Dilemma of first line regimens in metastatic pancreatic adenocarcinoma

Marwan Ghosn, Tony Ibrahim, Tarek Assi, Elie El Rassy, Hampig Raphael Kourie, Joseph Kattan

Abstract
Pancreatic cancer is one of the deadliest cancers, ranking fourth among cancer-related deaths. Despite all the major molecular advances and treatment breakthroughs, mainly targeted therapies, the cornerstone treatment of metastatic pancreatic cancer (mPC) remains cytotoxic chemotherapy. In 2016, more than 40 years after the introduction of gemcitabine in the management of mPC, the best choice for first-line treatment has not yet been fully elucidated. Two main strategies have been adopted to enhance treatment efficacy. The first strategy is based on combining non-cross resistant drugs, while the second option includes the development of newer generations of chemotherapy. More recently, two new regimens, FOLFIRINOX and gemcitabine/nab-paclitaxel (GNP), have both been shown to improve overall survival in comparison with gemcitabine alone, at the cost of increased toxicity. Therefore, the best choice for first-line therapy is a matter of debate. For some authors, FOLFIRINOX should be the first choice in patients with an Eastern Cooperative Oncology Group score (0-1) given its lower hazard ratio. However, others do not share this opinion. In this paper, we review the main comparison points between FOLFIRINOX and GNP. We analyze the two pivotal trials to determine the similarities and differences in study design. In addition, we compare the toxicity profile of the two regimens as well as the impact on quality of life. Finally, we present studies revealing real life experiences and review the advantages and disadvantages of possible second-line therapies including their cost effectiveness.

Key words: Review; Metastatic pancreatic cancer; FOLFIRINOX; Gemcitabine/nab-paclitaxel; Pivotal trials

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analyzes the effects these regimens have on toxicity profile, quality of life, real life experiences, choice of second-line therapy and cost.

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**INTRODUCTION**

Adenocarcinoma of the pancreas is one of the most aggressive human cancers, ranking fourth among cancer related deaths[1]. Recent biomolecular progress has led to a better comprehension of pancreatic carcinogenesis; however, the revolutionary targeted and immune therapies have not shown any significant results[2]. Subsequently, cytotoxic drugs remain the backbone of treatment for metastatic pancreatic cancer (mPC). Gemcitabine has been the standard of care in mPC since 1996, providing a limited survival of six months due to the intrinsic capacity of cancer cells and the surrounding microenvironment to resist cytotoxicity[3-5]. More aggressive regimens were developed to overcome these resistance mechanisms. The combination of non-cross resistant agents, GTX (gemcitabine, docetaxel and capecitabine) and PEFG (cisplatin, epirubicin, fluorouracil and gemcitabine), enhanced tumor shrinkage by acting on different stages of cell cycle and bypassing mechanisms of drug resistance[6-8].

In 2011, French investigators from the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup published the results of a phase II/III trial that revealed a clinically significant survival benefit and better quality of life for a regimen combining 5-FU/leucovorin, oxaliplatin and irinotecan (FOLFIRINOX) at the expense of increased toxicity[9]. Another option is nab-paclitaxel, which is a second generation chemotherapy agent that exploits the ability of albumin to deliver the hydrophobic molecule, paclitaxel, to targeted tissues. Nab-paclitaxel was combined with gemcitabine in the multinational MPACT phase III trial and added an OS benefit of 2.6 mo compared to single agent Gemcitabine[10,11]. Table 1 summarizes the efficacy of the FOLFIRINOX and gemcitabine/nab-paclitaxel (GNP) as published in the pivotal studies of ACCORD/PRODIGE and MPACT trials, respectively.

The best choice for first-line therapy is a matter of debate. The National Comprehensive Cancer Network (NCCN) panel considers FOLFIRINOX as the first choice for Eastern Cooperative Oncology Group (ECOG) 0-1 patients given its lower HR for death, whereas nab-paclitaxel should be reserved for ECOG 2 patients (NCCN 2016). Conversely, ASCO and ESMO consider both regimens as acceptable treatment options for ECOG 0-1 patients[12,13]. Indirect comparisons using the ESMO magnitude of clinical benefit scale show a higher score for the FOLFIRINOX regimen when compared to GNP (5/5 vs 2/5, with a higher score indicating a better regimen in terms of survival benefit and quality of life)[14]. In addition, a Bayesian meta-analysis comparing multiple systemic protocols in advanced pancreatic cancer showed a trend toward better survival with FOLFIRINOX compared to GNP[15]. In view of this debate, we conducted this review to discuss the main comparison points between FOLFIRINOX and GNP, including the design of the two pivotal trials, toxicity profiles, quality of life, real life experiences, choice of second-line therapy and cost effectiveness.

**TRIAL DESIGN: PRODIGE VS MPACT**

The PRODIGE and MPACT trials were both randomized controlled trials (RCTs) based on an intent to treat principle and included 342 and 861 patients with mPC, respectively. Both trials had nearly the same tumor characteristics[9,10]. Additionally, the median age (61 years for both trials) and sex ratio (1.6 for PRODIGE and 1.3 for MPACT) were nearly identical. However, the French trial included only patients less than 76 years old with good performance status based on the ECOG evaluation system (ECOG 0-1). In contrast, the MPACT trial did not specify an age limit (age ranged from 27 to 86 years) and included patients with intermediate performance status based on the KPS system (KPS < 90 in nearly 42% of patients). In addition, the PRODIGE trial only included patients from French centers while the MPACT trial was a multinational study including patients from North America (63%), Australia (14%), and Eastern (15%) and Western Europe (9%). In addition, patients in the Gemcitabine arm of the PRODIGE trial received only 6 mo of therapy even if they were not progressing (17%), nearly half of whom did not continue. While some authors do not consider these differences important given that the survival curves of the gemcitabine arm in the two trials are “superimposable”, others do not share this opinion. In fact, Gemcitabine is a well-known drug that is tolerated in the elderly population, even in intermediate health systems such as that of Eastern Europe. The same is not true when a new drug such as nab-paclitaxel is added to gemcitabine. In fact, the forest plot in the MPACT study clearly shows an effect of age and country on hazard ratio. In the same sense, Tehfe et al[17] published an analysis of patients from Canada (a subgroup of the MPACT trial) and showed an OS equal to 11.9 mo in the GNP arm compared to 7.1 mo in the gemcitabine arm with a hazard ratio of 0.76. However, this subgroup analysis included only 63 patients and was underpowered to detect a statistically significant result.
TOXICITY AND QUALITY OF LIFE

The toxicity profile of a chemotherapy regimen is a major contributor in its adoption. Based on the two trials, hematologic toxicity is in favor of the FOLFIRINOX regimen and includes a lower incidence of neutropenia (45% vs 38%) (although the use of G-CSF was more common), anemia (7.8% vs 13%), and thrombocytopenia (9.1% vs 13%). The remaining toxicities are listed in Table 1. Peripheral neuropathy attributed to Nab-paclitaxel is a particular debilitating toxicity; grade 3 peripheral neuropathy was encountered in 17% of the patients but improved to grade 1 toxicity or less in a median of 29 d. Real-life studies with a closer follow-up of patients showed fewer side effects compared to those reported in the clinical trials. Chemotherapy-induced hair loss is often a major determinant of the treatment regimen selected and was more commonly encountered in the GNP regimen (50% vs 11.2%) (although FOLFIRINOX did not relieve diarrhea), in the first two months of treatment. It also showed significantly increased time to physical or cognitive deterioration.

On the other hand, quality of life was not assessed in the MPACT trial. In contrast, GNP showed significant improvement in quality-adjusted survival in comparison to gemcitabine alone using the Quality-Adjusted Time Without Symptoms or Toxicities (Q-TWiST) methodology, despite the limitations of the Q-TWiST analysis and the lack of prospective quality of life data from the MPACT trial.

Because significant toxicity was not uncommon, more tolerable treatment regimens were created by modifying the administration or drug dosing schedule. In the modified FOLFIRINOX regimens, either the 5-fluorouracil bolus was omitted or the dose of irinotecan was reduced. Stein et al published solid data in a prospective study, enrolling both locally advanced and mPC patients who received a modified FOLFIRINOX regimen including a 25% dose reduction in 5-FU or irinotecan. These modifications successfully maintained the efficacy of the drugs while significantly decreasing the toxicity profile (decreased neutropenia, vomiting and fatigue). Additional exploratory analyses of the MPACT trial showed that patients who had dose delays or reductions (71% and 41%, respectively) had better outcomes. These practical changes are capable of modifying the tolerance profile of the drugs while preserving efficacy. Tables 2 and 3 compare the

Table 1 Comparison of the pivotal studies approving FOLFIRINOX and gemcitabine/nab-paclitaxel in metastatic pancreatic cancer

| Study characteristics | ACCORD/PRODIGE trial (FOLFIRINOX) | MPACT trial (GNP) |
|-----------------------|----------------------------------|------------------|
| Duration              | December 2005-October 2009       | May 2009-April 2012 |
| Location              | France                           | Multinational    |
| Number of patients    | 342                              | 861              |
| Study design          | Phase 2-3                        | Phase 3          |
| Control arm           | Gemcitabine                      | Gemcitabine      |
| Patient and tumor characteristics | | |
| Median age            | 61 years                         | 62 years         |
| Sex distribution      | Male (62%)                       | Male (57%)       |
| ECOG                  | PS 0 (37.4%)                     | PS 100 (74%)     |
|                       | PS 1 (61.3%)                     | PS 80-90 (77%)   |
|                       | PS 2 (0.6%)                      | PS 60-70 (7%)    |
| Tumor stage           | Metastatic                       | Metastatic       |
| Metastatic sites      | Liver (87.6%)                    | Liver (85%)      |
|                       | Lung (19.4%)                     | Lung (35%)       |
|                       | Peritoneum (19.4%)               | Peritoneum (4%)  |
|                       | Head (39.2%)                     | Head (44%)       |
| Response              | ORR (%)                          | 31.6             |
|                       | PR (%)                           | 31               |
|                       | SD (%)                           | 38.6             |
|                       | DCR (%)                          | 70.2             |
|                       | PFS (mo)                         | 6.4              |
|                       | OS (mo)                          | 11.1             |
|                       | 1-yr OS (%)                      | 48.4             |
| Safety (Grade 3-4 toxicities) | | |
| Neutropenia           | 45.7                             | 38               |
| Febrile neutropenia   | 5.4                              | 3                |
| Thrombocytopenia      | 9.1                              | 13               |
| Anemia                | 7.8                              | 13               |
| Fatigue               | 23.6                             | 17               |
| Peripheral neuropathy | 9                                | 17               |
| Diarrhea              | 12.7                             | 6                |
| Toxic death           | 9.6                              | 4                |
| Alopecia              | 11.2                             | 50               |
| G-CSF use             | 42.5                             | 26               |

DCR: Disease control rate; GNP: Gemcitabine/nab-paclitaxel; PR: Partial response; ORR: Overall response rate; OS: Overall survival; SD: Stable disease.
classical to the modified form of FOLFIRINOX and GNP respectively\(^{20-23}\).

### CHOICE OF SECOND-LINE

The optimal treatment sequence dictates the choice of first-line treatment for mPC. In fact, in the PRODIGE trial, only 47% of the patients were fit enough to receive second-line therapy while only 12.5% of patients received a second-line therapy after initially receiving a gemcitabine-based combination, yet the median OS was limited to 4.4 mo among those receiving second-line treatments. On the other hand, in the MPACT trial, 40% of the patients received additional therapy after GNP\(^{24}\). According to these data, similar numbers of patients were able to receive second-line therapy after either FOLFIRINOX or GNP.

Data on the administration of GNP after FOLFIRINOX failure in the literature is limited to a few retrospective studies with conflicting data. The AGEO trial, a prospective multicenter study, evaluated the use of GNP in the second-line setting after FOLFIRINOX failure. The disease control rate was 58% with a 17.5% overall response rate and OS of 8.8 mo. Twelve patients (21%) had an ECOG of 2, and 40% had grade 3-4 toxicities without any treatment-related deaths\(^{25}\).

In another retrospective study by Zhang et al\(^{26}\), 28 patients treated with the same regimen showed less satisfactory results, with an OS of 23 wk.

Small retrospective studies assessed the efficacy of FOLFIRINOX in the second line setting with a modest improvement in OS, but none evaluated its efficacy after GNP\(^{27,28}\). In fact, the only data available is from the exploratory analyses of the second line treatment of the MPACT trial, where FOLFIRINOX (despite demonstrating interesting data) was only administered to 18 patients (10.5% of the whole population), calling the use of this treatment sequence into question\(^{16}\).

Consequently, definitive recommendations concerning the optimal sequence of therapy cannot be made. The prospective data from the AGEO trial makes GNP a better and more plausible option as a second-line option after FOLFIRINOX administration. However, large RCTs are needed to create newer guidelines.

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### Table 2  Comparison of the FOLFIRINOX and modified FOLFIRINOX trials

| Location | Number of patients | Dosing | Tumor location | Response | Safety (grade 3-4 toxicities) | Additional information |
|----------|-------------------|--------|----------------|----------|-----------------------------|-----------------------|
| France   | 342               | Phase 2-3 Prospective | Head (39.2%) | ORR (%) 31.6 | Neutropenia 45.7 | Pegfilgastrim on each cycle |
| United States | 44               | Phase 2 Prospective | Head (54.8%) | ORR (%) 35.1 | Neutropenia 12.2 | Pegfilgastrim on each cycle |
| United States | 36               | No 5-FU bolus and 25% reduction in irinotecan doses | NA | PR (%) 31 | Febrile N. 3 | Pegfilgastrim on each cycle |
| United Kingdom | 18            | No 5-FU bolus and 25% reduction in irinotecan doses | Head (566%) | SD (%) 38.6 | Thrombocytopenia 9.1 | Pegfilgastrim on each cycle |

DCR: Disease control rate; PR: Partial response; ORR: Overall response rate; OS: Overall survival; SD: Stable disease.

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\(^{(9)}\) ACCORD/PRODIGE trial (FOLFIRINOX)\(^{(9)}\)  \(^{(10)}\) Stein et al\(^{20}\) Modified FOLFIRINOX  \(^{(11)}\) Mahaseth et al\(^{21}\) (Modified FOLFIRINOX)  \(^{(12)}\) Ghorni et al\(^{22}\) (Modified FOLFIRINOX)
COST-EFFECTIVENESS
In addition to weighing efficacy and safety, oncologists must evaluate financial considerations to choose the optimal chemotherapy regimen. In fact, the NCCN shows a tendency toward incorporating the financial burden of cancer drugs into its decision-making strategy. Cost-effectiveness of each regimen is largely dependent on the societal willingness-to-pay (WTP) threshold set by each country. For instance, setting the WTP in Canada at $130000 makes the FOLFIRINOX regimen the optimal strategy in mPC. However, decreasing the limit to $80000 renders Gemcitabine monotherapy the only possible therapeutic choice[29]. Similarly, the increased WTP threshold in Greece rendered the GNP protocol a potential option in the treatment of patients with mPC[30].

Both FOLFIRINOX and GNP showed consistent cost-effectiveness and cost-utility with superior survival efficacy in independent analytical studies[31,32]. However, it is not until recently that the values of each regimen were compared. The value of the different regimens in mPC was compared based on Medicare rates, which take into consideration the cost and administration of the drug, hospitalization and management of associated adverse events. The monthly costs of FOLFIRINOX and GNP were $7234 and $12221 respectively. However, the cost of the overall treatment based on progression free survival in each protocol was estimated at $46289 and $67216. FOLFIRINOX seemingly exhibits higher cost-effectiveness than GNP according to these results. However, it is worth mentioning that the cost of the FOLFIRINOX regimen is mainly due to its toxicity profile. Dosing modifications could limit the incidence of serious side effects and thus further increase the cost-effectiveness of this protocol (Monthly cost of FOLFIRINOX is $763 versus $9008 for the GNP protocol).

Consequently, in September 2015, the National Institute for Health and Care Excellence recommended against the use of GNP in patients with mPC due to the limited benefits in comparison to the cost of the drug. An alternative cheaper option that might be considered is modified GNP (which is yet to be validated), which has an overall treatment cost of $36226[33].

CONCLUSION
Overall, both FOLFIRINOX and GNP result in better overall survival and quality of life. In the absence of direct comparison, the treatment choice for patients with mPC is determined by physical toxicity and financial cost, both of which favor the FOLFIRINOX regimen. Further studies should aim to evaluate the modified schedules and dosing of both regimens in multinational RCTs and search for biomarkers that predict response to treatment[34]. In addition, the choice of first-line therapy in the future may not be limited to these two regimens, as newly developed drugs/therapeutic strategies should be tested in clinical trials to find more efficacious options for patients with good performance status.

REFERENCES
1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30 [PMID: 26742998 DOI: 10.3322/ caac.21332]
2 Kourie HR, Gharios J, Elkarak F, Antoun J, Ghosn M. Is metastatic pancreatic cancer an untargetable malignancy? World J Gastrointest Oncol 2016; 8: 297-304 [PMID: 26989465 DOI: 10.4251/wjgo.v8.i3.297]
3 Burriss HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in...
survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15: 2403-2413 [PMID: 9196156]

Rhim AD, Oberstein PE, Thomas DH, Mirek ET, Palermo CM, Sastri SA, Dekleva EN, Saunders T, Beerepoot CP, Tattersall IW, Westphalen CB, Kitaewski J, Fernandez-Barrena MG, Fernandez-Zapico ME, Iacobuzio-Donahue C, Olive KP, Stanger BZ. Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. Cancer Cell 2014; 25: 735-747 [PMID: 24856585 DOI: 10.1016/j.cccr.2014.04.021]

Fox RG, Lytle NK, Jaggush DV, Park FD, Ito T, Bajaj J, Koechlein CS, Zimdahl B, Yano M, Kopp JL, Kritzik M, Sicklick JK, Sander M, Grandgenett PM, Hollingsworth MA, Shibata S, Pizzo D, Valsek MA, Sasik R, Scadeng M, Okano Y, Kim Y, MacLeod AR, Lowy AM, Reya T. Image-based detection and targeting of therapy resistance in pancreatic adenocarcinoma. Nature 2016; 534: 407-411 [PMID: 27281208 DOI: 10.1038/nature17988]

De Jesus-Acosta A, Oliver GR, Blackford A, Kinsman K, Flores EL, Wilfong LS, Zheng L, Donehower RC, Cosgrove D, Laheru DL, De LT, Chung K, Diaz LA. A multicenter analysis of GTX chemotherapy in patients with locally advanced and metastatic pancreatic adenocarcinoma. Cancer Chemother Pharmacol 2012; 69: 415-424 [PMID: 21800112 DOI: 10.1007/s00280-011-1704-y]

Fine RL, Fogelman DR, Schreiber SM, Desai M, Sherman W, Strauss J, Guba S, Andrade R, Chabot J. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. Cancer Chemother Pharmacol 2008; 61: 167-175 [PMID: 17440727 DOI: 10.1007/s00280-007-0473-0]

Reni M, Wan Y, Solom C, Whiting S, Ji X, Botteman M. Quality-adjusted survival with combination nab-paclitaxel + gemcitabine vs gemcitabine alone in metastatic pancreatic cancer: a Q-TWIST analysis. J Med Econ 2014; 17: 338-346 [PMID: 24654922 DOI: 10.3111/13696998.2014.903122]

Corroy T, Dessegue F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoil J-L, Gourgou-Bourgade S, de la Fouchardiére C, Bennouna J, Bichet JB, Khermissa-Akouz F, Peré-Verdug D, Delbalbo C, Assenat E, Chauffu B, Michel P, Montoto-Grillot C, Ducrues M. FOLFIRINOX versus gemcitabine in patients with metastatic adenocarcinoma of the pancreas. N Engl J Med 2011; 364: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1119232]

Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Zhang H, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar VN, Maitra A, Hidalgo M. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase III trial. J Clin Oncol 2011; 29: 4548-4554 [PMID: 21969517 DOI: 10.1200/JCO.2011.37.5646]

Tefhe M, Dowden S, Kenecke H, El-Maraghi R, Lespereur B, Couture F, Letourneau R, Liu H, Romano M. nab-Paclitaxel Plus Gemcitabine Versus Gemcitabine in Patients with Metastatic Pancreatic Adenocarcinoma: Canadian Subgroup Analysis of the Phase III MPACT Trial. J Clin Oncol 2013; 31: 23-29 [PMID: 23213101 DOI: 10.1200/JCO.2012.44.4869]

Stein SM, James ES, Deng Y, Cong X, Kortmansky JS, Li J, Staaguard C, Indukula D, Boustani AM, Patel V, Cha CH, Salem RR, Chang B, Hochster HS, Lacy J. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer 2016; 114: 737-743 [PMID: 27022826 DOI: 10.1038/bjc.2016.45]

Mahaseth H, Butcher E, Kaul J, Hawk N, Kim S, Chen Z, Kooby DA, Mathiel SK, Landry J, El-Rayes BF. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas 2013; 42: 1311-1315 [PMID: 24152956 DOI: 10.1097/MPA.0b013e3182620f06]

Ghorani E, Wong HH, Hewitt C, Calder J, Corrie P, Basu B. Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience. Oncology 2015; 89: 291-297 [PMID: 26579208 DOI: 10.1159/000437917]

Krishna K, Blazer MA, Wei L, Ahn DH, Wu CS, Ciombrk KK, Mikhai S, Noonan AM, Goldberg RM, Bekaii-Saab TS. Modified gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer (MPC): A single-institution experience. J Clin Oncol 2015; 33: 366

Chiorean EG, Von Hoff DD, Tabernero J, El-Maraghi R, Ma WW, Reni M, Harris M, Whorf R, Liu H, Li JS, Manax V, Romano A, Liu B, Goldstein D. Second-line therapy after nab-paclitaxel plus gemcitabine or after gemcitabine for patients with metastatic pancreatic cancer. Br J Cancer 2016; 115: 188-194 [PMID: 27351217 DOI: 10.1038/bjc.2016.185]

Portal A, Pernot S, Tougeron D, Arbad A, Bidault AT, de la Fouchardiére C, Hammel P, Lecomte T, Dréané J, Cornet R, Bachtet JB, Dubreuil O, Marthey L, Dahan L, Tchouondjou B, Locher C, Lepère C, Bonnetain F, Taieb J. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after nab-paclitaxel failure: an AGEO prospective multicentre cohort. Br J Cancer 2015; 113: 989-995 [PMID: 26372701 DOI: 10.1038/bjc.2015.328]

Zhang Y, Hochster H, Stein S, Lacy J. Gemcitabine plus nab-paclitaxel for advanced pancreatic cancer after first-line FOLFIRINOX: a single institution retrospective review of efficacy and toxicity. Exp Hematol Oncol 2015; 4: 29 [PMID: 26451276 DOI: 10.1186/s40164-015-0025-y]

Assaf E, Verline-Carvalho M, Delbulco C, Grenier J, Sellam Z, et al
Pouessel D, Bouaita L, Baumgaertner I, Sobhani I, Tayar C, Paul M, Culiné S. 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with metastatic pancreatic adenocarcinoma. Oncology 2011; 80: 301-306 [PMID: 21778770 DOI: 10.1159/000329803]

Lee MG, Lee SH, Lee SJ, Lee YS, Hwang JH, Ryu JK, Kim YT, Kim DU, Woo SM. 5-Fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with advanced pancreatic cancer who have progressed on gemcitabine-based therapy. Chemotherapy 2013; 59: 273-279 [PMID: 24457620 DOI: 10.1159/000356158]

McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghriati K, Yasufuku K, Martel S, Lavelle F, Gingras M, Atkar-Khattra S, Berg CD, Evans K, Finley R, Yee J, English J, Nasute P, Goffin J, Puksa S, Stewart L, Tsai S, Johnston MR, Manos D, Nicholas G, Goss GD, English J, Nasute P, MacEachern P, Bhatia R, Tsao MS, Lam S. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med 2013; 369: 910-919 [PMID: 24004118 DOI: 10.1056/NEJMa1214726]

Fragoulakis V, Papakostas P, Pentheroudakis G, Dervenis C, Maniadakis N. Economic Evaluation of NAB-Paclitaxel Plus Gemcitabine Versus Gemcitabine Alone for the Management of Metastatic Pancreatic Cancer in Greece. Value Health 2014; 17: A632 [PMID: 27202246 DOI: 10.1016/j.jval.2014.08.2263]

Gharaibeh M, McBride A, Bootman JL, Abraham I. Economic evaluation for the UK of nab-paclitaxel plus gemcitabine in the treatment of metastatic pancreatic cancer. Br J Cancer 2015; 112: 1301-1305 [PMID: 25791875 DOI: 10.1038/bjc.2015.65]

Attard CL, Brown S, Alloul K, Moore MJ. Cost-effectiveness of folfoxirinox for first-line treatment of metastatic pancreatic cancer. Curr Oncol 2014; 21: e41-e51 [PMID: 24523620 DOI: 10.3747/co.21.1327]

Goldstein DA, Krishna K, Flowers CR, El-Rayes BF, Bekaii-Saab T, Noonan AM. Cost description of chemotherapy regimens for the treatment of metastatic pancreatic cancer. Med Oncol 2016; 33: 48 [PMID: 27067436 DOI: 10.1007/s12032-016-0762-8]

Jordeheim LP, Dumontet C. Do hENT1 and RRM1 predict the clinical benefit of gemcitabine in pancreatic cancer? Biomark Med 2013; 7: 663-671 [PMID: 23905902 DOI: 10.2217/bmm.13.48]

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