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#LBA87

THE INVICTUS TRIAL: RIPRETINIB AS ≥4TH-LINE THERAPY IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMORS (GIST)

Discussant:

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DISCLOSURE SLIDE

Orion Pharma (employee, stock owner), Neutron Therapeutics (chairman of the Scientific Advisory Board), Sartar Therapeutics (stock owner, past Board Member), Maud Kuistila Foundation (chairman of the Scientific Board).

SYSTEMIC TREATMENT OF ADVANCED GIST

- First line: Imatinib (since 2001)
- Second line: Sunitinib (since 2006)
- Third line: Regorafenib (since 2014)

These are Type II inhibitors (bind to the **inactive** conformation of the kinase)

A few Type I inhibitors are under investigation (bind to the **active** conformation)

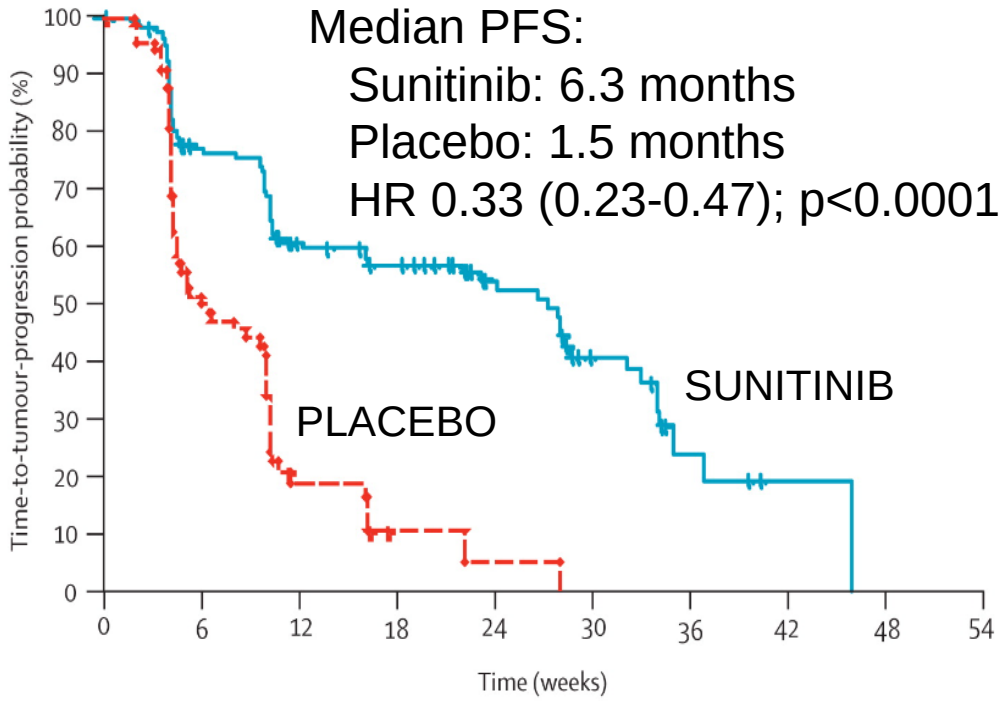
-Avapritinib (BLU-285)

-Crenolanib

APPROVED DRUGS AFTER IMATINIB FAILURE

Second-line: sunitinib[1]

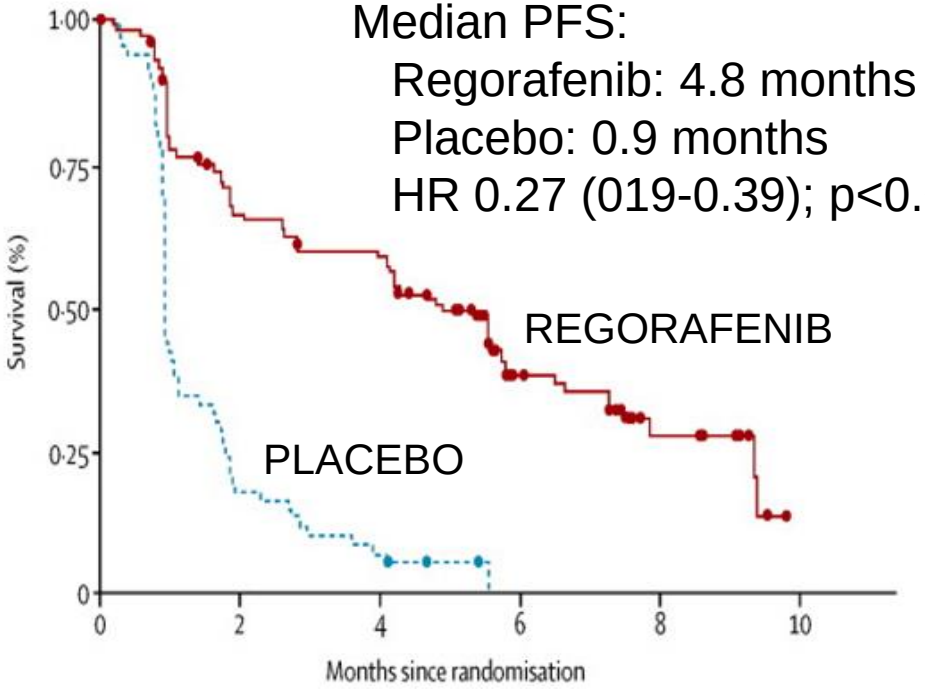
Median PFS:
Sunitinib: 6.3 months
Placebo: 1.5 months
HR 0.33 (0.23-0.47); p<0.0001



Number at risk									
Sunitinib	207	106	67	53	34	18	5	1	0
Placebo	105	36	9	2	1	0	0	0	0

Third-line: regorafenib[2]

Median PFS:
Regorafenib: 4.8 months
Placebo: 0.9 months
HR 0.27 (019-0.39); p<0.0001



Number at risk				
Regorafenib	82	72	27	9
Placebo	12	5	0	0

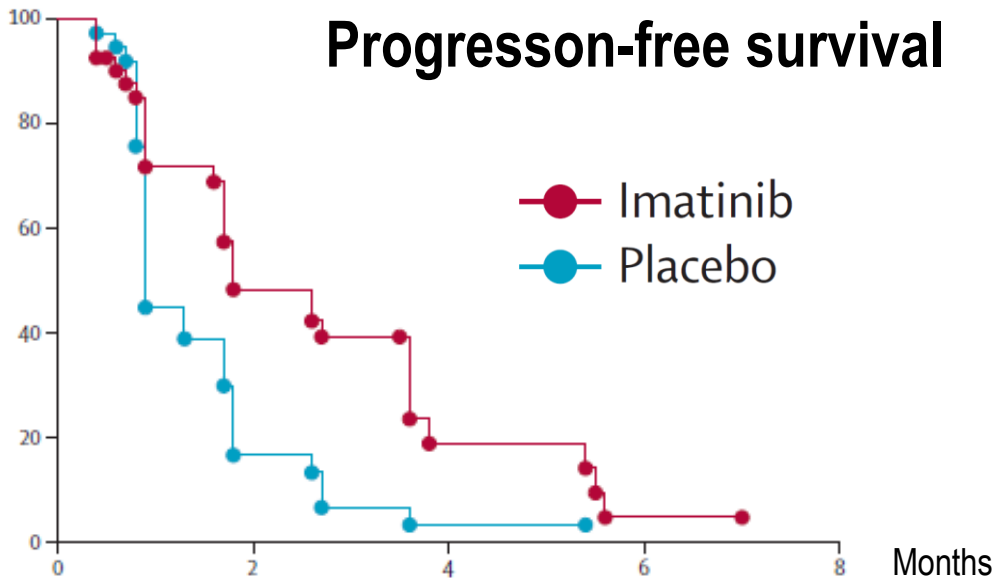
[1]NCT00075218. *Demetri GD et al. Lancet 2006;368:1329-38;*
[2]The GRID trial. *Demetri GD et al. Lancet 2013;381:295-302*

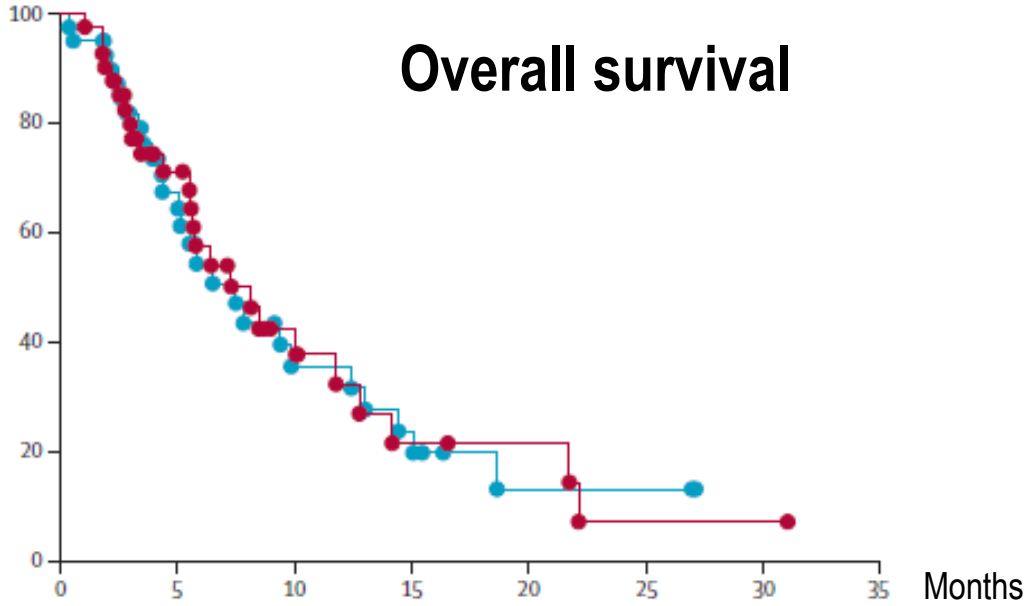
THE RIGHT TRIAL

Resumption to imatinib to control metastatic GIST after failure of imatinib and sunitinib[1]

- Trial compared imatinib to placebo
- 81 randomised patients
- Median progression-free survival:
  - Imatinib 1.8 months
  - Placebo 0.9 months (HR 0.46, p=0.005)
- 37 (93%) patients in the placebo group crossed over to open-label imatinib after progression

[1]*Kang Y-K et al. Lancet Oncol 2013; 14:1175–82*



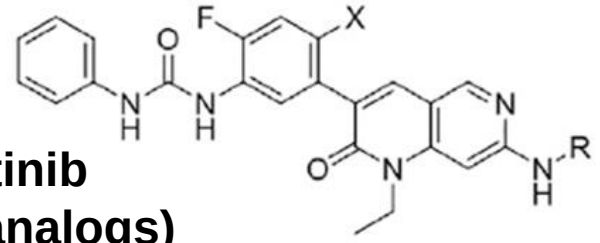


GIST MOLECULAR SUBTYPE INFLUENCES TREATMENT

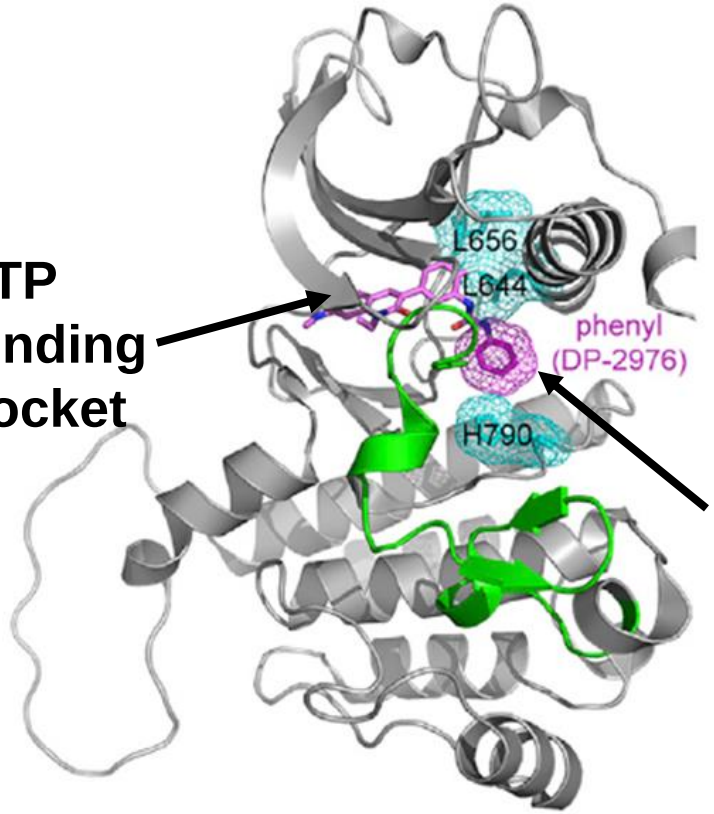
Molecular subtype	Frequency in advanced GIST	Efficacy of the approved agents
Primary *KIT* 11 mutation	Common (about 75%)	1L imatinib effective
Secondary *KIT* mutation (exons 13, 14, or 17/18)	Emerge in most patients treated with imatinib	PFS remains short with sunitinib and regorafenib
KIT exon 9 mutation	10%	Moderately imatinib sensitive, require a high dose
PDGFRA D842V	Rare (<5%)	Standard agents ineffective
No *KIT/PDGFRA* mutation	5-10%	Standard agents ineffective

1L = first line; *PDGFRA* = platelet-derived growth factor A; PFS = progression-free survival

RIPRETINIB (DCC-2618)



Ripretinib (and analogs)



ATP binding pocket

Switch pocket

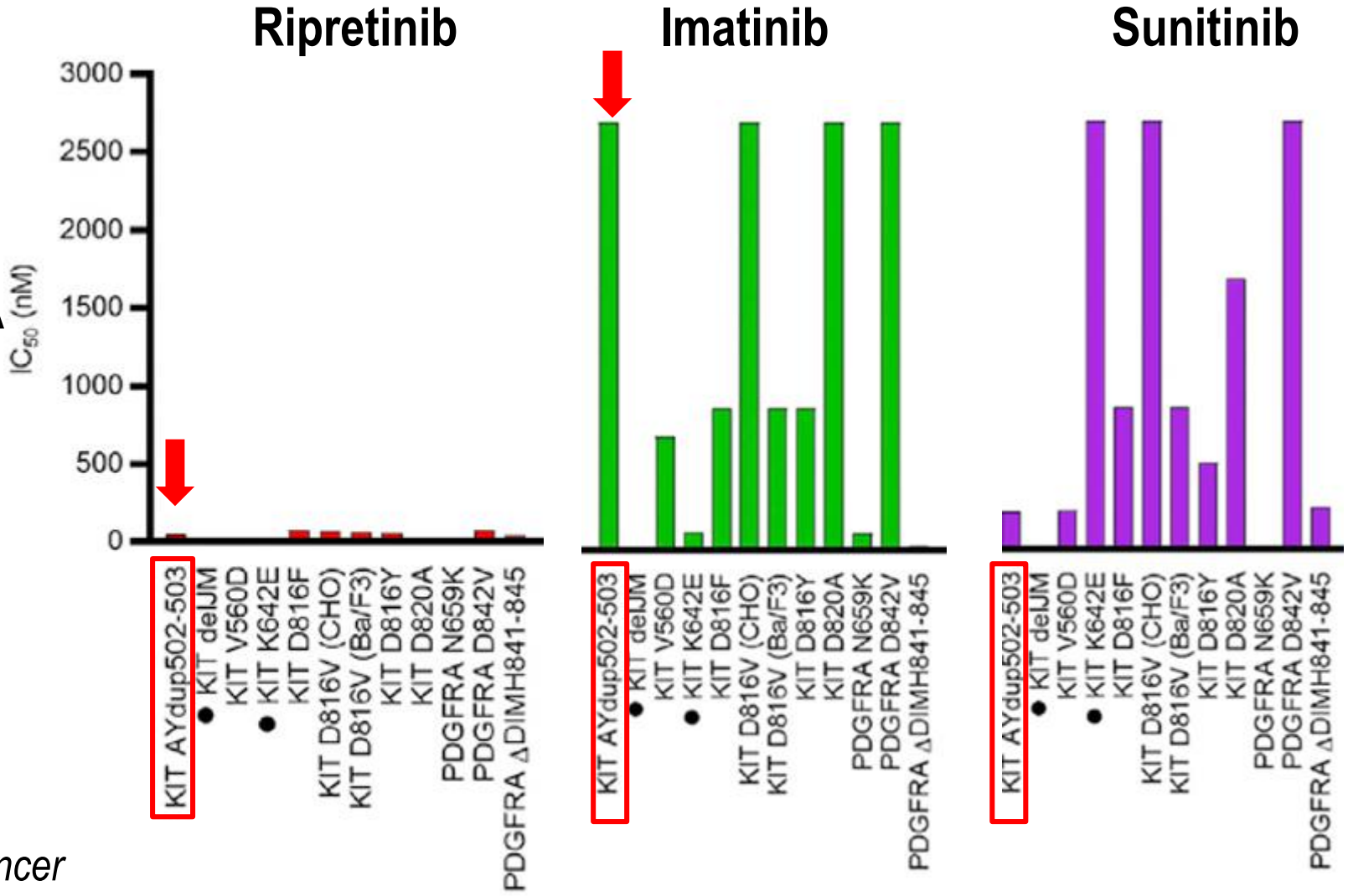
Ripretinib analog DP-2976 bound to KIT

- A novel switch-control inhibitor
- KIT and PDGFRA are dual-switch kinases
  - 1) Inhibitory switch in the juxtamembrane domain (JMD)
  - 2) Main activation loop switch
- Ripretinib
  - Restores the inhibitory (JMD) switch
  - Stabilizes the switches in an inactive (type II) state

Smith BD et al. Cancer Cell 2019;35:738-51

INHIBITION OF *KIT* AND *PDGFRA* MUTANTS IN CELL-BASED ASSAYS

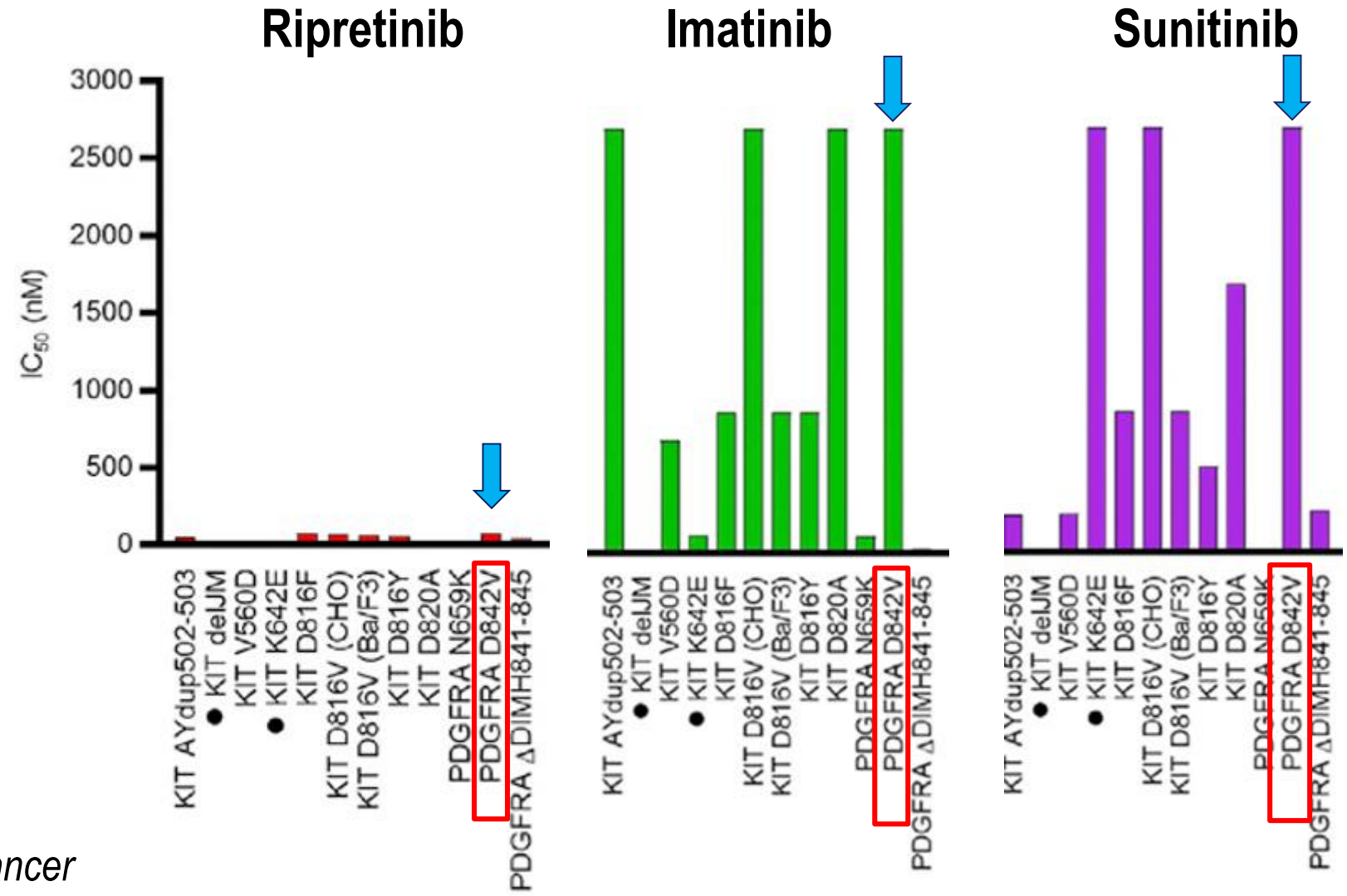
- Ripretinib effective for cells with a common KIT and PRGFRA mutation
- Includes the most common *KIT* exon 9 mutantion (AYdup502-503)



Adapted from *Smith BD et al. Cancer Cell 2019; 35:738-51*

INHIBITION OF *KIT* AND *PDGFRA* MUTANTS IN CELL-BASED ASSAYS

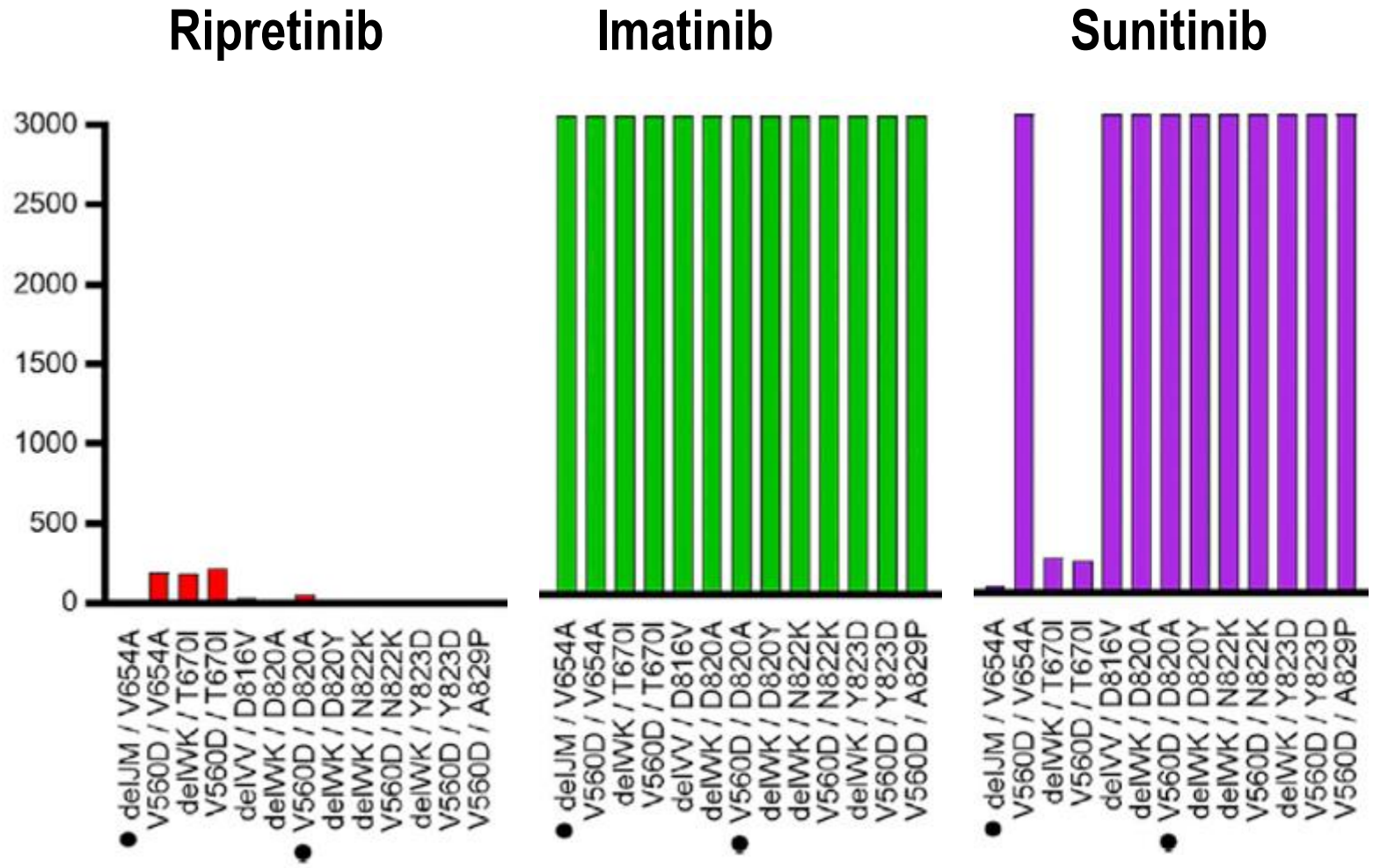
Ripretinib inhibits also the most common *PDGFRA* mutation (D842V) unlike imatinib and sunitinib



Adapted from *Smith BD et al. Cancer Cell 2019; 35:738-51*

RIPRENITIB INHIBITS SECONDARY IMATINIB RESISTANCE MUTATIONS IN CELL-BASED ASSAYS

- Mutated cells harbor both a primary *KIT* mutation and a secondary *KIT* resistance mutation
- These data suggest good riprenitib activity for imatinib-resistant GISTs



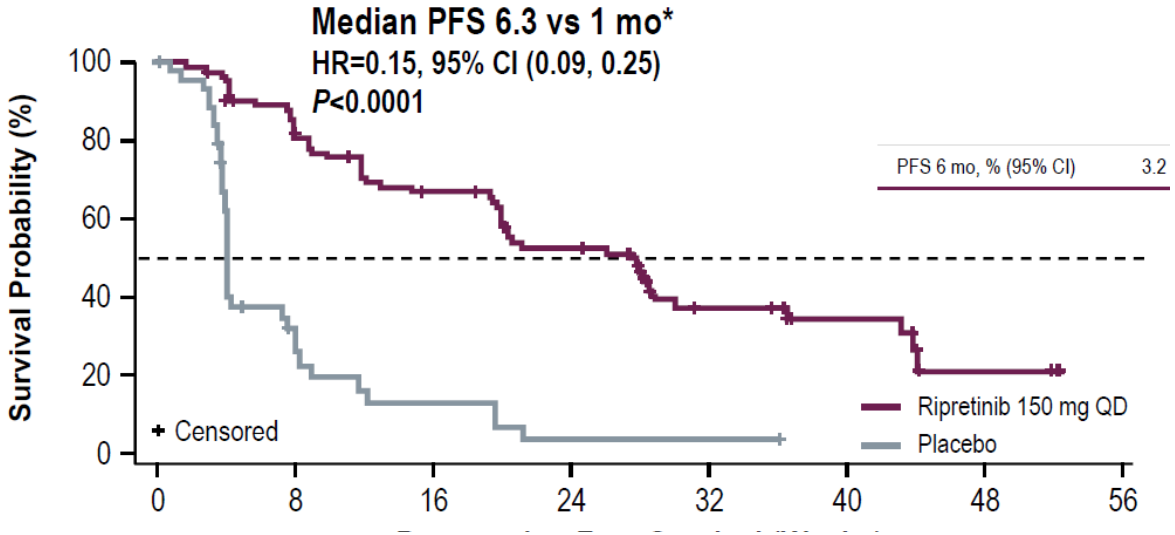
Adapted from *Smith BD et al. Cancer Cell 2019; 35:738-51*

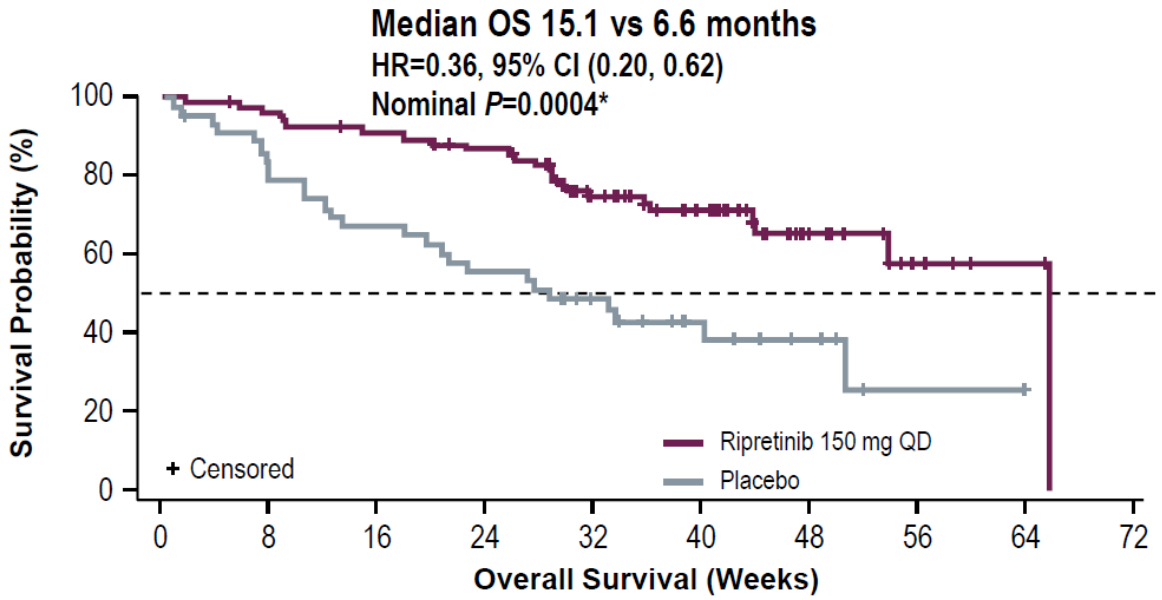
RIPRETINIB EFFICACY

Ripretinib was clearly effective:

- 5.3-month improvement in PFS
- 8.5-month improvement in OS*

*29 (66%) out of the 44 patients assigned to placebo crossed over





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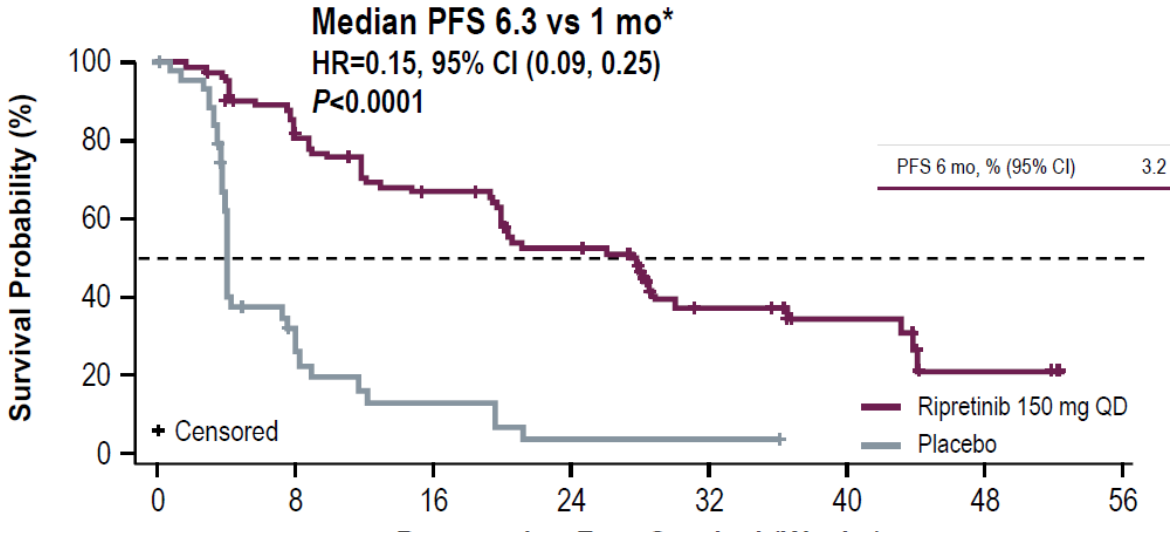
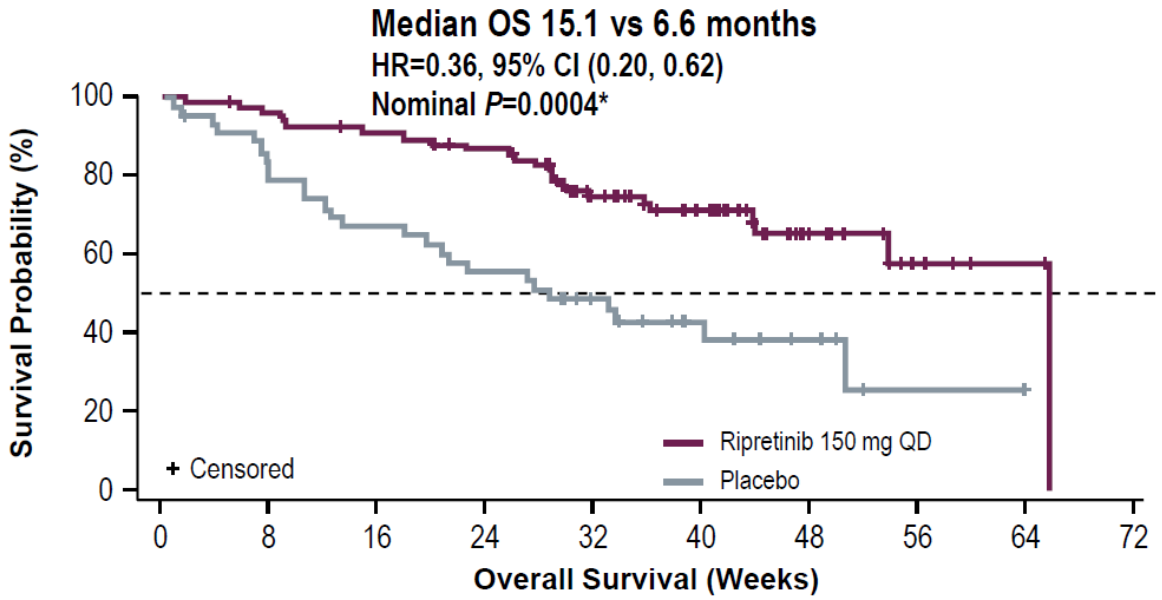
RIPRETINIB EFFICACY

- Efficacy results in different mutational subtypes pending
- Little is known about the resistance mechanisms to riprenitib





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RIPRETINIB EFFICACY COMPARED WITH THE APPROVED AGENTS AND IMATINIB RESUMPTION

Trial feature	Sunitinib (NCT00075218)[1]	Regorafenib (GRID trial)[2]	Imatinib resumption (RIGHT)[3]	Riprenitib (INVICTUS)[4]
Line	2nd	3rd	≥3	≥4
Control	Placebo	Placebo	Placebo	Placebo
No. of patients	312	199	81	129
Median PFS	6 vs. 1 mo HR 0.33; p<0.001	5 vs. 1 mo HR 0.27; p<0.001	2 vs. 1 mo HR 0.46; p=0.005	6 vs. 1 mo HR 0.15; p<0.001
Median OS; Cross-over	17 vs. 15 mo; Yes (extensive)	17 vs. 17 mo; Yes (extensive)	8 vs. 8 mo; Yes (extensive)	15 vs. 7 mo; Yes (extensive)
Response rate	7% vs. 0%	5% vs. 2%	0% vs. 0%	9% vs. 0%

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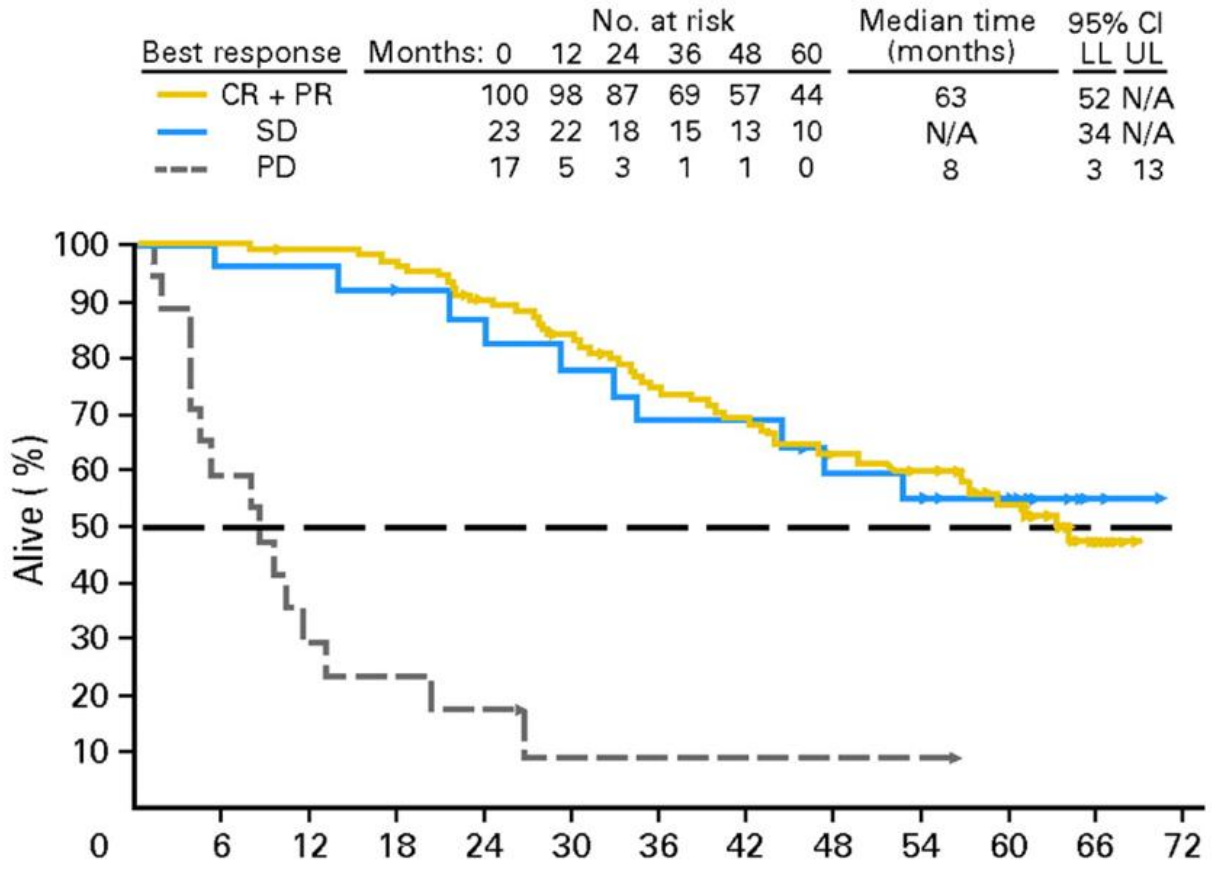
[1]Demetri GD et al. Lancet 2006;358:1329-38; [2]Demetri GD et al. Lancet 2013;381:295-302; [3]Kang YK et al. Lancet Oncol 2013;14:1175–82; [4]von Mehren M et al. ESMO 2019

WHY PFS AND OS BENEFIT DESPITE A LOW RESPONSE RATE?

- These response rates in ≥1st lines are clearly lower than those with first-line matinib (about 70%)
- Achieving stable disease is important in advanced GIST

Fist line imatinib for advanced GIST (B2222 trial)



Blanke CD et al. J Clin Oncol 2008;26:620-5

RIPRETINIB SAFETY

- 52% of the patients had alopecia, 21% had hand-foot syndrome, some GI tract toxicity (nausea, vomiting, diarrhea, constipation)
- Quality of life data not yet reported

SELECTED ADVERSE EFFECTS*

Adverse effect (any grade)	Sunitinib vs. placebo[1] (%)	Regorafenib vs. placebo[2] (%)	Riprenitib vs. placebo[3] (%)
Alopecia	Infrequent (<10%)	24 vs. 2	52 vs. 5
Fatigue	34 vs. 22	39 vs. 18	42 vs. 23
Hand-foot syndr.	13 vs. 2	56 vs. 14	21 vs. 0
Nausea	24 vs. 11	16 vs. 9	39 vs. 12
Vomiting	16 vs. 6	Infrequent (<10%)	21 vs. 7
Diarrhea	29 vs. 8	40 vs. 5	28 vs. 14
Constipation	Infrequent (<10%)	15 vs. 6	34 vs. 19

*The times on active drug and on placebo, the dose reduction schemes, and the methods of data collection likely differ between the trials

[1]Demetri GD et al. Lancet 2006;358:1329-38; [2]Demetri GD et al. Lancet 2013;381:295-302; [3]von Mehren et al. ESMO 2019

SUMMARY

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Ripretinib, a novel switch-control inhibitor

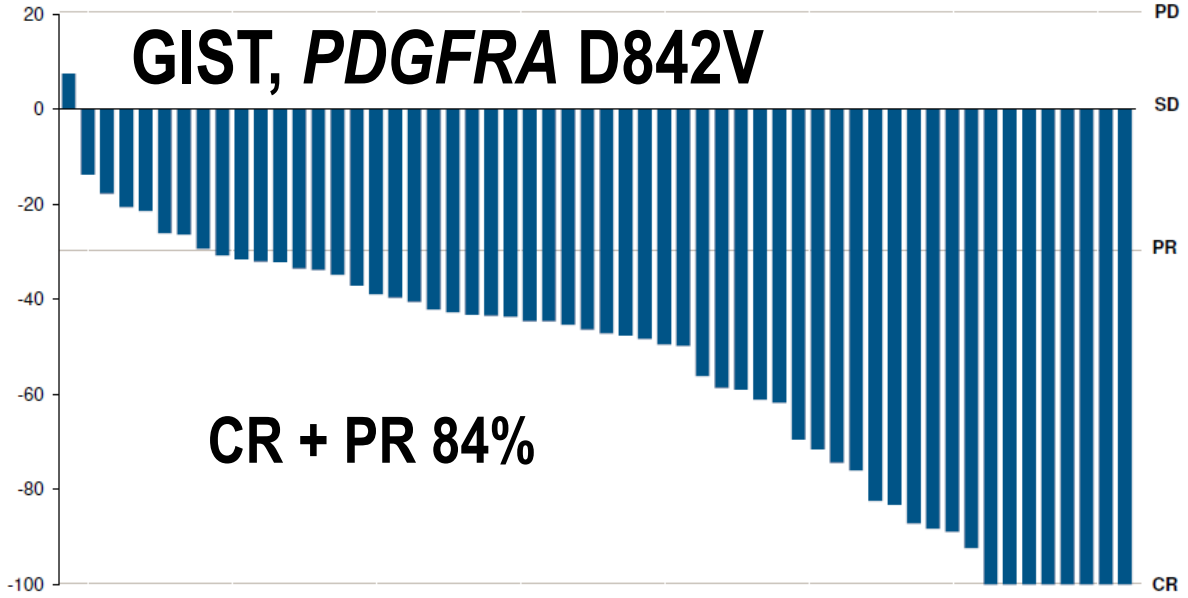
- Improves both PFS and overall survival in a GIST patient population of whose tumor has progressed on all 3 standard therapeutic agents (imatinib, sunitinib, and regorafenib)
- Has an acceptable adverse effect profile in this patient population
- These findings are likely practice changing

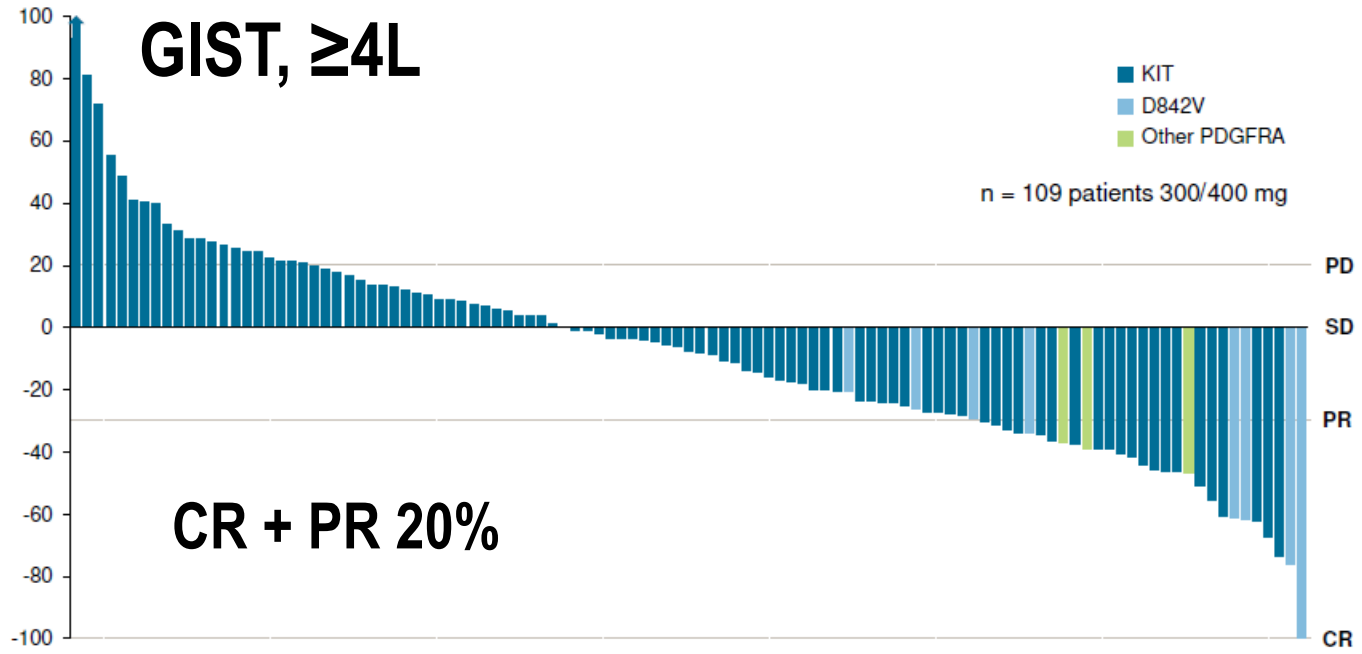
PFS = progression-free survival

AVAPRETINIB (BLU-285)

- A type I KIT/PDGFRA inhibitor
- Remarkably effective for GISTS with *PDGFRA* D842V[1]
- Relatively well tolerated; 26% had Grade 1 or 2 memory impairment, 20% had dizziness[1]
- Being compared to regorafenib in a phase 3 trial as 3L/4L treatment of advanced GIST (VOYAGER, NCT03465722)

[1]*Heinrich MC et al. CTOS, Nov. 15, 2018*





FINAL REMARKS #LBA87

- Results from the ongoing INTRIGUE trial[1] that compares ripretinib with sunitinib as the 2nd line treatment of advanced GIST are awaited with much intrest
- Switch control inhibitors of tyrosine kinases other than KIT/PDGFRA seem an interesting field for further drug development
- The current results are further good news to GIST patients

[1]Trial identifier NCT03673501