· Review ·

Nanoparticle drug delivery systems in solid tumor therapy

Yuan Dong[1,2,#], Xuanyi Yang[1#], Cen Yan[1], Yingmei Feng[1,2*]

[1]Department of Science and Technology, Beijing Youan Hospital, Capital Medical University, Beijing, 100069, China

[2]Laboratory for Clinical Medicine, Capital Medical University, Beijing, 100069, China

Abstract

Cancer is one of the leading causes of mortality that severely threatens life expectancy. Chemotherapy is the most common regimen for cancer patients. However, low drug availability in tumor site and its off-target effect elicit toxicity and attenuate the efficacy of chemotherapy. To overcome that, nanoparticles (NPs) have been delicately designed as carriers for tumor diagnosis and drug delivery. Being formulated and bioengineered such like chemical modification and conjugation of peptide and antibody, NPs hold distinct advantages for better biocompatibility, bioavailability and tumor cell targeting. Hereby, we first overviewed various NP formulations on cancer cell tracing and drug delivery system. Then, we performed PubMed search for NPs involved chemotherapy in clinical trials of advanced non-small-cell lung cancer (NSCLC) and breast cancer. When NPs drug system was applied for monotherapy or drug cocktail, patients were well tolerated and achieved better efficacy in most studies, as evidenced by few months of prolonged overall survival and progression-free-survival in patients among all ages. However, how to achieve long-time survival and better life quality is not covered yet. For perspectives, multimodal regimens are required to enhance targeting efficiency.in which NPs delivery system is synergized and integrated with pharmacological and physical treatment.

Keywords: nanoparticles, solid tumor, drug delivery, clinical trials, regimens

Introduction

Cancer ranks as one of the leading causes of mortality worldwide. According to the report from World Health Organization (WHO), an estimated 19.3 million new cancer cases occurred in 2020, accompanied with approximate 10.0 million cancer deaths. By 2024, the global cancer burden is expected to be 28.4 million cases with a 47% rise from 2020 [1, 2]. The therapeutic purpose of current anti-cancer agents could be achieved primarily by inhibition of tumor cell proliferation and induction of cell death. However, the chemotherapy promotes toxic effect on both cancerous and normal cells. Besides, chemical instability, poor cellular uptake and other side effects of conventional chemotherapeutic drugs also obstruct their progresses in the cancer treatment.

#Y. D. and X. Y. contributed equally to the study.

***Correspondence:**

Yingmei Feng; Email: yingmeif13@ccmu.edu.cn.

To improve the efficacy of cancer treatment with limited off-target effect, nanoparticles (NPs)-based drug delivery system has emerged as a promising therapeutic approach, especially for cancers. NPs are small particles, ranging from 1-1000 nm in diameter, preferably 5-200 nm [3]. NPs are big collections including inorganic NPs such as gold [4] or organic NPs like liposomes [5] to synthetic polymeric particles [6], which are of particular interest as their size, shape and surface chemistry can be readily tuned. NPs have distinct advantages for drug carriers, transporting the chemotherapeutic agents to tumors, increasing bioavailability, retention, and tissue distribution. They can be modified to target more specifically to tumor cells, avoiding normal tissues and reducing toxicity in the rest of the body [7]. In this review, we would summarize recent advances of NPs that have been applied in the treatment of solid tumor in clinical practice.

Types of nanoparticles for cancer diagnosis

Metallic nanoparticles

Metallic nanoparticles (mNPs) are the colloidal particles with the size of 1-100 nm, the small size of mNPs gives them unique properties compared to their corresponding bulk materials [8]. Drugs can be dispersed or encapsulated within a shell, or covalently attached to the surface of the NP, or encapsulated within a structure and then to be delivered to the targeted tumor cells [9, 10]. The most widely used mNPs include gold, silver, silica, and iron oxide. mNPs are promising nanocarriers for therapeutics due to their facile synthesis, ease of functionalization, biocompatibility, and inherent non-toxicity. Controversially, cytotoxicity potential, the difficulty of degradation and the elimination of metals from the organism [11], mNP incorporation [12] and other negative aspects also have gained attention at the same status of importance, influencing the applications of mNPs in nanomedicine.

Iron oxide nanoparticle

Iron oxide nanoparticles (IONPs) have found several applications in biomedicine field and most widely used as a contrast probe in MRI. For instance, SH U 555 is a contrast agent, comprising iron oxide microparticles (maghemite and magnetite coated with carboxydextran. Upon administration, they are sequestered mostly in liver and spleen where they maintain signals for detecting focal liver lesions with T2-weighted fast spin-echo MRI [13].

Of interest, tumor cells are featured with extreme high levels of receptors to mediate their aberrant cell growth. On the other hand, the distinct receptor patterns could assist us to discriminate tumor cells against normal healthy cells. When antibodies specific for these receptors are conjugated to INOPs, they act as magnetic probes to enhance image contrast signals by MRI for identification of tumor cells in the body. For instance, Cetuximab (C225, Erbitux®) is a chimeric human/murine monoclonal antibody that specifically targets the human EGFR with a 2-log higher affinity than EGFR [14]. Thus, Cetuximab competitively blocks EGFR signaling in tumor cells to trigger cell death. Taking this advantage, Tseng et al developed a therapeutic platform based on superparamagnetic iron oxide NPs (SPIONs) in which dextran-coated SPIONs were conjugated to anti-EGFR monoclonal antibody cetuximab (cet-PEG-dexSPIONs) via periodate oxidation [15]. More specifically, the dihydrazide-PEG linker was added to dextran-coated SPIONs via periodate oxidation of dextran. Then, active aldehyde functional groups were constructed onto EGFR antibody periodate oxidation. Afterward, Cetuximab was bioconjugated to PEG-dexSPIONs prior to intravenous injection.

Gold nanoparticles

Despite its diagnostic potential, SPIOs could trigger cell damage and inflammation and therefore, was not used in

clinics any more [16]. Instead, gold nanoparticles (AuNPs) are widely used as cancer diagnostic agents due to their physical properties and tailored surface functionalization. They are synthesized by chemical, physical, or biological methods. In chemical method, AuCl4 is reduced in citrating-containing water [17]. In physical method, AnNPs is synthesized by microwave-, ultraviolet-, and gamma-mediated radiation [18]. In biological method, metal salts are reduced by biosynthetic system such like fungi, bacteria, or plants to generate stable metals [19]. In a cross-sectional clinical trial, alveolar breaths were collected from 87 volunteers involving 22 head-and-neck cancer patients, 25 lung cancer patients, and 40 healthy controls. The subjects were inhaled nano-artificial nose containing five gold NPs sensors carrying tert-dodecanethiol, hexanethiol, 2-mercaptobenzoazole, 1-butanethiol, and 3-methyl-1-butanethiol ligands. The Exhaled alveolar breath GC-MS. samples were collected and separated by principle component analysis, five sensor NA-NOSE responses demonstrated distinct patterns among head-and-neck cancer, lung cancer as well as healthy controls [20].

To further improve tissue penetration, the size of AuNPs is reduced from 100 nm to 2-6 nm and surface modification further potentiates AuNPs uptake by tumor cells [21]. Due to small size, AuNPs could be not only easily uptake by host cells for diagnosis and but also cleared out from the body. In cultured tumor cells, anti-EGFR antibody coated with ultra-small AuNPs was added to cultured tumor cells, better cellular penetration and faster clearance were observed by Photoacoustic imaging [22]. These results confirmed that ultra-small AuNPs are one of the practical options for tumor diagnosis.

Magnetic nanoparticles

Magnetic nanoparticles (MNPs) are about 1-100 nm and the single-core MNPs consist of a single magnetic core coated by an organic or inorganic shell, while multi-core MNPs consist of several nanocrystals (magnetic cores) packed within a matrix. MNPs demonstrate the most superior property in nanomedicines is their magnetic characteristics. Because of no virtual magnetic background within biological samples, once MNPs-based carriers into the body can be easily measured due to their high sensitivity. In addition, MNPs effectiveness *in vivo* can be tailored by applying a safe and biocompatible coating such as polysaccharides, fatty acids, or other polymers [23], to increase their acceptability for a specific target in the human body. Besides, modifying the surface chemistry of MNPs to achieve the multifunctionality of them and the low toxicity make MNPs more popular in drug delivery nanomedicines [24]. Collectively, interesting physical properties of MNPs give great possibilities for their use in biological and biomedical applications.

Carbon nanotubes

Carbon nanotubes consist of nanoscale carbon particles with an average particle size of 150 nm, which are phagocytosed by macrophages after being injected into local tumor tissue under endoscopy or direct vision. These cylindrical structures only consist of carbon atoms with about a diameter of approximately 1–4 nm (depending on the number of graphene layers) and 1–10 nm in length. In general, CNTs contain single-wall CNTs and multiwall CNTs, favoring unique structural, electronic, optical, and mechanical properties [25]. Carbon nanoparticle suspension is an excellent tracer for lymph nodes and has a good safety profile [26]. Carbon nanoparticle suspension is used to trace lymph nodes not only in colorectal cancer, but also in breast cancer, thyroid cancer, gastric cancer and so on [27, 28]. Wei Ge et al. showed that injection of carbon nanoparticle suspensions in colorectal cancer patients resulted in better imaging of lymph nodes and more accurate of nodal staging [29].

Types of nanoparticles in cancer drug delivery

To achieve enhanced permeability and retention (EPR) in the tumor, NPs-mediated drug delivery systems have been used in the clinics [30]. Up to date, 28 NPs have been approved by Food and Drug Administration or European Medicines Agency for clinical use [31, 32]. In this section, we introduce different types of NPs that were used in cancer treatment.

Liposomes

Traced back to 1960s, lipid vesicles were the first NPs and later named as liposomes [33, 34]. Liposomes are self-assembled, uni-lamellar or multi-lamellar spherical phospholipids. They could encapsulate both hydrophilic and hydrophobic anti-cancer drugs. Hydrophilic drugs are encapsulated within the aqueous and hydrophobic drugs are in the lipid bilayer, which protect the drugs from the environmental degradation during systemic circulation [35]. The inherent advantages of liposomes including biocompatibility, low toxicity, high loading capacity, and controllable release kinetics make they are the most widely used and the most promising vehicles in the field of drug delivery systems [36]. Particularly, only a few anti-cancer drug NPs have been approved by Food and Drug Administration (FDA), liposomal formulations are dominant. Doxil, doxorubicin loaded liposomal formulation, is one such passive targeted drug delivery system and has been approved by the FDA using in the clinical treatment of Kaposi sarcoma [37]. Other liposomal formulations such as liposomal daunorubicin (DaunoXome), liposomal vincristine (Marqibo) and liposomal irinotecan (Onivyde) have also been approved by the FDA. In addition, non-polyethylene glycol (PEG)-ylated liposomal doxorubicin (Myocet) and liposomal mifamurtide (MEPACT) have been approved by the European Medicines Agency (EMA) [31].

However, liposomes are considered mainly as carriers of water-soluble drugs. Because the small space available in the membrane and the destabilization effect of the drug on the outer space, limiting the drug loading capacity of poorly soluble drugs [38, 39]. Besides, intravenous injection of liposomal drugs can cause the so-called "complement activation-related pseudoallergy" (CARPA), a drug-induced acute immune toxicity manifested in hypersensitivity reactions [40, 41]. Additionally, liposomes have some other limitations, such as problems with stability and industrial reproducibility, difficulties in sterilization, the oxidation of phospholipids, and the limited control of drug release [42].

Carbon nanotubes

Drugs entrapped within CNTs are less exposed to the enzymes in the body, avoiding from degradation and keeping drug stability even in in vivo and clinical studies [43]. In addition, compared to non-targeted CNTs, the functionalized surface of nanotubes can bind to different targeting molecules, enhancing tumor cell specificity of cytotoxic agents and overcoming the multidrug resistance [42, 44]. Albeit these encouraging advantages, no carbon nanotubes have been approved by FDA for clinical usage. The toxicity of CNTs hampers its utility in cancer therapy.

Polymeric nanocarriers

Polymeric nanocarriers have different structures including dendrimers, polymeric micelles, and capsules/particles (polymeric nanoparticles). In general, these polymeric nanocarriers have in common are composed with a hydrophobic core which contains poorly-water soluble anticancer drugs and a hydrophilic shell which allows the inclusion of hydrophilic drugs and provides stability to the nanocarriers [42]. Dendrimers consist of globular molecules, and these symmetrical molecules can be synthesized in a reproducible manner to adjust the

biocompability and the pharmacokinetics of the carriers, like a tree [45]. Polymeric micelles (PMs) are self-assembled, monolayer system which composed of amphiphilic block copolymers that form nanosized spheroidal micellar structures [46]. Polymeric nanoparticles (PNPs) are more advanced methods which used to form capsules with a liquid core and a shell made of fused polymer nano microparticles [47]. Drugs are encapsulated or physically entrapped within a polymeric matrix (nanospheres) or entrapped into a cavity surrounded by a polymeric membrane (nano capsules), being also possible the conjugation of the anticancer drug to the surface or the core of the particles [48, 49]. The various and available assembly methods of polymeric materials make these nanocarriers ideal for the drug delivery systems. Compare with other nanocarriers, polymeric nanocarriers hold unique advantages. Firstly, their outer surface can be modified with different functional groups to transport drugs into specific areas depending on the surface modifications. At the same time, they can be used for monitoring the state of cancerous organs as well as the progress of the curing process [50-52]. Secondly, polymeric nanocarriers can be used for visualizable diagnose. When they are attached by imaging agents, these particles can be visualized via magnetic resonance imaging [10], computed tomography [53] or X-ray, improving the effectiveness of targeting in cancer therapy [54]. Additionally, they are promising vehicles for long circulation times in blood, decreasing clearance by macrophages and the ability of accommodating a high number of drugs without risk of out leak [46].

There are also some drawbacks need more consideration. For example, these carriers share a limiting feature with polymer therapeutics: the multistep synthesis that increases production costs. Apart from that, changes in the physical-chemical properties of the nanocarriers in the systemic circulation such as change in particle size, aggregation behavior and premature drug release also limit their therapeutic applications [55].

Clinical NPs applications for cancer treatment

As reported in the Global Burden of Disease study, there

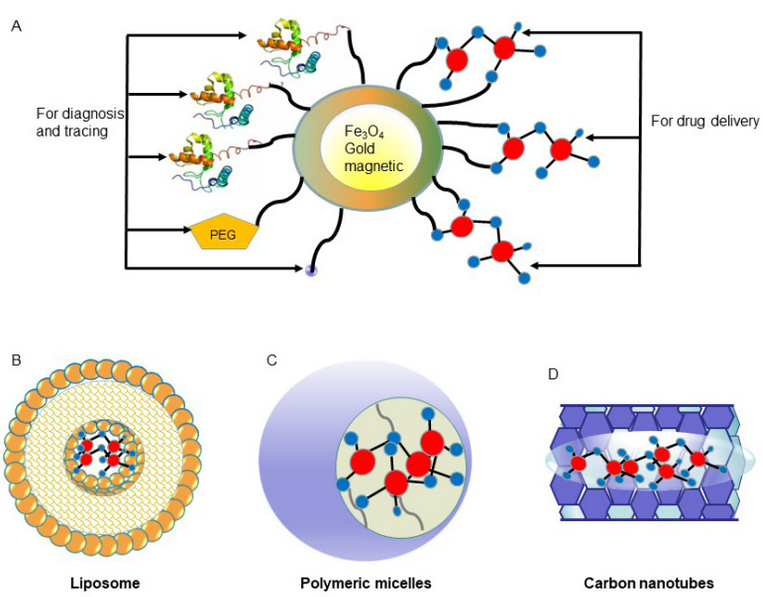


Figure 1. Representative structure of nanoparticles (NPs) for tumor diagnosis and anti-cancer agent delivery. A. Metal nanoparticles in cancer diagnosis and drug delivery. On the left side, metal NPs are conjugated with peptide or antibody for specific targeting and chemical modification for better retention. On the right side, drugs are linked to metal NPs and delivered to the tumor site. B-D, Liposomes, polymeric micelles, and carbon nanotubes used in anti-cancer drug delivery.

were 24.5 million incident cancer with 9.6 million cancer-related death in 2017. When dissected further nonmelanoma skin cancer, the incidence of tracheal, Bronchus, and Lung Cancer, breast cancer, colon and rectum cancer, stomach cancer and liver cancer were the global top 6 cancer [56]. Approximately, new cases of tracheal, Bronchus, and Lung Cancer, breast cancer, colon and rectum cancer, stomach cancer and liver cancer amounted to 2.2, 2.0, 1.8, 1.2, and 0.953 million, respectively. As the consequence, the cancer-related death was 1.9, 0.6, 0.896, 0.865, and 0.819 million for tracheal, Bronchus, and Lung Cancer, breast cancer, colon and rectum cancer, stomach cancer and liver cancer, respectively [56]. Excluding Nonmelanoma skin cancer and sex difference, lung cancer is the number one killer (18.4% of the total cancer cases), followed by breast cancer (11.6%), prostate cancer (7.1%), and colorectal cancer (6.1%) for incidence and colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) [57].

To evaluate the clinical results of NPs-mediated cancer drug delivery, we performed PubMed search in electronic databases including PubMed, China National Knowledge Infrastructure, and Google Scholar. Search terms included, but were not limited to, “cancer therapy”, “nanoparticles”, “drug delivery system”, “solid tumor”, “clinical trials”, “not mice”, “not rats”, “not review” and “not meta-analysis”. There are 372 published literatures searched relating to these key words in which NPs were more frequently applied for lung cancer and breast cancer among all patients. Below, we focused on the update of NPs application in lung cancer.

Lung cancer

The common cause of lung cancer is long-term smoking history or long-term exposure of tobacco smoke. Lung cancer is characterized by abnormal cell growth in lung tissues, these abnormal cells may spread to lymph nodes or other organs in the body, such as the brain. Based on histological features, lung cancer is divided into two major groups, the Small-Cell Lung Cancer and Non-Small-Cell Lung Cancer (NSCLC) [58]. Metastatic, squamous NSCLC is the most common type of lung cancer.

Nanoparticle albumin-bound-paclitaxel (nab-Pac)

Paclitaxel is an anti-microtubule agent and being the only drug approved by FDA for NSCLC therapy. To improve drug availability and reduce toxicity, nanoparticle 35 published clinical trials identified that assessed the effects and safety of NP-based drug delivery systems in the treatment of lung cancer (Figure 2A). Of 35 clinical trials, three are still ongoing and not finalized yet [59-61]. Among 32 finalized clinical trials, NSCLC patients were received either nanoparticle albumin-bound paclitaxel (nab-PTX) (n=30) [62-91] or nanoparticle polymeric micellar paclitaxel (n=2) [92, 93] (Figure 2B). albumin-bound (nab)-paclitaxel (nab-Pac) (Abraxane®) has been applied to patients since 2005 [94]. Nab-Pac is formulated with non-covalent link of albumin and paclitaxel. Instead, they are homogenized under high pressure, generating a NP particle with the size of 130 nm. Following injection, nab-Pac is dissolved and paclitaxel is bound to unbound albumin or other carriers in the blood for further transportation. As albumin is the most common and abundant carrier in the blood, nab-Pac construct is table with lest toxicity [95]. Among 33 clinical trials of nab-Pac involving 1789 NSCLC patients, there were 6 RCTs [60, 76, 77, 85, 87, 93], 24 single arms phase I-III [62-68, 70-72, 75, 78-82, 84, 86, 88-92, 96], and 3 retrospective studies (n=491) [69, 74, 97] (Table 1). Totaled 2280 NSCLC patients were received nab-Pac alone (n=553) [62, 74, 75, 79, 80, 82, 84, 90, 98], or combined with carboplatin (n=9) [60, 64, 67, 68, 70, 73, 86, 88, 99], or others (n=5) [72, 77, 81, 87, 93]. All the NSCLC patients recruited in the trials were in advanced stages and/or relapse from the previous treatment.

When nab-Pac was used as monotherapy, NSCLC patients were well-tolerated [62, 64, 73, 75, 86, 88, 99] and had high objective response rate (ORR), long median progression-free survival (PFS), and acceptable toxicity [90]. In a phase 3 RCT study, NSCLC patients were randomized 2:1 to maintenance nab-Pac plus best supportive care (BSC) or BSC alone. The primary endpoint was PFS. Secondary endpoints included safety and overall survival (OS). After 28.4 months of follow-up, the median OS was 17.61 months for nab-Pac plus BSC and 12.16 months for BSC (HR, 0.68; 95% CI, 0.47-0.98; nominal $P = 0.037$), showing a trend favoring nab-Pac plus BSC [85].

Same findings were found in old NSCLC patients received nab-Pac as monotherapy [82] or combined with other chemotherapy drugs [70, 72, 73, 88]. In a retrospective study in which 12 old patients who received nab-Pac as the first-line treatment (seven also received carboplatin), and 64 received nab-Pac as the latter-line treatment. The overall ORR, disease control rate, median PFS and median OS were 14.5%, 69.7%, 5.2 months, and 12.2 months, respectively, indicating a good clinical response profile in the elderly patients with stage IIIB-IV NSCLC [82].

The effect of nab-Pac was also assessed in NSCLC patients when used as dual therapy. In a RCT phase 3 trial, 559 untreated metastatic NSCLC patients were randomly received pembrolizumab or saline placebo for up to 35 cycles. In the first 4 circles, they were all administrated carboplatin with conventional paclitaxel or nab-Pac. After a median follow-up of 7.8 months, the median OS was 4.6 months longer for combination treatment group than place group (15.6 months vs. 13.2 months, $P<0.0001$). Moreover, the median PFS was 1.6 months longer for the combination groups compared with place (6.4 months vs. 4.8 months, $P<0.0001$) [76]. In a RCT phase 3 trial, 503 patients with advanced NSCLC were randomly allocated (1:1) to receive docetaxel (60 mg/m^2) in 60 minutes on day 1 every 3 weeks or nab-Pac (100 mg/m^2) in 30 minutes on days 1, 8, and 15 of a 21-day cycle every 3 weeks [87]. The primary end point was OR analyzed on an intention-to-treat basis. Results showed that median overall survival was 16.2 months for the 252 patients allocated to nab-Pac and 13.6 months for the 251 patients allocated to docetaxel. Median PFS was 4.2 months and 3.4 months, respectively. The ORR was increased and adverse events (AEs) of

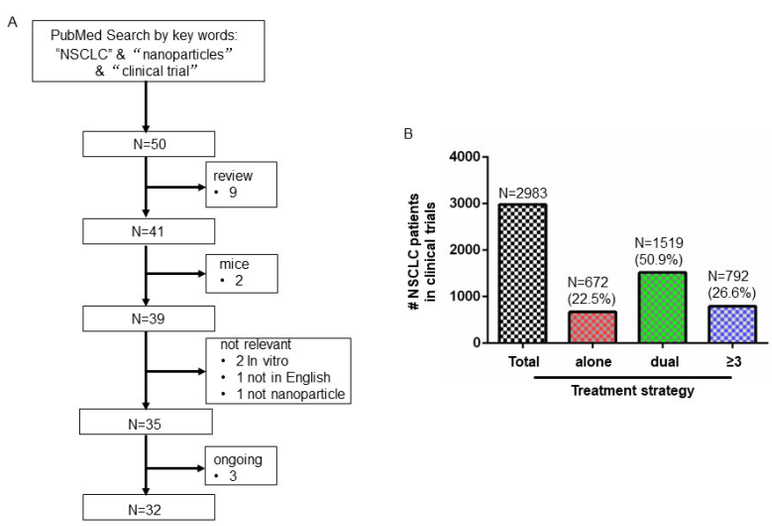


Figure 2. Clinical trials of nanoparticles-mediated drug treatment in NSCLC patients. A. A scheme of PubMed search of clinical trials involving nanoparticles-mediated drug delivery in NSLCL patients. B. number of NSCLC patients enrolled in the clinical trials. Alone, patients received only nanoparticle albumin-bound-paclitaxel (Nab-Pac) or nanoparticle polymeric micellar paclitaxel (Pm-Pac). Dual, patients received one more anti-cancer drug combined with nab-Pac or Pm-Pac; ≥3, patients received two or more than 2 anti-cancer drugs when combined with nab-Pac or Pm-Pac.

Table 1. List of clinical trials using NPs-mediated drug treatment in Non-Small-Cell Lung Cancer patients.

First authors	Type of clinical trial	Name of drug	Type of Patients	Number of patients	Treatment strategy	Main conclusions
Rizvi et al. [62]	Phase I/II	nab-PTX	advanced (Stage IV)	N=40	Nab-PTX 100 and 150 mg/m^2 without corticosteroid or antihistamine pre-medications on days 1, 8, and 15 of a 28-day cycle.	Nab-PTX was well tolerated and demonstrated encouraging single-agent activity.
Stinchcombe et al. [63]	Phase I	nab-PTX, gemcitabine	NSCLC (n = 8), SCLC (n = 6) and esophageal cancer (n =1)	N=15	gemcitabine 1000 mg/m^2 on days 1, 8 in all cohorts, and nab-PTX at doses of 260, 300, 340 mg/m^2 every 21 days depending on the treatment cohort.	The maximum tolerated dose of nab-PTX is 300 mg/m^2 in combination with gemcitabine 1000 mg/m^2 in previously treated NSCLC and SCLC patients.
Raynolds et al. [64]	Phase II	nab-PTX, carboplatin, bevacizumab	advanced (stage IIIB/IV)	N=50	Intravenous nab-PTX 300 mg/m^2, carboplatin at AUC of 6, and bevacizumab 15 mg/kg on day 1 of each 21-day cycle.	The combination of nab-PTX, carboplatin, and bevacizumab was well tolerated with moderate neutropenia.
Okamoto et al. [65]	Phase II	nab-PTX, carboplatin	advanced, stage III-IV, untreated, metastatic	N=18	Nab-PTX 100 mg/m^2 without steroid or antihistamine premedication once a week in combination with carboplatin at an AUC of 6 on day 1 of repeated 21-day cycles.	The combination of nab-paclitaxel (100 mg/m^2) administered weekly and carboplatin at an AUC of 6 every 3 weeks was well tolerated in Japanese patients with advanced NSCLC.
Ho et al. [66]	Phase I/II	pemetrexed plus nab-PTX	advanced	N=49	pemetrexed at 500 mg/m^2 on day 1 and nab-PTX day 1 at 180, 220, & 260 mg/m^2 every 21 days.	pemetrexed 500 mg/m^2 and nab-PTX 260 mg/m^2 day 1 every 21 days is a safe and feasible combination.
Ahn et al. [92]	Phase II	Cremorphor EL-free paclitaxel (Genexol-PM), gemcitabine	advanced	N=48	Genexol-PM 230 mg/m^2 on day 1 and gemcitabine 1,000 mg/m^2 on day 1 and day 8 of a 3-week cycle.	CrEL-free paclitaxel in combination with gemcitabine showed favorable antitumor but frequent grade 3/4 toxicities
Grilley-Olson et al. [67]	RCT, phase II	nab-PTX, carboplatin	Extensive stage	N=27	Arm A: carboplatin (AUC of 6) on day 1 and nab-PTX 300 mg/m^2 on day 1 every 3 weeks); arm B (carboplatin AUC of 6 on day 1 and nab-PTX 100 mg/m^2 on days 1, 8, and 15 every 21 days).	Carboplatin and nab-PTX demonstrated activity in ES-SCLC but required frequent dose adjustments.
Bertino et al. [68]	Phase III	nab-PTX, carboplatin	advanced	N=27 in the first stage; N=36 in the second stage	Nab-PTX 300mg/m^2 and reduced to 260 mg/m^2 followed by carboplatin (AUC of 6) administered on day 1 of a 21-day cycle.	Confirmed the activity of nab-PTX combined with carboplatin, particularly in squamous NSCLC.
Sexena et al. [69]	Retrospective analysis	nab-PTX	stage IV, relapsed	N=31	15 started at a dose of 260mg/m^2 on day 1 of a 21-day cycle; 6 started with a dose of 230mg/m^2 and 10 started at a dose of 200mg/m^2 every 21 days.	Single-agent nab-PTX was well tolerated and demonstrated efficacy in advanced NSCLC patients with relapsed or platinum-refractory disease.

Okuma et al. [70]	Phase II	nab-PTX	Advanced, untreated	N=10	Nab-PTX 100 mg/m^2 on days 1, 8, and 15 of each 21-day cycle, plus carboplatin (AUC of 6) 6 on day 1 of each 21-day cycle, for up to six cycles.	Nab-PTX plus carboplatin, without dose reduction is toxic and intolerable as first-line chemotherapy in elderly patients with advanced NSCLC.
Kaira et al. [71]	Phase II	nab-PTX, carboplatin, gemcitabine	Local advanced stage III	N=14	Weekly nab-PTX 30-40 mg/m^2 together with carboplatin (AUC of 2).	feasible and well tolerated for the treatment of patients with unresectable locally advanced NSCLC.
Miyauchi et al. [72]	Phase II	nab-PTX	advanced	N=32	CBDCA (AUC of 6 mg/mL/min) on day 1 and nab‐PTX 75 mg/m^2 on days 1, 8, and 15 every 4 weeks.	Modified CBDCA plus weekly nab‐PTX demonstrated significant efficacy and acceptable toxicities in elderly patients with advanced NSCLC.
Shiroyama et al. [73]	Phase II	nab-PTX, carboplatin	advanced, previous untreated	N=30	carboplatin (AUC of 6) on Day 1, and nab-PTX 100 mg/m^2 on Days 1, 8, and 15, every 28 days for ≤4 cycles.	Carboplatin plus weekly nab-PTX is effective and well tolerated as a first-line treatment for elderly patients with advanced squamous NSCLC.
Naito et al. [74]	Retrospective	nab-PTX	relapsed	N=14	As monotherapy: nab-PTX 100mg/m^2 weekly for 3 weeks in a 4-week cycle or weekly for 2 weeks in a 3 to 4-week cycle. As dual therapy: CBDCA (AUC of 6) plus nab-PTX 100 mg/m^2 weekly for 3 weeks in a 4-week cycle or for 2 weeks in a 3 to 4-week cycle.	a moderate clinical efficacy for nab-PTX chemotherapy regimens for relapsed SCLC, with an acceptable safety and tolerability profile.
Anzai et al. [75]	Phase II	nab-PTX	advanced	N=32	Nab-PTX 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle.	an active and well-tolerated regimen in previously treated NSCLC patients
Paz-Ares et al. [76]	RCT, phase III	pembrolizumab, nab-PTX, cisplatin	untreated metastatic, squamous NSCLC	N=559	200 mg of pembrolizumab or saline placebo on day 1 for up to 35 cycles. For the first 4 cycles, all the patients also received carboplatin (AUC of 6) on day 1 and either paclitaxel 200 mg/m^2 on day 1 or nab-PTX 100 mg/m^2 on days 1, 8, and 15.	The addition of pembrolizumab to carboplatin and either paclitaxel or nab-PTX resulted in longer overall survival and progression-free survival, a higher response rate, and a longer duration of response than chemotherapy alone, regardless of the level of PD-L1 expression.
Morgensztern et al. [77]	RCT, phase II	nab-Pac, CC-486 (an oral formulation of 5-azacytidine)	advanced	N=161	nab-PTX 100 mg/m^2 on days 8 and 15 plus CC-486 200 mg daily on days 1 to 14 or single-agent nab-PTX 100 mg/m^2 on days 1 and 8, with both regimens administered every 21 days	no benefit from the addition of CC-486 to nab-PTX.

Akiyama et al. [78]	Phase II	S-1, an oral fluoropyrimidine, carboplatin, nab-PTX	advanced, untreated	N=72	Four cycles of induction by carboplatin (AUC of 6) on day 1 of a 28-day cycle, and nab-PTX 100 mg/kg on days 1, 8, and 15. Then received maintenance therapy with S-1 (80 mg/m^2, days 1-14 of a 21-day cycle) until disease progression or unacceptable toxicity.	Switch maintenance therapy with S-1 after induction therapy with carboplatin and nab-paclitaxel was associated with moderate efficacy and acceptable safety and may represent a feasible treatment option for patients with advanced SCC.
Harada et al. [79]	Phase I/II	nab-PTX	pretreated advanced, without EGFR mutation and anaplastic lymphoma kinase rearrangement	N=5 in phase I; N=55 in phase II.	In phase I, a 4-week cycle (dose level 0: days 1, 8, 15 and 22 or dose level –1: days 1, 8 and 15) of 100 mg/m^2 nab-PTX until disease progression or unacceptable adverse events were observed. In phase II, nab-PTX was repeated as in phase I.	failed to meet predefined primary endpoints for patients with advanced NSCLC, although the PFS and OS were comparable with those in previous reports and toxicity was acceptable.
Kato et al. [80]	Phase II	nab-PTX	advanced	N=22	weekly nab-PTX administered 100 mg/m^2 intravenously on days 1, 8, and 15 every 3 weeks.	Nab-PTX may be a safe and effective later-line chemotherapeutic option for previously treated advanced NSCLC after standard of chemotherapies based on other trials.
Qin et al. [81]	Phase II,	nab-PTX plus cisplatin vs. gemcitabine plus cisplatin	advanced	N=84	100 mg/m^2 nab-PTX on day 1, 8 and 15 of a 28-day cycle, as well as cisplatin 75 mg/m^2 on day 1 every three weeks (nab-TP arm); or gemcitabine 1,000 mg/m^2 on day 1 and 8, plus cisplatin 75 mg/m^2 on day 1 every three weeks (GP arm).	Weekly nab-TP treatment has a similar efficacy and tolerability to GP treatment for patients who are undergoing their first-line treatment for NSCLC.
Weiss et al. [82]	Phase II	nab-PTX	Advanced, stage IV	N=42	Nab-PTX 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle.	Fit and prefrail older patients with stage IV NSCLC should be considered for treatment with nab-PTX after disease progression with doublet chemotherapy.
Wang et al. [83]	Retrospective analysis	nab-PTX	Elderly patients with advanced stage IIIB-IV NSCLC.	N=76	12 patients who received nab-PTX as the first-line treatment (seven also received carboplatin), and 64 received nab-PTX as the latter-line treatment.	Nab-PTX has a good clinical response profile in Chinese elderly (≥65 years) patients with stage IIIB - IV NSCLC, with acceptable and manageable adverse events.
Kotake et al. [84]	Phase II	nab-PTX	advanced, failed chemotherapy	N=35	nab-PTX 100 mg/m^2 on days 1, 8, and 15 of a 28-day cycle.	Nab-PTX may be a later-line chemotherapeutic option for previously treated advanced NSCLC.

Spigel et al. [85]	RCT, phase III	nab-PTX, carboplatin	advanced, untreated	N=420 for induction therapy; N=202 (nab-Pac plus BSC vs. BSC)	Four 21-day cycles of nab-PTX 100 mg/m^2 on days 1, 8, 15 plus carboplatin area under the curve 6 on day 1 as induction therapy. Patients without disease progression after induction were randomized 2:1 to maintenance nab-PTX 100 mg/m^2 (days 1 and 8 every 21 days) plus best supportive care (BSC) or BSC alone.	Although a trend in OS favoring nab-PTX was observed and maintenance therapy with nab-PTX might be feasible for patients with advanced squamous NSCLC, the interpretations must be tempered considering the recent findings with immune checkpoint inhibitors.
Tanaka et al. [86]	Phase I/II	nab-PTX, carboplatin	advanced, stage IIIA/IIIB	N=18 in phase I; N=6 in phase II	In the phase I, carboplatin (AUC of 4) and nab-PTX 60-100 mg/m^2 on days 1, 15, and 29. In the phase II part, carboplatin and nab-PTX on days 1, 15, and 29 as recommended.	Biweekly carboplatin and nab-PTX with concurrent RT were well-tolerated and exerted promising antitumor activity.
Yoneshima et al. [87]	RCT, phase III	nab-PTX, docetaxel	advanced	nab-PTX: N=252; docetaxel: N=252	docetaxel 60 mg/m^2 on day 1 every 3 weeks or nab-PTX 100 mg/m^2 in 30 minutes on days 1, 8, and 15 of a 21-day cycle every 3 weeks.	noninferior to docetaxel in terms of overall survival.
Omori et al. [88]	Phase I	nab-PTX, carboplatin	advanced, stage III	N=19	6 weeks of weekly carboplatin/nab-PTX and concurrent thoracic radiotherapy with a total dose of 64 Gy in 32 fractions. Carboplatin (AUC of 2) combined with 30 or 40 mg/m^2 nab-PTX	Carboplatin/nab-PTX and concurrent thoracic radiotherapy show good tolerability and exhibit promising efficacy in elderly patients with locally advanced NSCLC.
Miyauchi et al. [89]	Phase I/II	nab-PTX	Stage IV or postoperative recurrent, had two or more chemotherapy regimens	N=15 in phase I; N=18 in phase II	Biweekly nab-PTX 100-150 mg/m^2 and 12 patients in phase II were treated with 150 mg/m^2	Biweekly nab-PTX monotherapy was well tolerated and exhibited favorable antitumor activity in patients with previously treated NSCLC.
Yoshimura et al. [90]	Phase II	nab-PTX	advanced	N=30	nab-PTX at 80 mg/m^2 on days 1, 8, and 15 (21-d cycle).	high ORR, long median PFS, and acceptable toxicity
Lu et al. [93]	RCT, phase II	Sb-Pac, Pm-Pac, cisplatin	advanced	N=448; Sb-Pac plus cisplatin: N=148; Pm-Pac plus cisplatin: N=300	Pm-Pac at 230–300 mg/m^2 plus cisplatin at 70 mg/m^2; or Sb-Pac at 175 mg/m^2 plus cisplatin at 70 mg/m^2	prolonged progression-free survival, overall survival with a favored safety profile in advanced NSCLC patients without pleural metastasis.
Shoji et al. [91]	Phase II	nab-PTX	advanced, had chemotherapy regimens	N=65	nab-PTX 100 mg/m^2 intravenously on days 1, 8, and 15, every 4 weeks.	well tolerated and showed anti-tumor activity in patients with previously treated NSCLC

Abbreviations: nab-PTX, nab-paclitaxel; Sb-Pac, solvent-based paclitaxel; Pm-Pac, polymeric micellar paclitaxel; EGFR, epidermal growth factor receptor mutation; AUC 6, area under curve of 6 mg/ml/min; AUC 2, area under curve of 2 mg/ml/min.

grade greater than or equal to 3 was decreased in nab-Pac group. In a multicenter, single-arm, open-label phase II study, 30 elder NSCLC patients were administrated carboplatin on Day 1 and nab-Pac (100 mg/m^2) on Days 1, 8, and 15, every 28 days for no more than 4 cycles. After a median of 15 months of follow-up, the median progression-free and overall survival was 7.1 and 19.1 months, respectively. No treatment-related death was found and all treatment-associated adverse events were tolerable and reversible [73]. These data confirmed that nab-Pac as monotherapy or in combination with any chemotherapy were effective and well tolerated and could be used as first-line of treatment in NSCLC patients across all ages.

However, not all nab-Pac trials were successful. In a phase II open-label clinical study, 84 NSCLC patients were received either a weekly nab-Pac plus cisplatin (nab-TP arm) vs. gemcitabine plus cisplatin (GP arm), the median PFS, objective response rate as well as OS was similar between two groups [81]. In a noncomparative randomized phase II trial, 27 Patients were randomized to assign carboplatin plus nab-Pac or carboplatin alone for two cycles, the trial was withdrawn because of frequent dose reductions, treatment delays, and omission of the weekly therapy [67]. In line with that, in a phase I/II trial of weekly nab-Pac for pretreated NSCLC patients without epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangement, the objective response rate was 7.3 and failed to meet predefined primary endpoints [79].

Nanoparticle polymeric micellar paclitaxel

In 2007, Cremophor EL (CrEL)-free polymeric micelle formulation of paclitaxel, named Genexol-PM, was introduced in Korea for the treatment of metastatic NSCLC [100]. In this construct, paclitaxel was wrapped with the non-ionic surfactant polyethoxylated castor oil (Cremophor) and dehydrated alcohol. By doing so, polymeric micellar paclitaxel (pm-Pac) can be directly dissolved in solution. Moreover, PM-Pac is very small and in a size of 20 nm in diameter, which is easily distributed and cleared.

In a RCT phase II study, 448 advanced NSCLC Patients (n=448) were randomly assigned (2:1) to receive Pm-Pac plus cisplatin or solvent-based paclitaxel (Sb-Pac) plus cisplatin. The subgroup analysis was performed based on metastatic status to identify the potential benefit patients. In patients with 2 metastatic lesions, the median PFS was 7.31 months longer for patients treated with Pm-PAC plus cisplatin and 5.70 months for those received Sb-Pac plus cisplatin (P=0.0004). Likewise, in patients with 3 metastatic lesions, the PFS was 2.03 months longer in Pm-PAC/cisplatin group than Sb-Pac/cisplatin group (PFS: 6.26 months vs. 4.23 months, P= 0.0008). The results revealed that Pm-Pac potentially prolonged OS with a favorable safety profile in NSCLC patients without pleural metastasis [93].

In another phase II study, Cremorphor EL-free paclitaxel (Genexol-PM) and gemcitabine were used to treat advanced NSCLC patients. Genexol-PM is a polymeric micelle formulation of paclitaxel which allows higher-dose administration with less hypersensitivity. In this clinical trial, patients with advanced NSCLC received Genexol-PM combined gemcitabine for six cycles and gave the conclusion that CrEL-free paclitaxel in combination with gemcitabine demonstrated favorable antitumor activity with little emetogenicities in NSCLC patients. However, frequent grade 3/4 toxicities were observed, and safety should be evaluated thoroughly in future studies [92].

Breast cancer

Breast cancer is the most prevalent invasive cancer among women, accounting for more than 11.6% of all female cancers. Based on histological characteristics, molecular subtype, stage, and DNA-based alterations, breast cancer is classified into four main subtypes, namely, lu-

Table 2. List of clinical trials using NPs-mediated drug treatment in breast cancer.

First authors	Type of clinical trial	Name of drug	Type of Patients	Number of patients	Treatment strategy	Main findings
Chao et al. [102]	Phase II	Genetaxyl	Advanced, stage III or IV or recurrent	N=29	Genetaxyl 175 mg/m^2 every 3 weeks for 3-6 cycles	a 60% reduction of CrEL by Genetaxyl' s formulation does not affect the activity of paclitaxel.
Gradishar et al. [103]	Phase III	nab-PTX (ABI-007)	Metastatic	ABI-007: N = 229; standard paclitaxel: N = 225	ABI-007 at 260 mg/m^2; standard paclitaxel at 175 mg/m^2	ABI-007 demonstrated greater efficacy and a favorable safety profile compared with standard paclitaxel.
Roy et al. [104]	Phase II	nab-PTX, gemcitabine	untreated, metastatic	N= 50	Nab-PTX 125 mg/m^2 and gemcitabine at 1000 mg/m^2 were administered on days 1 and 8 of a 21-day cycle until disease progression.	All well-tolerated and only one patient developed febrile neutropenia. This strategy shows significant activity and good toxicity profile.
John et al. [105]	RCT, phase II	doxorubicin with cyclophosphamide, followed by nab-Pac or cf-Pac	metastatic	N=190	Nab-Pac at 260 mg/m^2 or cf-Pac at 175 mg/m^2	A 44% higher paclitaxel dose was delivered in the Nab-Pac compared with the cf-Pac arm, achieving a similar safety profile.
Ranade et al. [106]	RCT, Phase II	nanoparticle paclitaxel or Cremophor paclitaxel	advanced and/ or metastatic, after failure of anthracycline	N=195	nanoparticle paclitaxel 300 mg/m^2 or 220 mg/m^2 or Cremophor paclitaxel 175 mg/m^2	nanoparticle paclitaxel is well tolerated as Cremophor paclitaxel
Yardley et al. [107]	Phase II	nab-PTX, lapatinib	HER2 positive	N=55	Nab-PTX at 100 mg/m^2 on Day 1, 8, and 15 every 28 days	This combination is feasible with manageable and predictable toxicity and favors with other HER2-based combinations

Seidman et al.[108]	RCT, phase II	nab-PTX, filgrastim, Bevacizumab	metastatic	N=208
				arm A: N=75;
				arm B: N=54;
				arm C: N=79
					Arm A: nab-PTX 260 mg/m^2 q3k with bevacizumab;
					Arm B: filgrastim at 260 mg/m^2 q2w with bevacizumab;
					Arm C: filgrastim at 130 mg/m^2 weekly with bevacizumab
						Significant antitumor activity was observed in all the arms.
						Weekly nab-PTX with bevacizumab had the highest therapeutic index but with more severe sensory neuropathy, suggesting that a 3-weeks on and 1 week off schedule should be explored.

Hamilton et al. [109]	Phase II	paclitaxel, bevacizumab, carboplatin	triple negative metastatic	N=34	Nab-PTX at 100 mg/m^2 plus carboplatin (AUC of 2) on days 1, 8, 15, and bevacizumab 10 mg/kg on days 1 and 15 of a 28-day cycle.	efficacious and well tolerated as first-line treatment for TNMBC.

Sun et al.[110]	Phase II	paclitaxel, cisplatin	recurrent or metastatic	N=73	Nab-PTX weekly at 125 mg/m^2 on day 1, day 8, and day 15, followed by cisplatin at 75 mg/m^2 on day 1, repeated every 28 days	highly effective, with quick response, manageable toxicity, and possible equivalence across molecular subtypes in MBC patients.
Tanaka et al. [111]	Phase II	paclitaxel, trastuzumab	HER2 positive (stage I to IIIA)	N=45	epirubicin/cyclophosphamide or 5-fluorouracil/epirubicin/ cyclophosphamide every 3 weeks (q3w) for 4 cycles, followed by Nab-PTX at 260 mg/m^2 plus trastuzumab (q3w) for 4 cycles.	Neoadjuvant therapy using this combination appears to be effective and safe.
Park et al.[112]	RCT, Phase III	Genexol-PM	Recurrent or Metastatic HER2-Negative	N=212 Genexol-PM: N=105; Genexol: n=105	Genexol-PM at 260 mg/ m^2 or Genexol 175 mg/ m^2 intravenously every 3 weeks	Compared with standard paclitaxel, Genexol-PM demonstrated non-inferior and even superior clinical efficacy with a manageable safety profile in patients with metastatic breast cancer.
Sakaguchi et al. [113]	Phase I	paclitaxel, S-1	HER2-negative metastatic	N=9	Nab-PTX at 180-260 mg/m^2 on day 1 and S-1 at 65-80 mg/m^2 daily on days 1-14, repeated every 3 weeks	This combination therapy is effective and feasible.
Futamura et al. [114]	Phase II	paclitaxel, epirubicin, cyclophosphamide	Operable (stage IC-IIIA)	N=54	Four cycles of every-3-week (q3w) nab-PTX followed by four cycles of q3w an epirubicin plus cyclophosphamide	Preoperative NAC with nab-PTX followed by EC is effective and safe for operable breast cancer.
Schmid et al.[115]	RCT, Phase III	paclitaxel, atezolizumab	Advanced Triple-Negative	N=902; atezolizumab plus nab-Pac: N=451; lacebo plus nab-Pac: N=451	atezolizumab 800 mg on days 1 and 15, plus nab-PTX at 100 mg/m^2 on days 1, 8, and 15 of every 28-day cycle	Atezolizumab plus nab-PTX prolonged progression-free survival among patients.
Ota et al.[116]	Phase I	paclitaxel, cyclophosphamide	HER2-negative metastatic	N=5	Nab-PTX at 100-150 mg once a week for three weeks, repeated every 4 weeks, and cyclophosphamide 600 mg/ m^2 on day 1	The combination therapy with weekly nab-PTX and CPA was tolerable

Notes: Genetaxyl (Paclitaxel formulated in 50% Cremophor EL/absolute ethanol); Genexol-PM, a Cremophor EL-free formulation of low-molecular-weight, non-toxic, and biodegradable polymeric micelle-bound paclitaxel; Genexol: conventional paclitaxel; AUC of 6, area under curve 6 mg/ml/min.

minal breast cancer type A and type B, human epidermal growth factor receptor 2 (HER2) positive breast cancer, and triple-negative breast cancer [101].

Breast cancer is highly heterogeneous, making its treatment very complex. Precise treatment strategies are made that consider cancer stage, presence/absence of hormone receptors, genetic and epigenetic alterations, and biomarkers. These strategies include surgery, chemotherapy, radiation therapy, hormone therapy, immunotherapy, targeted therapy alone or in combination. For instance, neoadjuvant therapy is a standard of treatment (especially for HER2-positive and triple-negative breast cancer). Endocrine therapy and chemotherapy for ER-positive tumors for 5-10 years based on individual risk assessment [102]. However, conventional anti-cancer

drugs have poor bioavailability and short half-life as well as toxicity that limit their applications. There are 15 published clinical trials that assessed the effects and safety of NP-based drug delivery systems in the treatment of breast cancer [103-117].

Nab-Pac

Nab-Pac remains as the conventional drug to treat breast cancer. ABI-007 is the first solvent-free, biointeractive albumin-bound paclitaxel nanoparticle. In a phase III RCT study, 554 metastatic breast cancer patients were randomized assigned to three-week cycles of ABI-007 or standard paclitaxel. ABI-007 showed greater anti-tumor effect as evidenced by 1.7-fold response rate, 1.4-fold longer time to tumor progression. By contrast, grade 4 neutropenia was 60% lower in ABI-007 group than standard paclitaxel [104].

On top of nab-Pac, agents including cyclophosphamide, S-1, trastuzumab, bevacizumab, gemcitabine, cisplatin, lapatinib, and atezolizumab were often added to reinforce the anti-tumor activity [106, 109-112, 114-117]. In an open-label phase II RCT study, 208 metastatic breast cancer patients were randomized administered nab-Pac every 3 weeks (n=75), every 2 weeks (n=54) or weekly (n=79) in combination with bevacizumab, the overall response rate and neurotoxicity were comparable among three groups. Nevertheless, the median time to tumor progression was 9.0, 5.8, and 8.0 months for patients with weekly, every 2 weeks, or every 2 weeks of nab-Pac treatment group, respectively (P=0.105) [109]. In a RCT phase 3 trial, patients with untreated metastatic triple-negative breast cancer were randomized assigned to nab-Pac alone (n=451) or combined with atezolizumab (n=451) till signs of cancer progression or severe toxicity. By the intention-to-treatment analysis, the median progression-free survival was 1.7 months longer in patients received dual drugs than ones received nab-Pac alone (P=0.002). The overall survival was 3.7 months longer in dual drug treatment than nab-Pac alone (P=0.08) [118]. Likewise, in a phase II, multicenter trial, patients with triple negative metastatic breast cancer were treated with nab-Pac, carboplatin, and bevacizumab. The overall response rate was reached 85% and progression-free-survival was 9.2 months [110]. At present, the combination of nab-Pac, carboplatin, and bevacizumab is recommended as the first-line chemotherapy for the treatment of triple negative metastatic breast cancer.

Nanoparticle polymeric micellar paclitaxel

In a multicenter phase II study, 194 patients with advanced breast cancer were randomized assigned to 300 mg/m^2 or 200 mg/m^2 of Cremophor-free nanoparticle paclitaxel or 175 mg/m^2 Cremophor paclitaxel. Ultimately, they were all well tolerated in the patients with similar overall response rate ranging from 31% for Cremophor paclitaxel and 40% for nanoparticle paclitaxel [107]. Same findings were confirmed in another RCT study in which 212 patients with recurrent or metastatic HER2-negative breast cancer were randomized treated with Genexol-PM or conventional paclitaxel. Genexol-PM is a Cremophor EL-free formulated construct with low-molecular-weight, non-toxic, and biodegradable polymeric micelle-bound paclitaxel. After a median follow-up of 24.5 months, the overall response rate was 1.6-fold higher in Genexol-PM group than Genexol group (P=0.021). The overall survival rate and progression-free survival were comparable between two groups (P≥0.26) [113]. However, neutropenia was more frequently seen in Genexol-PM group compared with control (68.6% vs. 40.2%, P<0.01) [113].

New nanoparticles under investigation

The work of nanoparticles in the bioengineer of anti-tumor drugs for better efficacy and safety never stops. Ashley M Brinkman et al. engineered a unique unimolecular micelle nanoparticle [119] loaded with AF and conjugated with GE11, a 12 amino acid peptide targeting

epidermal growth factor receptor (EGFR), which can be an effective therapeutic option for EGFR-overexpressing triple-negative breast cancer [120]. Yu-Guo Yuan et al. synthesized palladium NPs from a novel biomolecule called R-paclitaxel and investigated the efficacy and safety with combined tubastatin A in human breast cancer cells [121]. The Metal-organic Nanoparticles MONs is composed of Cu (DDC)2 metal-organic complex core and surface decorated bovine serum albumin; it showed potent antitumor activity in breast cancer cell monolayers and three-dimensional cultures of tumor spheroids [122]. Curcumin is the most powerful compound to inhibit cancer cell proliferation. To increase its solubility, curcumin was combined with human albumin prior to incorporation into NPs. By doing so, it led to a significant increase in the toxicity of curcumin to cancer cells, without increasing its toxicity to normal cells [123]. All of which are currently tested in vitro and in animal models.

Conclusions and perspectives

Nanoparticles as vehicles of different anticancer drugs via active and passive transportation is a promising and advanced field, having a huge potential in cancer therapy. Apart from these data, numerous clinical trials are currently in development, and only a few nano-based anticancer drug carriers have reached the FDA approval. Up to date, most clinical trials are centered around Nab-Pac. There are many obstacles waiting for resolution and a vast field worth to be explored about nanoparticle drug delivery systems.

Acknowledgments

None.

Funding

This work was supported by National Natural Science Foundation of China (grant number 82200715) and Laboratory for Clinical Medicine, Capital Medical University to Yuan Dong.

Ethics, Consent to Participate, and Consent to Publish declarations

Not applicable.

Author contributions

Yuan Dong and Cen Yan contributed equally to this work. Yuan Dong and Cen Yan conceived and designed the study. Xuan-yi Yang collected and analyzed the literature. Ying-mei Feng supervised the project and revised the manuscript. Yuan Dong and Xuan-yi Yang drafted the initial version of the manuscript. All authors participated in the interpretation of data, critically revised the manuscript, and approved the final version for submission.

Conflicts of Interest

All authors declare no conflicts of interest.

Data Availability

Not applicable.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021 (71):209-249.

[2] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA

Cancer J Clin. 2024 (74):229-263.

[3] Hui Y, Yi X, Hou F, Wibowo D, Zhang F, Zhao D, et al. Role of nanoparticle mechanical properties in cancer drug delivery. ACS Nano. 2019 (13):7410-7424.

[4] Oh N, Kim Y, Kweon HS, Oh WY, Park JH. Macrophage-mediated exocytosis of elongated nanoparticles improves hepatic excretion and cancer phototherapy. ACS Appl Mater Interfaces. 2018 (10):28450-28457.

[5] Chen W, Goldys EM, Deng W. Light-induced liposomes for cancer therapeutics. Prog Lipid Res. 2020 (79):101052.

[6] Fan X, Yang J, Loh XJ, Li Z. Polymeric janus nanoparticles: Recent advances in synthetic strategies, materials properties, and applications. Macromol Rapid Commun. 2019 (40):e1800203.

[7] Jahangirian H, Lemraski EG, Webster TJ, Rafiee-Moghaddam R, Abdollahi Y. A review of drug delivery systems based on nanotechnology and green chemistry: Green nanomedicine. Int J Nanomedicine. 2017 (12):2957-2978.

[8] Tantakitti F, Burk-Rafel J, Cheng F, Egnatchik R, Owen T, Hoffman M, et al. Nanoscale clustering of carbohydrate thiols in mixed self-assembled monolayers on gold. Langmuir. 2012 (28):6950-6959.

[9] Ahmad MZ, Akhter S, Jain GK, Rahman M, Pathan SA, Ahmad FJ, et al. Metallic nanoparticles: Technology overview & drug delivery applications in oncology. Expert Opin Drug Deliv. 2010 (7):927-942.

[10] Neha D, Momin M, Khan T, Gharat S, Ningthoujam RS, Omri A. Metallic nanoparticles as drug delivery system for the treatment of cancer. Expert Opin Drug Deliv. 2021 (18):1261-1290.

[11] Kunrath MF, Campos MM. Metallic-nanoparticle release systems for biomedical implant surfaces: Effectiveness and safety. Nanotoxicology. 2021 (15):721-739.

[12] Al-Ahmady ZS, Donno R, Gennari A, Prestat E, Marotta R, Mironov A, et al. Enhanced intraliposomal metallic nanoparticle payload capacity using microfluidic-assisted self-assembly. Langmuir. 2019 (35):13318-13331.

[13] Liang Q, Wang YX, Ding JS, He W, Deng LL, Li N, et al. Intra-arterial delivery of superparamagnetic iron-oxide nanoshell and polyvinyl alcohol based chemoembolization system for the treatment of liver tumor. Discov Med. 2017 (23):27-39.

[14] Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (egfr) mutations in non-small cell lung cancer. Semin Cancer Biol. 2020 (61):167-179.

[15] Tseng SH, Chou MY, Chu IM. Cetuximab-conjugated iron oxide nanoparticles for cancer imaging and therapy. Int J Nanomedicine. 2015 (10):3663-3685.

[16] Vakili-Ghartavol R, Momtazi-Borojeni AA, Vakili-Ghartavol Z, Aiyelabegan HT, Jaafari MR, Rezayat SM, et al. Toxicity assessment of superparamagnetic iron oxide nanoparticles in different tissues. Artif Cells Nanomed Biotechnol. 2020 (48):443-451.

[17] Dong J, Carpinone PL, Pyrgiotakis G, Demokritou P, Moudgil BM. Synthesis of precision gold nanoparticles using turkevich method. Kona. 2020 (37):224-232.

[18] Lee KX, Shameli K, Yew YP, Teow SY, Jahangirian H, Rafiee-Moghaddam R, et al. Recent developments in the facile bio-synthesis of gold nanoparticles (aunps) and their biomedical applications. Int J Nanomedicine. 2020 (15):275-300.

[19] Sathiyaraj S, Suriyakala G, Dhanesh Gandhi A, Babujanarthanam R, Almaary KS, Chen TW, et al. Biosynthesis, characterization, and antibacterial activity of gold nanoparticles. J Infect Public Health. 2021 (14):1842-1847.

[20] Hakim M, Billan S, Tisch U, Peng G, Dvrokind I, Marom O, et al. Diagnosis of head-and-neck cancer from exhaled breath. Br J Cancer. 2011 (104):1649-1655.

[21] Fan M, Han Y, Gao S, Yan H, Cao L, Li Z, et al. Ultrasmall gold nanoparticles in cancer diagnosis and therapy. Theranostics. 2020 (10):4944-4957.

[22] Han S, Bouchard R, Sokolov KV. Molecular photoacoustic imaging with ultra-small gold nanoparticles. Biomed Opt Express. 2019 (10):3472-3483.

[23] Nowak-Jary J, Machnicka B. Pharmacokinetics of magnetic iron oxide nanoparticles for medical applications. J Nanobiotechnology. 2022 (20):305.

[24] Farzin A, Etesami SA, Quint J, Memic A, Tamayol A. Magnetic nanoparticles in cancer therapy and diagnosis. Adv Healthc Mater. 2020 (9):e1901058.

[25] Wang W, Zhu Y, Liao S, Li J. Carbon nanotubes reinforced composites for biomedical applications. Biomed Res Int. 2014 (2014):518609.

[26] Wang Q, Chen E, Cai Y, Chen C, Jin W, Zheng Z, et al. Preoperative endoscopic localization of colorectal cancer and tracing lymph nodes by using carbon nanoparticles in laparoscopy. World J Surg Oncol. 2016 (14):231.

[27] Liu Y, Li L, Yu J, Fan YX, Lu XB. Carbon nanoparticle lymph node tracer improves the outcomes of surgical treatment in papillary thyroid cancer. Cancer Biomark. 2018 (23):227-233.

[28] Yan J, Zheng X, Liu Z, Yu J, Deng Z, Xue F, et al. A multicenter study of using carbon nanoparticles to show sentinel lymph nodes in early gastric cancer. Surg Endosc. 2016 (30):1294-1300.

[29] Ge W, Li Q, Liu WJ, Zhang XQ, Fan XS, Shao LH, et al. Carbon nanoparticle suspension could help get a more accurate nodal staging for patient with rectal cancer. Sci Rep. 2021 (11):9933.

[30] Anselmo AC, Mitragotri S. Nanoparticles in the clinic: An update. Bioeng Transl Med. 2019 (4):e10143.

[31] Anselmo AC, Mitragotri S. Nanoparticles in the clinic. Bioeng Transl Med. 2016 (1):10-29.

[32] Tandon S, Burnand KM, De Coppi P, Mclaren CA, Roebuck DJ, Curry JI. Self-expanding esophageal stents for the management of benign refractory esophageal strictures in children: A systematic review and review of outcomes at a single center. J Pediatr Surg. 2019 (54):2479-2486.

[33] Bangham AD, Horne RW. Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. J Mol Biol. 1964 (8):660-668.

[34] Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. J Mol Biol. 1965 (13):238-252.

[35] Portney NG, Ozkan M. Nano-oncology: Drug delivery, imaging, and sensing. Anal Bioanal Chem. 2006 (384):620-630.

[36] Abu Lila AS, Ishida T. Liposomal delivery systems: Design optimization and current applications. Biol Pharm Bull. 2017 (40):1-10.

[37] Torchilin V. Tumor delivery of macromolecular drugs based on the epr effect. Adv Drug Deliv Rev. 2011 (63):131-135.

[38] Malam Y, Loizidou M, Seifalian AM. Liposomes and nanoparticles: Nanosized vehicles for drug delivery in cancer. Trends Pharmacol Sci. 2009 (30):592-599.

[39] Blanco E, Hsiao A, Mann AP, Landry MG, Meric-Bernstam F, Ferrari M. Nanomedicine in cancer therapy: Innovative trends and prospects. Cancer Sci. 2011 (102):1247-1252.

[40] Szebeni J. Complement activation-related pseudoallergy: A new class of drug-induced acute immune toxicity. Toxicology. 2005 (216):106-121.

[41] Fulop T, Kozma GT, Vashegyi I, Meszaros T, Rosivall L, Urbanics R, et al. Liposome-induced hypersensitivity reactions: Risk reduction by design of safe infusion protocols in pigs. J Control Release.

2019 (309):333-338.

[42] Perez-Herrero E, Fernandez-Medarde A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. Eur J Pharm Biopharm. 2015 (93):52-79.

[43] Al-Qattan MN, Deb PK, Tekade RK. Molecular dynamics simulation strategies for designing carbon-nanotube-based targeted drug delivery. Drug Discov Today. 2018 (23):235-250.

[44] Li R, Wu R, Zhao L, Wu M, Yang L, Zou H. P-glycoprotein antibody functionalized carbon nanotube overcomes the multidrug resistance of human leukemia cells. ACS Nano. 2010 (4):1399-1408.

[45] Somani S, Dufes C. Applications of dendrimers for brain delivery and cancer therapy. Nanomedicine (Lond). 2014 (9):2403-2414.

[46] Movassaghian S, Merkel OM, Torchilin VP. Applications of polymer micelles for imaging and drug delivery. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2015 (7):691-707.

[47] Kubiak T. Polymeric capsules and micelles as promising carriers of anticancer drugs. Polim Med. 2022 (52):37-50.

[48] Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug Discov Today. 2003 (8):1112-1120.

[49] Hillaireau H, Couvreur P. Nanocarriers' entry into the cell: Relevance to drug delivery. Cell Mol Life Sci. 2009 (66):2873-2896.

[50] Singh J, Jain K, Mehra NK, Jain NK. Dendrimers in anticancer drug delivery: Mechanism of interaction of drug and dendrimers. Artif Cells Nanomed Biotechnol. 2016 (44):1626-1634.

[51] Stanczyk M, Dziki A, Morawiec Z. Dendrimers in therapy for breast and colorectal cancer. Curr Med Chem. 2012 (19):4896-4902.

[52] Carvalho MR, Reis RL, Oliveira JM. Dendrimer nanoparticles for colorectal cancer applications. J Mater Chem B. 2020 (8):1128-1138.

[53] Khashab M, Tector AJ, Kwo PY. Epidemiology of acute liver failure. Curr Gastroenterol Rep. 2007 (9):66-73.

[54] Kumar V, Sahoo RK, Basak T, Yasmin T, Gupta U, Goyal AK. Diagnostic and therapeutic applications of smart nanocomposite dendrimers. Front Biosci (Landmark Ed). 2021 (26):518-536.

[55] Kumari P, Ghosh B, Biswas S. Nanocarriers for cancer-targeted drug delivery. J Drug Target. 2016 (24):179-191.

[56] Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. JAMA Oncol. 2019 (5):1749-1768.

[57] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 (68):394-424.

[58] Nooreldeen R, Bach H. Current and future development in lung cancer diagnosis. Int J Mol Sci. 2021 (22):8661.

[59] Yoneshima Y, Morita S, Ando M, Miura S, Yoshioka H, Abe T, et al. Treatment rationale and design for j-axel: A randomized phase 3 study comparing nab-paclitaxel with docetaxel in patients with previously treated advanced non-small-cell lung cancer. Clin Lung Cancer. 2017 (18):100-103.

[60] Otsubo K, Kishimoto J, Kenmotsu H, Minegishi Y, Ichihara E, Shiraki A, et al. Treatment rationale and design for j-sonic: A randomized study of carboplatin plus nab-paclitaxel with or without nintedanib for advanced non-small-cell lung cancer with idiopathic pulmonary fibrosis. Clin Lung Cancer. 2018 (19):e5-e9.

[61] Shiraishi Y, Kishimoto J, Shimose T, Toi Y, Sugawara S, Okamoto I. Phase ii study of carboplatin/nab-paclitaxel/atezolizumab combination therapy for advanced nonsquamous non-small cell lung cancer patients with impaired renal function: Restart trial. BMC Cancer. 2022 (22):964.

[62] Rizvi NA, Riely GJ, Azzoli CG, Miller VA, Ng KK, Fiore J, et al. Phase i/ii trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage iv non-small-cell lung cancer. J Clin Oncol. 2008 (26):639-643.

[63] Stinchcombe TE, Socinski MA, Lee CB, Hayes DN, Moore DT, Goldberg RM, et al. Phase i trial of nanoparticle albumin-bound paclitaxel in combination with gemcitabine in patients with thoracic malignancies. J Thorac Oncol. 2008 (3):521-526.

[64] Reynolds C, Barrera D, Jotte R, Spira AI, Weissman C, Boehm KA, et al. Phase ii trial of nanoparticle albumin-bound paclitaxel, carboplatin, and bevacizumab in first-line patients with advanced nonsquamous non-small cell lung cancer. J Thorac Oncol. 2009 (4):1537-1543.

[65] Okamoto I, Yamamoto N, Kubota K, Ohe Y, Nogami N, Murakami H, et al. Safety and pharmacokinetic study of nab-paclitaxel plus carboplatin in chemotherapy-naive patients with advanced non-small cell lung cancer. Invest New Drugs. 2012 (30):1132-1137.

[66] Ho C, Davies AM, Sangha RS, Lau D, Lara P, Jr., Chew HK, et al. Phase i/ii trial of pemetrexed plus nab-paclitaxel in advanced solid tumor patients with emphasis on non-small cell lung cancer. Invest New Drugs. 2013 (31):1587-1591.

[67] Grilley-Olson JE, Keedy VL, Sandler A, Moore DT, Socinski MA, Stinchcombe TE. A randomized phase ii study of carboplatin with weekly or every-3-week nanoparticle albumin-bound paclitaxel (abraxane) in patients with extensive-stage small cell lung cancer. Oncologist. 2015 (20):105-106.

[68] Bertino EM, Williams TM, Nana-Sinkam SP, Shilo K, Chatterjee M, Mo X, et al. Stromal caveolin-1 is associated with response and survival in a phase ii trial of nab-paclitaxel with carboplatin for advanced nsclc patients. Clin Lung Cancer. 2015 (16):466-474.

[69] Saxena A, Schneider BJ, Christos PJ, Audibert LF, Cagney JM, Scheff RJ. Treatment of recurrent and platinum-refractory stage iv non-small cell lung cancer with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) as a single agent. Med Oncol. 2016 (33):13.

[70] Okuma Y, Hosomi Y, Takahashi S, Nakahara Y, Watanabe K, Nagamata M, et al. A phase ii study of nanoparticle albumin-bound paclitaxel plus carboplatin as the first-line therapy in elderly patients with previously untreated advanced non-small cell lung cancer. Cancer Chemother Pharmacol. 2016 (78):383-388.

[71] Kaira K, Tomizawa Y, Imai H, Sakurai R, Matsuura M, Yoshii A, et al. Phase i study of nab-paclitaxel plus carboplatin and concurrent thoracic radiotherapy in patients with locally advanced non-small cell lung cancer. Cancer Chemother Pharmacol. 2017 (79):165-171.

[72] Miyauchi E, Inoue A, Usui K, Sugawara S, Maemondo M, Saito H, et al. Phase ii study of modified carboplatin plus weekly nab-paclitaxel in elderly patients with non-small cell lung cancer: North japan lung cancer study group trial 1301. Oncologist. 2017 (22):640-e659.

[73] Shiroyama T, Tamiya M, Minami S, Takata S, Masuhiro K, Futami-Nishijima Y, et al. Carboplatin plus weekly nanoparticle albumin-bound paclitaxel in elderly patients with previously untreated advanced squamous non-small-cell lung cancer selected based on mini nutritional assessment short-form scores: A multicenter phase 2 study. Cancer Chemother Pharmacol. 2017 (80):461-467.

[74] Naito Y, Tamiya A, Tamiya M, Kimura Y, Hamagu-

chi M, Saijo N, et al. Efficacy of nanoparticle albumin-bound paclitaxel regimens for relapsed small cell lung cancer: A retrospective analysis. Medicine (Baltimore). 2017 (96):e7884.

[75] Anzai M, Morikawa M, Okuno T, Umeda Y, Demura Y, Sonoda T, et al. Efficacy and safety of nanoparticle albumin-bound paclitaxel monotherapy as second-line therapy of cytotoxic anticancer drugs in patients with advanced non-small cell lung cancer. Medicine (Baltimore). 2017 (96):e9320.

[76] Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med. 2018 (379):2040-2051.

[77] Morgensztern D, Cobo M, Ponce Aix S, Postmus PE, Lewanski CR, Bennouna J, et al. Abound.2l+: A randomized phase 2 study of nanoparticle albumin-bound paclitaxel with or without cc-486 as second-line treatment for advanced nonsquamous non-small cell lung cancer (nsclc). Cancer. 2018 (124):4667-4675.

[78] Akiyama N, Karayama M, Inui N, Yasui H, Hozumi H, Suzuki Y, et al. Switch maintenance therapy with s-1 after induction therapy with carboplatin and nanoparticle albumin-bound paclitaxel in advanced lung squamous cell carcinoma. Invest New Drugs. 2019 (37):531-537.

[79] Harada D, Kozuki T, Nogami N, Bessho A, Hosokawa S, Fukamatsu N, et al. A phase i/ii trial of weekly nab-paclitaxel for pretreated non-small-cell lung cancer patients without epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangement. Asia Pac J Clin Oncol. 2019 (15):250-256.

[80] Kato Y, Okuma Y, Watanabe K, Yomota M, Kawai S, Hosomi Y, et al. A single-arm phase ii trial of weekly nanoparticle albumin-bound paclitaxel (nab-paclitaxel) monotherapy after standard of chemotherapy for previously treated advanced non-small cell lung cancer. Cancer Chemother Pharmacol. 2019 (84):351-358.

[81] Qin S, Yu H, Wu X, Luo Z, Wang H, Sun S, et al. Weekly albumin-bound paclitaxel/cisplatin versus gemcitabine/cisplatin as first-line therapy for patients with advanced non-small-cell lung cancer: A phase ii open-label clinical study. Chin J Cancer Res. 2019 (31):339-348.

[82] Weiss JM, Pennell N, Deal AM, Morgensztern D, Bradford DS, Crane J, et al. Nab-paclitaxel in older patients with non-small cell lung cancer who have developed disease progression after platinum-based doublet chemotherapy. Cancer. 2020 (126):1060-1067.

[83] Wang S, Liang Q, Chi Y, Zhuo M, An T, Duan J, et al. Retrospective analysis of the effectiveness and tolerability of nab-paclitaxel in chinese elderly patients with advanced non-small-cell lung carcinoma. Thorac Cancer. 2020 (11):1149-1159.

[84] Kotake M, Kuwako T, Imai H, Tomizawa Y, Kaira K, Yoshii A, et al. Phase ii study of weekly nanoparticle albumin-bound paclitaxel as second- or third-line therapy in patients with advanced non-small cell lung cancer. Chemotherapy. 2020 (65):21-28.

[85] Spigel DR, Jotte RM, Aix SP, Gressot L, Morgensztern D, Mccleod M, et al. Nanoparticle albumin-bound paclitaxel plus carboplatin induction followed by nanoparticle albumin-bound paclitaxel maintenance in squamous non-small-cell lung cancer (abound.Sqm): A phase iii randomized clinical trial. Clin Lung Cancer. 2021 (22):6-15 e14.

[86] Tanaka H, Hasegawa Y, Makiguchi T, Okumura F, Tabe C, Shiratori T, et al. A phase i/ii study of biweekly carboplatin and nab-paclitaxel with concurrent radiotherapy for patients with locally advanced unresectable stage iii non-small-cell lung cancer. Clin Lung Cancer. 2021 (22):42-48.

[87] Yoneshima Y, Morita S, Ando M, Nakamura A, Iwasawa S, Yoshioka H, et al. Phase 3 trial com-

paring nanoparticle albumin-bound paclitaxel with docetaxel for previously treated advanced nsclc. J Thorac Oncol. 2021 (16):1523-1532.

[88] Omori S, Harada H, Mori K, Hisamatsu Y, Tsuboguchi Y, Yoshioka H, et al. Phase i study of weekly nab-paclitaxel plus carboplatin and concurrent thoracic radiotherapy in elderly patients with unresectable locally advanced non-small cell lung cancer. Invest New Drugs. 2022 (40):106-114.

[89] Miyauchi E, Tanaka H, Nakamura A, Harada T, Nakagawa T, Morita M, et al. Phase i/ii study of biweekly nab-paclitaxel in patients with platinum-pretreated non-small cell lung cancer: Njlcg1402. Thorac Cancer. 2021 (12):2886-2893.

[90] Yoshimura N, Sawa K, Nakai T, Matsumoto Y, Mitsuoka S, Kimura T, et al. Phase ii study of the modified weekly nab-paclitaxel regimen in previously treated patients with advanced non-small cell lung cancer. Am J Clin Oncol. 2021 (44):613-618.

[91] Shoji S, Miura S, Watanabe S, Ohtsubo A, Nozaki K, Saida Y, et al. Phase ii study of nanoparticle albumin-bound paclitaxel monotherapy for relapsed non-small cell lung cancer with patient-reported outcomes (nlctg1302). Transl Lung Cancer Res. 2022 (11):1359-1368.

[92] Ahn HK, Jung M, Sym SJ, Shin DB, Kang SM, Kyung SY, et al. A phase ii trial of cremorphor el-free paclitaxel (genexol-pm) and gemcitabine in patients with advanced non-small cell lung cancer. Cancer Chemother Pharmacol. 2014 (74):277-282.

[93] Lu J, Gu A, Wang W, Huang A, Han B, Zhong H. Polymeric micellar paclitaxel (pm-pac) prolonged overall survival for nsclc patients without pleural metastasis. Int J Pharm. 2022 (623):121961.

[94] Feng L, Mumper RJ. A critical review of lipid-based nanoparticles for taxane delivery. Cancer Lett. 2013 (334):157-175.

[95] Yardley DA. Nab-paclitaxel mechanisms of action and delivery. J Control Release. 2013 (170):365-372.

[96] Shiroyama T, Tamiya M, Minami S, Takata S, Masuhiro K, Futami-Nishijima Y, et al. Carboplatin plus weekly nanoparticle albumin-bound paclitaxel in elderly patients with previously untreated advanced squamous non-sm all-cell lung cancer selected based on mini nutritional assessment short-form scores: A multicenter phase 2 study. Cancer Chemother Pharmacol. 2017 (80):461-467.

[97] Hui TW, Tang X, Loy CC. A lightweight optical flow cnn -revisiting data fidelity and regularization. IEEE Trans Pattern Anal Mach Intell. 2021 (43):2555-2569.

[98] Rosales-Mendoza S, Solis-Andrade KI, Marquez-Escobar VA, Gonzalez-Ortega O, Banuelos-Hernandez B. Current advances in the algae-made biopharmaceuticals field. Expert Opin Biol Ther. 2020 (20):751-766.

[99] Prokscha T, Chow KH, Stilp E, Suter A, Luetkens H, Morenzoni E, et al. Photo-induced persistent inversion of germanium in a 200-nm-deep surface region. Sci Rep. 2013 (3):2569.

[100] Kim DW, Kim SY, Kim HK, Kim SW, Shin SW, Kim JS, et al. Multicenter phase ii trial of genexol-pm, a novel cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. Ann Oncol. 2007 (18):2009-2014.

[101] Tong CWS, Wu M, Cho WCS, To KKW. Recent advances in the treatment of breast cancer. Front Oncol. 2018 (8):227.

[102] Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. Lancet. 2021 (397):1750-1769.

[103] Chao TC, Chu Z, Tseng LM, Chiou TJ, Hsieh RK, Wang WS, et al. Paclitaxel in a novel formulation containing less cremophor el as first-line therapy for advanced breast cancer: A phase ii trial. Invest New Drugs. 2005 (23):171-177.

[104] Gradishar WJ, Tjulandin S, Davidson N, Shaw H,

Desai N, Bhar P, et al. Phase iii trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol. 2005 (23):7794-7803.

[105] Roy V, Laplant BR, Gross GG, Bane CL, Palmieri FM, North Central Cancer Treatment Group. Phase ii trial of weekly nab (nanoparticle albumin-bound)-paclitaxel (nab-paclitaxel) (abraxane) in combination with gemcitabine in patients with metastatic breast cancer (n0531). Ann Oncol. 2009 (20):449-453.

[106] Pippen J, Paul D, Vukelja S, Clawson A, Iglesias J. Dose-dense doxorubicin and cyclophosphamide followed by dose-dense albumin-bound paclitaxel plus bevacizumab is safe as adjuvant therapy in patients with early stage breast cancer. Breast Cancer Res Treat. 2011 (130):825-831.

[107] Ranade AA, Bapsy PP, Nag S, Raghunadharao D, Raina V, Advani SH, et al. A multicenter phase ii randomized study of cremophor-free polymeric nanoparticle formulation of paclitaxel in women with locally advanced and/or metastatic breast cancer after failure of anthracycline. Asia Pac J Clin Oncol. 2013 (9):176-181.

[108] Yardley DA, Hart L, Bosserman L, Salleh MN, Waterhouse DM, Hagan MK, et al. Phase ii study evaluating lapatinib in combination with nab-paclitaxel in her2-overexpressing metastatic breast cancer patients who have received no more than one prior chemotherapeutic regimen. Breast Cancer Res Treat. 2013 (137):457-464.

[109] Seidman AD, Conlin AK, Bach A, Moynahan ME, Lake D, Forero A, et al. Randomized phase ii trial of weekly vs. Every 2 weeks vs. Every 3 weeks nanoparticle albumin-bound paclitaxel with bevacizumab as first-line chemotherapy for metastatic breast cancer. Clin Breast Cancer. 2013 (13):239-246 e231.

[110] Hamilton E, Kimmick G, Hopkins J, Marcom PK, Rocha G, Welch R, et al. Nab-paclitaxel/bevacizumab/carboplatin chemotherapy in first-line triple negative metastatic breast cancer. Clin Breast Cancer. 2013 (13):416-420.

[111] Sun S, Tang L, Zhang J, Lv F, Wang Z, Wang L, et al. Cisplatin improves antitumor activity of weekly nab-paclitaxel in patients with metastatic breast cancer. Int J Nanomedicine. 2014 (9):1443-1452.

[112] Tanaka S, Iwamoto M, Kimura K, Matsunami N, Morishima H, Yoshidome K, et al. Phase ii study of neoadjuvant anthracycline-based regimens combined with nanoparticle albumin-bound paclitaxel and trastuzumab for human epidermal growth factor receptor 2-positive operable breast cancer. Clin Breast Cancer. 2015 (15):191-196.

[113] Park IH, Sohn JH, Kim SB, Lee KS, Chung JS, Lee SH, et al. An open-label, randomized, parallel, phase iii trial evaluating the efficacy and safety of polymeric micelle-formulated paclitaxel compared to conventional cremophor el-based paclitaxel for recurrent or metastatic her2-negative breast cancer. Cancer Res Treat. 2017 (49):569-577.

[114] Sakaguchi K, Nakatsukasa K, Taguchi T. Phase i study of triweekly nab-paclitaxel combined with s-1 in patients with her2-negative metastatic breast cancer. Anticancer Res. 2016 (36):6515-6519.

[115] Futamura M, Nagao Y, Ishihara K, Takeuchi M, Nakada T, Kawaguchi Y, et al. Preoperative neoadjuvant chemotherapy using nanoparticle albumin-bound paclitaxel followed by epirubicin and cyclophosphamide for operable breast cancer: A multicenter phase ii trial. Breast Cancer. 2017 (24):615-623.

[116] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018 (379):2108-2121.

(Continued on page 59)