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EDITORIAL

- 5829 Role of tissue microenvironment resident adipocytes in colon cancer
Tabuso M, Homer-Vanniasinkam S, Adya R, Arasaradnam RP

REVIEW

- 5836 Ophthalmic manifestations in patients with inflammatory bowel disease: A review
Troncoso LL, Biancardi AL, de Moraes Jr HV, Zaltman C
- 5849 Laparoscopic appendectomy for acute appendicitis: How to discourage surgeons using inadequate therapy
Hori T, Machimoto T, Kadokawa Y, Hata T, Ito T, Kato S, Yasukawa D, Aisu Y, Kimura Y, Sasaki M, Takamatsu Y, Kitano T, Hisamori S, Yoshimura T
- 5860 Long non-coding RNAs in hepatocellular carcinoma: Potential roles and clinical implications
Niu ZS, Niu XJ, Wang WH

MINIREVIEWS

- 5875 Nano albumin bound-paclitaxel in pancreatic cancer: Current evidences and future directions
Giordano G, Pancione M, Olivieri N, Parcesepe P, Velocci M, Di Raimo T, Coppola L, Toffoli G, D'Andrea MR

ORIGINAL ARTICLE

Basic Study

- 5887 Comparison between tocotrienol and omeprazole on gastric growth factors in stress-exposed rats
Nur Azlina MF, Qodriyah HMS, Chua KH, Kamisah Y
- 5895 (-)-Epigallocatechin-3-gallate enhances poly I:C-induced interferon- λ 1 production and inhibits hepatitis C virus replication in hepatocytes
Wang YZ, Li JL, Wang X, Zhang T, Ho WZ
- 5904 Effects and mechanism of adenovirus-mediated phosphatase and tension homologue deleted on chromosome ten gene on collagen deposition in rat liver fibrosis
Xie SR, An JY, Zheng LB, Huo XX, Guo J, Shih D, Zhang XL

Retrospective Study

- 5913 Integrating *TYMS*, *KRAS* and *BRAF* testing in patients with metastatic colorectal cancer
Ntavatzikos A, Spathis A, Patapis P, Machairas N, Peros G, Konstantoudakis S, Leventakou D, Panayiotides IG, Karakitsos P, Koumariou A

Clinical Trials Study

- 5925 Characterizing gastrointestinal stromal tumors and evaluating neoadjuvant imatinib by sequencing of endoscopic ultrasound-biopsies

Hedenström P, Nilsson B, Demir A, Andersson C, Enlund F, Nilsson O, Sadik R

Observational Study

- 5936 Novel predictors for lymph node metastasis in submucosal invasive colorectal carcinoma

Yim K, Won DD, Lee IK, Oh ST, Jung ES, Lee SH

- 5945 Changes with aging in gastric biomarkers levels and in biochemical factors associated with *Helicobacter pylori* infection in asymptomatic Chinese population

Shan JH, Bai XJ, Han LL, Yuan Y, Sun XF

Prospective Study

- 5954 Modified *Helicobacter* test using a new test meal and a ¹³C-urea breath test in *Helicobacter pylori* positive and negative dyspepsia patients on proton pump inhibitors

Tepeš B, Malfertheiner P, Labenz J, Aygen S

- 5962 Real time endoscopic ultrasound elastography and strain ratio in the diagnosis of solid pancreatic lesions

Okasha H, Elkholy S, El-Sayed R, Wifī MN, El-Nady M, El-Nabawi W, El-Dayem WA, Radwan MI, Farag A, El-sherif Y, Al-Gemeie E, Salman A, El-Sherbiny M, El-Mazny A, Mahdy RE

- 5969 Efficacy and safety of sofosbuvir and daclatasvir in treatment of kidney transplantation recipients with hepatitis C virus infection

Xue Y, Zhang LX, Wang L, Li T, Qu YD, Liu F

Randomized Controlled Trial

- 5977 New botanical drug, HL tablet, reduces hepatic fat as measured by magnetic resonance spectroscopy in patients with nonalcoholic fatty liver disease: A placebo-controlled, randomized, phase II trial

Jeong JY, Sohn JH, Baek YH, Cho YK, Kim Y, Kim H

Randomized Clinical Trial

- 5986 Randomized clinical trial comparing fixed-time split dosing and split dosing of oral Picosulfate regimen for bowel preparation

Jun JH, Han KH, Park JK, Seo HL, Kim YD, Lee SJ, Jun BK, Hwang MS, Park YK, Kim MJ, Cheon GJ

META-ANALYSIS

- 5994 Systematic review and meta-analysis of colon cleansing preparations in patients with inflammatory bowel disease

Restellini S, Kherad O, Bessissow T, Ménard C, Martel M, Taheri Tanjani M, Lakatos PL, Barkun AN

CASE REPORT

- 6003** Postoperative inflammation as a possible cause of portal vein thrombosis after irreversible electroporation for locally advanced pancreatic cancer

Su JJ, Su M, Xu K, Wang PF, Yan L, Lu SC, Gu WQ, Chen YL

LETTERS TO THE EDITOR

- 6007** Comment on "Efficacy and adverse events of cold *vs* hot polypectomy: A meta-analysis"

Sun HH, Huang SL, Bai Y

ABOUT COVER

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Nano albumin bound-paclitaxel in pancreatic cancer: Current evidences and future directions

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Abstract

Pancreatic cancer (PDAC) is an aggressive and chemo-resistant disease, representing the fourth cause of cancer related deaths in western countries. Majority of patients have unresectable, locally advanced or metastatic disease at time of diagnosis and the 5-year survival rate in these conditions is extremely low. For more than a decade gemcitabine has been the cornerstone of metastatic PDAC treatment, although survival benefit was very poor. PDAC cells are surrounded by an intense desmoplastic reaction that may create a barrier to the drugs penetration within the tumor. Recently PDAC stroma has been addressed as a potential therapeutic target. Nano albumin bound (Nab)-paclitaxel is an innovative molecule depleting

tumor stroma, through interaction between albumin and secreted protein acidic and rich in cysteine. Addition of nab-paclitaxel to gemcitabine has showed activity and efficacy in metastatic PDAC first-line treatment improving survival and overall response rate *vs* gemcitabine alone in the MPACT phase III study. This combination represents one of the standards of care in advanced PDAC therapy and is suitable to a broader spectrum of patients compared to other schedules. Nab-paclitaxel is under investigation as a backbone of chemotherapy in novel combinations with target agents or immunotherapy in locally advanced or metastatic PDAC. In this article, we provide an updated and critical overview about the role of nab-paclitaxel in PDAC treatment based on the latest advances in preclinical and clinical research. Furthermore, we focus on the use of nab-paclitaxel within the context of metastatic PDAC treatment landscape and we discuss about future implications in the light of current clinical ongoing trials.

Key words: Nano albumin bound-paclitaxel; Pancreatic cancer; Metastatic disease; Gemcitabine; Folfirinox

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Core tip: In this article, we provide an updated and critical overview about the role of nano albumin bound (Nab)-paclitaxel in pancreatic cancer (PDAC) treatment based on the latest advances in preclinical and clinical research. Furthermore, we focus on the use of Nab-paclitaxel within the context of metastatic PDAC treatment landscape and we discuss about future implications in the light of current clinical ongoing trials.

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INTRODUCTION

Pancreatic cancer (PDAC) is a lethal disease with an incidence rate nearly equal to its mortality and it is the fourth cause of cancer-related death worldwide^[1,2]. Five-year survival rate is about 5% and it increases to 20% in patients receiving radical surgery, chemotherapy and radiation^[3-5]. The majority of patients have locally advanced or metastatic disease at the time of diagnosis and chemotherapy represents the only curative chance, even if prognosis remains very poor^[6]. For more than a decade, gemcitabine has been the cornerstone of treatment in metastatic setting, despite of a small advantage in terms of survival^[7]. Recently, PDAC stroma has been addressed as a possible target

for novel molecules^[8,9]. PDAC is characterized by an intense desmoplastic reaction that may explain its high chemoresistance. Tumor stroma contributes to poor vascularization and high intratumoral pressure resulting in reduced drugs penetration within cancer cells^[10,11]. Among stromal components, secreted protein acidic and rich in cysteine (SPARC) has been investigated as a potential therapeutic target because of its involvement in PDAC cells proliferation, migration, metastasization and escape mechanisms^[12-15]. Nano albumin bound (Nab)-paclitaxel is an innovative molecule obtained by the combination of paclitaxel with nano-particles of albumin^[16]. SPARC binds albumin and it has been postulated that "nab-technology" may enhance selective delivery and uptake of paclitaxel in cancer cells^[17]. Following the results of the MPACT phase III study, nab-paclitaxel in combination with gemcitabine has become a standard of care in metastatic PDAC first-line therapy^[18]. Accordingly, this doublet represents also a valid backbone for the new developing schedules. In this paper, we will focus on molecular structure, mechanism of action, preclinical data, clinical studies and future perspectives regarding nab-paclitaxel in PDAC treatment.

NAB-PACLITAXEL: MOLECULAR STRUCTURE AND MECHANISM OF ACTION

Nab-paclitaxel (ABI 007 or Abraxane[®]; Celgene) is a 130-nm, albumin-bound, formulation of paclitaxel without any solvents or ethanol^[19]. The Cremophor[®] EL free formulation reduces the incidence of infusion adverse reactions and makes premedication with steroids not necessary^[19]. This agent is prepared by homogenization of human serum albumin at 3%-4% concentration with paclitaxel^[20]. Nab-paclitaxel particles have a reduced diameter that enhances intracellular paclitaxel delivery and thus higher antitumor activity^[21]. This molecule has a greater distribution volume, higher concentration and a faster clearance than conventional paclitaxel^[22]. After administration of equal doses of nab-paclitaxel and radiolabeled paclitaxel-cremophor to MX-1 xenograft athymic mice, nab-paclitaxel had a more rapid tumor uptake. This resulted in overall increase in the area under the curve and a more effective intratumoral accumulation of nab-paclitaxel compared to paclitaxel-cremophor^[23]. Preclinical studies have shown that albumin facilitates transport of paclitaxel across endothelial cells through the gp60 albumin receptor/caveolin-1 pathway (Figure 1). Notably, endothelial transcytosis of nab-paclitaxel was inhibited by methyl β -cyclodextrin, a gp60/caveolin-1 transport inhibitor. *In vitro*, a significant 9.9 times increase of nab-paclitaxel binding to the endothelial cells of human umbilical vein compared to conventional paclitaxel was recorded. Accordingly, a 4.2 times increased endothelial transcytosis of paclitaxel linked

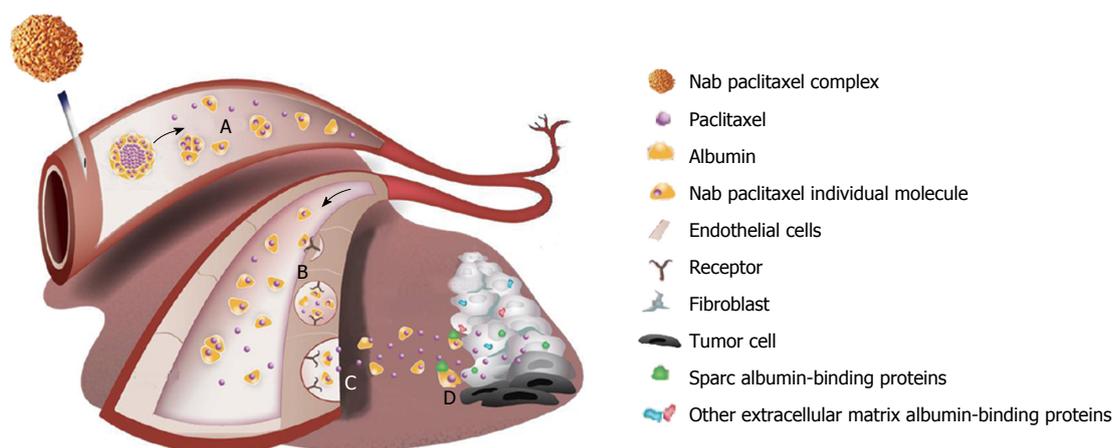


Figure 1 Nab-paclitaxel mechanism of action. A: After intravenous administration nab-paclitaxel is carried through bloodstream; B: Nab-paclitaxel binds gp60 albumin receptor on the endothelial cell; C: Endothelial transcytosis of nab-paclitaxel through the gp60 albumin receptor/caveolin - 1 pathway; D: Interaction between SPARC and nab-paclitaxel both on the pancreatic cancer cells and stromal fibroblasts. SPARC: Secreted protein acidic and rich in cysteine.

to nano-particles of albumin was demonstrated^[22,24]. Furthermore, passive transport through permeable peritumoral vessels could have a role in paclitaxel delivery to cancer cells^[25]. Peculiar and tumor-selective mechanism of action may be partially elucidated by interactions between SPARC and albumin (Figure 1). SPARC is an albumin-binding glycoprotein, also known as osteonectin, overexpressed in different types of tumor such as breast, lung, PDAC and melanoma^[26]. SPARC is expressed both in PDAC stroma and tumor cells, representing a potential target for nab-paclitaxel mechanism of action^[26]. Nevertheless, preclinical data on engineered mouse models (KPC models) demonstrated that SPARC had no role in nab-paclitaxel internalization in tumor cells^[27]. Consistently, tumor delivery of nab-paclitaxel was not related to SPARC expression in patient derived xenograft (PDX) PDAC murine models^[28].

DEVELOPMENT OF NAB-PACLITAXEL IN PDAC PRECLINICAL MODELS

In the context of a phase I - II study by Von Hoff *et al.*^[29], PDAC PDX murine models were randomly assigned to control, gemcitabine 100 mg/kg intraperitoneally on days 1 and 5 weekly for 4 wk, nab-paclitaxel 30 mg/kg per day intravenously for 5 consecutive days, and gemcitabine plus nab-paclitaxel in the preceding regimens for 4 wk. This study aimed to evaluate: (1) tumor progression; (2) changes in the pancreatic stroma; and (3) intratumoral drug penetration. Tumor regression was observed in 18%, 36% and 64% of xenografts treated with gemcitabine, nab-paclitaxel alone and both in combination, respectively. A depleted desmoplastic stroma, combined with dilated blood vessels, was found in each of nab-paclitaxel treatment group. Nab-paclitaxel plus gemcitabine resulted in 2.8 fold increased intratumor concentration of gemcitabine, compared to

gemcitabine alone^[29]. Another study investigated nab-paclitaxel, gemcitabine, docetaxel or control in PDAC cell-lines AsPC-1, BxPC-3, MIA PaCa-2 and Panc-1a. Addition of docetaxel or nab-paclitaxel at IC25, reduced gemcitabine IC50. Tumor growth inhibition after gemcitabine, docetaxel or nab-paclitaxel was 67%, 31% and 72%, respectively. Tumor stromal density, measured through reduction in α -smooth muscle actin, S100A4 and collagen 1 expression, was decreased by nab-paclitaxel better than docetaxel. In the same study, xenograft model was used to evaluate the efficacy of gemcitabine, docetaxel or nab-paclitaxel. Nab-paclitaxel followed by gemcitabine resulted in a longer median survival vs control or gemcitabine alone^[30]. Notably, combination of nab-paclitaxel and gemcitabine improved survival, reduced incidence of metastasis and increased intratumoral gemcitabine levels in KPC mouse models. Those effects were explained by the decrease of cytidine-deaminase, a gemcitabine-metabolizing enzyme^[31]. Engineered mice models of PDAC treated with nab-paclitaxel and gemcitabine, showed a distorted collagen with low cellular content in a preclinical-clinical study. Conversely, cancer-associated fibroblasts were increased in gemcitabine-treated mice. In the clinical section of this study, surgical specimen from patients with resectable PDAC, receiving preoperative treatment with two cycles of nab-paclitaxel and gemcitabine were studied to determine the collagen content and cancer associated fibroblasts density. Tumor samples of patients treated with nab-paclitaxel plus gemcitabine, showed a less abundant fibrillar collagen matrix around the tumor. Consistently, cancer associated fibroblasts were decreased in number, without effects on their activity^[32]. Recently, a preclinical study definitively demonstrated that nab-paclitaxel was superior to conventional paclitaxel in blocking primary tumor progression, depletion of tumor stroma and resulted in a longer survival in PDAC murine models^[33].

NAB-PACLITAXEL AND GEMCITABINE: A STANDARD OF CARE IN METASTATIC PDAC TREATMENT

Combination of nab-paclitaxel and gemcitabine in metastatic PDAC patients was investigated in an open label phase I -II study conducted in four United States centers. In the phase I part of this trial, primary endpoint was to identify the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of gemcitabine 1000 mg/m² followed by nab-paclitaxel 100, 125 or 150 mg/m² administered intravenously on day 1, 8 and 15 of a 28 d cycle. DLTs were sepsis and neutropenia and the MTD was fixed at level 2 (nab-paclitaxel 125 mg/m²). Phase II part of this study continued accrual at MTD to evaluate activity and safety of this combination. A cohort of 67 patients was enrolled and 44 received treatment at MTD. Median overall survival (OS) and progression free survival (PFS) in patients treated at MTD were 12.2 and 7.9 mo, respectively. Overall response rate (ORR) was 48% and overall disease control rate (DCR) was 68%. Most common grade ≥ 3 toxicities were represented by neutropenia (67%), leukopenia (44%), thrombocytopenia (23%), fatigue (21%) and neuropathy (15%). SPARC levels analysis was performed by immunohistochemistry in 36 tumor samples and patients were classified into high-SPARC and low-SPARC. High-SPARC was related to longer OS than low-SPARC (17.8 mo vs 8.1 mo, $P = 0.0431$) and it was significant predictor for OS at multivariate Cox regression model ($P = 0.041$)^[29]. Phase I -II studies have been performed also in Asian patients. In Japanese population, no differences were observed in grade 3 or higher toxicities compared to the American phase I -II study, using the same schedule^[34]. A Chinese phase I -II trial evaluated a different schedule of nab-paclitaxel plus gemcitabine. MTD was fixed at nab-paclitaxel 120 mg/m² in combination with gemcitabine 1000 mg/m² on day 1 and 8 every 3 wk^[35].

MPACT phase III trial

The MPACT trial was an international, multicenter, open label, randomized phase III study involving 11 countries worldwide. Eligible patients were randomly assigned 1:1 to receive either nab-paclitaxel 125 mg/m² plus gemcitabine 1000 mg/m² on days 1, 8, 15 every 4 wk or gemcitabine alone weekly for 7 of 8 wk during first cycle and days 1, 8, 15 every 4 wk in subsequent cycles. Treatment was administered until disease progression or unacceptable toxicity. Eight-hundred sixty-one patients (431 in the experimental arm) were enrolled and stratified according Karnofsky Performance Status (KPS), presence of liver metastases and geographic region. Primary end-point was OS; secondary objectives were PFS and ORR.

Age, gender, race, region and KPS were comparable in both study arms. No significant differences in pancreatic tumor site, location of metastases, number of metastatic sites, median CA19.9 levels, previous surgical or medical treatment and biliary stent implantation were observed between nab-paclitaxel plus gemcitabine and single agent gemcitabine groups. In the experimental arm, median duration of treatment was 3.9 mo and median dose intensity was 81% for nab-paclitaxel and 75% for gemcitabine. Addition of nab-paclitaxel to gemcitabine increased significantly median OS over gemcitabine alone (8.5 mo, 95%CI: 7.89-9.53 vs 6.7 mo, 95%CI: 6.01-7.23) with a 28% reduced risk of death (HR = 0.72, 95%CI: 0.62-0.82, $P < 0.001$). One and two-year survival rates were significantly higher in nab-paclitaxel and gemcitabine group compared to gemcitabine alone (35% vs 22%, $P < 0.001$ and 9% vs 4%, $P = 0.02$, respectively). Median PFS was prolonged by combination schedule (5.5 mo, 95%CI: 4.5-5.9 vs 3.7 mo, 95%CI: 3.6-4.0; HR = 0.69, 95%CI: 0.58-0.82, $P < 0.001$) with a significantly higher 12 mo- PFS rate than single agent gemcitabine (16% vs 9%). ORR was increased by addition of nab-paclitaxel to gemcitabine vs gemcitabine alone as assessed both by independent and investigator review (23% vs 7%, $P < 0.001$ and 29% vs 8%, $P < 0.001$, respectively). Notably, DCR, as evaluated by independent review, was higher in combination than single agent arm (48% vs 33%). Nab-paclitaxel and gemcitabine combination benefit was consistent across the different subgroups in terms of OS and PFS. Patients with more advanced disease, poorer PS, presence of liver metastases, more than 3 metastatic sites and CA19.9 higher than 59 times the upper limit of the normal range had the highest reduction in risk of death. Most common grade 3-4 hematologic events in the experimental arm were neutropenia (38%), leukopenia (31%), thrombocytopenia (13%) and most common non-haematological events were fatigue (17%) and peripheral neuropathy (17%)^[18]. An updated analysis of MPACT trial with a longer median follow-up (13.9 mo) confirmed the superior OS in nab-paclitaxel plus gemcitabine vs single agent gemcitabine group (8.7 mo vs 6.6 mo, respectively) and identified 10%, 4% and 3% of long survivors in the combination arm at 24, 36 and 42 mo, respectively^[36].

MPACT study: post hoc analyses

Nab-paclitaxel plus gemcitabine remained an independent predictor of improved OS and PFS also after correction for prognostic factors. In fact, MPACT investigators evaluated the effect of treatments according stratification factors and known prognostic factors (age, sex, KPS, peritoneal carcinomatosis, primary tumor location, pulmonary metastases, liver metastases, Whipple procedure, biliary stent implantation, stage at diagnosis, CA19.9 level).

Combination regimen was more effective than gemcitabine in a larger spectrum of patients^[37]. In addition, an elevated neutrophil to lymphocytes ratio (NLR \geq 5) at baseline resulted as an independent prognostic factor related to a worse OS in an updated multivariate analysis^[36]. Nab-paclitaxel plus gemcitabine combination showed activity both on primary and metastatic lesions in terms of tumor shrinkage benefit in a further analysis^[38]. In MPACT trial, baseline CA19.9 levels were not a significant predictor of survival; conversely, CA19.9 decrease was related to better outcomes in both arms. An exploratory analysis confirmed the CA19.9 decrease at 8 wk as an early marker of treatment efficacy in terms of OS and ORR^[39]. A pre-specified analysis evaluated the role of metabolic response detected by PET scan and compared metabolic response rate with treatment efficacy. Metabolic response rates at 8 wk as well as best metabolic response were higher in nab-paclitaxel plus gemcitabine arm. Metabolic response appeared as predictor of longer OS in both study arms^[40]. Nab-paclitaxel plus gemcitabine was related to 54% of any grade neuropathy. Majority of patients experiencing grade 3 neuropathy, improved to grade 1 or less within one-month. Patients who developed peripheral neuropathy received a longer treatment and obtained a longer OS. Survival benefit increased according to the grade of peripheral neuropathy^[41]. An exploratory analysis was performed in order to gain insight the role of SPARC expression as prognostic or predictive factor of survival. Neither baseline plasma SPARC levels, nor changes from baseline were predictors of OS. Stromal and tumor levels of SPARC, measured by immunohistochemistry had no correlation with OS^[42]. Nab-paclitaxel plus gemcitabine increased OS, PFS and ORR, compared to gemcitabine alone in patients treated until disease progression. Accordingly, more than 50% of patients treated until progression received a second line therapy^[43]. In the MPACT study 41% of patients had a nab-paclitaxel dose reduction, 71% had a dose delay, mostly after two cycles of treatment. In nab-paclitaxel plus gemcitabine arm, those modifications led to a longer treatment exposure and OS respect of patients who did not receive reductions or delays^[44]. Forty-percent of patients treated in nab-paclitaxel and gemcitabine group received a second line treatment, mostly (74%) with fluoropyrimidines in combination regimens. Second line therapies were related to a significant benefit in OS in both study arms compared to patients without second line therapy. Notably, OS was significantly increased in patients treated with first line nab-paclitaxel plus gemcitabine vs gemcitabine alone (12.8 mo vs 9.0 mo, HR = 0.76, $P = 0.015$)^[45].

NOVEL INVESTIGATIONS WITH NAB-PACLITAXEL IN PDAC

Hypoxia represents a common feature of several

malignancies and it correlates with a worse prognosis and resistance to chemo- and radio-therapy^[46,47]. TH-302 is a bromo-isophosphoramidate mustard that works under conditions of hypoxia. The triplet containing nab-paclitaxel, gemcitabine and TH-302 exhibited superior efficacy in reducing stromal density and cell proliferation compared to TH-302 alone or nab-paclitaxel plus gemcitabine, in human PDAC xenograft models^[48]. Combination of nab-paclitaxel with the oral fluoropyrimidine S-1 demonstrated to inhibit proliferation in PDAC cell lines and to decrease relative tumor volume in murine xenograft models^[49,50]. An important pathway involved in PDAC stem cells maintenance is represented by Notch signaling^[51]. Recently, the oncolytic adenovirus AdNuPARmE1A has showed to interfere with Notch pathway. In PDAC PDX mouse models, administration of nab-paclitaxel and gemcitabine combined with AdNuPARmE1A resulted in a higher therapeutic response than nab-paclitaxel plus gemcitabine combination and AdNuPARmE1A alone^[52]. Tumor microenvironment plays a crucial role in PDAC aggressiveness and drug-resistance^[53,54]. In this context, pancreatic stellate cells have been addressed as responsible for fibrosis and they have similar characteristics to the monocyte-macrophage lineage. Pamidronate and zoledronic acid are nitrogen-containing bisphosphonates that have showed *in vitro* anti-proliferative and pro-apoptotic activity on macrophages. *In vivo*, antitumor effect of nab-paclitaxel is enhanced by the combination with bisphosphonates in PDAC PDX mouse models^[55]. Depending on predominant signals within the tumor microenvironment, macrophages can adopt a variety of functional states. In particular, macrophages with M2 phenotype acquire immuno-suppressive and tumor-promoting features^[56]. *In vitro* and *in vivo* studies showed that nab-paclitaxel is internalized by macrophages *via* macro-pinocytosis, leading to a polarization towards a potentially tumoricidal M1 phenotype^[57]. Insulin-like growth factor (IGF) signaling proteins are overexpressed in PDAC, predicting poor prognosis and higher aggressiveness. A small IGF-1 receptor and Insulin receptor reversible inhibitor (BMS-754807) reduced PDAC relative volume when combined with nab-paclitaxel in PDX mouse models^[58].

Phase I-II studies

Several clinical trials in locally advanced or metastatic PDAC treatment included nab-paclitaxel in new therapeutic schedules. A phase I study has investigated the combination of FOLFOX plus nab-paclitaxel in a cohort of 35 patients, aiming to establish the nab-paclitaxel MTD. A dose of 150 mg/m² every 2 wk was identified as MTD and a 20% reduction in oxaliplatin dose was recommended in patients who developed grade 2 neuropathy. This schedule showed a promising activity with 60% response rate and median survival of 15 mo^[59]. The four-drug schedule combining

cisplatin, nab-paclitaxel, capecitabine and gemcitabine (PAXG) has been tested in unresectable or borderline resectable PDAC patients. The PAXG regimen was investigated in a phase I trial on 24 patients with the objective to define the recommended phase 2 dose (RP2D) of nab-paclitaxel. A dose of 150 mg/m² every 2 wk resulted as RP2D and major grade 3-4 toxicities were represented by neutropenia (31%), anemia (12%), fatigue (19%), hand-foot syndrome (12%). Disease control was obtained in all 21 patients and 67% of them showed a partial response. Six- and twelve-months PFS rates were 96% and 50% respectively^[60]. This novel combination was evaluated in a randomized phase II study in which PAXG was compared to standard nab-paclitaxel plus gemcitabine. Fifty-four patients with unresectable or borderline resectable PDAC were randomized and 26 received PAXG. Primary endpoint of the study was resectability rate and each regimen would have been considered active if at least 4 patients per arm underwent to surgical resection. Both schedules resulted to be active and 5 patients in each arm underwent to surgery^[61]. Combination of nab-paclitaxel and gemcitabine has been tested as a therapeutic backbone with target agents. A phase Ib trial evaluated the addition of erlotinib to nab-paclitaxel and gemcitabine in previously untreated advanced PDAC patients. The triplet was not feasible at standard dose of each single agent and it was necessary to reduce both nab-paclitaxel and erlotinib doses to 75 mg/m² and 75 mg/d, respectively. Due to the small number of patients treated at dose level 3, no valid information about activity outcomes were obtained^[62]. Recently, combination of nab-paclitaxel with both oral and intravenous fluoropyrimidines has been investigated. A single arm phase II trial evaluated the combination of capecitabine 825 mg/m² orally bis in die on days 1-15 and nab-paclitaxel 125 mg/m² intravenously on days 1 and 8 every 3 wk as a first line treatment in 30 PDAC patients. In patients without relevant adverse reaction after first cycle, the nab-paclitaxel dose was escalated to 100 mg/m² on days 1, 8, 15 every 4 wk. ORR and DCR were 41.4% and 76%, respectively. Major grade 3 toxicities were peripheral neuropathy (23%), neutropenia (17%), hand-foot syndrome (13%), and phototoxic skin reaction (10%)^[63]. A randomized phase II study compared the combination of nab-paclitaxel 125 mg/m², leucovorin 400 mg/m², 5-fluorouracil 400 mg/m² bolus, followed by 2400 mg/m² given as 46 h continuous infusion on day 1 and 15 every 4 wk (NABFU schedule) vs standard nab-paclitaxel plus gemcitabine. One hundred-fourteen patients were included with 2:1 randomization in favor of experimental arm. PFS at 4 mo was the primary endpoint. No differences were observed between the experimental arm and the standard treatment (55% vs 54%). NABFU regimen resulted in a higher median OS, as well as higher OS rates at 12 and 18 mo vs

nab-paclitaxel plus gemcitabine (11.4 mo vs 9.2 mo, 48% vs 41% and 34% vs 31% respectively). Safety profile was similar in both study arms, except for grade 3 mucositis and diarrhea that were higher in the NABFU treatment group, reflecting the fluorouracil-related toxicities^[64,65].

PUTTING NAB-PACLITAXEL IN PDAC LANDSCAPE: PAST, PRESENT...

Despite of promising preclinical and “early” clinical activity, paclitaxel and docetaxel have never showed superiority compared to gemcitabine in PDAC therapy^[66]. Conversely, nano-technology improved bioavailability and intratumoral delivery of paclitaxel as well as avoided effects due to cremophor and therefore premedication with steroids. The albumin-bound formulation, acts on tumor microenvironment and depletes stroma through interaction between SPARC and albumin. This mechanism of action favors gemcitabine increased intratumoral concentration, making nab-paclitaxel an ideal partner for this drug. Nab-paclitaxel plus gemcitabine was the first combination to increase survival and response rates in metastatic PDAC treatment compared to gemcitabine alone. This schedule represents one of the standards of care in advanced PDAC first line treatment together with FOLFIRINOX and single agent gemcitabine^[7,67,68]. Among these schedules, the most appropriate therapeutic choice should be guided by patient-related features (age, performance status, comorbidities, preferences), disease characteristics (tumor burden, metastatic sites, biliary stent implantation, bilirubin levels), also taking into consideration previous therapies and cost-effectiveness. In this context, FOLFIRINOX, according to the ACCORD/PRODIGE phase II -III study, could be an option in young, healthy and good performance status patients. Single agent gemcitabine could be used in unfit patients, with poor performance status and few comorbidities where a doublet or a triplet would not be feasible. Nab-paclitaxel and gemcitabine combination appears suitable for a broader spectrum of patients. In fact, MPACT trial was performed on a larger and more heterogeneous population than FOLFIRINOX and gemcitabine pivotal trials (Table 1). This study demonstrated that nab-paclitaxel plus gemcitabine improved survival in metastatic PDAC patients regardless to age, gender, geographic region, KPS, primary tumor location, presence of liver metastases, number of metastatic sites and baseline CA19.9 PDAC incidence is higher in elderly patients although this population is scarcely included in clinical trials^[69]. Patients aged ≥ 75 years were not enrolled in the ACCORD/PRODIGE study; conversely they represented 10% of the MPACT population. Nab-paclitaxel plus gemcitabine showed efficacy and improved survival regardless age at a cut-off of 65 years; nevertheless data about “truly elderly”

Table 1 Patients characteristics in metastatic pancreatic cancer pivotal trials

	Gemcitabine	FOLFIRINOX	Nab-paclitaxel + gemcitabine
Trial (yr)	Gemcitabine <i>vs</i> 5-fluorouracil (1997)	FOLFIRINOX <i>vs</i> Gemcitabine (2011)	Nab-paclitaxel <i>vs</i> Gemcitabine (2013)
Phase	I ¹	II-III	III
Countries	United states- Canada- United Kingdom	France	Worldwide
Patients	126	342	861
Median age	61.5	61	62
Elderly (≥ 75 yr)	Yes		Yes
ECOG PS 0-1	Yes	Yes	Yes
ECOG PS 2	Yes		Yes
Biliary Stent	Yes	Yes	Yes
Multiple metastatic sites	Yes	Yes	Yes

¹Phase not specified in the full paper. ECOG PS: Eastern Cooperative Oncology Group Performance Status.

patients, aged over 75 years were available only on a small proportion of subjects. Real life experiences, with the limitation of retrospective series, suggest that the combination schedule was feasible, active, effective and well tolerated in elderly patients aged more than 70 and 75^[70,71]. No data are available about the use of FOLFIRINOX in patients with poor performance status, in fact only subjects with ECOG PS 0-1 were included in the pivotal trial. Addition of nab-paclitaxel to gemcitabine did not improve survival in the KPS 70 (corresponding to ECOG PS of 2) compared to single agent gemcitabine, although these results were limited only to the 8% of MPACT study population. In order to make the best therapeutic choice in this population, physicians should differentiate between ECOG PS 2 due to "tumor burden" or due to comorbidities. In fact, as stated by European Society for Medical Oncology Guidelines for PDAC treatment, nab-paclitaxel plus gemcitabine could be considered an option in patients with ECOG PS 2 due to "heavy tumor load" for best chance of response^[72]. Feasibility and flexibility of nab-paclitaxel plus gemcitabine combination allow to treat patients until disease progression. Data from MPACT study post-hoc analysis confirm that the higher exposure to both drugs correlates to better outcomes. Metastatic PDAC subjects treated until disease progression as well as receiving dose delays or modifications within the study, had a longer OS than patients who did not. Introduction of new, active schedules in PDAC first line treatment let to higher proportion of patients to benefit also from further lines of therapy. In fact, in ACCORD/PRODIGE and MPACT study population, 46% and 40% of patients received a second line chemotherapy in the FOLFIRINOX and nab-paclitaxel plus gemcitabine arm, respectively. Real

life data show that this number is even higher in nab-paclitaxel and gemcitabine treated subjects, reaching more than 50%^[73]. Second-line options that have demonstrated efficacy are oxaliplatin plus fluoro-folate (OFF schedule) and nano-liposomal irinotecan plus fluoro-folate according to CONKO-003 and NAPOLI-1 phase III trials results, respectively^[74-76]. The choice of nab-paclitaxel as a first-line regimen allows the use of a non-cross-resistant second-line chemotherapy both with oxaliplatin and nano-liposomal irinotecan, whereas FOLFIRINOX does not. Finally, the optimal first-line therapeutic decision should take into account treatment-related costs. Recent data show that patient who initiated first line therapy with nab-paclitaxel plus gemcitabine has similar treatment duration but lower all-cause costs than FOLFIRINOX^[77].

CONCLUSION

Innovative technology, peculiar mechanism of action and clinical activity of nab-paclitaxel have made this molecule an intriguing weapon for further studies in PDAC treatment. Several phase I, II and III trials are actually recruiting patients in PDAC therapy in order to investigate nab-paclitaxel based chemotherapy plus immunotherapy or target agents in the metastatic setting (Table 2). Furthermore, recent data from a randomized phase II trial suggest that sequential administration of nab-paclitaxel on day 1, 8, 15 and gemcitabine day 2, 9, 16 every 4 wk as first-line therapy in metastatic PDAC, may be more effective than a concomitant schedule and this approach warrants further studies^[78]. Notably, combination of nab-paclitaxel and gemcitabine is under investigation in adjuvant setting (Table 3). AFACT is a phase III, multicenter, open label, randomized study of nab-paclitaxel plus gemcitabine *vs* gemcitabine alone in subjects with surgically resected PDAC. This trial planned to enroll 846 patients evaluating the disease free survival as primary endpoint and study results are expected in the next future. Several studies are ongoing in the locally advanced, borderline resectable or unresectable PDAC (Table 3). In particular, LAPACT is a phase II, international, multicenter, open label, single-arm study in subjects with unresectable, locally advanced PDAC who have not received prior treatment. Nab-paclitaxel and gemcitabine was administered for a maximum of six cycles as induction therapy. Only in patients without disease progression or unacceptable toxicity, the investigator could choose among different options: (1) continuing chemotherapy with the same schedule; (2) chemo-radiation; and (3) surgical resection. Primary end-point was the time to treatment failure (time from the first day of treatment and disease progression or death). An interim analysis evaluated preliminary safety and efficacy data on 47 of 110 planned patients. Induction phase was completed in 60% of patients and 40% discontinued treatment,

Table 2 Principal clinical trials with nab-paclitaxel in metastatic pancreatic cancer

Study ID	Setting	Study drugs	Phase	Status
NCT02993731	Metastatic	Nab-paclitaxel + Gemcitabine +/-Napabucasin	III	Recruiting
NCT02101021	Metastatic	Nab-paclitaxel + Gemcitabine +/- Momelotinib	III	Active not recruiting
NCT02715804	Metastatic	Nab-paclitaxel + Gemcitabine +/-PEGPH20	III	Recruiting
NCT02436668	Metastatic	Nab-paclitaxel + Gemcitabine +/- Ibrutinib	II-III	Recruiting
NCT02827201	Metastatic	Sequential Nab-paclitaxel + Gemcitabine /FOLFIRI	II	Active not recruiting
NCT02767557	Metastatic	Nab-paclitaxel + Gemcitabine +/-tocilizumab	II	Recruiting
NCT03086369	Metastatic	Nab-paclitaxel + Gemcitabine +/- Olaratumab	II	Not yet recruiting
NCT02879318	Metastatic	Nab-paclitaxel + Gemcitabine +/- Durvalumab + Tremelimumab	II	Recruiting
NCT02399137	Metastatic	Nab-paclitaxel + Gemcitabine + MM-141	II	Recruiting
NCT02340117	Metastatic	Nab-paclitaxel + Gemcitabine + SGT-53	II	Recruiting
NCT02124317	Metastatic	Nab-paclitaxel + S-1	II	Active not recruiting
NCT03076216	Metastatic	Nab-paclitaxel + Gemcitabine + ONCOSil	II	Not yet recruiting
NCT02905578	Metastatic	Nab-paclitaxel + Gemcitabine + High-dose ascorbate	II	Not yet recruiting
NCT02732938	Metastatic	Nab-paclitaxel + Gemcitabine + PF-04136309	II	Recruiting
NCT02551991	Metastatic	Nal-Iri or Gemcitabine + Nab-paclitaxel	II	Recruiting
NCT03009058	Metastatic	Nab-paclitaxel + Gemcitabine + IMM 101	I - II	Not yet recruiting
NCT02559674	Metastatic	Nab-paclitaxel + Gemcitabine + ALT-803	I - II	Recruiting
NCT02705196	Metastatic	Nab-paclitaxel + Gemcitabine + LOAd703 oncolytic virus	I - II	Recruiting
NCT01834235	Metastatic	Nab-paclitaxel + Gemcitabine + NPC-1C	I - II	Active not recruiting
NCT01730222	Metastatic	Nab-paclitaxel + Gemcitabine + Capecitabine + Cisplatin	I - II	Recruiting
NCT02620800	Metastatic	Nab-paclitaxel + 5-fluorouracil + Leucovorin + Bevacizumab + Oxaliplatin	I - II	Recruiting
NCT01506973	Metastatic	Nab-paclitaxel + Gemcitabine + Hydroxychloroquine	I - II	Recruiting
NCT02504333	Metastatic	Nab-paclitaxel + Gemcitabine followed by FOLFOX	I - II	Recruiting
NCT02050178	Metastatic	Nab-paclitaxel + Gemcitabine + OMP-54F28	I	Active not recruiting
NCT02309177	Metastatic	Nab-paclitaxel + Nivolumab +/- Gemcitabine	I	Recruiting
NCT02514031	Metastatic	Nab-paclitaxel + Gemcitabine + ARQ-761	I	Recruiting
NCT01934634	Metastatic	Nab-paclitaxel + Gemcitabine + LCL161	I	Active not recruiting
NCT02101580	Metastatic	Nab-paclitaxel + Gemcitabine + ADI-PEG 20	I	Active not recruiting
NCT02138383	Metastatic	Nab-paclitaxel + Gemcitabine + Enzalutamide	I	Active not recruiting
NCT02975141	Metastatic	Nab-paclitaxel + Gemcitabine + Afatinib	I	Recruiting
NCT02227940	Metastatic	Nab-paclitaxel + Gemcitabine + Ceritinib	I	Recruiting
NCT02231723	Metastatic	Nab-paclitaxel + Gemcitabine + BBI608	I	Recruiting
NCT02501902	Metastatic	Nab-paclitaxel + Palbociclib	I	Recruiting

Nal-Iri: Nanoliposomal irinotecan.

due to adverse events in the majority of cases. DCR was 80% and 13% of patients underwent to surgical resection. Major grade 3-4 toxicities were neutropenia (45%), anemia (13%) and fatigue (11%)^[79]. Clinical trials in neo-adjuvant treatment or in locally advanced disease are evaluating integrated strategies containing nab-paclitaxel with both intensity modulated, image guided and stereotactic radiotherapy (Table 3). Actually there are no predictive biomarkers that may guide therapeutic choice in PDAC treatment and may help clinicians to choose the best regimen for each patient. An intense research is ongoing in order to investigate the potential role of micro-RNA as predictive of sensitivity and resistance to the drugs included in the FOLFIRINOX and nab-paclitaxel plus gemcitabine schedules^[80].

Introduction of nab-paclitaxel in Oncologist's portfolio of drugs has represented a very important step forward in PDAC treatment. Nab-paclitaxel plus gemcitabine is one of the standards of care in advanced PDAC therapy and this combination is suitable for a wide spectrum of patients with different features and clinical presentations. This scenario could change rapidly as the result of nab-paclitaxel anticipation in "early settings" and further studies could be required in order to investigate a "re-challenge" in the metastatic disease.

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Table 3 Principal clinical trials with nab-paclitaxel in pancreatic cancer “early settings”

Study ID	Setting	Study drugs	Phase	Status
NCT01964430	Adjuvant	Nab-paclitaxel + Gemcitabine <i>vs</i> Gemcitabine	III	Recruiting
NCT02506842	Adjuvant	Nab-paclitaxel + Gemcitabine <i>vs</i> OFF	III	Recruiting
NCT02023021	Adjuvant	Nab-paclitaxel + Gemcitabine	II	Recruiting
NCT02125136	Neoadjuvant	Nab-paclitaxel + Gemcitabine <i>vs</i> FOLFIFINOX	II	Recruiting
NCT02243007	Neoadjuvant	Nab-paclitaxel + Gemcitabine <i>vs</i> FOLFIFINOX	II	Recruiting
NCT02717091	Neoadjuvant/borderline resectable	Nab-paclitaxel + Gemcitabine <i>vs</i> FOLFIFINOX	II	Recruiting
NCT02481635	NEO/adjuvant	Nab-paclitaxel + Gemcitabine + radiotherapy	I - II	Recruiting
NCT01431794	Neoadjuvant	Nab-paclitaxel + Gemcitabine + LDE-225	I - II	Active not recruiting
NCT02588443	NEO/adjuvant	Nab-paclitaxel + Gemcitabine + RO7009789	I	Recruiting
NCT02272738	Neoadjuvant	Nab-paclitaxel + Gemcitabine + radiotherapy	I	Recruiting
NCT02506803	Neoadjuvant	Nab-paclitaxel + Gemcitabine	I	Recruiting
NCT02427841	Resectable	Nab-paclitaxel + Gemcitabine followed by radiotherapy	II	Recruiting
NCT02550327	Resectable	Nab-paclitaxel + Gemcitabine + Cisplatin + Anakinra	I	Recruiting
NCT02210559	Locally advanced	Nab-paclitaxel + Gemcitabine + FG-3019	I - II	Recruiting
NCT02394535	Locally advanced	Nab-paclitaxel + Capecitabine + radiotherapy	I	Recruiting
NCT02124369	Borderline unresectable	Nab-paclitaxel + Gemcitabine	II	Recruiting
NCT02043730	Unresectable locally advaced	Nab-paclitaxel + Gemcitabine	II	Recruiting
NCT02207465	Unresectable locally advanced	Nab-paclitaxel + Gemcitabine + radiotherapy	I	Recruiting
NCT02272738	Unresectable locally advanced	Nab-paclitaxel + Gemcitabine	I	Recruiting
NCT01978184	Preoperative	Nab-paclitaxel + Gemcitabine + Hydroxychloroquine	II	Recruiting
NCT02427841	Preoperative	Nab-paclitaxel + Gemcitabine + radiotherapy	II	Recruiting
NCT02723331	Preoperative	Nab-paclitaxel + Gemcitabine followed by SBRT	II	Recruiting
NCT02930902	Preoperative	Nab-paclitaxel + Gemcitabine + Pembrolizumab + Paricalcitol	I	Recruiting

SBRT: Stereotactic body radiotherapy; OFF: Oxaliplatin plus fluoro-folate.

paclitaxel mechanism of action from their educational slides kit.

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