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Randomized phase II study of capecitabine and cisplatin with or without sorafenib in patients with metastatic gastric cancer: STARGATE study

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On behalf of the STARGATE investigators

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Disclosure

- Min-Hee Ryu: No relevant conflict of interest to disclose

Background (I)

- Gastric cancer (GC) is the 3rd leading cause of cancer death worldwide[1]

- Capecitabine + cisplatin (XP) is one of the most commonly used 1st line regimens for advanced GC
  - Non-inferiority of XP vs 5-FU + cisplatin (FP) shown in ML17032 study[2] (median PFS 5.6mo vs 5.0mo; HR 0.81)
  - A commonly used backbone chemotherapy for combining targeted agents in advanced GC

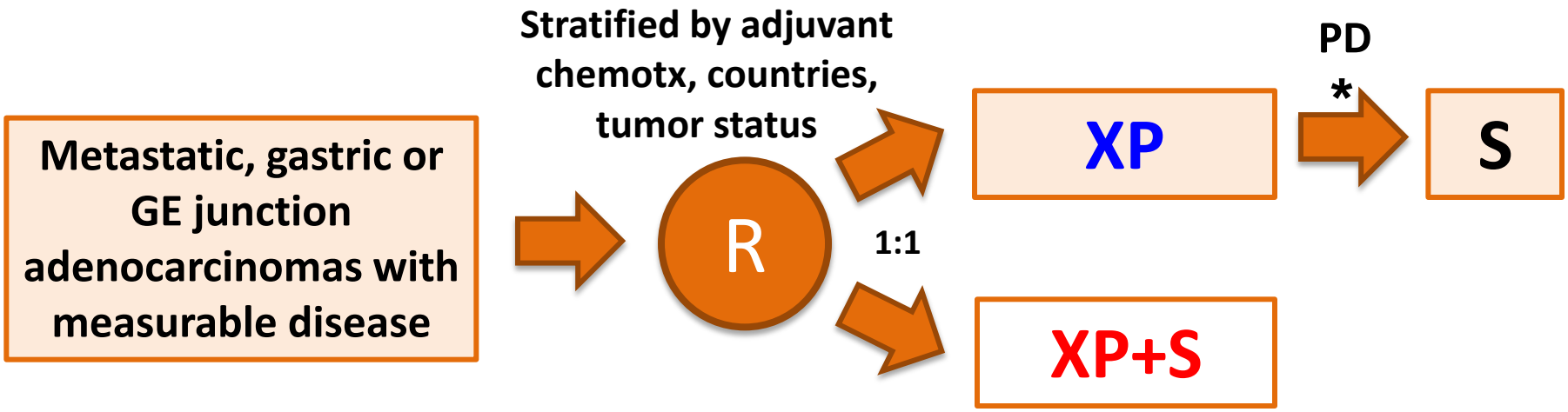
1. GLOBOCAN 2012 2. Kang et al, Ann Oncol 2009

Background (II)

- Sorafenib: multikinase inhibitor of VEGFR and RAF-MEK-ERK
  - Approved in HCC, RCC, and RAI refractory TC
  - Encouraging efficacy was suggested in AGC when combined with cytotoxic chemotherapy (DP[1], XP[2])
- Recommended dose for sorafenib + XP in a Phase I study[2]
  - Sorafenib (400 mg bid D1-21) + capecitabine (800 mg/m^2 bid D1-14) + cisplatin (60 mg/m^2 D1), every 3 weeks

1. Sun et al, J Clin Oncol 2010
2. Kim et al, Invest New Drugs 2012

Study Design



- **XP** every 3 wks
  - Capecitabine 1000mg/m^2 p.o. bid D1-14
  - Cisplatin 80mg/m^2 i.v. D1
  - Until 8 cycles

- **XP+S** every 3 wks
  - Capecitabine 800mg/m^2 p.o. bid D1-14
  - Cisplatin 60mg/m^2 i.v. D1
  - Sorafenib 400mg p.o. bid D1-21
  - Until 8 cycles, and then S alone

* Allowed to cross-over to S after PD

Endpoints & Statistical Assumption

- Primary endpoint: PFS by independent central review
  - Expected median PFS: 5.6 mo (**XP)** vs 7.4 mo **(XP + S)**
  - 2 yr of accrual and 1 yr of follow-up
  - 80% power, one-sided alpha 0.05, 10% drop out
  - Planned total N = 194

- Secondary endpoints
  - OS, RR, and safety of XP vs XP+S
  - RR and PFS of 2nd line sorafenib in XP arm
  - Biomarker analyses

Study Conduct

- A total of 195 patients were randomized from 12 centers in 3 countries (10 in Korea, 1 in China, 1 in Taiwan) between Jan 2011 and Feb 2013

- Safety interim analysis with 30 patients in Oct 2011

- Data cut-off for final analysis with 154 events in Nov 2013

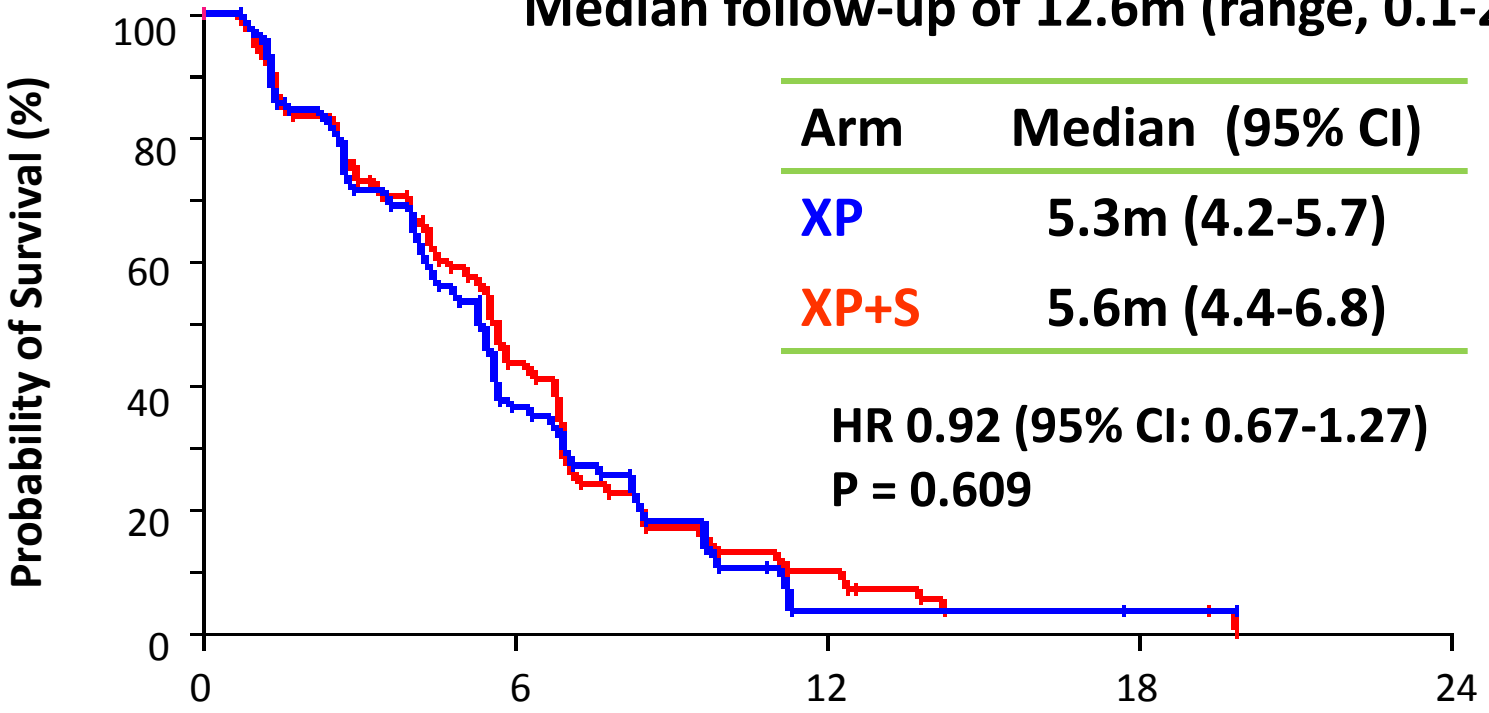
Baseline Characteristics (I)

		XP (n=98)	XP+S (n=97)	
		n (%)	n (%)	P-value
Median age (range)		56 (19-73)	55 (19-72)	0.605
Gender	Male	69 (70)	76 (78)	0.204
	Female	29 (30)	21 (22)	
ECOG PS	0	29 (30)	32 (33)	0.609
	1	69 (70)	65 (67)	
Disease Status	Metastatic	86 (88)	85 (88)	0.979
	Recurrent	12 (12)	12 (12)	
Primary Site	GE junction	10 (10)	**20 (21)**	**0.044**
	Gastric	88 (90)	77 (79)	
Differentiation	Well	3 (3)	6 (7)	0.433
	Moderately	34 (39)	38 (44)	
	Poorly	50 (57)	43 (49)	

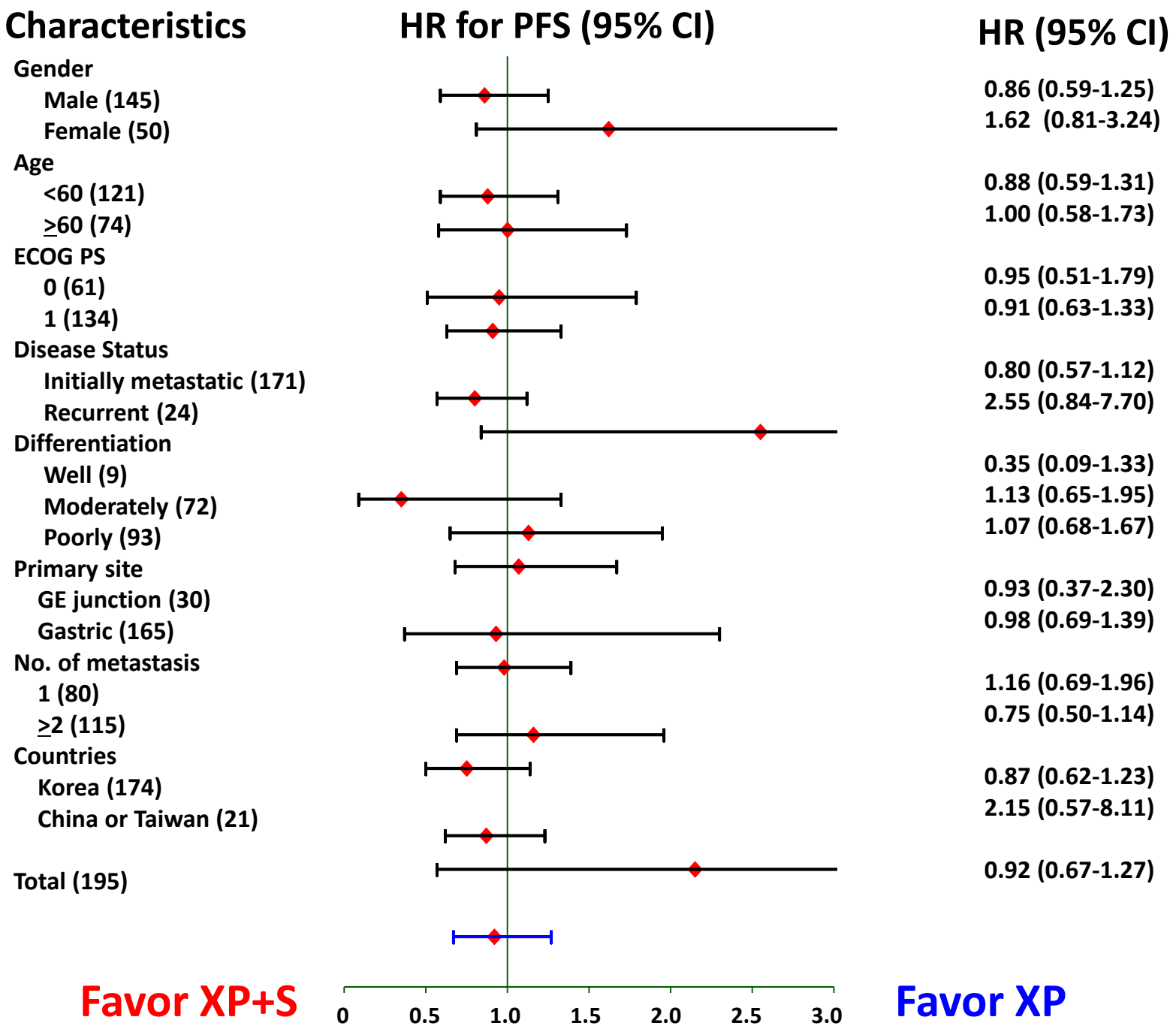
Baseline Characteristics (II)

		XP (n=98)	XP+S (n=97)	
		n (%)	n (%)	P-value
No. of metastasis	1	38 (39)	42 (43)	0.521
	≥2	60 (61)	55 (57)	
Metastatic sites	Liver	52 (53)	44 (45)	0.282
	Peritoneum	29 (30)	26 (27)	0.665
	Lymph node	78 (80)	78 (80)	0.886
	Lung	6 (6)	3 (3)	0.497
	Bon	3 (3)	5 (5)	0.497
Adjuvant chemotherapy		7 (7)	7 (7)	0.984
Countries	Korea	87 (89)	87 (90)	0.837
	China or Taiwan	11 (11)	10 (10)	

Primary Endpoint: PFS (by Independent Review)

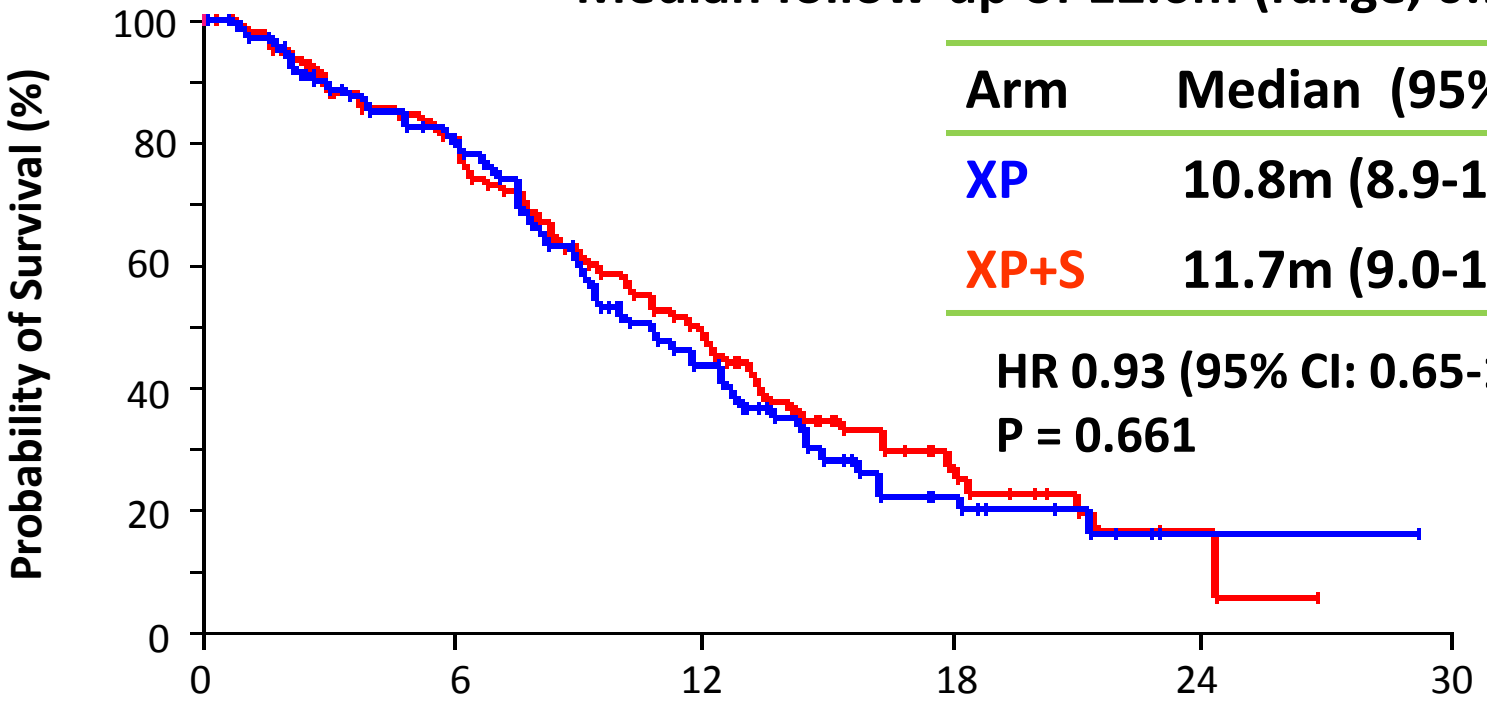


Number at risk					
XP	98	27	2	1	0
XP+S	97	31	7	2	0


Characteristics
HR for PFS (95% CI)
HR (95% CI)
Gender
Male (145)
0.86 (0.59-1.25)
Female (50)
1.62 (0.81-3.24)
Age
<60 (121)
0.88 (0.59-1.31)
≥60 (74)
1.00 (0.58-1.73)
ECOG PS
0 (61)
0.95 (0.51-1.79)
1 (134)
0.91 (0.63-1.33)
Disease Status
Initially metastatic (171)
0.80 (0.57-1.12)
Recurrent (24)
2.55 (0.84-7.70)
Differentiation
Well (9)
0.35 (0.09-1.33)
Moderately (72)
1.13 (0.65-1.95)
Poorly (93)
1.07 (0.68-1.67)
Primary site
GE junction (30)
0.93 (0.37-2.30)
Gastric (165)
0.98 (0.69-1.39)
No. of metastasis
1 (80)
1.16 (0.69-1.96)
≥2 (115)
0.75 (0.50-1.14)
Countries
Korea (174)
0.87 (0.62-1.23)
China or Taiwan (21)
2.15 (0.57-8.11)
Total (195)
0.92 (0.67-1.27)
Favor XP+S
0
0.5
1.0
1.5
2.0
2.5
3.0
Favor XP

Overall Survival

Median follow-up of 12.6m (range, 0.1-29.2)



Arm	Median (95% CI)
XP	10.8m (8.9-12.7)
XP+S	11.7m (9.0-13.5)

HR 0.93 (95% CI: 0.65-1.31)
P = 0.661

Number at risk

XP	98	66	32	9	1
XP+S	97	70	40	12	3

Response by RECIST v1.1
(by Independent Review)

Best Response	XP (n=98)	XP+S (n=97)
CR	1 (1%)	1 (1%)
PR	50 (51%)	51 (53%)
SD	28 (29%)	24 (25%)
PD	11 (11%)	13 (13%)
Not evaluable	8 (8%)	8 (8%)
ORR*	52%	54%

*P = 0.826

Adverse Events ≥ Grade 3 in ≥5%

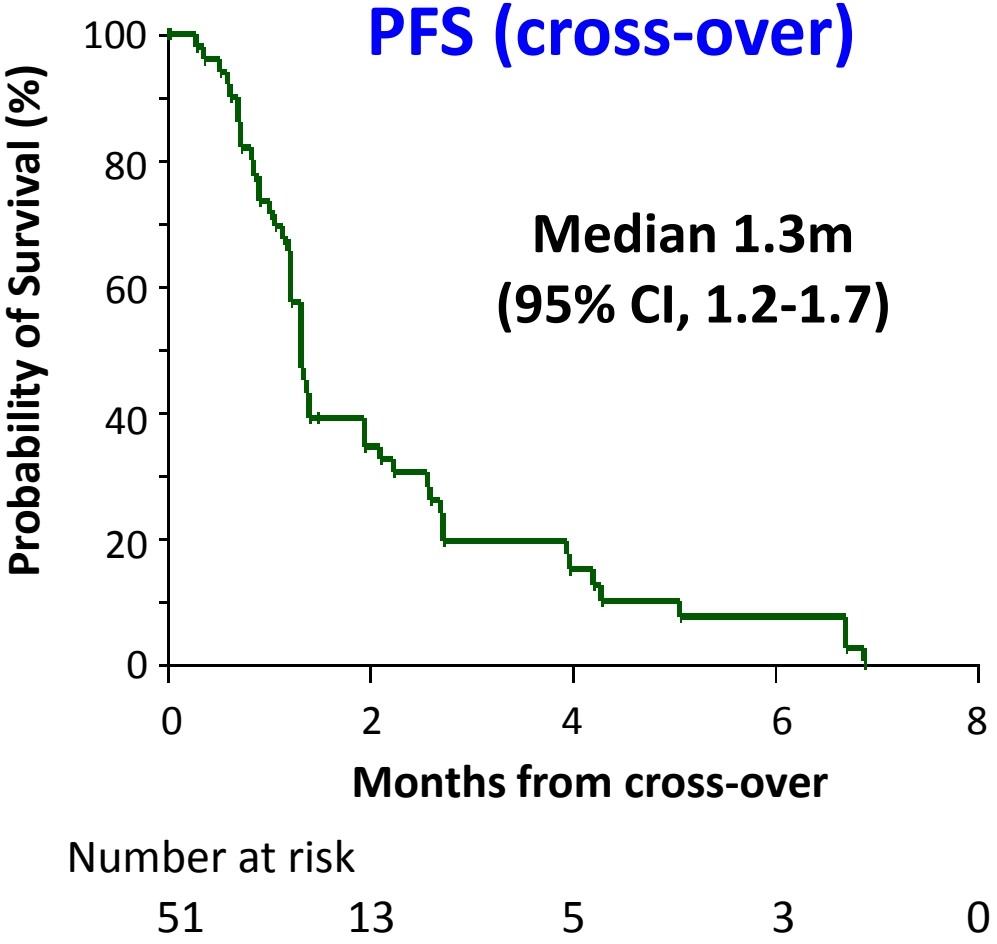
	XP (n=96)	XP+S (n=97)	P-value
Leucopenia	6.3%	2.1%	0.144
Neutropenia	**36.5%**	20.6%	**0.015**
Anemia	13.5%	10.3%	0.488
Thrombocytopenia	5.2%	8.2%	0.400
Febrile neutropenia	6.3%	2.1%	0.144
Thromboembolic events	5.2%	5.2%	0.987
Hand Foot Skin Reaction	1.0%	**7.2%**	**0.031**
Fatigue	5.2%	3.1%	0.461
Bilirubin increase	2.1%	5.2%	0.254
Anorexia	**5.2%**	0.0%	**0.023**

Dose Intensity and Modification

	XP	XP+S
Median number of cycles	6	6
Relative dose intensity		
Capecitabine	85%	83%
Cisplatin	82%	85%
Sorafenib	-	90%
Dose reductions due to toxicity		
Capecitabine	68%	63%
Cisplatin	68%	57%
Sorafenib	-	20%
Discontinuation due to toxicity	3%	10%

Cross-over to Sorafenib in XP arm

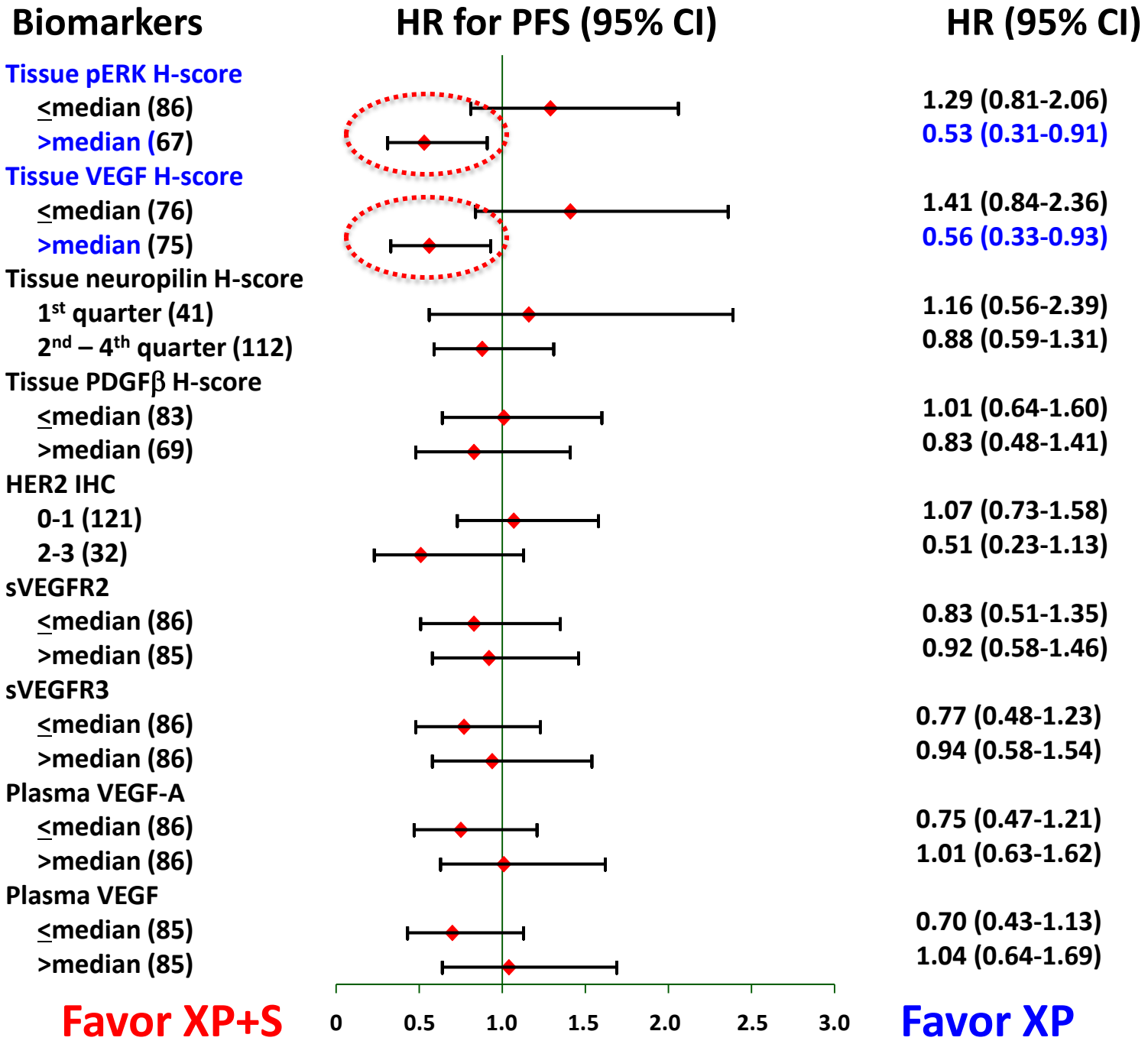
Best Response	Cross-over (n=51)
CR	0 (0%)
PR	0 (0%)
SD	19 (37%)
PD	30 (59%)
NE	2 (4%)



Biomarkers for Sorafenib

	Plasma soluble protein	Tumor Tissue*
Angiogenesis	sVEGFR1,2,3 VEGF-A, VEGF bFGF, TIE-1 PDGFRβ	VEGF, VEGFR2 PDGFβ Neuropilin
RAF-MEK-ERK		pERK
Others		HER2

***by H-score for angiogenesis and RAF-MEK-ERK**


Biomarkers
HR for PFS (95% CI)
HR (95% CI)
Tissue pERK H-score
≤median (86)
>median (67)
Tissue VEGF H-score
≤median (76)
>median (75)
Tissue neuropilin H-score
1st quarter (41)
2nd – 4th quarter (112)
Tissue PDGFβ H-score
≤median (83)
>median (69)
HER2 IHC
0-1 (121)
2-3 (32)
sVEGFR2
≤median (86)
>median (85)
sVEGFR3
≤median (86)
>median (86)
Plasma VEGF-A
≤median (86)
>median (86)
Plasma VEGF
≤median (85)
>median (85)
1.29 (0.81-2.06)
0.53 (0.31-0.91)
1.41 (0.84-2.36)
0.56 (0.33-0.93)
1.16 (0.56-2.39)
0.88 (0.59-1.31)
1.01 (0.64-1.60)
0.83 (0.48-1.41)
1.07 (0.73-1.58)
0.51 (0.23-1.13)
0.83 (0.51-1.35)
0.92 (0.58-1.46)
0.77 (0.48-1.23)
0.94 (0.58-1.54)
0.75 (0.47-1.21)
1.01 (0.63-1.62)
0.70 (0.43-1.13)
1.04 (0.64-1.69)
Favor XP+S
0
0.5
1.0
1.5
2.0
2.5
3.0
Favor XP

Conclusions

- Combination of sorafenib with XP was tolerable, but not more effective than XP alone in unselected patients with advanced GC.
- Sorafenib does not appear to be effective after failure of XP.
- Tissue expression level of pERK and VEGF may have a predictive role for PFS with XP + sorafenib.

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