Ripretinib Intra-Patient Dose Escalation Following Disease Progression Provides Clinically Meaningful Progression-Free Survival in Gastrointestinal Stromal Tumor in Phase 1 Study

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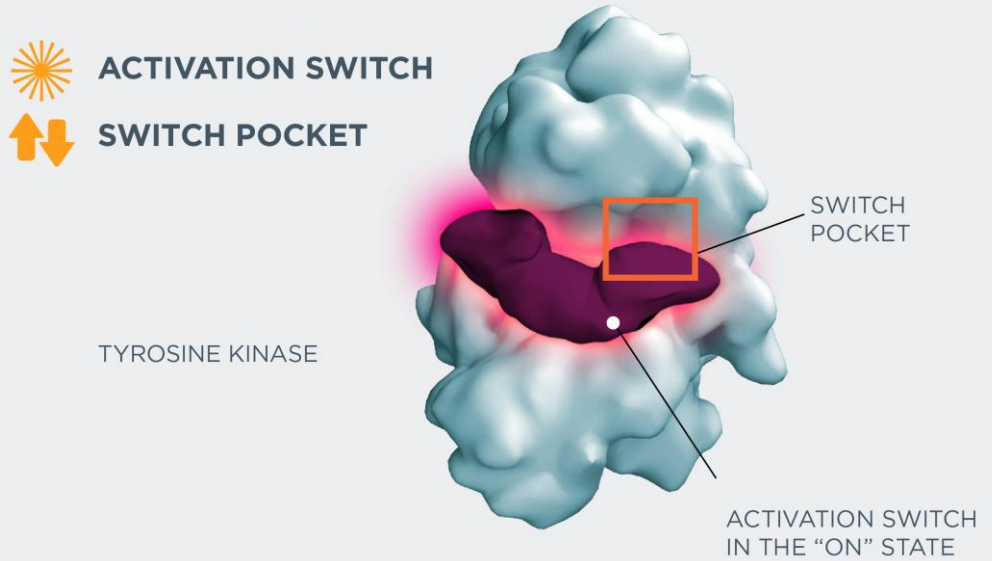
Disclosure information

Dr. Suzanne George

- Institution receives research support from Bayer, Blueprint Medicines, Deciphera Pharmaceuticals, Novartis, and Pfizer
- Is, or has been, a consultant or on the Scientific Advisory Boards of AstraZeneca, Bayer, Blueprint Medicines, Daiichi Sankyo, Deciphera Pharmaceuticals, Eli Lilly, and Exelixis
- Has a leadership role in Alliance Foundation
- Receives licensing royalties from Wolters Kluwer Health
- Is a shareholder/stockholder of Abbott Labs and Allergan

Ripretinib mechanism of action

Kinase activation requires the interaction of two critical regions:

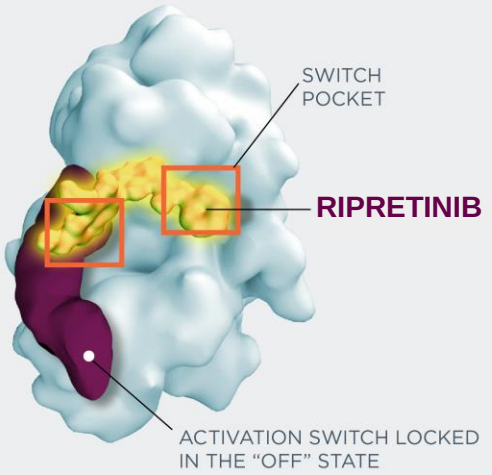


As shown in preclinical studies, ripretinib:

BINDS
to both the activation switch and switch pocket, regardless of where mutations arise

LOCKS
the kinase in the inactive ("off") state, inhibiting downstream signaling and cancer cell proliferation

In vitro studies not designed to assess clinical efficacy

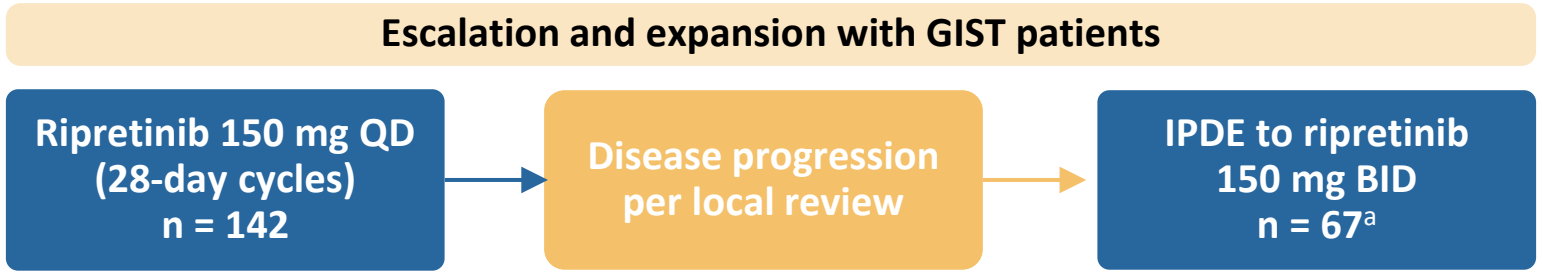


- Ripretinib is a novel **switch control** tyrosine kinase inhibitor engineered to broadly inhibit KIT and PDGFRA mutated kinases by using a unique **dual mechanism of action** that regulates the kinase switch pocket and activation loop

Smith BD, et al. *Cancer Cell.* 2019;35:738–51.

Ripretinib phase 1 intra-patient dose escalation study design

- Patients may dose escalate to ripretinib 150 mg BID after disease progression



Efficacy endpoint

PFS (per RECIST v1.1 based on **local review**)

- **PFS1**: PFS on ripretinib 150 mg QD defined as Cycle 1, Day 1 to progression
- **PFS2**: PFS on ripretinib 150 mg BID defined as the date of IPDE to progression or death

- All patients with radiologic disease progression had the option to dose escalate
- Data from the escalation and expansion phases were pooled for this presentation
- In this presentation, we review GIST patients who started at ripretinib 150 mg QD and dose escalated to 150 mg BID

Data cutoff
8 May 2020

ClinicalTrials.gov: NCT02571036

[a]Three patients were dose escalated without progression per RECIST (clinical progression per investigator, n = 2; debulking surgery for nonresponding lesions prior to progression n = 1).
BID, twice daily; GIST, gastrointestinal stromal tumor; IPDE, intra-patient dose escalation; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline characteristics for IPDE patients

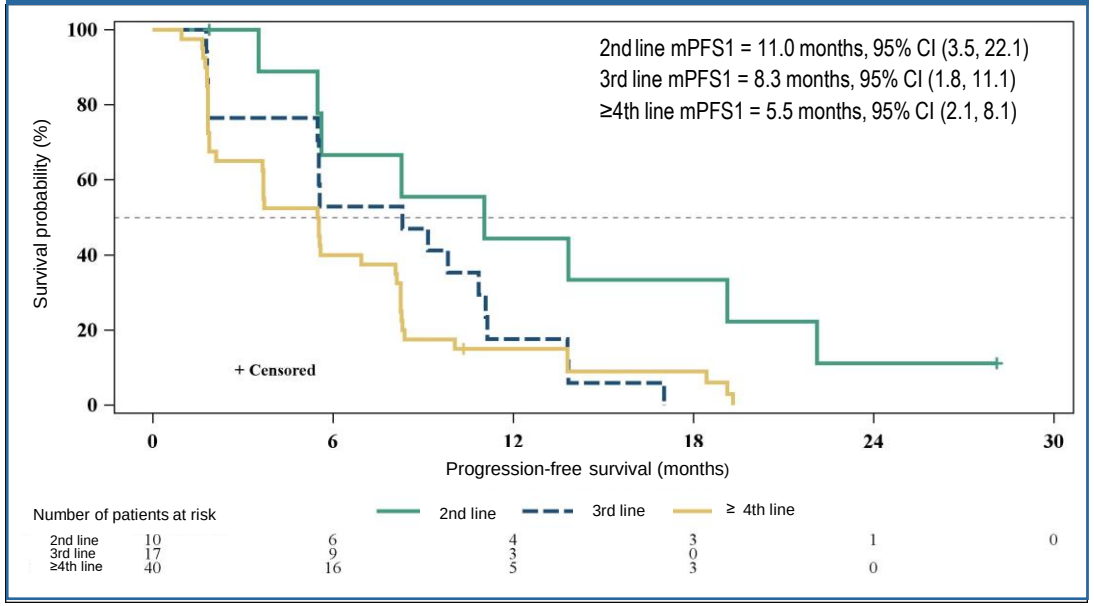
Characteristics	2nd line (n = 10)	3rd line (n = 17)	≥4th line (n = 40)	Total (N = 67)
Age at informed consent (years)				
Mean (SD)	59.6 (13.57)	64.6 (8.66)	59.9 (10.03)	61.1 (10.35)
Median	60.0	64.0	59.0	60.0
Min, max	32, 80	51, 82	39, 87	32, 87
Age category (years)				
≥18–≤64	6 (60)	9 (53)	30 (75)	45 (67)
≥65	4 (40)	8 (47)	10 (25)	22 (33)
Sex				
Male	3 (30)	10 (59)	30 (75)	43 (64)
Female	7 (70)	7 (41)	10 (25)	24 (36)
ECOG status				
0	8 (80)	9 (53)	19 (48)	36 (54)
1	2 (20)	8 (47)	20 (50)	30 (45)
2	0	0	1 (3)	1 (2)
Mutation				
KIT exon 11	8 (80)	12 (71)	28 (70)	48 (72)
KIT exon 9	1 (10)	5 (29)	8 (20)	14 (21)
KIT other exons	0	0	2 (5)	2 (3)
PDGFRA	1 (10)	0	2 (5)	3 (5)

Data presented as n (%) unless otherwise indicated. Percentages were rounded to the nearest whole number.
ECOG, Eastern Cooperative Oncology Group; IPDE, intra-patient dose escalation; max, maximum; min, minimum; PDGFRA, platelet-derived growth factor receptor alpha; SD, standard deviation.

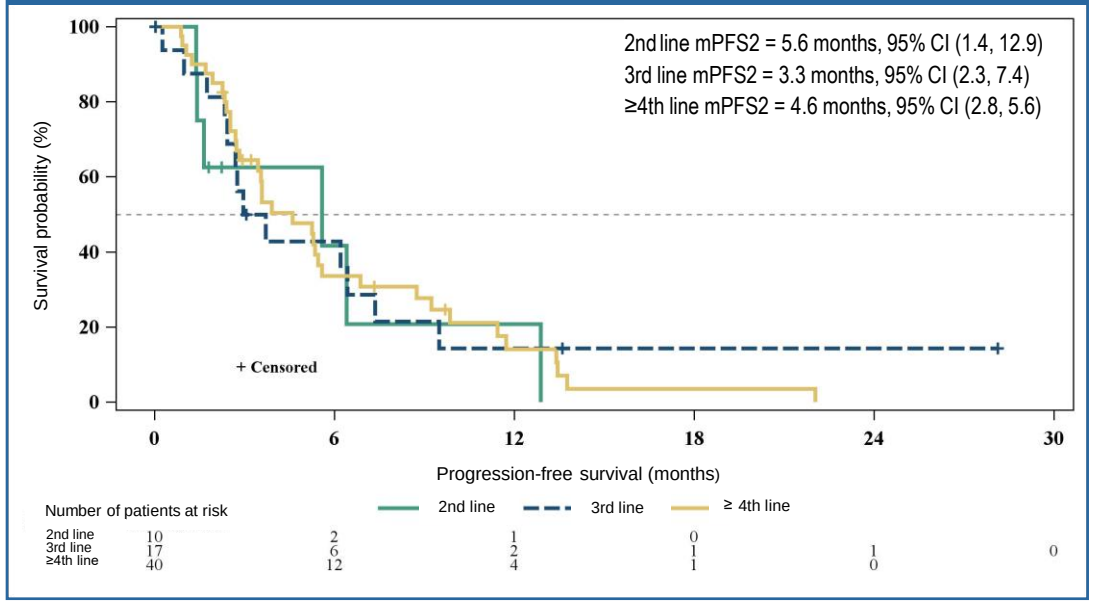
Kaplan-Meier plots of PFS for GIST IPDE patients

- Patients with GIST who received ripretinib 150 mg QD and dose escalated to 150 mg BID

Ripretinib 150 mg QD
PFS1, by line of therapy



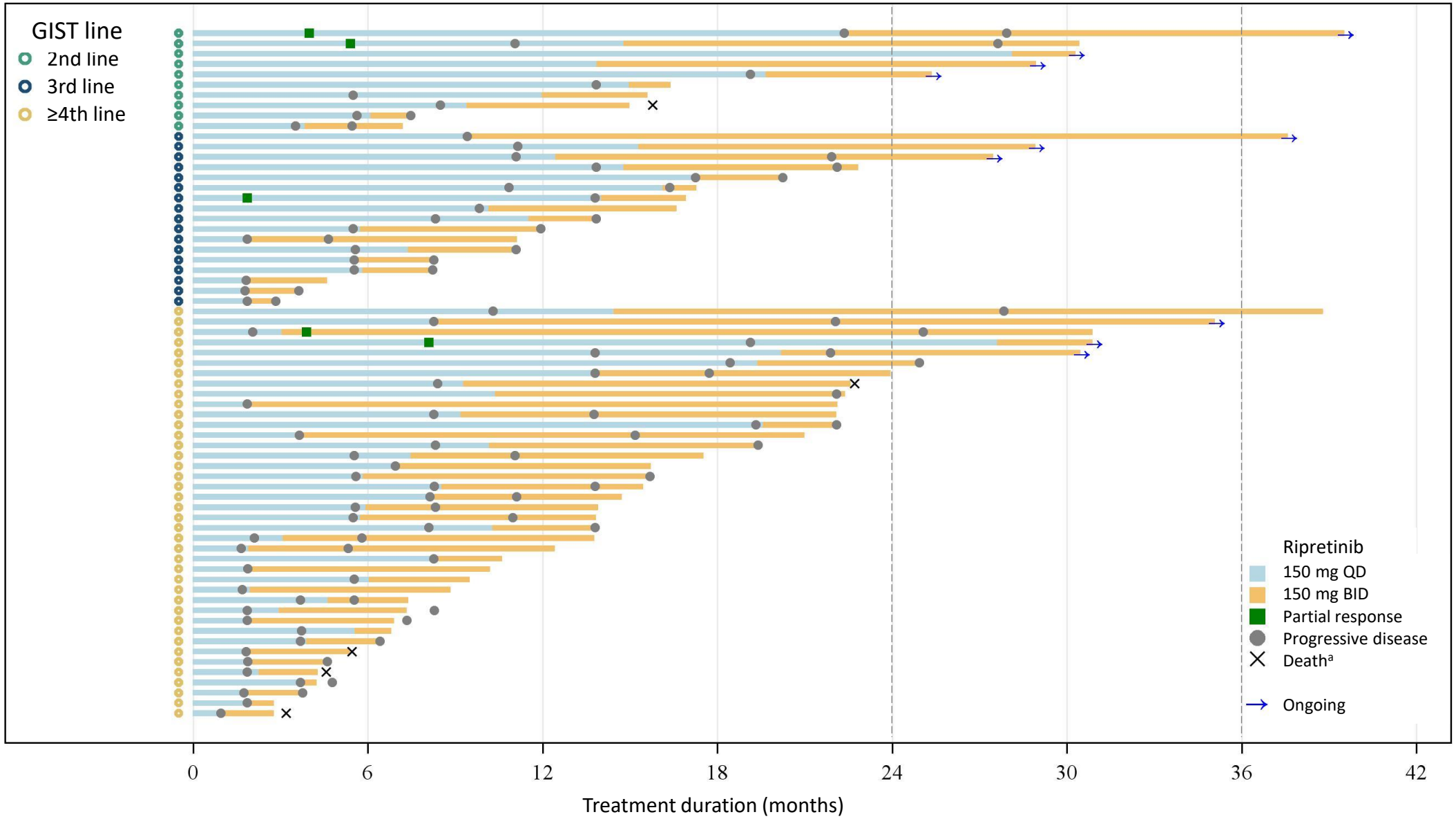
Ripretinib 150 mg BID
PFS2, by line of therapy



Ripretinib 150 mg BID (n = 67)			
Line of therapy	**2nd line (n = 10)**	**3rd line (n = 17)**	**≥4th line (n = 40)**
mPFS, months	mPFS1, 11.0 mPFS2, 5.6	mPFS1, 8.3 mPFS2, 3.3	mPFS1, 5.5 mPFS2, 4.6
mPFS2/mPFS1	51%	40%	84%

BID, twice daily; CI, confidence interval; GIST, gastrointestinal stromal tumor; IPDE, intra-patient dose escalation; m, median; PFS, progression-free survival; QD, once daily.

Total duration of treatment in the GIST IPDE population



[a] Deaths noted were those counted as PFS events. Dashed lines indicate 2- and 3-year marks. BID, twice daily; GIST, gastrointestinal stromal tumor; IDPE, intra-patient dose escalation; PFS, progression-free survival; QD, once daily.

Treatment-emergent adverse events

- Patients with GIST who received ripretinib 150 mg QD and dose escalated to 150 mg BID

TEAEs occurring in >20% of patients in the total dosing period

Parameters, n (%)	Ripretinib 150 mg QD period (n = 67)		Ripretinib 150 mg QD + 150 mg BID period (n = 67)	
	All grades	Grade 3/4	All grades	Grade 3/4
Alopecia	41 (61)	0	49 (73)	0
Fatigue	23 (34)	0	35 (52)	2 (3.0)
Myalgia	33 (49)	0	35 (52)	0
Nausea	24 (36)	0	35 (52)	0
PPES	24 (36)	0	33 (49)	0
Diarrhea	13 (20)	1 (1.5)	28 (42)	2 (3.0)
Abdominal pain	15 (22)	0	27 (40)	7 (10)
Muscle spasms	19 (28)	0	27 (40)	0
Lipase increased	22 (33)	14 (21)	25 (37)	16 (24)
Weight decreased	19 (28)	0	24 (36)	0
Constipation	18 (27)	0	23 (34)	0
Decreased appetite	11 (16)	0	22 (33)	1 (1.5)
Hypertension	14 (21)	2 (3.0)	18 (27)	3 (4.5)
Anemia	3 (4.5)	0	17 (25)	4 (6.0)
Dry skin	11 (16)	0	17 (25)	0
Rash	13 (19)	0	17 (25)	0
Vomiting	9 (13)	0	16 (24)	0
Back pain	10 (15)	0	15 (22)	0
Cough	12 (18)	0	15 (22)	0
Actinic keratosis	14 (21)	0	14 (21)	0
Dyspnea	5 (7.5)	0	14 (21)	2 (3.0)
Headache	8 (12)	0	14 (21)	1 (1.5)
Hypokalemia	8 (12)	1 (1.5)	14 (21)	2 (3.0)

Dose modifications

Parameters, n (%)	Ripretinib 150 mg QD period (n = 67)	Ripretinib 150 mg QD period + 150 mg BID period (n = 67)
Any dose interruption	24 (36)	40 (60)
Any dose reduction	4 (6.0)	9 (13)
Any TEAE leading to treatment discontinuation	N/A	10 (15)

BID, twice daily; GIST, gastrointestinal stromal tumor; N/A, not applicable; PPES, palmar-plantar erythrodysesthesia syndrome; QD, once daily; TEAE, treatment-emergent adverse event.

Ripretinib phase 1 IPDE: Conclusions

- In this phase 1 study, dose escalation to ripretinib 150 mg twice daily after disease progression on ripretinib 150 mg daily provided additional clinically meaningful benefit for patients with advanced GIST
  - This benefit was demonstrated for patients with GIST receiving second-, third-, and ≥fourth-line therapy
- Comparison of reported TEAEs demonstrate that the safety profile for ripretinib 150 mg BID is similar to ripretinib 150 mg QD
- Ripretinib 150 mg daily is approved for the treatment of patients with fourth-line GIST in the United States (FDA), Canada (Health Canada), and Australia (TGA)

Enrollment is ongoing in INTRIGUE, a phase 3, randomized, multicenter, open-label study of ripretinib vs sunitinib in patients with advanced GIST after treatment with imatinib (NCT03673501)

BID, twice daily; FDA, Food and Drug Administration; GIST, gastrointestinal stromal tumor; IPDE, intra-patient dose escalation; QD, once daily; TEAE, treatment-emergent adverse event; TGA, Therapeutic Goods Administration.

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