GIST metastásico

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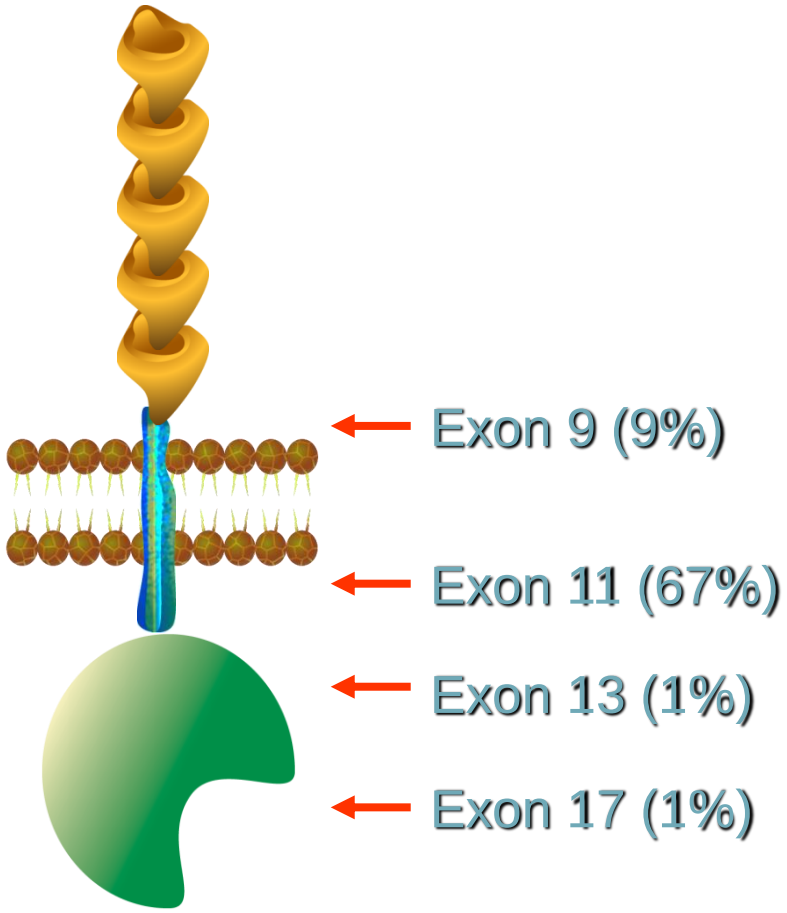
GEIS
GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS

Máster en Tumores Musculoesqueléticos

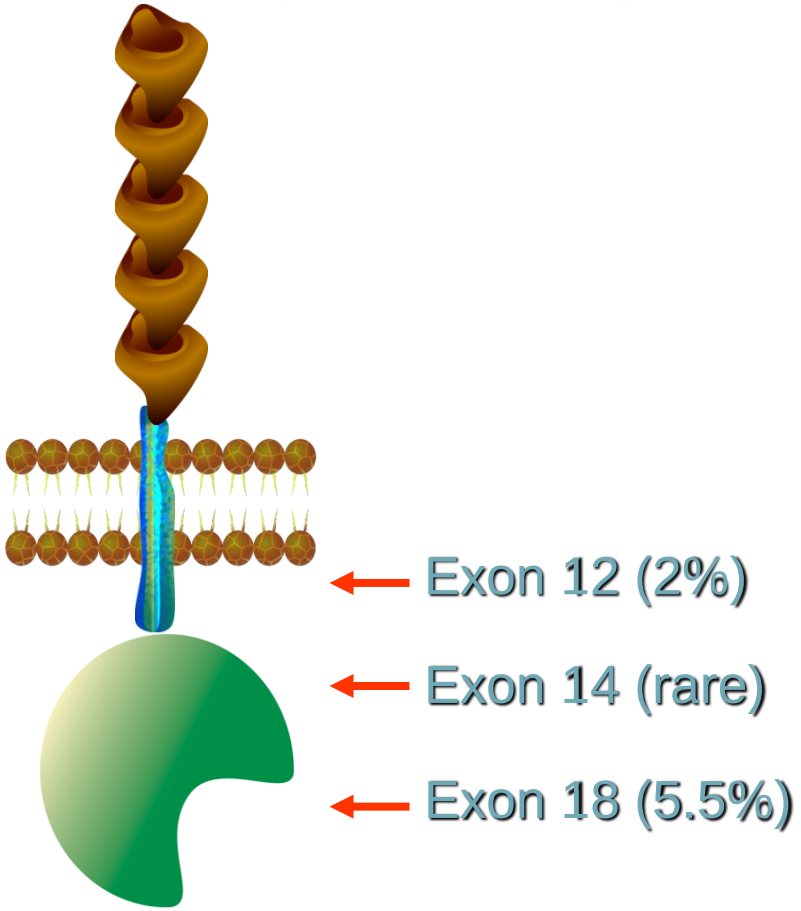
KIT and PDGFRA gain-of-function mutations are primary drivers of oncogenic signal in GIST

Overall Mutation Frequency (950 GISTs): 86%

KIT (78.5%)



PDGFRA (7.5% total)



Courtesy of Jonathan A. Fletcher

Approved agents for the treatment of locally-advanced or metastatic GIST

KIT/PDGFRA-mutant GIST

PDGFRA D842V-mutant GIST

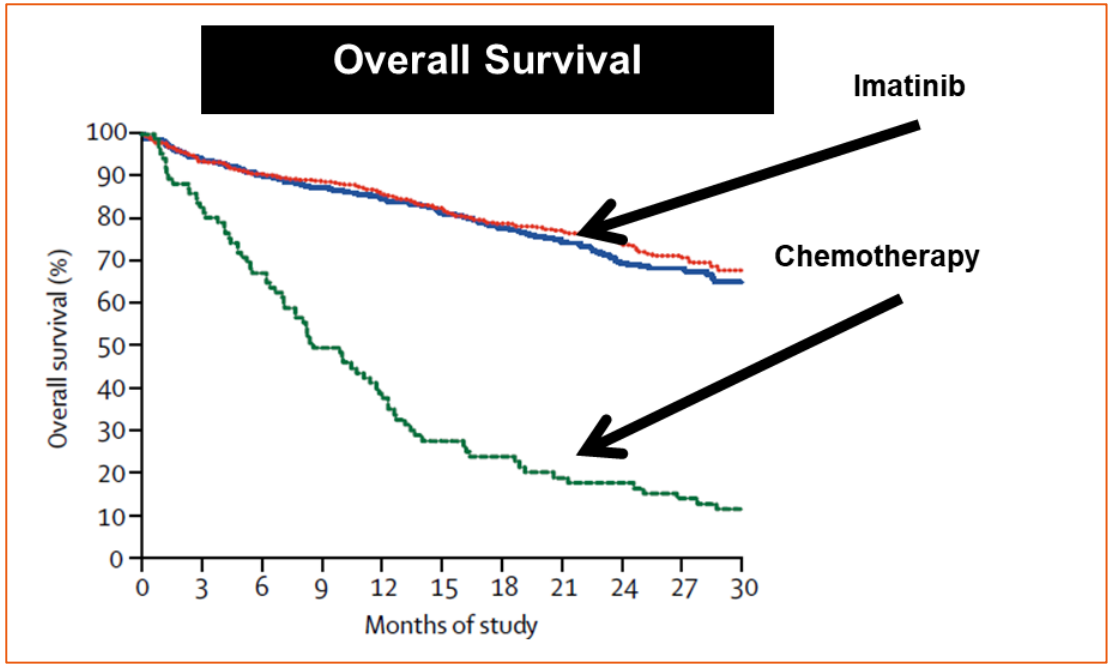
Approved agents for the treatment of locally-advanced or metastatic GIST: IMATINIB

IMATINIB 2001

mPFS 24 mo
ORR 68.1%

KIT/PDGFRA-mutant GIST

PDGFRA D842V-mutant GIST



Demetri, *NEJM* 2002
Blanke, *J Clin Oncol* 2008

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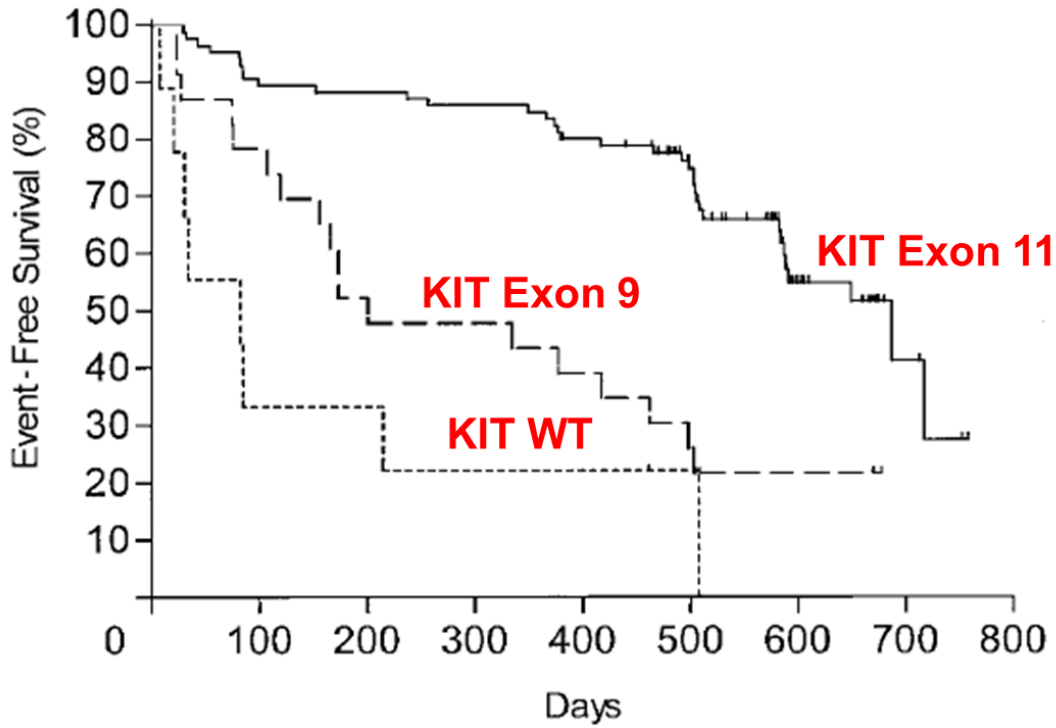
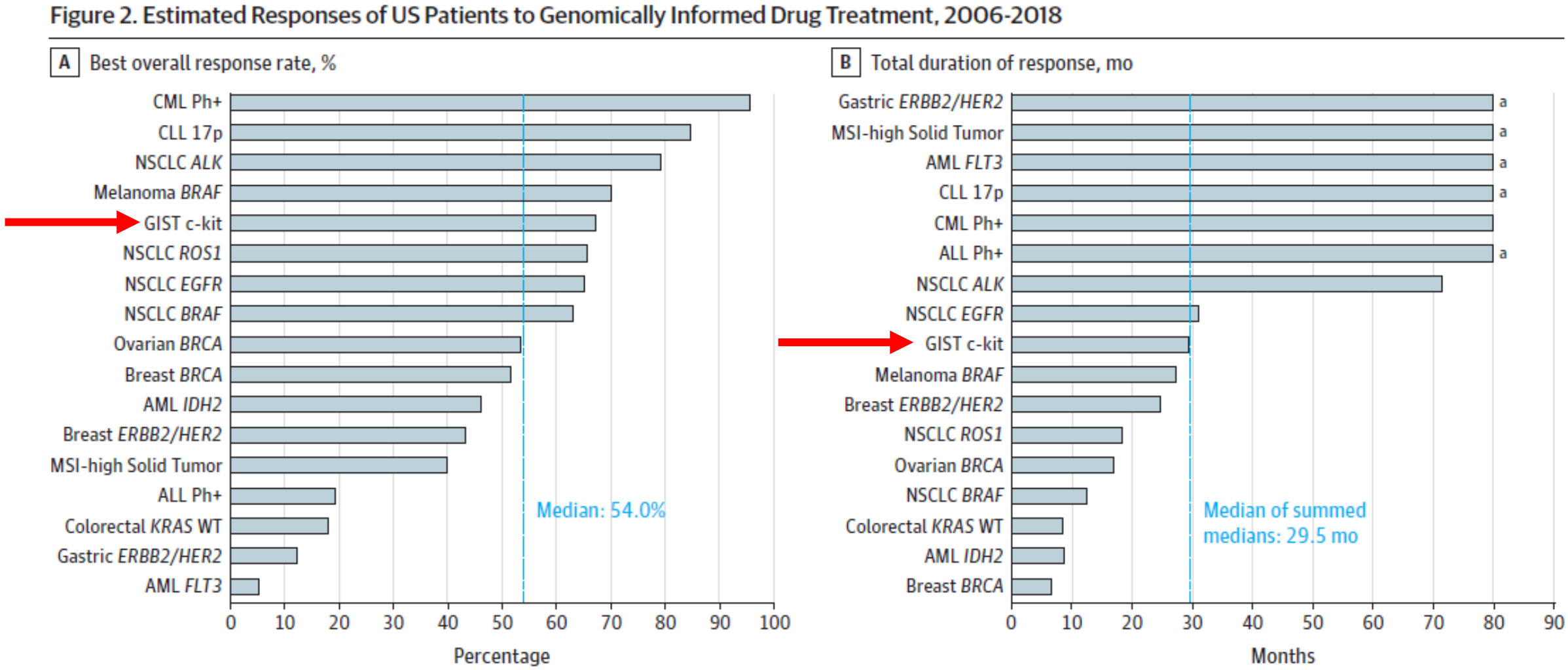
PDGFRA D842V-mutant GIST

KIT primary genotype predicts the activity of first-line imatinib



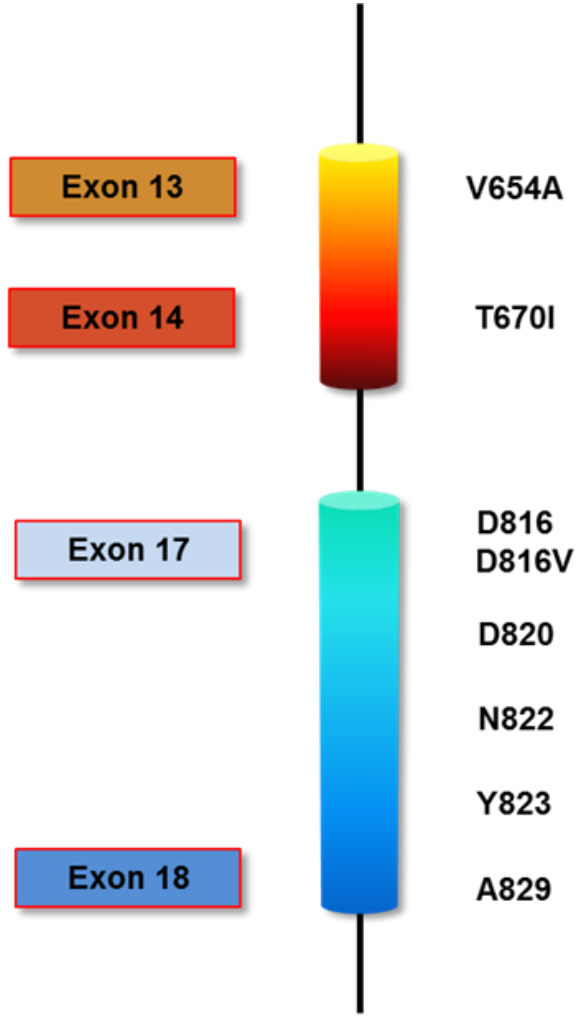
Heinrich, *J Clin Oncol* 2003

Approved agents for the treatment of locally-advanced or metastatic GIST: IMATINIB

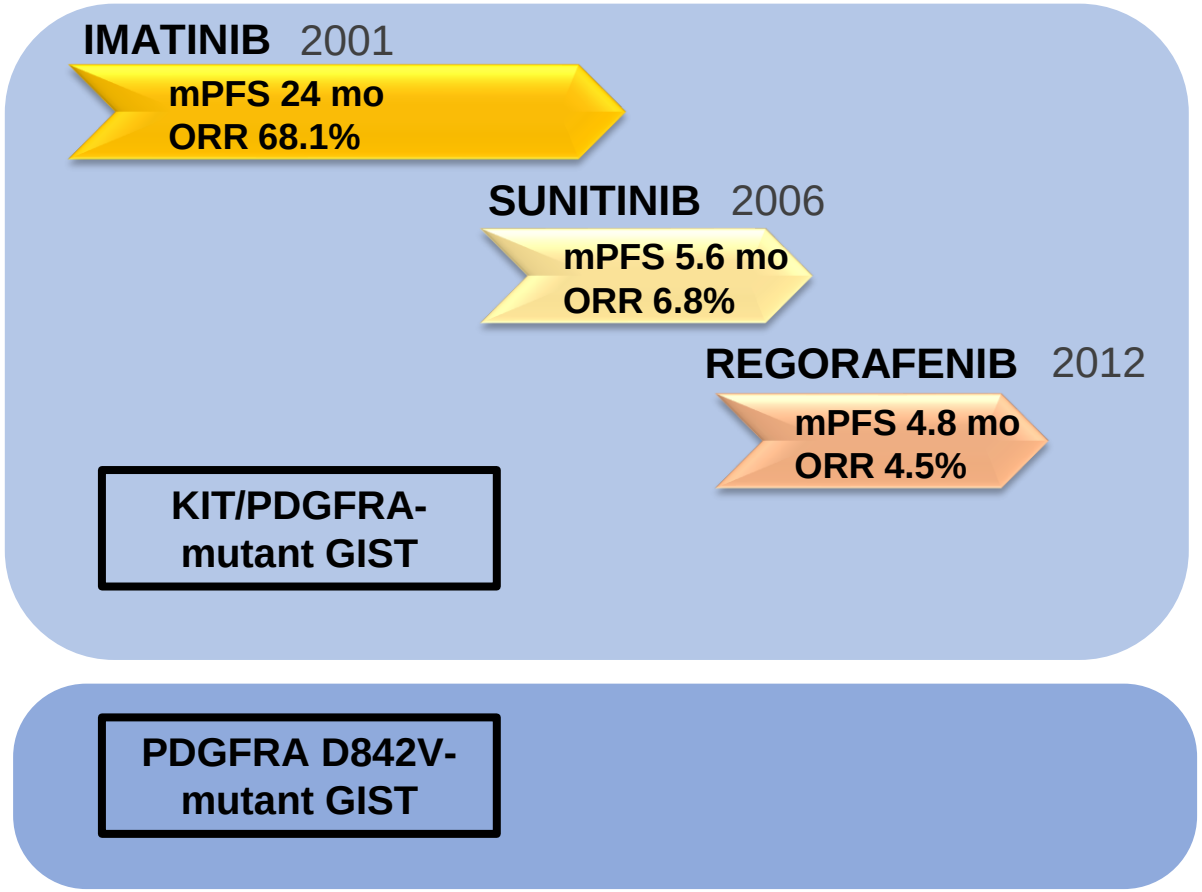


Marquart, *JAMA Oncol* 2018

Imatinib resistance: KIT secondary mutations



Approved agents for the treatment of locally-advanced or metastatic GIST: SUNITINIB y REGORAFENIB



Demetri, *Lancet* 2006
Demetri, *Lancet* 2013

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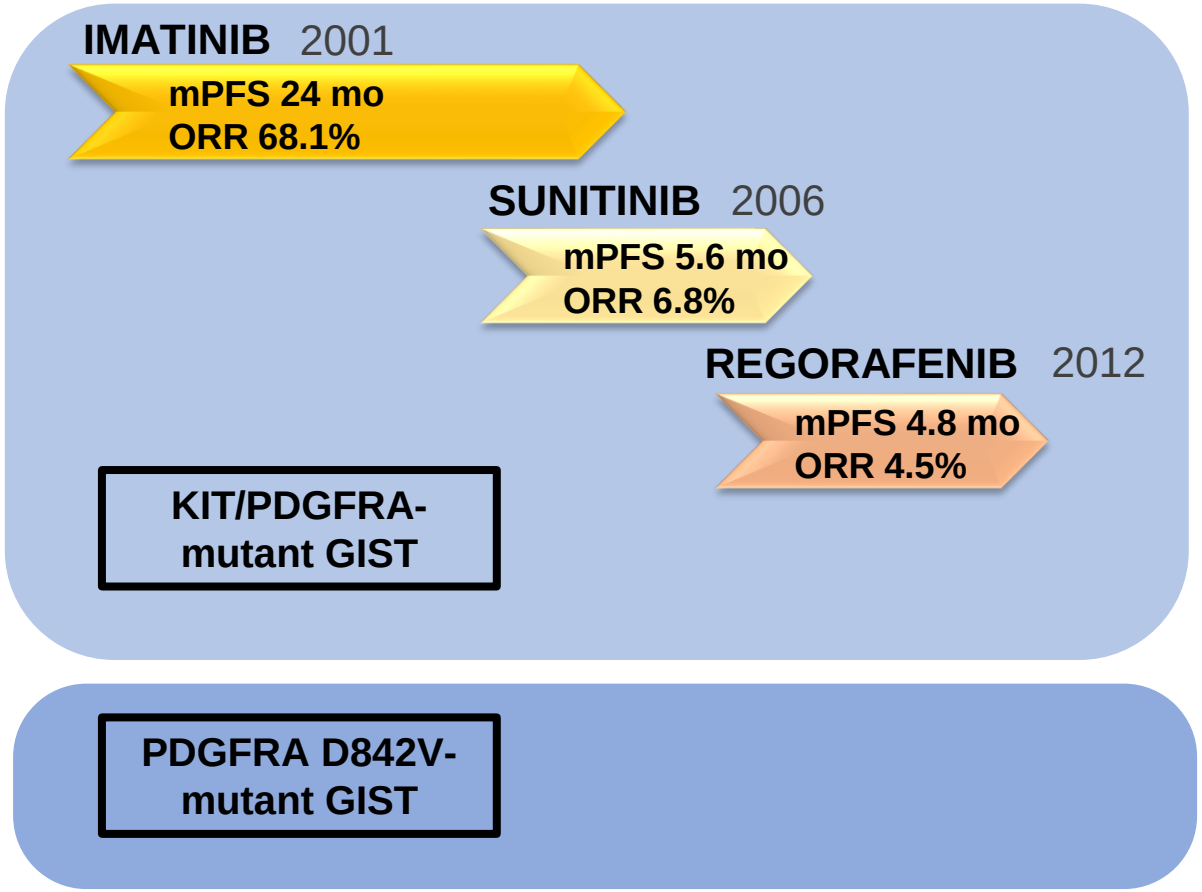


	Imatinib (n=147)	Sunitinib (n=207)	Regorafenib (n=133)
ORR	68.1%	6.8%	4.5%
$SD_{12\ weeks}$	15.6%	53%	48.1%
TTP/PFS	24 mo	5.6 mo	4.8 mo

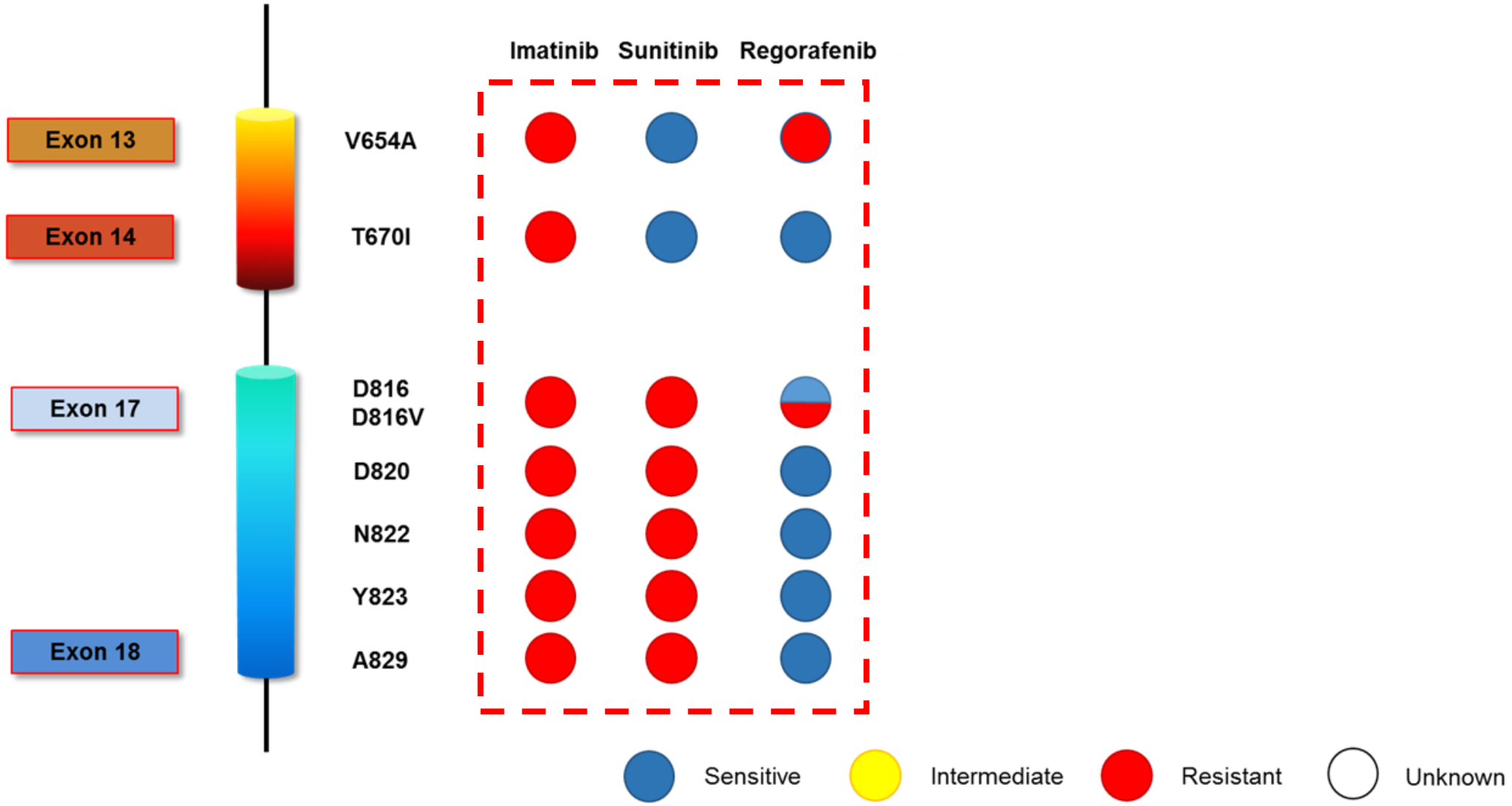
Demetri, *Lancet* 2006
Demetri, *Lancet* 2013

Approved agents for the treatment of locally-advanced or metastatic GIST: OTHER TKIs

Drug	Clinical Trial	Setting Treatment Line	ORR (%)	mPFS (mo)	Phase
Avapritinib	Kang (2021)[78]	Third/fourth	17	4.2	III-R
Cabozantinib	Schöffski (2020)[79]	Third	14	5.5	II
Dasatinib	Schuetze (2018)[80]	Second or more	4	2.9	II
Dovitinib	Kang (2013)[81]	Third or more	3	3.6	II
	Joensuu (2017)[82]	Third or more	5	4.6	II
Masitinib	Adenis (2014)[83]	Second	NA	3.7	II
Nilotinib	Montemurro (2009)[84]	Third or more	10	2.8	II
	Sawaki (2011)[85]	Third	3	3.7	II
	Cauchi (2012)[86]	Third or more	0	2.0	II
	Reichardt (2012)[87]	Third	< 1	3.6	III-R
Pazopanib	Ganjoo (2014)[88]	Second or more	0	1.9	II
	Mir (2016)[89]	Second or more	0	3.4	II-R
	Eriksson (2021)[90]	Third/fourth	3	4.5	II
Ponatinib*	George (2022)[91]	Second or more	8	4.3	II
Sorafenib	Kindler (2011)[92]	Second or more	13	5.2	II
	Park (2012)[93]	Third or more	13	4.9	II

Schaefer, DeMatteo and Serrano, *ASCO EdBook* 2022

KIT / PDGFRA 2nd genotype predicts response to TKIs



Heinrich, *JCO* 2008; Serrano, *BJC* 2019; Serrano, *Oncotarget* 2019

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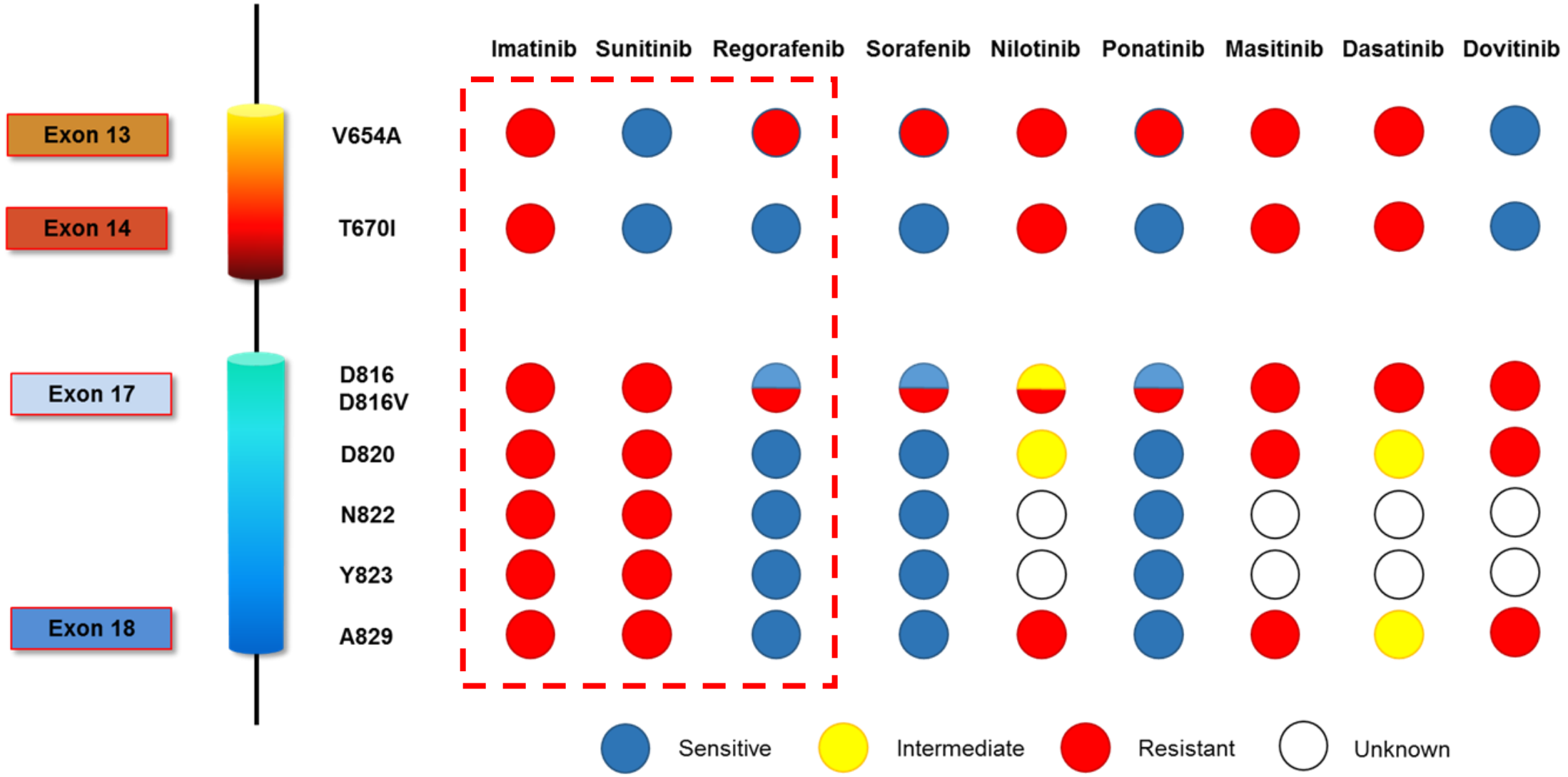

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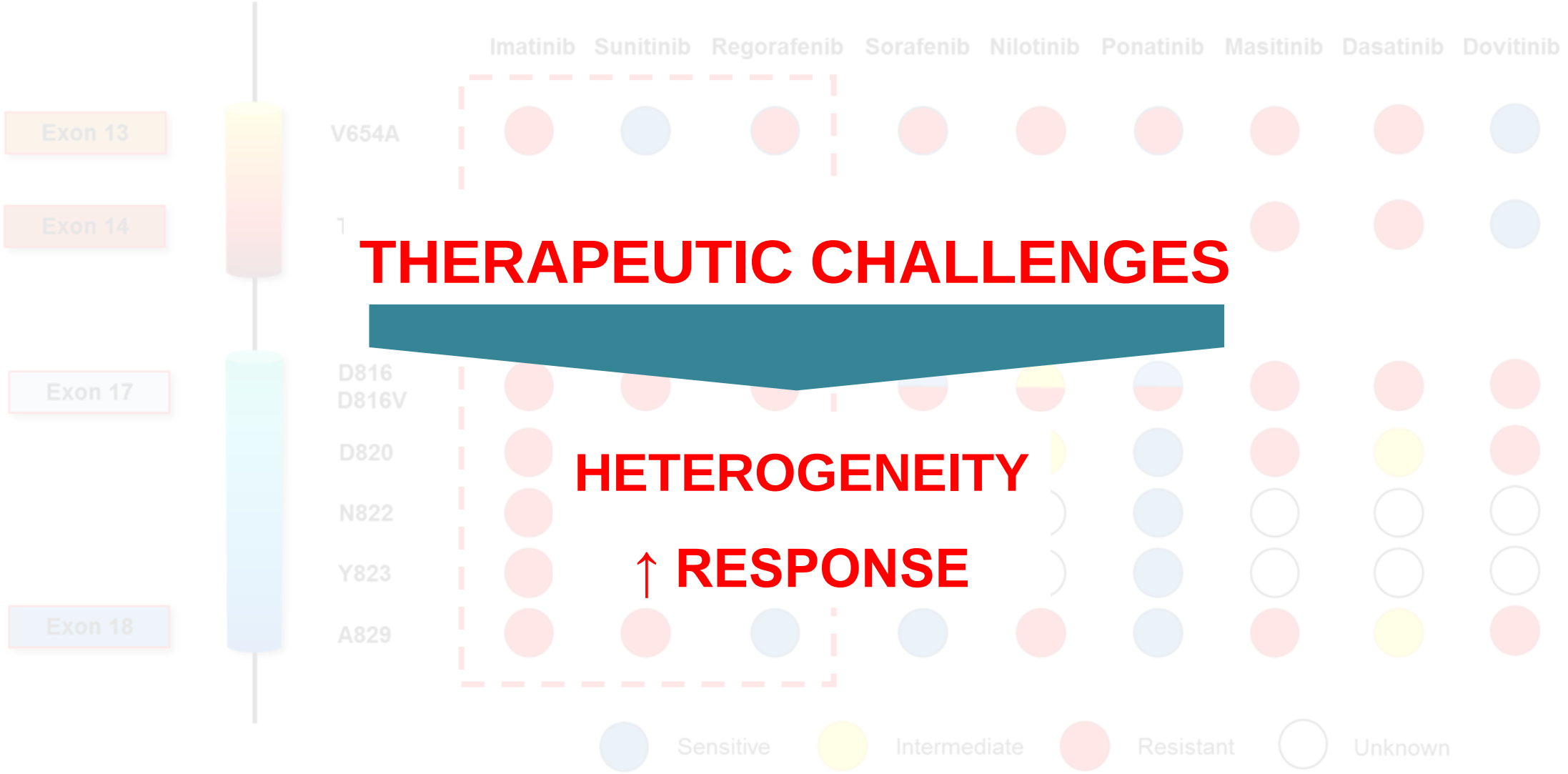
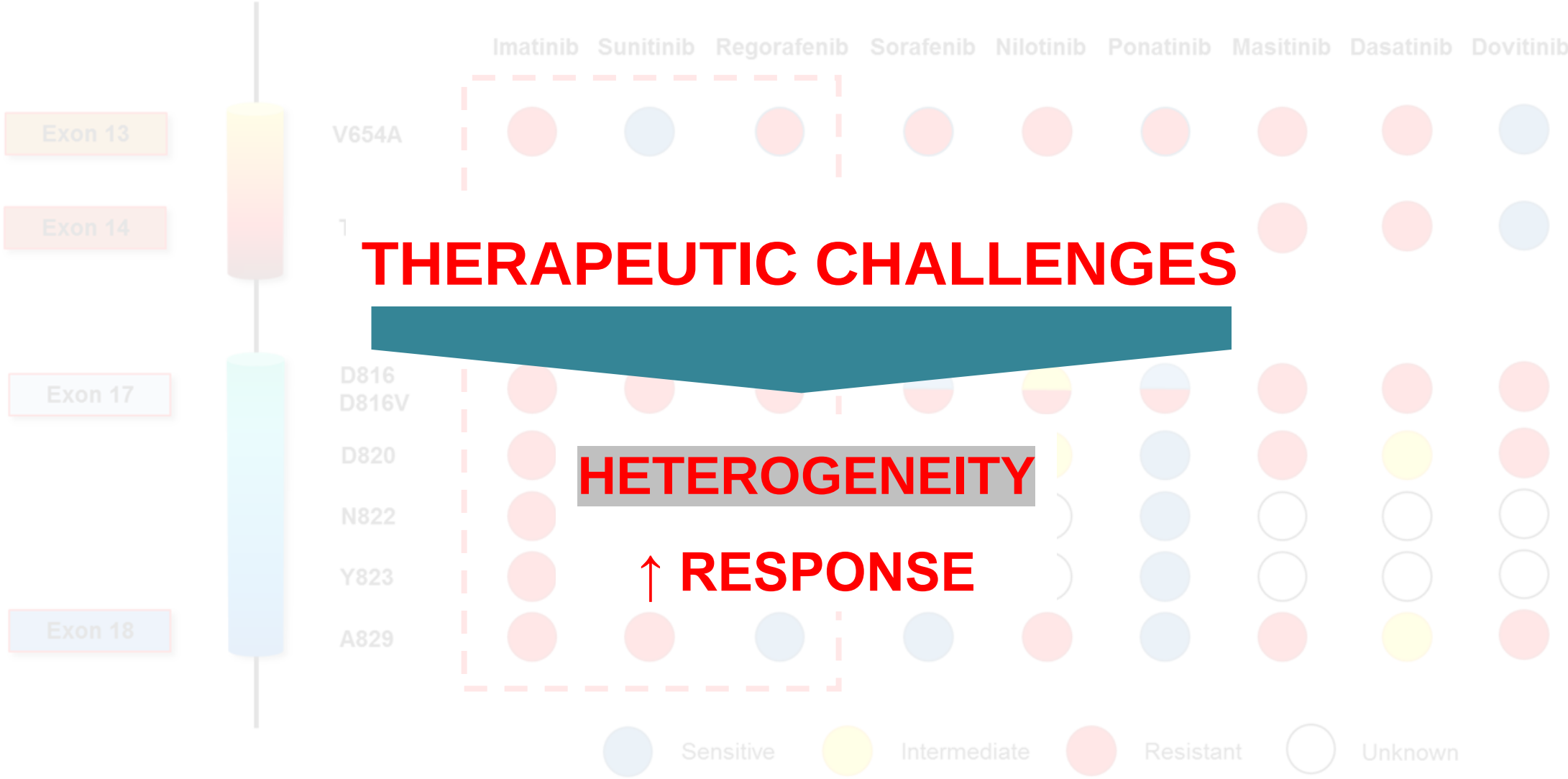


THERAPEUTIC CHALLENGES

HETEROGENEITY

↑ RESPONSE

KIT / PDGFRA 2nd genotype predicts response to TKIs



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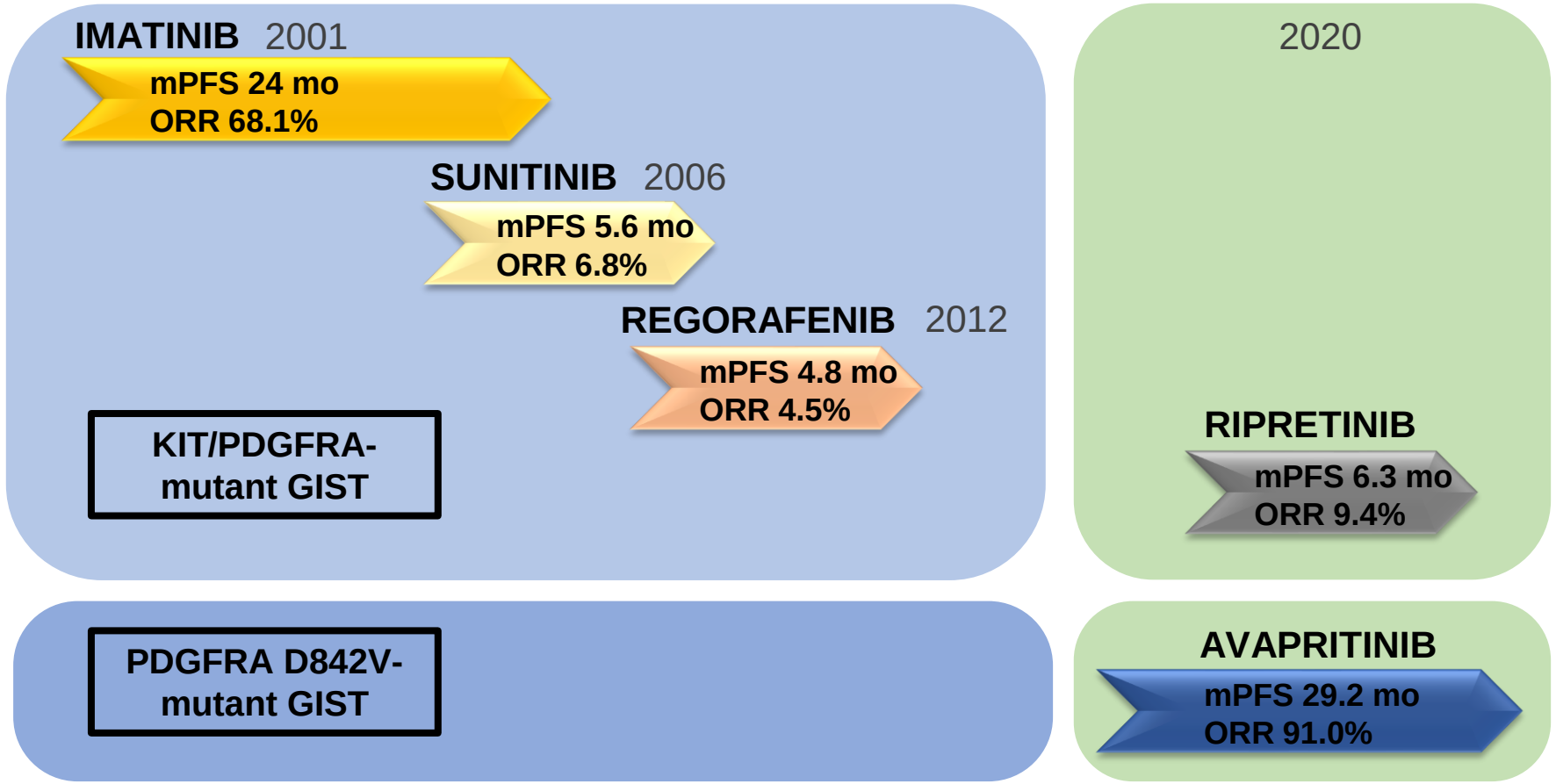

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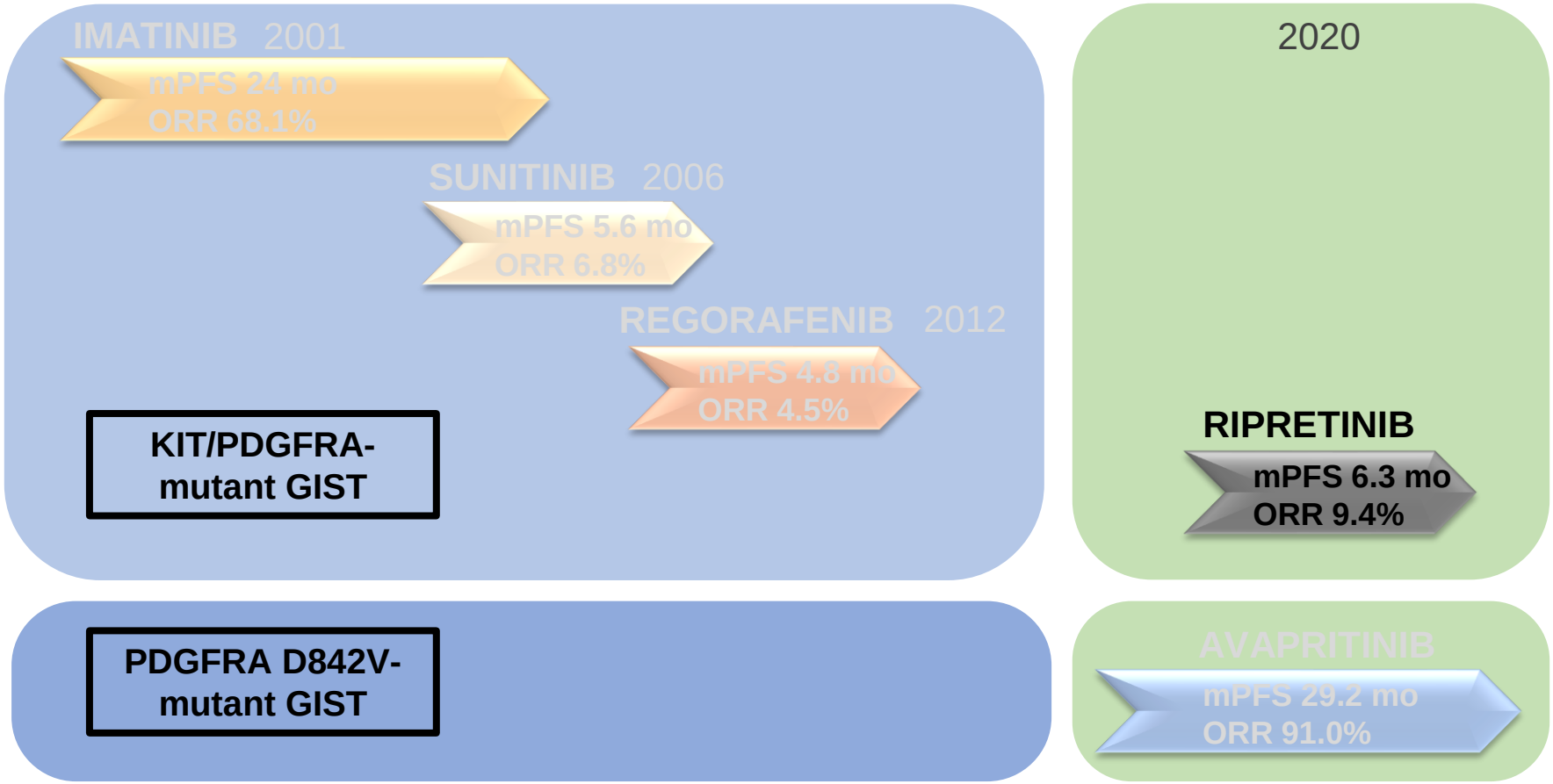
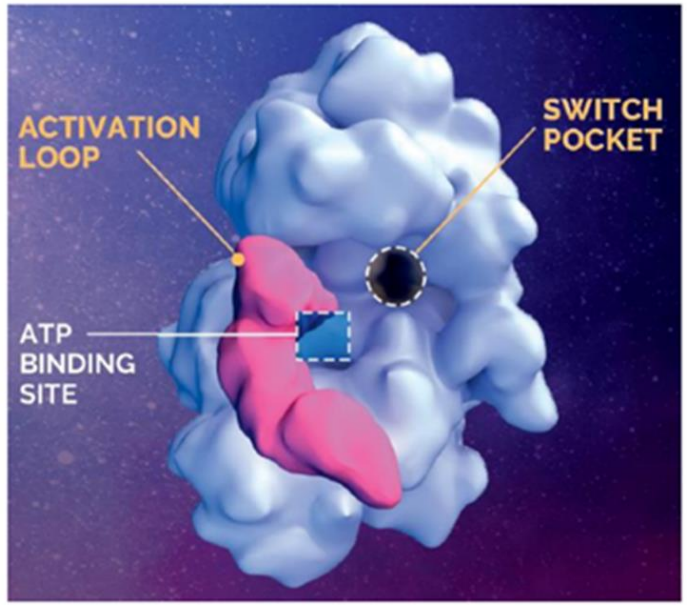


HETEROGENEITY

↑ RESPONSE

RIPRETINIB has broad activity against KIT/PDGFRA mutants



- **Switch control** kinase inhibition
- **Ripretinib** binds to the activation loop and the switch pocket
- Lock the kinase in the **inactive state**

Smith, *Cancer Cell* 2019

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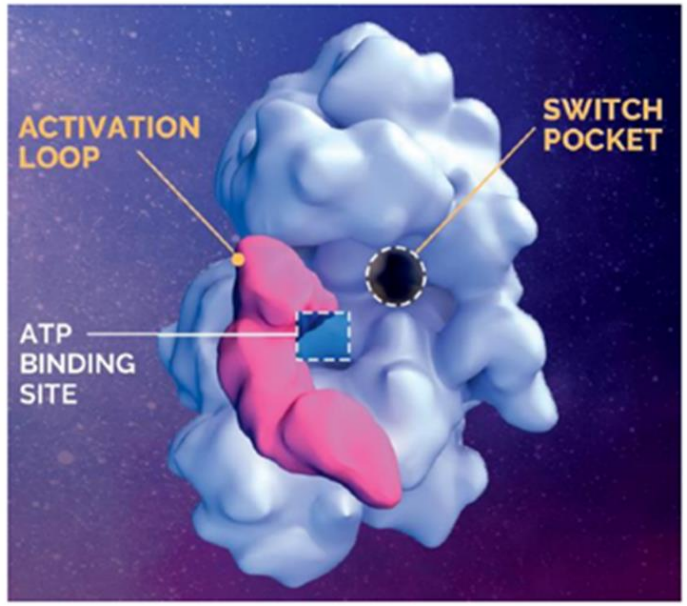

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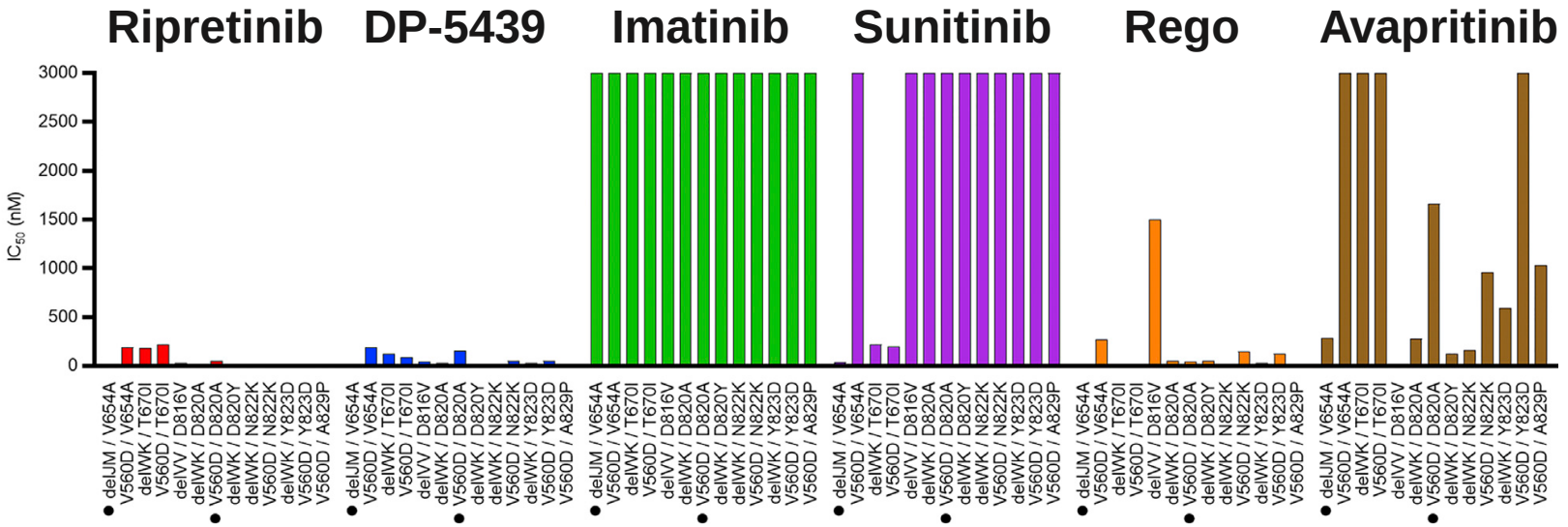
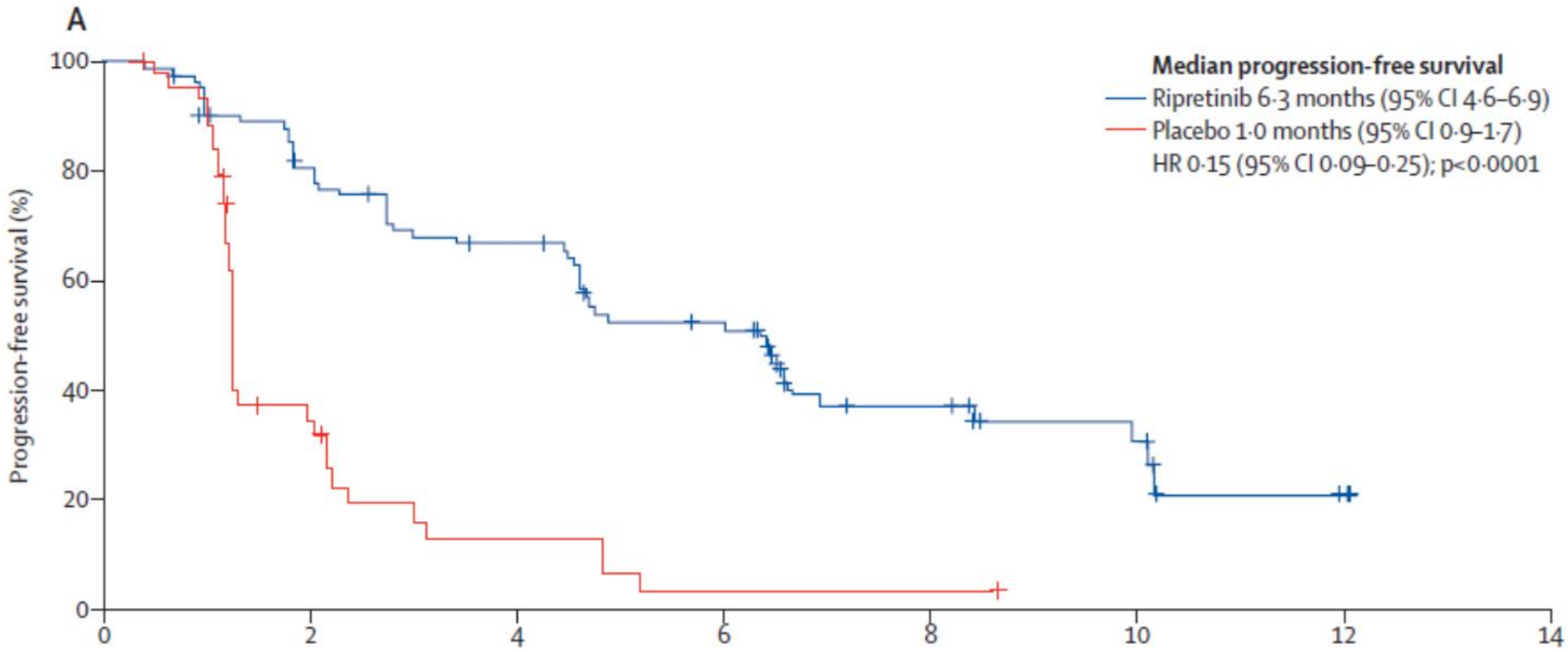


Inhibition of KIT and PDGFRA mutants in transfected CHO or Ba/F3 cells IC50 values

Smith, *Cancer Cell* 2019

Phase III INVICTUS trial: ripretinib v. placebo ≥ 4L

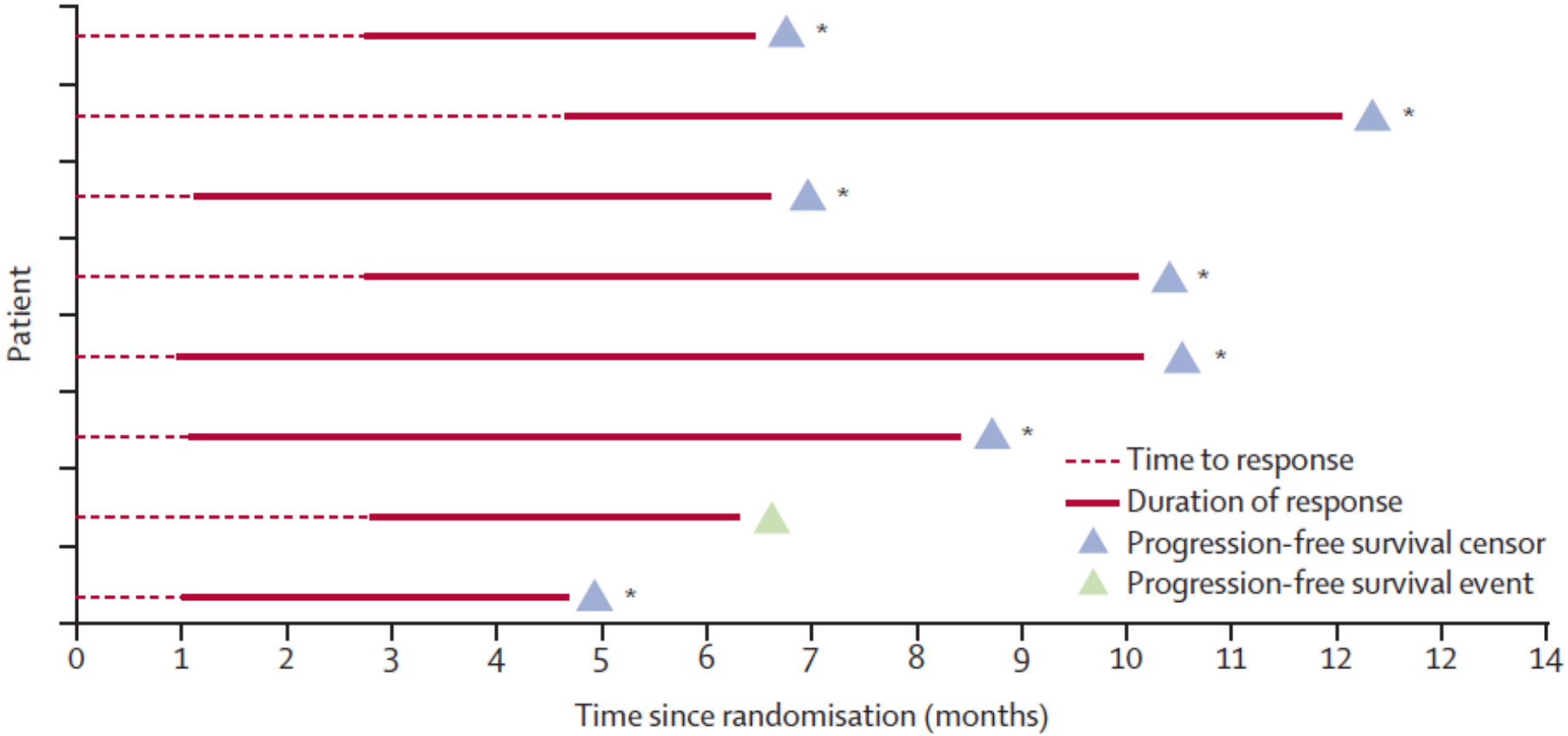
❖ **Benefit in mPFS**: ripretinib (6.3 mo) v. placebo (1.0 mo)



Blay, *Lancet Oncol* 2020

Phase III INVICTUS trial: ripretinib v. placebo ≥ 4L

- **ORR 9.4%,** comparable with other TKIs in IM-resistant GIST

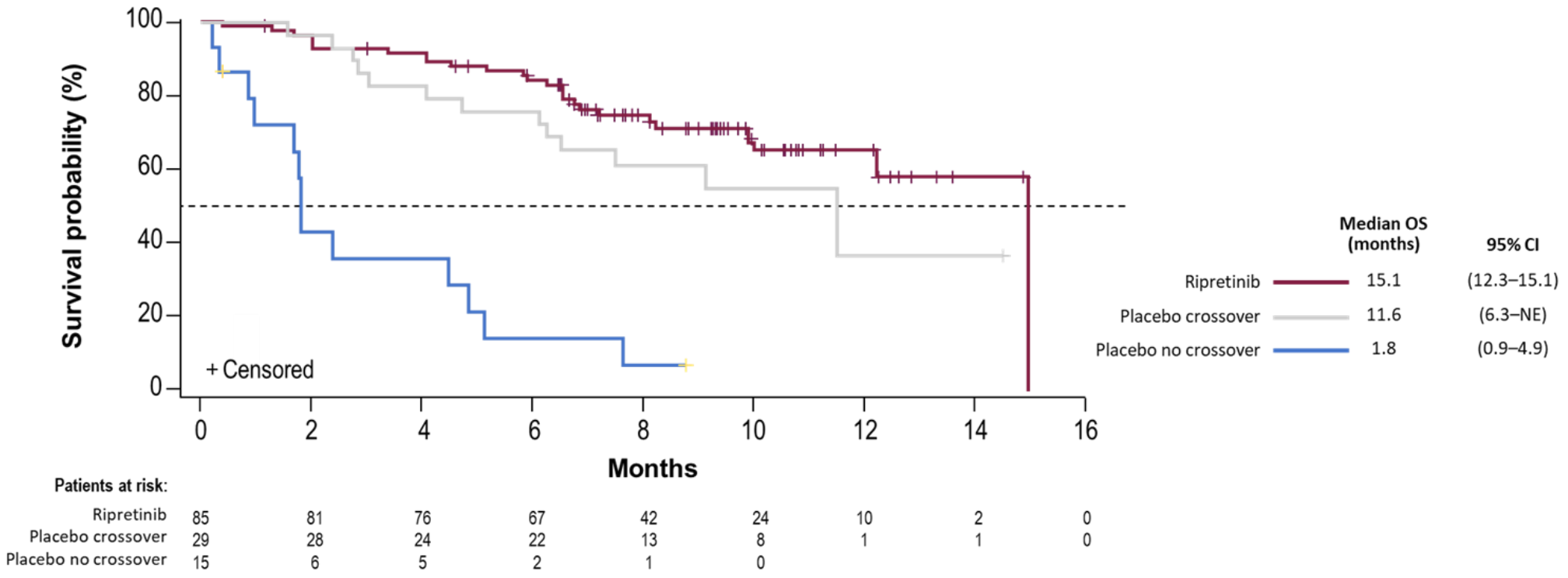


Blay, *Lancet Oncol* 2020

Phase III INVICTUS trial: ripretinib v. placebo ≥ 4L

❖**OS benefit:** 11.6 months with crossover v. 1.8 months without crossover

→ GIST becomes a highly aggressive disease over time



Serrano, *ESMO GI* 2020

Phase III INVICTUS trial: ripretinib v. placebo ≥ 4L

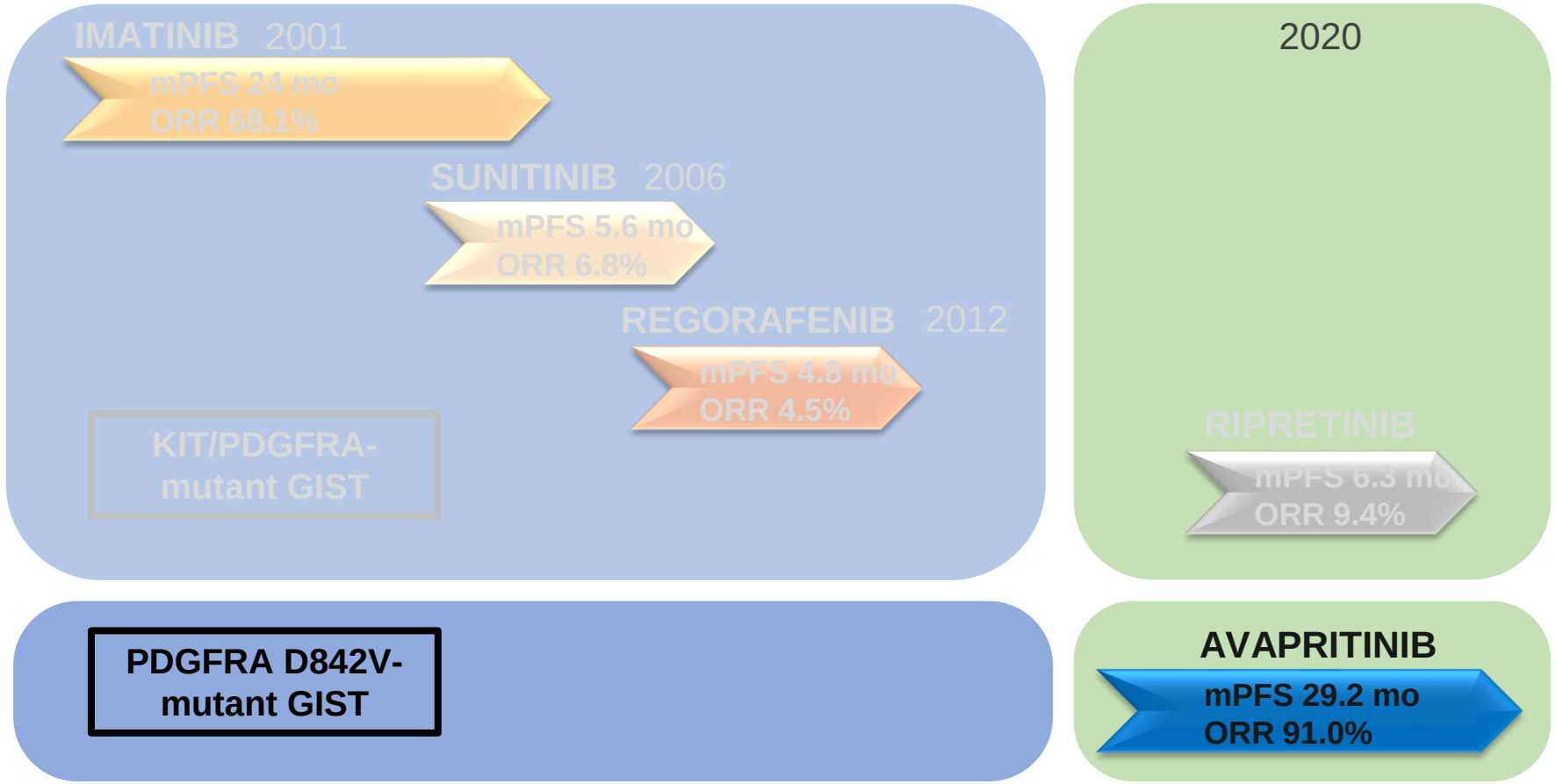
❖ **Safety profile:** treatment-related adverse events (≥ 5%)

	Ripretinib group (n=85)			
	Grade 1–2	Grade 3	Grade 4	Grade 5
Alopecia	42 (49%)†	..	..	..
Myalgia	23 (27%)	1 (1%)	..	..
Nausea	21 (25%)	1 (1%)	..	..
Fatigue	20 (24%)	2 (2%)	..	..
Palmar–plantar erythrodysesthesia syndrome	18 (21%)	0	..	..
Diarrhoea	17 (20%)	1 (1%)	0	0
Constipation	13 (15%)	0	0	0
Decreased appetite	12 (14%)	1 (1%)	0	0
Weight loss	13 (15%)	0	..	..
Blood bilirubin increased	12 (14%)	0	0	..
Arthralgia	10 (12%)	0	..	..
Muscle spasms	10 (12%)	0	..	..
Hypertension	4 (5%)	3 (4%)	0	0
Lipase increase	4 (5%)	4 (5%)	0	..
Pain in extremity	5 (6%)	1 (1%)	..	..
Hypophosphataemia	3 (4%)	2 (2%)	0	0

Blay, *Lancet Oncol* 2020

Musculoesqueléticos

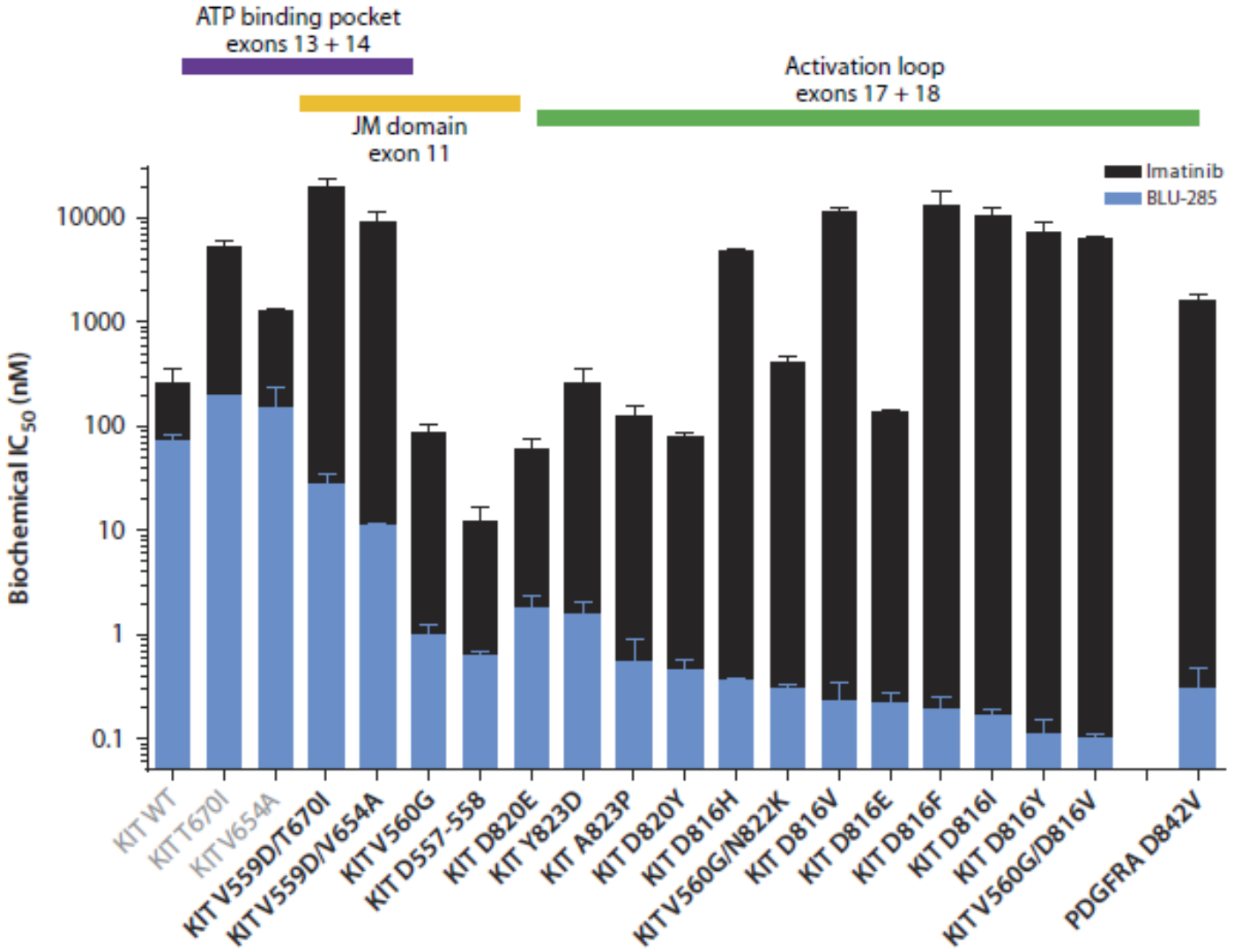
Approved agents for the treatment of locally-advanced or metastatic GIST



HETEROGENEITY

↑ RESPONSE

AVAPRITINIB is a type I TKI highly active against mutations in *PDGFRA* exon 18 D842V

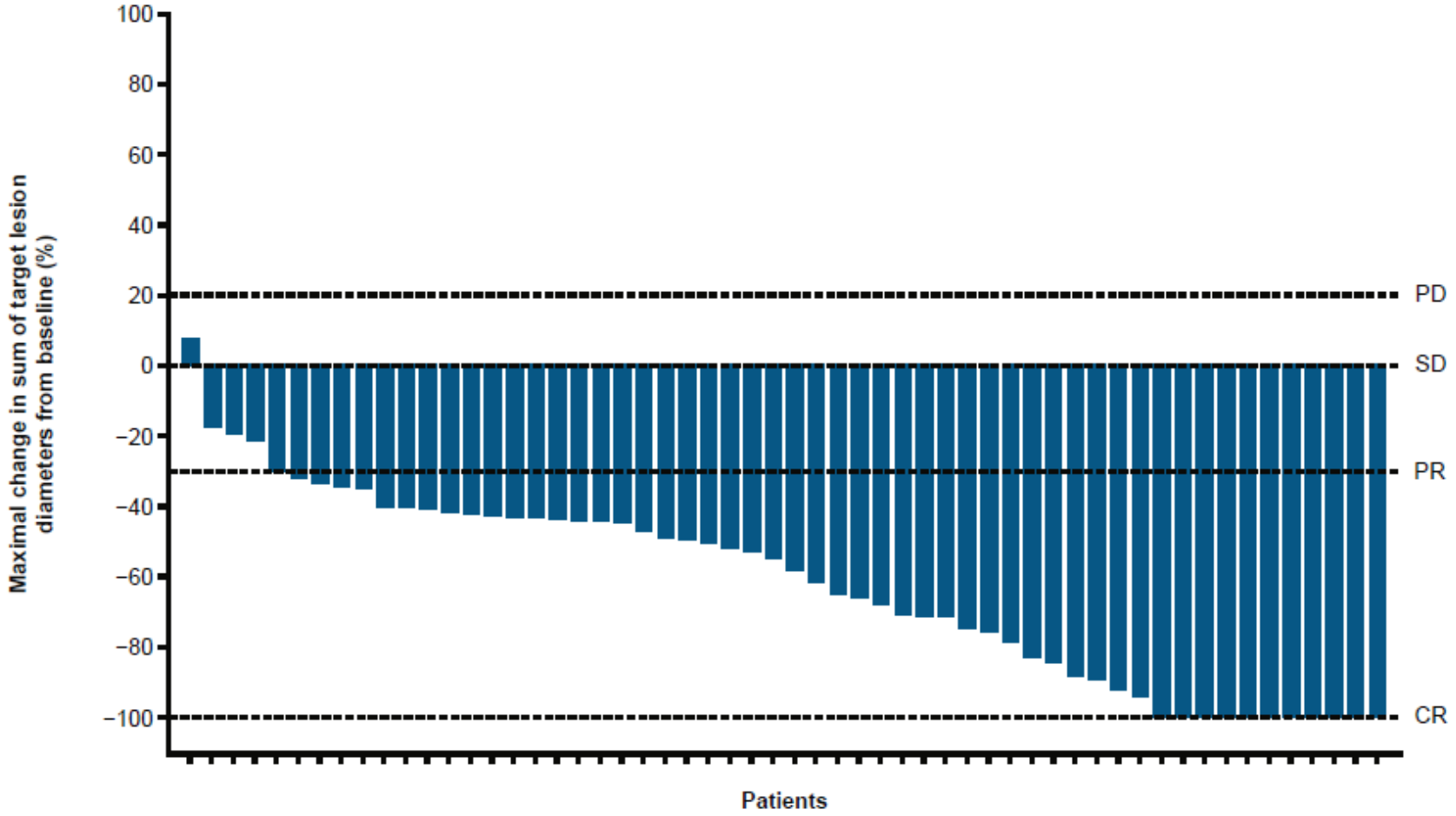


- Selective activity against **mutations in the activation loop**
- **Type I TKI:** binds to the active conformation of the kinase

Evans, *Sci Transl Med* 2017

Phase I NAVIGATOR trial: avapritinib in PDGFRA D842V GIST

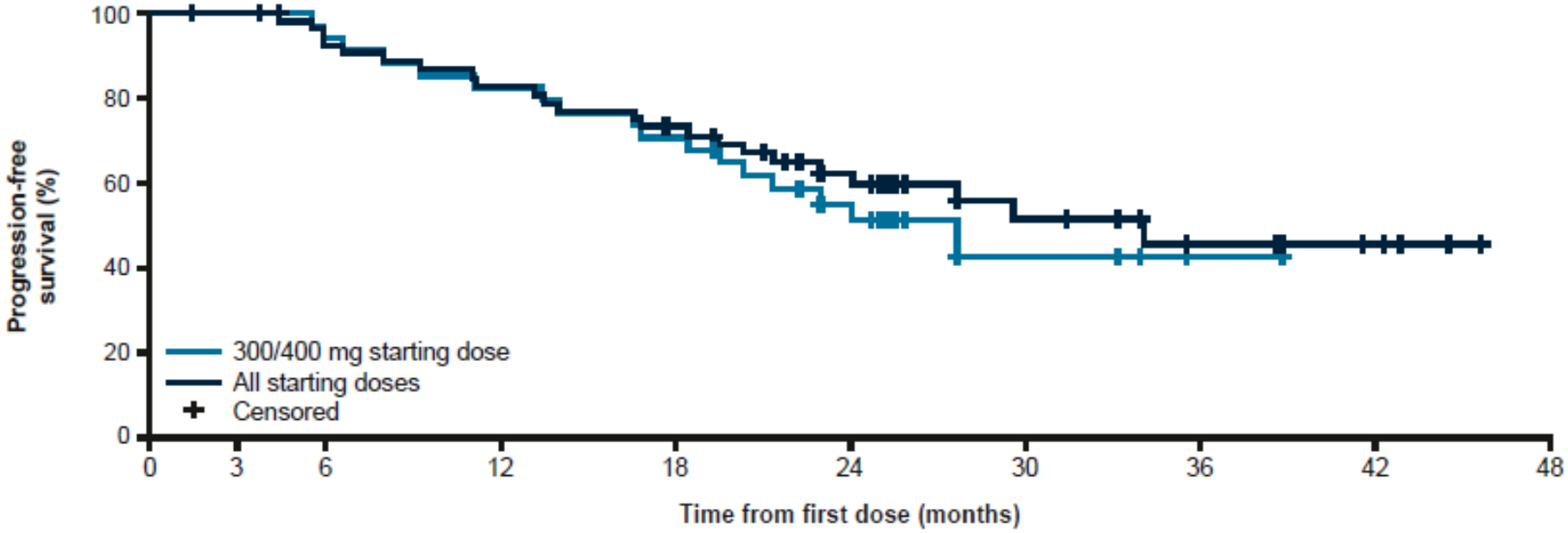
- ORR **91%**, Disease control rate ≥ 16 weeks, **100%**



Heinrich, *Lancet Oncol* 2020; Jones, *Eur J Can* 2021

Phase I NAVIGATOR trial: avapritinib in PDGFRA D842V GIST

- mPFS (all patients) **34.0 months**



Number at risk									
300/400 mg starting dose	38	37	32	28	24	14	4	1	0
All starting doses	56	55	48	43	36	23	12	7	4	0

Heinrich, *Lancet Oncol* 2020; Jones, *Eur J Can* 2021

Phase I NAVIGATOR trial: avapritinib in PDGFRA D842V GIST

❖**Safety profile:** all-cause adverse events (≥ 20%)

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)

Preferred term, n (%)	*PDGFRA* D842V population (n = 56)	Safety population (N = 250)
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)

Heinrich, *Lancet Oncol* 2020; Jones, *Eur J Can* 2021

Phase I NAVIGATOR trial: avapritinib in PDGFRA D842V GIST

❖ **Safety profile:** cognitive effects

	Patients (*n* = 167)				
	AE incidence				AEs leading to permanent treatment discontinuation
	Grade 1	Grade 2	Grade 3	Total[a]	
Cognitive effects, *n* (%)	47 (28.1)	15 (9.0)	5 (3.0)	67 (40.1)	10 (6.0)
Memory impairment	36 (21.6)	8 (4.8)	1 (<1.0)	45 (26.9)	1 (<1.0)
Cognitive disorder[b]	12 (7.2)	8 (4.8)	1 (<1.0)	21 (12.6)	5 (3.0)
Confusional state	7 (4.2)	2 (1.2)	2 (1.2)	11 (6.6)	2 (1.2)
Encephalopathy	0	0	1 (<1.0)	1 (<1.0)	2 (1.2)

[a]No patient experienced grade 4 or 5 cognitive effects.
[b]Cognitive disorders leading to permanent treatment discontinuation included acute psychotic episode, worsening cognitive disturbances, mental status change, and delirium.

Joseph, *The Oncol* 2021

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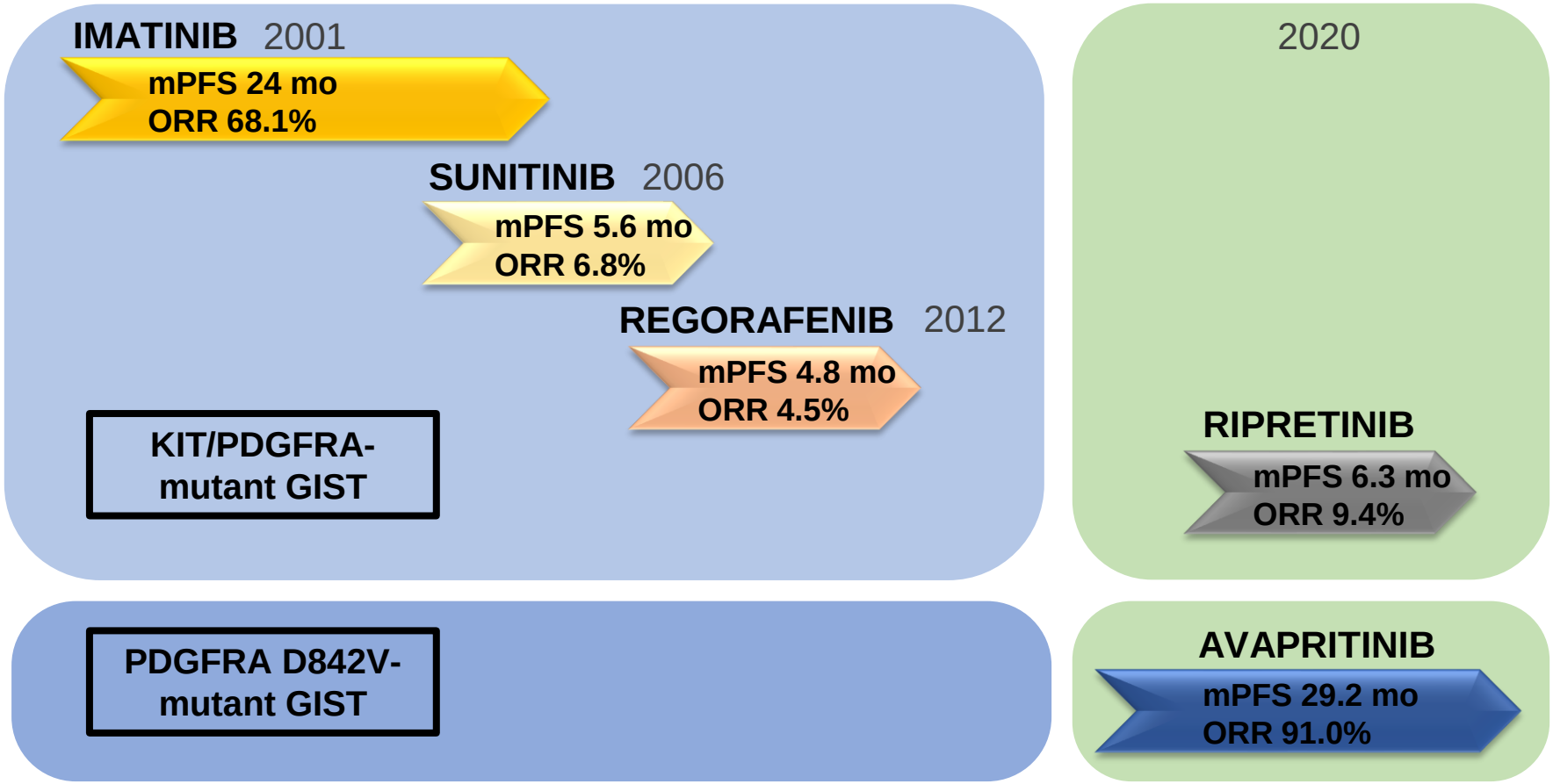

Modified from Serrano, *Clin Can Res* 2020

New clinical trials ongoing or shortly ongoing

Phase	Trial	Treatment	Setting
III	PEAK	SU vs SU + Bezuclastinib	2nd
III	INSIGHT	RI vs SU – ctDNA KIT ex 11 + ex 17	2nd
I	IDRX-42-001	IDRX-42 (pan KIT/PDGFRA)	>1st
I	NB003-01	NB003 (pan KIT/PDGFRA)	>1st
II	MK-6482	MK-6482 (HIF2a inh)	Any

CONCLUSIONS / TAKE-HOME MESSAGES

- We are currently assisting to a golden-age with **paradigm-shifting drugs** tested in clinical trials.
- **Avapritinib** targets for the first-time ever *PDGFRA* D842V mutation.
- **Ripretinib** has a broader activity against KIT receptor heterogeneity.
- Future efforts will focus on **combination of agents** and **ctDNA-based strategies** aiming to overcome KIT/PDGFRA heterogeneity.

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