MUSCULOSCELETAL TUMOR UNIT
MedUni Wien | AKH Wien

COMPREHENSIVE CANCER CENTER VIENNA

GIST

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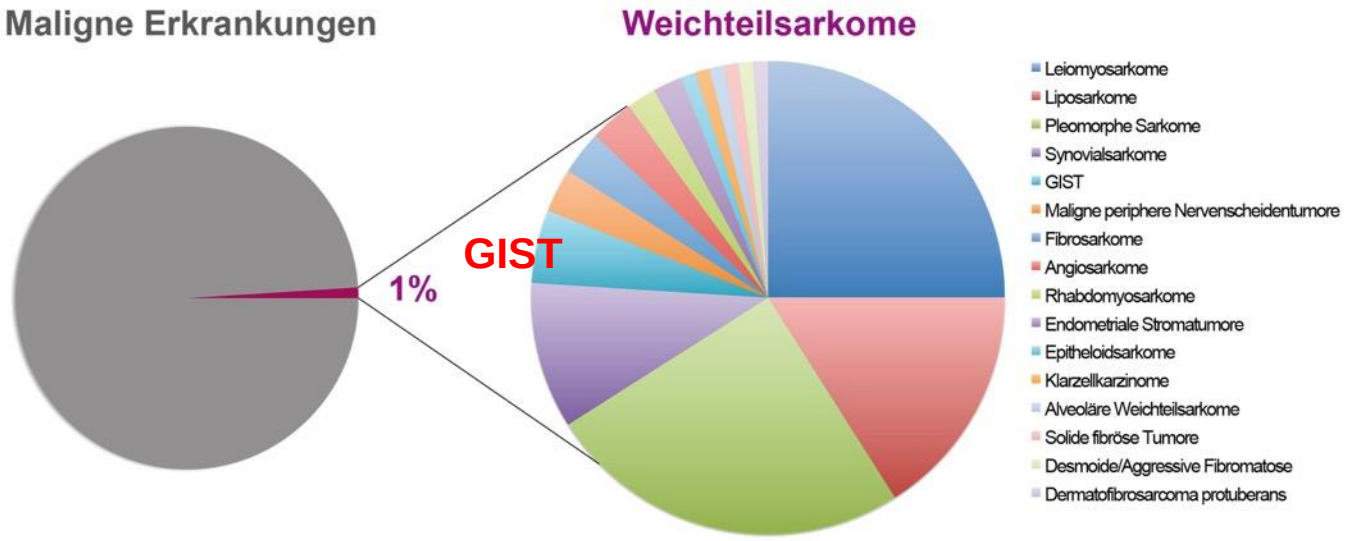
GastroIntestinal Stromal Tumor (GIST)

...a rare tumor!



15 pro 1 Million EinwohnerInnen (in Österreich etwa 120 Neuerkrankungen pro Jahr)
Etwa **10% Metastasen bei Diagnosestellung**

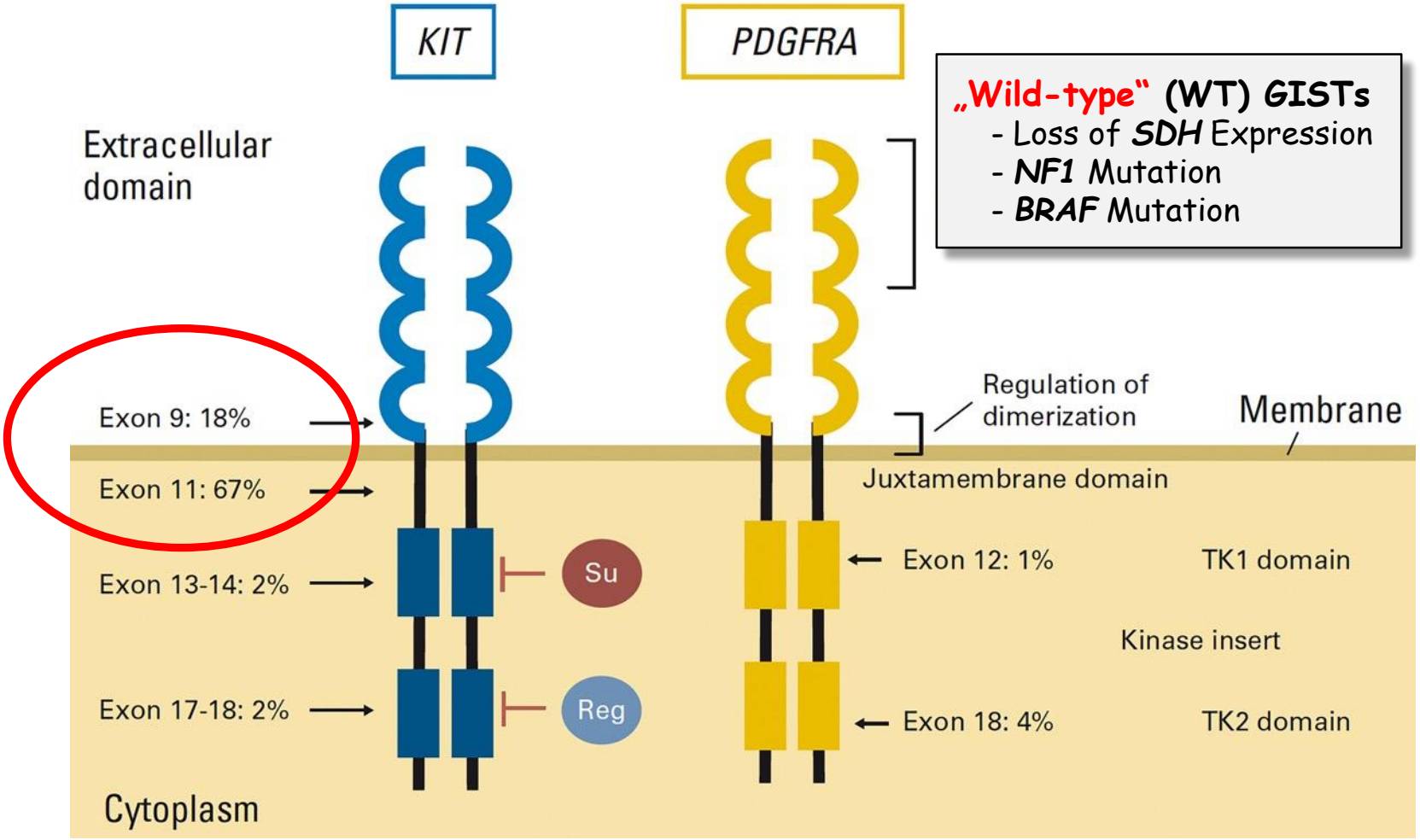
...mit eingeschränkten Therapieoptionen?

...bis zur Jahrtausendwende: **< 5% ansprechen auf Chemotherapie**
mittlere Überlebenszeit 14 Monate

Identifizierung von **onkogenen „Driver-Mutationen"** und **„Targeted Therapy"**

Onkogene „Driver-Mutationen“

85% der GISTs - aktivierende Mutation in ***KIT oder PDGFRα***



Cioffi&Maki, JCO, 2015

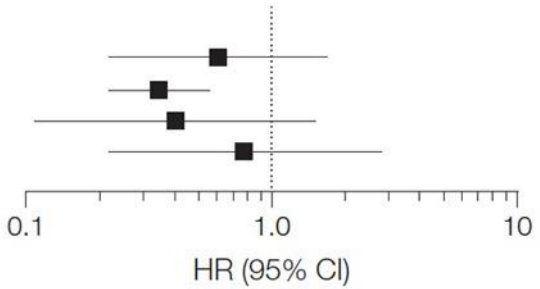
GIST – adjuvante Therapie

SSGX-VIII/AIO Studie

Imatinib 400mg/d
1 Jahr vs. 3 Jahr
high-risk GIST Patienten

Subgruppenanalyse

Tumor mutation site						
KIT exon 9	12	14	8	8	0.61 (0.22-1.68)	.34
KIT exon 11	129	127	55	28	0.35 (0.22-0.56)	<.001
Wild type	19	14	9	3	0.41 (0.11-1.51)	.17
Other	28	23	6	4	0.78 (0.22-2.78)	.70



Keine adjuvante Therapie in

- low-risk GIST
- WT-GIST
- *PDGFRα D842V* Mutation

KIT exon 9 Mutation
Kein Konsensus bisher zu **Imatinib 800mg/d?**

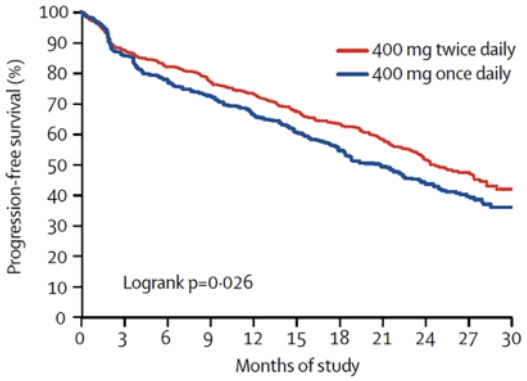
Joensuu *et al.*, JAMA, 2012

GIST – M1

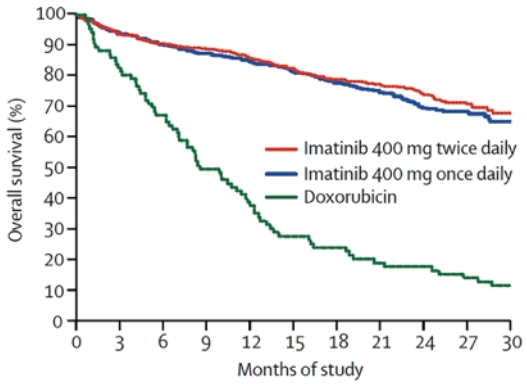
lokal fortgeschritten / inoperabel ± metastasiert

EORTC-ISG-AGITG

Progression free survival



Overall survival



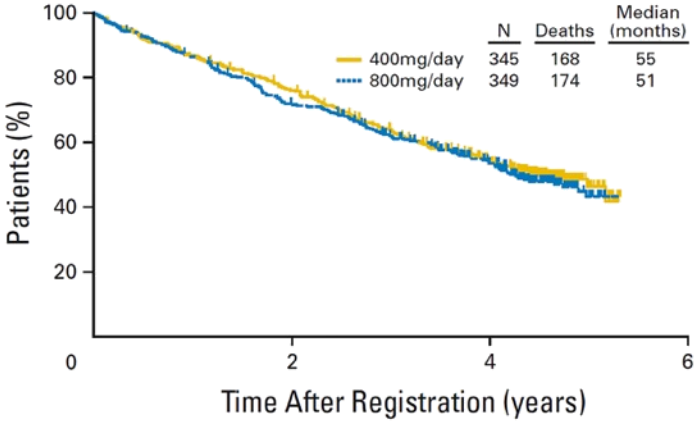
Verweij *et al.*, Lancet, 2004

Zwei Phase III Studien

Imatinib 400mg/d vs. **800mg/d**

NASG-S0033

Overall survival



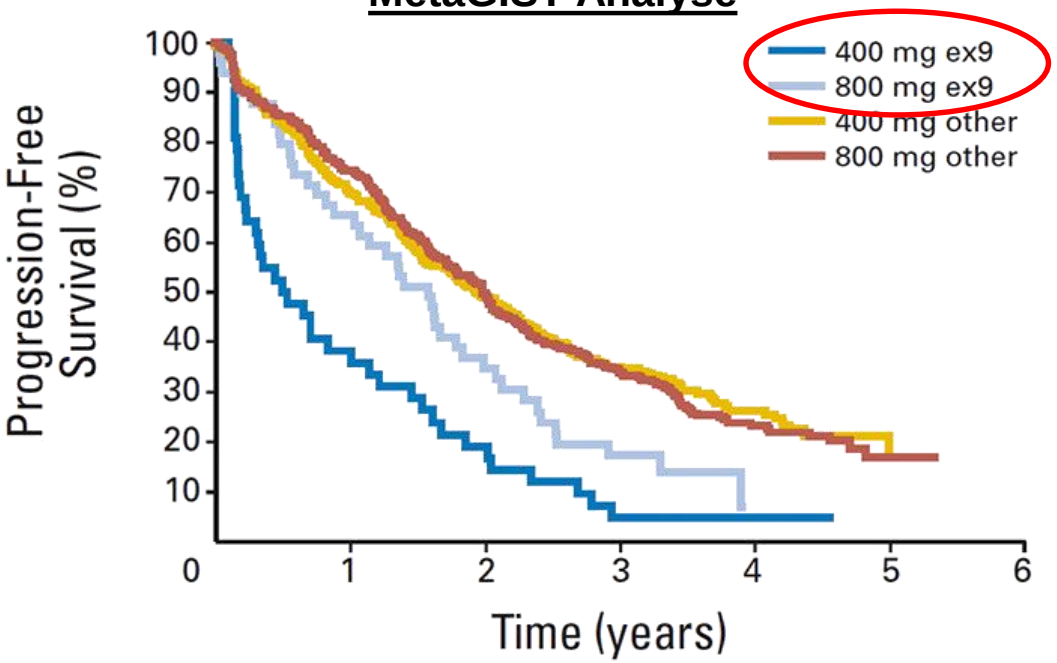
400mg äquivalent zu 800mg
im overall survival

Blanke *et al.*, JCO, 2008

GIST – M1

Therapie entsprechend Mutationsstatus?

MetaGIST Analyse



KIT Exon9 Mutation

signifikanter **Vorteil im PFS** (p=0,017) für **Imatinib 800mg/d**

kein signifikanter Vorteil im OS

→ 1st-line Therapie: **Imatinib 800mg/d**

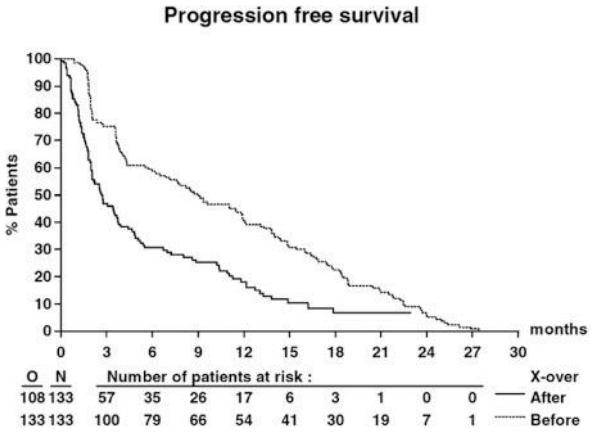
Van Glabbeke *et al.*, JCO, 2010

GIST – M1

Progressive Disease unter Imatinib 400mg/d?

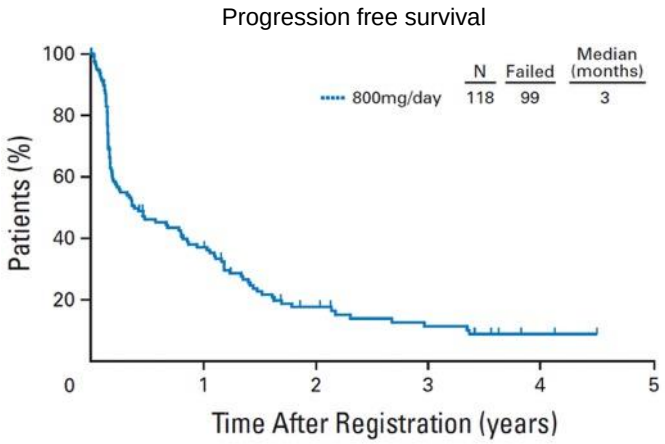
Analyse **Cross-over 400mg zu 800mg nach PD** in zwei Phase III Studien

EORTCISG-AGITG study



Zalcberg *et al.*, EJC, 2005

American Intergroup study S0033



Blanke *et al.*, JCO, 2008

→ Erneutes **Therapieansprechen** nach **Dosiseskalation** von 400mg/d auf **800mg/d Imatinib**

mittlere progressionsfreie Zeit **3-4 Monate**

gering vermehrte Nebenwirkungen: v.a. **Anämie & Fatigue**

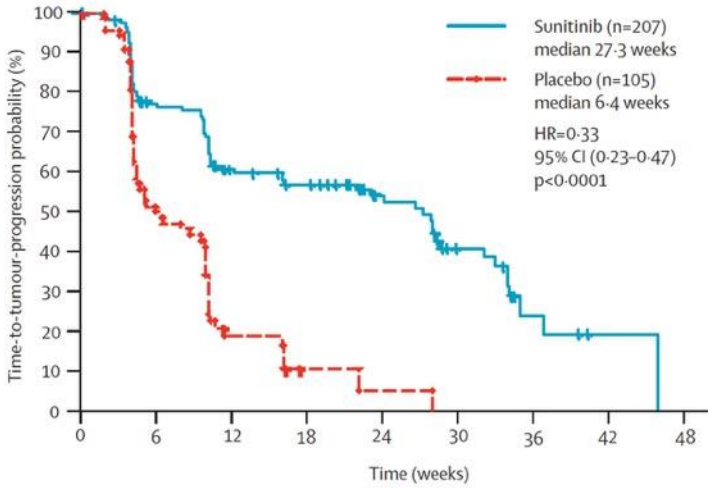
GIST – M1

2nd-line Therapie nach Imatinib?

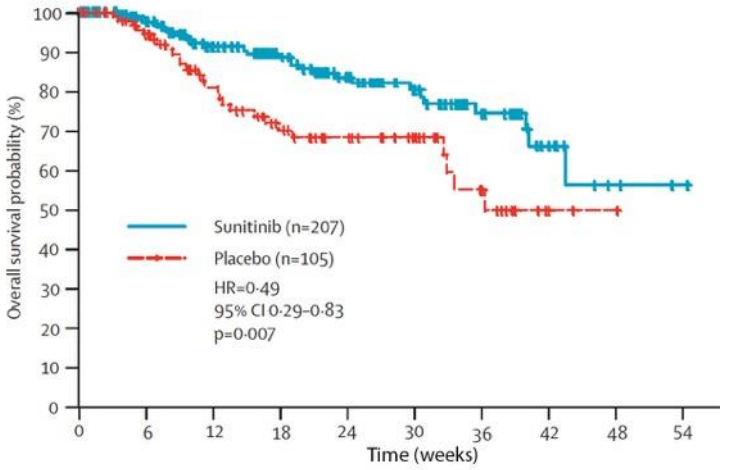
Phase III Studie – **Sunitinib** vs. Placebo

Sunitinib 50mg/d; d1-28; q42

Progression free survival



Overall survival



→ signifikanter **Vorteil** für **Sunitinib** in **PFS** (HR 0,33) und **OS** (HR 0,49)

Alternatives Therapieprotokoll:

Sunitinib 37,5mg/d; kontinuierlich

(George et al, EJC, 2009)

Demetri *et al.*, Lancet, 2006

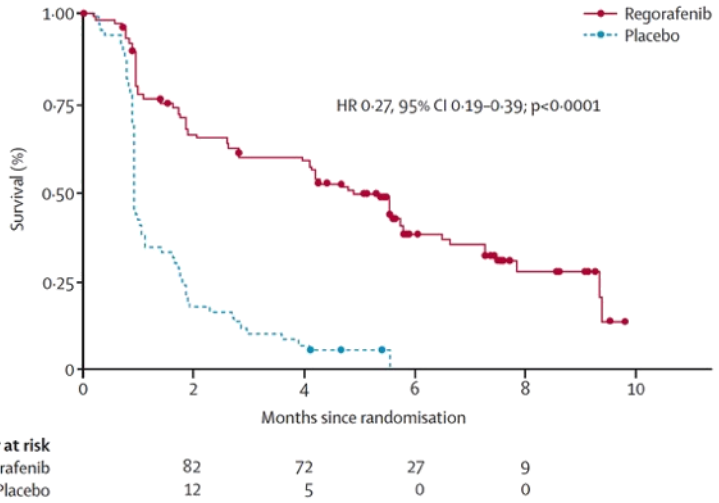
GIST – M1

3rd-line Therapie – Therapieversagen Imatinib & Sunitinib?

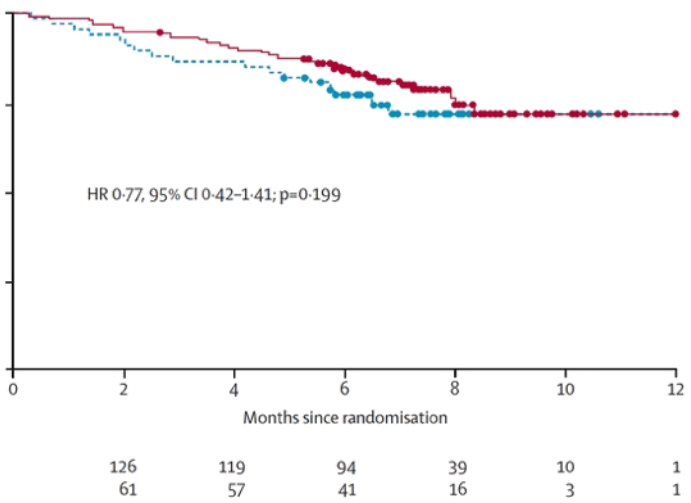
Phase III Studie – **Regorafenib** vs. Placebo

Regorafenib 160mg/d; d1-21; q28

Progression free survival



Overall survival



→ signifikanter **Vorteil** für **Regorafenib** in **PFS** (HR 0,27)

mittleres PFS 4,8 vs. 0,9 Monate

Demetri *et al.*, Lancet, 2013

Therapieempfehlung GIST

Neoadjuvante Therapie

Einzelfallentscheidung im Rahmen **interdisziplinären Tumorboardes**
Imatinib 400mg/d (*KIT exon9 Mut*: 800mg/d)

Adjuvante Therapie

Imatinib 400mg/d für 3 Jahre in high-risk GIST Patienten
(**NICHT** bei *PDGFRα D842V* und *WT*-GIST)

Palliative Therapie

1st-line: **Imatinib 400mg/d**, Dauertherapie; (*KIT exon9 Mut*: 800mg/d)
Dosiseskalation bei **PD** auf 800mg/d

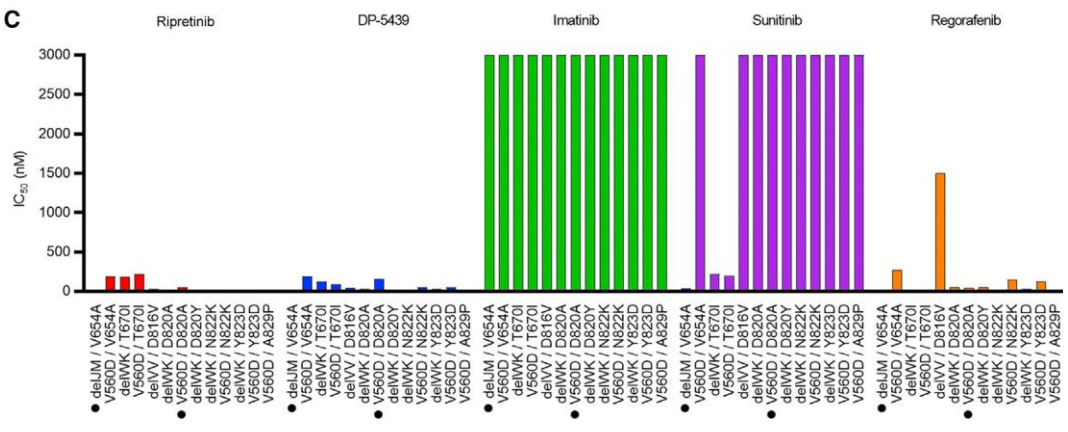
2nd-line: **Sunitnib** 50mg/d (d1-28; q42)
37,5mg/d (Dauertherapie)

3rd-line: **Regorafenib** 160mg/d (d1-21; q28)

→ Mutationsanalyse bei jedem GIST

Novel KIT/PDGFRA inhibitors

Ripretinib (DCC-2618)



Ongoing clinical trials

INVICTUS
≥4th line

INTRIGUE
2nd-line

Article

Cancer Cell

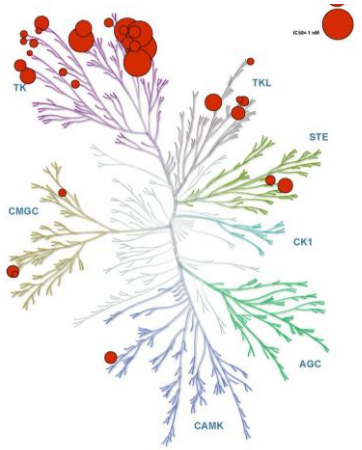
Ripretinib (DCC-2618) Is a Switch Control Kinase Inhibitor of a Broad Spectrum of Oncogenic and Drug-Resistant KIT and PDGFRA Variants

Highlights

- Ripretinib broadly inhibits primary and drug-resistant KIT/PDGFRA mutants
- KIT/PDGFRA inhibitor of all known activation loop mutations

Authors

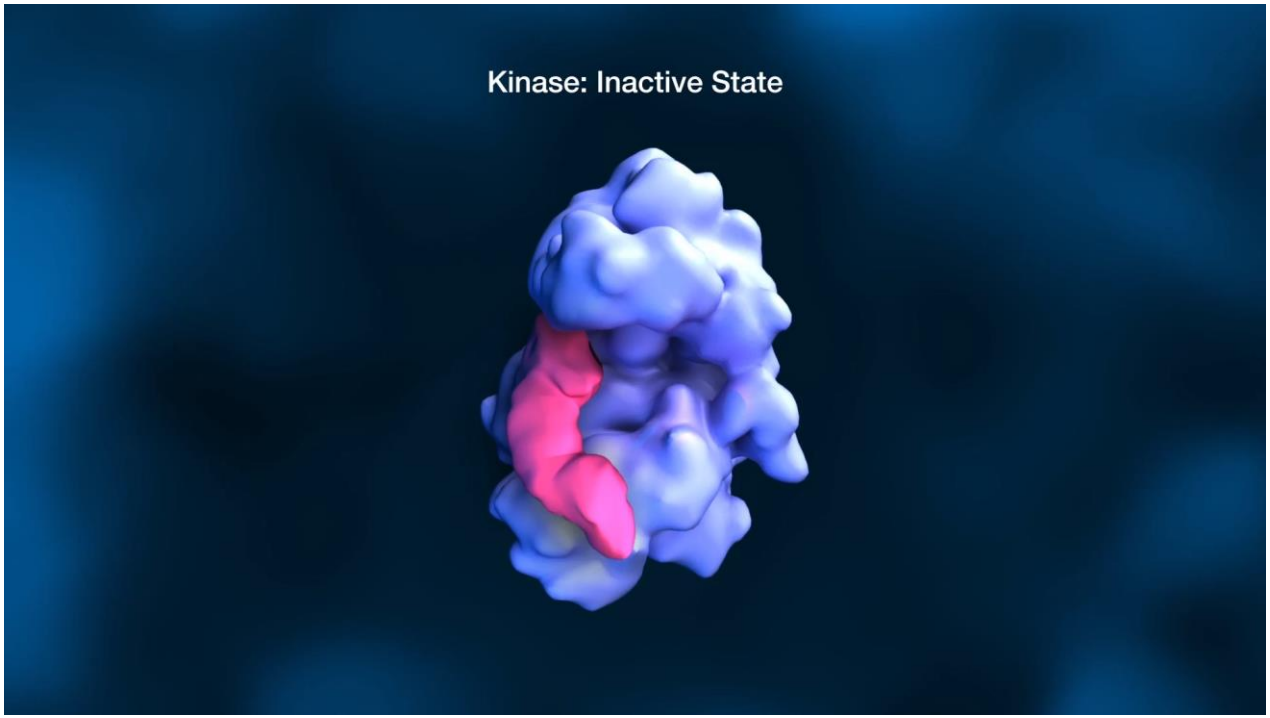
Bryan D. Smith, Michael D. Kaufman, Wei-Ping Lu, ..., Oliver Rosen, Michael C. Heinrich, Daniel L. Flynn



Ripretinib kinome selectivity

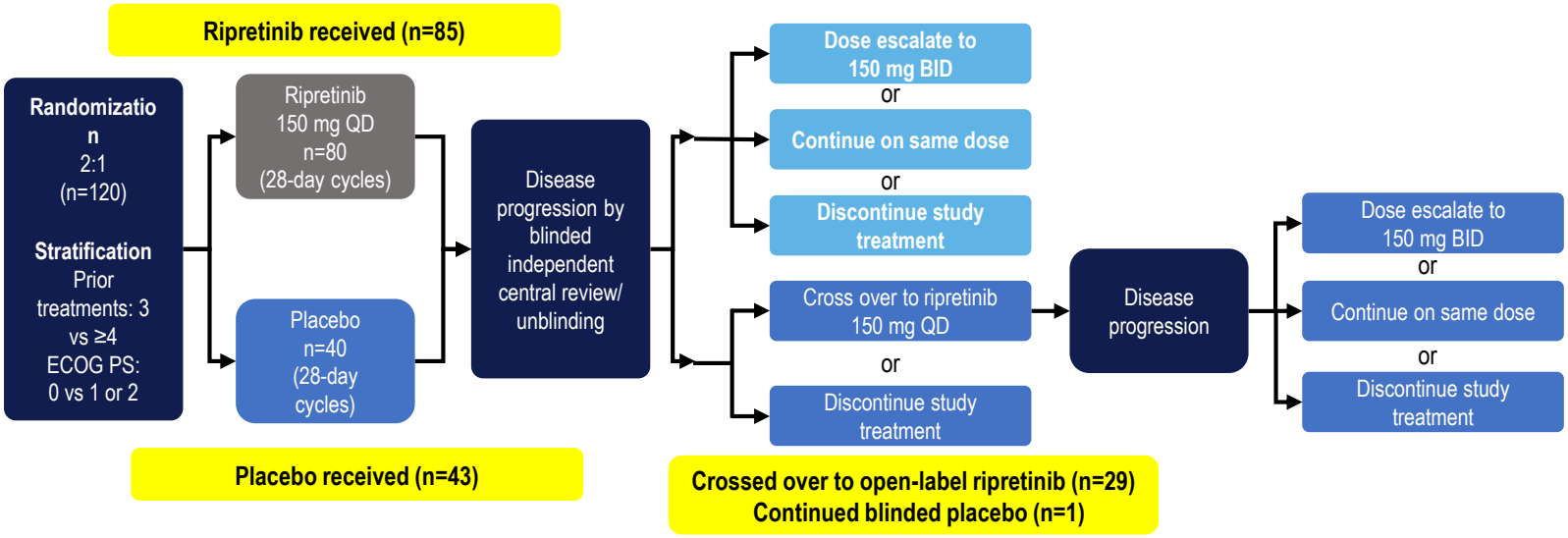
Smith BD, et al. *Cancer Cell*. 2019;35:738-751.

Ripretinib Mechanism of Action



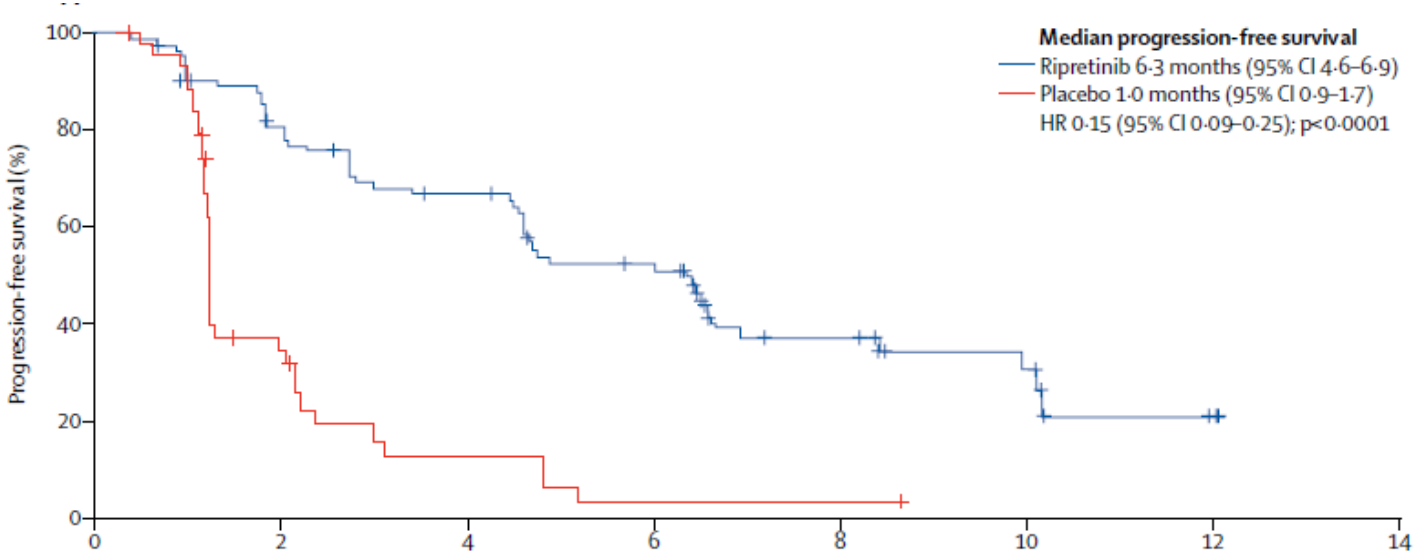
Smith BD, et al. *Cancer Cell*. 2019;35:738-751.

INVICTUS: Randomized Phase III Trial (≥4th line)



Endpoints: PFS → ORR → OS

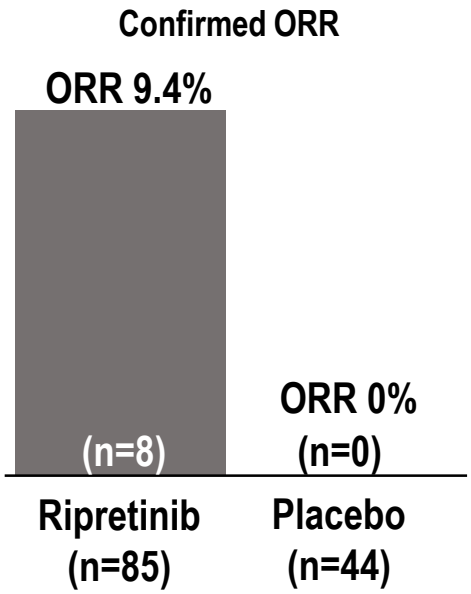
INVICTUS: Randomized Phase III Trial (≥4th line)
PFS analysis



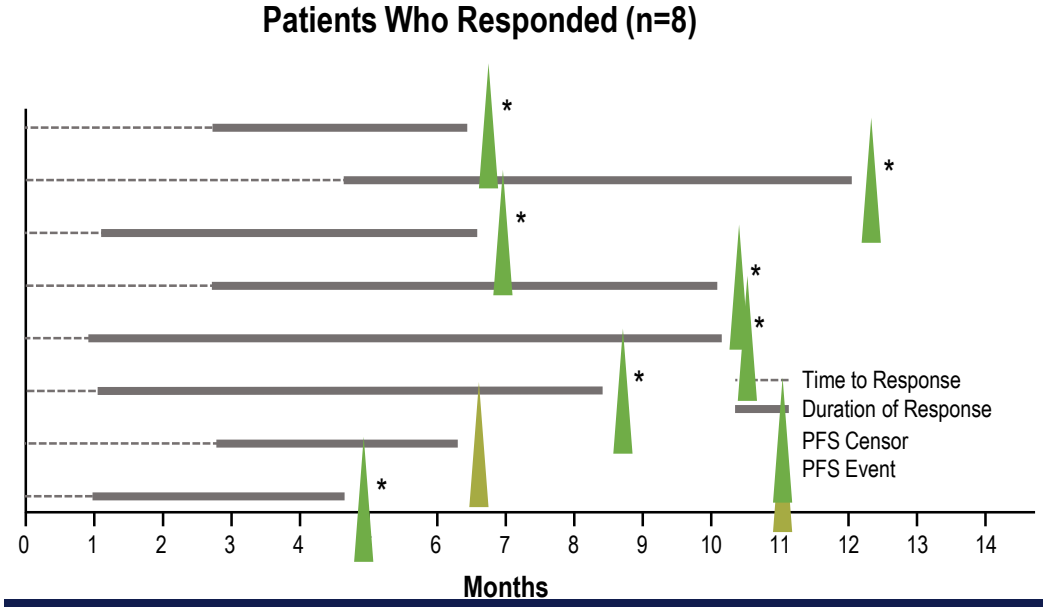
85% risk reduction of disease progression or death compared to placebo

INVICTUS: Randomized Phase III Trial (≥4th line)

Response rate



***P*=0.0504**



- 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

PFS Benefit in all patient subgroups

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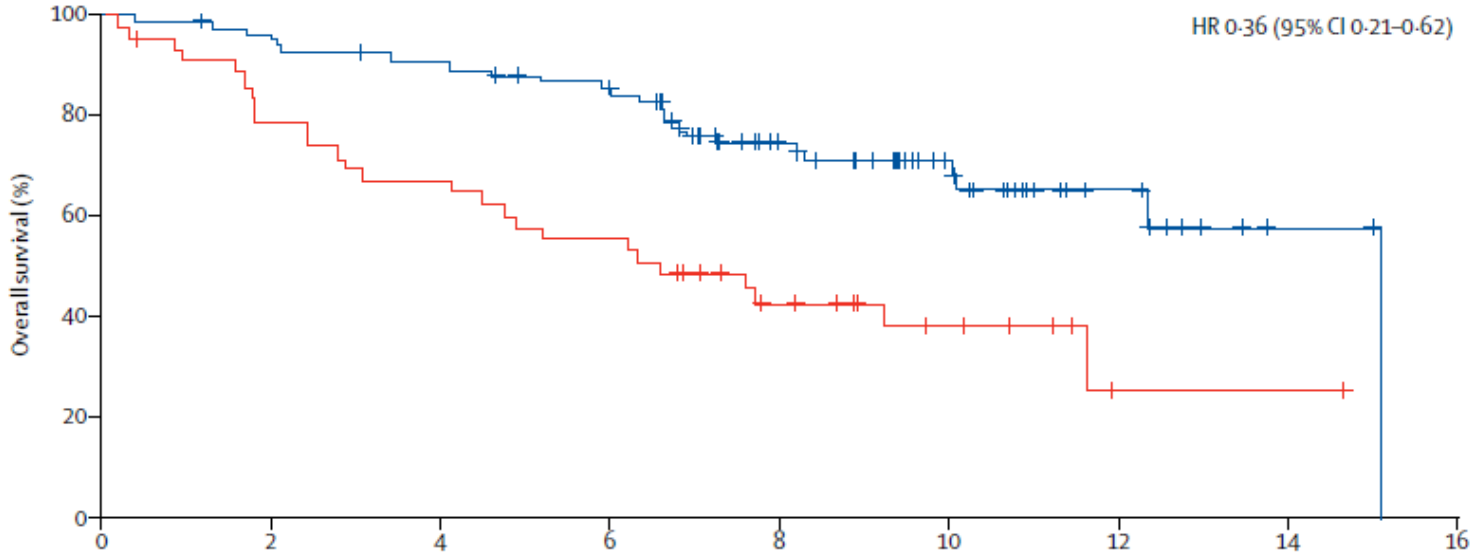
INVICTUS: Randomized Phase III Trial (≥4th line)
Overall survival



Median OS 15.1 vs 6.6 months

HR=0.36 (95% CI, 0.20–0.62) **Nominal *P*=0.0004***

*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.

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INVICTUS: Randomized Phase III Trial (≥4th line)

TEAEs in >10% of patients

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

INVICTUS: Randomized Phase III Trial (≥4th line)

Grade 3/4 TEAEs

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%)
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Headache	16 (18.8%)	0	2 (4.7%)	0
Weight decreased	16 (18.8%)	0	5 (11.6%)	0

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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.

Ripretinib
Next Steps

Clinical Trial Protocol

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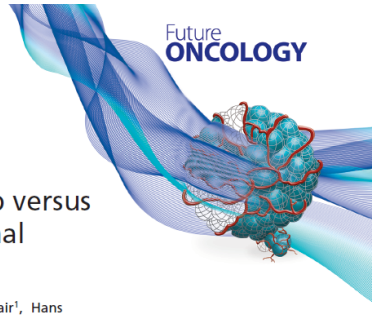
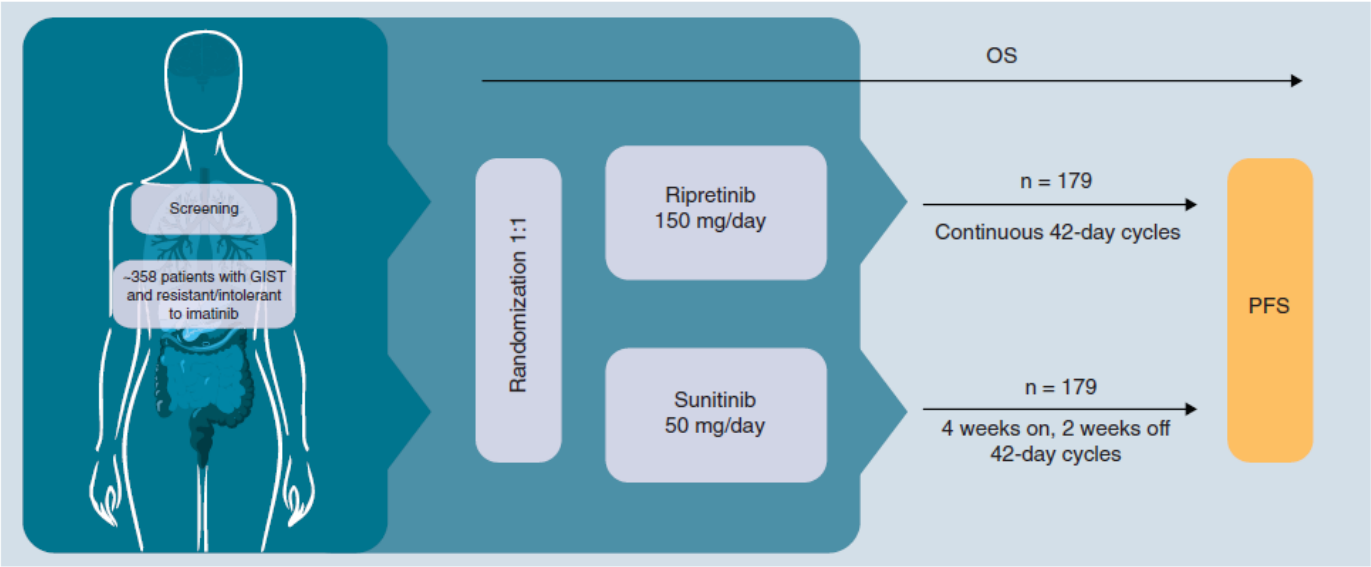
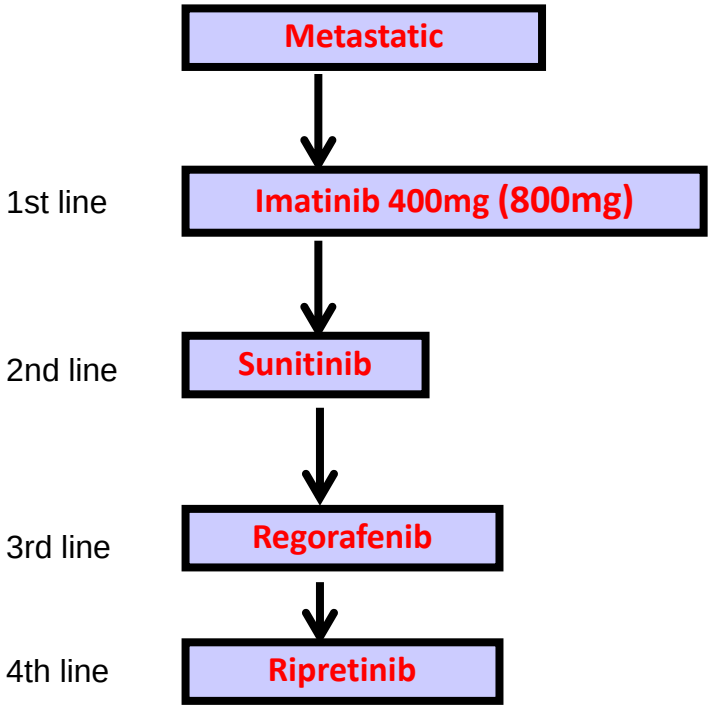


Intrigue: Phase III study of ripretinib versus sunitinib in advanced gastrointestinal stromal tumor after imatinib

John Nemunaitis*[,1,2], Sebastian Bauer[3], Jean-Yves Blay[4], Khalil Choucair[1], Hans Gelderblom[5], Suzanne George[6], Patrick Schöffski[7], Margaret von Mehren[8], John Zalcberg[9], Haroun Achour[10], Rodrigo Ruiz-Soto[10] & Michael C Heinrich[11]



Therapeutic Algorithm GIST (KIT/PDGFRAnon-D842V) 2021



INTRIGUE-Trial