Pancreatic ductal adenocarcinoma (PDAC) remains one of the most difficult-to-treat cancers, with a 5-year survival rate of only 8%, one of the lowest of all cancers. Even if the cancer is resected in a curative way and the patient is treated with intense adjuvant chemotherapy for 6 months, most patients relapse and die of disease; median survival in the recent ESPAC-4 trial was 28 months [1]. Almost half of patients present with metastatic disease and face a median overall survival of less than 12 months [2].

The development of effective systemic therapy has lagged behind that of other tumor types. Much effort was required to identify chemotherapy regimens that could significantly improve survival over gemcitabine alone. A major step forward was the identification of the combination chemotherapy regimen FOLFIRINOX, which improved survival (11.1 months versus 6.8 months over gemcitabine alone in the PRODIGE study [3]). A second study, the MPACT trial, identified the addition of nab-paclitaxel to gemcitabine as effective, with an 8.5-month overall survival for the combination versus 6.7 months for gemcitabine alone [4]. Although FOLFIRINOX appears to have greater benefit, it is a more intense regimen, and a number of modified regimens are being adopted, although without clear data supporting equivalence with the original regimen [5–9]. Given that the patient population on the MPACT trial was older and was weighted toward poorer performance status, some investigators consider the two regimens, FOLFIRINOX and gemcitabine plus nab-paclitaxel, to be more similar than different [10]. A small study from Japan comparing the two regimens found a median progression-free survival of 3.7 months for FOLFIRINOX versus 6.5 months for gemcitabine plus nab-paclitaxel [11]. Similarly, in a retrospective analysis, modified FOLFIRINOX (dose-reduced irinotecan and 5-FU bolus omitted) compared with gemcitabine/nab-paclitaxel showed a median progression-free survival of 5.7 versus 6.5 months and a median overall survival of 11.5 versus 14 months, respectively [12].

Considering the two regimens likely comparable, many investigators have turned their efforts toward improving the gemcitabine/nab-paclitaxel combination by the addition of a third agent. The fact that gemcitabine/nab-paclitaxel is well-tolerated, even in the elderly [13], offers an attractive platform toward improving the gemcitabine/nab-paclitaxel combination by the addition of a third agent. Numerous trials were performed attempting to improve over gemcitabine monotherapy—summarizing several meta-analyses, almost 14,000 patients across 47 trials were invested in this effort [2, 15–19]. Whether it will require 14,000 patients to make another incremental step over gemcitabine/nab-paclitaxel remains to be determined.

Also in this issue, O’Reilly et al. report another trial using gemcitabine/nab-paclitaxel as a platform [20]. Necuparanib, a heparan sulfate considered to have antitumor and antimetastatic activity, was studied in combination with gemcitabine/nab-paclitaxel in a phase I study in 39 patients, with a partial response rate of 38% and a median survival of 15.6 months in those who received at least one cycle. These results supported continuation of the study into a randomized phase II design that was discontinued at an interim analysis, as the three-drug combination did not achieve a sufficient level of activity to warrant trial continuation.

In the randomized double-blinded phase II trial, Ko et al. evaluated the efficacy of gemcitabine/nab-paclitaxel plus either apatorsen, an antisense oligonucleotide targeting mRNA of the heat shock protein 27 (Hsp27), or placebo in patients with previously untreated metastatic PDAC [14]. The rationale for this study was that Hsp27, a protein chaperone that promotes cell survival under stress conditions, is induced by chemotherapy, radiation, and oxidative stress [21]. In vitro data suggested that Hsp27 may play a key role in resistance to gemcitabine [22]. Apatorsen is an antisense oligonucleotide that binds to Hsp27 mRNA and blocks its translation [23]. In this trial, 132 patients with metastatic PDAC were enrolled, 66 in the apatorsen arm and 66 in the control arm. Median PFS and OS were disappointingly poor, 2.7 and 5.3 months, in the apatorsen arm versus 3.8 and 6.9 months in the gemcitabine/nab-paclitaxel only arm, respectively. The authors were not able to identify prognostic factors that might explain the poorer overall survival at 6.9 months for the gemcitabine/nab-paclitaxel only arm, relative to the original MPACT data. It may be that increasing confidence in the use of gemcitabine/nab-paclitaxel has led to treatment of patients with worse performance status and disease characteristics than in the original trial.

On closer inspection of the trial, one does observe a trend in the poor prognostic subgroup with high serum levels of Hsp27 toward longer PFS and OS with apatorsen, 3.3 and 3.3 months versus 0.9 and 1.0 months in the gemcitabine/nab-
paclitaxel only arm. Although the number of subjects was too small to draw any conclusions, the findings seem to indicate that this subgroup could benefit from inhibition of Hsp27, suggesting that the question deserves a second look.

One proposed hypothesis for chemotherapy failure in PDAC is the formation of a dense stroma around the tumor cells that blocks drug access to the tumor. A nanopiposomal formulation of irinotecan aims to overcome the stromal barrier and improve drug delivery to the tumor. The NAPOLI-1 trial showed that the combination of nanopiposomal irinotecan with 5-FU/leucovorin improved OS over either of these therapies alone in patients previously treated with gemcitabine/nab-paclitaxel [24]. An alternate approach to overcoming the dense stroma is the use of PEGylated recombinant hyaluronidase (PEGPH20), which reduces the accumulation of hyaluronic acid (HA) in the tumor stroma. A randomized phase II trial showed that the addition of PEGPH20 to gemcitabine plus nab-paclitaxel led to a 46% overall response rate, compared with 34% with the two chemotherapy drugs alone in patients with HA-high PDAC [25]. A confirmatory randomized phase III trial is ongoing.

Systemic genomic sequencing has revealed that PDAC is not typically a heavily mutated tumor [26]. The most consistently mutated genes are KRAS, CDKN2A, TP53, and SMAD4/DPC4 [27]. Mutational signatures have also been cataloged—relating profiles of actual nucleotide variants to cancer-causing processes—identifying 4 signatures: age-related, double-strand break repair (DSBR)-deficient, mismatch repair (MMR)-deficient, and an ill-defined group [28]. DSBR-deficient (11% of cases) and MMR-deficient (2% of cases) signatures were associated with evidence of increased immunogenicity. These signatures could eventually aid identification of agents to add to the nab-paclitaxel/gemcitabine platform, including immunotherapy strategies [26]. The fact that most tumors bore age-related and not immunogenic signatures speaks to the need to find altogether different approaches to therapy.

In summary, the presented study points to the importance of reporting “negative” clinical trials—so valuable for what can be learned. Indeed, this study can be viewed in the context of all the studies that attempted to improve over gemcitabine monotherapy. The lower overall survival in the treatment population in the study by Ko et al. points to the importance of continuing to run randomized trials in pancreatic cancer, which is demanded by the variable complexity and heterogeneous nature of the patient population. It also points to the important role of the oncology community in supporting these trials through referral of patients for clinical trials whenever possible. Numerous clinical trials are currently available for patients with PDAC, ranging from neoadjuvant to refractory metastatic disease, and we strongly encourage participation in such trials [29].

DISCLOSURES
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REFERENCES
1. Neoptolemos JP, Palmer DH, Ghanek P et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): A multi-centre, open-label, randomised, phase 3 trial. Lancet 2017;389:1011–1024.
2. Bates SE. Pancreatic cancer: Challenge and inspiration. Clin Cancer Res 2017;23:1628.
3. Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–1825.
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):1691–1703.
5. Blazer M, Wu C, Goldberg RM et al. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. Ann Surg Oncol 2015;22:1153–1159.
6. Ghorani E, Wong HH, Hewitt C et al. Safety and efficacy of modified FOLFIRINOX for advanced pancreatic adenocarcinoma: A UK single-centre experience. Oncology 2015;89:281–287.
7. Katz MH, Shi Q, Ahmad SA et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for Clinical Trials in Oncology Trial A021101. JAMA Surg 2016;151:e161317.
8. Nanda RH, El-Rays B, Maithel SK et al. Neoadjuvant modified FOLFIRINOX and chemoradiation therapy for locally advanced pancreatic cancer improves resectability. J Surg Oncol 2015;111:1028–1034.
9. Stein SM, James ES, Deng Y et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br J Cancer 2016;114:737–743.
10. El Rassy E, Assi T, El Karak F et al. Could the combination of nab-paclitaxel plus gemcitabine salvage metastatic pancreatic adenocarcinoma after FOLFIRINOX failure? A single institutional retrospective analysis. Clin Res Hepatol Gastroenterol 2017;41:e26–e28.
11. Muranaka T, Kuwatan M, Komatsu Y et al. Comparison of efficacy and toxicity of nab-paclitaxel plus gemcitabine in unresectable pancreatic cancer. J Gastrointest Oncol 2017;8:556–567.
12. Watanabe K, Hashimoto Y, Umemoto K et al. Clinical outcome of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel as first line chemotherapy in metastatic pancreatic cancer. J Clin Oncol 2017;35(suppl 45): abstract 438.
13. Bedge J, Haertel N, Chi-Kern J et al. A multicenter phase 4 geriatric assessment directed trial to evaluate gemcitabine ± nab-paclitaxel in elderly pancreatic cancer patients J Clin Oncol 2017;35(suppl 45):abstract TPS10124.
14. Ko AH, Murphy PB, Peyton JD et al. A randomized, double-blinded, phase II trial of gemcitabine and nab-paclitaxel plus apatmosen or placebo in patients with metastatic pancreatic cancer: The RAINIER trial. The Oncologist 2017;22:1427–1428.
15. Banu E, Banu A, Fodor A et al. Meta-analysis of randomised trials comparing gemcitabine-based doublets versus gemcitabine alone in patients with advanced and metastatic pancreatic cancer. Drugs Aging 2007;24:865–879.
16. Chan K, Shah K, Lien K et al. A Bayesian meta-analysis of multiple treatment comparisons of systemic regimens for advanced pancreatic cancer. PLoS One 2014;9:e108749.
17. Giliberto D, Botta C, Correale P et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: A meta-analysis of randomised trials. Eur J Cancer 2013;49:593–603.
18. Gresham GK, Wells GA, Gill S et al. Chemotherapy regimens for advanced pancreatic cancer: A systematic review and network meta-analysis. BMC Cancer 2014;14:471.
19. Xie DR, Yang Q, Chen DL et al. Gemcitabine-based cytotoxic doublets chemotherapy for advanced pancreatic cancer: Updated subgroup meta-analyses of overall survival. Jpn J Clin Oncol 2010;40:432–441.
20. O’Reilly EM, Roach JM, Miller P et al. Saietry, Pharmacokinetics, Pharmacodynamics, antitumor activity of necuparanib combined with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer: Phase I results. The Oncologist 2017;22:1429–1430.
21. Garrido C, Brunet M, Didecot C et al. Heat shock proteins 27 and 70: anti-apoptotic proteins with tumorigenic properties. Cell Cycle 2006;5:2592–2601.
22. Kuramitsu Y, Wang Y, Tabo K et al. Heat-shock protein 27 plays the key role in gemcitabine-resistance of pancreatic cancer cells. Anticancer Res 2012;32:2295–2299.
23. Kamada M, So A, Muramaki M et al. Hsp27 knockdown using nucleotide-based therapies inhibit tumor growth and enhance chemotherapy in human bladder cancer cells. Mol Cancer Ther 2007;6:299–308.
24. Wang-Gillam A, Li CP, Bodoky G et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in
metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLE1): A global, randomised, open-label, phase 3 trial. Lancet 2016; 387:545–557.

25. Hingorani SR, Bullock AJ, Seery TE et al. Randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine vs nab-paclitaxel plus gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. J Clin Oncol 2017; 35(suppl):abstract 4008.

26. Borazanci E, Dang CV, Robey RW et al. Pancreatic cancer: “A Riddle Wrapped in a Mystery Inside an Enigma”. Clin Cancer Res 2017;23:1629–1637.

27. Oldfield LE, Connor AA, Gallinger S. Molecular events in the natural history of pancreatic cancer. Trends Cancer 2017;3:336–346.

28. Connor AA, Denroche RE, Jang GH et al. Association of distinct mutational signatures with correlates of increased immune activity in pancreatic ductal adenocarcinoma. JAMA Oncol 2017;3:774–783.

29. Manji GA, Olive KP, Saenger YM et al. Current and emerging therapies in metastatic pancreatic cancer. Clin Cancer Res 2017;23:1670–1678.

Editor’s Note:
See the related articles, “A Randomized, Double-Blinded, Phase II Trial of Gemcitabine and Nab-Paclitaxel Plus Apatersen or Placebo in Patients with Metastatic Pancreatic Cancer: The RAINIER Trial,” by Andrew H. Ko et al. on page 1427 and “Safety, Pharmacokinetics, Pharmacodynamics, antitumor activity of necuparanib combined with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer: Phase I results” by Eileen M. O’Reilly et al., on page 1429.