Journal of Gastrointestinal Cancer (2019) 50:519–524
https://doi.org/10.1007/s12029-018-0116-1

ORIGINAL RESEARCH

Efficacy of Docetaxel and Oxaliplatin Regimen as a Second-Line Therapy for Patients with Advanced Pancreatic Adenocarcinoma

Amal Rayan[1] · Ola N. Abdel Fattah[1] · Ahmed Soliman[2] · Hosam A. Hasan[3] · Asmaa M. Zahran[4]

Published online: 25 May 2018

Abstract

Background and Aim of Work Pancreatic cancer is the deadliest of the 21 most common cancers, largely because it is often identified at a late stage, we aimed to determine the control rates, and PFS for patients who received docetaxel-oxaliplatin regimen as a 2nd line therapy.

Patients and Methods Twenty-five patients with advanced cancer pancreas progressed or failed on 1st line treatments and justified the inclusion criteria were eligible to receive Docetaxel 75 mg/m^2 over 1h iv infusion on day 1, Oxaliplatin 80 mg/m^2 over 2 h iv infusion on day 2, the cycle was repeated every 3 weeks for 6-8 cycles unless disease progression or severe toxicity appeared.

Results No patients achieved complete response (CR), and the control rate (control rate = partial response (PR = 6/25, 24%) + stable disease (SD = 9/25, 36%) was 60% while disease progression (DP) was demonstrated in (10/25) 40% of patients, the median PFS was 7 ± 0.777 ms (95% confidence interval: 5.467-8.524 ms), grade 3 neutropenia, fatigue, diarrhea, and vomiting were developed in 12%, 8%, 12% and 8% of patients respectively.

Conclusions Docetaxel-oxaliplatin regimen was an active regimen in advanced cancer pancreas based on our encouraging results without occurrence of grade four toxicities.

Keywords Advanced cancer pancreas · Oxaliplatin · Docetaxel · Survival

Introduction

Pancreatic adenocarcinoma represents the tenth most common cancer and the second leading cause of death in the USA [1], while worldwide, it ranks the 12th most common cancer, and the fourth leading cause of death [2].

Over the last 40 years, survival for many cancers had improved except for cancer pancreas with only 7.2% of patients surviving up to 5 years following diagnosis.

✉ Amal Rayan
amal3774rayan@gmail.com

[1] Department of clinical oncology, Assiut University Hospital, Assiut University, Assiut 71515, Egypt

[2] Department of surgery, Assiut University Hospital, Assiut University, Assiut, Egypt

[3] Department of diagnostic radiology, Assiut University Hospital, Assiut University, Assiut, Egypt

[4] Department of clinical pathology, South Egypt Cancer Institute, Assiut University, Assiut, Egypt

Chemotherapy is the primary treatment modality for patients with locally advanced pancreatic cancers. Although gemcitabine has long been considered the standard regimen, newer chemotherapy regimens have recently emerged.

Many phase III studies have evaluated a combination regimen with either a platinum analog (cisplatin or oxaliplatin) or fluoropyrimidine versus single-agent gemcitabine [3]. No one of these phase III trials has demonstrated a statistically significant advantage favoring the use of combination chemotherapy in the first-line treatment of metastatic pancreatic cancer.

However, nab-paclitaxel and gemcitabine when compared with gemcitabine alone in the multicenter international phase III trial [4] significantly increased the median overall survival (OS) from 6.7 to 8.5 months (HR 0.72; 95% CI, 0.62–0.83; $P < .001$), and also increased progression-free survival (PFS) from 3.7 to 5.5 months (HR 0.69; 95% CI, 0.58–0.82; $P < .001$), but with more grade 3 toxicities compared to gemcitabine alone, and based on these results, nab-paclitaxel and gemcitabine regimen was considered a standard treatment option for patients with advanced pancreatic cancer.

FOLFORINOX regimen [5] significantly increased OS and PFS when also compared to gemcitabine alone from 6.8

to 11.1 months (HR = 0.57; 95% CI, 0.45–0.73; $P < .001$) and from 3.3 to 6.4 months (HR = 0.47; 95% CI, 0.37–0.59; $P < .001$) respectively with significantly impaired quality of life and neutropenia. FOLFORINOX is considered a standard treatment option for advanced cancer pancreas.

The options for second-line chemotherapy are limited as patient's performance status is an important poor prognostic factor; notably, only 40% of patients can receive an additional line of therapy after failure or progression on first-line chemotherapy.

Even so, second-line treatment for those tolerating further chemotherapy is associated with improved outcomes in advanced cancer pancreas compared to best supportive care [6].

Objectives

This study was a phase II prospective single-arm efficacy one, and was done at the clinical oncology department, Assiut University Hospital; the study was approved by the Institutional Review Board of our faculty, Assiut University.

Patients and Methods

This trial is a phase II prospective single-arm efficacy trial, and was done at clinical oncology department, Assiut university hospital, the study was approved by the Institutional Review Board of our faculty, Assiut university.

Inclusion Criteria

Patients with histologically or cytologically confirmed metastatic or unresectable locally advanced pancreatic adenocarcinoma (a biopsy was needed in some cases to confirm metastasis when there was a doubt; patients with solitary hepatic focal lesion or solitary lung nodule were confirmed to be metastatic by needle biopsy especially when elevated CA19-9 or clinical deterioration did not occur; in addition, biopsy was taken when facilitated diffusion pattern on diffusion MRI exhibited), age ≥ 18 years, taxane naïve, after failure of first-line treatment due to progression during treatment or within 3 months after treatment, with KPS≥70% , adequate life expectancy, adequate BM reserve (granulocytic count ≥ 1.5*10(9)/L, HB ≥ 9 g/dl, platelet count ≥ 100*10(9)/L), liver functions with serum bilirubin < 2 times ULN, transaminases < 2.5 times ULN, and renal functions with serum creatinine ≤ 1.5 times ULN were eligible; previous radiotherapy was allowed and informed consent from all eligible patients was taken.

Exclusion Criteria

Patients with more than two sites of metastases and cerebral metastases were excluded.

Treatment

Docetaxel 75 mg/m2 over 1 h iv infusion on day 1 and oxaliplatin 80 mg/m2 over 2 h iv infusion on day 2 were given; the cycle was repeated every 3 weeks for 6–8 cycles and stopped when disease progression or grade 4 toxicity developed. Premedication by antiemetic therapy and 8 mg dexamethasone on the day before treatment and on days 2 and 3 after docetaxel, and 16 mg dexamethasone on the day of infusion of docetaxel. One gram calcium gluconate and 1 g magnesium were administered just before and after oxaliplatin infusion, aprepitant was given 1 h before docetaxel and oxaliplatin infusions in the 1st and 2nd days and continued for another 1 day, and ondansetron 8 mg iv before docetaxel and oxaliplatin infusions (4 doses every 12 h over 2 days). Treatment delay for 1–2 weeks was done when grade 2 or 3 toxicities developed like neutropenia, thrombocytopenia, diarrhea, vomiting, and neuropathy, and dose reductions ≤ 50% were allowed when these toxicities were not corrected by delaying the treatment; the treatment was stopped when these toxicities repeated in subsequent cycles; also, the treatment was stopped if grade 4 toxicities appeared. Toxicities were determined according to CTCAE ver.3.

All eligible patients underwent the following:

- Laboratory tests: (CBC, LFTs, RFTs, electrolytes, CA19-9)
- Imaging: contrasted MSCT Chest, contrasted MSCT pelvi-abdomen or diffusion MRI in some cases, bone scan (PET-CT in some cases), MRI brain to exclude brain metastases

Assessment of the response clinically every cycle to evaluate the subjective improvement, and by MSCT chest and pelvi-abdomen, and CA19-9 test every two cycles to evaluate the objective response till completion of 6–8 cycles. Follow-up was done monthly by clinical examination, and laboratory tests (CBC, LFTs, RFTs) if needed (especially if toxicities developed), and by MSCT abdomen and CA19-9 every 2 months to determine the PFS.

Statistics

Descriptive statistics as mean, median, range, and percentages were used; Kaplan-Meier test was used for determination of PFS.

PFS was defined as the time from registration in docetaxel-oxaliplatin regimen to objective tumor progression or death.

RECIST criteria were used that defined tumor progression as appearance of one or more new lesions, or increase in the size of target lesions.

Clear, unequivocal increase in non-target lesions which may be measurable or non-measurable, worsening of signs and symptoms of the tumor and increase in tumor marker CA19-9 were also considered disease progression.

Pearson's chi-square and log-rank tests were used to determine the significance of different patients' characteristics on PFS.

Results

This trial was done at the clinical oncology department of Assiut University Hospital during the period from the start of July 2014 to the end of July 2016 and involved 25 patients with locally advanced or metastatic pancreatic adenocarcinoma primarily diagnosed by biopsy and elevated CA19-9 or after radical surgery (some cases previously underwent Whipple's operation, total pancreatectomy, and distal pancreatectomy) and received systemic chemotherapy with or without radiotherapy in the first-line setting; these patients then became eligible to receive second-line chemotherapy due to disease progression or relapse (in some cases, a biopsy was required to confirm metastases) and the clinical characteristics of these patients were demonstrated in Table 1.

Response of 25 Patients Receiving Docetaxel and Oxaliplatin Regimen

No patients achieved complete response (CR), and the control rate (control rate = partial response (PR = 6/25, 24%) + stable disease (SD = 9/25, 36%) was 60% while disease progression (DP) occurred in (10/25) 40% of patients, the minimum number of cycles was 2 while the median number of cycles was 5, patients exhibited DP were discontinued to receive this regimen and treated with either supportive care or metronomic chemotherapy if they had acceptable PS Figs. 1 and 2.

Progression-Free Survival for 25 Patients Receiving Docetaxel and Oxaliplatin Regimen

The median PFS was 7 ± 0.777 ms (95% confidence interval 5.467–8.524 ms) Fig. 3.

Among the previously mentioned demographic and clinical characteristics of the study patients, younger age ≤ 58.8 ys ($P < 0.033$), PS > 70% ($P < 0.01$), having locally advanced disease ($P < 0.007$), number of cycles >5 ($P < 0.000$), previous radical surgery ($P < 0.038$), previous definitive radiotherapy ($P < 0.03$), and achieving PR ($P < 0.000$) all had a significant effect on PFS

Toxicity of the Regimen

No patients developed grade 4 toxicity, while grade 3 was common; grade 3 neutropenia, fatigue, diarrhea, and vomiting were developed in 12%, 8%, 12%, and 8% of patients respectively (Table 2).

Treatment delay was done in almost all patients while reductions of the dose up to 50% occurred in about half of the patients, during delay patients were treated with growth factors like G-CSF, and synthetic erythropoitin, blood transfusion, liver support medications, antiemetics, and neurotonics all were allowed according to the toxicity developed. Furthermore, prophylactic growth factors were also given 48 hours after nearly each cycle.

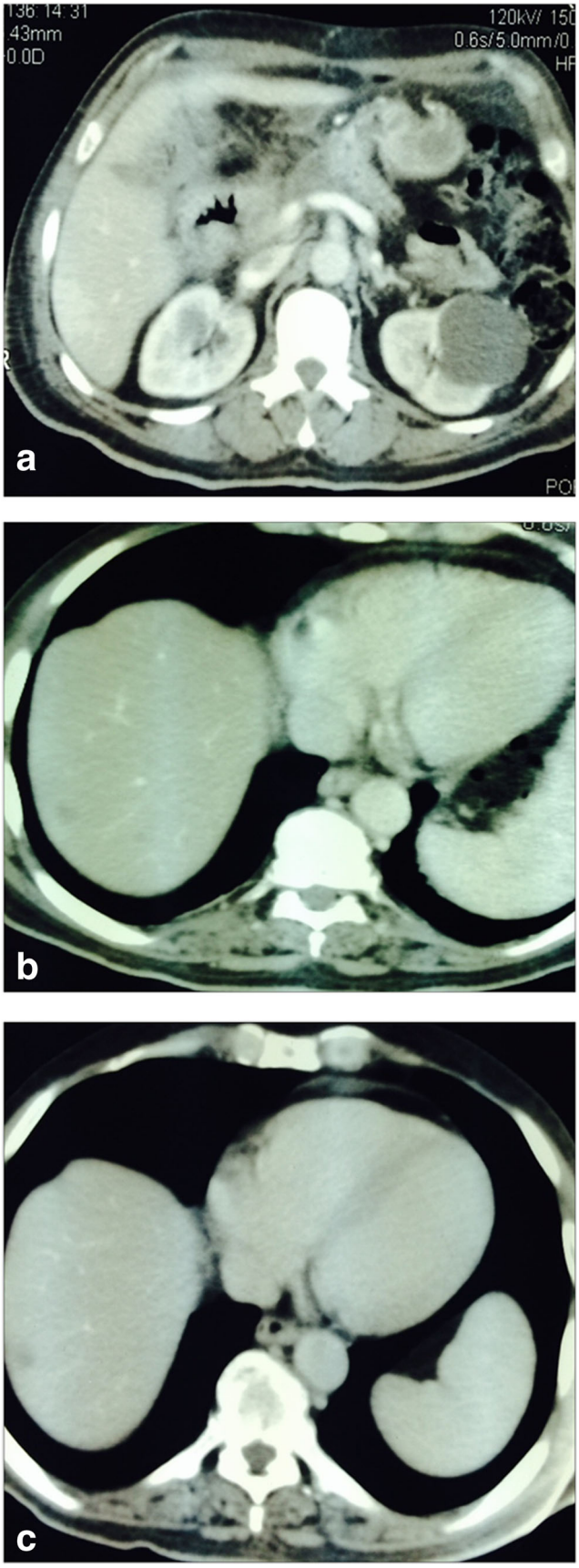
Table 1 Clinical characteristics of 25 patients eligible for docetaxel-oxaliplatin regimen

Age	
Mean ± SD	58.8 ± 1.698 years
Min.–max.	39–76 years
Gender	
Male	18 (72%)
Female	7 (28%)
KPS	
> 70%	16 (64%)
≤ 70%	9 (36%)
Site	
Head	14 (56%)
Body	8 (32%)
Tail	3 (12%)
Stage	
Locally advanced	7 (28%)
Metastatic	18 (72%)
Site of metastasis:	
Liver	9 (36%)
Non regional LN	4 (16%)
Liver and non-regional LN	3 (12%)
Bone	1 (4%)
Lung	1 (4%)
No metastasis	7 (28%)
First-line chemotherapy	
Gemcitabine + cisplatin/or oxaliplatin	16 (64%)
Gemcitabine alone	7 (28%)
5 FU + LV	1 (4%)
Capecitabine	1 (4%)
Pre-regimen CA19-9	
Elevated	17 (68%)
Not elevated	6 (24%)
Not done	2 (8%)
Prior radical surgery	5 (20%)
Prior definitive radiotherapy	7 (28%)
Median no of cycles	5 cycles
Min–max. no of cycles	2–8 cycles

LN lymph nodes, *5-FU* 5-fluorouracil, *LV* leucovorin

Discussion

Pancreatic cancer is the deadliest of the 21 most common cancers, largely because it is often identified at a late stage.



◀ **Fig. 1** **a** Male patient with Whipple's operation receiving adjuvant treatment then HFL appeared followed by 2nd-line docetaxel-oxaliplatin with SD. **b** Single HFL in the right lobe before second-line treatment. **c** The same HFL in the right lobe with SD after docetaxel-oxaliplatin regimen

The efficacy of oxaliplatin-based regimens in gemcitabine-refractory patients were studied mainly in three randomized studies; the CONKO-01 study that demonstrated a small significant advantage in the median OS for OFF regimen compared to BSC (4.8 vs. 2.3 months) despite its premature accrual closure [7]. The CONKO-003 trial also confirmed the efficacy of OFF regimen compared to 5-FU with lower toxicities [6]. But the PANCREOX study [8] terminated this hope of treatment with its detrimental results that favored 5-FU and leucovorin compared to FOLFOX6 regimen (the median OS 6.1 vs. 9.9 months, $P = 0.02$).

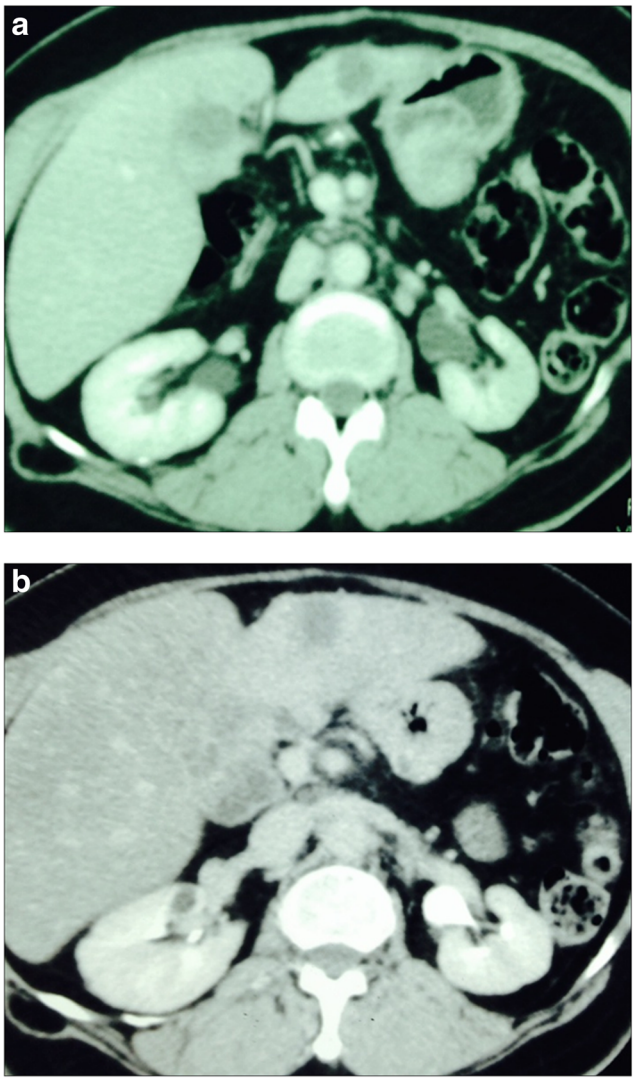


Fig. 2 **a**:Two HFLs in the right and left lobes before start of 2nd line CTR. **b** PR after 6 cycles of docetaxel-oxaliplatin with disappearance of right HFL

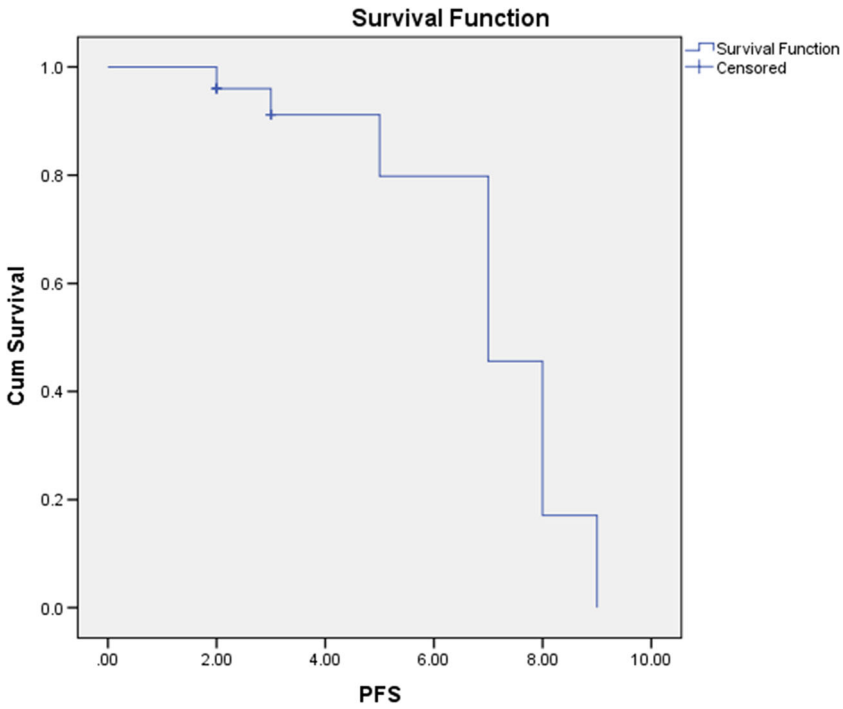


Fig. 3 The median PFS for 25 patients with advanced cancer pancreas receiving docetaxel and oxaliplatin as a second-line chemotherapy was 7 ± 0.777 months (95% CI 5.467–8.524)

Table 2 Toxicity profile in 25 patients with advanced cancer pancreas receiving second-line docetaxel-oxaliplatin chemotherapy

Toxicity	No.	%
Neutropenia		
GI	7	28
GII	6	24
GIII	3	12
Anemia		
GI	5	20
GII	7	28
Thrombocytopenia		
GI	4	16
Fatigue		
GI	20	80
GII	3	12
GIII	2	8
Diarrhea		
GI	8	32
GII	2	8
GIII	3	12
Vomiting		
GI	11	44
GII	6	24
GIII	2	8
Peripheral neuropathy		
Mild	12	48
Moderate	3	12

Saif et al. [9] retrospectively evaluated the role of docetaxel in patients with gemcitabine-refractory cancer pancreas whether it was given weekly at a dose of 25 mg/m^2 or 3-weekly at a dose 75 mg/m^2 (docetaxel alone, docetaxel-gemcitabine-capecitabine, and docetaxel-gemcitabine regimens) and demonstrated mild activity of docetaxel with 6% objective response rate, median PFS of 8 weeks, and median OS of 4 months without severe toxicities.

A study was done by Ettrich TJ et al. [10] to evaluate the activity of docetaxel and oxaliplatin combination as a second line after failure of gemcitabine, docetaxel 75 mg/m2 and oxaliplatin 80 mg/m2; no complete responses, partial response was achieved in 15.9% of patients, disease control rate was 48%, median PFS was 1.82 months, and the median OS was 10.1 months.

In this study, the control rate was 60% with no complete responses, partial response was achieved in 24%, the median PFS was 7 months with no more than grade 3 toxicities, and grade 3 toxicities developed in only 8–12% of patients.

The results of this study were better than those achieved by Ettrich TJ et al. and may be attributed to good PS as most patients had KPS ≥ 70%; heavily pretreated patients were excluded; patients with more than two sites of metastases and heavily metastasized patients were also excluded.

Conclusion

Docetaxel-oxaliplatin regimen is an active regimen in advanced cancer pancreas based on these encouraging results

and is needed to be evaluated in a multicentric large study to determine the actual survival benefits of this regimen.

References

1. American Cancer Society, 2015; SEER, 2015.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65:5–29.
3. Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. J Clin Oncol. 2010;28(10):1645–51.
4. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
5. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
6. Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, et al. Second line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil versus gemcitabine refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol. 2014;32:2423–9.
7. Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, et al. 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;47:1676–81.
8. 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.
9. Saif MW, Syrigos K, Penney R, Kaley K. Docetaxel second-line therapy in patients with advanced pancreatic cancer: a retrospective study. Anticancer Res. 2010;30:2905–9.
10. Ettrich TJ, Perkhofer L, von Wichert G, Gress TM, Michl P, Hebart HF, et al. 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. https://doi.org/10.1186/s12885-016-2052-4.