THE ROLE OF *FGFR2* AMPLIFICATION AND EXPRESSION IN PATIENTS WITH ADVANCED OR METASTATIC GASTRIC CANCER RECEIVING FLUOROPYRIMIDINE-BASED CHEMOTHERAPY

Skupińska M[1], Jesiotr M[2], Chrom P[3], Mróz A[4], Cierniak S[2], Winiarek M[5], Wyrwicz L[5], Pieczykolan J[1], Wieczorek M[1], Stańczak A[1], Bodnar L[3]

1 –Preclinical Development Department; Celon Pharma S.A; 2 –Department of Pathology, Military Institute of Medicine; Warsaw, Poland; 3 – Department of Oncology, Military Institute of Medicine; 4 – Department of Pathology and Laboratory Diagnostics, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology; Warsaw, Poland ; 5 – Department of Oncology and Radiotherapy, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology; Warsaw, Poland

corresponding author: monika.skupinska@celonpharma.com; presentation numer: 647P

CELON PHARMA

Shape the future of healthcare.

INTRODUCTION

Fibroblast growth factors (FGFs) and their receptors are complex intracellular pathway that controls cellular proliferation, tumor growth and invasion. FGFR alterations have been shown to be associated with the initiation and progression of gastric cancer (GC) [1-5]. We investigated correlations of the *FGFR2* amplification and expression with clinicopathological characteristics and outcomes in advanced/metastatic gastric cancer patients who received systemic chemotherapy based on fluoropyrimidine.

MATERIALS AND METHODS

Patients` characteristics

Table 1. Clinicopathological characteristics of patients

Parameter	Number of patients	%
Gender		
male	78	63
female	45	37
Age, median, range (in years)	63.8	29-84
Gastrectomy		
No	55	44
Yes	68	55
Ascites		
No	112	91
Yes	11	9
Performance status (ECOG):		
0	31	25
1	75	61
2	17	14
Local recurrence		
No	65	53
Yes	58	47
Lung metastases:		
No	108	88
Yes	15	12
Liver metastases:		
No	75	61
Yes	48	39
Peritoneal metastases		
No	70	57
Yes	53	43
Number of metastasis sites:		
1	26	21
2	73	59
3	13	11
4	5	4
5	5	4
6	1	1

Materials

FFPE tumor samples were obtained from patients with advanced/metastatic gastric cancer who received systemic chemotherapy based on fluoropyrimidyne diagnosed at two cancer centers between 2010 and 2016.

Fluorescence *in* situ hybridization (FISH)

FGFR2 gene copy number was assessed by FISH method using probes specific for the 10q26 locus and the chromosome 10 centromere (CEN 10) Zyto*Light* SPEC FGFR2/CEN 10 Dual Color Probe (ZytoVision). Amplification was defined as FGFR2/CEN10≥2.0

Immunohistochemistry (IHC)

FGFR2 protein expression was determined by immunohistochemistry. Tissue slides were subjected to antigen retrieval in Target Retrieval Solution, pH 9 (DAKO) with PT Link (DAKO). Tissues were incubated with anti-FGFR2 rabbit polyclonal antibody (Abcam). Detection was done with EnVision TM+ system (DAKO). Overexpression was defined as complete membrane staining intensity ≥2+ (graded from 0 to 3+) in ≥10% tumor cancer cells.

Statistical analysis

Analyses were done using Statistica Statsoft version 12.0. The Kaplan-Meier method was used to estimate medians for PFS and OS. Multivariate Cox proportional hazards regression was used to identify factors independently associated with PFS and OS.

The study was approved by local ethical committee.

RESULTS

FGFR2 Amplification and Expression Patterns

From the cohort consisting of 186 gastric cancer patients, FFPE tumor samples were available from 123 patients. *FGFR2* amplification was found in 4/123 (3.3%) patients with FGFR2/CEN10 and the mean FGFR2/CEN10 ratio was 1.16 ±1.77 (range: 0.8-20.0). FGFR2 overexpression was observed in 5/123 (4.1%) patients.

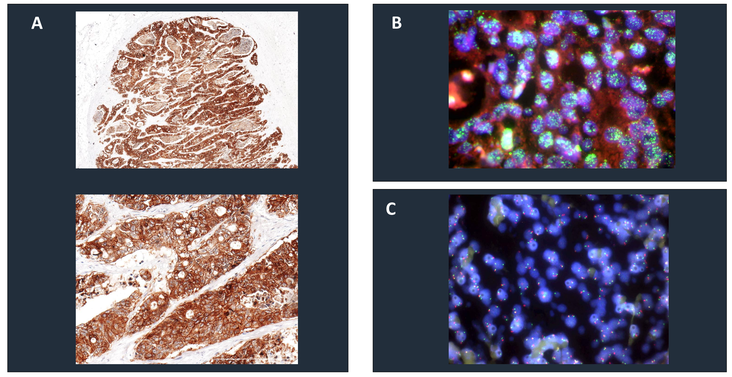

Figure 1. Representative example of FGFR2 expression and amplification in gastric cancer patient. (**A**) Strong cytoplasmic and membrane staining (IHC 3+); (**B**) *FGFR2* amplification (FGFR2/CEN10 =20); (**C**) *FGFR2* no amplification (FGFR2/CEN10 = 1,05).

The FISH and IHC results were consistent in 99.8 % gastric cancer patients (n=123), including 4/123 (3.3%) double-positive and 118/123 (95.93%) double-negative tumors. In 1/123 patient result was discordant: IHC(+) FISH(-).

Table 2. Samples of FISH and/or IHC positve results.

No	FGFR2/CEN10 ratio	FISH results	IHC score	IHC results
1	20,00	FISH (+)	3+	IHC (+)
2	1,00	FISH (-)	3+	IHC (+)
3	10,46	FISH (+)	3+	IHC (+)
4	14,02	FISH (+)	3+	IHC (+)
5	18,80	FISH (+)	3+	IHC (+)

STRATEGMED

The National Centre for Research and Development

The research was co-financed by the National Center of Research and Development and pharmaceutical company Celon Pharma S.A., project "CELONKO", grant number STRATEGMED2/266776/17/NCBR/2015

RESULTS

Progression-free survival and overall survival

FGFR2 amplification had no statistically significant impact on overall survival (OS) and progression free survival (PFS) in comparison to those without *FGFR2* amplification (respectively, HR=1.43, 95% CI 0.54 to 4.04, p=0.4426 and HR=3.06, 95%CI 0.94 to 9.97, p=0.0628). There was no prognostic significance observed for FGFR2 overexpression on OS and PFS (respectively, HR=1.27, 95%CI 0.52 to 3.15, p=0.5961 and HR=2.44, 95%CI 0.88 to 6.78, p=0.0863).

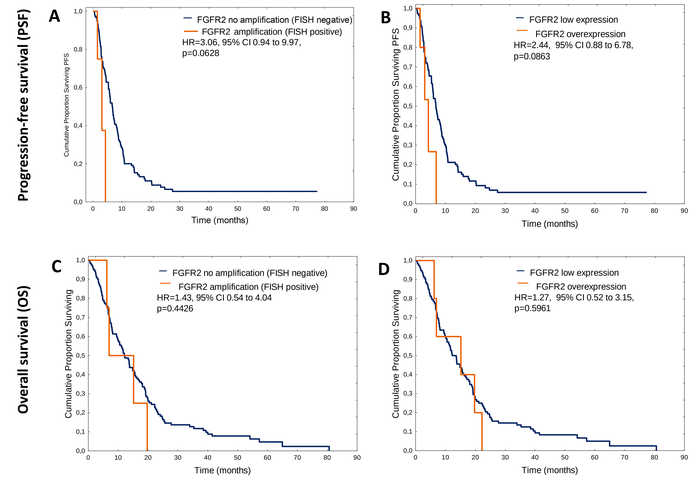

Figure 2. Progression-free survival (A, B) and overall survival (C,D). Cumulative proportion surviving (Kaplan–Meier method).

CONCLUSIONS

The rate of GC patients with tumors positive for *FGFR2* amplification or expression was consistent with the data published in the literature. However, *FGFR2* amplification and overexpression have no prognostic significance in advanced/metastatic gastric cancer patients who received systemic chemotherapy based on fluoropyrimidine. Therefore, further investigation on a larger population is required.

REFERENCES

[1] M. Inokuchi *et al.* Therapeutic targeting of fibroblast growth factor receptors in gastric cancer, *Gastroenterol. Res. Pract.*15 (2015)

[2] S. Ahn *et al.* FGFR2 in gastric cancer: protein overexpression predicts gene amplification and high *H*-index predicts poor survival, *Modern Pathol* 1-9 (2016)

[3] S. Seo et *al.* Prognostic impact of fibroblast growth factor receptor 2 gene amplification in patients receiving fluoropyrimidine and platinum chemotherapy for metastatic and locally advanced unresectable gastric cancers, *Oncotarget* (2016)

[4] K. Matsumoto *et al. FGFR2* gene amplification and clinicopathological features in gastric cancer, *Brit J Cancer.* 106 (2012)

[5] H. Murase *et al.* Prognostic significance of the co-overexpression of fibroblast growth factor receptors 1, 2 and 4 in gastric cancer, *Mol. Clin. Oncol.* 2 (2014)