Current Treatment Options

Yoon-Koo Kang

Asan Medical Center, University of Ulsan, Seoul, Korea

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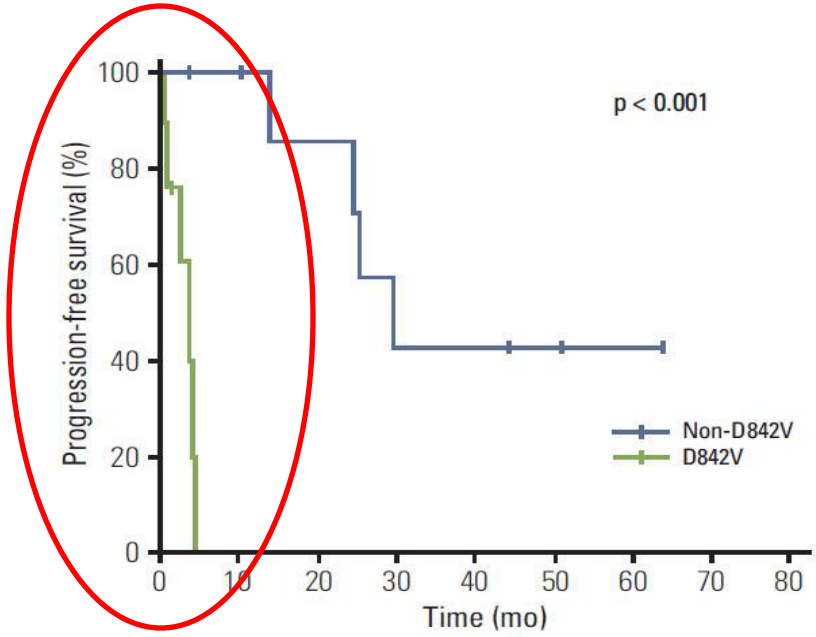
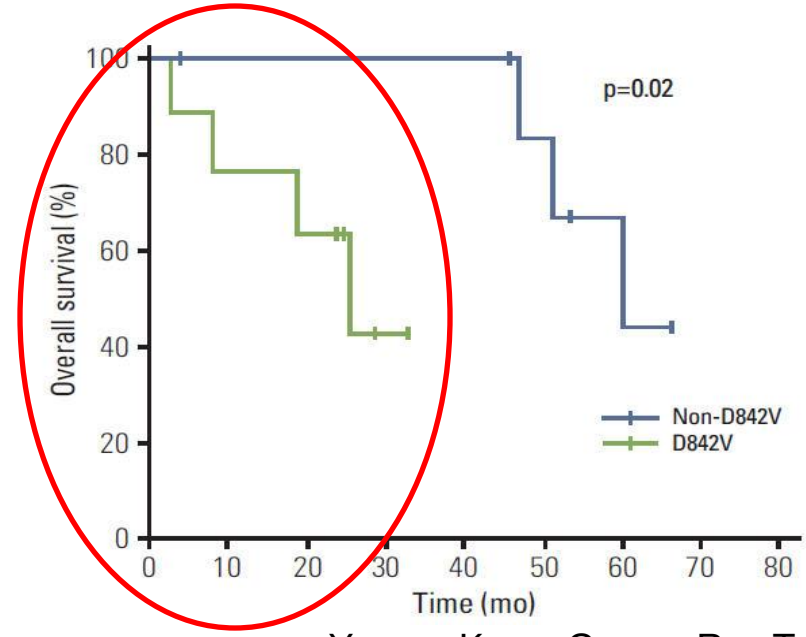
- New agent proven effective
  - Avapritinib for pdgfra exon 18 D842V mutant GIST
- Resumption of Imatinib after failure of all available effective treatment
- Surgical resection of residual lesions after control with imatinib

No efficacy of Standard TKIs for PDGFRα D842V Mutant GIST

Efficacy of **Imatinib** for PDGFRA mutant GIST

Response	Type of mutation			
	D842V exon 18	Non-D842V exon 18	Exon 12	Overall
Complete response	0	0	0	0
Partial response	0	4 (100)	1 (33)	5 (42)
Stable disease	1 (20)	0	2 (67)	3 (25)
Progressive disease	4 (80)	0	0	4 (33)





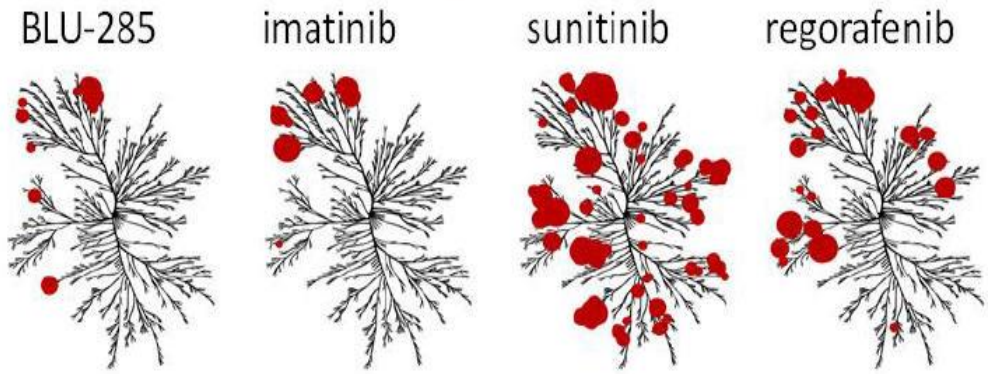
Yoo, --- Kang. Cancer Res Treat 2016

BLU-285 is a highly potent and selective inhibitor of KIT and PDGFRα activation loop mutants

BLU-285:
Avapritinib

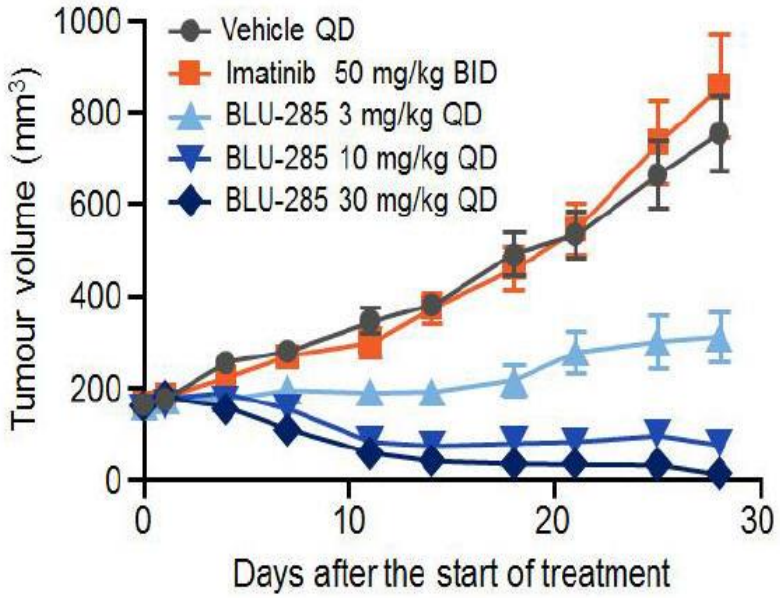
Biochemical profiles

	Activation loop		JM domain/ activation loop
	Exon 18	Exon 17	Exon 11/17
Compound	PDGFRα D842V IC_{50} nM	KIT D816V IC_{50} nM	KIT V560G/D816V IC_{50} nM
BLU-285	0.24	0.27	0.10
imatinib	759	8150	6145
sunitinib	120	207	97.2
regorafenib	810	3640	1685



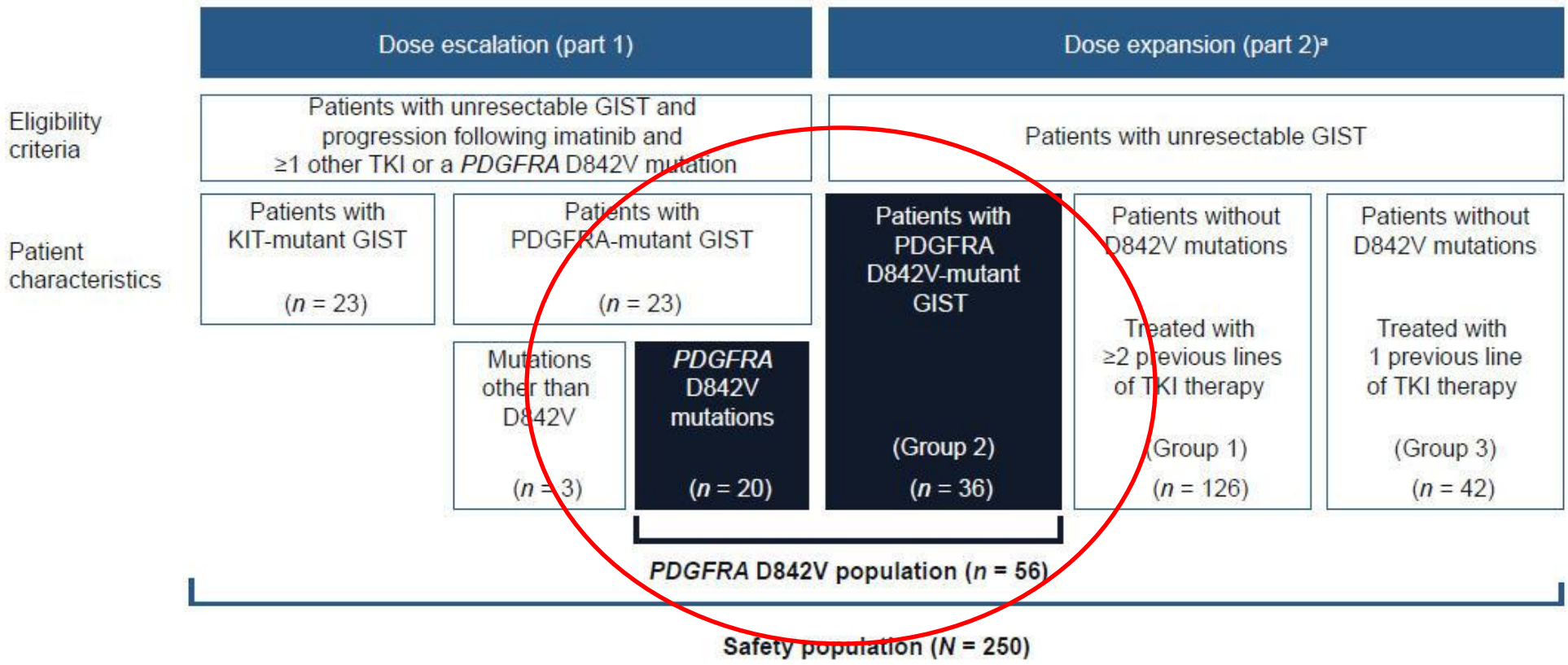
BID, twice daily; IC_{50}, half maximal inhibitory concentration; PDX, patient derived xenograft; QD, once daily
Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)

Tumor regression in KIT exon 11/17* mutant GIST PDX



*del556-558/Y823D

NAVIGATOR: Phase I trial of Avapritinib in unresectable or metastatic GIST

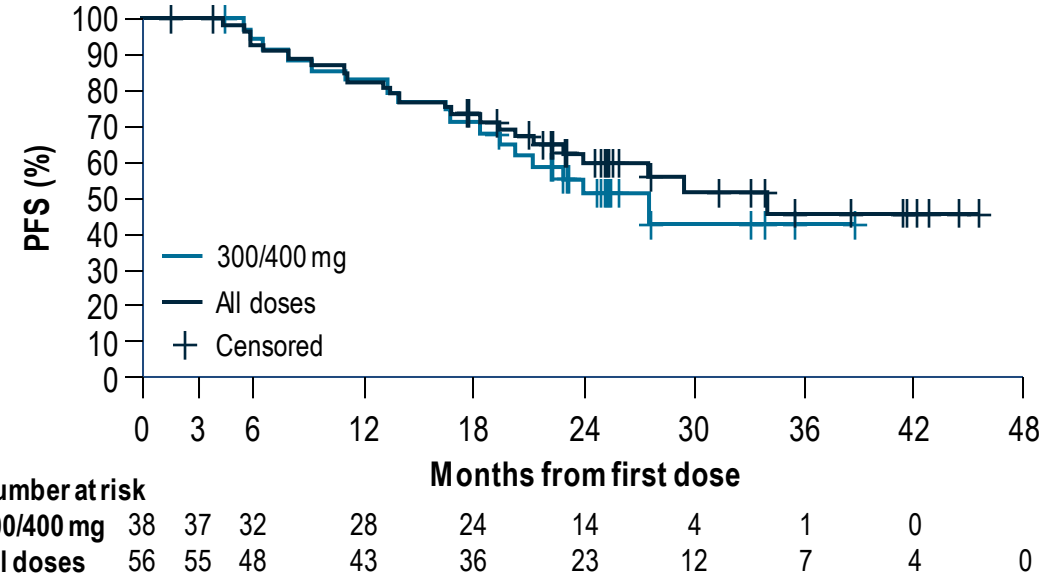


Heinrich, et al. Lancet Oncol 2020; Jones, et al. Eur J Cancer 2021

NAVIGATOR trial: Avapritinib

• 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.

•PDGFRA D842V-mutant GIST: Most common AEs and AEs of special interest

Most common AEs (any cause and grade) in ≥30% of patients, n (%)	D842V population 300/400 mg starting dose (n=38)	Safety population All starting doses (N=250)
Nausea	28 (74)	161 (64)
Anemia	26 (68)	136 (54)
Diarrhea	25 (66)	112 (45)
Fatigue	22 (58)	157 (63)
Memory impairment	18 (47)	81 (32)
Periorbital edema	17 (45)	110 (44)
Decreased appetite	15 (39)	101 (40)
Increased lacrimation	13 (34)	88 (35)
Vomiting	12 (32)	106 (42)
Peripheral edema	12 (32)	80 (32)
Abdominal pain	12 (32)	64 (26)
Increased blood bilirubin	12 (32)	54 (22)
Hypokalemia	12 (32)	48 (19)

AESI (any cause and grade), n (%)	D842V population 300/400 mg starting dose (n=38)	Safety population All starting doses (N=250)
Cognitive effects	24 (63)	115 (46)
Memory impairment	18 (47)	81 (32)
Confusional state	7 (18)	17 (7)
Cognitive disorder	5 (13)	28 (11)
Encephalopathy	1 (3)	5 (2)
Intracranial bleeding	2 (5)	7 (3)
Intracranial hemorrhage	2 (5)	3 (1)
Cerebral hemorrhage	0	1 (<1)
Subdural hematoma	0	3 (1)

- Overall, 13 (34%) patients receiving avapritinib 300/400 mg starting dose in the *PDGFRA* D842V population discontinued treatment due to AEs of any cause
  - 8 (21%) of patients discontinued due to treatment-related AEs
- Dose interruption and/or reduction was an effective method of improving Grade ≥2 cognitive effect AEs, in a median of 12 days[1]

Enrollment as of a data cut-off March 9, 2020. AE, adverse event; AESI, adverse event of special interest.

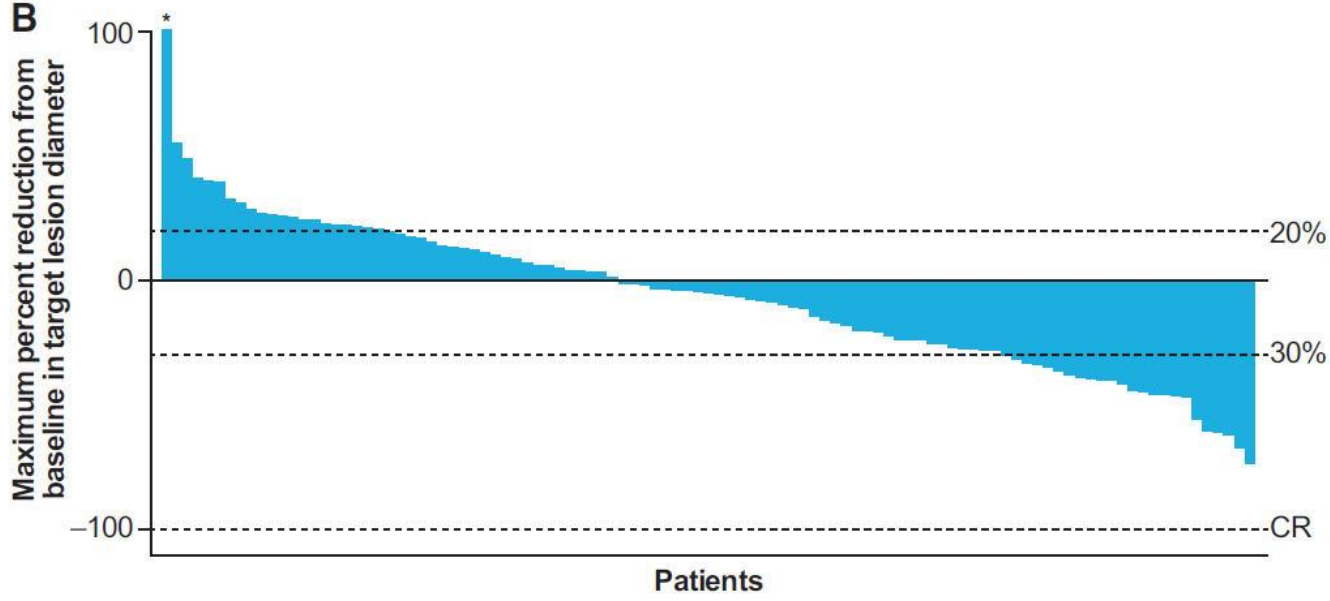
1. Joseph CP et al. Presented at the Connective Tissue Oncology Society Annual Meeting, November 13-16, 2019, Tokyo, Japan.

Efficacy of Avapritinib in patients with advanced GIST following ≥ 3 prior lines of therapy

A

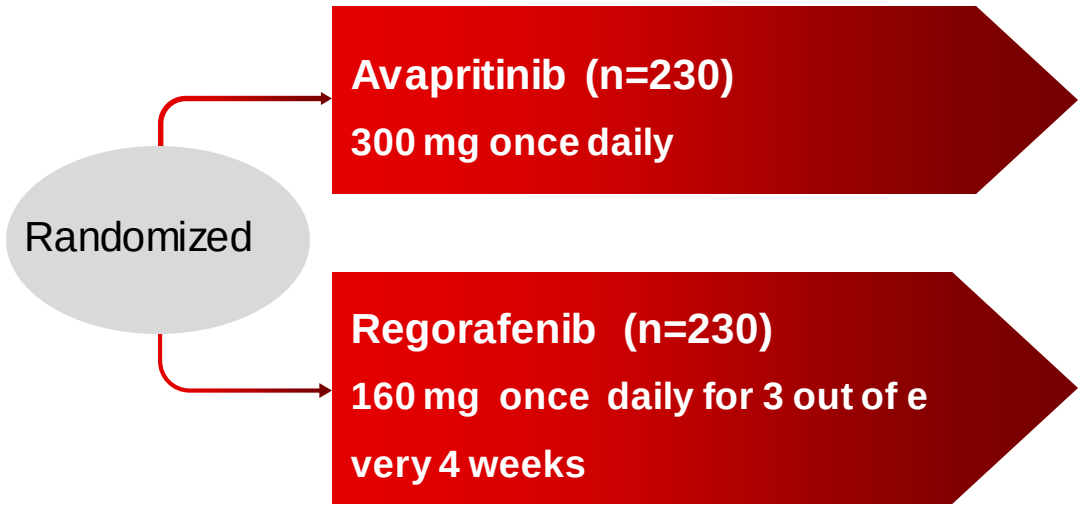
	Efficacy population			Response-evaluable population		
	Avapritinib starting dose			Avapritinib starting dose		
Best overall response, *n* (%)[a]	300 mg (*n* = 78)	400 mg (*n* = 35)	300/400 mg (*n* = 113)	300 mg (*n* = 70)	400 mg (*n* = 33)	300/400 mg (*n* = 103)
Complete response	0	0	0	0	0	0
Partial response	12 (15)	5 (14)	17 (15)	12 (17)	5 (15)	17 (17)
Stable disease	34 (44)	18 (51)	52 (46)	33 (47)	18 (55)	51 (50)
Progressive disease	26 (33)	10 (29)	36 (32)	25 (36)	10 (30)	35 (34)
ORR, % (95% CI)[b]	15 (8–25)	14 (5–30)	15 (9–23)	17 (9–28)	15 (5–32)	17 (10–25)
CBR, % (95% CI)[c]	35 (24–46)	34 (19–52)	35 (26–44)	39 (27–51)	36 (20–55)	38 (29–48)

B



George, et al. The Oncologist 2021

Phase III VOYAGER Trial of Avapritinib vs Regorafenib for Patients with 3rd or 4th line GIST



Primary end point: progression-free survival

Design

- Open-label, randomized, phase Ⅲ clinical trial
- Patients assigned to receive regorafenib may cros s over to receive Avapritinib following confirmed dis ease progression

Eligibility

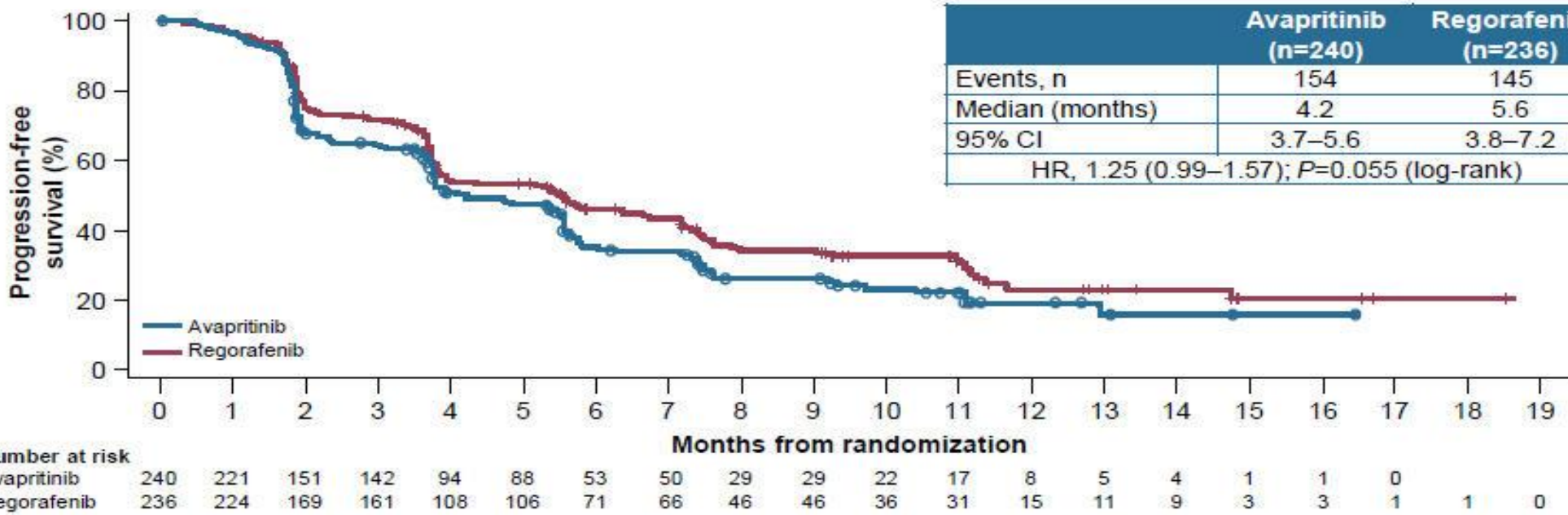
- Aged 18 years or older
- Metastatic and/or unresectable GIST
- Have received imatinib and 1 or 2 other kinase inh ibitors

Kang, et al. J Clin Oncol 2021

Progression-free survival

- The primary endpoint for this study was not met, as there was no significant difference in median PFS between avapritinib and regorafenib (HR 1.25 [95% CI 0.99–1.57]; median PFS 4.2 versus 5.6 months; *P*=0.055 (**Figure 3**)

Figure 3: Progression-free survival



	Avapritinib (n=240)	Regorafenib (n=236)
Events, n	154	145
Median (months)	4.2	5.6
95% CI	3.7–5.6	3.8–7.2
HR, 1.25 (0.99–1.57); *P*=0.055 (log-rank)		

Number at risk																			
Avapritinib	240	221	151	142	94	88	53	50	29	29	22	17	8	5	4	1	1	0	
Regorafenib	236	224	169	161	108	106	71	66	46	46	36	31	15	11	9	3	3	1	1	0

Overall survival

- At the cut-off date, OS data were immature with a median follow-up of 8.5 months for avapritinib and 9.6 months for regorafenib. At 12 months, KM OS estimates were similar for avapritinib (68%) and regorafenib (67%)

Kang, et al. J Clin Oncol 2021

Avapritinib

- **Highly effective for pdgfra exon 18 D842V mutant GIST**
  - Approved in USA for the treatment of pdgfra exon 18 mutant GIST, in Europe for pdgfra exon 18 D842V mutant GIST
  - Not better than regorafenib for the 3rd line treatment
- **Management of Adverse events[1]**
  - Early recognition of adverse events and tailored dose modification appear to be effective
  - Dose reduction does not appear to result in reduced efficacy.
  - Patients' cognitive function should be assessed at baseline and monitored carefully throughout treatment.
  - Dose interruption is recommended at the first sign of any cognitive effect, including grade 1 events.
- **D842V mutant GIST often has very indolent progression**

1. Joseph, et al. The Oncologist 2021

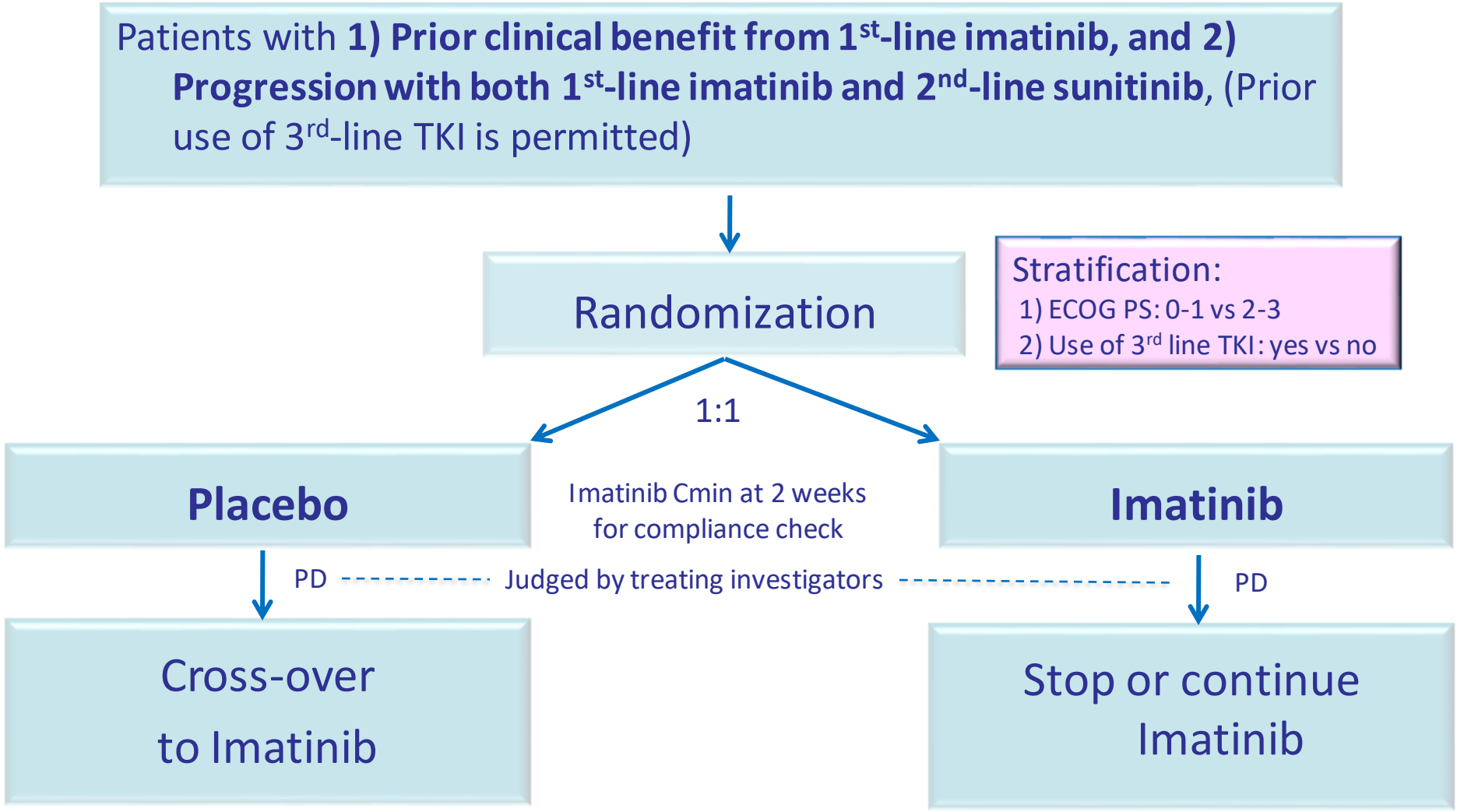
Resumption of imatinib after failure of all available TKIs: Rationale

- **According to principles of oncology, rechallenge of any chemotherapeutic agents is not recommended if those agents had failed previously in the patient.**

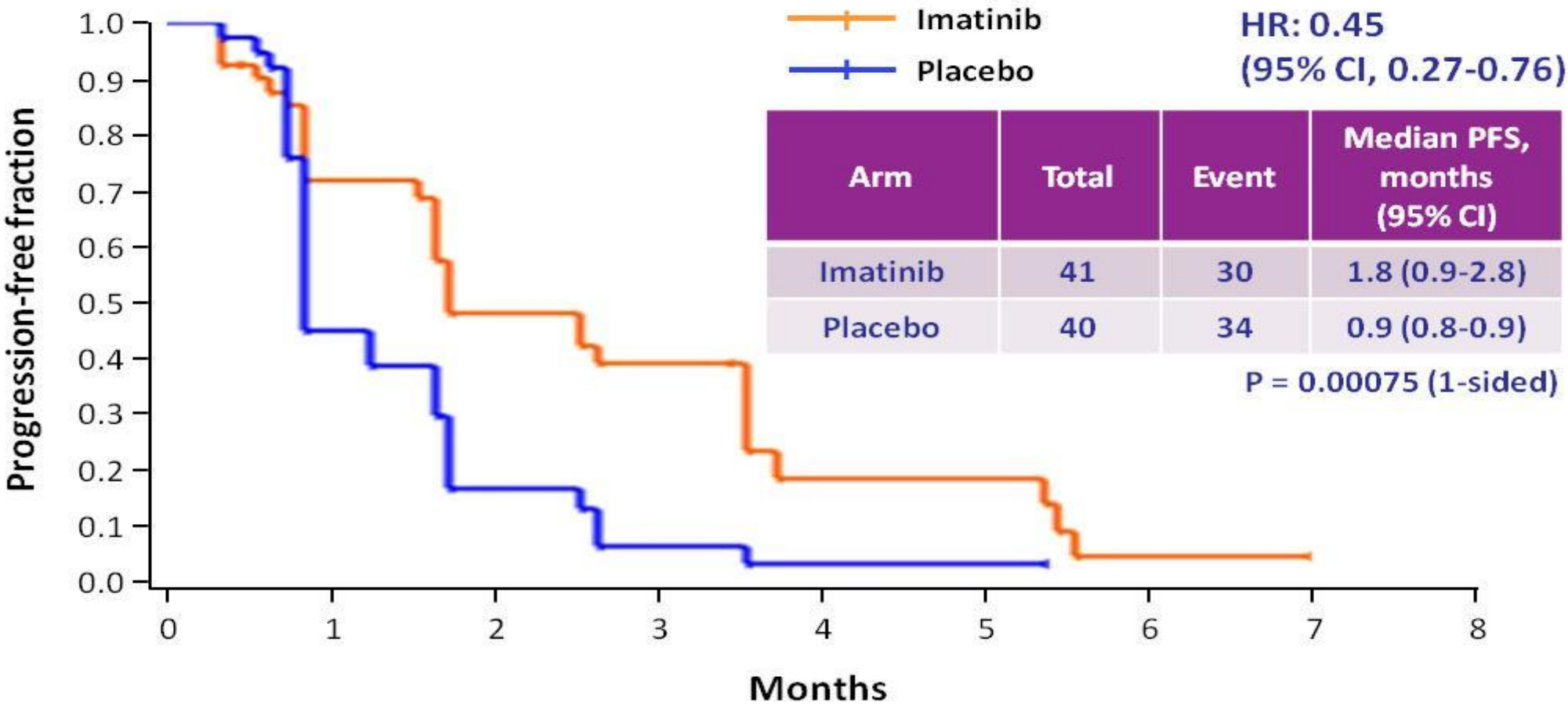
- **Expert consensus recommending rechallenge of TKIs that failed previously in GIST**
  - **Flare-up on PET after discontinuation of TKI**
  - **Among multiple clones, some are still sensitive to TKI even in the case of PD**
  - **Retrospective studies suggested potential benefit from rechallenge of TKIs after prior failure**

Study Design: RIGHT

(Rechallenge of Imatinib in GIST Having no effective Treatment)



Imatinib rechallenge prolongs PFS after failure of all available therapy: RIGHT



Arm	Total	Event	Median PFS, months (95% CI)
Imatinib	41	30	1.8 (0.9-2.8)
Placebo	40	34	0.9 (0.8-0.9)

P = 0.00075 (1-sided)

Kang, et al. Lancet Oncol 2013

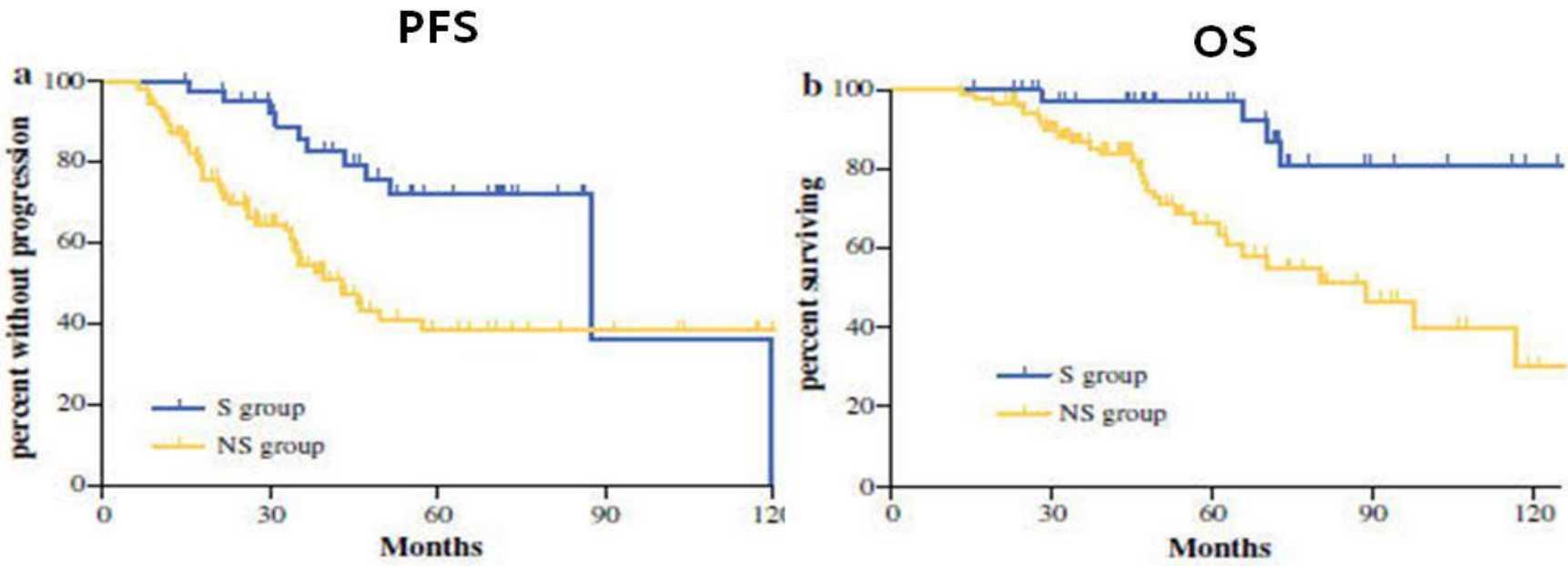
Surgical resection of residual disease after control with imatinib: Rationale

- Pathologic examination reveals that most of the grossly residual lesions contain suppressed but viable cancer cells.

- Clinical resistance to imatinib can develop from these viable cancer cells present in grossly residual lesions (if not resected).

- Resection of these residual lesions can prevent or delay the emergence of clinical resistance to imatinib.

Surgical resection of residual disease after control with imatinib: A retrospective study



134 patients (42 in S group, 92 in NS group) with metastatic or recurrent GIST who had SD for > 6 months after responding to imatinib

Park, ---- Kang. Ann Surg Oncol 2014

Received: 9 October 2018 | Revised: 11 December 2018 | Accepted: 8 January 2019

DOI: 10.1002/cam4.1994

ORIGINAL RESEARCH

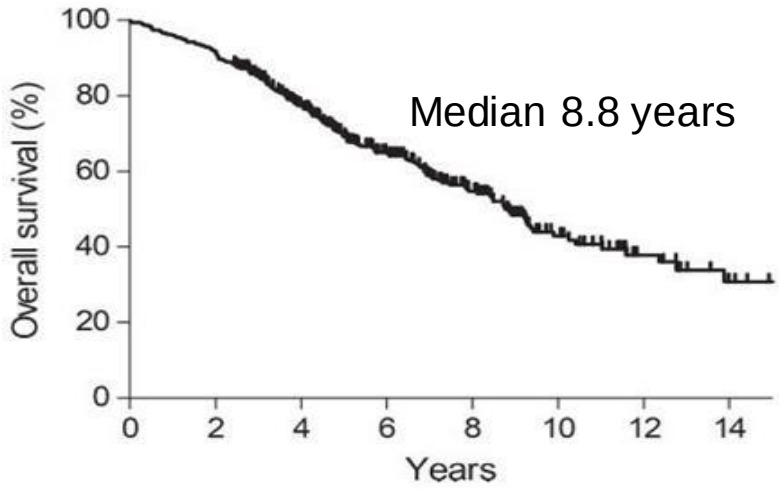
WILEY Cancer Medicine Open Access

Long-term survival outcome with tyrosine kinase inhibitors and surgical intervention in patients with metastatic or recurrent gastrointestinal stromal tumors: A 14-year, single-center experience

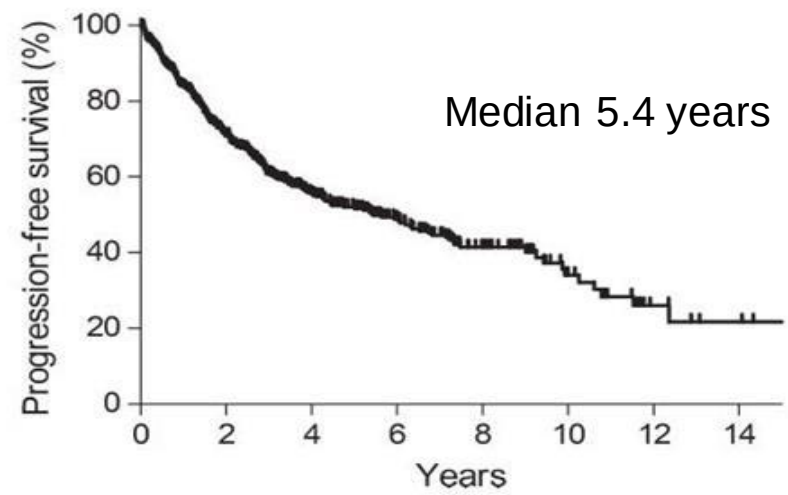
（N=379 patients with metastatic or recurrent GIST who started standard dose of imatinib at AMC between 2001 and 2014）

imatinib

Overall survival

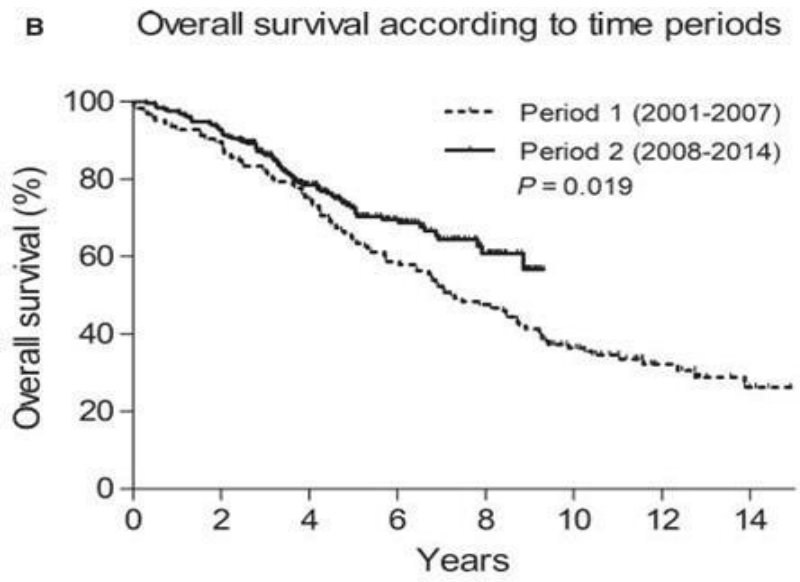


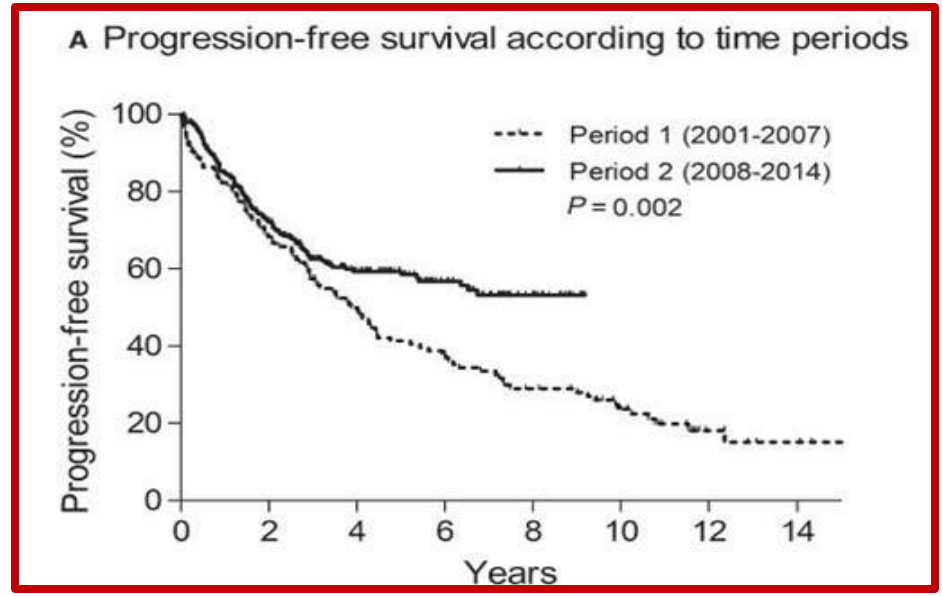
Progression-free survival



1. Kim JH, et al. Cancer Med 2019;8(3):1034-1043

Comparison of treatment results between early and late periods in AMC retrospective study[1]





Surgical resection of residual lesions after control with imatinib
Total: 20.8% of patients
Period 1: 12.7%
Period 2: 24.9%

1. Kim JH, et al. Cancer Med 2019;8(3):1034-1043

Summary

- Avapritinib is highly effective for the treatment of patients with pdgfra D842V mutant GIST.
- Resumption of imatinib is a treatment option after failure of all available effective treatment.
- Surgical resection of residual lesions is beneficial after control with imatinib of metastatic GIST.

Thank you.