Nanoparticle albumin-bound paclitaxel: a big nano for the treatment of gastric cancer

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Abstract
Gastric cancer (GC) is the third cause of cancer-related death worldwide. Patients with unresectable GC can be treated with chemotherapy such as paclitaxel, which is a microtubule stabilizer. The use of nanoparticle albumin-bound paclitaxel (nab-ptx) avoids hypersensitivity reactions due to the absence of solvent needed to dissolve paclitaxel and it can be administered at higher doses. The ABSOLUTE randomized phase-3 clinical trial showed the non-inferiority of the nab-ptx used every week compared to the solvent-based paclitaxel used every week. This review describes the current advancements of the use of nab-ptx in GC in preclinical and clinical study investigations. The possibility of combining nab-ptx with other medications to improve response of patients to their specific molecular needs will also be debated.

Introduction

In the last decade, gastric cancer (GC) is the third most common cause of cancer-related mortality worldwide, accounting for 723,000 or 8.2% of cancer deaths yearly [1]. The terminology "gastric cancer" refers to a certain type of tumor that extends from the external mucosa wall until the whole stomach, meaning that over 90% of these types of tumors are adenocarcinoma. Because of the asymptomatic nature of the disease, GC is often diagnosed at a late stage when it cannot be surgically removed. When the disease is ascertained at its earliest stages, it can be surgically removed and subsequently treated with radiotherapy and chemotherapy, resulting in a 5-year survival of 90% [2]. However, the delay in diagnosis causes the progression of GC to more advanced stages, in some cases precluding surgical resection, and it can invade adjacent tissues and/or metastasize into different organs [3].

Regimens which combine a fluoropyrimidine with a platinum-based agent remain the most widely used first-line chemotherapy for unresectable GC [4, 5]. The use of second-line chemotherapy using taxanes [mainly paclitaxel (ptx)] and irinotecan has shown clinical benefits [6–8]. However, the monoclonal antibody against vascular endothelial growth factor receptor 2 (VEGFR2) ramucirumab, alone or in combination with paclitaxel has increased survival and is considered the gold standard for second line of treatment [9, 10]. Additionally, other agents have increased survival in third or subsequent lines of treatment [11–13].

Paclitaxel is a chemotherapeutic agent belonging to the class of taxanes. The antitumor activity of ptx is mainly due to the suppression of the dynamics of the tubulin microtubule, by stabilizing the GDP-bound tubulin in the microtubule, destabilizing, therefore, the fast-dividing neoplastic cell and resulting in the deregulation of mitosis, as well as in the blockade of cell division, and eventually in the induction of apoptosis [6]. However, the use of solvent-based ptx may result in hypersensitivity and anaphylactic reactions related to the solvent Cremophor EL (polyoxyl 35 castor oil) required for administration, in many cases being

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a polyethoxylated oil [14, 15]. Thus, the use of ptx requires the use of premedications to reduce adverse effects, such as steroids and histamine H2 receptor blockers [14, 15]. Nanoparticle entailing albumin-bound (nab) paclitaxel provides a solvent-free formulation of ptx, minimizing, therefore, the risk of hypersensitivities [16, 17]. In this review, we describe the nab-ptx molecule and the current pre- and clinical evidences on its efficacy in the treatment of GC. The combination of this drug with other targeted therapies and the need of biomarkers of responsiveness will be further debated.

The nab-paclitaxel molecule

The nanoparticle albumin-bound paclitaxel (nab-ptx) formulation does not require premedications since it does not need a solvent for its administration [16, 17]. nab-ptx consists of nanometric (130 nM) particle of ptx stabilized with human albumin through hydrophobic interactions. This condition facilitates ptx delivery across the endothelial cell by binding to the albumin-specific receptor glycoprotein (gp60). The binding to gp60 initiates the caveolar-mediated endothelial transport through transcytosis. Finally, caveolae will release ptx into the tumour interstitial space. It has also been suggested that SPARC (secreted protein, acidic and rich in cysteine) protein, present in tumor stromal, might have mediated this process [14]. However, the role of SPARC in enhancing the delivery of nab-ptx into the tumor microenvironment has not been fully clarified [18–20]. After the nab-ptx enters the cells, the vesicular transport will move it into the subendothelial space, allowing nab-ptx to reach the tumor. Using passive and active targeting, the nab-ptx complex model has a more efficient delivery system, reducing dangerous side effects and toxic outcomes for the patient since albumin is a natural carrier for other body molecules, and it is abundant in the body (Fig. 1). Furthermore, nab-ptx can be administered at higher doses over a shorter infusion time vs solvent-based ptx. After administering the two drugs at equal doses, the ptx dose reaching the tumor was 33% higher for the nab-ptx versus the solvent-based ptx, indicating that the nab-ptx was more efficient in reaching and accumulating inside the intratumoral microenvironment [21, 22]. Moreover, since there is no need for a

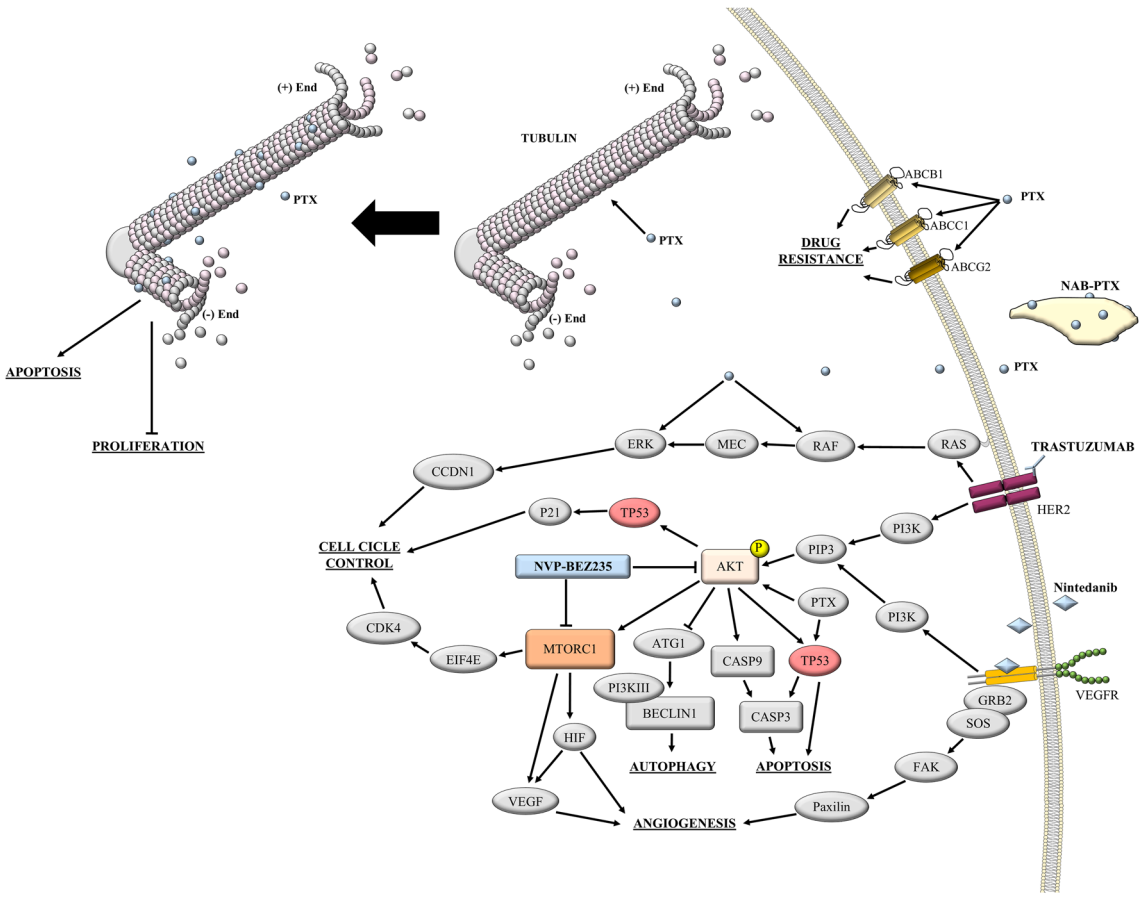

Fig. 1 Mode of action of albumin-bound paclitaxel and targeted therapies inhibiting the PI3 K/mTOR and angiogenesis in the treatment of gastric cancer

hydrated ethanol solvent, the nab-ptx can be administered to alcohol-intolerant patients.

Preclinical models

Zhang et al. [23] showed in gastric cell lines (AGS, NCI-N87 and SNU16) that nab-ptx inhibited cell proliferation with a half-maximal inhibitory concentration (IC_{50}) of 5 nM in SNU16, 23 nM in AGS, and 49 nM in NCI-N87 after a 72-h treatment. These IC_{50} were lower than those observed for oxaliplatin (1.05–1.51 μM) and epirubucin (0.12–0.25 μM). Furthermore, they showed in vivo that after 2 weeks of treatment with nab-ptx, epirubicin or oxaliplatin, the average local tumor growth inhibition rates were 77%, 21.7%, and 17.2%, respectively ($p = 0.002$). Additionally, treatment with nab-ptx significantly increased animal survival compared to controls ($p = 0.0007$), the use of oxaliplatin ($p = 0.0007$) or the use of docetaxel ($p = 0.0416$). However, the authors did not investigate the IC50 of free ptx in their tumor models. In line with this study, Kinoshita et al. [24] used nude mice bearing GC OCUM-2MD3 cell subcutaneous xenografts to evaluate at equitoxic doses for the therapeutic efficacy of nab-ptx compared to conventional solvent-based ptx. The drugs were administered in mice either intraperitoneally (i.p.) or intravenously (i.v.). They observed a significantly greater reduction in the size of subcutaneous tumors and weight of ascites and peritoneal burden in mice treated with nab-ptx compared to usual ptx ($p < 0.05$). In both i.p. and i.v. treated groups, complete regressions were observed. The survival benefit was higher in both the intraperitoneal and in the subcutaneous nab-ptx groups compared to control ptx ($p = 0.034$ and $p = 0.047$, respectively) [24].

In addition, the use of nab-ptx and trastuzumab in human epidermal growth factor receptor 2 (HER2)-positive GC cell lines demonstrated a higher cytotoxic activity of the combination compared with nab-ptx alone. In fact, the IC50 for GC cell lines was 0.13 ± 0.03 and 0.048 ± 0.01 μg/ml of nab-ptx and trastuzumab/nab-ptx, respectively [25]. Also, the combination of nab-ptx and trastuzumab led to the highest reduction of tumor volume in GC xenograft models [25]. Therefore, the combination of trastuzumab with nab-ptx could be a promising option to be explored for the treatment of HER2-positive GC.

Awasthi et al. [26] proved that the combination of nab-ptx with anti-angiogenic drugs improved the survival of mice models of gastric adenocarcinoma. Subcutaneous gastric adenocarcinoma cell-derived models or patient-derived xenografts were tested with combinations of nab-ptx with anti-angiogenic drugs, i.e., DC101 (murine version of ramucirumab), cabozantinib, and nintedanib. The combination of nab-ptx with nintedanib was the most effective in improving the survival of the animal models. In addition, cell-derived subcutaneous xenografts of mice treated with nab-ptx plus nintedanib showed significant reduction in tumor growth over single agents alone [26]. Therefore, the combination of nab-ptx with nintedanib is promising and warrants clinical evaluation.

Finally, the activity of a novel dual PI3 K/mTOR inhibitor, NVP-BEZ235, has been investigated alone and in combination with nab-ptx in GC by Zhang et al. [27]. Interestingly, the authors showed that after treatment with nab-ptx, the phosphorylation levels of mTOR and 4E-BP1 were higher in cultured human GC cell line SNU16 and SNU16 tumor tissues. This lasts because 4E-BP1 is a member of a family of translation repressor proteins, and a well-known substrate of the mechanistic target of mTOR signaling pathway [27]. Potential taxane resistance associated with the activation of mTOR through phosphorylation makes a strong rationale for the use of nab-ptx with an mTOR inhibitor. In this study, the use of BEZ235 was capable to effectively inhibit cell proliferation in cultured human GC cell line SNU16 and SNU16 tumor tissues, as observed by immunostaining, with a synergistic effect observed with the combination of nab-ptx and BENZ235. The combination of BEZ235 and nab-ptx resulted in a 97% inhibition in net tumor growth of SNU16 tumor-bearing mice ($p < 0.0001$), compared with control group. In addition, the authors showed that the net local tumor growth inhibition for the BEZ235, nab-ptx, and BEZ235 + nab-ptx was 45.1, 77.9, and 97% compared to controls. The median survival of the animal models was significantly higher for the nab-ptx ($p = 0.0001$) and for the BEZ235 + nab-ptx combination treatment groups ($p = 0.001$) compared to controls [27].

Clinical developments

The available evidence on the use of nab-ptx in the treatment of GC comes from phase I and II trials, retrospective studies, and a phase III trial. A summary of the most relevant studies is reported in Tables 1 and 2.

A phase II study investigated for the first time the efficacy and safety of nab-ptx given every 3 weeks at a dose of 260 mg/m^2 on day 1 to patients with unresectable or recurrent GC who previously had received fluoropyrimidine-containing chemotherapy. The primary endpoint was overall response rate (ORR), secondary endpoint included overall survival (OS), progression-free survival (PFS), and safety. Based on an Independent Review Committee (IRC), the ORR was 27.8% (15/54; 95% CI, 16.5–41.6) and the disease control rate (DCR) was 59.3% (32/54; 95% CI, 45.0–72.4). As to secondary endpoints, PFS and OS were of 2.9 months (95% CI, 2.4–3.6) and 9.2 months (95% CI, 6.9–11.4), respectively. The evidence from this clinical trial showed that nab-ptx given every 3 weeks has relatively promising activity in GC with well-tolerated toxicities [28].

Table 1 Characteristics of the analyzed trials

Study	Phase	Primary endpoint	Experimental drug	Number of patients	Setting of disease	Line of treatment
Sasaki et al. (NCT00661167)	2	ORR (RECIST 1.0)	Nab-ptx 260 mg/m^2 (day 1 of each 21-day cycle)	56	Unresectable/metastatic or recurrent GC	2
Bando et al. (JapicCTI-153088)	2	ORR (RECIST 1.1)	Nab-ptx 100 mg/m^2 (days 1, 8 and 15 of each 28-day cycle) Ramucirumab 8 mg/kg (days 1 and 15 of each 28-day cycle)	45	Unresectable/metastatic or recurrent GC	2
Katsaounis et al. (NCT02251951)	2	ORR (RECIST 1.1)	Nab-ptx 150 mg/m^2 (days 1, 8 and 15 of each 28-day cycle)	39	Unresectable/metastatic or recurrent GC	2
Kanazawa et al.	R	Safety	Nab-ptx 260 mg/m^2 (day 1 of each 21-day cycle)	14	Unresectable/metastatic or recurrent GC	≥2
Fukuchi et al.	R	Safety and efficacy	Nab-ptx 260 mg/m^2 (day 1 of each 21-day cycle)	37	Unresectable/metastatic or recurrent GC	2
Sato et al. (UMIN000016973)	2	ORR (RECIST 1.1)	Nab-ptx 180 mg/m^2 (day 1 of each 21-day cycle)	37	Unresectable/metastatic or recurrent GC	≥2
Watson et al. (NCT02486601) FOXAGAST trial	2	pCR (Mandard TRG)	Nab-ptx 150 mg/m^2 plus FOLFOX4 q2w for six cycles	60	Resectable GC, HER2-	Perioperative
Shitara et al. (JapicCTI-132059) ABSOLUTE trial	3	OS	Nab-ptx 260 mg/m^2 (day 1 of each 21-day cycle) Nab-ptx 100 mg/m^2 (days 1, 8 and 15 of each 28-day cycle)	741	Unresectable/metastatic or recurrent GC	2
Nakayama et al. (JapicCTI-121987)	1	MTD and RD	Dose escalation: nab-ptx 180, 220, and 260 mg/m^2 (day 1 of each 21-day cycle) plus S-1 80 mg/m^2/day (days 1–14 of each 21-day cycle)	16	Unresectable/metastatic or recurrent GC	1

ORR overall response rate; nab-ptx: nab-paclitaxel, *GC* gastric cancer, *R* retrospective, *pCR* pathological complete response, *OS* overall survival; tolerated dose (MTD); recommended dose (RD)

Table 2 Data on overall survival, progression-free survival, tumour response of the included studies

Study	OS (months)	PFS (months)	Objective response rate (%)	Disease control rate (%)
Sasaki et al. [28] (NCT00661167)	9.2	2.9	27.8	59.3
Bando et al. [29] (JapicCTI-153088)	Not reached	7.6	54.8	92.9
Katsaounis et al. [30] (NCT02251951)	6.8	3	23.1	51.3
Kanazawa et al. [31]	10.5	6	28.5	64.2
Fukuchi et al. [32]	10.4	4.8	24.3	59.5
Sato et al. [33] (UMIN000016973)	9.2	2.4	5.9	47.1
Watson et al. [34] (NCT02486601) FOXAGAST trial	Not reached	Not reached	NA	NA
Shitara et al. [35] (JapicCTI-132059) ABSOLUTE trial	10.3 vs 11.1 vs 10.9	3.8 vs 5.3 vs 3.8	25 vs 33 vs 24	67 vs 78 vs 72
Nakayama et al. [37] (JapicCTI-121987)	NA	5.8	54.5	81.8

OS overall survival, *PFS* progression-free survival, *NA* not available

A phase II study made of 45 patients refractory to first-line chemotherapy investigated nab-ptx 100 mg/m^2 intravenously on days 1, 8, and 15 with ramucirumab 8 mg/kg administered on days 1 and 15 of a 28-day cycle. The primary endpoint of the study was the ORR assessed by an IRC and was 54.8% (90% confidence interval [CI] 41.0–68.0). The DCR was 92.9% (95% CI 80.5–98.5). The PFS assessment through IRC was 7.6 months (95% CI 5.4–8.1). However, the median OS of the study was not reached at data cutoff. The main treatment-related grade 3 or 4 adverse events were neutropenia (76.7%) and leukopenia (27.9%). These results show that the combination of nab-ptx plus ramucirumab is a promising combination, both effective and tolerable in Japanese pretreated AGC patients [29].

The phase II study of the Hellenic Oncology Research Group investigated nab-ptx at the dose of 150 mg/m^2 on days 1, 8, 15 of every 28 days in 33 pretreated GC patients with taxane-based regimens and in six GC patients co-treated with fluoropyrimidines plus cisplatin. Partial response (PR) was observed in nine patients (23.1%; 95% CI 10.1–37.2%), stable disease (SD) in 11 (28.2%), and disease progression in 18 (46.2%). The DCR was 51.3%. The median PFS and OS were of 3.0 months and 6.8 months, respectively [30].

The retrospective study of Kanazawa et al. [31] evaluated the clinical safety and efficacy of nab-ptx in 14 GC patients. Four out of 14 patients achieved PR. They showed that ORR and DCR were 28.5% and 64.2%, respectively. Moreover, they observed that patients having high relative dose intensity (RDI) ($\geq$80%) had longer PFS and OS than those with low RDI ($\leq$80%), which were of 11.8 vs. 4.0 months ($p=0.02$) and 14.3 vs. 8.2 months ($p=0.03$), respectively [31].

The retrospective study of Fukuchi et al. [32] investigated the clinicopathological and survival data of 37 patients with unresectable or recurrent GC treated with second-line nab-ptx mono-therapy at the dose of 260 mg/m^2 on day 1 of each 21-day cycle. The ORR was 24.3% and the DCR 59.5%. The median PFS and OS were 4.8 months and 10.4 months, respectively. The authors showed that cycle of chemotherapy $\geq$5 was the only significant independent predictive factor of longer PFS (odds ratio, 0.20; 95% CI, 0.08–0.50; $p<0.01$) [32].

The antitumor efficacy of nab-ptx against GC was demonstrated in a multicenter, single-arm, phase II study made of 34 patients. Patients were treated with low doses of 180 mg/m^2 nab-ptx on day 1 of each of the 21-day cycle. The primary endpoint, ORR, was 5.9%. Secondary endpoints, PFS and OS, were 2.4 months and 9.2 months, respectively. As to safety, the most common grade 3/4 toxicities were anemia (9.8%), neutropenia (5.9%), appetite loss (5.9%), and peripheral sensory neuropathy (5.9%) [33].

FOXAGAST was an open-label, phase II, non-randomized study that investigated tumor regression grade rate of the use of nab-ptx with oxaliplatin and 5-fluorouracil (FOLFOX) as perioperative regimen in 49 GC patients. Of the 42/44 resected tumors (95.5% of patients), the classification by pathological review categorized as tumor regression grading (TRG1) and TRG2 a total of 8 (16.3%; 95% CI 5.8–26.8) and 11 (22.5%; 95% CI 10.6–34.4) patients, respectively. As to adverse events, the most common ones were neutropenia (22.4%), nausea (10.2%), vomiting (10.2%), diarrhea (8.2%), and neuropathy (12.2%). With 16% of TRG1, the study met its primary endpoint [34]. Of note, this is the first study investigating nab-ptx in the perioperative setting.

The ABSOLUTE trial is a phase III, open-label, randomized, non-inferiority clinical trial comparing nab-ptx every 3 weeks (on day 1 of a 21-day cycle) at the dose of 260 mg/m^2, with weekly nab-ptx at the dose of 100 mg/m^2, on days 1, 8, and 15 of a 28-day cycle or weekly solvent-based ptx at the dose of 80 mg/m^2, on days 1, 8, and 15 of a 28-day cycle in 741 advanced GC patients refractory to a fluoropyrimidine-containing first-line chemotherapy regimen. The primary endpoint of the study was the median OS, which was 10.3 months (95% CI 8.7–11.4) in the group receiving every 3 weeks nab-ptx, 11.1 months (9.9–13.0) in the group receiving every week nab-ptx, and 10.9 months (9.4–11.8) in the group receiving every week solvent-based ptx (control arm). There was a non-inferiority result between the nab-ptx group and the solvent-based ptx group (HR 0.97, 97.5% CI 0.76–1.23; non-inferiority one-sided $p=0.0085$). On the other hand, nab-ptx given every 3 weeks group was not non-inferior compared to the solvent-based ptx group (1.06, 95% CI 0.87–1.31; one-sided non-inferiority $p=0.062$) [35]. Therefore, data from this randomized clinical trial show that giving nab-ptx every week was non-inferior than giving solvent-based ptx every week. Successively, an exploratory analysis of the ABSOLUTE trial divided patients into apparent peritoneal metastasis group (PM group) and no apparent peritoneal metastasis group (no PM group). The study included 240 and 243 patients in the weekly nab-ptx and solvent-based ptx, respectively. In the PM group, the median OS was 9.9 months (95% CI 7.5–12.9) and 8.7 months (95% CI 7.7–9.2) in the weekly nab-ptx ($n=140$) vs. the weekly solvent-based ptx ($n=152$) arm (HR 0.63; 95% CI 0.45–0.88; $p=0.0060$), respectively. The results were adjusted for prognostic factors and the HR for OS in the weekly nab-ptx arm versus the solvent-based ptx arm was 0.59 (95% CI 0.42–0.83; $p=0.0023$; PM group) and 1.34 (95% CI 1.101–1.78; $p=0.0414$; no PM group), with a significantly different interaction between the efficacy of the treatment and the presence of peritoneal metastasis between PM and no PM groups ($p=0.0003$) [36].

Nakayama et al. assessed the safety of the combination of an oral fluoropyrimidine (S-1) with nab-ptx in a study made of 16 patients with unresectable or recurrent GC. The study established the recommended dose (RD) at level 3a (S-1

80 mg/m^2 twice daily plus nab-ptx at 260 mg/m^2 on day 1). Neutropenia (62.5%) was the most common grade 3/4 toxicity. The ORR was 54.5%. Intriguingly, the authors found that the pharmacokinetic profiles of co-administrated S-1 and ptx were similar to those of nab-ptx or S-1 as single agents [37]. Therefore, the combination of the therapies was well tolerated and showed an antitumor efficacy in advanced GC.

Moreover, the SNOW study was a dose-escalation phase I/II study (UMIN000016788) administering a combination of S-1, nab-ptx, and oxaliplatin every 2 weeks in advanced GC. The dose-limiting toxicity and maximum tolerated dose were identified to pave the way for a subsequent ongoing phase II study. On this basis, the SNOW regimen represented by the triplet made of S-1, nab-ptx and oxaliplatin could be a promising therapeutic option [38]. Results from larger clinical trials assessing the efficacy of the SNOW regimen in patients are eagerly awaited to see if the triplet can improve the survival of patients.

The PFS of GC patients treated with nab-ptx together with S-1 versus SOX (S-1 and oxaliplatin) as first-line therapy has been investigated as the primary endpoint in a randomized, open-label, phase III clinical trial made of 294 patients. Secondary endpoints of the study are ORR, OS and safety (NCT03801668).

The pathological complete response of the use of nab-ptx versus FOLFOX has been investigated as the primary endpoint in an open-label, phase II study made of 55 patients. Among secondary endpoints, there are DFS, OS, and Quality of Life (QoL; NCT02486601). Table 3 summarizes all the ongoing clinical trials investigating nab-ptx alone or in combination with other drugs for the treatment of GC (NCT02486601).

Discussion

To date, nab-ptx has shown remarkable clinical activity for several cancers, including breast, lung, and pancreatic cancer [39–41]. Interestingly, the use of nab-ptx in metastatic pancreatic cancer, albeit associated with poor prognosis, has led to a long-term survivor (> 3 years) group of about 4% of treated patients [41].

Nanoparticle albumin-bound ptx is a molecule that allows a better solubility in the blood circulation than free ptx. As a consequence, higher doses of nab-ptx can be administered in a shorter time than solvent-based ptx. Moreover, the nab-ptx composition does not require a hydrated ethanol solvent and, therefore, it can be administered to alcohol-intolerant patients. These chemical improvements to the molecule, which brought to the investigation of the drug in pre- and clinical studies, showed that the use of nab-ptx is relatively safe. Moreover, its use every week was non-inferior than solvent-based ptx given every week. In the near future, the use of nab-ptx will be investigated with targeted drugs according to the positive results obtained in in vitro and in vivo experiments. First, the nab-ptx in preclinical models of HER2-positive GCs improved the efficacy of monoclonal antibody trastuzumab [25]. Hence, on this basis, the combination of trastuzumab and nab-ptx should be tested in clinical trials for GC patients. Second, nab-ptx with the anti-angiogenic drug nintedanib was capable to induce tumor regression in animal models [26]. These combinations warrant clinical evaluation. Third, the dual inhibitor of PI3 K/mTOR NVP-BEZ235 with nab-ptx resulted in a 97% inhibition in vivo [27], a result that also deserves clinical validation.

In an era that has been contemplating the advent of personalized medicine, the use of combinations of nab-ptx with a targeted therapy is an interesting root that deserves further investigation. In fact, the use of trastuzumab, nintedanib, and NVP-BEZ235 together with nab-ptx could provide improvements for patients. Interestingly, as shown in Fig. 1, the three different drugs that increase the effectiveness of nab-ptx in preclinical models target the PI3 K/mTOR signaling pathway. This pathway could be important for improving the efficacy of GC therapy in future clinical therapies.

After genetic profiling of GCs, sub-populations of patients could be selected that would most likely benefit from nab-ptx in combination with targeted. For example, HER2-positive GC patients could mostly benefit from trastuzumab and nab-ptx combination. Some ongoing clinical trials are testing the use of nab-ptx with S1, immunotherapies, or chemotherapies.

In conclusion, although the heterogeneity of the treatment schedules used in preliminary trials that investigated the use of nab-ptx in GC and the relatively small size of the populations preclude a precise estimate of the benefit of nab-ptx, we deem that this could be an intriguing option for GC replacing and adding novel efficacy compared with the old ptx formulation. Meanwhile, clinical trials investigating the biomarkers of responsiveness of GC patients to nab-ptx are warranted.

Table 3 Ongoing clinical trials using nab-paclitaxel for gastric cancer patients

Clinical trial identifier	Phase	Administered drug(s) (target)	Primary endpoint	Status
NCT03801668	3	Nab-paclitaxel plus S-1 Oxaliplatin plus S-1	PFS	Not yet recruiting
NCT02486601	2	Nab-paclitaxel FOLFOX	pCR	Recruiting
NCT03283761	2	Nab-paclitaxel Oxaliplatin 5-FU Leucovorin	ORR	Recruiting
NCT03162510	1	Oxaliplatin Nab-paclitaxel S-1 Leucovorin	MTD of oxaliplatin DLT	Recruiting
NCT02574663	1	TGR-1202 Nab-paclitaxel + gemcitabine Oxaliplatin + folinic acid + fluorouracil Oxaliplatin + folinic acid + fluorouracil + bevacizumab	AE	Active, not recruiting
NCT03668418	N/A	Fluorouracil Lederfolin Oxaliplatin Irinotecan Docetaxel Cisplatin Epirubicin Gemcitabine Nab-paclitaxel	Correspondence with chemo-sensitivity data collected in zebrafish model	Recruiting
NCT02658214	1	Paclitaxel + carboplatin Carboplatin + etoposide Gemcitabine + carboplatin Nab-paclitaxel (paclitaxel-albumin) + carboplatin Oxaliplatin + 5-FU + leucovorin (calcium folinate/folinic acid) Durvalumab Tremelimumab Nab-paclitaxel (paclitaxel-albumin) + gemcitabine Cisplatin + 5-FU		Active, not recruiting
UMIN000016788 (SNOW)	1/2	S-1 Nab-paclitaxel Oxaliplatin	MTD, RD	Recruiting

PFS Progression-free survival, *pCR* pathological complete response, *MTD* maximum tolerated dose, *RD* recommended dose, *DLT* dose-limiting toxicity, *AEs* adverse events, *ORR* overall response rate, *5-FU* 5-fluorouracil, *S-1* fluoropyrimidine

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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