AIGOM
ASSOCIAZIONE ITALIANA
GRUPPI ONCOLOGICI MULTIDISCIPLINARI

GIST:
dalla diagnosi al trattamento

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

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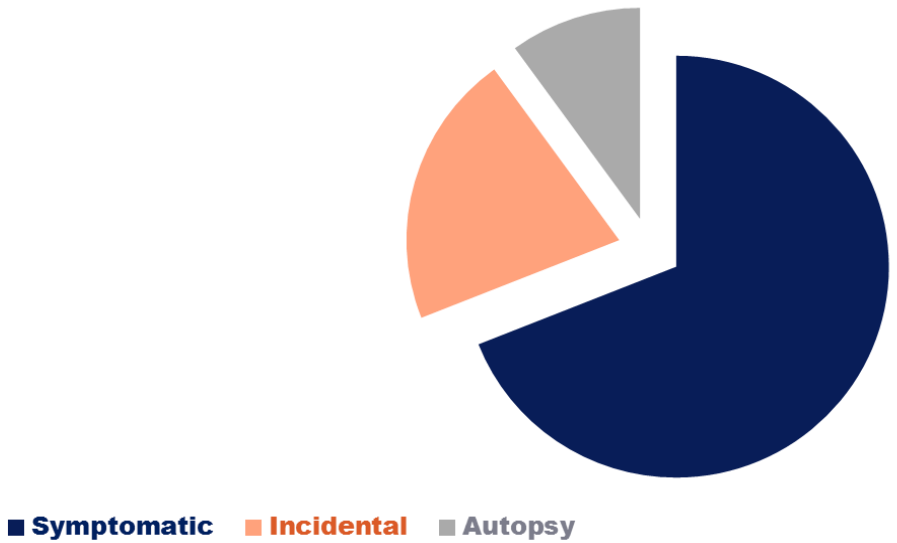
Gastrointestinal Stromal Tumors: The Incidence, Prevalence, Clinical Course, and Prognostication in the Preimatinib Mesylate Era

A Population-Based Study in Western Sweden



B. Nilsson et al., Cancer 2005

Gastrointestinal Stromal Tumors: Recent Advances in Understanding of Their Biology

MARKKU MIETTINEN, MD, MAARIT SARLOMO-RIKALA, MD, AND JERZY LASOTA, MD

Gastrointestinal stromal tumor (GIST) is the preferred term for mesenchymal tumors specific for the gastrointestinal tract (60% in stomach, 30% small intestine, 10% elsewhere). GISTs include most tumors previously designated as leiomyoma, cellular leiomyoma, leiomyoblastoma, and leiomyosarcoma. However, in the esophagus, leiomyoma is the most common mesenchymal tumor. GISTs are composed of spindle (70%) or epithelioid (30%) cells, and 10%-30% are malignant showing intra-abdominal spread or liver metastases. They are immunohistochemically positive for c-kit (CD117), CD34, and sometimes for actin but are almost always negative for desmin and S100-protein. The malignant GISTs especially show activating mutations in the c-kit gene. GISTs and gastrointestinal autonomic nerve tumors (GANT) overlap. The cell of origin is not fully understood, but resemblance to the interstitial cells of Cajal, expression of some smooth muscle markers, and occurrence outside of the GI-tract suggest origin from multipotential cells that can differentiate into Cajal and smooth muscle cells. HUM PATHOL 30:1213-1220.

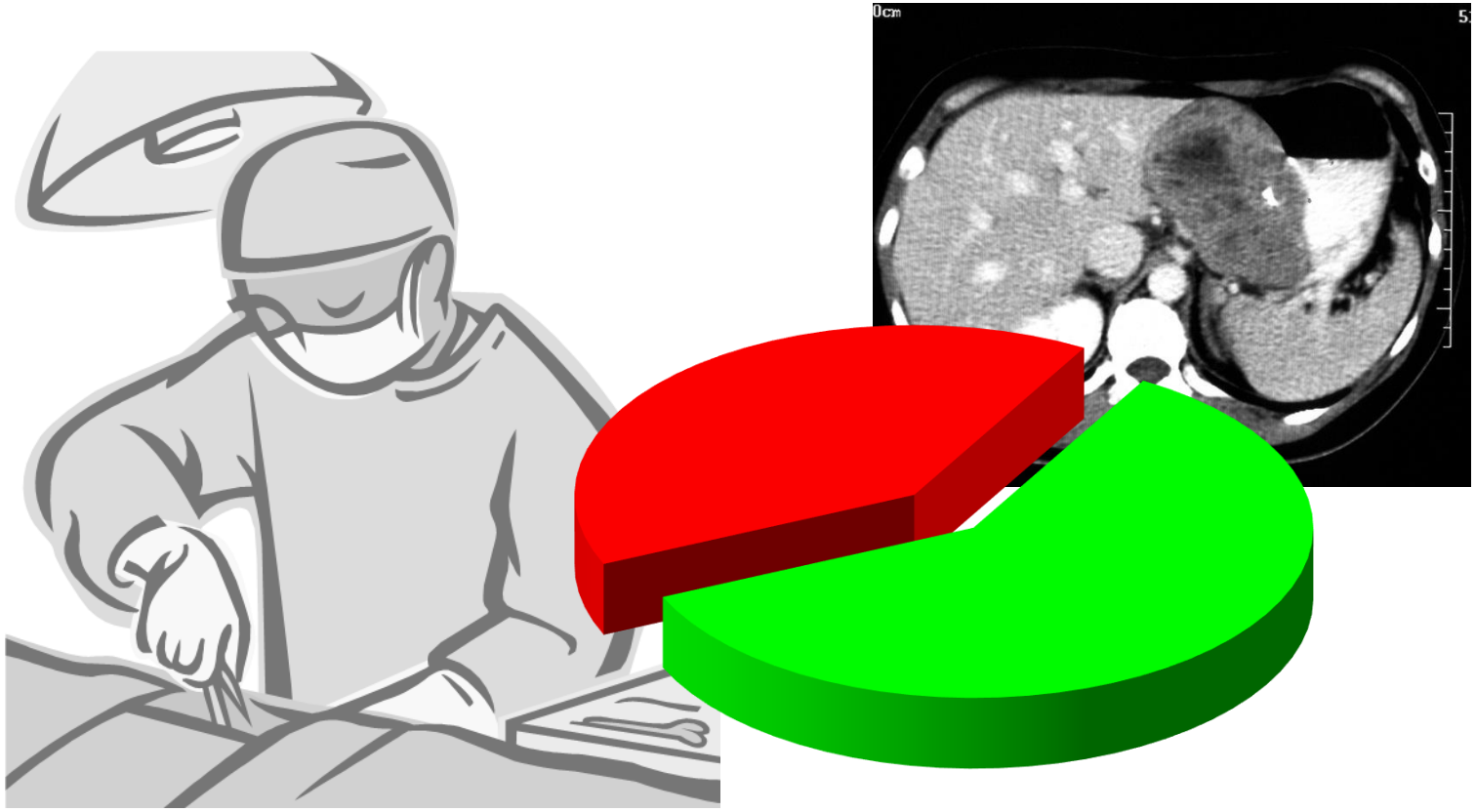
Key words: leiomyosarcoma, GIST, pathology, c-kit, genetics.

Abbreviations: GI, gastrointestinal; AFIP, Armed Forces Institute of Pathology; GIST, gastrointestinal stromal tumor; HPF, high-power field; HCD, heavy-molecular-weight caldesmon; PCNA, proliferating cell nuclear antigen; GANT, gastrointestinal autonomic nerve tumor; CGH, comparative genomic hybridization.

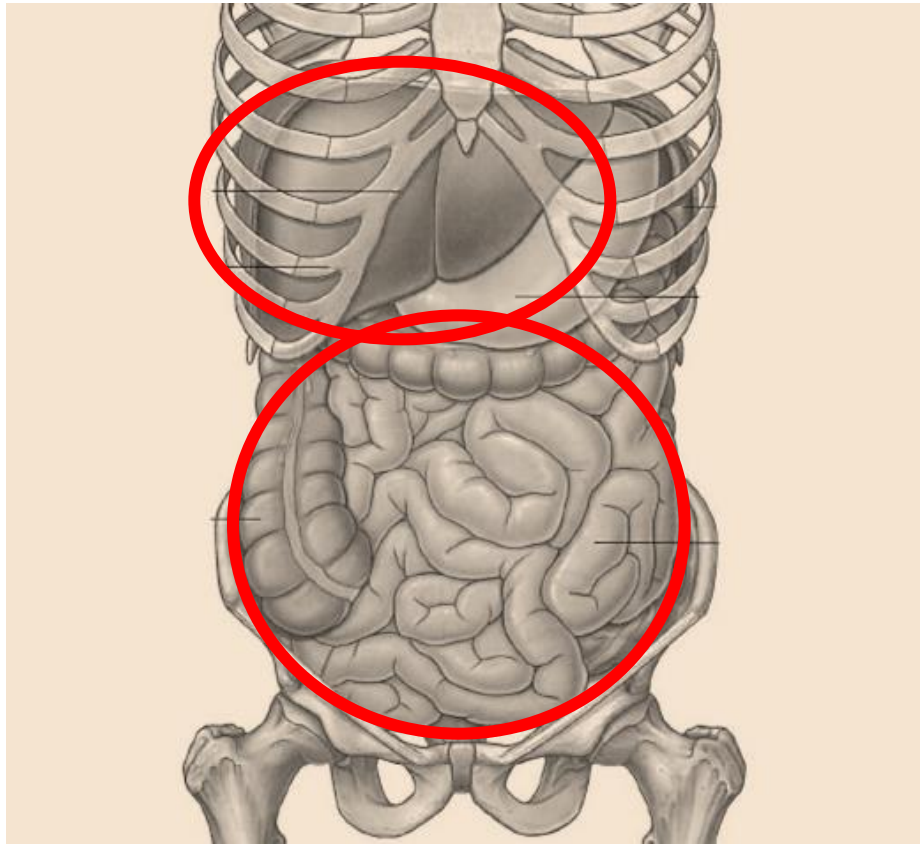
- Symptomatic: signs/symptoms related to location and size of tumor
  - Vague GI pain or discomfort
  - GI hemorrhage
  - Anemia
  - Anorexia, weight loss, nausea, fatigue, and additional GI complaints
  - Acute intraperitoneal bleeding or perforation

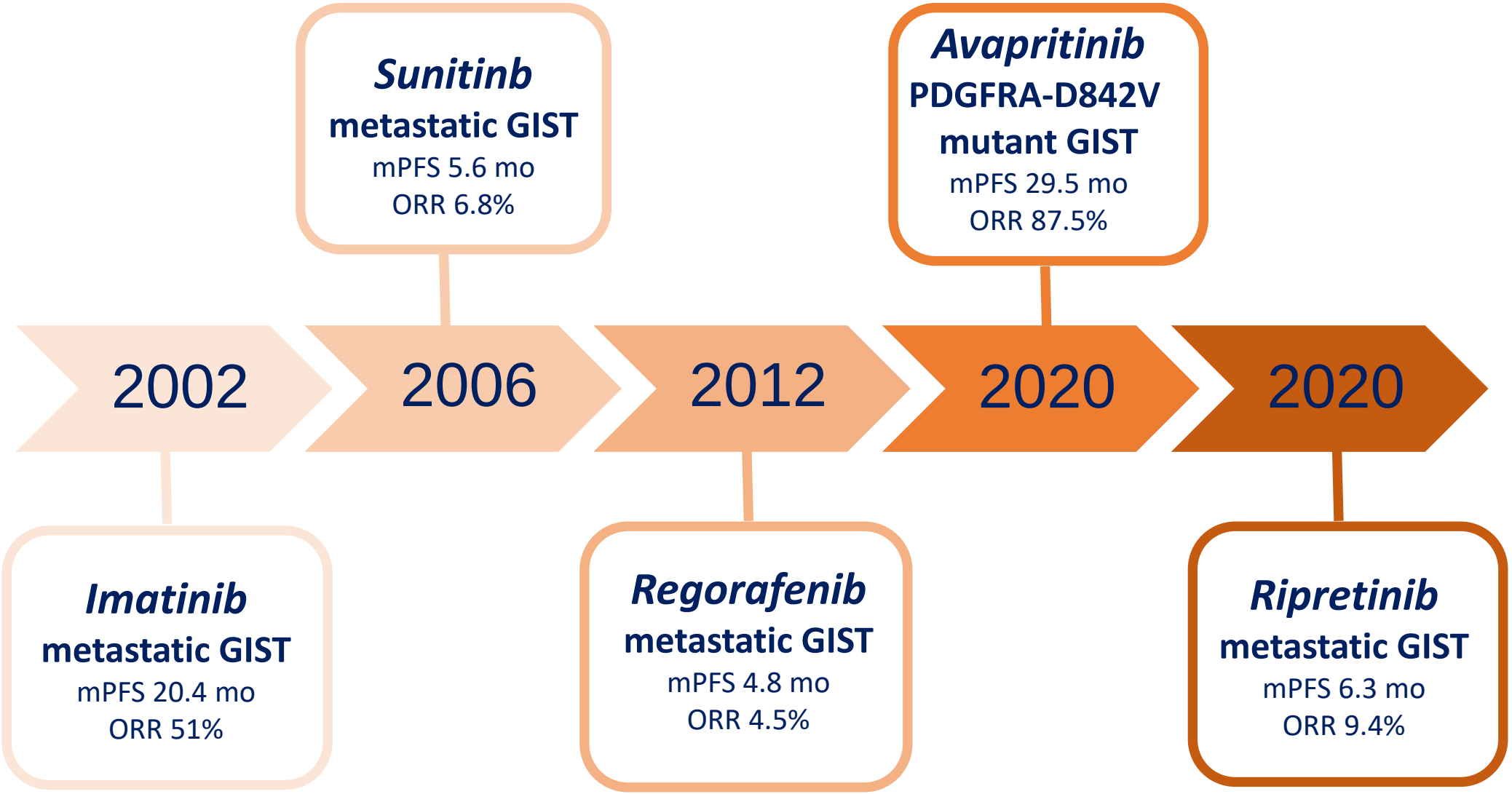
Hum Pathol. 1999

GIST: standard treatment



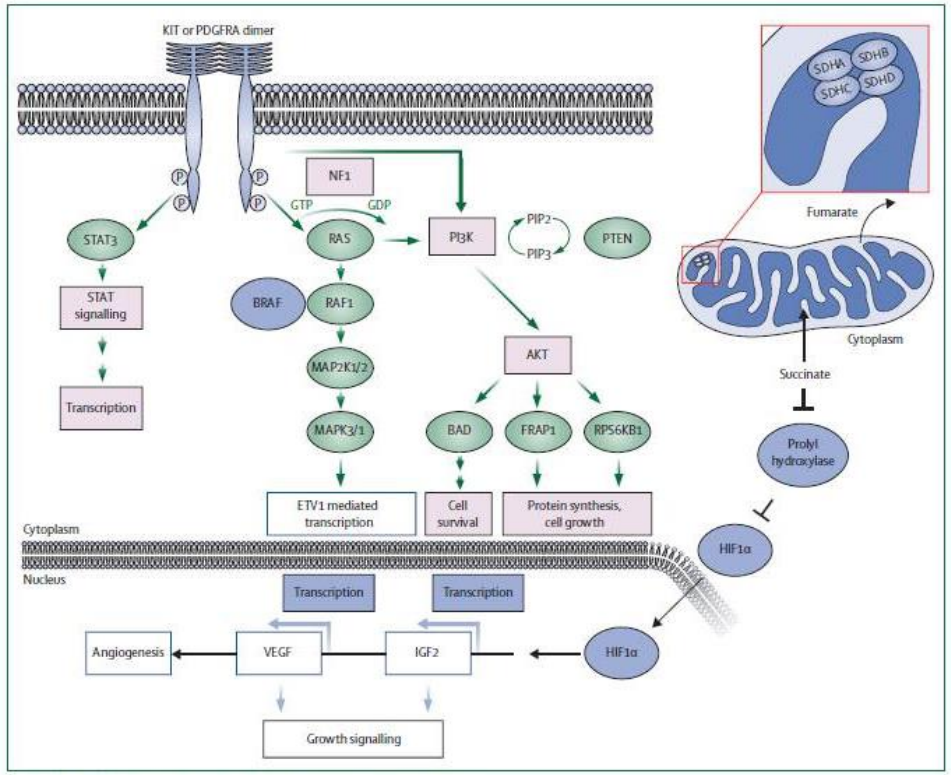
Relapse patterns



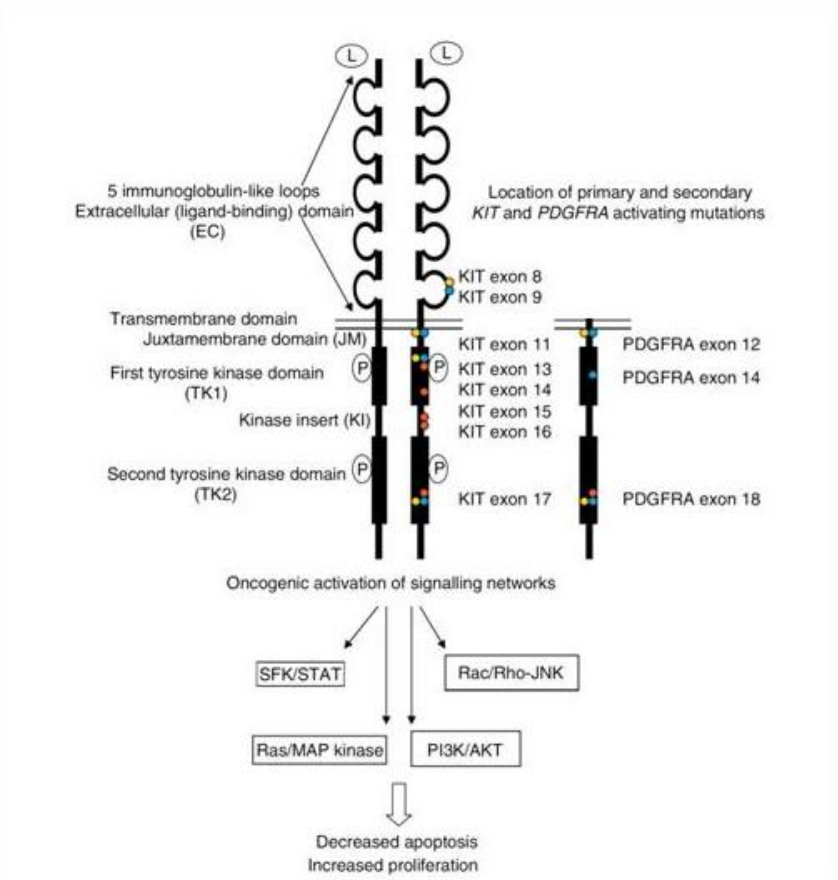


Verweji J et al. Lancet 2004
Demetri GD et al. Lancet 2006
Demetri GD et al. Lancet 2013
Blay JY et al. Lancet Oncol 2020
Heinrich MC et al. Lancet Oncol 2020

Molecular biology



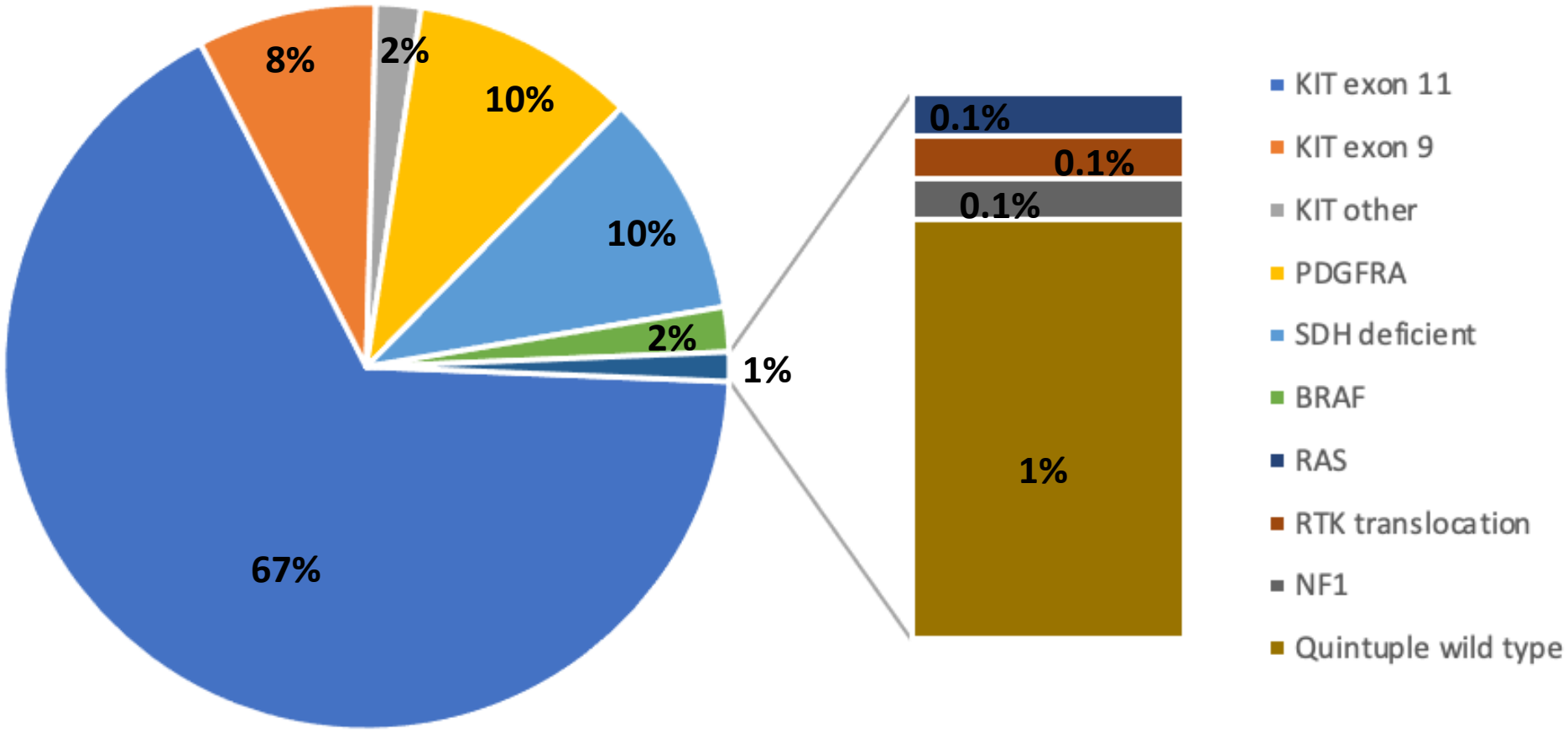
KIT **PDGFRA**



Joensuu *H et al. Lancet 2013*

Lasota J et al, Histopathology 2008

GIST KIT/PDGFRA *WT*



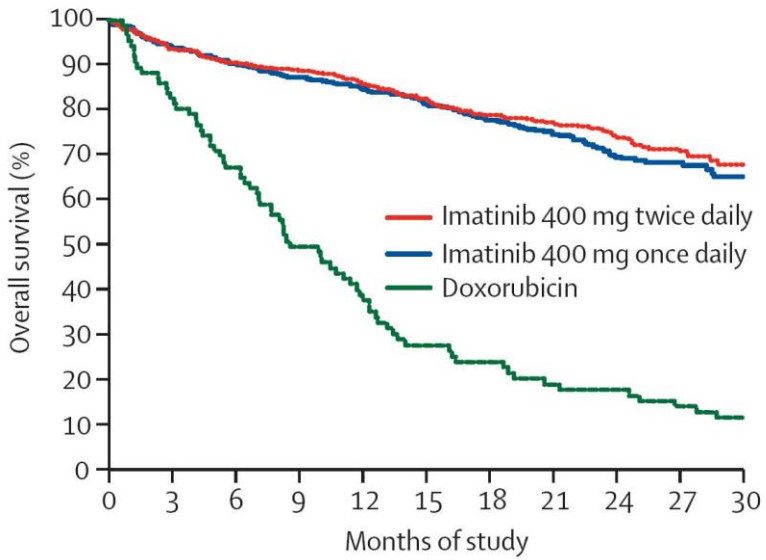
Adattato da C.M. Kelly et al, J Hematol Oncol 2021

Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

*Jaap Verweij, Paolo G Casali, John Zalcberg, Axel LeCesne, Peter Reichardt, Jean-Yves Blay, Rolf Issels, Allan van Oosterom, Pancras C W Hogendoorn, Martine Van Glabbeke, Rossella Bertulli, Ian Judson, for the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group**

Lancet 2004; 364: 1127–134
See Comment page 1101

*Study investigators listed at end of report



	400 mg once a day (n=470)				400 mg twice a day (n=472)			
Grade	1	2	3	4	1	2	3	4
Any side-effect	98	215	123	29	41	190	201	36
Anaemia	257	128	26	7	195	187	55	24
Leucopenia	128	59	13	-	138	77	10	2
Granulocytopenia	96	63	20	13	89	81	22	11
Thrombocytopenia	18	3	5	2	19	6	2	4
Oedema	236	86	13	1	200	169	41	2
Fatigue	201	90	28	-	177	146	50	1
Fever	39	13	4	-	60	15	6	-
Pruritus	55	17	4	-	70	36	7	-
Rash	80	34	11	-	121	74	24	1
Anorexia	76	37	8	1	119	63	8	-
Constipation	52	18	4	1	61	19	7	-
Diarrhoea	160	58	7	1	170	73	25	-
Nausea	170	47	12	-	170	101	15	-
Vomiting	86	25	12	1	107	60	13	-
Bleeding	34	4	12	1	64	3	30	8
Infection	34	34	12	1	41	36	21	1
Dizziness	44	7	1	-	50	9	2	-
Arthralgia	50	11	-	-	56	15	4	-
Headache	59	15	1	-	54	8	4	-
Myalgia	87	27	1	-	91	35	5	-
Pleuritic pain	159	60	19	2	143	83	33	1
Cough	52	8	1	-	53	13	1	-
Dyspnoea	-	39	14	1	-	62	16	5
Renal or genitourinary	43	16	2	1	48	22	10	3

Data are number of patients who started per-protocol treatment.

Table 3: Side-effects by grade of toxic effect

IMATINIB

400mg/die

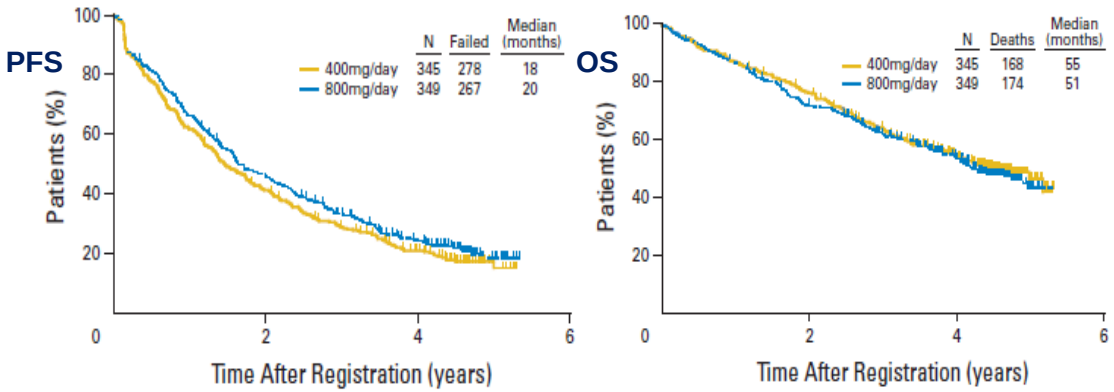
Lancet 2004;364:1127

VOLUME 26 · NUMBER 4 · FEBRUARY 1 2008

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase III Randomized, Intergroup Trial Assessing Imatinib Mesylate At Two Dose Levels in Patients With Unresectable or Metastatic Gastrointestinal Stromal Tumors Expressing the Kit Receptor Tyrosine Kinase: S0033

Charles D. Blanke, Cathryn Rankin, George D. Demetri, Christopher W. Ryan, Margaret von Mehren, Robert S. Benjamin, A. Kevin Raymond, Vivien H.C. Bramwell, Laurence H. Baker, Robert G. Maki, Michael Tanaka, J. Randolph Hecht, Michael C. Heinrich, Christopher D.M. Fletcher, John J. Crowley, and Ernest C. Borden

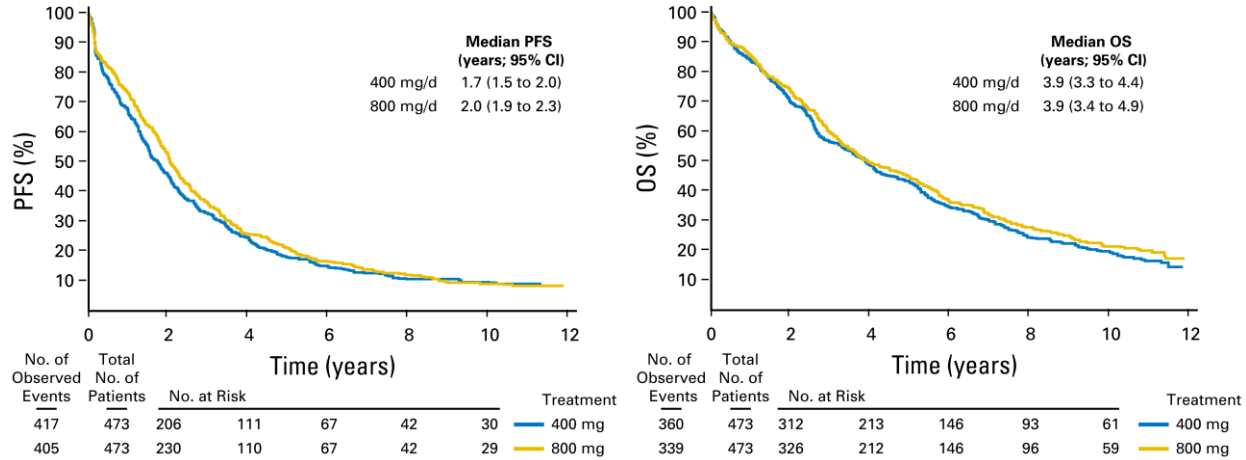


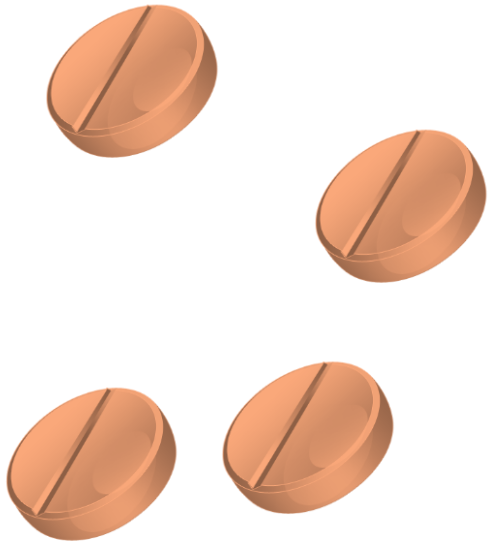
VOLUME 35 · NUMBER 15 · MAY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

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





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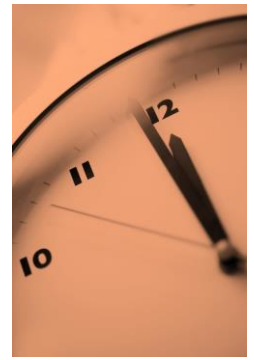
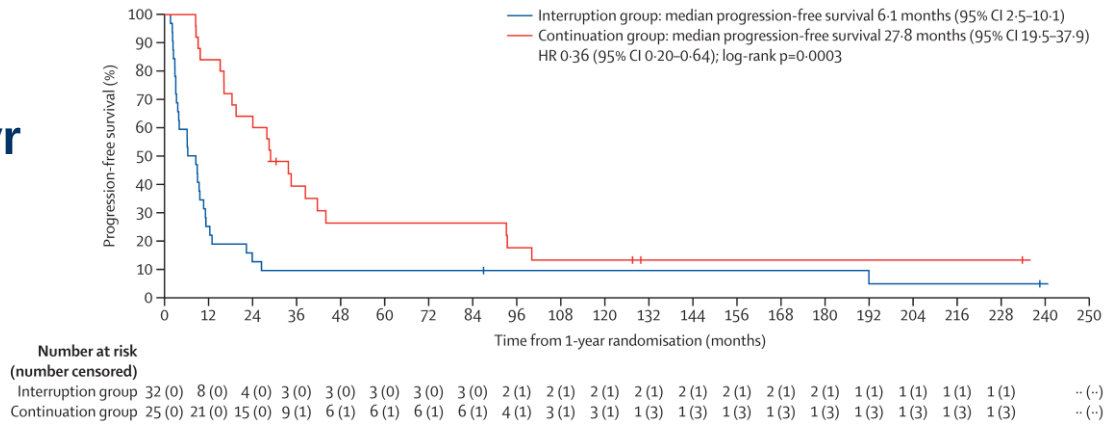


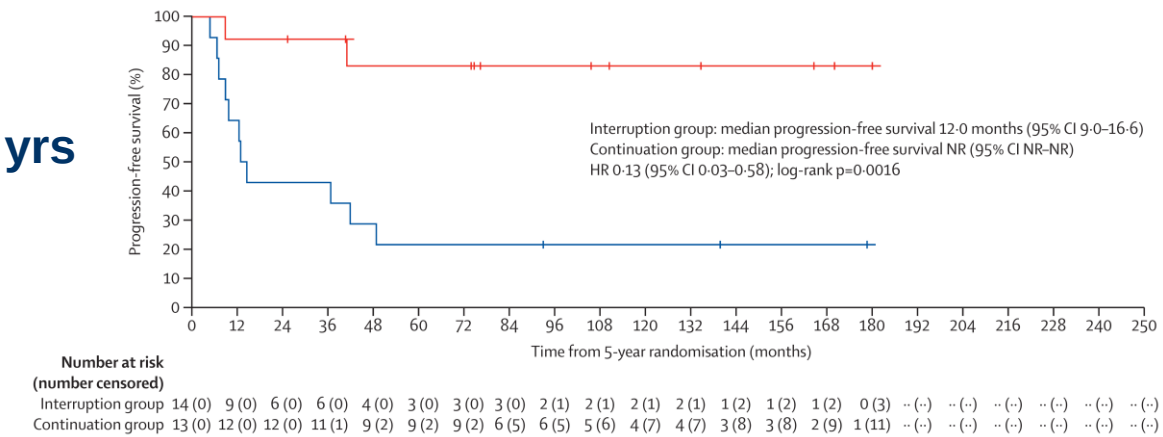
Discontinuation versus continuation of imatinib in patients with advanced gastrointestinal stromal tumours (BFR14): exploratory long-term follow-up of an open-label, multicentre, randomised, phase 3 trial

Jean-Yves Blay, Quentin Devin*, Florence Duffaud, Maud Toulmonde, Nelly Firmin, Olivier Collard, Emmanuelle Bompas, Benjamin Verret, Isabelle Ray-Coquard, Sebastien Salas, Clemence Henon, Charles Honoré, Mehdi Brahmi, Armelle Dufresne, Marc Pracht, Alice Hervieu, Nicolas Penel, Francois Bertucci, Maria Rios, Esma Saada-Bouzid, Pauline Soibinet, David Perol, Sylvie Chabaud, Antoine Italiano, Axel Le Cesne*

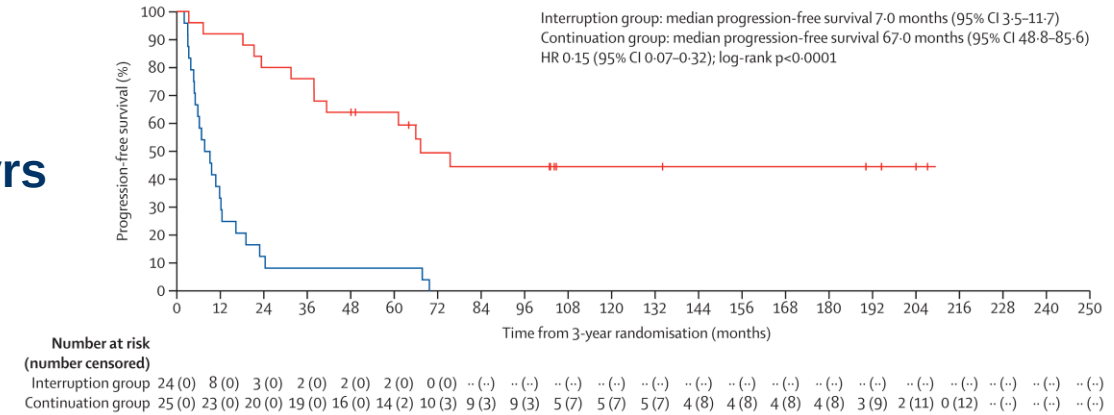
1 yr



5 yrs

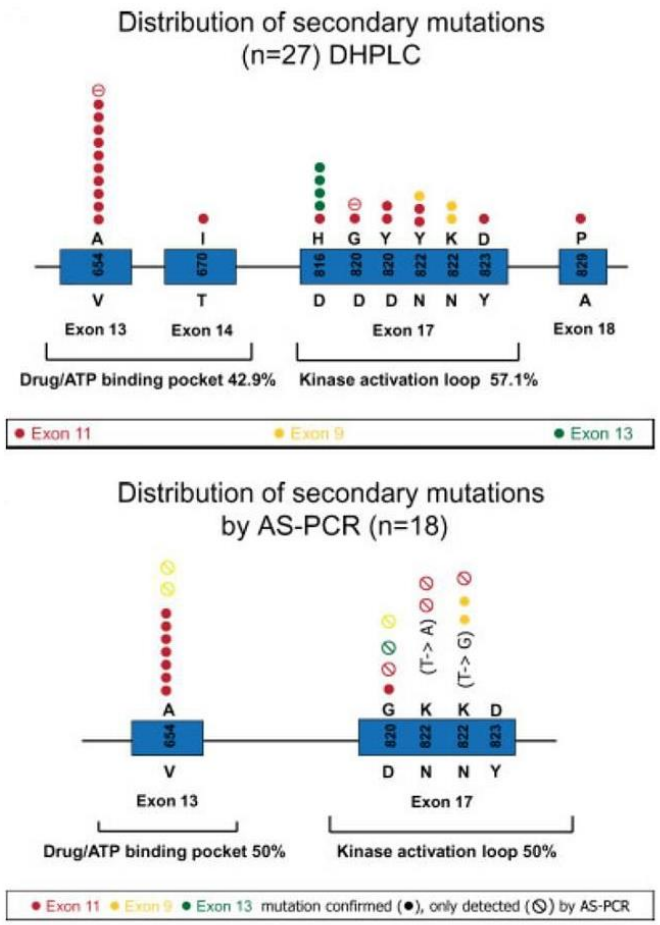


3 yrs



Lancet Oncology 2024

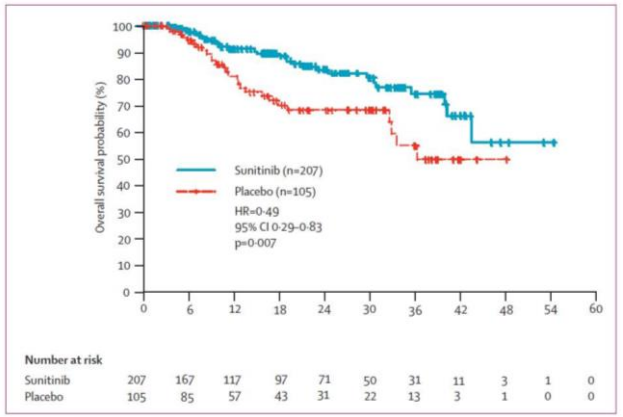
Secondary resistance: molecular heterogeneity

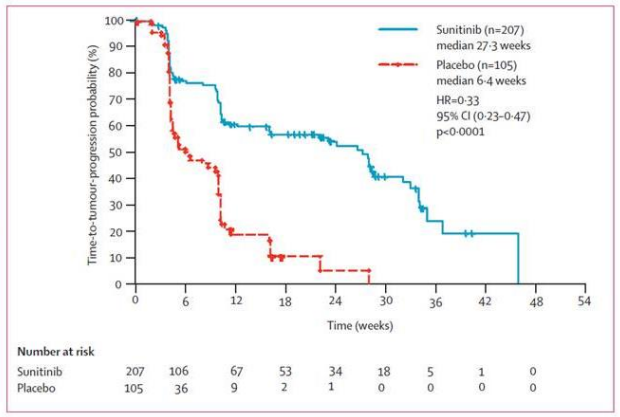


Liegl B, J Pathol, 2008

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





	Sunitinib (n=202)			Placebo (n=102)		
	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Non-haematological*						
Fatigue	58 (29%)	10 (5%)	0 (0%)	20 (20%)	2 (2%)	0 (0%)
Diarrhoea	52 (26%)	7 (3%)	0 (0%)	8 (8%)	0 (0%)	0 (0%)
Skin discolouration	50 (25%)	0 (0%)	0 (0%)	6 (6%)	0 (0%)	0 (0%)
Nausea	47 (23%)	1 (1%)	0 (0%)	10 (10%)	1 (1%)	0 (0%)
Anorexia	38 (19%)	0 (0%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Dysgeusia	36 (18%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Stomatitis	30 (15%)	1 (1%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Vomiting	30 (15%)	1 (1%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Hand-foot syndrome	19 (9%)	9 (4%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Rash	24 (12%)	2 (1%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Asthenia	18 (9%)	6 (3%)	0 (0%)	2 (2%)	2 (2%)	0 (0%)
Mucosal inflammation	24 (12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dyspepsia	22 (11%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Hypertension	15 (8%)	6 (3%)	0 (0%)	4 (4%)	0 (0%)	0 (0%)
Epistaxis	14 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hair-colour changes	14 (7%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Dry mouth	13 (6%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Glossodynia	11 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Haematological						
Anaemia†	117 (58%)	7 (4%)	0 (0%)	59 (58%)	2 (2%)	0 (0%)
Leucopenia	104 (52%)	7 (4%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Neutropenia	86 (43%)	17 (8%)	3 (2%)	4 (4%)	0 (0%)	0 (0%)
Lymphopenia	80 (40%)	18 (9%)	1 (1%)	31 (30%)	2 (2%)	1 (1%)
Thrombocytopenia	72 (36%)	8 (4%)	1 (1%)	4 (4%)	0 (0%)	0 (0%)

Data are number (%). *Treatment-related. †Anaemia was included in the table, despite a difference of less than 5% between the treatment groups, because of its frequency and clinical relevance in GIST.

Table 2: **Adverse events that occurred with a frequency of at least 5% greater on sunitinib than on placebo in per-protocol population**

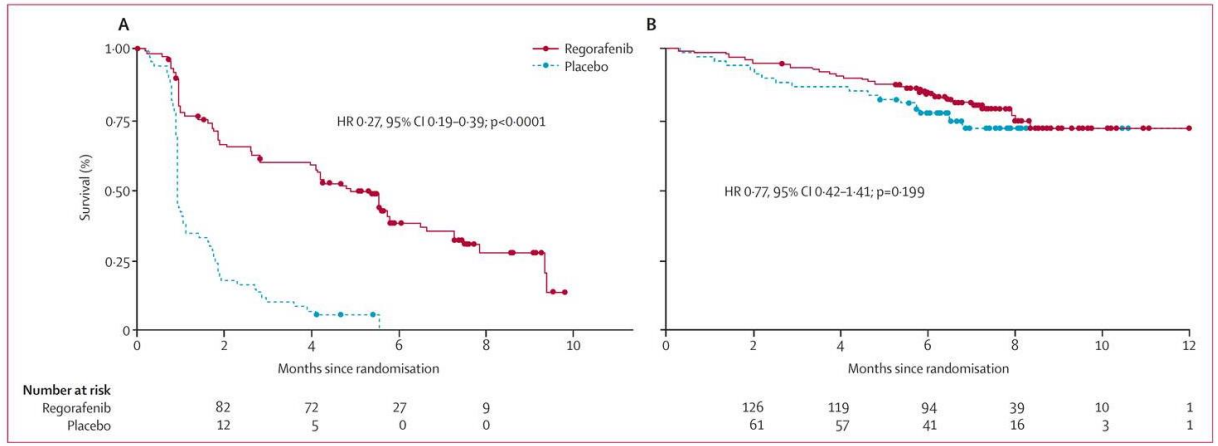
50 mg/die, 4 settimane on, 2 settimane off

37.5 mg/die

Lancet 2006;368:1329

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 G Casali, on behalf of all GRID study investigators**



	Regorafenib (N=132*)			Placebo (N=66)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any event	130 (98%)	77 (58%)	2 (2%)	45 (68%)	5 (8%)	1 (2%)
Hand-foot skin reaction	74 (56%)	26 (20%)	0	9 (14%)	0	0
Hypertension	64 (49%)	30 (23%)	1 (1%)	11 (17%)	2 (3%)	0
Diarrhoea	53 (40%)	7 (5%)	0	3 (5%)	0	0
Fatigue	51 (39%)	3 (2%)	0	18 (27%)	0	0
Oral mucositis	50 (38%)	2 (2%)	0	5 (8%)	1 (2%)	0
Alopecia	31 (24%)	2 (2%)	0	1 (2%)	0	0
Hoarseness	29 (22%)	0	0	3 (5%)	0	0
Anorexia	27 (21%)	0	0	5 (8%)	0	0
Rash, maculopapular	24 (18%)	3 (2%)	0	2 (3%)	0	0
Nausea	21 (16%)	1 (1%)	0	6 (9%)	1 (2%)	0
Constipation	20 (15%)	1 (1%)	0	4 (6%)	0	0
Myalgia	18 (14%)	1 (1%)	0	6 (9%)	0	0
Voice alteration	14 (11%)	0	0	2 (3%)	0	0

Data are n (%). *Excluding one patient who did not receive study treatment.

Table 2: Drug-related adverse events in ≥10% of patients during double-blind treatment period

REGORAFENIB

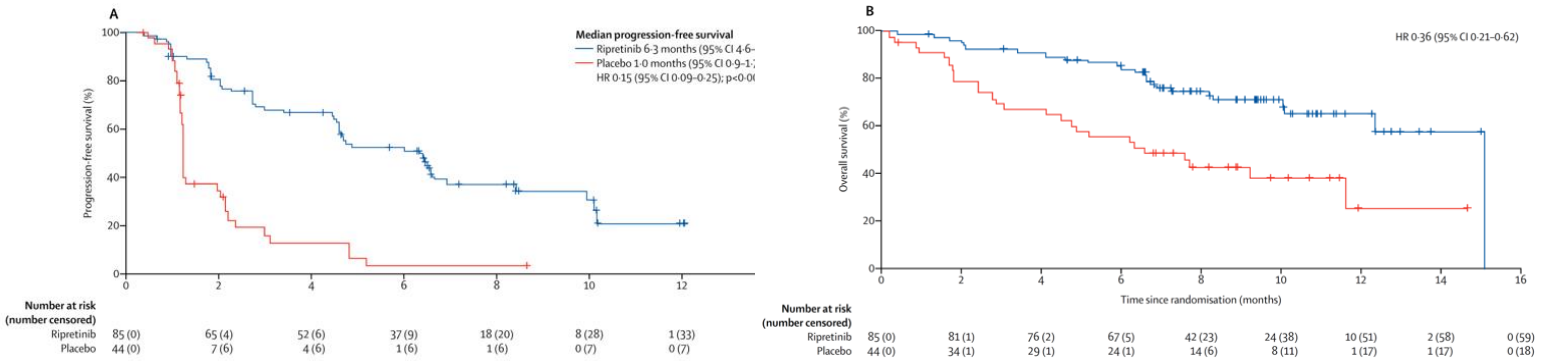
160 mg/day**, 3 settimane on, 1 settimana off**

Lancet 2013;381:295

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

Lancet Oncol 2020; 21: 923-34



	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

RIPRETINIB

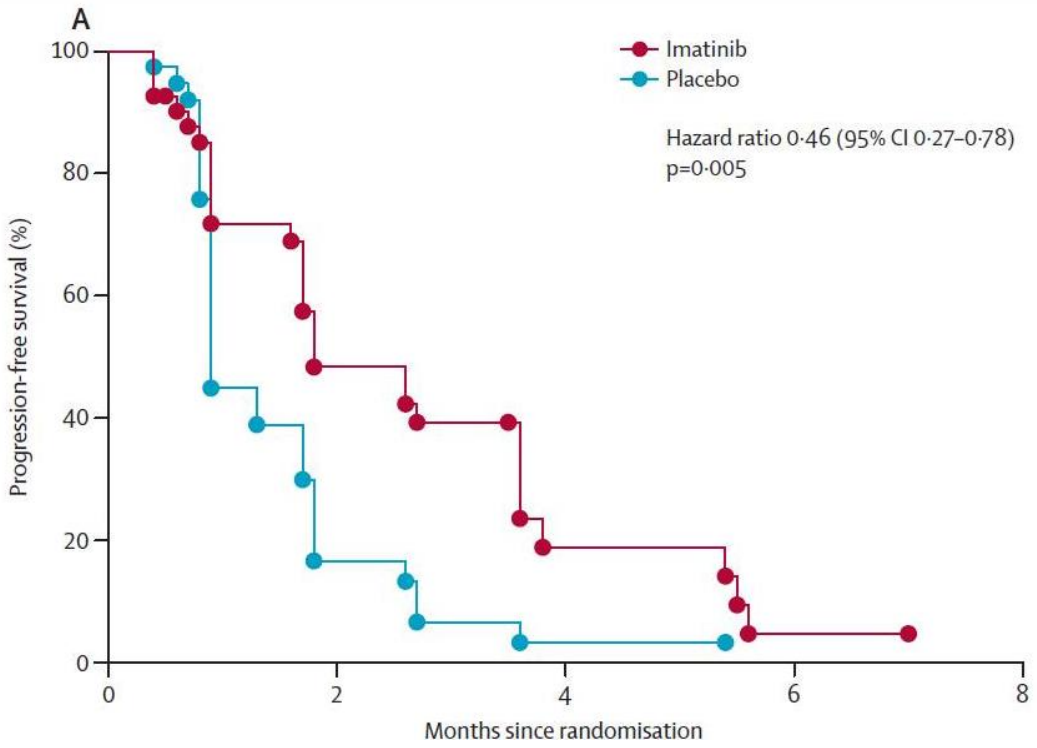
150 mg/die

Lancet Oncol 2020; 381:295

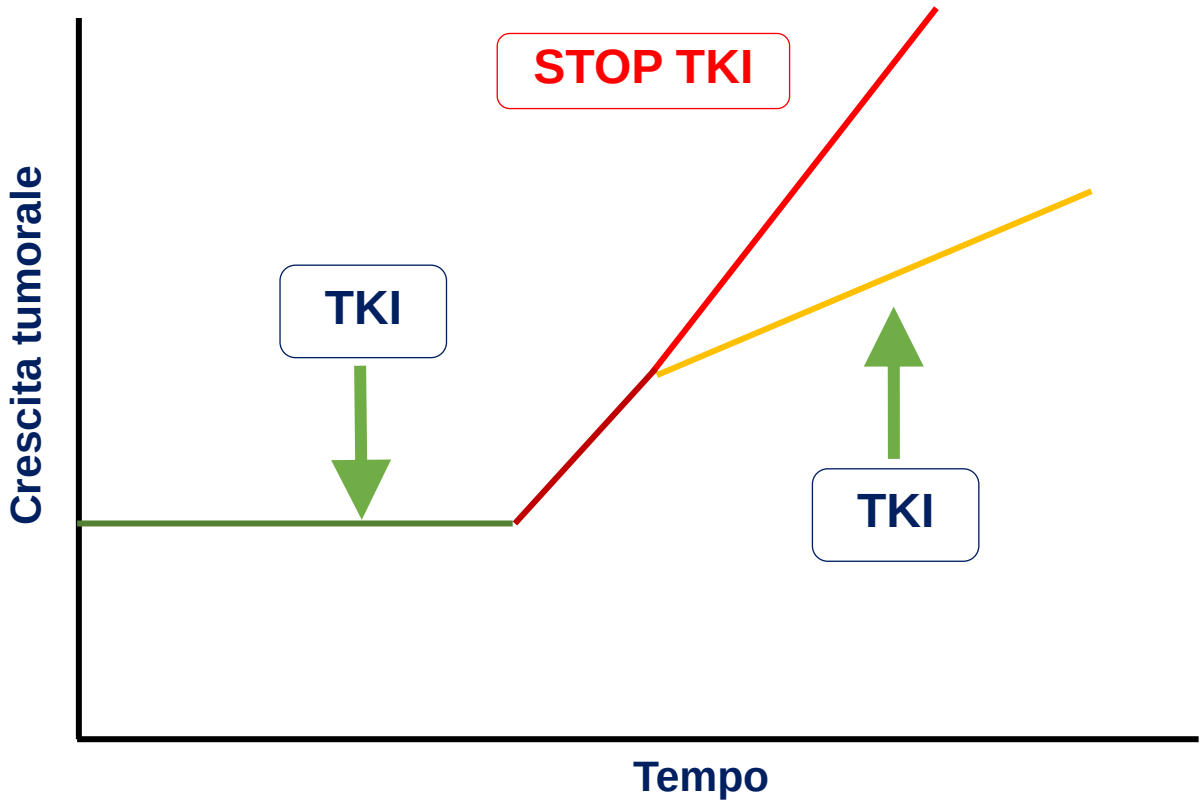
TKIs beyond progression

Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial

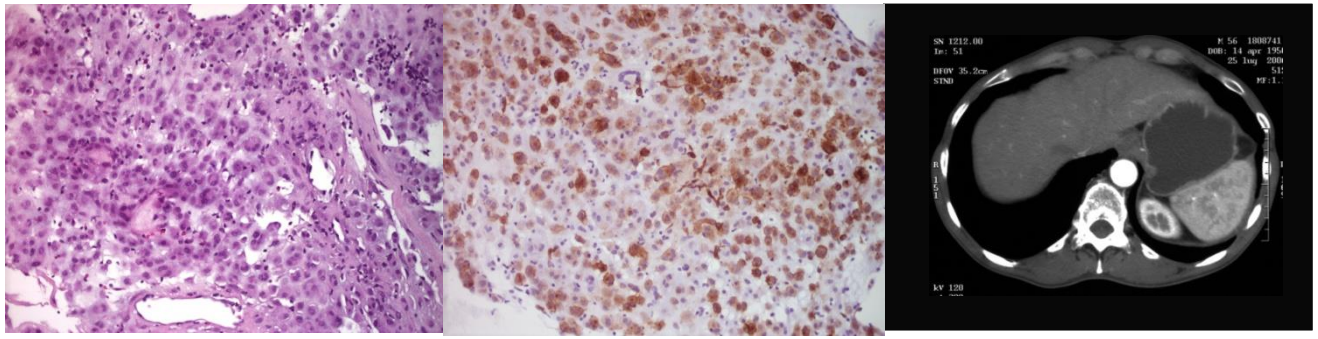
Yoon-Koo Kang, Min-Hee Ryu, Changhoon Yoo, Baek-Yeol Ryoo, Hyun Jin Kim, Jong Jin Lee, Byung-Ho Nam, Nikhil Ramaiya, Jyothi Jagannathan, George D Demetri

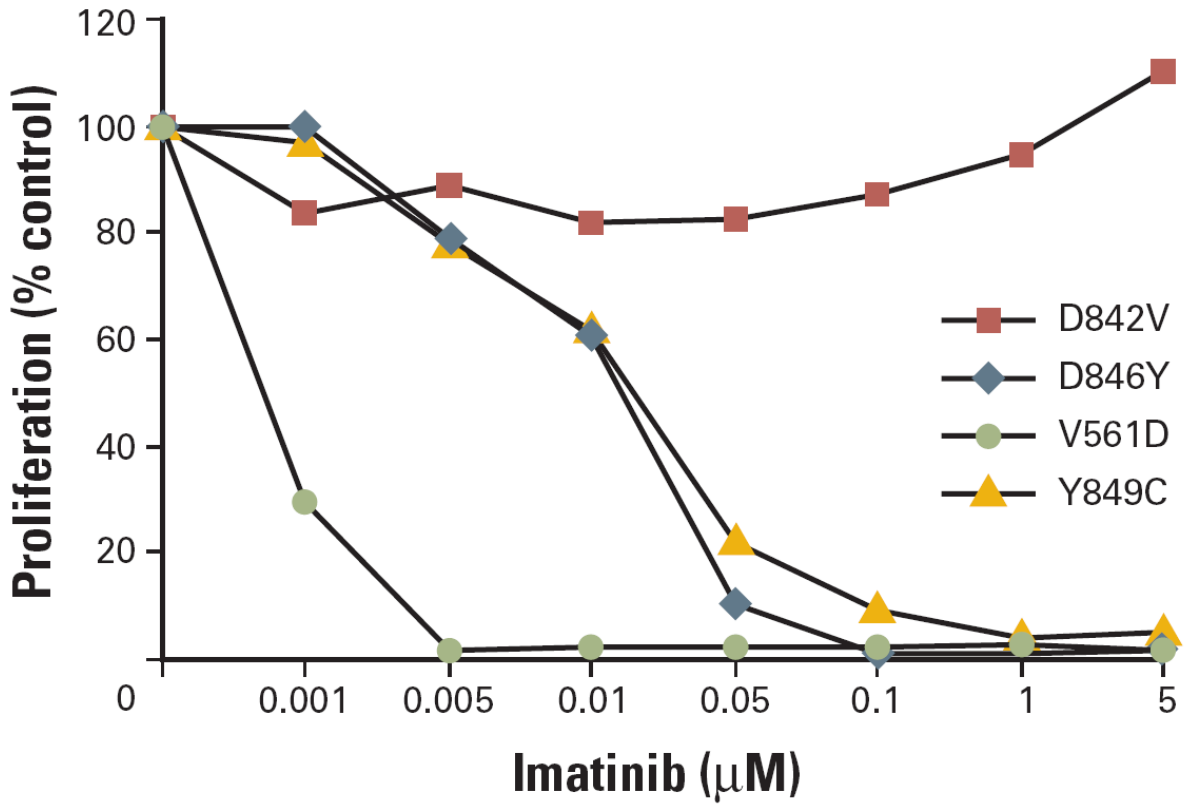


Lancet Oncol 2013



PDGFRA





Corless CL, J Clin Oncol 2005

Avapritinib in D842V

European Journal of Cancer 145 (2021) 132–142

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

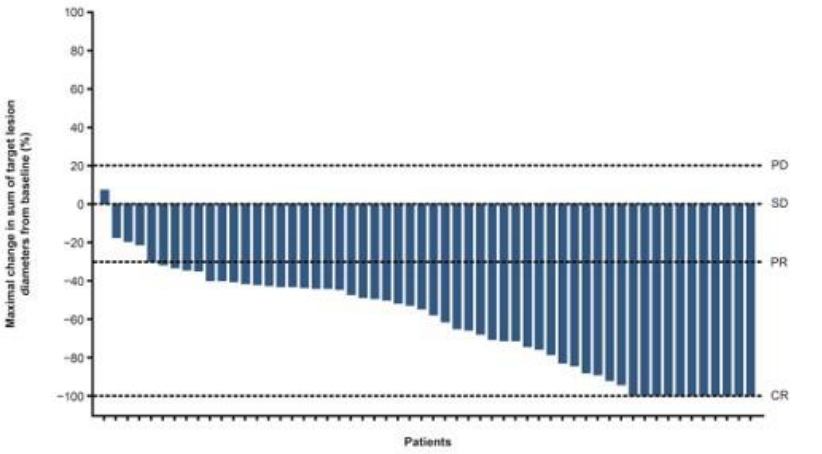
Original Research

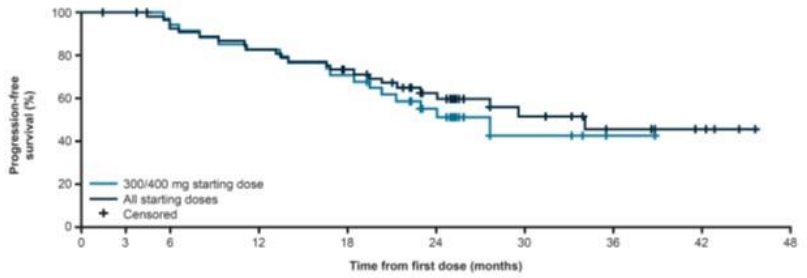
Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: Long-term efficacy and safety data from the NAVIGATOR phase I trial

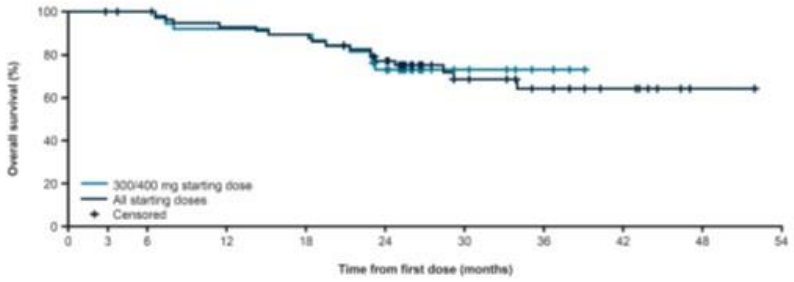
Robin L. Jones [a,*], César Serrano [b], Margaret von Mehren [c], Suzanne George [d], Michael C. Heinrich [e], Yoon-Koo Kang [f], Patrick Schöffski [g], Philippe A. Cassier [h], Olivier Mir [i], Sant P. Chawla [j], Ferry A.L.M. Eskens [k], Piotr Rutkowski [l], William D. Tap [m], Teresa Zhou [n], Maria Roche [n], Sebastian Bauer [o]

AVAPRITINIB

300 mg/die



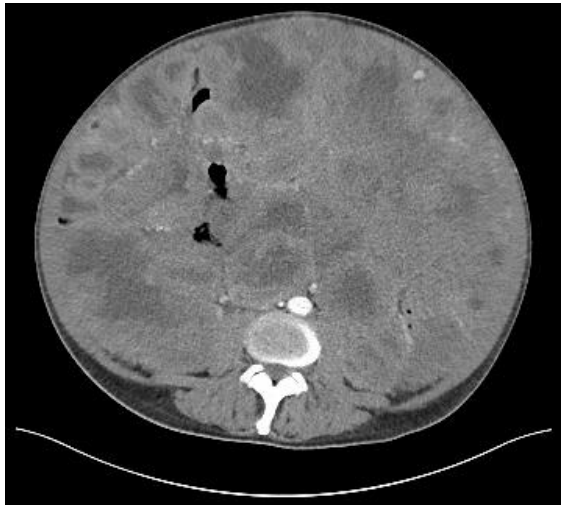




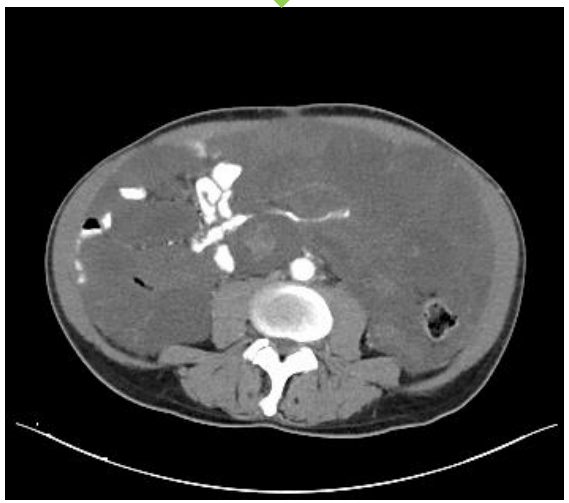
Any-cause adverse events occurring in ≥20% of patients in the safety population and the *PDGFRA* D842V population.

Preferred term, n (%)	*PDGFRA* D842V population (n = 56)	Safety population (N = 250)
Nausea	38 (68)	161 (64)
Fatigue	35 (63)	157 (63)
Anaemia	37 (66)	136 (54)
Diarrhoea	37 (66)	112 (45)
Periorbital oedema	27 (48)	110 (44)
Vomiting	21 (38)	106 (42)
Decreased appetite	23 (41)	101 (40)
Increased lacrimation	21 (38)	88 (35)
Memory impairment	23 (41)	81 (32)
Peripheral oedema	21 (38)	80 (32)
Abdominal pain	19 (34)	64 (26)
Constipation	12 (21)	64 (26)
Hair colour changes	16 (29)	62 (25)
Dizziness	16 (29)	59 (24)
Face oedema	13 (23)	57 (23)
Increased blood bilirubin	16 (29)	54 (22)
Hypokalaemia	14 (25)	48 (19)
Headache	13 (23)	48 (19)
Dysgeusia	13 (23)	47 (19)
Decreased weight	15 (27)	46 (18)
Dyspepsia	13 (23)	44 (18)
Cough	15 (27)	39 (16)
Neutropenia	14 (25)	29 (12)
Upper respiratory tract infection	12 (21)	27 (11)

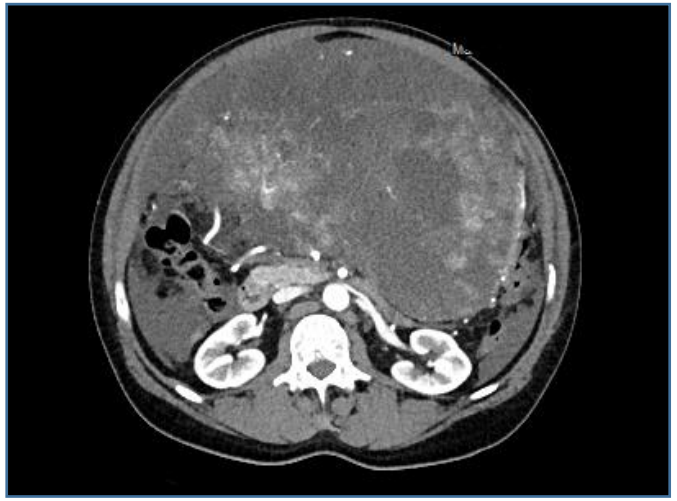
Imatinib



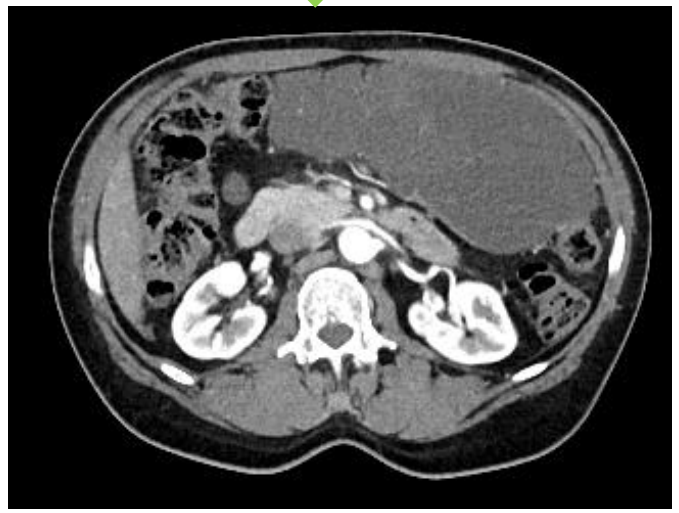
+ 1 month

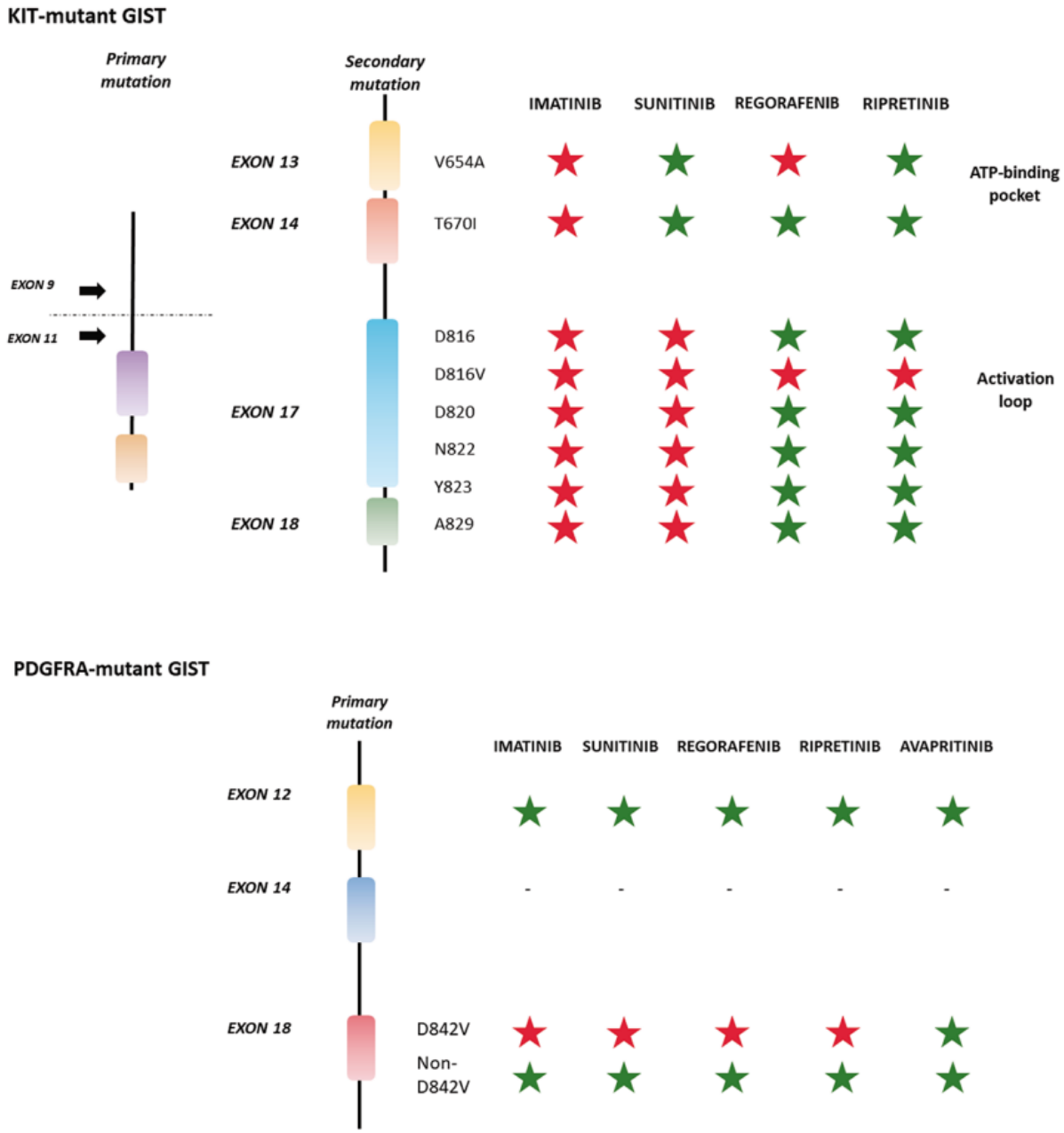


Avapritinib in D842V

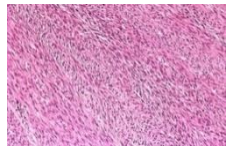


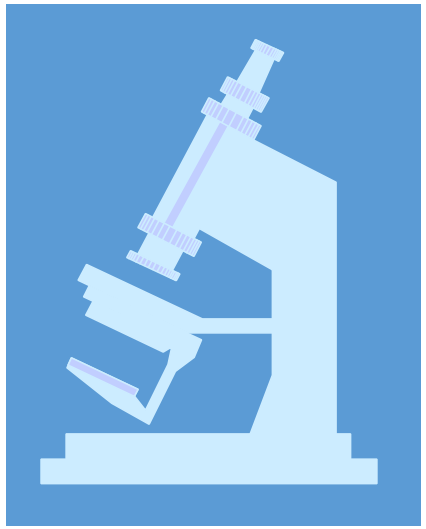
+ 2 months

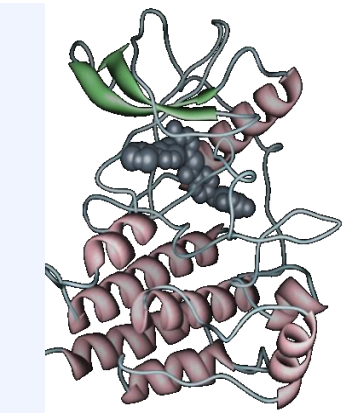


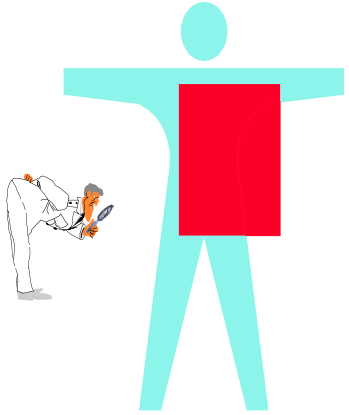


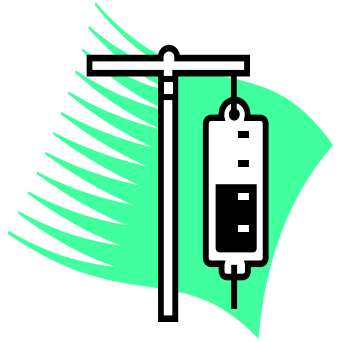
Lostes MJ et al. Ther Adv Med Oncol 2021











VOLUME 25 · NUMBER 13 · MAY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

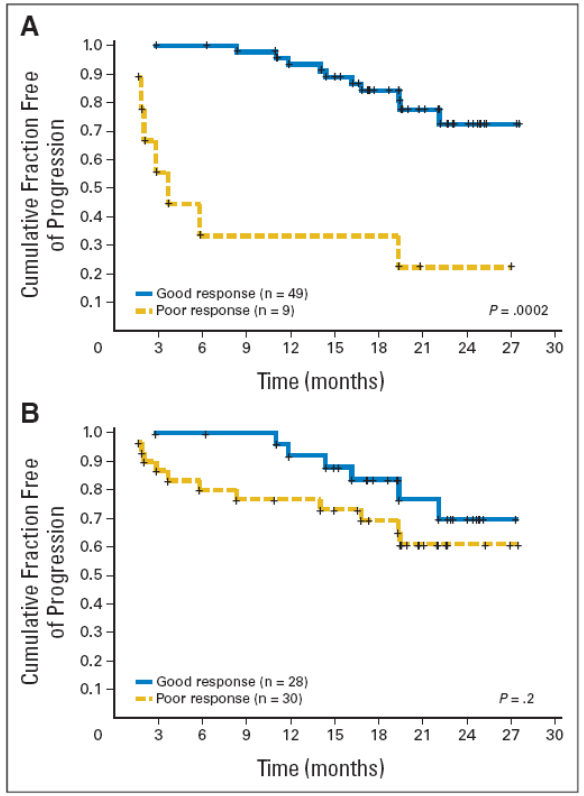
ORIGINAL REPORT

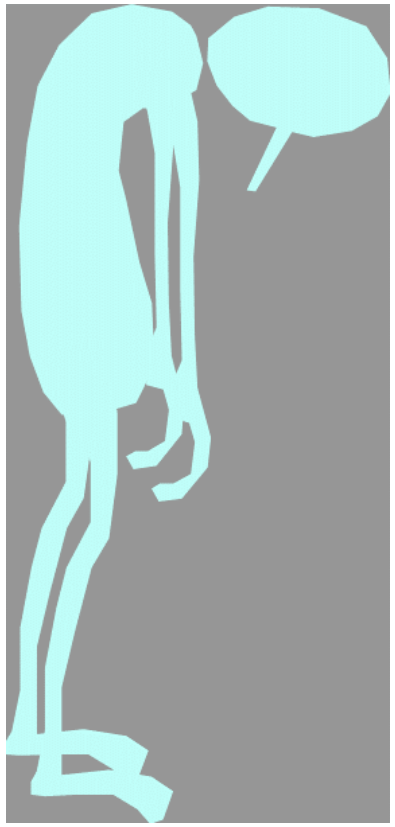
We Should Desist Using RECIST, at Least in GIST

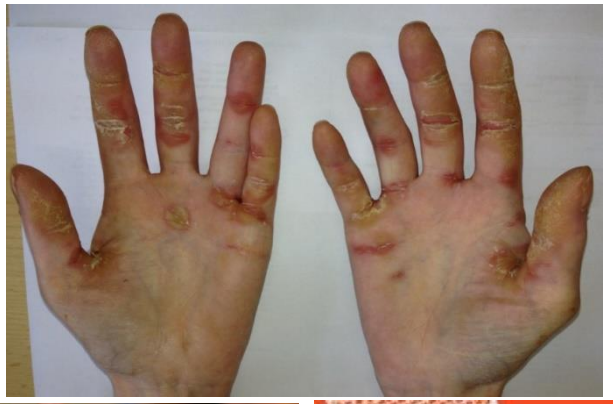
Robert S. Benjamin, Haesun Choi, Homer A. Macapinlac, Michael A. Burgess, Shreyaskumar R. Patel, Lei L. Chen, Donald A. Podoloff, and Chuslip Charnsangavej

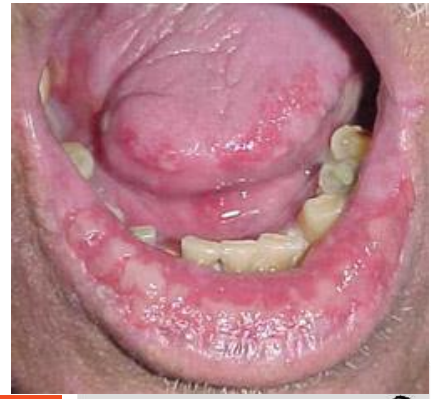
Choi's

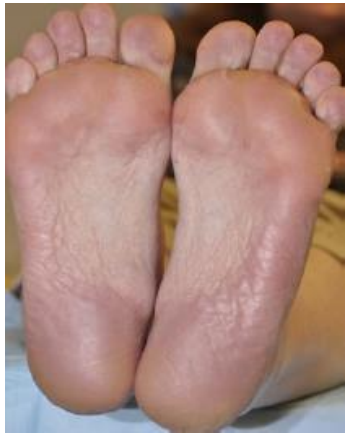
RECIST

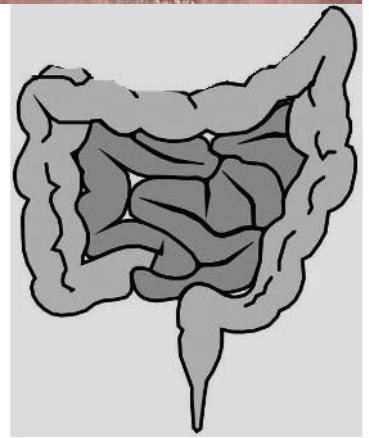












The Oncologist®

Gastrointestinal Cancer

Optimizing Tyrosine Kinase Inhibitor Therapy in Gastrointestinal Stromal Tumors: Exploring the Benefits of Continuous Kinase Suppression

Axel Le Cesne,[a] Jean-Yves Blay,[b] Peter Reichardt,[c] Heikki Joensuu[d]

ONCOLOGY LETTERS 8: 1793-1799, 2014

Alternative schedules or integration strategies to maximise treatment duration with sunitinib in patients with gastrointestinal stromal tumours

MARISTELLA SAPONARA[1,2], CRISTIAN LOLLI[1], MARGHERITA NANNINI[1], VALERIO DI SCIOSCIO[3], CARLA SERRA[4], ANNA MANDRIOLI[1], MARIA CATERINA PALLOTTI[1], GUIDO BIASCO[1,2] and MARIA ABBONDANZA PANTALEO[1,2]

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ESMO OPEN | CANCER HORIZONS

ORIGINAL RESEARCH

Standard versus personalized schedule of regorafenib in metastatic gastrointestinal stromal tumors: a retrospective, multicenter, real-world study

M. Nannini[1*†], A. Rizzo[1‡], M. C. Nigro[1], B. Vincenzi[2], A. Mazzocca[2], G. Grignani[3], A. Merlini[3], L. D'Ambrosio[3], F. Tolomeo[3], G. Badalamenti[4], L. Incorvaia[4], A. Bonasera[4], E. Fumagalli[5], D. Miliziano[5], F. Ligorio[5], A. Brunello[6], B. Chiusole[6], S. Gasperoni[7], M. Novelli[8] & M. A. Pantaleo[1,9]

The Oncologist®

Symptom Management and Supportive Care

Optimizing Treatment Outcomes With Regorafenib: Personalized Dosing and Other Strategies to Support Patient Care

Axel Grothey,[a] Suzanne George,[b] Eric van Cutsem,[c] Jean-Yves Blay,[d] Alberto Sobrero,[e] George D. Demetri[b]

[a]Mayo Clinic, Rochester, Minnesota, USA; [b]Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA; [c]University Hospital Gasthuisberg/Leuven, Leuven, Belgium; [d]Léon Bérard Centre and Claude Bernard University, Lyon, France; [e]IRCCS San Martino, Genoa, Italy

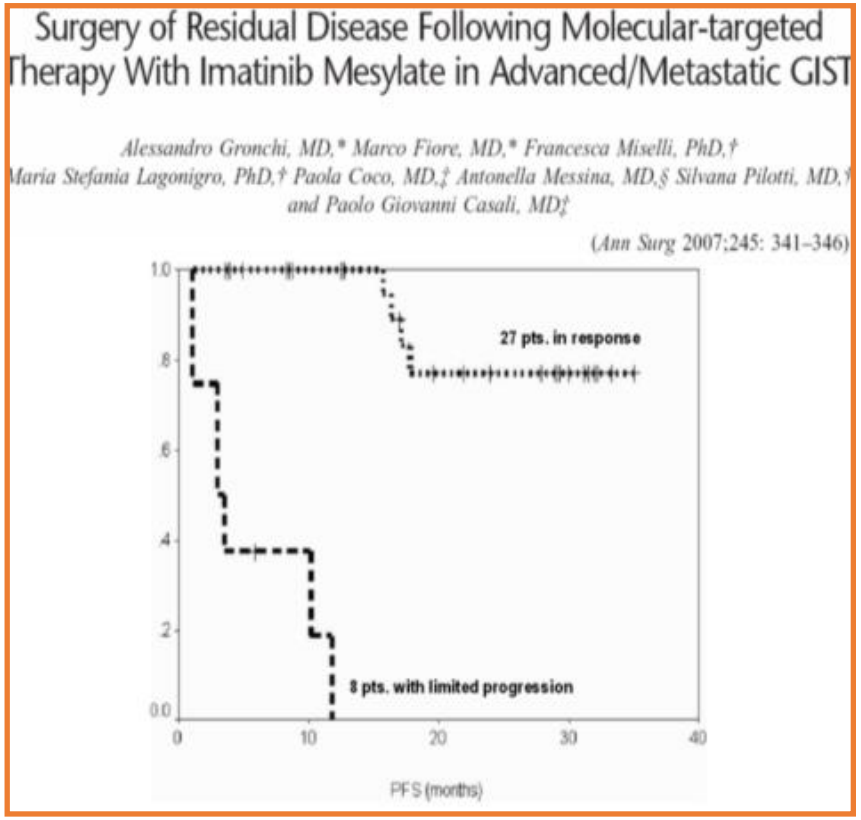
Surgery
of responding residual disease

VOLUME 24 · NUMBER 19 · MAY 20 2006

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Surgical Management of Advanced Gastrointestinal Stromal Tumors After Treatment With Targeted Systemic Therapy Using Kinase Inhibitors

Chandrajit P. Raut, Matthew Posner, Jayesh Desai, Jeffrey A. Morgan, Suzanne George, David Zahrieh, Christopher D.M. Fletcher, George D. Demetri, and Monica M. Bertagnolli

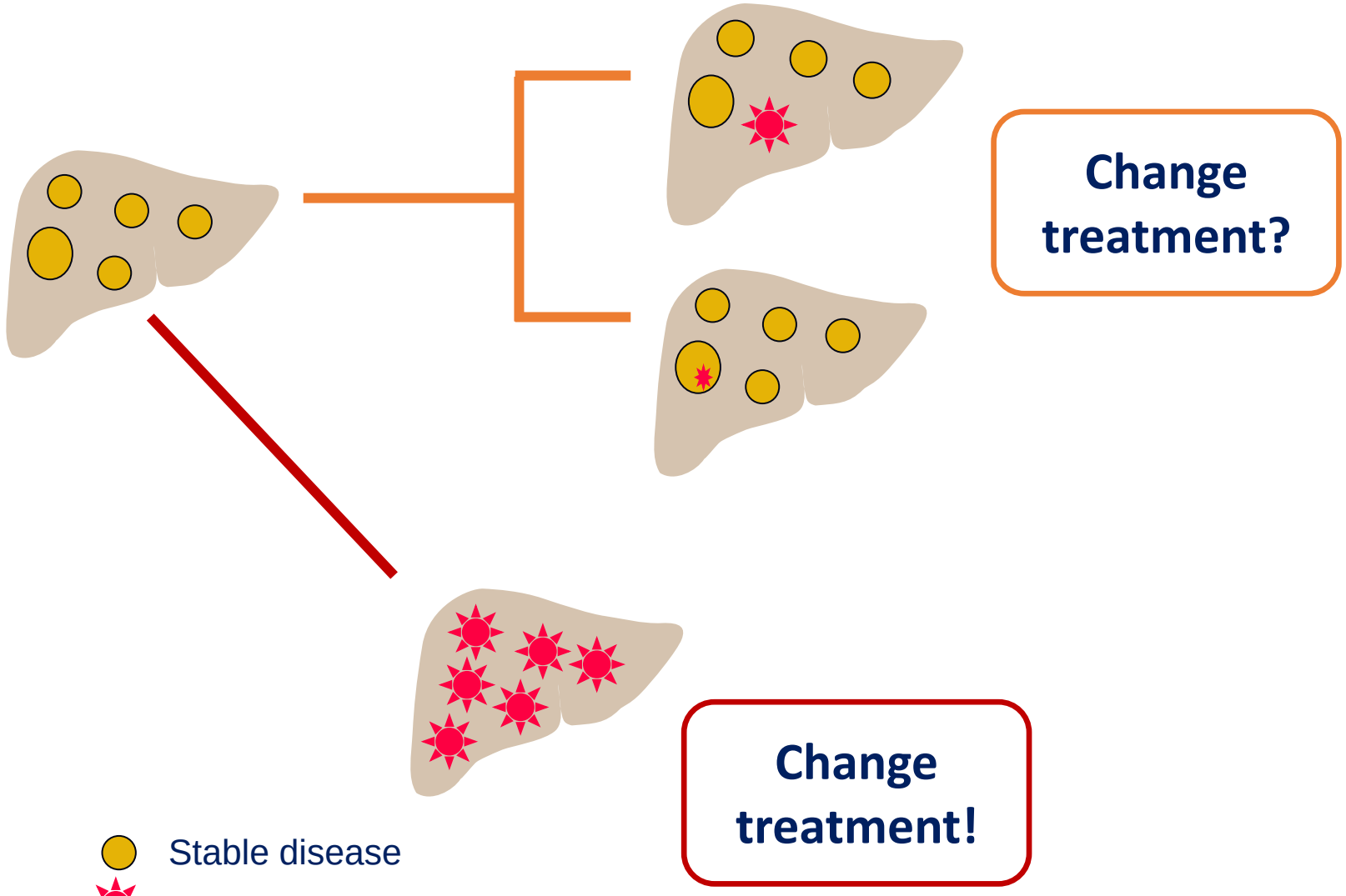


Surgery of Residual Disease Following Molecular-targeted Therapy With Imatinib Mesylate in Advanced/Metastatic GIST

Alessandro Gronchi, MD, Marco Fiore, MD,* Francesca Miselli, PhD,† Maria Stefania Lagonigro, PhD,† Paola Coco, MD,‡ Antonella Messina, MD,§ Silvana Pilotti, MD,¶ and Paolo Giovanni Casali, MD‡*

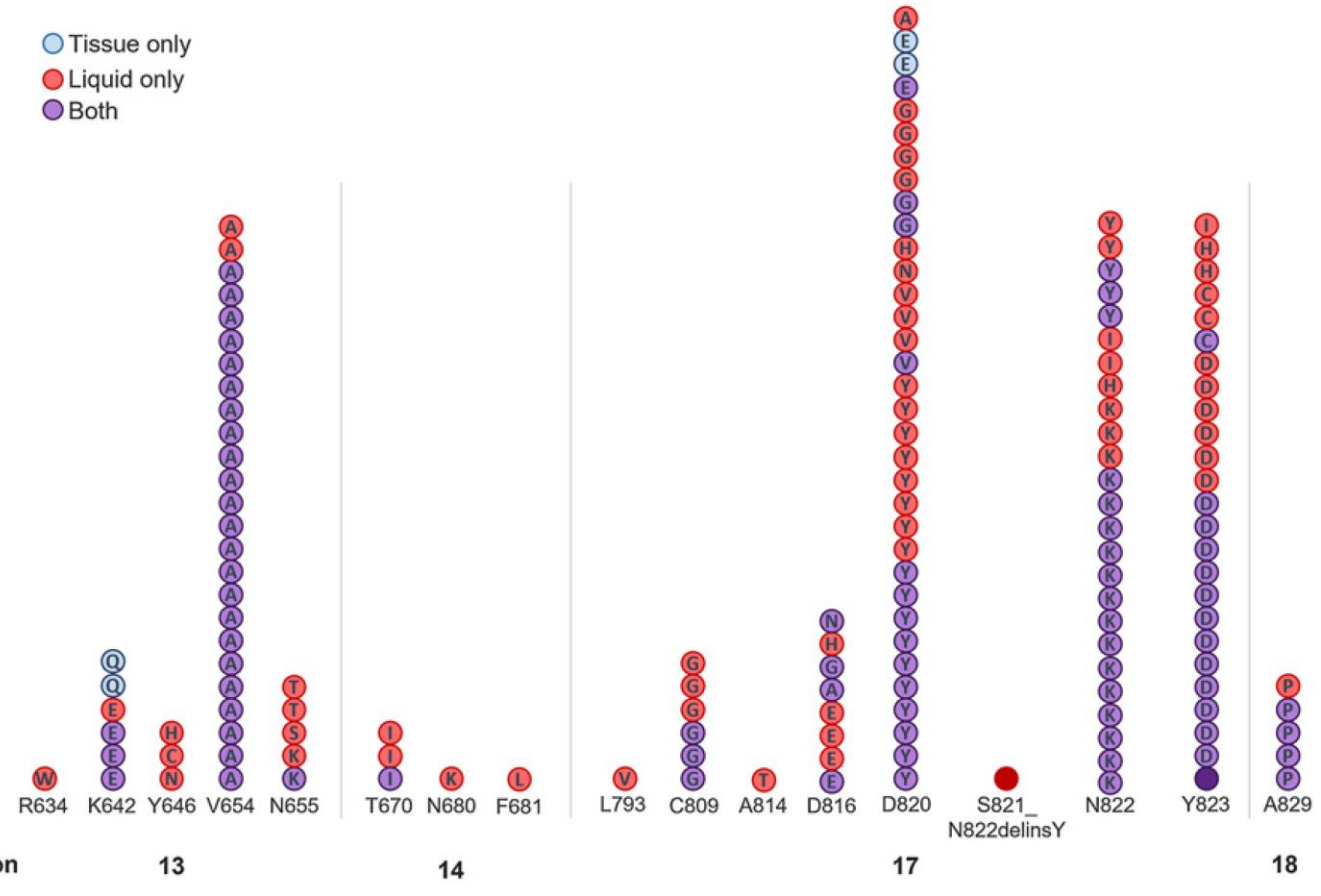
(*Ann Surg* 2007;245: 341–346)

Surgery of progressing disease



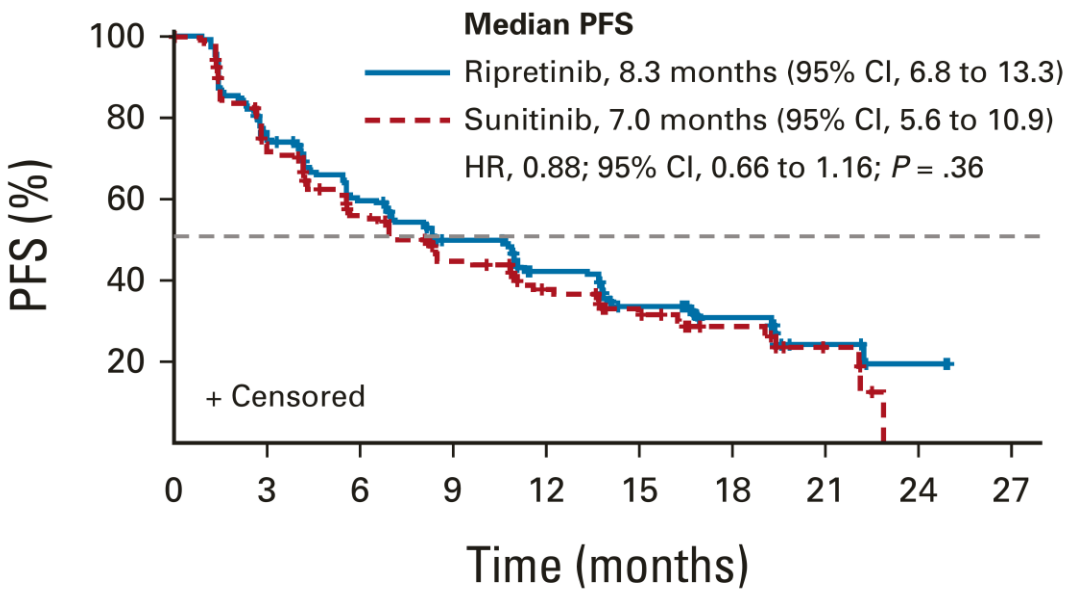
Clinical Activity of Ripretinib in Patients with Advanced Gastrointestinal Stromal Tumor Harboring Heterogeneous *KIT/PDGFRA* Mutations in the Phase III INVICTUS Study

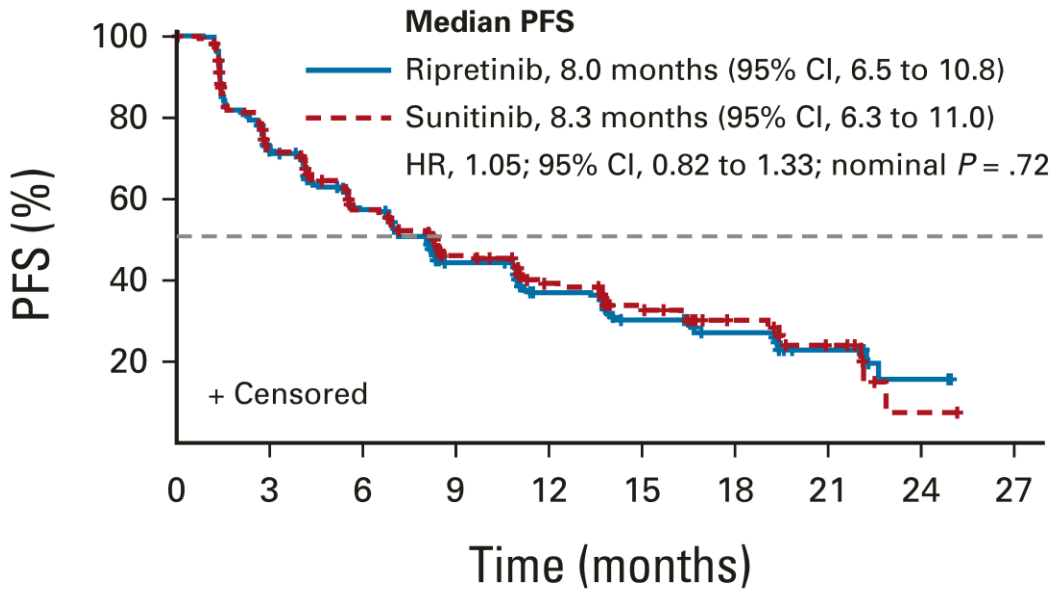
Sebastian Bauer[1,2], Michael C. Heinrich[3,4], Suzanne George[5], John R. Zalcberg[6], César Serrano[7], Hans Gelderblom[8], Robin L. Jones[9], Steven Attia[10], Gina D'Amato[11], Ping Chi[12], Peter Reichardt[13], Julie Meade[14], Ying Su[14], Rodrigo Ruiz-Soto[14], Jean-Yves Blay[15], Margaret von Mehren[16], and Patrick Schöffski[17]



Ripretinib Versus Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumor After Treatment With Imatinib (INTRIGUE): A Randomized, Open-Label, Phase III Trial

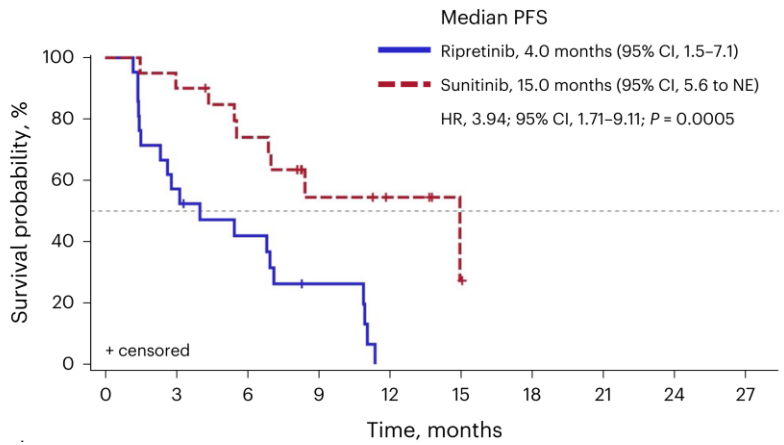
Sebastian Bauer, MD[1,2]; Robin L. Jones, MD, MBBS[3]; Jean-Yves Blay, MD, PhD[4]; Hans Gelderblom, MD, PhD[5]; Suzanne George, MD[6]; Patrick Schöffski, MD[7]; Margaret von Mehren, MD[8]; John R. Zalcberg, MD, PhD[9]; Yoon-Koo Kang, MD, PhD[10]; Albiruni Abdul Razak, MRCP, MBBCh[11]; Jonathan Trent, MD, PhD[12]; Steven Attia, DO[13]; Axel Le Cesne, MD[14]; Ying Su, MD, PhD[15]; Julie Meade, MD[15]; Tao Wang, PhD[15]; Matthew L. Sherman, MD[15]; Rodrigo Ruiz-Soto, MD[15]; and Michael C. Heinrich, MD[16,17]

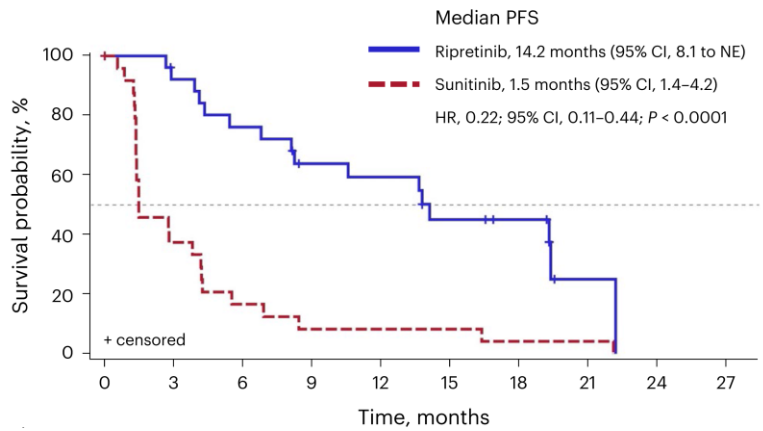


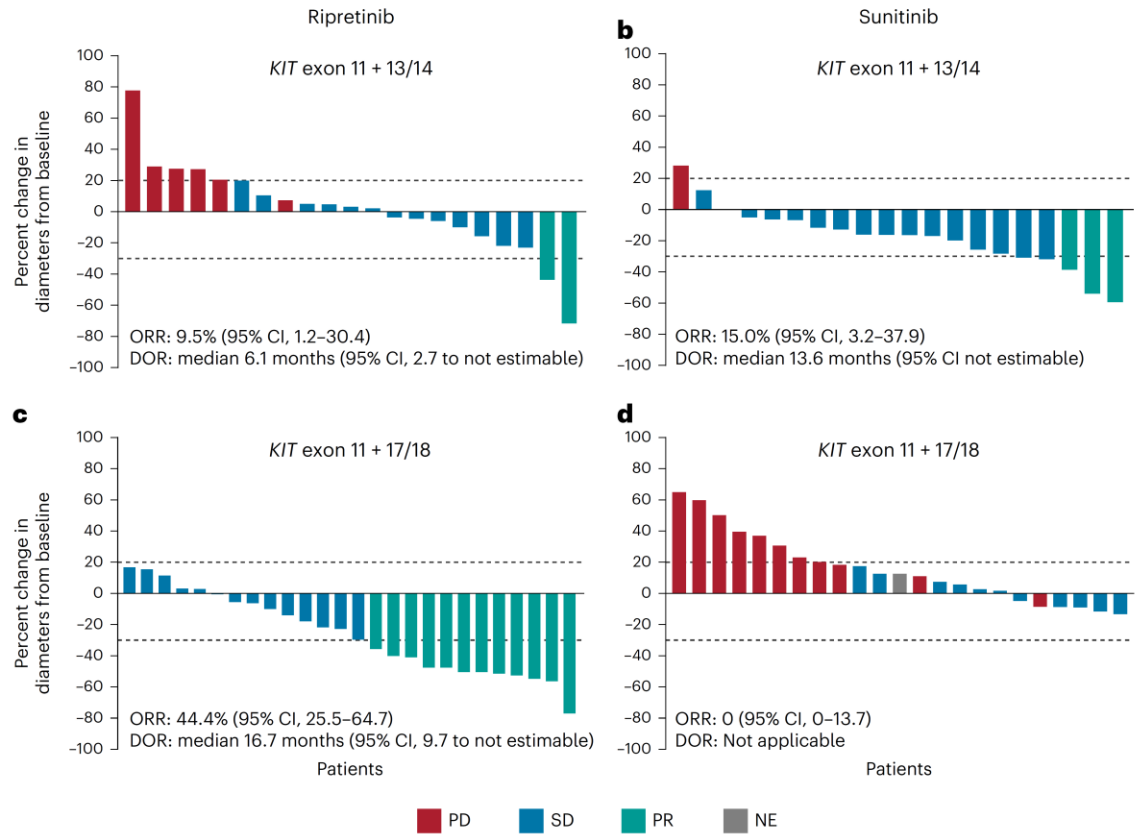


https://doi.org/10.1038/s41591-023-02734-5

Ripretinib versus sunitinib in gastrointestinal stromal tumor: ctDNA biomarker analysis of the phase 3 INTRIGUE trial

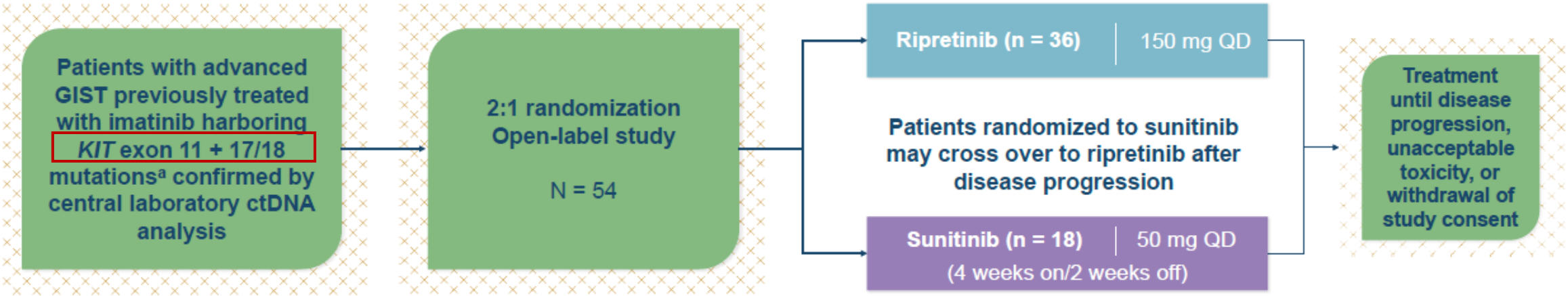




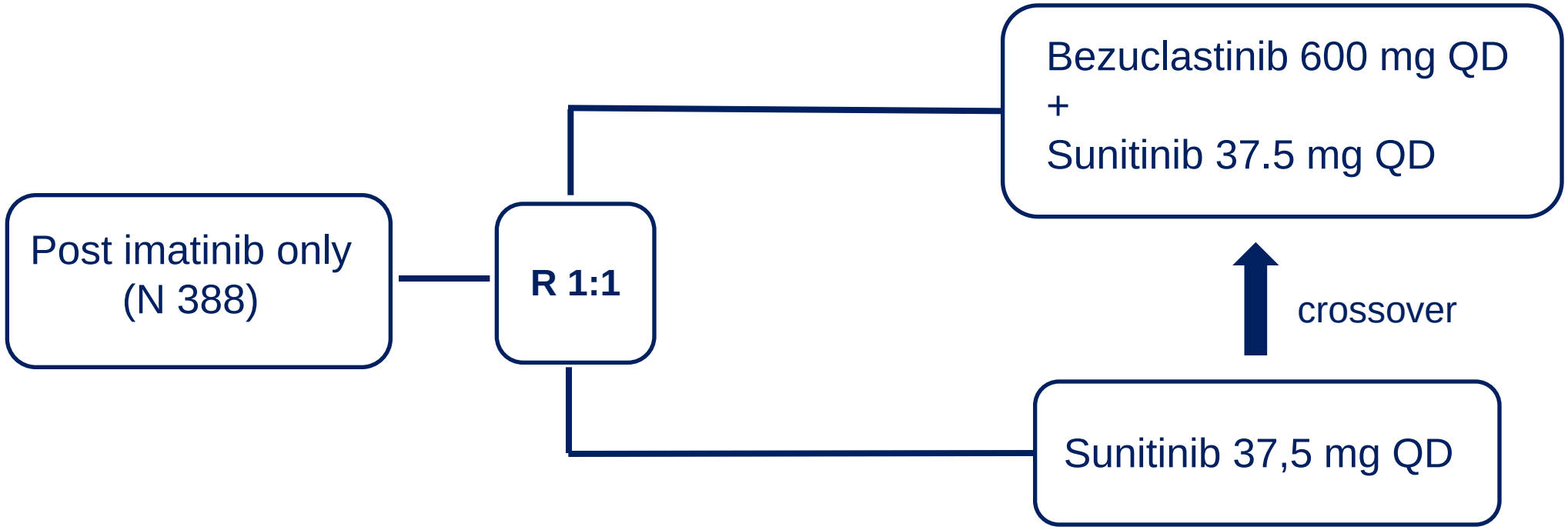


Heinrich M et al, Nature Medicine 2024

INSIGHT: phase 3, randomized, global, multicenter, open-label study



PEAK Study: a Phase 3, Randomized, Open-Label, Multicenter Clinical Study of Bezuclastinib (CGT9486) and Sunitinib Combination Versus Sunitinib in Patients with Gastrointestinal Stromal Tumors (GIST)



THE NOVEL KIT INHIBITOR IDRX-42 SHOWS PROMISING ACTIVITY IN 2ND AND LATER-LINE GASTROINTESTINAL STROMAL TUMORS: RESULTS FROM A PHASE 1 STUDY (STRATEGIST 1)

Suzanne George[1], Michael Heinrich[2], Jonathan Trent[3], César Serrano[4], Sebastian Bauer[5], Margaret von Mehren[6], Neeta Somaiah[7], Peter Reichardt[8], George Demetri[1], Nick Lydon[9], David Kerstein[9], Jaap Verweij[9], Vivek Kadambi[9], Jessica Christo[9], Sean Kim[9], Debbie Johnson[9], James Shao[9], Patrick Schöffski[10]

Suzanne George, MD
Chief, Division of Sarcoma
Dana-Farber Cancer Institute
Boston, MA USA

2024 ANNUAL MEETING

IDRX-42: a KIT TKI designed to address unmet need in GIST

- *KIT* mutations drive most GIST, with resistance to TKIs due to diverse secondary mutations in the ATP-binding pocket and activation loop
- No approved TKI inhibits the full spectrum of these mutations[1]
  - Response rates with 2nd line sunitinib, 3rd line regorafenib, and 4th line ripretinib are approximately 18%, 5%, and 9%, respectively [2,3,4]
- IDRX-42 is an investigational KIT TKI which has shown:
  - Superior *in vivo* activity vs standard TKIs in xenograft mouse models with exon 9, 11, 13 and 17 mutations[5,6]
  - Selectivity over off-target kinases, sparing VEGFR-2 and FLT3[5]

FLT3, fms-like tyrosine kinase 3; TKI, tyrosine kinase inhibitor; VEGFR-2, vascular endothelial growth factor receptor 2; Sources: 1. Kelly CM et al. J Hematol Oncol. 2021;14(1):2; 2. Bauer et al. J Clin Oncol. 2022;40(34):3918-3928; 3. Demetri et al. Lancet. 2013;381(9863):295-302; 4. Blay et al. Lancet Oncol. 2020 (7):923-934.; 5. Blum A et al. J Med Chem. 2023;66:(4):2386-2395; 6. De Sutter L et al. Clin Cancer Res. 2023;29(15):2859-2868

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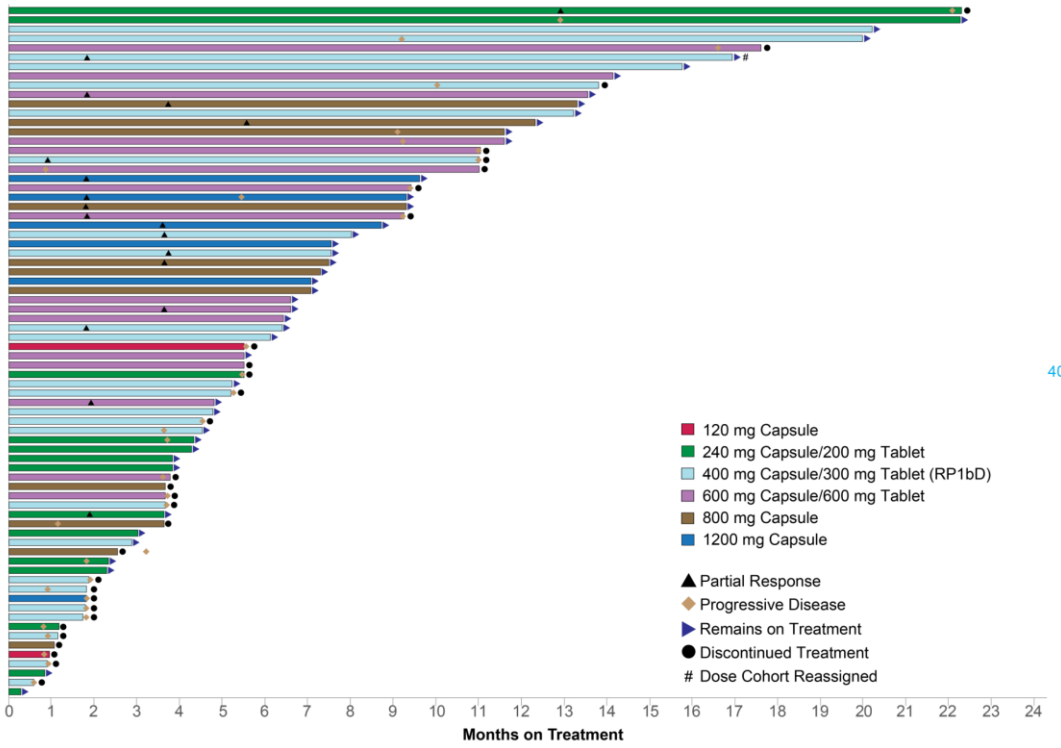
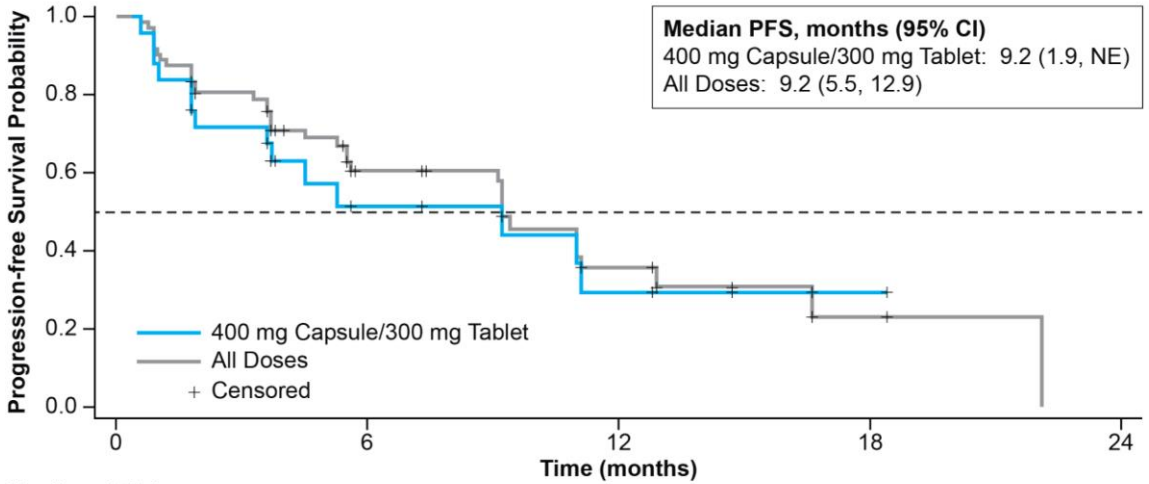
Duration of Treatment and Response
≥ 3 rd Line Patients



Progression Free Survival
≥ 3 rd Line Patients

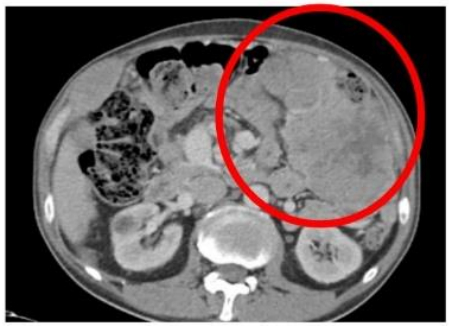


Progression-Free Survival (PFS)

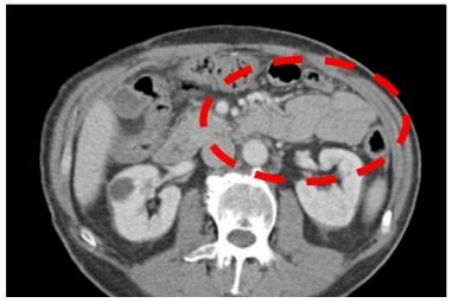
	3rd Line		≥4th Line No Prior Ripretinib	
	N	Median PFS, months (95%CI)	N	Median PFS, months (95%CI)
All Doses	10	12.9 (0.8, NE)	25	9.2 (3.7, NE)
400 mg capsule/ 300 mg tablet (RP1bD)#	4	NE (1.9, NE)	10	11.0 (0.6, NE)

George S et al, CTOS 2024

Radiographic response in *KIT* exon 9 and 17 mutant GIST (6th Line)

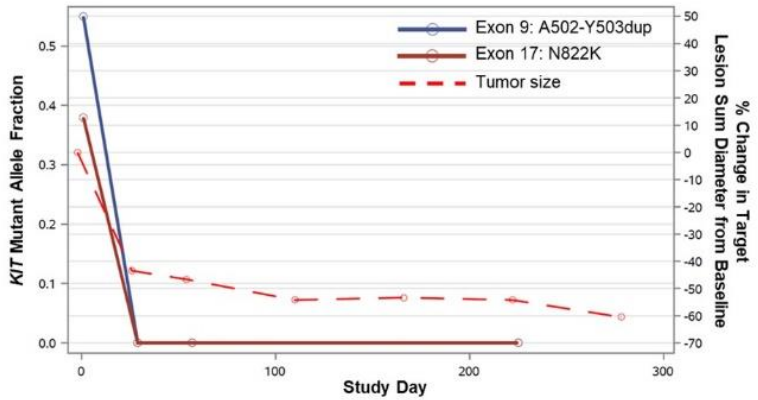


Baseline



Study Day 54

- 60 year old male (400 mg QD)
- Prior imatinib, sunitinib, regorafenib, cabozantinib, and regorafenib rechallenge
- No known response to prior therapy
- PR by mRECIST at 4 weeks
- Currently on treatment >10 months



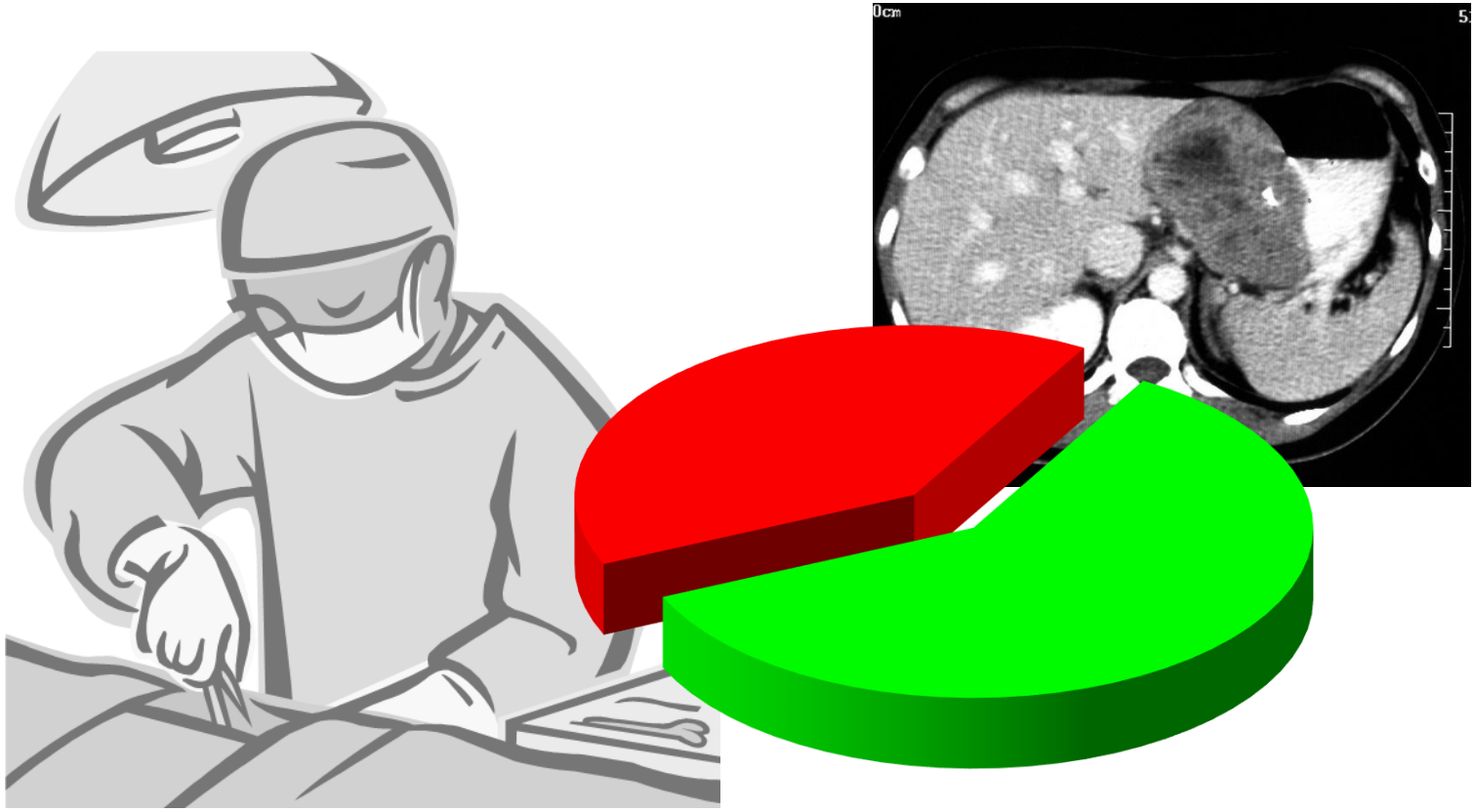
Radiographic images provided by César Serrano, Vall d'Hebron Institut d'Oncologia (VHIO)

mRECIST; modified RECIST; PR, partial response; QD, once daily; Data cutoff date: 28 April 2024

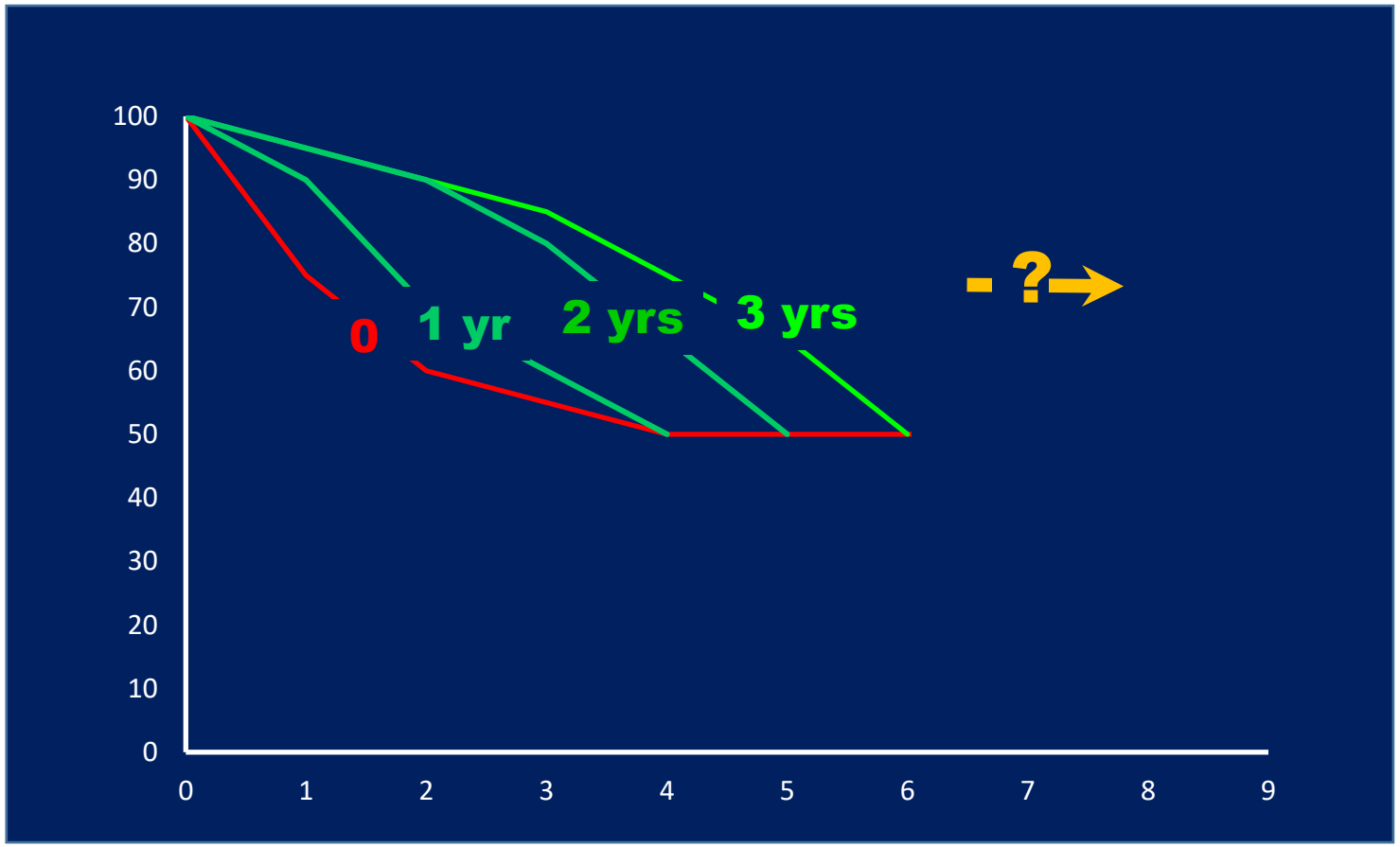
PRESENTED BY: Dr. Patrick Schöffski

Schoffski P et al, ASCO 2024

GIST: standard treatment



GIST - Adjuvant



De Matteo RP et al. Lancet 2009
Casali PG et al. J Clin Oncol 2015
Joensuu H et al. J Clin Oncol 2016

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

A randomized study of 6 versus 3 years of adjuvant imatinib in patients with localized GIST at high risk of relapse

J.-Y. Blay[1,*], C. Schiffler[1], O. Bouché[2], M. Brahmi[1], F. Duffaud[3], M. Toulmonde[4], B. Landi[5], W. Lahlou[5], D. Pannier[6], E. Bompas[7], F. Bertucci[8], L. Chaigneau[9], O. Collard[10], M. Pracht[11], C. Henon[12], I. Ray-Coquard[1], K. Armoun[2], S. Salas[3], M. Spalato-Ceruso[4], A. Adenis[6,13], B. Verret[13], N. Penel[6], C. Moreau-Bachelard[7], A. Italiano[4], A. Dufresne[1], S. Metzger[1], S. Chabaud[1], D. Perol[1] & A. Le Cesne[12]

[1]Centre Léon Bérard & Université Claude Bernard Lyon I, Lyon; [2]CHU & Université de Reims, Reims; [3]Hôpital La Timone & Université Aix-Marseille, Marseille; [4]Institut Bergonié, Bordeaux; [5]Hôpital Européen George Pompidou, Paris; [6]Centre Oscar Lambret & Université Lille, Lille; [7]Institut Cancérologie de l'Ouest, Nantes; [8]Institut Paoli-Calmette & Université Aix-Marseille, Marseille; [9]CHU Besançon, Besançon; [10]Hôpital Privé de la Loire, Saint-Etienne; [11]Centre Eugene Marquis, Rennes; [12]Institut Gustave Roussy, Villejuif; [13]Institut de Cancerologie de Montpellier & CLCC Val d'Aurelle, Montpellier, France

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Background: The administration of adjuvant imatinib during 3 years is indicated after resection of primary localized GIST at high risk of recurrence, but many patients relapse afterwards.

Methods: IMADGIST (NCT02260505) was a multicenter, open-label, randomized phase III study evaluating the maintenance of imatinib for 3 more years (6-year arm) compared with interruption (3-year arm) from the day of randomization, conducted in the French Sarcoma Group. The primary endpoint was intent-to-treat disease-free survival. Secondary endpoints included overall survival, time to imatinib resistance, response after imatinib reintroduction at relapse, and safety.

Results: From 24 December 2014 to 4 April 2023, 136 patients aged $\geq$18 years, Eastern Cooperative Oncology Group performance status $\leq$2, with a localized gastrointestinal stromal tumor with an R0 or R1 surgery, and a risk of tumor recurrence $\geq$35% according to National Comprehensive Cancer Network (NCCN) risk classification were randomized in 14 centers. Sixty-five patients were randomized to the 3-year arm versus 71 to the 6-year arm. There were 68 males and females. Primary sites were gastric and small bowel in 60 (44%) and 64 (47%) patients, respectively. Respectively, 52 (38%) and 71 (52%) patients had a risk of relapse of 35%-70% and >70%. With a median follow-up of 55 months (interquartile range 46-59 months) after randomization, disease-free survival was significantly superior in the 6-year arm [hazard ratio: 0.40 (0.20-0.69), $P = 0.0008$]. Time to imatinib resistance, survival, adverse events, and quality of life were not different in the two arms.

Conclusions: Three additional years of adjuvant imatinib reduces the risk of relapse in patients who have received 3 years of adjuvant imatinib with an acceptable tolerance.

Key words: adjuvant therapy, gastrointestinal stromal tumors, imatinib mesylate, randomized clinical trial

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common sarcoma and also a paradigmatic model for precision medicine in solid tumors, with the tyrosine kinase inhibitor imatinib as a standard first-line treatment in the advanced phase and as adjuvant treatment in *KIT*- or *PDGFRA*-mutated GIST.[1,2]

Three randomized clinical trials established that imatinib mesylate prescribed in the adjuvant setting significantly reduces the risk of relapse of GIST at high risk of relapse.[3-5] A duration of 3 years of adjuvant imatinib treatment was demonstrated to improve relapse-free survival (RFS) and overall survival of patients at high risk of relapse over a duration of 1 year and is now recommended as standard in guidelines.[4,6-8] The EORTC STBSG 62024 study which provided 2 years of adjuvant treatment demonstrated that adjuvant treatment is not associated with a faster emergence of secondary resistance to imatinib.[5] The recommended dose of imatinib in the adjuvant setting is 300-400 mg/day.[6-8] An 800 mg dose is an option in GIST with *KIT* exon 9 mutation in the advanced phase, but did not show superiority at >400

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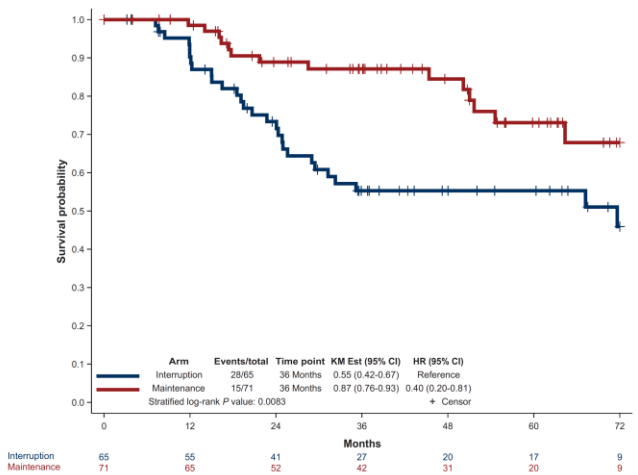
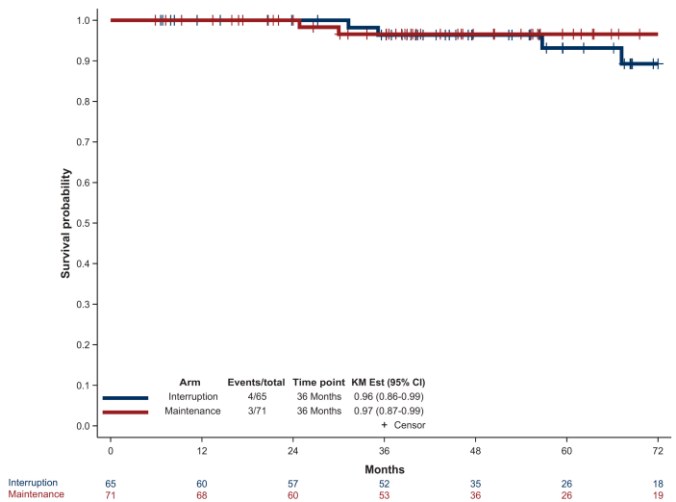
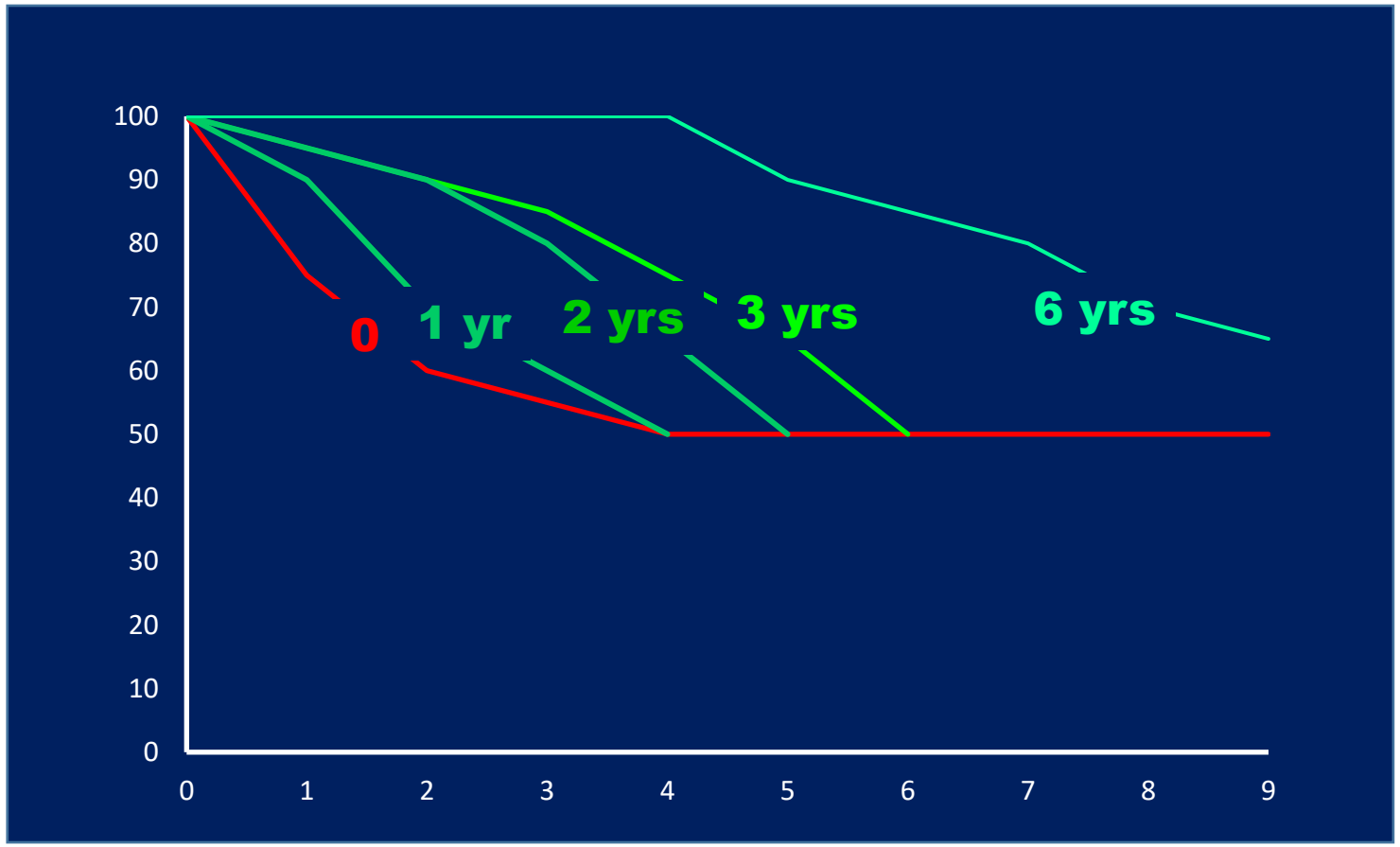


Disease Free Survival



Overall Survival

GIST - Adjuvant



De Matteo RP et al. Lancet 2009
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Joensuu H et al. J Clin Oncol 2016
JY Blay et al. Ann Oncol 2024

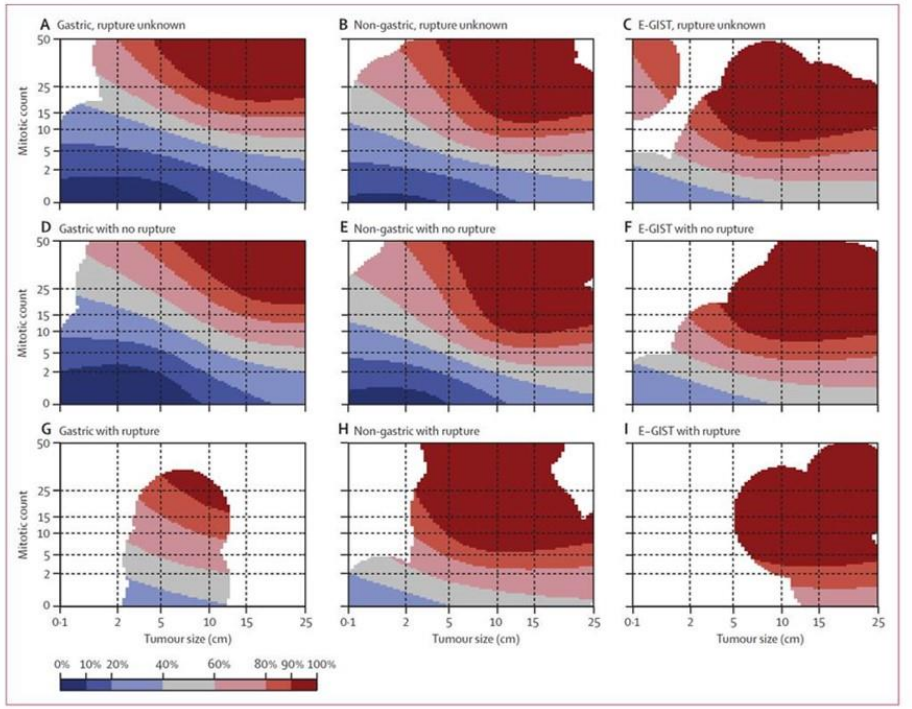
GIST: prognostic factors

- mitoses
- size
- site

- [genotype]

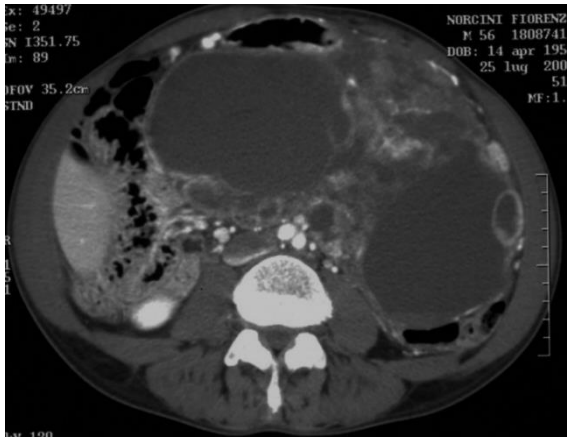
Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts

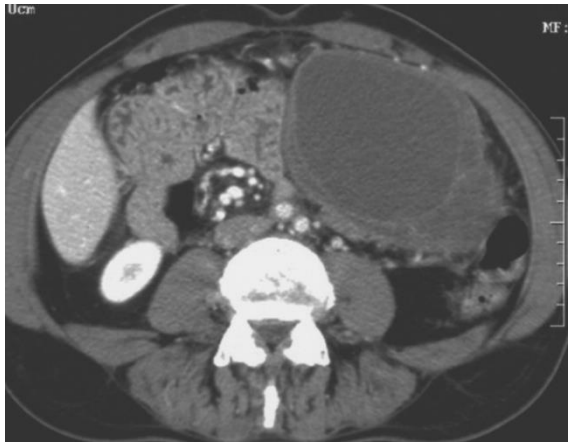
Heikki Joensuu, Aki Vehtari, Jaakko Riihimäki, Toshirou Nishida, Sonja E Steigen, Peter Brabec, Lukas Plank, Bengt Nilsson, Claudia Cirilli, Chiara Braconi, Andrea Bordoni, Magnus K Magnusson, Zdenek Linke, Jozef Sufliarsky, Massimo Federico, Jon G Jonasson, Angelo Paolo Dei Tos, Piotr Rutkowski

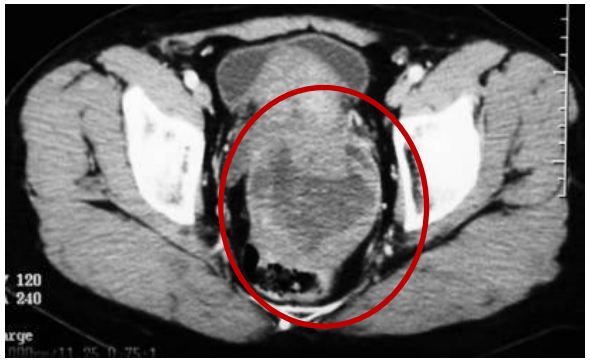


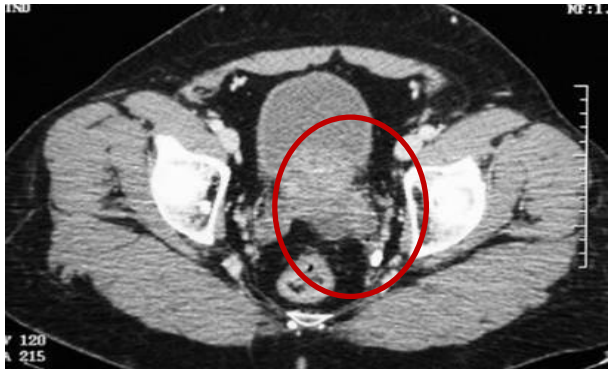
Lancet Oncol 2012;13:265

Cytoreductive therapy









Linee guida

SARCOMI DEI TESSUTI MOLLI E GIST

Edizione 2024

Aggiornata al 17/04/2024

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Italian Sarcoma Group

Società Italiana di Chirurgia

SICO Società Italiana di Chirurgia Oncologica

SIGO Società Italiana di Ginecologia e Ostetricia

Società Italiana di Radiologia Medica e Interventistica

ESMO

ANNALS OF ONCOLOGY

SPECIAL ARTICLE

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

P. G. Casali[1,2], J. Y. Blay[3], N. Abecassis[4], J. Bajpai[5], S. Bauer[6], R. Biagini[7], S. Bielack[8], S. Bonvalot[9], I. Boukovinas[10], J. V. M. G. Bovee[11], K. Boye[12], T. Brodowicz[13], A. Buonadonna[14], E. De Álava[15,16], A. P. Dei Tos[17], X. G. Del Muro[18], A. Dufresne[19], M. Eriksson[20], A. Fedenko[21], V. Ferrari[22], A. Ferrari[23], A. M. Frezza[1], S. Gasperoni[24], H. Gelderblom[25], F. Gouin[26], G. Grignani[27], R. Haas[28,29], A. B. Hassan[30], N. Hindi[31], P. Hohenberger[32], H. Joensuu[33], R. L. Jones[34], C. Jungels[35], P. Jutte[36], B. Kasper[37], A. Kawai[38], K. Kopeckova[39], D. A. Krákorová[39], A. Le Cesne[40], F. Lo Giorgio[41], E. Lugis[42], A. Leithner[43], A. Lopez-Pousa[44], J. Martin-Broto[31], O. Merimsky[45], C. Messiou[46], A. B. Miah[47], O. Mir[48], M. Montemurro[49], C. Morosi[50], E. Palmerini[51], M. A. Pantaleo[52], R. Piana[53], S. Piperno-Neumann[54], P. Reichardt[55], P. Rutkowski[56], A. A. Safwat[57], C. Sangalli[58], M. Sbaraglia[17], S. Scheipl[59], P. Schöffski[60], S. Sleijfer[61], D. Strauss[62], S. J. Strauss[63], K Sundby Hall[12], A. Tamm[64], M. Unk[56], M. A. J. van de Sande[65], W. T. A. van der Graaf[66,67], W. J. van Houdt[68], T. Frebourg[67†], A. Gronchi[69] & S. Stacchiotti[1], on behalf of the ESMO Guidelines Committee, EURACAN and GENTURIS*

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Key words: GIST, clinical practice guidelines, gastrointestinal stromal tumour, surgery, tyrosine kinase inhibitor

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†Deceased.

GIST: «Tumor board»

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