Abstract # 1257P
2022 ESMO

Apatinib plus POF (paclitaxel plus FOLFOX) in patients (pts) with treatment-naïve advanced gastric cancer(TNAGC): Update from the phase I study (SYLT-FNF007)

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BACKGROUND

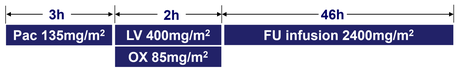
- POF (paclitaxel, oxaliplatin, fluorouracil, and leucovorin) regimen (reported in 2007, 2008, 2009, 2010 ASCO,ASCO-GI 2019) has shown impressive efficacy and well tolerated in patients with AGC, especially in the first-line treatment.
- Our data (ASCO-GI 2017, ASCO 2018, ESMO-ASIA 2018, ESMO 2020) suggests that apatinib combined with chemotherapy may cause synergistic effects by inhibiting cell membrane–bound ABC transporters.
- Apatinib can be safely administered up to 750mg daily combined with POF for pts with TNAGC in the first-line treatment.(ESMO 2019).
- Apatinib can be safely administered up to 850 mg daily plus POF for pts with TNAGC. The dose level possibly relates with the response (ESMO 2020).

METHODS

This was a phase I single center study with standard 3+3 design for pts with TNAGC. The primary endpoints are determining dose limiting toxicities (DLT) and maximum tolerated dose (MTD). Secondary endpoints include overall survival (OS), progression free survival (PFS), response rate (RR), and quality of life (QOL). Initial plan was to enroll pts in 5 escalating dose levels of apatinib (250mg, 375mg, 500mg, 625mg, 750mg and 850mg daily) plus POF (consisted of paclitaxel 135 mg/m^2, followed by mFOLFOX6 omitted 5-Fu bolus, every 14 days repeated). Eligible pts had ECOG PS 0-1, age 18-70, and adequate organ function. DLT was any treatment-related hematologic ≥ grade 4 toxicity (except for neutropenia lasting for ≤ 5 days), or non-hematologic ≥ grade 3 toxicity (except for nausea and vomiting that could be improved with optimal supportive care, escalation of alkaline phosphatase). The study design is shown in **Figure 1.**

Figure 1: Treatment Regimen

POF regimen:



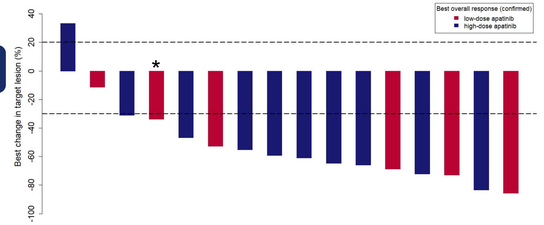
Apatinib dose level:250mg, 375mg, 500mg, 625mg, 750mg and 850mg daily

RESULTS

- From 2 Feb. 2018, 23 petients were enrolled (cut-off date of Mar 30, 2022). Patients characteristics was shown in the **Table1**.
- Twenty three participants were recruited from 2/2018 to 06/2019.The baseline characteristics are shown in Table1.
- The median follow-up time was 19.5 (range 3.9–41) months.
- The reasons for termination of treatment are shown in Table 2.
- Of 16 evaluable pts, 13 (81.25%) were PR, 1 was SD, 2 was PD. Median PFS was 10.6m (95%CI 6.91-14.29m). Median OS was 18.667m (95%CI 10.443-26.891m).
- Patients with the high-dose apatinib (625mg, 750，850mgmg daily) plus POF were associated with higher ORR(90% 9/10), DCR(90% 9/10) and longer mPFS (10.67m 95%CI 10.16-11.18m) and mOS (19.9m 95%CI 14.75-25.05m) .

Table 1 Patient characteristics

	All patients (n=23)
Age (years), median (range)	55 (25–69)
Male, n (%)	16 (69.6)
ECOG PS, n (%)	
0	14 (60.9)
1	9 (39.1)
No. of involved organs (metastasis), n (%)	
≤ 1	14 (60.9)
> 1	9 (39.1)
History of gastrectomy, n (%)	
Yes	5 (21.7)
No	18 (78.3)
History of radiotherapy, n (%)	
No	23 (100)
Site of primary tumor	
Gastroesophageal junction	4 (17.4)
Stomach	19 (82.6)
Site of metastases	
Lymph node	14 (60.9)
Liver	6 (26.1)
Lung	6 (26.1)
Peritoneum	8 (34.8)



* This patient developed brain metastases during treatment,

Figure 2: Best change from baseline in sum of longest target lesion diameters evaluable patient.

Efficacy

The efficacy was shown in the **Table2,Figure2, Figure3, Figure4, Figure5.**

Table 2. Best response of patients

	All patients (n=23)	low-dose apatinib (n=6)	high-dose apatinib (n=10)
Best overall response, n			
CR	0	0	0
PR	13	4	9
SD	1	1	0
PD	2	1	1
NE	7	3	4
ORR	81.25%	66.7%	90%
DCR	87.5%	83.3%	90%

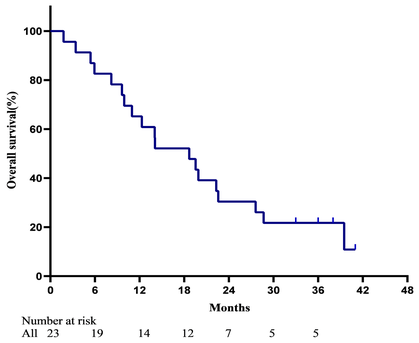


Figure 3 Overall survival（OS）

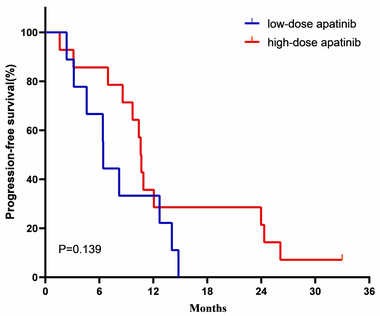


Figure 4: PFS comparison of low-dose and high-dose apatinib

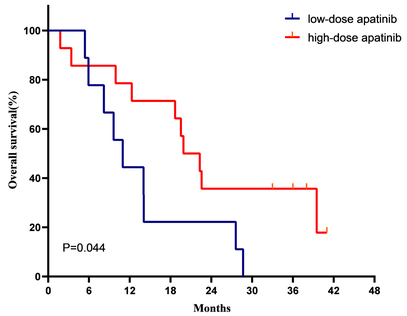


Figure 5: OS comparison of low-dose and high-dose apatinib

Safety

- All pts were evaluated for toxicity, 21 were evaluable for DLT.
- During apatinib with POF treatment in the first 28 days, one DLTs were observed at dl 850 mg with herpes in perineum and grade 3 stomatitis. Per protocol, the cohort expanded to six patients to be enrolled at the same starting dose, and all of the patients at this dose level didn't have DLTs.
- AEs occurring in ≥ 10% of patients either during treatment with apatinib with POF in the first 28 days and entire period under apatinib with POF are listed in **Table 3.**

Table 3. AEs occurring ≥ 10%in patients

AEs n (%)	Apatinib+POF (n=23)			
	First 28 days		Entire period	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Anemia	16 (69.6)	0 (0.0)	19 (82.6)	0 (0.0)
Hypoalbuminemia	14 (60.9)	0 (0.0)	18 (78.3)	0 (0.0)
Neutropenia	11 (47.8)	6(26.1)	19 (82.6)	7(30.4)
Leukopenia	10 (43.5)	0 (0.0)	13 (56.5)	0 (0.0)
Prolonged prothrombin time	8 (47.1)	0 (0.0)	10 (43.5)	0 (0.0)
Elevated aspartate aminotransferase	8 (34.8)	0 (0.0)	9 (39.1)	0 (0.0)
Diarrhea	6 (26.1)	0 (0.0)	6 (26.1)	0 (0.0)
Proteinuria	6 (26.1)	0 (0.0)	16 (69.6)	1 (4.35)
Hypochloremia	5 (21.7)	0 (0.0)	5 (21.7)	0 (0.0)
Elevated alanine aminotransferase	5 (21.7)	0 (0.0)	10 (43.5)	0 (0.0)
Hypophosphatemia	4 (17.4)	0 (0.0)	7 (30.4)	0 (0.0)
Elevated gamma-glutamyl transferase	3 (13.0)	0 (0.0)	5 (21.7)	0 (0.0)
Elevated lactate dehydrogenase	3 (13.0)	0 (0.0)	9 (39.1)	0 (0.0)
Hyponatremia	3 (13.0)	0 (0.0)	4 (17.4)	0 (0.0)
Hyperbilirubinemia	3 (13.0)	0 (0.0)	7 (30.4)	0 (0.0)
Constipation	3 (13.0)	0 (0.0)	5 (21.7)	0 (0.0)
Mucositis	3 (13.0)	1(4.35)	10 (43.5)	4(17.4)
Elevated alkaline phosphatase	3 (13.0)	0 (0.0)	7 (30.4)	0 (0.0)
Hypocalcemia	2 (8.7)	0 (0.0)	2 (8.7)	0 (0.0)
Vomiting	2 (8.7)	0 (0.0)	4 (17.4)	0 (0.0)
Asthenia	2 (8.7)	0 (0.0)	7 (30.4)	1 (4.35)
Dizziness	2 (8.7)	0 (0.0)	3 (13.0)	0 (0.0)
Hand-foot syndrome	0 (0.0)	0 (0.0)	10(43.5)	3 (13)
Hypertension	0 (0.0)	0 (0.0)	4 (17.4)	1 (4.35)
peripheral neuropathy	0 (0.0)	0 (0.0)	13 (56.5)	2 (8.7)

CONCLUSIONS

Apatinib in combination with POF had a manageable safety profile. High dose Apatinib combined with POF had encouraging antitumor activity in patients with TNAGC, which warrants additional investigations in larger cohorts.

CLINICAL TRAIL IDENTIFICATION

The trial protocol number is ClinicalTrials.gov: NCT03244774.

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