Gemcitabine as second-line chemotherapy after Folfirinox failure in advanced pancreatic adenocarcinoma: A retrospective study

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Abstract

Background: Pancreatic adenocarcinoma (PA) is diagnosed in most cases at an advanced stage requiring chemotherapy. Folfirinox is the standard first-line treatment. After Folfirinox failure, gemcitabine alone is routinely used as second-line therapy without data supporting this attitude.

Aim: Determine the response rate and outcome of patients with advanced PA treated with gemcitabine after Folfirinox failure.

Methods: We retrospectively analyzed all consecutive patients treated with gemcitabine after Folfirinox failure for a locally advanced or metastatic PA between 2009 and 2015. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method. Response rate, control rate and tolerability were assessed.

Results: 96 patients were included (male,51%; median age,62; performance status (PS) 0-1, 47%). Median duration on gemcitabine was 2.1 months. The overall disease control rate was 40%. Median OS was 3.7 months (95%CI: 2.5-5.2) and median PFS was 2.1 months (95%CI: 2.0-2.6). Reasons for treatment discontinuation were mostly progression (51%). Age at diagnosis and PS were independently associated with OS in multivariate analysis (HR of 1.86; p=0.0055 and 2.42; p<0.0001 respectively). 34 patients experienced a grade 3 adverse event.

Conclusions: This study suggests that gemcitabine is not beneficial to all patients failing on Folfirinox first-line therapy and should be restricted to young patients with good PS.

Keywords: Advanced pancreatic cancer, Folfirinox, gemcitabine, second-line chemotherapy

Background

Pancreatic adenocarcinoma is a frequent malignancy worldwide[1] associated with a five-year overall survival (OS) rate between 5% and 7% in USA and Europe respectively[2,3]. At the time of diagnosis, most patients present with a locally advanced or metastatic disease precluding surgical resection. For these patients, survival without any treatment is less than 5 months[4] and palliative chemotherapy is the only therapeutic option, associated with median OS durations between 6 and 11 months[5–7].

Current standards in first-line treatment of fit patients with an advanced disease are Folfirinox and nab-paclitaxel plus gemcitabine regimens, both having shown their superiority over gemcitabine alone in two phase III studies[5,6]. Until recently, after progression during first-line therapy, there was no standard second-line treatment although literature suggests that an increasing number of patients (40 to 60%) would be able to receive a second-line therapy[5,6,8].

Only one phase III study from the German CONKO-study group compared a second-line chemotherapy including fluorouracil, folinic acid and oxaliplatin to best supportive care (BSC) in this setting and showed an improvement of second-line OS (4.8 vs 2.3 months; p=0.031) without major toxicities but failed by insufficient accrual[9]. The same regimen significantly improved OS and PFS when compared to fluorouracil/ folinic acid alone in another phase III study from the same group that included 168 gemcitabine-refractory patients (5.9 vs 3.3 months, p=0.01 and 2.9 vs 2.0 months, p=0.019 respectively)[10]. These

results suggested the interest of an oxaliplatin-based second-line therapy but were not confirmed by the Canadian PANCREOX trial who compared modified FOLFOX6 and infusional FU/leucovorin and found no difference in PFS (3.1 vs 2.9 months, p=0.99) and inferior OS in patients assigned to mFOLFOX6 (6.1 vs 9.9 months, p=0.02)[11]. Recently, nanoliposomal irinotecan in combination with fluorouracil/ folinic acid has shown a significant improvement of median OS (6.1 vs 4.2 months), progression-free survival (PFS) and objective response rate over fluorouracil/ folinic acid alone in the NAPOLI-1 phase III study[12]. Other studies have reported median OS between 3 and 9 months, suggesting a benefit of chemotherapy compared to BSC and a meta-analysis of 34 studies confirmed this impression by showing a survival benefit of 3.2 months (p=0.013) in patients treated compared to those who only received BSC[13]. However, most of these studies have been performed before the era of Folfirinox and nab-paclitaxel-gemcitabine in patients progressing on gemcitabine alone.

Since the publication of the study by Conroy et al., Folfirinox has become the reference regimen in Europe and USA for the first-line treatment of advanced pancreatic cancer patients with a good performance status (PS) and a level of bilirubin ≤1.5 ULN[14,15]. After failure on Folfirinox, a gemcitabine-based chemotherapy is recommended according to ASCO and ESMO clinical practice guidelines but with a low level of evidence[14,15] as poor data are available in this setting[16–19].

The aim of this retrospective multicenter study was to determine the response rate and outcome of patients with advanced pancreatic adenocarcinoma treated with gemcitabine alone as second-line treatment after failure on Folfirinox and to identify prognostic factors in this setting.

Methods

Patients

All consecutive patients with a histological proven metastatic or locally advanced pancreatic adenocarcinoma treated with gemcitabine after Folfirinox failure between October 2009 and December 2015 in 3 centers (Rennes University Hospital, Eugène Marquis Cancer Center and Jean Mermoz private hospital) were retrospectively enrolled.

Medical records of patients were reviewed to collect relevant data on demographics, tumor characteristics, pancreatic surgery, adjuvant gemcitabine chemotherapy, biliary stenting, pancreatic radiation, Eastern Cooperative Oncology Group (ECOG) PS and serum levels of carbohydrate antigen 19-9 (CA 19-9) before the start of second-line chemotherapy. The following first-line Folfirinox characteristics were collected: number of cycles, best response (RECIST v1.1) and reasons for treatment cessation.

Second-line treatment and outcome measures

Each cycle of gemcitabine consisted of a 30 min intravenous infusion of gemcitabine at a dose of 1000 mg per m^2 on days 1, 8, and 15 every 4 weeks. This regimen was delivered until disease progression, unacceptable toxicity or patient refusal.

The following data regarding second-line-gemcitabine were collected: date of first and last infusions, number of cycles, potential dose reductions and their reasons, and reasons for treatment cessation.

Tolerability was assessed by analyzing all chemotherapy-related adverse events reported during the second-line treatment and if specified, their grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) V4.0.

Tumor response was assessed in patients with measurable disease every 2 months by chest–abdomen–pelvis by means of computed tomography or magnetic resonance imaging according to the RECIST version 1.1 criteria[20] .

Any third-line chemotherapy administered after disease progression was also recorded. After progression, all patients were followed up until death.

Statistical analysis

Quantitative variables were expressed as medians and range. Categorical variables were presented as counts and percent of the cohort.

PFS was calculated from the date of gemcitabine initiation to the date of disease progression or death, whichever came first. Surviving patients without disease progression were censored at the date of last follow up. OS was calculated from the date of gemcitabine initiation to death. Surviving patients were censored at the date of last follow up.

PFS and OS curves were estimated by the Kaplan Meier method. For univariate and multivariate analysis, Cox's proportional hazards model was used to calculate hazard ratios (HR) with 95% confidence intervals (CI) for PFS and OS. All tests were two-sided and p-value <0.05 was considered to be statistically significant.

This study was approved by the Rennes University Hospital Ethics Committee for all participating centers.

Results

Patient and tumor characteristics

Among a total of 206 patients treated between October 2009 and December 2015 by Folfirinox in first-line, 96 (47%) patients received gemcitabine alone in second-line. Baseline characteristics of study population are depicted in **Table 1**. The median age of patients was 62 years and 51% of them were male. Most tumors were located in the head of pancreas and most patients had a metastatic disease, preferentially located in the liver. A total of 12 patients (13%) had previously undergone a pancreatic surgery, including 6 who received

gemcitabine as adjuvant chemotherapy. Patients have received Folfirinox in first-line for a median duration of 5.9 months and 64% of them were treated for more than 4 months, with an objective response rate of 40%.

Of note, prior to second-line chemotherapy, only 47% of patients had a PS of 0-1. Most patients showed an elevated CA19-9 serum level (> 400 UI/ml) among the 65 patients in whom this data was available. Gemcitabine was usually started because of disease progression (84%, table 1).

Toxicity

Median duration on gemcitabine was 2.1 months (range 0.2-15.8). Patients received a median number of 2 cycles (range 1-14). There was no treatment-related death. A total of 34 patients experienced at least one grade 3 toxicity, which was mainly hematologic and/or asthenia. Toxicities are described in **Table 2**.

A total of 23 patients (24%) required a dose reduction, mainly due to asthenia (14 patients, 61%) or hematologic toxicities (9 patients, 39%). Chemotherapy was adjourned at least one time in 30 patients (31%).

Tumor response and Survival

The tumor response was assessable in 80 patients with measurable disease. There was no complete response. 8 patients achieved a partial response (10%) and 24 (30%) a stable disease. The overall disease control rate was 40% (**Table 3**).

After a median follow-up of 10.9 months (1.2-51) since the beginning of Folfirinox and 3.7 months (0.2-19.7) since the beginning of gemcitabine, the median OS from the start of second-line therapy was 3.7 months (95%CI:2.5-5.2). The 6-months and 12-months OS rates were 35% (95%CI: 26.2-45.8) and 10% (95%CI: 5.4-19.4) respectively (**Figure 1**). The median PFS from the start of second-line therapy was 2.1 months (95%CI:2.0-2.6). The 6-months and

12-months PFS rates were 16% (95%CI:10.2-25.8) and 2% (95%CI:0.6-8.5) respectively (**Figure 2**). The median OS from the start of first-line chemotherapy was 11.2 months (95%CI:10.4-14.0). The 12-months and 24-months OS rates were 46 % (95%CI: 36.6-57) and 13% (95% CI :7.6-22.6) respectively.

Reasons for gemcitabine discontinuation were disease progression (n=49, 51%), side effects (n=15, 16%), patient death (n=24, 25%) and patient preference (n=5;5%). 3 patients were still on treatment at the end of the follow up and 33 patients (34%) received a third-line therapy.

Prognostic factors

In univariate analysis, age at diagnosis [>62 years versus ≤ 62 years; HR=1.05, 95%CI: 0.68-1.63; p=0.0049] and ECOG-PS score [>1 versus ≤ 1; HR=2.40, 95%CI: 1.56-3.71; p<0.0001] were the only factors significantly associated with OS in these patients treated with gemcitabine second-line therapy. Sex, tumor stage, number of metastatic sites, CA 19-9 level and even response to first-line chemotherapy were not associated with OS.

In multivariate analysis, age at diagnosis and ECOG-PS were still significantly and independently associated with OS with a HR of 1.86 (95%CI: 1.20-2.88; p=0.0055) and 2.42 (95%CI: 1.56-3.75; p<0.0001) respectively (**Table 4**). OS was thus 6.48 months (95%CI: 4.18-9.86) among PS 0-1 patients and 2.47 months (95%CI: 1.68-2.79) among PS 2-3 patients.

We also evaluated the association between these factors and the PFS. In univariate analysis, ECOG-PS score (>1 versus ≤ 1; HR=1.77, 95%CI: 1.17-2.67; p=0.0069) and CA 19.9 level (>400 versus ≤ 400; HR=2.06, 95%CI: 1.12-3.80; p=0.0205) were the only factors associated with PFS, of which, only ECOG-PS was still independently associated with PFS in multivariate analysis with a HR of 2.39 (95%CI: 1.42-4.03; p=0.0011). PFS was thus 2.66 months

(95%CI:2.04-4.07) among PS 0-1 patients and 1.84 months (95%CI:1.28-2.27) among PS 2-3 patients.

Discussion

Folfirinox has become the treatment of choice in first-line treatment of fit patients with metastatic pancreatic adenocarcinoma[5,14,15]. Despite the increasing use of this regimen, there is a lack of data regarding second-line therapy and no consensus second-line treatment after Folfirinox failure in patients with good PS[14,15]. However, gemcitabine is routinely used in this setting, based on its efficacy in first line of advanced pancreatic cancer where this molecule was for 15 years the standard treatment [21].

This study provides results about gemcitabine efficacy as second-line chemotherapy after Folfirinox failure. To our knowledge, it represents the largest reported experience with gemcitabine alone after Folfirinox failure in the literature. Median second-line OS and PFS were relatively short (3.7 and 2.1 months respectively), particularly compared to the median OS of 5.6 months found in first line with this drug in the pivotal study of Burris et al.[21], and were generally lower than those reported in first studies evaluating other second-line chemotherapy regimen after gemcitabine failure (OS: 3.3 to 6.6 months; PFS 2.0 to 5.0 months)[8–11]. This retrospective study reflects routine practices as no selection has been made among patients receiving gemcitabine as second-line treatment, with 25% of patients older than 70 years and 53% of them with an ECOG-PS score of 2 or 3 before starting treatment. This high proportion of old and/or frail patients in our study could explain the poor results of gemcitabine we found.

Some previous studies investigated second-line chemotherapy regimen after Folfirinox failure and often found better survival rates than ours. A phase II study of the AGEO group

evaluated the combination of nab-paclitaxel plus gemcitabine in 57 patients and found median OS and PFS of 8.8 and 5.1 months respectively[16]. In the same way, Zhang et al. found median OS and PFS of 5.3 and 2.7 months respectively in a small series of 28 patients treated with the same combination[17]. Better patient outcomes reported in these studies might be explained by the superiority of nab-paclitaxel plus gemcitabine over gemcitabine alone demonstrated in first-line[6]. Moreover, patients included in these studies were younger and had a better PS than our patients (79% and 96% of patients with PS 0-1 respectively).

Two other studies found similar results than ours. An Italian study investigated 40 patients who received second-line single agent (gemcitabine, docetaxel, nab-paclitaxel) or doublets (gemcitabine with either nab-paclitaxel, capecitabine, cisplatin or docetaxel) after Folfirinox failure. The exact number of patients that received gemcitabine alone was unknown but median PFS and OS of all patients were 2.7 and 3.4 months respectively, without significant difference between single agents and doublets[18]. Finally, a small Portuguese study investigated gemcitabine alone after Folfirinox failure in 20 patients and found median PFS and OS of 2.0 and 5.7 months respectively. To our knowledge, this is the only other published study investigating gemcitabine alone after Folfirinox failure but it included very few patients and most of them had still a good PS[19].

As shown in others studies, we observed that ECOG-PS score was an independent prognostic factor. PS 0-1 patients had a longer OS than PS 2-3 patients. Previous studies had already shown the prognostic value of this parameter in other cancers, including advanced biliary tract cancers[22,23]. The other independent prognostic factor associated with better outcomes in our study was a young age. Young people are supposed to benefit most from chemotherapy than elders even if we lack of data regarding elderly. In most studies reported above, patients were less than 75 years and multivariate analysis was not significant for this

parameter. We did not find any other prognostic factor, particularly, response to gemcitabine was not influenced by prior response to Folfirinox. One lesson we could learn from the prognostic analysis is that we have to better select patients who could most benefit from second-line chemotherapy and exclude elderly and/or frail patients.

This study had several limitations: the retrospective design first, that caused a lack of data such as the CA 19-9 baseline level in 31 patients or others potential prognostic factors such as albumin concentration; the limited number of centers participating to the study and finally, the lack of selection of patients who received second-line gemcitabine, which is however a reflection of clinical routine practices.

In the future, beside chemotherapy, management of pancreatic adenocarcinoma will have to take into account new therapeutic options such as the PEGylated recombinant human hyaluronidase that showed promising results combined to nab-paclitaxel/gemcitabine in previously untreated stage IV pancreatic cancer patients[24].

Conclusions

Gemcitabine alone as second-line chemotherapy after Folfirinox failure in patients treated for a pancreatic adenocarcinoma is not a satisfying option regarding to our results. Although retrospective, our study suggests that gemcitabine alone is not beneficial to all patients and that a better selection of patients, based on age and general condition is crucial. Nab-paclitaxel plus gemcitabine could be a promising option in this setting but it has to be confirmed in prospective and large trials. New drugs are needed to expect a survival improvement of these patients. In the future, since approaches targeting EGFR and angiogenesis have been disappointing, management of advanced pancreatic adenocarcinoma will have to take into account other therapeutic classes.

List of abbreviations used

OS, overall survival – BSC, best supportive care – PFS, progression-free survival – PS, Performance Status - ECOG, Eastern Cooperative Oncology Group – CA 19-9, carbohydrate antigen 19-9 – RECIST, Response Evaluation Criteria in Solid Tumors – HR, Hazard Ratio – CI, Confidence Interval.

Competing interests

The authors declare that they have no competing interests.

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Figures legends

Figure 1 Kaplan Meier analysis of overall survival from the start of gemcitabine second-line chemotherapy

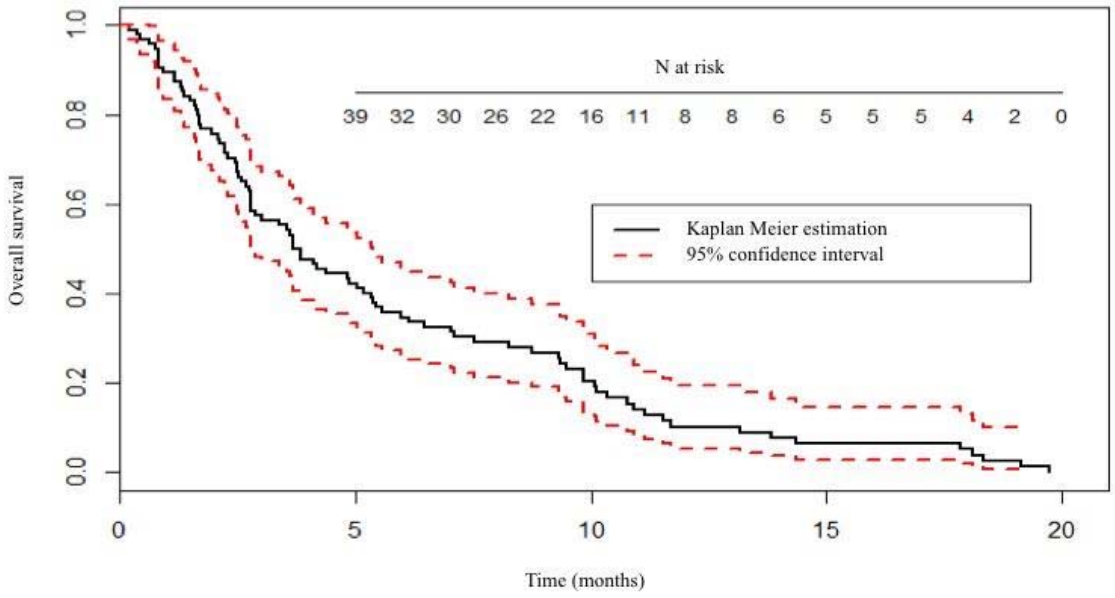

Figure 2 Kaplan Meier analysis of progression-free survival from the start of gemcitabine second-line chemotherapy

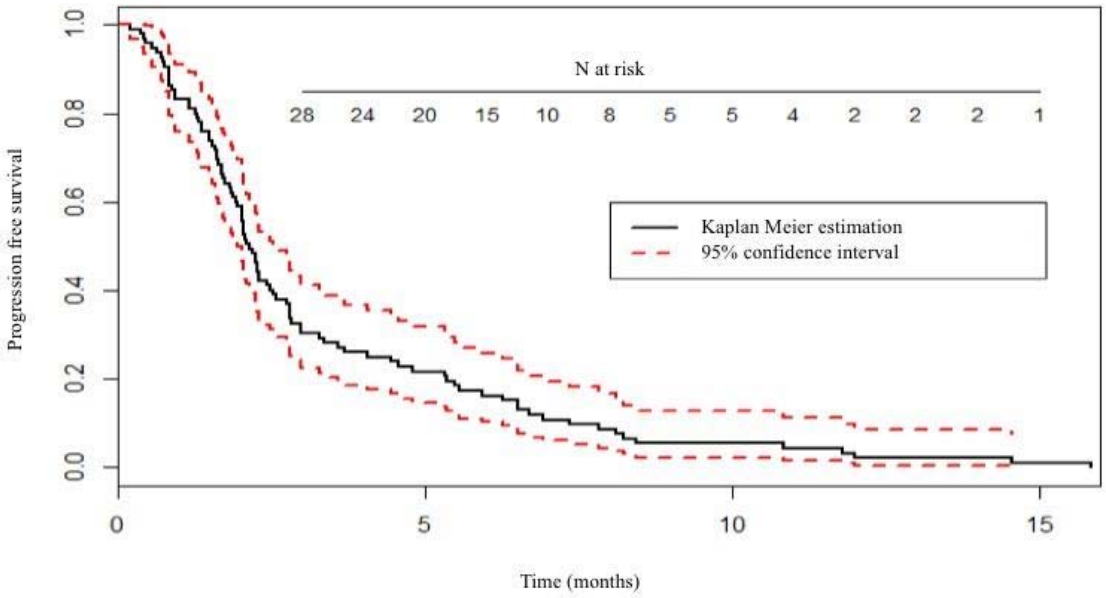

Table 1 Patient and tumor characteristics

Number of patients	96
Median Age [range], years	62 [38-80]
Gender n (%)	
Male	49 (51)
Female	47 (49)
ECOG-PS score n (%)	
0	11 (12)
1	34 (35)
2	45 (47)
3	6 (6)
Pancreatic tumor location n (%)	
Head	44 (46)
Body	31 (32)
Tail	21 (22)
Metastatic sites n (%)	
- Number of metastatic sites	
0	9 (10)
1	57 (59)
≥ 2	30 (31)
- Location of metastasis	
Liver	68 (71)
Lung	23 (24)
Peritoneum	23 (24)
Other	10 (10)
Baseline CA 19-9 serum level n (%)	
≤ 400 UI/ml	18 (19)
> 400 UI/ml	47 (49)
unknown	31 (32)
median [range], UI/ml	1561 (0-1233720)
Biliary stent n(%)	26 (27)
First line Folfirinox chemotherapy characteristics	
- Number of cycles, median [range]	7 [1-24]
- Duration, months, median [range]	5.9 [0.9-38]
- Tumor response, n (%)	
complete response	0 (0)
partial response	38 (40)
stable disease	28 (29)
progression disease	25 (26)
non-evaluable	5 (5)
- Reasons for treatment cessation, n (%)	
Progression	81 (84)
Toxicity	15 (16)
Prior adjuvant gemcitabine chemotherapy n (%)	6 (6)

ECOG-PS, Eastern Cooperative Oncology Group Performans status; CA 19-9, Carbohydrate Antigen 19-9.

Table 2 Toxicities

	No. of patients (%)			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic event				
Neutropenia	5 (5)	8 (8)	11 (11)	1 (1)
Thrombocytopenia	21 (22)	6 (6)	5 (5)	1 (1)
Anemia	35 (37)	17 (18)	3 (3)	0 (0)
Non hematologic event				
Asthenia	16 (17)	17 (18)	19 (20)	0 (0)
Nausea/vomiting	12 (13)	5 (5)	2 (2)	0 (0)
Mucitis	5 (5)	0 (0)	0 (0)	0 (0)
Diarrhea	8 (8)	0 (0)	0 (0)	0 (0)
Neurotoxicity	5 (5)	1 (1)	0 (0)	0 (0)
Hand Foot syndrome	0 (0)	0 (0)	0 (0)	0 (0)
Alopecia	3 (3)	0 (0)	0 (0)	0 (0)

Toxicities were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0)

Table 3 Tumor Response to gemcitabine and Survival

Tumor response (No. of Patients) (%)	
Total of assessable patients	80
Complete response	0 (0)
Partial Response	8 (10)
Stable disease	24 (30)
Progression disease	48 (60)
Median progression free survival (months) [95%CI]	2.1 [2.0-2.6]
Median overall survival (months) [95%CI]	3.7 [2.5-5.2]

Table 4 Univariate and Multivariate analysis for overall survival

		Univariate analysis			Multivariate analysis		
Variables	N	HR	95% CI	*p*	HR	95% CI	*p*
Sex (female vs male)	96	1.07	[0.70-1.62]	*0.7651*			
Age at diagnosis (>62 vs ≤ 62 years)	96	1.05	[0.68-1.63]	*0.0049*	1.86	[1.20-2.88]	*0.0055*
ECOG-PS score (> 1 vs 0-1)	96	2.40	[1.56-3.71]	*<0.0001*	2.42	[1.56-3.75]	*<0.0001*
Tumor Stage (metastatic vs locally advanced)	96	1.29	[0.64-2.63]	*0.4787*			
Number of metastatic sites (>1 vs ≤ 1)	96	1.08	[0.68-1.71]	*0.7412*			
CA 19-9 level (> 400 vs ≤ 400UI/ml)	65	1.14	[0.75-1.73]	*0.5543*			
First-line response							
disease control vs progression	91	1.47	[0.90-2.39]	*0.1204*			
objective response vs no response	91	1.21	[0.78-1.87]	*0.3982*			
First line PFS (> 4 vs ≤ 4 months)	96	0.79	[0.51-1.23]	*0.2976*			

Abbreviations: HR, Hazard Ratio; 95%CI, 95% confidence Interval; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; CA 19.9, Carbohydrate Antigen 19.9; PFS, Progression Free Survival.