



## ORIGINAL ARTICLE

# FOLFIRINOX is a cost-effective combination chemotherapy in first-line for advanced pancreatic Cancer

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## ABSTRACT

**Objectives:** The analysis was conducted to assess the effect of front-line combination chemotherapies on progression free survival (PFS).

**Methods:** The analysis was restricted to phase III randomized controlled trials (RCTs) in first-line therapy for advanced pancreatic cancer. The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) was applied to the above phase III RCTs. We have also calculated differences in PFS between the different arms of each trial and the pharmacological costs necessary to get the benefit in PFS, for each trial.

**Results:** Our study evaluated 11 phase III randomized controlled trials (RCTs), including 4572 patients. Combining the costs of therapy with the measure of efficacy represented by the PFS, we have obtained 74.12 € per month of PFS gained for 5-FU, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX), 90.14 per month of PFS gained for gemcitabine and oxaliplatin (GEMOX) and 4708.70 € per month of PFS gained for the combination of gemcitabine plus nab-paclitaxel against gemcitabine alone.

**Conclusions:** Combining pharmacological costs with the measure of efficacy represented by PFS, FOLFIRINOX is a cost-effective first-line for advanced pancreatic cancer.

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## Introduction

Pancreatic cancer (3% of all cancers) is an aggressive malignant disease, with incidence that nearly mirrors its mortality rate with only 1–4% of the patients that are alive 5 years after diagnosis [1,2]. Prevalent histology (>80%) is ductal pancreatic adenocarcinoma (much more aggressive), followed by neuroendocrine tumours and other very rare histotypes [3]. In metastatic disease, gemcitabine alone or in association with other drugs was considered the gold standard for more than 10 years, with a median survival of 6.2 months and a response rate less than 20% [4,5]. European Society for Medical Oncology (ESMO)-European Society of Digestive Oncology (ESDO) Clinical Practice Guidelines have recommended the combination of 5-FU, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) as a novel therapeutic option for patients ≤75 years of age with a good PS (0 or 1) and a level of bilirubin ≤1.5 ULN [3], based on the results of a phase III randomized controlled trial (RCT)

[6]. More recently, a new combination therapy (nab-paclitaxel plus gemcitabine) has been proposed as a new standard treatment based on another phase III RCT [7].

The introduction of active new agents for the treatment of advanced pancreatic cancer is associated with a relevant increase of costs and it might be interesting to make a balance between the costs of treatment and the added value represented by the improvement of the clinical parameters of interest such as progression free survival (PFS). The analysis was conducted to assess the effect of front-line combination chemotherapies on PFS.

## Materials and methods

The analysis was conducted according to the following steps: 1) definition of the outcomes (definition of the question the analysis was designed to answer); 2) definition of the search strategy; 3) definition of the trial selection criteria and data extraction; 4) results; 5) discussion.

## Outcome definition

The analysis was conducted to assess the effect of first-line

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combination chemotherapies on PFS, separately, on each arm of the evaluated trials. The present evaluation was restricted to phase III RCTs in first-line therapy for advanced pancreatic cancer. We have subsequently applied the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) [8] to the above phase III RCTs, to derive a relative ranking (from grade 1 to grade 5) of the magnitude of clinically meaningful benefit that can be expected from front-line therapy for advanced pancreatic cancer (different forms of evaluation were used to evaluate noncurative interventions, depending on which overall survival (OS), PFS, quality of life (QoL), toxicity or response rate (RR) were primary outcomes and for non-inferiority studies); adjustments (upgrade or down-grade) are planned based on QoL or grade 3–4 toxicities impacting daily well-being [8]. We have also calculated differences in PFS (expressed in months) between the different arms of each trial. Then, we calculated the pharmacological costs necessary to get the benefit in PFS, for each trial, referring to the median number of cycles reported in each phase III RCT. Calculations were based on an “ideal patient” (BSA 1.8 sqm; weight 70 Kg). The costs of drugs are at the Pharmacy of our Hospital and are expressed in euros (€). We assumed the following costs for 1 cycle: gemcitabine = 44.82 €, GEMOX = 26.76 €, FOLFIRINOX = 49.87 €, gemcitabine plus nab-paclitaxel = 2152.53 €

### Search strategy

Deadline for trial publication and/or presentation was June 30th, 2017. Full reports and updates of phase III RCTs that compared at least front-line combination chemotherapy regimens for advanced pancreatic cancer patients were obtained through Medline (PubMed: [www.ncbi.nlm.nih.gov/PubMed](http://www.ncbi.nlm.nih.gov/PubMed)), American Society of Clinical Oncology (ASCO, [www.asco.org](http://www.asco.org)), and European Society for Medical Oncology (ESMO, [www.esmo.org](http://www.esmo.org)) website searches. Keywords used for searching were: advanced pancreatic cancer, first-line, phase III, randomized. In addition to computer browsing, review and original papers were also scanned in the reference section to look for missing trials.

### Trial identification criteria and data extraction

All phase III RCTs published in peer-reviewed journals up to June 30th, 2017 in which previously untreated patients affected by advanced pancreatic cancer were prospectively randomized to receive at least two front-line combination chemotherapy regimens were considered. Data regarding first-line therapies in advanced pancreatic cancer was extracted; the last available update of each trial was considered as the original source. All data were reviewed by 2 investigators (J.G., A.B.) and separately computed by 2 investigators (J.G., A.B.).

### Results

Our study evaluated 11 phase III RCTs, including 4572 patients. The primary objective of the evaluated studies was OS in all 11 RCTs. The main reported outcomes (OS and PFS) of the analyzed phase III RCTs are reported in Fig. 1 and Fig. 2. OS and PFS value obtained according to the regimen administered and to the specific trial are summarized in Table 1. OS and PFS range from 5.4 to 2.2 months of gemcitabine alone [9], respectively, to 11.1 and 6.4 months of FOLFIRINOX [6], respectively. The main difference in gain of OS was for FOLFIRINOX [6], with 4.3 months against gemcitabine alone (in this trial crossover was allowed). The best hazard ratio (HR) was for FOLFIRINOX [6], with 0.57 (95% C.I. 0.45–0.73).

The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) has reached a grade 2 of magnitude of clinical benefit for GEMOX [10], a grade 3 for the combination of gemcitabine plus nab-paclitaxel [7]

and a grade 4 for FOLFIRINOX [6]. All other phase III RCTs have reached a grade 1 of magnitude of clinical benefit (from the low grade 1 to the high grade 5).

Combining the difference in PFS for the different arms of the phase III RCTs with the highest ESMO-MCBS scores with the pharmacological costs necessary to get the benefit in PFS for each trial (Table 2), we have obtained 74.12 € per month of PFS gained for FOLFIRINOX [6], 90.14 per month of PFS gained for GEMOX [10] and 4708.70 € per month of PFS gained for the combination of gemcitabine plus nab-paclitaxel [7] against gemcitabine alone.

### Discussion

Since RCT of Burris et al. [4], gemcitabine was considered the reference drug for first-line treatment in advanced pancreatic cancer. The role of gemcitabine combination chemotherapies was confirmed by two meta-analysis. Sultana et al. [5], in a meta-analysis of 51 randomized controlled trials (including 9970 patients), have examined the different therapeutic approaches comparing chemotherapy versus (vs.) best supportive care, 5-fluorouracil (5FU) vs. 5FU combination chemotherapy, gemcitabine vs. FU and gemcitabine vs. gemcitabine combination chemotherapy. They found that chemotherapy improved survival compared with best supportive care (hazard ratio [HR] = 0.64), FU-based combination chemotherapy did not result in better OS compared with FU alone (HR = 0.94) and there was insufficient evidence of a survival difference between gemcitabine and FU; survival was improved after gemcitabine combination chemotherapy compared with gemcitabine alone (HR = 0.91), supporting the use of gemcitabine-based combination chemotherapy in the treatment of advanced pancreatic cancer. The same results were confirmed by Heinemann et al. [11] in their meta-analysis of 15 trials (including 4465 patients) with a significant survival benefit for gemcitabine plus X with a pooled HR = 0.91 ( $p = 0.004$ ). Recently, new combinations chemotherapies have been introduced in daily clinical practice, such as FOLFIRINOX [6] and the combination of nab-paclitaxel plus gemcitabine [7]. More recently, Goldstein et al. [12] have updated analysis of OS from MPACT [7] with an extended data cutoff (eight months longer) at the time the trial was closed. The median OS was 8.7 months in the nab-paclitaxel plus gemcitabine vs. 6.6 months in the gemcitabine group (HR = 0.72;  $p < 0.001$ ), with long-term (>three-year) survivors in the nab-paclitaxel plus gemcitabine arm only (4%). In particular, nab-paclitaxel plus gemcitabine was favored in poor-prognosis cancer patients over gemcitabine alone (HR = 0.612,  $p < 0.001$  for CA19-9 level  $\geq$  median and HR = 0.81,  $p = 0.079$  for neutrophil-to-lymphocyte ratio  $> 5$ ).

But these data are not unique in definitely consider the combination chemotherapies used to date (eg. GEMOX) as outdated. In facts, we have to consider that only few patients are candidated to either FOLFIRINOX or nab-paclitaxel gemcitabine, due to restrictive eligibility requirements, such as ECOG PS, age, bilirubin level and cardiac function, as confirmed by Peixoto et al. [13].

In addition, it would be interesting to examine the magnitude of the clinical benefit from new therapeutic approaches derived from randomized phase III RCTs for advanced pancreatic cancer, using the ESMO-MCBS [8]. Concerning the “old-combination chemotherapies”, only GEMOX [10] has reached a grade 2 ESMO-MCBS. The new combination therapies, FOLFIRINOX [6] and gemcitabine plus nab-paclitaxel [7], have reached respectively a grade 4 and 3 ESMO-MCBS (Table 1). To this must be added that ESMO-MCBS has some criticism, such as the lack of consideration of toxicities in the definition of the grade of magnitude of clinical benefit. Considering more critically the efficacy data, OS were similar between GEMOX [10] and gemcitabine plus nab-paclitaxel, respectively with 8.8

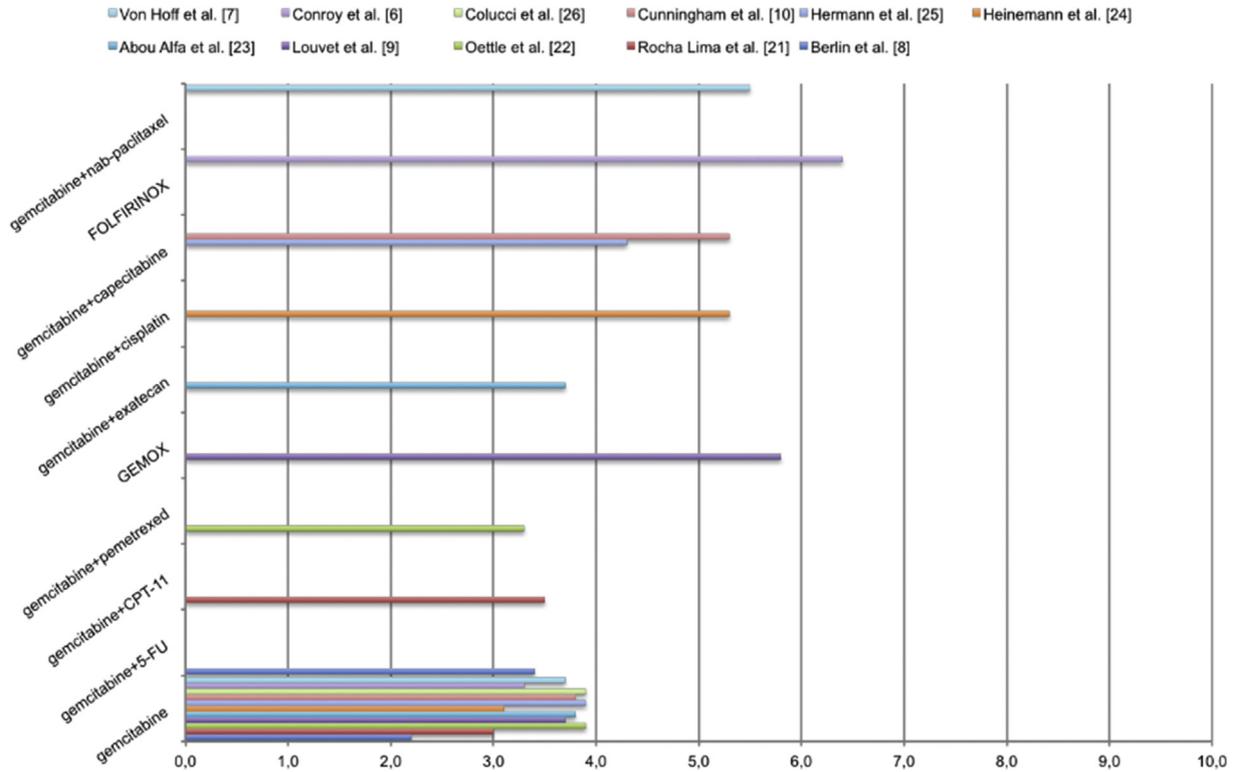


Fig. 1. PFS (months) in phase III RCTs concerning combination chemotherapies in first-line for advanced pancreatic cancer.

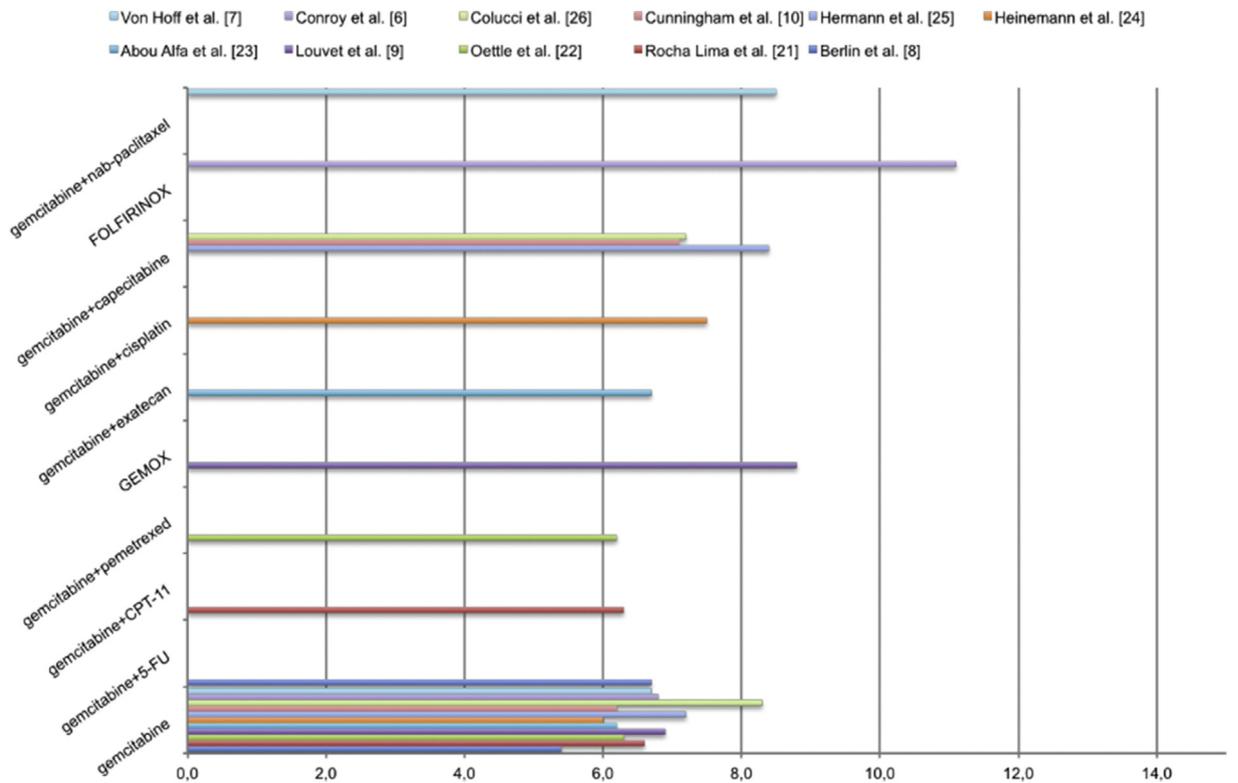


Fig. 2. OS (months) in phase III RCTs concerning combination chemotherapies in first-line for advanced pancreatic cancer.

**Table 1**  
Main outcomes of the considered phase III RCTs.

Authors	Comparative Regimens	N° of patients	Primary endpoint	OS (months)	p-value	OS gain (months)	OS HR (95% C.I.)	Gain (%) at 24 months	PFS (months)	p-value	ESMO-MCBS
Berlin et al. [8]	gemcitabine	162	OS	5.4	NS	1.3	NR	NR	2.2	<b>0.022</b>	<b>1</b>
	gemcitabine plus 5-FU	160		6.7					3.4		
Rocha Lima et al. [23]	gemcitabine	180	OS	6.6	NS	−0.3	NR	NR	3.0	NS	<b>1</b>
	gemcitabine plus CPT-11	180		6.3					3.5		
Oettle et al. [24]	gemcitabine gemcitabine plus pemetrexed	282 283	OS	6.3 6.2	NS	−0.1	0.98 (0.82–1.18)	NR	3.9 3.3	NS	<b>1</b>
Louvet et al. [10]	gemcitabine GEMOX	163 163	OS	6.9 8.8	NS	1.9	1.18 (0.94–1.51)	NR	3.7 5.8	<b>0.04</b>	<b>2</b>
Abou Alfa et al. [25]	gemcitabine	174	OS	6.2	NS	0.5	NR	NR	3.8	NS	<b>1</b>
	gemcitabine plus exatecan	175		6.7					3.7		
Heinemann et al. [26]	gemcitabine	97	OS	6.0	NS	1.5	0.80 (NR)	NR	3.1	NS	<b>1</b>
	gemcitabine plus cisplatin	98		7.5					5.3		
Hermann et al. [27]	gemcitabine	159	OS	7.2	NS	1.2	NR	NR	3.9	NS	<b>1</b>
	gemcitabine plus capecitabine	160		8.4					4.3		
Cunningham et al. [28]	gemcitabine	266	OS	6.2	NS	1.1	0.86 (0.72–1.02)	NR	3.8	<b>0.026</b>	<b>1</b>
	gemcitabine plus capecitabine	267		7.1					5.3		
Colucci et al. [29]	gemcitabine	199	OS	8.3	NS	−1.1	1.10 (0.89–1.19)	NR	3.9	NS	<b>1</b>
	gemcitabine plus cisplatin	201		7.2					3.8		
Conroy et al. [6]	gemcitabine	171	OS (crossover allowed)	6.8	<b>&lt;0.001</b>	4.3	0.57 (0.45–0.73)	NR	3.3	<b>&lt;0.001</b>	<b>4</b>
	FOLFIRINOX	171		11.1					6.4		
Von Hoff et al. [7]	gemcitabine	430	OS	6.7	<b>&lt;0.001</b>	1.8	0.72 (0.61–0.83)	5%	3.7	<b>&lt;0.001</b>	<b>3</b>
	gemcitabine plus nab-paclitaxel	431		8.5					5.5		

**Legend:** N = number; OS = overall survival; PFS = progression free survival; HR = hazard ratio; 95% C.I. = 95% Confidence Interval; ESMO-MCBS = European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (from grade 1 to grade 5); NS = not significant; NR = not reported; 5-FU = 5-fluorouracil; CPT-11 = irinotecan; GEMOX = gemcitabine and oxaliplatin; FOLFIRINOX = oxaliplatin, irinotecan, leucovorin and 5-FU.

**Table 2**  
Pharmacological costs and difference in PFS with the different treatment regimens of the considered phase III RCTs in first-line for advanced pancreatic cancer with the highest ESMO-MCBS scores.

Authors	Comparative Regimens	N° of patients	PFS (months)	p-value	Costs of therapy (€)	Difference in PFS (months)	Difference in costs (€)	Difference in costs per month-PFS gained (€)
Louvet et al. [10]	gemcitabine	163	3.7	<b>0.04</b>	403.38	2.1	189.30	90.14
	GEMOX	163	5.8		214.08			
Conroy et al. [6]	gemcitabine	171	3.3	<b>&lt;0.001</b>	268.92	3.1	230.18	74.12
	FOLFIRINOX	171	6.4		498.70			
Von Hoff et al. [7]	gemcitabine	430	3.7	<b>&lt;0.001</b>	134.46	1.8	8475.66	4708.70
	gemcitabine plus nab-paclitaxel	431	5.5		8610.12			

**Legend:** N = number; PFS = progression free survival; GEMOX = gemcitabine and oxaliplatin; FOLFIRINOX = oxaliplatin, irinotecan, leucovorin and 5-FU.

months and 8.5 months and with a OS gain towards gemcitabine alone respectively of 1.9 months and 1.8 months; also PFS was similar between the 2 combinations, with 5.8 months for GEMOX and 5.5 months for gemcitabine plus nab-paclitaxel. The higher grade of ESMO-MCBS for the combination of gemcitabine and nab-paclitaxel was related to percentage of long survivors at 24 months (gain of 5%). The best results in terms of OS and the highest grade magnitude of clinical benefit were reached by FOLFIRINOX [6], with 11.1 month and a gain in OS of 4.3 months against gemcitabine. Concerning toxicity, both GEMOX that FOLFIRINOX that gemcitabine plus nab-paclitaxel have demonstrated a statistically significant grade 3–4 toxicities impacting daily well-being against gemcitabine single-agent, such as vomiting (8.9% vs. 3.2%) and peripheral sensory neuropathy (19.1% vs. 0.0%) for GEMOX [10], peripheral sensory neuropathy (17% vs. 1%), fatigue (17% vs. 7%) and diarrhea (6% vs. 1%) for gemcitabine and nab-paclitaxel [7], peripheral

sensory neuropathy (9.0% vs. 0.0%) and diarrhea (12.5% vs. 1.8%) for FOLFIRINOX [6].

All this we must add the topic of pharmacological costs. In facts, in light of the relevant expenses of pharmacological interventions it might be interesting to make a balance between the cost of the new drugs administered and the difference in PFS for the different arms of the trials with the highest ESMO-MCBS scores concerning combination chemotherapies in first-line for advanced pancreatic cancer [6,7,10]. PFS values obtained according to the chemotherapeutic regimen administered and to the specific trial are summarized in Table 2. Combining the costs of therapy with the measure of efficacy represented by the PFS, we get the costs for obtaining the advantage in PFS, for each arm of the analyzed trials. The best results in terms of pharmacological costs per month-PFS gained were obtained by FOLFIRINOX with 74.12 € per month of PFS gained, followed by GEMOX with 90.14 per month of PFS gained and the

combination of gemcitabine plus nab-paclitaxel with 4708.70 € per month of PFS gained. Obviously, this evaluation based on pharmacological cost has several limitations. First, PFS is influenced by a number of factors, which are difficult to standardize. Moreover, we have considered only the direct costs, but there are other important cost elements that are not considered here (e.g. outpatient/inpatient administration costs or treatment-related adverse event costs or health-related quality of life between different first-line treatments). To this must be added the fact that there is no information concerning the extension of the estimated costs to the OS benefit (which it is however limited in the pancreatic cancer). Conversely, the use of PFS allows us to have a quick measure of effectiveness on which to calculate the costs of different therapies in first-line for advanced pancreatic cancer, also in daily clinical practice. In addition, the analysis presented here is not a real cost-effectiveness analysis (that would imply not only direct medical costs, but also indirect medical costs), but an analysis of pharmacological costs of the most effective combination chemotherapies used first-line regimens for the treatment of advanced pancreatic cancer.

Poor results have been shown by randomized phase III RCTs on targeted biological agents, such as marimastat [14], tipifarnib [15], bevazumab [16], cetuximab [17] and axitinib [18] and erlotinib [19].

The relevant expenses of pharmacological interventions have stressed the importance to make a balance between pharmacological costs and the added value represented by the improvement of the clinical parameters of interest such as PFS. The pharmacological costs are transferred to the Italian reality and, more generally, to Europe (free movement of patients and goods). The idea is to emphasize not only the cost topic, but also the method, which is to combine the pharmacological costs of drugs with the measure of efficacy represented by the PFS and the clinical benefit expressed by the ESMO-MCBS, in order to achieve a given objective as possible. The ESMO-MCBS, due to its easy use in daily clinical practice, can help to better determine this choice with the definition of the magnitude of the clinical benefit from each treatment, also from a health economics perspective. This method incorporates a structured, rational and valid approach to data interpretation and analysis that can help clinicians to weigh the relative merits of competing relevant therapeutic options in situations in which there is no direct comparative data comparing the available therapeutic options. So, the ESMO-MCBS scale has a public health perspective: ranking the clinical benefit of oncologic drugs to identify those agents that should be available in every EU country (this scale is being adopted for reimbursement purposes in several European regions) [20]. Finally, it remains the difficult and heavy topic of costs [21,22] and it also remains to understand how justified are both an increase in costs that an increase in toxicities compared to a minimum of survival gain for a disease with a so poor prognosis (median OS less than 12 months) and this could be of social importance, considering that median age of patients in pivotal phase III RCTs of FOLFIRINOX [6] and nab-paclitaxel [7] are not to be considered of elderly patients (61 and 62 years old, respectively).

In recent years new combination chemotherapies, such as FOLFIRINOX and gemcitabine plus nab-paclitaxel, have been added in first-line for advanced pancreatic cancer, based on results of phase III RCTs. The best results both in terms of OS that PFS are undoubtedly those obtained from FOLFIRINOX [6], but with more heavy results in terms of toxicity. Similar results both in terms of OS that PFS were obtained by GEMOX [10] and gemcitabine plus nab-paclitaxel [7], with different toxicities impacting daily well-being (similar peripheral sensory neuropathy, but a high incidence of vomiting for GEMOX and fatigue and diarrhea for gemcitabine plus nab-paclitaxel). In conclusion, combining pharmacological costs

with the measure of efficacy represented by PFS, FOLFIRINOX is a cost-effective first-line for advanced pancreatic cancer. The price of newly registered oncologic drugs is continuously increasing posing a serious threat to the sustainability of the National Health Systems, especially in Countries in which the public control and oversight over the prices is limited. Medical Oncologists and the society as a whole are becoming more and more concerned with the issues of the costs of the cure of cancer patients and are able to bring attention to the “just price” of new treatments that must reflect the reality of their true benefits and societal and personal costs.

### Conflicts of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

### Research involving human participants and/or animals

No human participants and/or animals were involved.

### Informed consent

Not needed (no human participants were involved).

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