



## Nanovectors for anti-cancer drug delivery in the treatment of advanced pancreatic adenocarcinoma

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### Abstract

Liposome, albumin and polymer polyethylene glycol are nanovector formulations successfully developed for anti-cancer drug delivery. There are significant differences in pharmacokinetics, efficacy and toxicity between pre- and post-nanovector modification. The alteration in clinical pharmacology is instrumental for the future development of nanovector-based anticancer therapeutics. We have reviewed the results of clinical studies and translational research in nanovector-based anti-cancer therapeutics in advanced pancreatic adenocarcinoma, including nanoparticle albumin-bound paclitaxel and nanoliposomal irinotecan. Furthermore, we have appraised the ongoing studies incorporating novel agents with nanomedicines in the treatment of pancreatic adenocarcinoma.

**Key words:** Pancreatic adenocarcinoma; Nanovector; Nanoparticle albumin-bound paclitaxel; Nanoliposomal irinotecan; Biomarker

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**Core tip:** The nanovector-based anti-cancer therapeutics play important role in the treatment of advanced pancreatic adenocarcinoma. Data from completed clinical trials are reviewed, and important ongoing studies are presented. Biomarkers for patient selection and personalized medicine are discussed.

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## INTRODUCTION

Nanomedicines are pharmaceuticals prepared by manipulating matter at the nanoscale ( $< 1000$  nm); *i.e.*, manipulations at less than  $1000^{\text{th}}$  of a millimeter. The vast majority of nanomedicines are the result of the packaging of pharmacologically active compounds within nanovectors (5-800 nm). The chemical compounds used to construct these nanomedicines include low molecular weight self-assembling amphiphilic polymers, polymer-drug conjugates, water insoluble polymers/cross-linked polymers, dendrimers, inorganic chemistries and carbon nanotubes. Targeting of solid tumors by most of the nanomedicines is achieved by passive means known as enhanced permeability and retention (EPR) effect. Because of their size and surface properties, nanomedicines can easily travel through leaky blood vessel walls in the tumors, with enhanced retention due to impaired lymphatic drainage. This gives rise to a significant increase in the accumulation of attached drug by nanovectors in tumor tissue compared to that achieved with the free-form drug<sup>[1]</sup>. Nanovector formulation of anticancer compounds has several potential advantages over the free-form drugs: protecting drugs from being degraded in the body before they reach their target, enhancing uptake of drugs into tumor, allowing for better control over the timing and distribution of drugs to tumor tissue, and preventing drugs from interacting with normal cells thus decreasing the toxicities.

Adenocarcinoma of pancreas is the fourth most common cause of cancer-related death among United States men and women, and the seventh leading cause of cancer mortality worldwide, causing more than 300000 deaths globally every year<sup>[2]</sup>. Due to lack of specific symptoms and effective screening modality, about 80% of cases are diagnosed at an advanced stage with locally advanced or metastatic disease. Surgery remains the only curative therapy; however, most patients die within two years of diagnosis, and the 5-year survival rate is less than 5%<sup>[3]</sup>.

Gemcitabine was approved for advanced pancreatic adenocarcinoma in late 1990. Further studies have confirmed a 2-wk gain of overall survival (OS) by adding erlotinib, a tyrosine kinase inhibitor of epidermal growth factor receptor, to gemcitabine<sup>[4]</sup>, and a 7-wk gain of survival with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine vs gemcitabine<sup>[5]</sup>. The combination of 5-fluorouracil (5-FU), leucovorin (LV), irinotecan, and oxaliplatin (FOLFIRINOX) has also demonstrated improved overall

survival by 4 to 5 mo vs gemcitabine alone in a phase III study (ACCORD11/PRODIGE4) involving more than 340 patients with metastatic pancreatic cancer<sup>[6]</sup>. In October 2015, nanoliposomal irinotecan (nal-IRI, MM-398) has been approved by the United States Food and Drug Administration (FDA) to be used in combination with 5-FU and LV in patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Carbohydrate antigen 19-9 (CA 19-9) is currently used as a marker for following patients during treatment for pancreatic adenocarcinoma. Only about 80% to 85% of patients with pancreatic adenocarcinoma can demonstrate an elevated CA 19-9 level<sup>[7]</sup>. Retrospective analyses of clinical trials have shown that pretreatment serum CA 19-9 concentration is an independent prognostic factor for survival. In patients with advanced pancreatic cancer receiving either gemcitabine or gemcitabine and capecitabine, median OS for patients with baseline CA 19-9 level  $\geq$  the median value [ $59 \times$  upper limit of normal (ULN)] was significantly shorter than that for patients whose baseline CA 19-9 level  $<$  median (5.8 mo vs 10.3 mo,  $P < 0.0001$ )<sup>[8]</sup>. Retrospective analysis of CA 19-9 decrease in patients with metastatic pancreatic adenocarcinoma treated with FOLFIRINOX or gemcitabine in ACCORD11/PRODIGE4 indicated that an 8-wk CA 19-9 decrease  $\geq 20\%$  was correlated with an improved OS compared to an 8-wk CA 19-9 decrease  $< 20\%$  (10.3 mo vs 7.8 mo,  $P = 0.002$ )<sup>[9]</sup>.

Here, we have reviewed the mechanism of action and clinical studies of the 2 United States FDA approved nanomedicines in pancreatic adenocarcinoma and the utility of biomarkers such as CA 19-9 in correlation with clinical outcomes and population pharmacokinetic studies in different ethnic groups. Furthermore, we have examined ongoing investigations incorporating novel agents with nab-paclitaxel and gemcitabine platform. We have also looked back at previous nanomedicines studied in pancreatic adenocarcinoma.

## NANOPARTICLE ALBUMIN-BOUND PACLITAXEL

### *Mechanism of action and SPARC*

Nanoparticle albumin-bound paclitaxel (Nab-paclitaxel) is a Cremophor EL-free, albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers, and is the first in its class of biologically interactive albumin-bound forms of chemotherapy<sup>[10]</sup>. This formulation results in enhanced intra-tumoral concentration of paclitaxel by a receptor-mediated transport process. This albumin-specific receptor mediated process involves the binding of a specific receptor, gp60, on the endothelial cell wall, yielding the activation of a protein caveolin-1, which initiates an opening in the endothelial wall with transport

of the albumin-bound chemotherapeutic complex to the underlying tumor interstitium<sup>[11]</sup>.

Secreted protein acidic and rich in cysteine (SPARC), a calcium-binding glycoprotein also known as osteonectin, is a nonstructural matricellular protein, secreted by the tumor and involved in cell-matrix interaction during tissue remodeling, embryonic development, cell migration, and angiogenesis<sup>[12]</sup>. SPARC has an affinity for binding albumin<sup>[13]</sup>. It has been postulated that SPARC binds and entraps the albumin, and may help to accumulate nab-paclitaxel inside tumor interstitium, allowing release of the hydrophobic drug to the tumor cell membrane. The transport of nab-Paclitaxel *via* this gp-60/caveolin-1/caveolae/SPARC pathway potentially increases intratumoral concentration of drug while reducing toxicity to normal tissue. Preclinical studies comparing nab-paclitaxel to paclitaxel demonstrated lower toxicities, with a maximum tolerated dose approximately 50% higher for nab-paclitaxel compared to paclitaxel. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma<sup>[14]</sup>.

Overexpression of SPARC in many cancer types such as squamous cell carcinoma of head and neck, esophageal and urothelial cancers is associated with poor prognosis<sup>[15]</sup>. Interestingly, in certain tumor types such as non-small cell lung cancer and pancreatic adenocarcinoma, strong expression of SPARC has been detected predominantly in the stroma adjacent to the cancer cells<sup>[16,17]</sup>. In a retrospective analysis of patients with resectable pancreatic adenocarcinoma, Infante *et al.*<sup>[18]</sup> found that the presence of SPARC in stromal fibroblasts was associated with worse OS and the presence of SPARC in tumor cells did not significantly impact OS. A subgroup analysis from CONKO-001, a phase III trial showing improved survival from adjuvant gemcitabine therapy in patients with resectable pancreatic adenocarcinoma, confirmed the prognostic significance of SPARC expression after resection of pancreatic cancer; however, the negative prognostic impact was restricted to patients who received adjuvant treatment with gemcitabine, suggesting SPARC as a predictive marker for response to gemcitabine<sup>[19]</sup>.

In preclinical studies of combination of nab-paclitaxel and gemcitabine in mice bearing human tumor xenograft, nab-paclitaxel depleted the desmoplastic stroma of pancreatic adenocarcinoma, and increased intratumoral concentration of gemcitabine by 2.8-fold when compared to gemcitabine alone<sup>[20]</sup>. Moreover, nab-paclitaxel reduced the levels of cytidine deaminase protein in cultured tumor cells through reactive oxygen species-mediated degradation, resulting in the increased stabilization and levels of gemcitabine<sup>[21]</sup>. Early-phase clinical studies of nab-paclitaxel and gemcitabine in metastatic pancreatic adenocarcinoma have shown that overexpression of SPARC correlated

with increased RR and OS<sup>[20]</sup>.

### **MPACT trial and analyses of biomarkers**

A randomized phase III study, MPACT, in 861 patients with metastatic pancreatic adenocarcinoma has demonstrated an increased median OS with nab-paclitaxel plus gemcitabine vs gemcitabine (8.5 mo vs 6.7 mo,  $P < 0.001$ )<sup>[5]</sup>. For patients who received nab-paclitaxel/gemcitabine vs gemcitabine, the median progression-free survival (PFS) was 5.5 mo compared to 3.7 mo ( $P < 0.001$ ), and the overall RR was 23% vs 7% ( $P < 0.001$ ), respectively. Patients who received nab-paclitaxel/gemcitabine had more grade 3 or higher toxicities in neutropenia, fatigue, and neuropathy but similar incidences of grade 3 toxicities in anemia and thrombocytopenia, when compared with gemcitabine.

Retrospective analysis of SPARC levels in the phase III MPACT trial showed no association between stromal SPARC level and OS in either treatment arm. Neither tumor epithelial SPARC nor plasma SPARC was associated with OS<sup>[22]</sup>. This exploratory analysis does not support making treatment decisions regarding nab-paclitaxel plus gemcitabine or gemcitabine alone in metastatic pancreatic adenocarcinoma based on SPARC expression.

Goldstein *et al.*<sup>[23]</sup> have performed a post hoc analysis of the MPACT trial with data collected by May 9, 2013. In this extended follow-up study, they found that the median OS for nab-paclitaxel plus gemcitabine group was more than 2 mo longer than gemcitabine alone (8.7 mo vs 6.6 mo, HR = 0.72,  $P < 0.001$ ); 4% of nab-paclitaxel plus gemcitabine compared to 0% of gemcitabine alone survived more than 36 mo. They further identified baseline CA 19-9 level and neutrophil-to-lymphocyte ratio (NLR) as prognostic markers for OS. An elevated NLR, which is a marker of systemic inflammation, has been associated with angiogenesis and metastasis resulting in adverse outcomes in many solid tumor malignancies including pancreatic cancer<sup>[24]</sup>. Retrospective analyses have demonstrated baseline NLR greater than five predicts worse OS in patients with advanced pancreatic cancer receiving palliative chemotherapy<sup>[25-27]</sup>. In the pooled treatment arm analysis of the MPACT trial, 543 patients with baseline NLR  $\leq 5$  had a significantly longer OS than 309 patients whose baseline NLR  $> 5$  (9.1 mo vs 5.0 mo, HR = 1.839,  $P < 0.001$ ). In patients with baseline NLR  $\leq 5$ , better OS was noted in the nab-paclitaxel and gemcitabine group compared to gemcitabine alone (10.9 mo vs 7.9 mo, HR = 0.67,  $P < 0.001$ ); however, there was no significant OS difference in patients whose baseline NLR  $> 5$ , treated with nab-paclitaxel plus gemcitabine or gemcitabine alone (5.6 mo vs 4.3 mo, HR = 0.81,  $P = 0.079$ ).

The median baseline CA 19-9 level for all patients in MPACT trial was 2470 U/mL; 15% of patients had normal baseline CA 19-9 level, and 52% of patients had baseline CA 19-9 level  $\geq 59 \times$  ULN, equally distributed between 2 treatment arms. In patients with

**Table 1** Selected ongoing trials with nab-paclitaxel in pancreatic adenocarcinoma

Trial	Trial phase	Treatment regimen	Primary endpoint	Planned patients number
NCT01964430 (APACT) after resection	III	Adjuvant nab-paclitaxel and gemcitabine <i>vs</i> gemcitabine alone	Disease-free survival	800
NCT02562716 (SWOG 1505) in resectable disease	II	Perioperative nab-paclitaxel and gemcitabine <i>vs</i> FOLFIRINOX	2-yr overall survival	112
NCT02047513 (NEONAX) in resectable disease	II	Perioperative nab-paclitaxel and gemcitabine <i>vs</i> adjuvant nab-paclitaxel and gemcitabine	Disease-free survival	166
NCT01921751 (RTOG 1201) in locally advanced disease	II	Upfront nab-paclitaxel and gemcitabine followed by standard <i>vs</i> high intensity radiation	2-yr overall survival	346
NCT02301143 (LAPACT) in locally advanced disease	II	Upfront treatment with nab-paclitaxel and gemcitabine	Time to treatment failure	110
NCT02436668 (RESOLVE) in metastatic disease	III	1 <sup>st</sup> -line with nab-paclitaxel and gemcitabine $\pm$ ibrutinib	Progression-free survival	326
NCT02715804 (HALO-301) in metastatic disease	III	1 <sup>st</sup> -line with nab-paclitaxel and gemcitabine $\pm$ PEGPH20	Progression-free and overall survival	420
NCT02399137 (CARRIE) in metastatic disease	II	1 <sup>st</sup> -line with nab-paclitaxel and gemcitabine $\pm$ istiratumab	Progression-free survival	260
NCT02551991 in metastatic disease	II	1 <sup>st</sup> -line nab-paclitaxel and gemcitabine, <i>vs</i> nal-IRI/LV/5-FU $\pm$ oxaliplatin	Progression-free survival rate at 24 wk	168

a baseline CA 19-9 level  $\geq$  median, the nab-paclitaxel plus gemcitabine arm had a significantly longer OS than the gemcitabine arm (HR = 0.612,  $P < 0.001$ ). In the gemcitabine arm, OS was longer in patients whose baseline CA 19-9 level  $<$  median compared to patients whose baseline CA 19-9 level  $\geq$  median (HR = 0.773,  $P = 0.001$ ); however OS was similar regardless of baseline CA 19-9 level in patients treated with nab-paclitaxel and gemcitabine. A higher proportion of patients with baseline CA 19-9 level  $\geq 59 \times$  ULN survived 2 years or longer in the nab-paclitaxel and gemcitabine group than in the gemcitabine group (55% *vs* 15%). Thus, nab-paclitaxel may reduce the negative impact of elevated baseline CA 19-9 level on OS for patients with metastatic pancreatic adenocarcinoma receiving nab-paclitaxel and gemcitabine as upfront treatment.

Chiorean *et al.*<sup>[28]</sup> further examined the CA 19-9 decrease at 8 wk as a predictor of OS in the MPACT study. Combining both treatment arms for analysis, patients with any CA 19-9 decline *vs* those without (20% of combined treatment patients) had improved OS (median 11.1 mo *vs* 8.0 mo,  $P = 0.005$ ). In the nab-paclitaxel plus gemcitabine arm, patients with *vs* without (18% of this treatment arm) any CA 19-9 decrease at week 8 had a confirmed overall RR of 40% *vs* 13%, and a median OS of 13.2 mo *vs* 8.3 mo ( $P = 0.001$ ), respectively. In the gemcitabine arm, patients with *vs* without (21% of this treatment arm) CA 19-9 decrease at week 8 had a confirmed ORR of 15% *vs* 5%, and median OS of 9.4 mo *vs* 7.1 mo ( $P = 0.404$ ), respectively. This analysis demonstrated that in patients with pancreatic adenocarcinoma receiving nab-paclitaxel and gemcitabine as front-line treatment, any CA 19-9 decrease at week 8 can be a predictive marker for chemotherapy efficacy and improved clinical outcomes including survival benefit.

### Current investigation

Nab-paclitaxel and gemcitabine is currently under active investigation in neoadjuvant and adjuvant settings for patients with resectable pancreatic adenocarcinoma (Table 1). Furthermore, many studies in different phases have explored the combination of novel therapeutics with nab-paclitaxel/gemcitabine in the metastatic setting. These novel agents include Bruton tyrosine kinase inhibitor (ibrutinib, NCT02436668), pegylated recombinant human hyaluronidase (PEGPH20, NCT02715804), antibody against programmed death receptor 1 (PD-1) (nivolumab, NCT02309177), cancer stemness inhibitor (BB1-608, NCT02231723), phosphatidylinositol 3-kinase (PI3K) inhibitor (BYL719, NCT02155088), antibody against IGF-1R and ErbB3 (istiratumab, NCT02399137), *etc.* The combination of nab-paclitaxel and gemcitabine has become the platform of research for combining targeted agents in advancing the management of pancreatic adenocarcinoma.

PEGPH20 removes hyaluronan or hyaluronic acid (HA). HA is a glycosaminoglycan, which is the major component of extracellular matrix. Many solid tumors including pancreatic adenocarcinoma, have been shown to secrete high levels of HA, which can lead to unusually elevated interstitial fluid pressure collapsing the tumor's blood vessels. This in turn attenuates the delivery of chemotherapeutic agents into tumor tissues<sup>[29]</sup>. In preclinical studies, PEGPH20 removed HA from tumors, reduced tumor interstitial fluid pressure, and enhanced the effects of chemotherapy in mouse models of pancreatic adenocarcinoma<sup>[30,31]</sup>.

In a randomized phase II study in metastatic pancreatic adenocarcinoma investigating nab-paclitaxel/gemcitabine with or without PEGPH20 as a first-line therapy, patients with HA-high tumors showed significant improvement in PFS and a trend toward



improved OS after receiving nab-paclitaxel/gemcitabine and PEGPH20 combination<sup>[32]</sup>. This study enrolled 135 patients, 74 received the 3-drug combination while 61 received nab-paclitaxel and gemcitabine. Forty-four patients had HA-high tumors; PFS was 9.2 mo in 23 patients treated with the 3-drug combination vs 4.3 mo in 21 patients treated with nab-paclitaxel/gemcitabine (HR = 0.39,  $P = 0.05$ ). The global phase III study has been launched in early 2016 to assign patients with HA-high metastatic pancreatic adenocarcinoma to nab-paclitaxel/gemcitabine with or without PEGPH20 as first-line treatment (NCT02715804).

## NANOLIPOSOMAL IRINOTECAN (NAL-IRI, PEP02, MM-398)

### **Mechanism of action**

Irinotecan has a complicated pharmacology that causes it to have a narrow therapeutic index. Irinotecan exists in a pH and serum protein dependent equilibrium between the active lactone form (stable in acidic pH) and the inactive carboxylate form (stable in neutral to basic pH)<sup>[33]</sup>. Therefore, in normal physiologic pH, the lactone form rapidly hydrolyzes and is inactivated. This instability of the active drug molecule at physiological pH is a major obstacle in attaining efficacy. Moreover, only a small fraction of irinotecan is converted to its more potent metabolite SN-38, which requires metabolism by carboxylesterases (CES) in the liver with variability among patients. It has been shown that more than 50% of pancreatic adenocarcinoma express CES, and high CES2 expression in tumor tissue was associated with longer overall survival in resectable and borderline resectable patients who underwent neoadjuvant FOLFIRINOX treatment<sup>[34]</sup>.

SN-38 is eliminated by the biliary system, after glucuronidation from the uridine diphosphate glucuronosyl-transferase (UGT)1A1 enzyme. The glucuronidated SN-38 can be converted back to SN-38 by beta-glucuronidase enzymes secreted from the intestinal flora in the gut. Retrospective analyses have demonstrated that individuals who are homozygous for UGT1A1\*28 are at an increased risk of developing irinotecan-related neutropenia and diarrhea toxicities<sup>[35,36]</sup>. This UGT1A1\*28 polymorphism is characterized by the presence of an additional TA repeat in the TATA sequence of the UGT1A1 promoter, causing markedly decreased expression of UGT1A1, which leads to slower SN-38 glucuronidation, and a greater SN-38 plasma concentration over time. It is estimated that about 10% of Caucasians may be homozygous for UGT1A1\*28, and the prevalence is lower in Asians. Other variants have been reported and characterized; UGT1A1\*6 which occurs at exon 1 and reduces catalytic function of UGT1A1 by 60% is more commonly seen in Asians and can cause severe neutropenia after irinotecan treatment<sup>[37]</sup>.

In an attempt to overcome these pharmacological limitations of irinotecan with the goals of improved

efficacy and decreased toxicity, nal-IRI was developed<sup>[38]</sup>. This is a novel formulation that encapsulates irinotecan in an approximately 100 nm spherical liposome with high drug load (approximately 80000 molecules of irinotecan per liposome) and high stability that surpasses previously developed liposomal formulations (including liposomal anthracyclines). This is done using novel gradient based drug loading technology with a highly charged, nonpolymeric anion sucrose octasulfate. The liposome formulation allows for protection of irinotecan in its lactone form from hydrolysis in the serum until it reaches the tumor site. The end result of this nanoliposomal formulation on irinotecan pharmacology is slower drug elimination, lower plasma concentration, and enhanced accumulation of the drug into the tumor site. The formulation of nal-IRI has been shown to improve the pharmacokinetics and tumor bio-distribution of both irinotecan and its active metabolite SN-38 with less toxicity in mouse xenograft study<sup>[39-41]</sup>. Moreover, nal-IRI demonstrated increased efficacy compared to free irinotecan in pancreatic cancer xenograft study<sup>[42]</sup>.

### **Clinical studies**

The first-in-human phase I study conducted in advanced refractory solid tumors confirmed the favorable pharmacokinetics of the liposomal formulation of irinotecan<sup>[43]</sup>. The maximum tolerated dose (MTD) of nal-IRI intravenously for 90 min every 3 wk was 120 mg/m<sup>2</sup> (equivalent to 100 mg/m<sup>2</sup> of free irinotecan); the toxicity profile remained similar to that of free-form irinotecan, with diarrhea and myelosuppression being the dose limiting toxicities. This study observed slow release of irinotecan from liposomes, small volume of distribution in plasma, slow clearance, prolonged terminal half-life of circulating total irinotecan, and a favorable pharmacokinetics of the active metabolite SN-38. Two patients achieved partial response, including one patient with pancreatic cancer who failed prior gemcitabine-based treatment. This promising result was further observed in another phase I trial in advanced solid tumors studying dose-escalating nal-IRI in combination with weekly 24-h infusion of high-dose LV/5-FU<sup>[44]</sup>. The MTD of nal-IRI in combination with weekly 24-h infusion of high-dose LV/5-FU given every-3-wk was 80 mg/m<sup>2</sup> (equivalent to 70 mg/m<sup>2</sup> free irinotecan). In these two phase I trials, 7 pancreatic cancer patients who failed gemcitabine-based regimen received nal-IRI with or without weekly 24-h infusion of high-dose LV/5-FU. There was 1 patient with partial response, 4 patients with stable disease, and 2 patients with progressive disease. This indicated a potential activity of nal-IRI as a second-line treatment in patients with gemcitabine-refractory advanced pancreatic adenocarcinoma<sup>[45]</sup>.

Based on the promising activity from phase I and preclinical studies, a phase II study of nal-IRI was conducted in 40 patients with metastatic pancreatic

adenocarcinoma following progression on gemcitabine-based therapy<sup>[46]</sup>. Patients were given nal-IRI 120 mg/m<sup>2</sup> every 3 wk with a primary end point of 3-mo OS. The study met its primary endpoint with 75% of patients surviving at least 3 mo and 25% reaching 1 year. The median PFS was 2.4 mo and OS was 5.2 mo. Three patients (7.5%) achieved an objective response, with an additional 17 (42.5%) demonstrating stable disease. Ten (31.3%) of 32 patients with an elevated baseline CA 19-9 had a > 50% biomarker decline. In terms of safety, nal-IRI was generally well tolerated with gastrointestinal and hematologic toxicities being the most common toxicities, as well as fatigue and abdominal pain. Twenty-six patients (65%) experienced at least one grade 3 or higher adverse event. Dose modification due to adverse events was required in 11 patients (27.5%). The results implied the feasibility and activity of nal-IRI in gemcitabine-refractory advanced pancreatic adenocarcinoma.

The combination of nal-IRI and LV/5-FU was compared to free-form irinotecan and LV/5-FU (FOLFIRI) in a multicenter, open-label, noncomparative, randomized phase II study (PEPCOL) as second-line treatment in patients with metastatic colorectal cancer<sup>[47]</sup>. Patients who had failed one prior oxaliplatin-based first-line therapy were randomized to every 14-d FOLFIRI or nal-IRI with LV/5-FU (nal-IRI 80 mg/m<sup>2</sup> IV over 90 min, followed by LV 400 mg/m<sup>2</sup> iv over 2 h, then 5-FU 2400 mg/m<sup>2</sup> continuous infusion over 46 h). Bevacizumab (5 mg/kg every 14 d) was allowed in both arms. The primary endpoint was 2-mo response rate (RR). Fifty-five patients were randomized (FOLFIRI, *n* = 27; nal-IRI/LV/5-FU, *n* = 28), and the 2-mo RR was 7.4% and 10.7% in the FOLFIRI and nal-IRI/LV/5-FU, respectively. The most common grade 3-4 adverse events reported in the FOLFIRI and nal-IRI/LV/5-FU were diarrhea (33% vs 21%), neutropenia (30% vs 11%), mucositis (11% vs 11%), and grade 2 alopecia (26% vs 25%). The results of the PEPCOL study suggested that the nal-IRI/LV/5-FU regimen was more active than the standard FOLFIRI regimen in patients with oxaliplatin-pretreated metastatic colorectal cancer with an acceptable safety profile. Based on the preliminary results of the PEPCOL study, the nal-IRI/LV/5-FU combination regimen was added as the third arm of the phase III NAPOLI-1 study in metastatic pancreatic cancer.

The pivotal NAPOLI-1 study was an open label, randomized, international phase III study that enrolled 417 patients across 76 sites in 14 countries worldwide<sup>[48]</sup>. In version 1 of the protocol, it assigned patients with metastatic pancreatic adenocarcinoma that progressed on first-line gemcitabine-based therapy in a 1:1 ratio to receive either nal-IRI 120 mg/m<sup>2</sup> alone over 90 min every 3 wk, or the control arm with LV 200 mg/m<sup>2</sup> infused over 30 min followed by 5-FU 2000 mg/m<sup>2</sup> over 24 h, every week for the first 4 wk of each 6-wk cycle. Sixty-three patients were enrolled on version 1 of the protocol: 33 in nal-

IRI and 30 in the control arm. After the PEPCOL study demonstrated the feasibility of nal-IRI/LV/5-FU (nal-IRI 80 mg/m<sup>2</sup> IV over 90 min, followed by LV 400 mg/m<sup>2</sup> IV over 2 h, then 5-FU 2400 mg/m<sup>2</sup> continuous infusion over 46 h, every 14 d), this combination regimen was added as a third arm in version 2 of the protocol. There were 117 patients assigned to nal-IRI/LV/5-FU, 119 patients assigned to the control arm, and 118 patients assigned to nal-IRI alone on version 2 of the protocol. For all the efficacy comparisons, the 117 patients assigned to the combination arm were compared to 119 patients assigned to the control arm on version 2 of the protocol, whereas patients assigned to nal-IRI were compared to the control arm under both version 1 and 2 of the protocol. It demonstrated a statistically significant increase in OS for the combination of nal-IRI/LV/5-FU (6.1 mo) vs the control arm (4.2 mo) (HR=0.57, 95%CI: 0.41-0.80, and *P* = 0.0009).

The objective RR was 7.7% vs 0.8%, for the combination and control, respectively. For those with baseline CA 19-9 levels of > 30 U/mL at baseline (84% in the combination arm), there was a ≥ 50% reduction in the marker for 29% of patients treated with the nal-IRI/LV/5-FU vs 9% in the control arm (*P* = 0.0006). Nal-IRI monotherapy did not demonstrate superior efficacy compared with LV/5-FU. The rates of diarrhea were 12.8% vs 21.1% and the rates of vomiting were 11.1% vs 13.6% for the nal-IRI combination vs single-agent, respectively. Additionally, febrile neutropenia occurred in 1.7% of patients in the combination arm compared with 4.1% with nal-IRI alone, and not at all with the control arm. Nal-IRI alone was associated with more adverse events compared with the nal-IRI/LV/5-FU, indicating that nal-IRI should only be used in combination with LV/5-FU in pancreatic adenocarcinoma.

An expanded analysis was conducted in the per-protocol population, which was defined as patients who received ≥ 80% of the protocol defined dose and were able to remain on treatment for at least 6 wk<sup>[49]</sup>. This analysis further validated the initial data results with a median OS of 8.9 mo for the combination arm vs 5.1 mo for the control (HR = 0.47 95%CI: 0.29-0.77, and *P* = 0.0018). Moreover, there was a significant increase in PFS (overall and at 3 mo), overall RR, and CA 19-9 response for the combination vs the control. The safety profile was manageable with most frequent grade 3 or 4 adverse effects being neutropenia, fatigue, and GI effects (diarrhea and vomiting) in the combination arm. Based on the NAPOLI-1, nal-IRI in combination with 5-FU/LV has been approved by United States FDA in October 2015 for patients with metastatic pancreatic adenocarcinoma who have progressed from gemcitabine-based treatment.

An open-label phase II comparative study is currently underway to explore the safety and efficacy of adding oxaliplatin to nal-IRI/LV/5-FU as 1<sup>st</sup>-line treatment in metastatic pancreatic adenocarcinoma

**Table 2** Selected nanomedicines studied in clinical trials for pancreatic adenocarcinoma

Nanomedicine	Nanoplatfrom	Status	Reference/trial information
Nanoplatin (NC-6004)	Polymeric nanoparticle (PEG-polyaspartate) of cisplatin	Phase III on going in advanced disease as 1 <sup>st</sup> -line; 290 patients expected	NCT02043288; gemcitabine ± NC6004
EndoTAG-1	Cationic liposome encapsulated paclitaxel	Phase II (with gemcitabine <i>vs</i> gemcitabine) published in 2012	Löhr <i>et al</i> <sup>[56]</sup> 2012/NCT00377936
Genexol-PM	Methoxy-PEG-poly(D,L-lactide) based formulation of paclitaxel	Phase II monotherapy published in 2010	Saif <i>et al</i> <sup>[65]</sup> 2010/NCT00111904
Rexin-G	Pathotropic nanoparticle with cytotoxic cyclin G1 construct	Phase I / II monotherapy published in 2010	Chawla <i>et al</i> <sup>[66]</sup> 2010/NCT00504998
Lipoplatin	Liposomal formulation of cisplatin	Phase I / II (with gemcitabine) published in 2006	Stathopoulos <i>et al</i> <sup>[67]</sup> 2006
Caelyx/Doxil	Liposomal formulation of doxorubicin	Phase II monotherapy published in 1995 and 2001	Schwartz <i>et al</i> <sup>[68]</sup> 1995; Halford <i>et al</i> <sup>[69]</sup> 2001

(NCT02551991)<sup>[50]</sup>. This study will initiate part 1 as a safety and tolerability run-in of nal-IRI/LV/5-FU/LV and oxaliplatin combination. About 6 to 18 patients are enrolled on a traditional dose escalation design to confirm the target dose of oxaliplatin. Part 2 is a randomized, efficacy study to assign approximately 160 patients to 3 treatment arms: (1) nal-IRI/LV/5-FU and oxaliplatin; (2) nal-IRI/LV/5-FU; and (3) nab-paclitaxel and gemcitabine (control arm). The primary endpoint is PFS rate at 24 wk, and secondary endpoints are OS, PFS, and RR. Additionally, pharmacokinetic data will be collected in part 1 of the study.

#### Analyses of biomarker and pharmacokinetics

A biomarker analysis at the 2016 ASCO GI Cancers Symposium looked specifically at the impact of CA 19-9 levels on the efficacy in NAPOLI-1<sup>[51]</sup>. In this analysis, there was a greater treatment effect from nal-IRI/LV/5-FU on OS with higher CA 19-9 level relative to the control 5-FU/LV. Median OS was similar between the nal-IRI/LV/5-FU combination arm and the control for those with CA 19-9 levels < 120 U/mL (7.6 mo *vs* 7.2 mo; HR = 1.12). As CA 19-9 levels increased, the benefit with nal-IRI combination became more dramatic. In those with CA 19-9 levels ≥ 12815 U/mL, median OS was 4.6 *vs* 1.9 mo in the nal-IRI/LV/5-FU (*n* = 26) *vs* the control arm (*n* = 26; HR = 0.35; 95%CI: 0.19-0.64). The CA 19-9 serum level provided important information with regards to overall survival in NAPOLI-1.

The population pharmacokinetics and exposure-safety relationship of nal-IRI were evaluated in 353 patients with advanced solid tumors receiving nal-IRI 60-120 mg/m<sup>2</sup> on 6 clinical studies<sup>[52]</sup>. Both age (28 to 87 years) and gender after adjusting for body surface area (BSA) had no clinically meaningful effect on the exposure of irinotecan and SN-38. Mild-to-moderate renal impairment had no effect on the exposure of total SN-38 after adjusting for BSA. SN-38 maximum plasma concentration (C<sub>max</sub>) was associated with incidence of severe neutropenia and anemia (grade 3 or higher), and IRI C<sub>max</sub> was associated with incidence of severe

diarrhea (grade 3 or higher). Compared to Caucasians, Asians had a 0.5-fold lower IRI C<sub>max</sub>, corresponding to a 5% lower predicted severe diarrhea. In contrast, Asians had a 1.5-fold higher SN-38 C<sub>max</sub> than Caucasians, corresponding to a 7% higher predicted severe neutropenia. Compared to patients with bilirubin < 1 mg/dL, patients with bilirubin 1-2 mg/dL had a 1.4-fold higher SN-38.

#### OTHER NANOMEDICINES

We have summarized 6 frequently mentioned nanomedicines that have been clinically studied in pancreatic adenocarcinoma (Table 2). Among these 6 compounds, only nanoplatin (NC-6004) is still under active investigation in pancreatic adenocarcinoma. Nanoplatin is a novel cisplatin-incorporating polymeric micelle formulation that retains the activity but avoids the renal toxicity and neurotoxicity caused by the high peak C<sub>max</sub> concentrations of cisplatin<sup>[53,54]</sup>. A phase I / II trial of nanoplatin in combination with gemcitabine in patients with advanced pancreatic adenocarcinoma was conducted in Asia and reported in 2012 ESMO congress. Among 19 patients enrolled, partial response was found in 1 (5.9%) and stable disease in 10 (58.8%) patients; the disease control rate was 64.7%. The combination of nanoplatin and gemcitabine was well tolerated and demonstrated modest efficacy in patients with advanced pancreatic adenocarcinoma. Therefore a phase III study in advanced pancreatic adenocarcinoma comparing nanoplatin with gemcitabine *vs* gemcitabine alone as front-line therapy was launched in 2014 with expected accrual of 290 patients and completion in 2017.

EndoTAG-1 is a formulation in which paclitaxel is embedded in a cationic liposome membrane. The positively charged liposomes have a high affinity to the endothelial cells of tumor blood vessels, leading to selective targeting and delivery of paclitaxel to the tumor microenvironment<sup>[55]</sup>. An open-label, randomized, controlled multicenter phase II trial was conducted in order to evaluate the safety and efficacy of EndoTag-1 in treatment naïve patients with locally

advanced or metastatic pancreatic adenocarcinoma<sup>[56]</sup>. Two hundred and twelve patients were randomly assigned to one of four treatment arms: gemcitabine monotherapy or a combination of gemcitabine and EndoTAG-1 administered at 3 different dose levels: 11 mg/m<sup>2</sup> (Endo11), 22 mg/m<sup>2</sup> (Endo22) and 44 mg/m<sup>2</sup> (Endo44). Median overall survival rates were higher in the combination arms at 8.1 mo for Endo11 (HR = 0.93), 8.7 mo for Endo22 (HR = 0.69), and 9.3 mo for Endo44 (HR = 0.66) vs 6.8 mo for gemcitabine alone. Similarly, PFS times were longer in the combination arms with PFS of 4.1 mo for Endo11 (HR = 0.84), 4.6 mo for Endo22 (HR = 0.58), and 4.4 mo for Endo44 (HR = 0.74) vs 2.7 mo for gemcitabine monotherapy. The 12-mo survival rates were also higher at 21%, 35%, and 30% for Endo11, Endo22, and Endo44, respectively, compared to 15% for gemcitabine alone. In terms of safety, there were marginal additive adverse reactions in the combination groups compared to gemcitabine monotherapy. Combination therapy resulted in a dose dependent increase in the severity of thrombocytopenia as well as the frequency of infusion-related reactions (mainly pyrexia and chills). There was no evidence of clinically relevant organ toxicity or neurotoxicity or deaths relating to the study medication. Moreover, there was no cumulative toxicity of EndoTAG-1 in combination with gemcitabine after repeated treatment cycles or additive effects to gemcitabine's liver toxicity. This randomized phase II study demonstrated a better efficacy for the combination of gemcitabine and EndoTag-1 with acceptable toxicity profiles. A phase III trial has been planned to confirm these results and identify a potential role for EndoTAG-1 in combination with gemcitabine in advanced pancreatic adenocarcinoma<sup>[57]</sup>.

## CONCLUSIONS AND PLACE IN THERAPY

The systemic treatment of pancreatic adenocarcinoma remains a daunting task but improved survival has been more obvious since early 2010 when FOLFIRINOX and nab-paclitaxel/gemcitabine have become standard first-line treatment options. Since October 2015, nal-IRI/LV/5-FU has been approved as second-line therapy in advanced pancreatic adenocarcinoma after failing gemcitabine-based treatment. Retrospective analysis of MPACT trial showed second-line treatment was feasible and extended patients' survival after failing front-line therapy<sup>[58]</sup>. Patients who received any second-line therapy after progression had a median OS of 12.8 mo if their initial treatment was nab-paclitaxel and gemcitabine compared with 9.9 mo if they received gemcitabine alone in the first line setting. This has echoed the recommendation from NCCN guideline in metastatic pancreatic adenocarcinoma for patients with good performance status, *i.e.*, ECOG 0-1 with adequate pain control and nutritional status and without obstructive jaundice, to continue on systemic

treatment after failing first-line treatment. The keys to successful second-line treatment are patient selection and regimen selection. Therefore clinical trials with novel therapeutics/strategies will be ideal for patients to participate in if there is no standard of care such as progression after FOLFIRINOX. A phase II study reported by French investigators with nab-paclitaxel/gemcitabine as second-line treatment showed promising activity in patients with rapid progression (PFS less than 248 d) from FOLFIRINOX as first-line treatment<sup>[59]</sup>.

Identification of prognostic and predictive markers can personalize treatment and select patients for target-driven therapy. CA 19-9, NLR, HA and CES2 seem to provide useful predictive information for systemic treatment in pancreatic adenocarcinoma, but require perspective study to confirm. Elevated C-reactive protein (CRP) levels in the plasma at diagnosis correlate with higher tumor stage and grading and poorer clinical outcome in pancreatic adenocarcinoma<sup>[60]</sup>. The CRP level could be a useful marker for patient stratification, and the JAK inhibitor ruxolitinib may improve clinical outcome in patients with elevated CRP. An ongoing phase III study, known as JANUS 2, is examining the role of a JAK inhibitor as a second-line treatment option in patients with advanced pancreatic adenocarcinoma<sup>[61]</sup>.

A hallmark of pancreatic adenocarcinoma is the presence of a dense desmoplastic stroma that consist largely of fibroblasts, immune cells, endothelial cells, pancreatic stellate cells, extracellular matrix proteins, *etc.*<sup>[62]</sup>. This provides an excellent milieu to test novel therapeutics including nanomedicines (with EPR effect) and immune checkpoint inhibitors such as antibody against PD-1. The PD-1 is primarily expressed by activated T-cells as negative co-stimulatory receptor; binding of PD-1 to its ligands, PD-L1 and PD-L2, downregulates T-cells and the immune system<sup>[63]</sup>. Many tumor cells express PD-L1 and PD-L2 which is a mechanism which allows escape from immune destruction of the tumor cells. The combination of nanomedicine and antibody against PD-1 seems to provide a good stroma targeting effect and will be tested in pancreatic adenocarcinoma (NCT02309177)<sup>[64]</sup>.

Besides delivery through EPR effect, nanomedicines can be harnessed with targeting system to reach the malignant tissue or cells more promptly and precisely. With the advance of technology and better understanding of cancer biology, we are confident that the next-generation nanomedicines will greatly advance cancer treatment and improve patients' outcome.

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