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Development of new therapies for metastatic pancreatic cancer: are they better than FOLFIRINOX?

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Metastatic pancreatic adenocarcinoma (mPAC) is a fatal disease. Palliative chemotherapy has been the only treatment option for patients; a modest benefit on overall survival (OS) has been well established with single-agent gemcitabine or 5-FU since the 1990s. Nearly two decades later, in 2011, Conroy *et al*[1] showed the superiority of the FOLFIRINOX regimen over gemcitabine alone (median OS, 11.1 vs 6.8 months; p<0.001). In 2013, Von Hoff *et al*[2] demonstrated the OS benefit of gemcitabine+nab-paclitaxel (Gem-Nab) over gemcitabine alone (8.5 vs 6.7 months; HR 0.72; 95% CI 0.62 to 0.83; p<0.001). Currently, both regimens have been used in high-income countries, but nab-paclitaxel is less widely available in low- and middle-income countries.

Despite several efforts, no targeted therapy has shown improvement in OS in phase III trials, with the exception of a minimal benefit from adding erlotinib to gemcitabine.[3] Recent data with PARP inhibitors in pancreatic tumours with *BRCA* or *PALB2* mutations[4] have shown promising results but only as maintenance therapy after palliative chemotherapy. In addition, even if such improvements are confirmed in phase III trials, only a minority of patients with pancreatic cancer harbour these mutations. Unfortunately, very few patients with pancreatic cancer benefit from current tumour-agnostic approaches, such as immunotherapy or NTRK inhibitors for those who harbour a microsatellite instability-high tumour or NTRK fusion, respectively.

Because of its poor prognosis and high incidence,[5] there is substantial interest in developing better therapies to treat mPAC. Currently, there are 326 clinical trials registered at ClinicalTrials.gov investigating therapeutic regimens in mPAC. Among those, 36 are in the context of first-line therapy, and of those, only seven are investigating FOLFIRINOX, while 29 are investigating Gem-Nab as the backbone therapy. Notably, among the seven trials using FOLFIRINOX, only one is active, while two were withdrawn and none were recruiting or completed. Moreover, nearly all new therapies have been tested in combination with the Gem-Nab regimen.

In our opinion, this observation is worrisome for the following reasons: (1) nab-paclitaxel is not as readily available as drugs included in the FOLFIRINOX regimen in low-income and middle-income countries, and (2) there are no data showing that Gem-Nab is as effective as FOLFIRINOX. While it is inappropriate to compare results from two independent clinical trials, data from the FOLFIRINOX regimen have shown a 'stronger' HR than that associated with the Gem-Nab regimen; moreover, nab-paclitaxel failed in the adjuvant setting (APACT trial—NCT01964430), in which FOLFIRINOX has resulted in the longest OS yet reported for patients with resected pancreatic cancer.[6] Since then, FOLFIRONOX has become the current standard-of-care for suitable patients. Thus, there are reasons to believe that treatment with FOLFIRINOX can yield better outcomes than can treatment with Gem-Nab.

There is no compelling reason to not use FOLFIRINOX as a backbone chemotherapy in combination with novel agents. Notably, despite the toxicity associated with FOLFIRONOX, this regimen has been combined successfully and safely with targeted therapies for the treatment of colorectal cancer. Therefore, we would like to warn the medical oncology community about the risks attendant on developing new therapies in combination therapy that is not commonly used worldwide and that may not be the best first-line option. In addition, we believe that FOLFIRINOX should be the control arm of all relevant first-line trials. Importantly, we do not aim to remove Gem-Nab from our first-line arsenal,

but we do need to reconcile providing the best clinical care developing new therapies. Any experimental arm that is shown to be superior to Gem-Nab will likely raise the question "*Is it better than FOLFIRINOX*?".

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