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Efficacy And Safety Of Ripretinib In Chinese Patients With Advanced Gastrointestinal Stromal Tumors: A real-world, multicenter, observational study

FNP:

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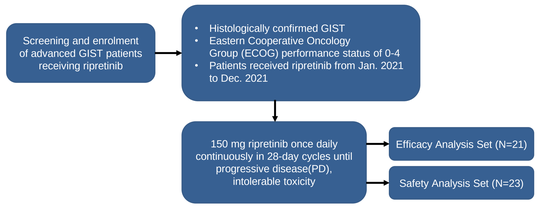
Introduction

- Gastrointestinal stromal tumors (GISTs), are responsible for 1% to 2% of malignant gastrointestinal tumors globally with incidence rate 0.40 per 100,000 person-years in China.
- Tyrosine kinase inhibitors (TKIs) have revolutionized the multi-line treatment of non-resectable and/or metastatic GIST. However, advanced GIST treatment is still challenging due to drug resistance.
- Ripretinib, a novel switch-control kinase inhibitor that broadly inhibits KIT proto-oncogene, receptor tyrosine kinase (KIT) or platelet-derived growth factor receptor A (PDGFRA) kinase signaling. Ripretinib was approved for advanced GIST patients who had received ≥3 lines of prior TKI treatment in the China, US, Hong Kong and other countries/regions (1,2).
- INTRIGUE study demonstrated comparable efficacy and improved safety of ripretinib compared to sunitinib as second-line (2L) treatment (3).
- Even though several clinical trials have well established the clinical benefit of ripretinib, real-world data on efficacy and safety of ripretinib in China is scarce.

Objective

- To evaluate the efficacy and safety of ripretinib in Chinese patients with advanced GIST in this real-world, multicenter, observational study.

Methods



Endpoints

Primary endpoint:
- Progression-free survival (PFS)

Secondary endpoint:
- Overall survival (OS)
- Objective response rate (ORR)
- Disease control rate (DCR)
- Safety

Statistical analysis

- Comparison between groups: Cochran-Mantel-Haenszel-χ2 (CMH-χ2) test, Fisher's exact test or Wilcoxon rank sum test.
- Survival analysis: Kaplan–Meier method and log-rank test with 95% confidence interval (CI).
- p<0.05: statistically significant

Results

Baseline characteristics

- A total of 23 patients with advanced GIST were enrolled in the study (FAS), while 21 patients were included in EAS for efficacy evaluation. Baseline and clinical characteristics are given in Table 1.
- There were 61.9% males and 38.1% female with median age of 64 years (range, 45–90) and 47.62% were aged ≥65 years.
- Median duration of patient follow up and ripretinib treatment was 12 months and 7.3 months respectively.

Table 1: Baseline demographic and clinical characteristics

Parameter	Efficacy analysis set (EAS) N=21
Age (years)	
Median age of patients receiving ripretinib (min, max)	64 (45, 90)
< 65 years old, n (%)	11 (52.38)
≥ 65 years old, n (%)	10 (47.62)
Sex, n (%)	
Male	13 (61.90)
Female	8 (38.10)
Primary tumor site at first diagnosis, n (%)	
Stomach	5 (23.81)
Small intestine	13 (61.9)
Rectum	2 (9.53)
Other	1 (4.76)
Number of previous treatment lines, n (%)	
≤ 2 lines	7 (33.33)
≥ 3 lines	14 (66.67)
Median (min, max)	3 (0, 4)
Previous treatment drugs, n (%)	
Imatinib	20 (95.24)
Sunitinib	18 (85.71)
Regorafenib	14 (66.67)
Avapritinib	2 (9.52)
Other	1 (4.76)

Parameter	Efficacy analysis set (EAS) N=21
Previous duration of sunitinib, n (%)	
≤ 6 months	6 (35.29)
>6 months	11 (64.71)
Previous duration of regorafenib, n (%)	
≤ 6 months	9 (69.23)
>6 months	4 (30.77)
ECOG performance score at study enrolment, n (%)	
0	3 (14.28)
1	8 (38.10)
2	8 (38.10)
3	1 (4.76)
4	1 (4.76)
Site of metastasis at study enrolment, n (%)	
Liver	16 (76.19)
Peritoneum	3 (14.29)
Other	16 (76.19)
Tumor mutation*, n (%)	
KIT 9	8 (38.10)
KIT 11	8 (38.10)
KIT 13/14/17/18	13 (61.90)
PDGFRA12/18	1 (4.76)
Unknown	1 (4.76)

Efficacy outcomes

- Overall mPFS was 7.1 months (95% CI: 4.9–NR). A better trend of improvement in mPFS was observed in patients who switched to ripretinib within the time interval of ≤1 month (mPFS not reached) than >1 month (mPFS: 5.0 months (95% CI: 3.9–NR) (p=0.054) (Figure 1).
- Patients with KIT11 mutation showed a mPFS of 7.1 months (95% CI: 5.1-NR), while it was 3.9 months (95% CI: 3.7-NR) in patients with KIT9 mutation.
- All the patients who progressed on ripretinib 150 mg QD did not receive dose escalation to ripretinib 150 mg b.i.d., and the mOS was 12.0 months (95% CI: 9.2 – NR). Patients switched to ripretinib in ≤1 month had significantly longer mOS (Not reached) than >1 month (mOS: 8.3 months (95% CI: 7.3–NR) (p = 0.046) (Table 2, Figure 2).
- In the EAS, patients had an ORR and DCR of 9.52% and 85.71%.
- mPFS, ORR and DCR of subgroups have been represented in Table 2.

Table 2:Efficacy outcomes

Subgroup	No. of cases	PR, n (%)	SD, n (%)	PD, n (%)	ORR, n (%)	DCR, n (%)	mPFS, month (95% CI)
EAS	21	2 (9.52)	16 (76.19)	3 (14.28)	2 (9.52)	18 (85.71%)	7.1 (4.9, NR)
≤2 previous lines of treatment	7	1 (14.29)	3 (42.85)	3 (42.85)	1 (14.29)	4 (57.14)	7.1 (2.0, NR)
≥3 previous lines of treatment	14	1 (7.14)	13 (92.86)	0	1 (7.14)	14 (100.00)	9.2 (4.6, NR)
KIT 11	8	2 (25.00)	6 (75.00)	0	2 (25.00)	8 (100.00)	7.1 (5.1, NR)
KIT 9	8	0	5 (62.50)	3 (37.5)	0	5 (62.50)	3.9 (3.7, NR)
PDGFRA mutation	1	0	1 (100.00)	0	0	1 (100.00)	NR
Genotype unknown	1	0	1 (100.00)	0	0	1 (100.00)	NR

Safety

- Safety set showed alopecia and asthenia as the most common AEs of any grade (30.43% each). While abdominal pain and decreased lymphocyte count (8.70% each) were the most common grade 3 treatment-emergent adverse events (TEAEs). No grade 4/5 TEAEs were recorded. (Table 3).

Table 3: Adverse events (safety set)

		N=23	
Adverse events, n (%)	**Any grade**	**Grade 1-2**	**Grade 3**
Alopecia	7 (30.43)	7 (30.43)	0
Asthenia	7 (30.43)	6 (26.09)	1 (4.35)
Palmar–plantar erythrodysesthesia syndrome	3 (13.04)	3 (13.04)	0
Hypertension	3 (13.04)	3 (13.04)	0
Diarrhoea	3 (13.04)	2 (8.70)	1 (4.35)
Abdominal pain	3 (13.04)	1 (4.35)	2 (8.70)
Decreased lymphocyte count	3 (13.04)	1 (4.35)	2 (8.70)
Decreased appetite	2 (8.70)	2 (8.70)	0
Hyperpigmentation of skin	2 (8.70)	2 (8.70)	0
Myalgia	2 (8.70)	1 (4.35)	1 (4.35)
Vomiting	1 (4.35)	1 (4.35)	0
Rash	1 (4.35)	1 (4.35)	0
Palpitation	1 (4.35)	1 (4.35)	0
Nausea	1 (4.35)	1 (4.35)	0
Perianal pain	1 (4.35)	1 (4.35)	0
Limb pain	1 (4.35)	1 (4.35)	0
Skin Itch	1 (4.35)	1 (4.35)	0
Skin induration	1 (4.35)	1 (4.35)	0
Intestinal obstruction	1 (4.35)	0	1 (4.35)
AEs leading to dose adjustment			
Type of AE, n (%)	**Total no. of cases**		
Dose reduction due to any AE	2 (8.70)		
Grade 3 myalgia	1 (4.35)		
Grade 3 perianal pain	1 (4.35)		

Conclusion

Efficacy and safety of ripretinib in advanced GIST patients under real-world setting in China is consistent with the global RCT studies.

Early switching to ripretinib following disease progression may provide more significant clinical benefits in advanced GIST patients.

Figure 1: KM plots for progression free survival

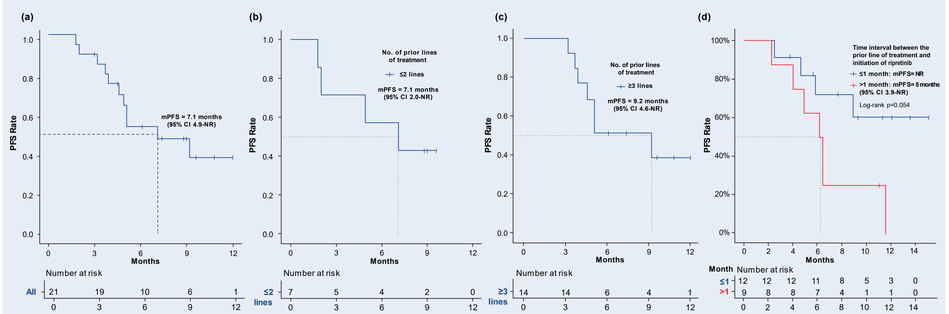
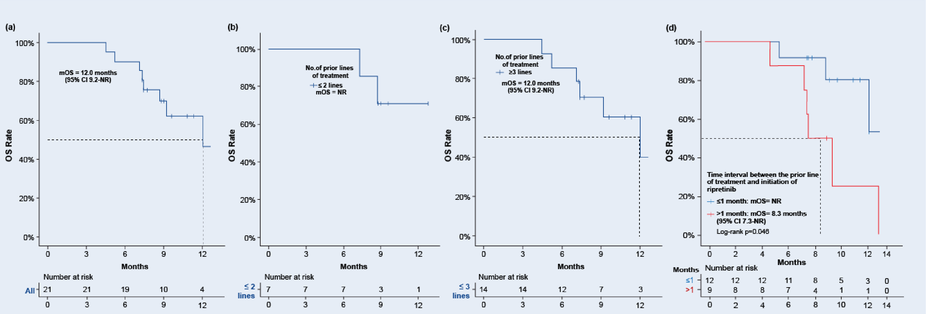


Figure 2: KM plots for overall survival



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Abbreviations: ECOG - Eastern Cooperative Oncology Group; KIT - KIT proto-oncogene, receptor tyrosine kinase; PDGFRA - Platelet-derived growth factor receptor-α; CI – Confidence interval; PR – Partial response; SD – Stable disease; PD – Progressive disease.

References:

1. Center for Drug Evaluation, State Drug Administration. Accessed December 20, 2022.
2. Blay JK et al, 2020. Lancet Oncol. 21:923–34.
3. Bauer S et al, 2022. J. Clin. Oncol. 40(34):3918-3928.

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