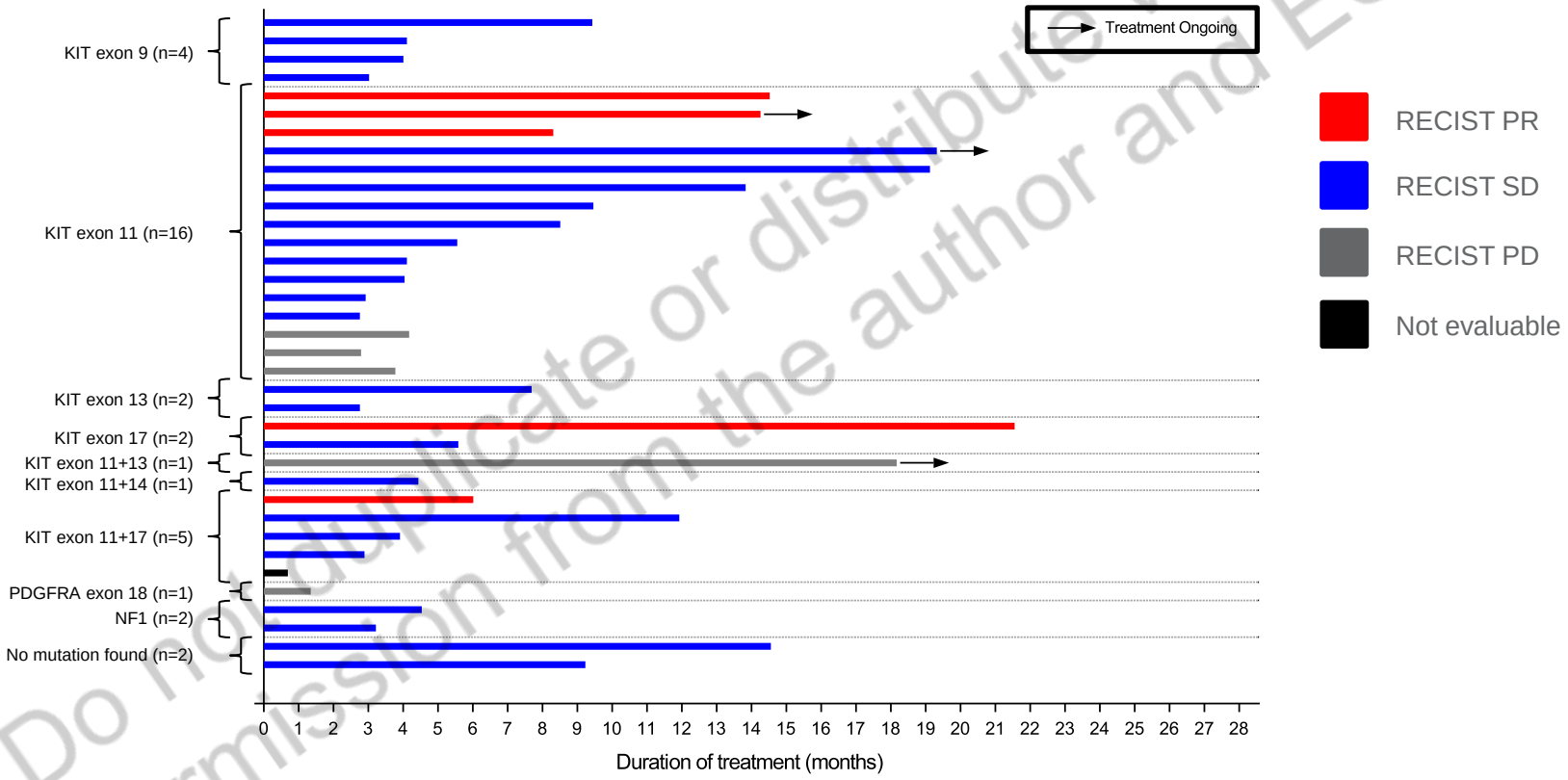
Events/Total	Median (95% CI)
47/50	5.5 (3.6-6.9)

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

Shadow represents 95%CI

Centrally assessed GIST genotype, duration of treatment and best RECIST response



(Central mutational analysis not performed in 14 pts)

Larotrectinib Efficacy and Safety in Patients with TRK Fusion Sarcomas

George D. Demetri[1], Catherine M. Albert[2], Daniel S. W. Tan[3], Stefan Bielack[4], Daniel Orbach[5], Steven G. DuBois[6], Noah Federman[7], Birgit Geoerger[8], Shivaani Kummar[9], Theodore W. Laetsch[10], Ramamoorthy Nagasubramanian[11], Alexander Drilon[12], David S. Hong[13], David M. Hyman[12], Ulrik Lassen[14], Ray McDermott[15], Alberto Pappo[16], Neerav Shukla[12], Shivani Nanda[17], Barrett H. Childs[17], Leo Mascarenhas[18], Cornelis M. van Tilburg[19]

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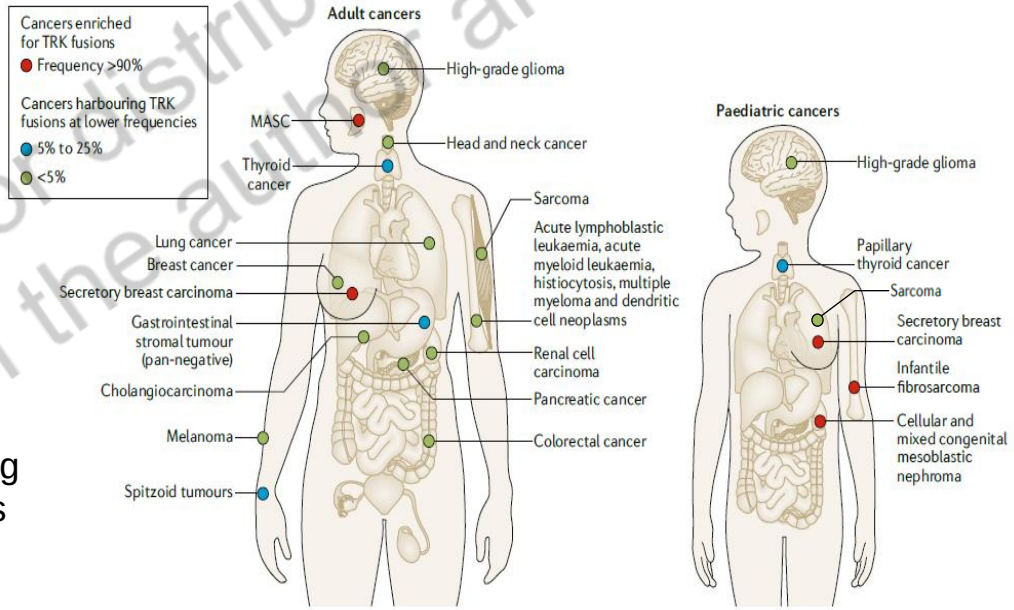
Larotrectinib is Highly Active Against Cancers Harbour

- Larotrectinib is a first-in-class, highly selective TRK inhibitor[1]
  - High potency against all TRK isoforms (TRKA, TRKB, and TRKC) [5]
  - ≥100-fold selectivity for TRK kinases versus 229 other kinases[5]
- FDA- and EMA-approved for the treatment of paediatric and adult patients with solid tumours harbouring *NTRK* gene fusions[3,4]
  - Activity reported in CNS disease[2]
- Selitrectinib is a next-generation inhibitor targeting mutations that confer resistance to TRK inhibitors (NCT03215511)

Frequency of *NTRK* gene fusions in adult and paediatric cancers[6]

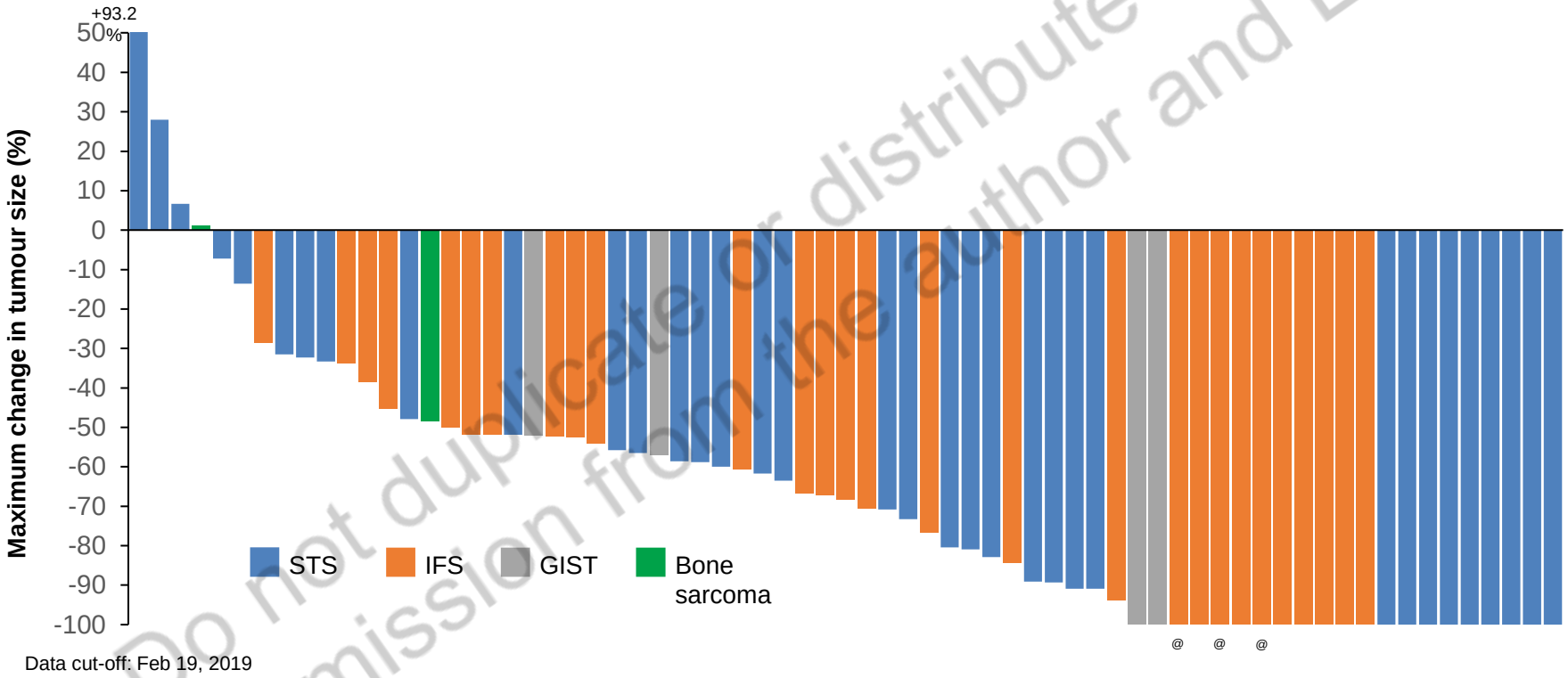


CNS, central nervous system; EMA, European Medicines Agency; FDA, Food and Drug Administration; IC_{50}, half maximal inhibitory concentration; MASC, mammary analogue secretory carcinoma; *NTRK*, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.

1. Drilon A, et al. *N Engl J Med*. 2018;378:731–739. 2. Drilon A, et al. Presented at ASCO 2019. Abstract #2006. 3. VITRAKVI Prescribing Information. Nov 2018. 4. VITRAKVI SmPC. Jul 2019. 5. Doebele RC, et al. *Cancer Disc*. 2015;5:1049–1057. 6. Cocco E, et al. *Nat Rev Clin Oncol*. 2018;15:731–747.

Efficacy of Larotrectinib in Sarcomas Harbouring TRK fusions: Best Change in Target Lesions

(Investigator assessed)

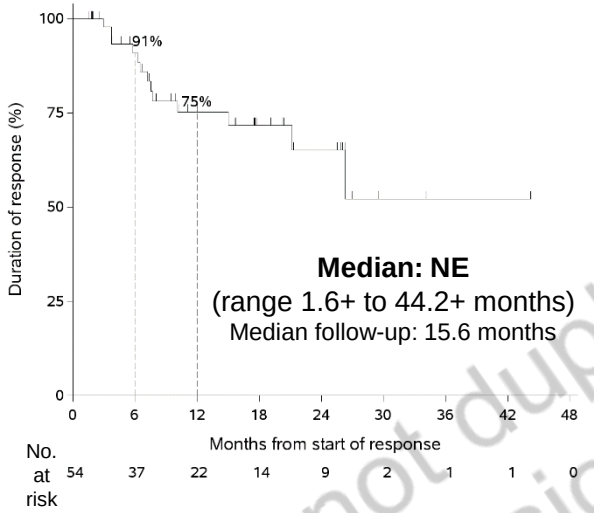


Data cut-off: Feb 19, 2019

Tumour responses in patients with measurable disease and tumour values recorded at data cut-off, based on RECIST 1.1 sum of longest diameter.
Excludes one patient because post-baseline assessments were not yet done at data cut-off; one patient continued on treatment. @Patients with a pathological complete response.
GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; RECIST, Response Evaluation Criteria in Solid Tumors; STS, soft tissue sarcoma.

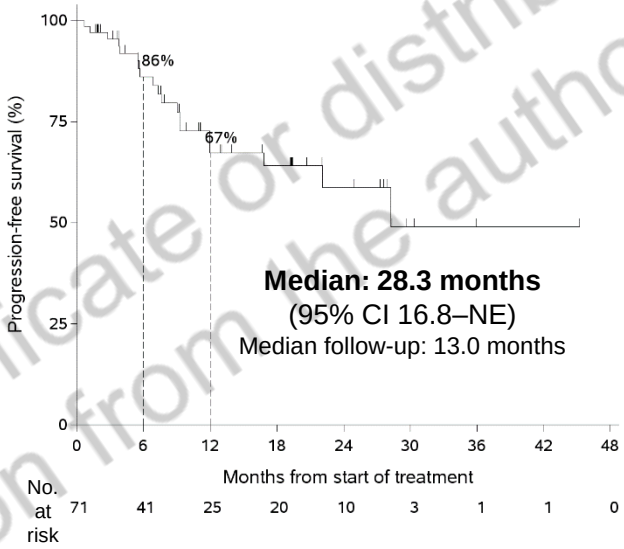
Efficacy Endpoints

Duration of response



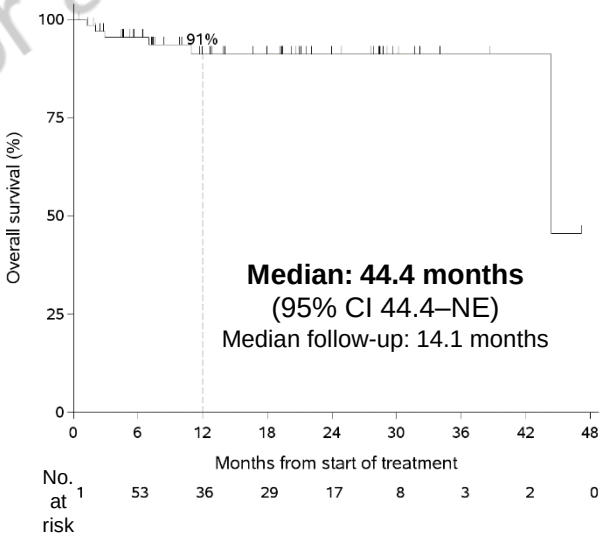
Median: NE
(range 1.6+ to 44.2+ months)
Median follow-up: 15.6 months

Progression-free survival



Median: 28.3 months
(95% CI 16.8–NE)
Median follow-up: 13.0 months

Overall survival



Median: 44.4 months
(95% CI 44.4–NE)
Median follow-up: 14.1 months

Data cut-off: Feb 19, 2019

Vertical tick marks represent censored patients. NE, not estimable.

Ongoing?

- 4+ line (post ripretinib) lenvatinib vs placebo
- 4+ line : imatinib vs imatinib +atezolizumab
- TKI in phase I & phase II

Conclusions : GISTs

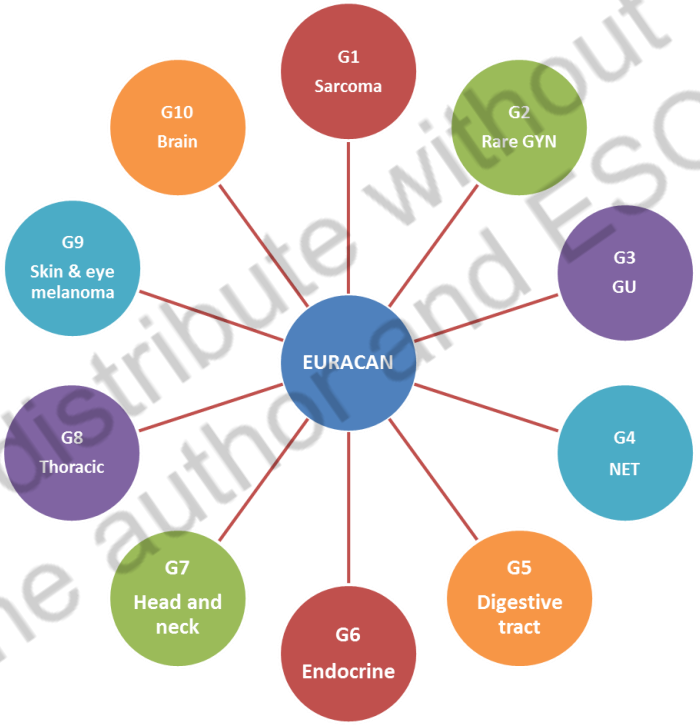
- Molecular characterization routine
  - Different diseases
- Localized phase: SURGERY and adjuvant medical treatment
- Advanced phase: MEDICAL TREATMENT (Im, Su, Re) and surgery
- Five new drugs in advanced phase

European Reference Network

for rare or low prevalence complex diseases

Network Adult Cancers (ERN EURACAN)

EURACAN



Melanoma Patient Network Europe

RARE SOLID ADULT CANCERS