**Name of journal: *World Journal of Gastrointestinal Oncology***

**ESPS Manuscript NO: 25950**

**Manuscript Type: TOPIC HIGHLIGHT**

**2016 Pancreatic Cancer: Global view**

**Pancreatic cancer: New hopes after first line treatment**

Aroldi F *et al*. Second line therapy for pancreatic cancer

**Francesca Aroldi, Paola Bertocchi, Giordano Savelli, Edoardo Rosso, Alberto Zaniboni**

**Francesca Aroldi, Paola Bertocchi,** **Alberto Zaniboni,** Department of Medical Oncology, Poliambulanza Foundation, 25124 Brescia, Italy

**Giordano Savelli,** Department of Nuclear Medicine, Poliambulanza Foundation, 25124 Brescia, Italy

**Edoardo Rosso,** Department of General Surgery, Poliambulanza Foundation, 25124 Brescia, Italy

**Author contributions:** Aroldi F, Bertocchi P, Savelli G and Rosso E contributed equally to this work and wrote the paper, while Zaniboni A made critical revisions related to important intellectual content of the manuscript and approved the final version of the article.

**Conflict-of-interest statement:** The authors declare that they do not have any conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Correspondence to: Alberto Zaniboni, MD,** Department of Medical Oncology, Poliambulanza Foundation, via Bissolati 57, 25124 Brescia, Italy. anib@numerica.it

**Telephone**: +39-30-3515553

**Fax**: +39-30-3518270

**Received:** March 26, 2016

**Peer-review started:** March 27, 2016

**First decision:** May 17, 2016

**Revised:** June 7, 2016

**Accepted:** July 14, 2016

**Article in press:**

**Published online:**

**Abstract**

Pancreatic cancer is the fourth leading cause of cancer-related death worldwide. Extensive research has yielded advances in first-line treatment strategies, but there is no standardized second- line therapy. In this review, we examine the literature trying to establish a possible therapeutic algorithm.

**Key words:** Pancreatic cancer; Second line; Algorithm; Nab-paclitaxel; Nal-iri

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Pancreatic cancer is an emerging disease. In this review a possible therapeutic algorithm for second line treatment is hypothesized.

Aroldi F, Bertocchi P, Savelli G, Rosso E, Zaniboni A. Pancreatic cancer: New hopes after first line treatment. *World J Gastrointest Oncol* 2016; In press

**INTRODUCTION**

Pancreatic cancer (PDA) is an emerging disease and is the fourth leading cause of cancer death worldwide[1]. The prognosis is very poor; the 5-year survival rate is 5%, and the life expectancy of patients with metastatic PDA is approximately 2.8-5.7 mo[2]. These poor outcomes are likely due to resistance to chemotherapy and PDA biology. PDA often presents with micro-metastatic lesions at diagnosis, which are subsequently confirmed by radiological evidence. The mechanisms underlying PDA development and progression have not been fully elucidated, hindering the development of therapeutic strategies for disease management. National Comprehensive Cancer Network (NCCN) guidelines recommend 5-fluorouracil-oxaliplatin-irinotecan (FOLFIRINOX) or nab-paclitaxel plus gemcitabine as first-line therapy. Gemcitabine (alone or in combination) is recommended as second-line therapy, with capecitabine or fluoropyrimidine plus oxaliplatin as the final option[3]. In fact gemcitabine seems to be more effective than fluoropyrimidine[4]. Second-line therapy is not standardized and depends on patient performance status (PS) (which frequently worsens after first-line therapy), comorbidities, previous treatments, and residual toxicities. Notably, only 40% of patients can receive an additional line of therapy after the first treatment[5].

However, active treatment has been linked to improved outcomes in PDA compared to best supportive care (BSC)[6].

In this review, we focus on significant second-line studies and subsequently propose a therapeutic algorithm for PDA.

**SECOND-LINE THERAPY**

Although studies of efficient target therapies are promising, the backbone of second-line strategies for PDA involves a combination of chemotherapeutic agents. Currently, gemcitabine-based chemotherapy or fluoropyrimidine-based therapy, depending on previous drug regimens, remains the standard of care in the second-line setting.

***Target therapy***

PDA is a heterogeneous cancer and identifying plausible therapeutic targets is consequently difficult. The efficacies of a variety of drugs targeting different pathways have been evaluated, including targets in angiogenesis, farnesyl-transferases, cancer stem cells, hyaluronic acid, EGFR-MEK, m-TOR, and JAK-STAT pathways. Bevacizumab has been investigated in PDA therapy due to the favourable results achieved in other gastrointestinal cancers. Although the addition of bevacizumab to gemcitabine in first-line therapy failed to improve overall survival (OS), it has been evaluated in second-line settings. A small randomized trial comparing bevacizumab monotherapy to the combination of bevacizumab (10 mg-kg q14) plus docetaxel (35 mg-m2 day 1.8.15 q 28) reported a detrimental effect of combination therapy[7]. The only targeted therapy approved by the Food and Drug Administration for PDA treatment is erlotinib. This drug produced a small advantage in first-line treatment and also demonstrated activity (4.1 months in OS) in second-line treatment[8]. However, the combination of erlotinib with bevacizumab failed to improve patient outcomes[9].

The EGFR and VEGFR pathways play major roles in PDA carcinogenesis and have been investigated as potential targets for second-line treatment. Inhibition of MEK1/2 by selumetinib failed to improve OS in gemcitabine-refractory patients compared to capecitabine[10], most likely due to activation of the EGFR pathway. On the contrary, a phase II trial with a small sample size, demonstrated that the combination of erlotinib and selumetinib achieved better outcomes (7.3 mo OS)[11]. The EGFR inhibitor gefitinib failed to produce satisfactory results when used in combination with docetaxel using different schedules[12-13]. The JAK-STAT inhibitor ruxolitinib achieved promising outcomes in preclinical and phase II trials[14], but the subsequent phase III trial was terminated prematurely due to inefficacy. Instead encouraging results (median OS 9.8 mo) were reported with the use of olaparib, a poly (ADP-ribose) polymerase inhibitor, in BRCA1 and BRCA2 (BRCA1/2) mutated patients prior exposed to at least one line of therapy[15]. Reni *et al*[16] investigated the maintenance with sunitinib in advanced pancreatic cancer not progressed after six months of first line therapy, reporting an interesting result: an high 2 years OS, 22.9% *vs* 7.1 % with sunitinib and placebo respectively.

***Immunotherapy***

Recent studies have focused on the new and attractive field of immunotherapy, which has achieved excellent results in the treatment of other malignancies. A variety of strategies had been tested in the following therapeutic settings: vaccines, immune checkpoint blockade, anti-cytotoxic T-lymphocytes-associate protein 4 inhibitors, anti- PD-1 and anti- PDL1 inhibitors, and oncolytic virotherapy[17]. Good outcomes have not been obtained, most likely due to the immune suppressive nature of the PDA microenvironment, which is characterized by desmoplastic reactions. Predictive biomarkers are not available but are actively being sought[18].

***Chemotherapy***

Extensive data on potential treatments for gemcitabine-refractory patients are available because gemcitabine was previously the most frequently used agent for PDA. The roles of oxaliplatin and irinotecan in PDA have been evaluated due to the effectiveness of these drugs for other gastrointestinal cancers. Based on the promising results of a phase II trial[16], three phase III randomized studies have investigated the efficacy of oxaliplatin-based regimens in gemcitabine-refractory patients. The CONKO-01 trial compared the efficacy of oxaliplatin, folinic acid (LLV), and 5-fluorouracil (5-FU) 24 h (OFF) with BSC. Although the patient cohort was small due to premature accrual closure, the study represents the first second-line trial demonstrating an advantage of chemotherapy over BSC (median OS 4.8 vs. 2.3 months). Patient randomization was terminated early because of the hesitation of the clinicians to administer BSC when a potentially active therapy was available[19].

Afterwards in the CONKO-003 trial the OFF arm was compared to an active control arm (5FU). The results of this study confirmed OFF schedule efficacy. OS increased significantly in the experimental arm (5.9 mo *vs* 3.3 mo), and there was a low rate of adverse events[6]. These data are more reliable than those of the CONKO-01 trial because of the high number of randomized patients (168). Smaller, non-randomized studies reported similar results (approximately 5 months in OS) for combination oxaliplatin-capecitabine (xelox)[20].

However, PANCREOX, which randomized 108 patients to oxaliplatin and 5-FU, the FOLFOX6m schedule, or 5-FU plus leucovorin, demonstrated a detrimental effect of FOLFOX6m on both OS and quality of life (median OS 6.1 mo *vs* 9.9 mo, *P* = 0.02), although the high OS in the 5-FU arm appears disputable[21].

Other schedules after progression to gemcitabine-based therapy have been investigated in non-randomized studies. The combination of oxaliplatin plus raltitrexed[22] or gemcitabine[23] led to OS of 5.2 and 6 mo, respectively. A recent small phase II study reported outstanding OS (10.4 mo) for the combination of oxaliplatin and docetaxel[24]. The use of docetaxel was suggested by the result of a previous retrospective trial that reported OS of 4.0 months with docetaxel monotherapy[25]. By contrast, the combination of docetaxel with irinotecan yielded disappointing outcomes, with OS of 4.1 mo, comparable to the median OS for other schedules in this setting[26].

Limited experience with docetaxel[27], paclitaxel[28], and eribulin[29] monotherapies has not yielded satisfactory results.

Similar to oxaliplatin, irinotecan has been evaluated in association with other agents such as raltitrexed, resulting in OS of 6.5 mo[30]. Patients pre-treated with platinoid therapy frequently experienced peripheral neuropathy, limiting therapy options. Irinotecan monotherapy exhibited moderate activity and an acceptable safety profile as second-line treatment[31]. A subsequent multicentre phase II study was conducted to investigate the combination of irinotecan with fluoropyrimidine using the FOLFIRI schedule (irinotecan 180 mg/m2, leucovorin 200 mg/m2, 5-FU 400 mg/m2 bolus and 5-FU 600 mg/m2 for 22 h). This schedule was well tolerated and led to acceptable outcomes (OS 5 mo)[32].

Recent interesting data emerging from two relevant studies (PRODIGE 4, ACCORD 11) of FOLFIRINOX first-line therapy suggest an important impact of this schedule on OS; approximately 45% of patients underwent second-line therapy, despite the high rate of adverse events in the experimental arm compared to the gemcitabine control arm, including febrile neutropenia (5.4% *vs* 1.2%), neutropenia (45.7% *vs* 21%) and diarrhoea grade 3–4 (12.7% *vs* 1.8%)[33].

The optimal treatment choice after FOLFIRINOX progression has not been established. The PRODIGE intergroup reported the most common second-line therapy administered to patients progressing in the FOLFIRINOX arm was gemcitabine (82.5%) or a gemcitabine-based combination (12.5%). Conversely, in the gemcitabine-resistant group, the second-line treatment was FOLFOX (49.4%), gemcitabine plus oxaliplatin (17.6%), fluorouracil and leucovorin plus cisplatin (16.5%) or FOLFIRINOX (4.7%)[34]. Studies have also investigated nab-paclitaxel plus gemcitabine[35-36] and gemcitabine alone[37] after first-line FOLFIRINOX. In gemcitabine-refractory patients, second-line therapy with FOLFIRINOX is marginally effective and less manageable in terms of toxicities[38].

The most accepted hypothesis explaining rapid PDA progression during chemotherapy is the presence of a dense stroma surrounding the tumour cells that prevents drug activity. To overcome this obstacle, a new formulation of paclitaxel (nab-paclitaxel) was used in combination with gemcitabine as a first-line regimen[39]. This combination exhibited activity in the second-line setting both in gemcitabine-refractory patients[40-41] and after progression on FOLFIRINOX[42]. Nab-paclitaxel exhibited a clinical benefit and is also feasible in elderly patients[43]. Based on these results, irinotecan encapsulated in liposome nanoparticles was evaluated. A phase II trial of nanoliposomal irinotecan (nal-iri) monotherapy reported OS of 5.2 mo[44]. The phase III study (NAPOLI-1) randomized (1:1:1) 417 patients worldwide to nanoliposomal irinotecan monotherapy, 5-FU and leucovorin, or nanoliposomal irinotecan plus 5-FU and leucovorin. The reported median OS was 4.9, 4.2 and 6.1 months, respectively[45]. This multicentre study had a large accrual, and nanoliposomal irinotecan plus 5-FU and leucovorin achieved the highest OS reported (Tables 1 and 2). Nanoliposomal irinotecan monotherapy was comparable to the combination of other chemotherapy agents.

All available agents have been tested in PDA therapy in different combinations and schedules. However, as in other cancers, the sequence of treatments and the optimization of the few efficient agents are critical. Therefore, it is very important to define an algorithm based on PS, patient age, and comorbidities for the first line decision (Figure 1).

To determine the first-line therapy, patients can be classified into three categories depending on age, PS, and comorbidities: patients with PS 0–1 and < 65 years can be treated with FOLFIRINOX; patients with PS 0–1 and > 65 years can receive nab-paclitaxel; and patients with PS > 1 elderly patients, or patients with serious comorbidities receive gemcitabine monotherapy. The selection of subsequent therapies is affected by previous treatment and depends on residual toxicities, PS after first-line therapy, and patient preference.

Based on the literature, we hypothesize that patients treated with FOLFIRINOX can receive nab-paclitaxel plus gemcitabine or gemcitabine monotherapy. However, patients treated with first-line gemcitabine have additional options, including fluoropyrimidine and irinotecan.

There are currently no studies assessing treatment progression following nab-paclitaxel. However, if the patient recovers from peripheral neurotoxicity, we suggest platinoid-based chemotherapy or irinotecan-based therapy. A recent post hoc analysis of the MPACT trial showed that second-line therapy is feasible and more beneficial in patients previously treated with an efficient first-line treatment, particularly nab-paclitaxel plus gemcitabine, than in patients treated with gemcitabine alone[46].

Improved outcomes may be obtained by treatment with all active agents (nab-paclitaxel, gemcitabine, irinotecan, oxaliplatin, fluoropyrimidine) during the entire patient history.

**CONCLUSION**

Many drugs have been investigated for PDA treatment, but outstanding OS results have only recently been obtained in the second-line setting. The median OS remains approximately 5 months that is a good results in comparison with that achieved by BSC. Current targeted therapies have not demonstrated efficacy in phase III trial, and future studies must strengthen the efficacy of current chemotherapy agents. Drugs such as nal-iri and nab-paclitaxel represent the first real change in this landscape and may provide new hope for PDA treatment.

**REFERENCES**

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac]

2 **Carrato A**, Falcone A, Ducreux M, Valle JW, Parnaby A, Djazouli K, Alnwick-Allu K, Hutchings A, Palaska C, Parthenaki I. A Systematic Review of the Burden of Pancreatic Cancer in Europe: Real-World Impact on Survival, Quality of Life and Costs. *J Gastrointest Cancer* 2015; **46**: 201-211 [PMID: 25972062 DOI: 10.1007/s12029-015-9724-1]

3 **National Comprehensive Cancer Network**. NCCN pancreatic guideline. Available from: URL: http: //www.nccn.org/professionals/physician\_gls/pdf/pancreatic

4 **Burris 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]

5 **Smyth EN**, Bapat B, Ball DE, André T, Kaye JA. Metastatic Pancreatic Adenocarcinoma Treatment Patterns, Health Care Resource Use, and Outcomes in France and the United Kingdom Between 2009 and 2012: A Retrospective Study. *Clin Ther* 2015; **37**: 1301-1316 [PMID: 25907619 DOI: 10.1016/j.clinthera.2015.03.016]

6 **Oettle H**, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, Görner M, Mölle M, Greten TF, Lakner V, Bischoff S, Sinn M, Dörken B, Pelzer U. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol* 2014; **32**: 2423-2429 [PMID: 24982456 DOI: 10.1200/JCO.2013.53.6995]

7 **Astsaturov IA**, Meropol NJ, Alpaugh RK, Burtness BA, Cheng JD, McLaughlin S, Rogatko A, Xu Z, Watson JC, Weiner LM, Cohen SJ. Phase II and coagulation cascade biomarker study of bevacizumab with or without docetaxel in patients with previously treated metastatic pancreatic adenocarcinoma. *Am J Clin Oncol* 2011; **34**: 70-75 [PMID: 20458210 DOI: 10.1097/COC.0b013e3181d2734a]

8 **Renouf DJ**, Tang PA, Hedley D, Chen E, Kamel-Reid S, Tsao MS, Tran-Thanh D, Gill S, Dhani N, Au HJ, Wang L, Moore MJ. A phase II study of erlotinib in gemcitabine refractory advanced pancreatic cancer. *Eur J Cancer* 2014; **50**: 1909-1915 [PMID: 24857345 DOI: 10.1016/j.ejca.2014.04.008]

9 **Ko AH**, Venook AP, Bergsland EK, Kelley RK, Korn WM, Dito E, Schillinger B, Scott J, Hwang J, Tempero MA. A phase II study of bevacizumab plus erlotinib for gemcitabine-refractory metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 2010; **66**: 1051-1057 [PMID: 20130876 DOI: 10.1007/s00280-010-1257-5]

10 **Bodoky G**, Timcheva C, Spigel DR, La Stella PJ, Ciuleanu TE, Pover G, Tebbutt NC. A phase II open-label randomized study to assess the efficacy and safety of selumetinib (AZD6244 [ARRY-142886]) versus capecitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy. *Invest New Drugs* 2012; **30**: 1216-1223 [PMID: 21594619 DOI: 10.1007/s10637-011-9687-4]

11 **Ko AH**, Bekaii-Saab T, Van Ziffle J, Mirzoeva OM, Joseph NM, Talasaz A, Kuhn P, Tempero MA, Collisson EA, Kelley RK, Venook AP, Dito E, Ong A, Ziyeh S, Courtin R, Linetskaya R, Tahiri S, Korn WM. A Multicenter, Open-Label Phase II Clinical Trial of Combined MEK plus EGFR Inhibition for Chemotherapy-Refractory Advanced Pancreatic Adenocarcinoma. *Clin Cancer Res* 2016; **22**: 61-68 [PMID: 26251290 DOI: 10.1158/1078-0432.CCR-15-0979]

12 **Brell JM**, Matin K, Evans T, Volkin RL, Kiefer GJ, Schlesselman JJ, Dranko S, Rath L, Schmotzer A, Lenzner D, Ramanathan RK. Phase II study of docetaxel and gefitinib as second-line therapy in gemcitabine pretreated patients with advanced pancreatic cancer. *Oncology* 2009; **76**: 270-274 [PMID: 19258727 DOI: 10.1159/000206141]

13 **Ignatiadis M**, Polyzos A, Stathopoulos GP, Tselepatiotis E, Christophylakis C, Kalbakis K, Vamvakas L, Kotsakis A, Potamianou A, Georgoulias V. A multicenter phase II study of docetaxel in combination with gefitinib in gemcitabine-pretreated patients with advanced/metastatic pancreatic cancer. *Oncology* 2006; **71**: 159-163 [PMID: 17646699]

14 **Hurwitz HI**, Uppal N, Wagner SA, Bendell JC, Beck JT, Wade SM, Nemunaitis JJ, Stella PJ, Pipas JM, Wainberg ZA, Manges R, Garrett WM, Hunter DS, Clark J, Leopold L, Sandor V, Levy RS. Randomized, Double-Blind, Phase II Study of Ruxolitinib or Placebo in Combination With Capecitabine in Patients With Metastatic Pancreatic Cancer for Whom Therapy With Gemcitabine Has Failed. *J Clin Oncol* 2015; **33**: 4039-4047 [PMID: 26351344 DOI: 10.1200/JCO.2015.61]

15 **Kaufman B,** Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, Mitchell G, Fried G, Stemmer SM, Hubert A,Rosengarten O, Steiner M, Loman N, Bowen K, Fielding A, Domchek SM. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015; **33**: 244-250 [PMID: 25366685 DOI: 10.1200/JCO.2014.56.2728]

16 **Reni M,** Cereda S, Milella M, Novarino A, Passardi A, Mambrini A, Di Lucca G, Aprile G, Belli C, Danova M, Bergamo F, Franceschi E, Fugazza C, Ceraulo D,Villa E. Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: a phase II randomised trial. *Eur J Cancer* 2013; **49**: 3609-3615 [DOI: 10.1016/j.ejca.2013.06.041]

17 **Ibrahim AM**, Wang YH. Viro-immune therapy: A new strategy for treatment of pancreatic cancer. *World J Gastroenterol* 2016; **22**: 748-763 [PMID: 26811622 DOI: 10.3748/wjg.v22.i2.748]

18 **Androulakis N**, Syrigos K, Polyzos A, Aravantinos G, Stathopoulos GP, Ziras N, Mallas K, Vamvakas L, Georgoulis V. Oxaliplatin for pretreated patients with advanced or metastatic pancreatic cancer: a multicenter phase II study. *Cancer Invest* 2005; **23**: 9-12 [PMID: 15779862]

19 **Pelzer U**, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, Riess H, Oettle H. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011; **47**: 1676-1681 [PMID: 21565490 DOI: 10.1016/j.ejca.2011.04.011]

20 **Blesa JG,** Alberola-Candel B, Marco VG. Phase II trial of second line chemotherapy in metastatic pancreas cancer with the combination of oxaliplatin (OX) and capecitabine (CP). *J Clin Oncol* 2009; **27** suppl: abstr e15561

21 **Gill S,** Ko YJ, Cripps MC, BeauDOIn A, Dhesy-Thind SK, Zulfiqar M. PANCREOX: a randomised phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT). *J Clin Oncol* 2014; **32**: abstr 4022

22 **Reni M**, Pasetto L, Aprile G, Cordio S, Bonetto E, Dell'Oro S, Passoni P, Piemonti L, Fugazza C, Luppi G, Milandri C, Nicoletti R, Zerbi A, Balzano G, Di Carlo V, Brandes AA. Raltitrexed-eloxatin salvage chemotherapy in gemcitabine-resistant metastatic pancreatic cancer. *Br J Cancer* 2006; **94**: 785-791 [PMID: 16508631]

23 **Demols A**, Peeters M, Polus M, Marechal R, Gay F, Monsaert E, Hendlisz A, Van Laethem JL. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. *Br J Cancer* 2006; **94**: 481-485 [PMID: 16434988]

24 **Ettrich TJ**, Perkhofer L, von Wichert G, Gress TM, Michl P, Hebart HF, Büchner-Steudel P, Geissler M, Muche R, Danner B, Kächele V, Berger AW, Güthle M, Seufferlein T. DocOx (AIO-PK0106): a phase II trial of docetaxel and oxaliplatin as a second line systemic therapy in patients with advanced pancreatic ductal adenocarcinoma. *BMC Cancer* 2016; **16**: 21 [PMID: 26772812 DOI: 10.1186/s12885-016-2052-4]

25 **Saif MW**, Syrigos K, Penney R, Kaley K. Docetaxel second-line therapy in patients with advanced pancreatic cancer: a retrospective study. *Anticancer Res* 2010; **30**: 2905-2909 [PMID: 20683031]

26 **Ko AH**, Dito E, Schillinger B, Venook AP, Bergsland EK, Tempero MA. Excess toxicity associated with docetaxel and irinotecan in patients with metastatic, gemcitabine-refractory pancreatic cancer: results of a phase II study. *Cancer Invest* 2008; **26**: 47-52 [PMID: 18181045 DOI: 10.1080/0735900701681483]

27 **Cereda S**, Reni M. Weekly docetaxel as salvage therapy in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Chemother* 2008; **20**: 509-512 [PMID: 18676234]

28 **Oettle H**, Arnold D, Esser M, Huhn D, Riess H. Paclitaxel as weekly second-line therapy in patients with advanced pancreatic carcinoma. *Anticancer Drugs* 2000; **11**: 635-638 [PMID: 11081455]

29 **Renouf DJ**, Tang PA, Major P, Krzyzanowska MK, Dhesy-Thind B, Goffin JR, Hedley D, Wang L, Doyle L, Moore MJ. A phase II study of the halichondrin B analog eribulin mesylate in gemcitabine refractory advanced pancreatic cancer. *Invest New Drugs* 2012; **30**: 1203-1207 [PMID: 21526355 DOI: 10.1007/s10637-011-9673-x]

30 **Ulrich-Pur H**, Raderer M, Verena Kornek G, Schüll B, Schmid K, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Scheithauer W. Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. *Br J Cancer* 2003; **88**: 1180-1184 [PMID: 12698181]

31 **Yi SY**, Park YS, Kim HS, Jun HJ, Kim KH, Chang MH, Park MJ, Uhm JE, Lee J, Park SH, Park JO, Lee JK, Lee KT, Lim HY, Kang WK. Irinotecan monotherapy as second-line treatment in advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2009; **63**: 1141-1145 [PMID: 18839175 DOI: 10.1007/s00280-008-0839-y]

32 **Zaniboni A**, Aitini E, Barni S, Ferrari D, Cascinu S, Catalano V, Valmadre G, Ferrara D, Veltri E, Codignola C, Labianca R. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: a GISCAD multicenter phase II study. *Cancer Chemother Pharmacol* 2012; **69**: 1641-1645 [PMID: 22576338 DOI: 10.1007/s00280-012-1875-1]

33 **Gourgou-Bourgade S**, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Boige V, Bérille J, Conroy T. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013; **31**: 23-29 [PMID: 23213101 DOI: 10.1200/JCO.2012.44.4869]

34 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]

35 **Berger AK**, Weber TF, Jäger D, Springfeld C. Successful treatment with nab-paclitaxel and gemcitabine after FOLFIRINOX failure in a patient with metastasized pancreatic adenocarcinoma. *Onkologie* 2013; **36**: 763-765 [PMID: 24356569 DOI: 10.1159/000356811]

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

37 **da Rocha Lino A**, Abrahão CM, Brandão RM, Gomes JR, Ferrian AM, Machado MC, Buzaid AC, Maluf FC, Peixoto RD. Role of gemcitabine as second-line therapy after progression on FOLFIRINOX in advanced pancreatic cancer: a retrospective analysis. *J Gastrointest Oncol* 2015; **6**: 511-515 [PMID: 26487945 DOI: 10.3978/j.issn.2078-6891.2015.041]

38 **Kobayashi N.** Second-line chemotherapy by FOLFIRINOX with unresectable pancreatic cancer (phase I, II study). *J Clin Oncol* 2016; 34 suppl 4S: abstr 297

39 **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, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]

40 **Bertocchi P**, Abeni C, Meriggi F, Rota L, Rizzi A, Di Biasi B, Aroldi F, Ogliosi C, Savelli G, Rosso E, Zaniboni A. Gemcitabine Plus Nab-Paclitaxel as Second-Line and Beyond Treatment for Metastatic Pancreatic Cancer: a Single Institution Retrospective Analysis. *Rev Recent Clin Trials* 2015; **10**: 142-145 [PMID: 25881637]

41 **Hosein PJ**, de Lima Lopes G, Pastorini VH, Gomez C, Macintyre J, Zayas G, Reis I, Montero AJ, Merchan JR, Rocha Lima CM. A phase II trial of nab-Paclitaxel as second-line therapy in patients with advanced pancreatic cancer. *Am J Clin Oncol* 2013; **36**: 151-156 [PMID: 22307213 DOI: 10.1097/COC.0b013e3182436e8c]

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

43 **Giordano G,** Vaccaro V, Lucchini E, Musettini G, Bertocchi P, Bergamo F, Giommoni E, Santoni M, Russano M, Campidoglio S, Santini S, Zaniboni A, Zagonel V, Cascinu S, Vasile E, Melisi D, Milella M, Febbraro A Nab-paclitaxel (Nab-P) and gemcitabine (G) as first-line chemotherapy (CT) in advanced pancreatic cancer (APDAC) elderly patients (pts): A “real-life” study. *J Clin Oncol* 2015; **33** suppl 3: abstr 424

44 **Ko AH**, Tempero MA, Shan YS, Su WC, Lin YL, Dito E, Ong A, Wang YW, Yeh CG, Chen LT. A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer. *Br J Cancer* 2013; **109**: 920-925 [PMID: 23880820 DOI: 10.1038/bjc.2013.408]

45 **Wang-Gillam A**, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, Macarulla T, Lee KH, Cunningham D, Blanc JF, Hubner RA, Chiu CF, Schwartsmann G, Siveke JT, Braiteh F, Moyo V, Belanger B, Dhindsa N, Bayever E, Von Hoff DD, Chen LT. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 2016; **387**: 545-557 [PMID: 26615328 DOI: 10.1016/S0140-6736(15)00986-1]

46 **Goldstein D**, Chiorean G E, Tabernero J, Hassan R. Outcome of second-line treatment (2L Tx) following nab-paclitaxel (nab-P) gemcitabine (G) or G alone for metastatic pancreatic cancer (MPC). *J Clin Oncol* 2016; **34**: suppl 4S: abstr 333

**P-Reviewer:** Buanes TA, Kleeff J, Miyoshi E **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Table 1 Randomized second line studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref. | Year | Study | Regimens | Patients | OS (mo) |
| Pelzer *et al*[18] | 2011 | CONKO-01 | OFF *vs* BSC | 23 | 4.8 *vs* 2.3 |
| Oettle *et al*[6] | 2014 | CONKO-003 | OFF *vs* 5-FU | 76 | 5.9 *vs* 3.3 |
| Gillam *et al*[43] | 2015 | NAPOLI 1 | Nal-iri + 5-FU+LLV *vs* Nal-iri *vs* 5-FU+LLV *vs* | 417 | 6.1 *vs* 4.9 *vs* 4.2 |
| Ulrich-Pur *et al*[29] | 2003 |  | Raltitrexed+irinotecan *vs* raltitrexed | 38 | 6.5 *vs* 4.3 |

**Table 2 Most significant not randomized second line studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Ref. | Year study | Regimens | Patients | OS (mo) |
| Reni *et al*[21] | 2006 | Oxaliplatin +Raltitrexed | 41 | 5.2 |
| Demols *et al*[22] | 2006 | Oxaliplatin+ Gemcitabine | 33 | 6 |
| Saif *et al*[24] | 2010 | Docetaxel | 17 | 4 |
| Cantore | 2004 | Oxaliplatin+irinotecan | 30 | 5.9 |
| Yi *et al*[30] | 2009 | Irinotecan | 33 | 6.6 |
| Zaniboni *et al*[31] | 2012 | Folfiri | 50 | 5 |
| Bertocchi *et al*[38] | 2015 | Abraxane+ gemcitabine | 23 | 5 |

**Second line therapy**

**Patients characteristics**

**First line therapy**

Nab-paclitaxel+gemcitabine

FOLFOXIRI FOLFIRINOX

PS 0-1

<65 years

no comorbidities

Gemcitabine

Platonid based therapy (+- Fluoropyrimidine):

* Xelox
* Gemox
* OFF

PS 0-1

>65 years

Nab-paclitaxel+gemcitabine

Irinotecan based therapy (+- Fluoropyrimidine):

* FOLFIRI
* Nal-iri
* Nal-iri+ 5FU-LLV

Fluoropyrimidine

Fluoropyrimidine

PS >1

>65 years

Serious comorbidities

Gemcitabine

Irinotecan

**Figure 1 Proposed algorithm of pancreatic cancer therapy.**