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The battle of "nano" paclitaxel

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ABSTRACT

Paclitaxel (PTX) is one of the three most widely used chemotherapeutic agents, together with doxorubicin and cisplatin, and is first or second line treatment for several types of cancers. In 2000, Taxol, the conventional formulation of PTX, became the best-selling cancer drug of all time with annual sales of 1.6 billion. In 2005, the introduction of the albumin-based formulation of PTX, known as Abraxane, ended Taxol's monopoly of the PTX market. Abraxane's ability to push the Taxol innovator and generic formulations aside attracted fierce competition amongst competitors worldwide to develop their own unique, new and improved formulation of PTX. At this time there are at least 18 companies focused on pre-clinical and/or clinical development of nano-formulations of PTX. These pharmaceutical companies are investing substantial capital to capture a share of the lucrative global PTX market. It is hoped that any formulation that dominates the market will result in tangible benefits to patients in terms of both survival and quality of life. Given all of this activity, here we address the question: Who is going to win the battle of "nano" paclitaxel?

Contents

1. Paclitaxel formulations: big money deals and promising data

Large pharmaceutical and small biotech companies (18 in total, Fig. 1) have pursued formulation development, manufacturing, acquisition of distribution rights and/or company mergers with a goal towards conquering the paclitaxel (PTX) market. Funds exchanged in business deals have ranged from a few million USD, for acquisition of distribution rights, to several billion USD, for company acquisitions. The motivation driving these deals is simple: PTX has been established worldwide as the number one chemotherapeutic agent [1], and these companies are aiming to obtain a profitable share of the PTX market. The US dominates the global oncology market (i.e. 39%) while North America, Europe, Japan and BRIC (Brazil, Russia, India, China) together comprise 88% [2]. There is tremendous potential for an efficacious formulation of PTX, that is approved in all four markets, to become a financial and clinically meaningful success.

1.1. Taxol® vs Abraxane®

PTX has been formulated and marketed as Taxol since receiving FDA approval in 1992. By 2000, Taxol had become the best-selling anti-

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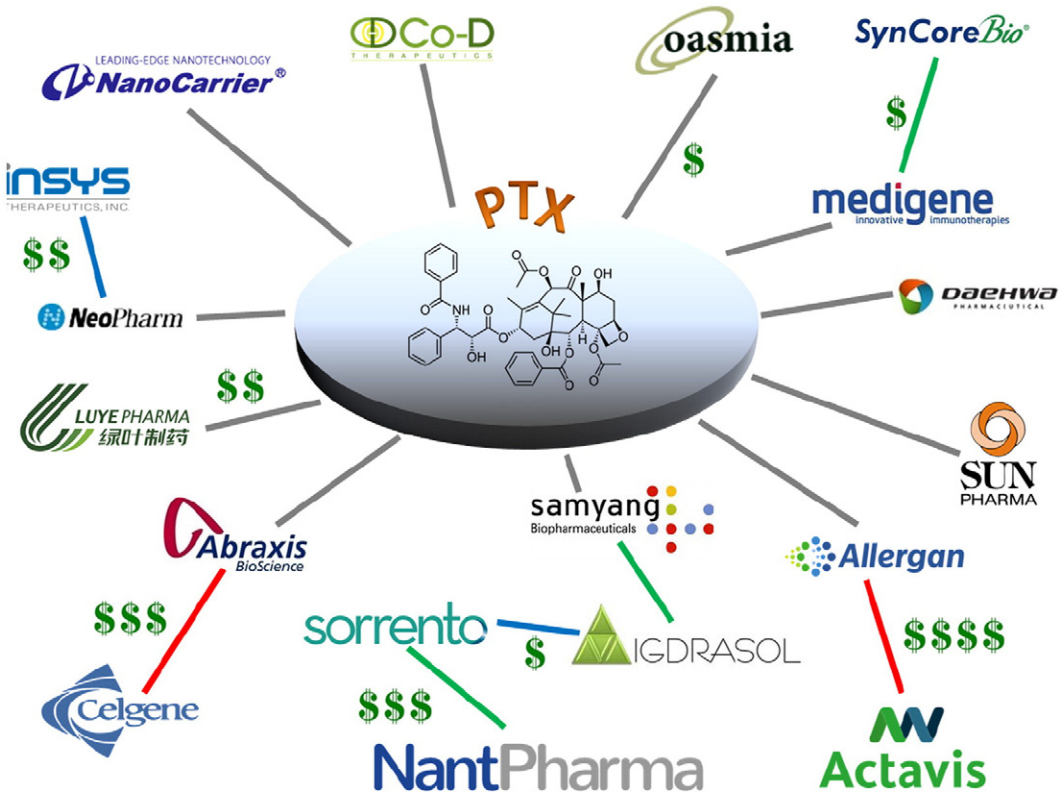

Fig. 1. Industrial competitors in the global PTX market. PTX is one of the most widely used chemotherapeutic agents. Many companies have developed and manufactured nanotechnology-based formulations of PTX. As well, companies have been involved in large financial deals that have provided an entry point to the PTX-market. Gray lines: formulation development and/or manufacturing; green lines: acquisition of drug formulation or distribution rights; blue lines: merger between companies; red lines: company acquisition; $: deal bellow 0.1 billion; $$: deal between 0.1 and 1 billion; $$$: deal between 1 and 10 billion; $$$$ deal over 10 billion.

cancer drug of all time with annual sales of $1.6 billion [3]. Since 2002, seven generic Taxol formulations have been launched by the following companies Gland Pharma, Actavis, Fresenius Kabi Oncol, Mylan Labs, Sandoz, Teva Pharms, and West-Ward Pharms. This has significantly reduced the revenue resulting from sales of the innovator product [4]. The Taxol formulations rely on the use of Cremophor EL (alt. name Kolliphor EL, Macrogolglycerol ricinoleate, PEG-35 castor oil, Polyoxyl 35 hydrogenated castor oil and Polyoxyl-35 castor oil), a synthetic, nonionic surfactant that acts as a solubilizer for PTX. Taxol is clinically approved for treatment of breast cancer (BC), metastatic breast cancer (MBC), ovarian cancer (OC), non-small cell lung cancer (NSCLC), bladder cancer, prostate cancer, melanoma, esophageal cancer, and other types of solid tumors [5]. In 2005, the introduction of Abraxane to the marketplace ended the monopoly of the innovator and generic versions of the Taxol formulation [6].

Abraxane, manufactured by Abraxis Bioscience, was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2005 and 2008, respectively, as second-line therapy for MBC patients with resistance to an anthracycline plus taxane regimen [6,7]. Importantly, the clinical data leading to approval of Abraxane demonstrated superiority relative to Taxol in terms of a reduction in toxicity which in turn resulted in a significantly higher maximum tolerated dose (MTD) for Abraxane [8]. In 2010, Celgene Corporation acquired Abraxane/Abraxis Bioscience for $2.9 billion [9]. The outlook for Abraxane then changed significantly following successful Phase III clinical trials (NCT00540514: comparison of Abraxane and carboplatin versus Taxol and carboplatin, and NCT00844649: Abraxane and gemcitabine versus gemcitabine) [10,11] which led to the 2012 FDA approval of the drug as first-line treatment for NSCLC in combination with carboplatin, and approval by the FDA and EMA in 2013 as first-line treatment in combination with gemcitabine for metastatic pancreatic adenocarcinoma [7]. Abraxane sales have increased significantly from $387 million in 2011 [12] to $967 million in 2015 [13] and $973 million in 2016 [14] with projections as high as $1.9 billion by 2020 [15]. These figures suggest that Abraxane has the potential to surpass the incredible success of Taxol. As shown in Fig. 2, Taxol's domination of the market peaked around 2000 and decreased beyond that following expiration of its US patent in 2001 [16,17]. The current leader in the PTX-formulation market is certainly Abraxane. Nevertheless, Celgene recently provided an updated estimate of projected revenues for 2017 that indicated a decrease from an initial projection of >$1.5 billion to $1 billion, raising questions as to whether it will be feasible to reach $1.9 billion in sales by 2020 [18].

One of the major factors behind the success of Abraxane is its simplicity. Abraxane includes six or seven PTX molecules bound non-covalently [19] to an albumin molecule forming a PTX-albumin primary aggregate of 4–14 nm [20,21]. These then further aggregate to form an albumin-PTX particle of approximately 130 nm in diameter [22]. Preclinical studies have shown that Abraxane improves efficacy, in comparison to Taxol, due to an increase in tumor accumulation of drug [23,24]. An increase in tumor accumulation, following administration of Abraxane relative to Taxol, has not been confirmed clinically. However, clinical studies have shown that the absence of Cremophor EL reduces the toxicity of the formulation, enabling a 49% higher dose of drug to be administered without corticosteroid premedication [8,25]. Table 1 highlights many of the strengths of Abraxane including ease of administration, reduction in hypersensitivity reactions, better overall response and survival, as well as improvements in life years gained (LYG) and quality-adjusted life years gained (QALYG) [8,26–30]. With respect to the toxicity profile, even though Abraxane shows a decrease in the incidence of neutropenia, an increase in incidence of neurotoxicity has been reported when Abraxane is administered in combination with Gemcitabine for treatment of pancreatic cancer (PC) [31]. In 2015, the National Institute of Health and Care Excellence (NICE) in the UK

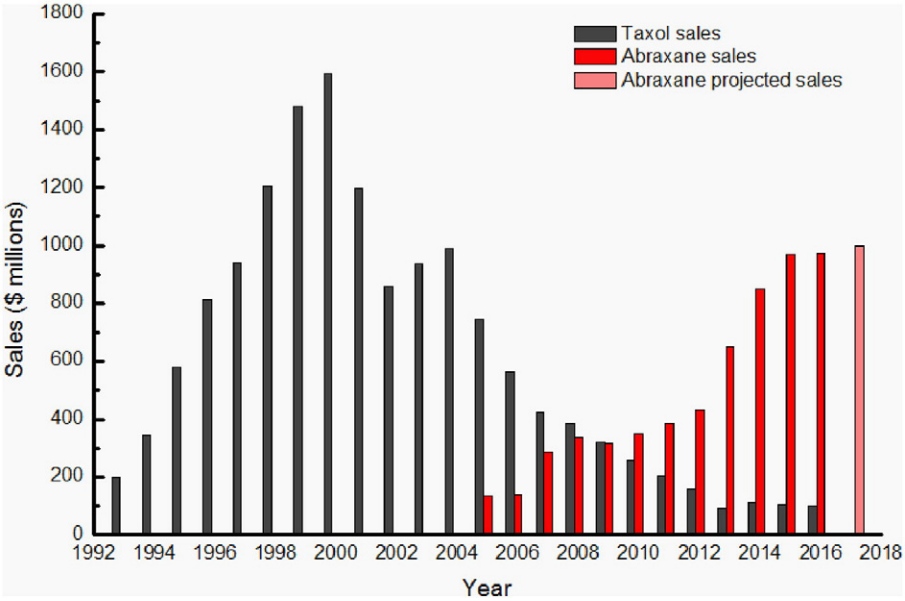

Fig. 2. Sales of Taxol and Abraxane. Global sales (in millions of USD) for Taxol (black) and Abraxane (red) from 1992 to 2016 with projected sales for 2017 (light red). Data for Taxol sales from 2009 to 2012 and 2016 are estimated [14,16,17].

recommended that Abraxane not be funded in this disease setting "on grounds that the cost does not justify its limited benefit" [32,33]. However, this decision was over-ruled in Wales and Scotland wherein patients with metastatic pancreatic cancer continued to be provided access to Abraxane [34,35]. In 2016, following advocacy by patient groups in England and the proposal of a patient access scheme by Celgene, NICE announced a reappraisal of Abraxane for treatment of this patient population [36].

1.2. The competitors

At this time, the most immediate threat to Abraxane's market leadership is Cynviloq™ (also known as Genexol-PM). Cynviloq was originally developed by Samyang Biopharmaceuticals Corporation and approved in South Korea for the treatment of several types of cancer [37] (i.e. BC, OC, NSCLC). In 2013, Sorrento Therapeutics merged with IgDraSol (transaction valued at about $28 M) [38] and obtained exclusive distribution rights for Cynviloq in North America, the European Union, Australia [39,40] and South America in 2015 [41]. In May of 2015, Cynviloq was acquired from Sorrento by NantPharma in a deal valued at $1.3 billion ($90 million upfront cash plus $1.2 billion in milestone payments) [42,43]. The increase in value of Cynviloq has largely been attributed to preliminary positive results obtained in the TRIBECA trial. A trial designed to evaluate bioequivalence (BE) between Cynviloq and Abraxane in patients with MBC or locally recurrent BC. Indeed, initial PK results from the first eight patients enrolled in the TRIBECA™ clinical trial (NCT02064829) [44] demonstrated comparable BE between the two formulations [45–47]. The study has now been completed; however, at this point the additional data obtained has not yet been disclosed. These studies may support approval through the 505(b)(2) new drug application (NDA) regulatory pathway, a hybrid between the new entities regulatory pathway (i.e. 505(b)(1) NDA) and the abbreviated new drug application (ANDA, 505(j)) [47,48]. As a reminder, the 505(b)(1) commonly includes a full non-clinical and clinical data set on the safety and effectiveness of the therapeutic. An ANDA is a type of NDA that is used to demonstrate that a generic is comparable to an innovator drug product. Generally, an ANDA 505(j) does not include data to establish safety and toxicity, rather the focus is on confirmation of pharmaceutical equivalence and demonstration of bioequivalence. Thus, an ANDA is able to rely on the innovator's data for safety and efficacy [49]. Given Sorrento's initial indication of pursuit of the 505(b)(2) regulatory pathway and the positive preliminary BE data already in hand in BC patients, it is conceivable that Cynviloq could soon be on the market competing with Abraxane. It is worth noting that a nanomedicine has not yet been approved through the 505(b)(2) pathway and to date few oncology products have been approved via this route [48]. Further, in March of 2015, Celgene filed a Citizen's petition that states that "Abraxane is a novel nanotechnology agent" and that "nanotechnologies possess unique and complex characteristics" [50]. In the petition they request that "the FDA establish stringent standards with respect to any ANDA relying on approval of Abraxane as a reference listed drug and any 505(b)(2) new drug application for any similar product referencing Abraxane or paclitaxel". Further, the petition "requests that any such applicant's product including nanoparticle formulations clinically demonstrate safety and

Table 1
A comparison between Taxol and Abraxane for the treatment of (metastatic) breast cancer.
Abraxane treatment results in an improvement in overall response and survival, as well as a reduction in side effects. Despite its higher treatment cost, Abraxane increases life years gained (LYG) and improves quality of life. Costs are calculated based on cost-effectiveness analysis for studies performed in China, Spain, Italy, UK and Canada and pertain to the treatment of (metastatic) breast cancer [8,26–30]. *Overall response, overall survival, and toxicity rates for Taxol and Abraxane were retrieved from studies using doses of 175 mg/m^2 and 260 mg/m^2, respectively [26]. **The USD values (rounded in hundreds) are fixed based on inflation between the year of the study and July 28, 2016 and the conversion rate of July 28, 2016. (LYG: life years gained, QALYG: quality-adjusted life years gained).

	Taxol	Abraxane
Administration	q3w	q3w
Infusion time (min)	120–180	20–30
Dose (mg/m^2)	175	260
Premedication	Yes	No
Overall response (%)	25.2 (±5.1)*	33.2
Overall survival (months)	12.48	15.24
Neutropenia (%)	47.0 (±4.6)	30
Neurotoxicity (%)	6.0 (±2.6)	10
Hypersensitivity (%)	2	0
Cost per course ($ USD)**	10000 (±5500)	16700 (±2600)
LYG from use of Abraxane	0.25 (±0.04)	
Cost per LYG ($ USD)**	31300 (±19800)	
QALYG from use of Abraxane	0.19 (± 0.2)	
Cost per QALYG ($ USD)**	35500 (±14900)	
Conclusion	Abraxane is a cost-effective alternative to Taxol	

effectiveness". To our knowledge, the FDA has not yet responded to the filed petition. Their response will have implications for all nanomedicine formulations that aim to pursue the ANDA or 505(b)(2) routes for approval of an Abraxane "equivalent". Meanwhile, a recent Phase III clinical trial (NCT00876486) [51] conducted in South Korea demonstrated superior clinical efficacy in comparison to a conventional Cremophor-EL based PTX formulation in patients with MBC, likely, due to the higher allowed dose (i.e. 260 mg/m^2 and 175 mg/m^2 for Cynviloq and the conventional formulation, respectively) [52]. Moreover, Cynviloq is currently also being evaluated for treatment of OC (NCT02739529 - Phase I trial currently recruiting [53] and NCT00877253 - Phase I clinical trial completed [54]), PC (NCT02739633 - a Phase II clinical trial currently in the pre-recruiting process [55]) and bladder cancer (NCT01426126 - a completed Phase II study [56]). Cynviloq (patent US20150366806 A1) is a relatively straightforward formulation that includes PTX solubilized in block copolymer micelles of 25 nm in diameter and formed from mPEG-*b*-poly(D,L-lactide) copolymer, with an average molecular weight of 1766–2000 Da wherein 50–60 wt.% of the copolymer is comprised of the hydrophilic block [46,57]. The absence of albumin in this formulation is beneficial, as it does not require an albumin donor and has a reduced risk of microbial growth [22]. A final advantage favouring Cynviloq is that patients can safely be treated in the range of 300–435 mg/m^2 [46,58,59] in comparison to Abraxane which has an MTD of 300 mg/m^2 [60,61].

Another recent entrant into the nano-PTX arena is Paclical®, developed by Oasmia Pharmaceutical AB whose 2015 initial public offering (IPO) raised $23 million [62]. Paclical is based on the proprietary excipient XR-17, a vitamin A derivative mixture composed of N-(all-trans-retinoyl)-L-cysteic acid methyl ester sodium salt and N-(13-cis-retinoyl)-L-cysteic acid methyl ester sodium salt that is reported to form micelles of 20–60 nm for solubilization of hydrophobic drugs such as PTX [63]. A Phase III clinical trial in OC patients (NCT00989131) [64] demonstrated improved overall survival for Oasmia's Paclical in combination with carboplatin compared to Taxol plus carboplatin [65]. In 2015, Paclical received approval for treatment of OC in combination with carboplatin in the Russian Federation [66]. Oasmia has applied to the EMA for market authorization [67], and has received orphan drug designation from the FDA for future use in the treatment of OC [68]. Furthermore, a head-to-head clinical study comparing Paclical and Abraxane showed similar PK profiles for these formulations, suggesting the opportunity for global approval of Paclical for treatment of BC [69,70]. Of note, Oasmia is also interested in veterinary oncology with development of Paccal Vet®-CA1 as a companion animal therapeutic, conditionally approved by the FDA [71]. This is an area that is not accessible to Celgene Corporation given the inclusion of human albumin in Abraxane.

China has contributed its own PTX-formulation, Lipusu®, also known as *Paclitaxel Liposome for Injection*, consisting of PTX solubilized in liposomes of 400 nm in diameter formed from lecithin and cholesterol in a ratio of 87:13 wt.% [72]. Lipusu was originally created by LuyePharma Group, whose Hong Kong IPO in 2014 raised $764 million [73]. Further clinical trials on Lipusu were carried out by both LuyePharma Group and Nanjing Sike Pharmaceutical [74]. Lipusu is approved in China as first-line chemotherapy for OC patients, first-line therapy for NSCLC patients who are not candidates for radiotherapy or surgery, and also for BC patients following doxorubicin treatment or in combination with cisplatin following disease recurrence [75]. Currently, there are two Phase IV clinical trials that are recruiting patients: NCT02142790 [76] in MBC patients and NCT02142010 [77] for evaluation of Lipusu in combination with cisplatin as neoadjuvant therapy in patients with BC. The MTD of Lipusu has not yet been determined; however, a Phase IV study, NCT01994031 [78], is recruiting patients for this purpose. A previous Phase I study of Lipusu (NCT00606515) [79] employed a dose of 175 mg/m^2, presumably to match the commonly used dose of Taxol. The only publicly available data on the pharmacokinetics of PTX administered as Lipusu is from preclinical studies [80].

PICN (Paclitaxel Injection Concentrate for Nanodispersion) is a formulation of PTX that was developed in India by Sun Pharma Advanced Research Company (SPARC) [81]. The PICN formulation is based on SPARC's Nanotecton® technology, which utilizes nanoparticles of 100–110 nm in diameter that are formed from polyvinyl-pyrrolidone, cholesteryl sulfate and caprylic acid [82]. PICN is approved in India for the treatment of MBC [83] and has demonstrated equivalent efficacy and toxicity to Abraxane in a Phase II/III study [82] in BC patients. Given the significant success in India, additional clinical trials are now planned in order to seek FDA approval [81]. PICN is currently in Phase III (NCT02597465) evaluation in the United States for the treatment of billiary tract carcinoma [84]. PICN has also shown positive tolerability results when administered in combination with carboplatin in a Phase I trial (NCT01304303) [85,86].

NanoCarrier, a pharmaceutical company focused on employing nanomedicines for cancer therapy, has a market capitalization of $500 million (4571:Tokyo Stock Exchange) and currently has eight ongoing clinical trials in the oncology field [87]. Its contribution to the battle of nano-PTX is a polymeric micelle formulation of PTX known as NK105 that has been licensed to Nippon Kayaku. The NK105 polymeric micelles, of about 85 nm in diameter, are comprised of an amphiphilic copolymer that includes PEG as the hydrophilic block and polyaspartate modified by esterification with 4-phenyl-1-butanol as the hydrophobic block [88]. The core-forming block of this copolymer was designed to create a microenvironment within the micelle core that enables a high degree of drug loading and good drug retention with the ultimate goal of creating a true carrier that retains the drug following i.v. administration. NK105 is based on NanoCarrier's first generation technology (i.e. passive entrapment of drug in micelles). The company currently has a number of nano-formulations in clinical development that are based on their second-generation technology that includes drug covalently conjugated or chelated to the core-forming block of the micelles. NK105, based on the company's, first generation technology prolonged the half-life of the drug to more than 10 h, relative to about 30 min for Taxol, and as a result the company was expecting this formulation to make a positive contribution [89]. However, it was recently announced that a Phase III clinical trial (NCT01644890) [90] evaluating NK105 for treatment of patients with MBC or recurrent BC missed its primary endpoint [89]. The company is now pursuing a Phase I study in combination with carboplatin for the treatment of solid tumors [91]. Moreover, a Phase II clinical trial of this formulation as a treatment for patients with gastric cancer showed sufficient activity and tolerability [91,92].

SB05 (formerly Endotag®-1) is a PTX formulation that is comprised of liposomes of about 200 nm in diameter that are formed from the cationic phospholipid DOTAP and neutral phospholipid DOPC in a 53:47 molar ratio [93–95]. The formulation was developed by MediGene AG [96] and sold to the Taiwanese company SynCore Biotechnology at the end of 2015 [97] in a deal that included $5.5 million in upfront cash and opportunity for future milestone payments [98]. The acquisition of Endotag-1 by Syncore was likely motivated by results emerging from Phase II clinical trials evaluating Endotag-1 for treatment of HER2-negative BC (NCT01537536) [99], TNBC (NCT00448305) [100], PC in combination with gemcitabine (NCT00377936) [101], and hepatic metastases (NCT00542048) [102]. Current plans are to enter a Phase III clinical trial for the treatment of TNBC [94].

Another liposomal PTX formulation is LEP-ETU (Liposome Entrapped Paclitaxel Easy to Use) which includes liposomes of about 150 nm in diameter that are composed of DOPC, cholesterol, and cardiolipin in a 90:5:5 molar ratio [93,103,104]. Developed by NeoPharm, LEP-ETU underwent its first clinical trials in 2004, NCT00080418 [105] and NCT00100139 [106], which revealed a high MTD of 325 mg/m^2 [107] and an equivalent PK profile to that of Taxol [108]. However, despite promising preliminary data, the company's $90 million operating loss between 2005 and 2007 [109], and subsequent delisting from the NASDAQ stock exchange in 2009 [110], significantly delayed progress. In 2010, Neopharm merged with Insys Therapeutics in a deal valued at

$135 million [109,111]. In 2010, Insys Therapeutics ran a Phase II clinical trial evaluating LEP-ETU for treatment of MBC, with 275 mg/m^2 as the selected dose [103]. LEP-ETU has recently received orphan drug designation for the treatment of gastric cancer [112] and OC [113] from the FDA.

Although not strictly reliant on nanotechnology, an oral PTX formulation is also undergoing advanced clinical development. DHP107 is being developed by Daehwa Pharmaceutical of South Korea. This formulation is composed of PTX, monoolein, tricaprylin, and Tween 80, in a ratio of 1: 55: 27.5: 16.5 wt.%, which are mixed together to form an emulsion following sonication [114]. Upon oral administration, it is postulated that this formulation interacts with bile acids and spontaneously forms "micelles" of about 10 μm in diameter in the intestine [115]. In 2007, oral administration of PTX in DHP107 was shown to result in a significantly improved distribution of drug to the gastro-enteric area (i.e. stomach, jejunum, ileum, colon), compared to systemic therapy with Taxol, exhibiting a 30–2000 times higher AUC_{0-24} in this compartment in murine studies [115]. As a result, a Phase I clinical trial on DHP107 was conducted in patients with advanced solid tumors refractory to all standard treatments with comparison to a 175 mg/m^2 intravenous dose of Taxol. In these patients, DHP107 was found to be relatively safe at all doses administered (i.e. up to 600 mg/m^2) with no reported DLTs and no grade 4 neutropenia [116]. In 2015, the Phase III DREAM (NCT01839773) clinical study [117] demonstrated equivalent progression-free survival for oral 200 mg/m^2 DHP107 compared to IV 175 mg/m^2 Taxol [118]. This study showed for the first time that a classical chemotherapeutic agent can result in equivalent efficacy, when the appropriate formulation is used following, oral and intravenous administration (for the treatment of gastric cancer). As the oral route of administration may be more appropriate for gastric cancers compared to other indications, this strategy could facilitate treatment and patient compliance in the management of gastric cancer. Daehwa Pharmaceutical received approval for DHP107 for the treatment of gastric cancer in South Korea in September of 2016 and is now planning expansion to other markets [119,120]. The oral route of administration, and the absence of a post-Taxol approved formulation of PTX for the treatment of gastric cancer could well allow DHP107 to capture a successful share of the market.

Despite the significant number of PTX formulations that are approved for clinical use or are undergoing clinical development, there are a number of new formulations that are expected to quickly reach late stage pre-clinical development and enter into clinical translation [121,122].

Co-D Therapeutics has developed Triolimus, a polymeric micelle formulation that encapsulates a triple drug combination. Triolimus is comprised of PEG-*b*-PLA micelles of 30–40 nm in diameter [123]. In addition to PTX, the encapsulated combination of drugs includes the mTOR inhibitor rapamycin and the Hsp90 inhibitor tanespimycin (17-AAG) which together have been shown to exert synergistic activity [121]. Triolimus was granted orphan drug designation for treatment of angiosarcoma in 2015 and is currently in late stage preclinical evaluation for treatment of BC, NSCLC and angiosarcoma [124]. With regards to the upcoming Triolimus clinical trials, it is noteworthy that a polymeric nanomedicine delivering a combination of drugs is close to entering the market. Celator Pharmaceuticals announced successful data from their Phase III clinical trial which evaluated VYXEOS™ (formerly CPX-351), a liposome formulation co-encapsulating a synergistic ratio of cytarabine and daunorubicin, for treatment of high-risk acute myeloid leukemia [125]. Celator was acquired by Jazz Pharmaceuticals in 2016 in a deal valued at $1.5 billion [126].

Another potential threat to Abraxane is the potential introduction of a generic version of this formulation. This may not seem likely to happen soon given that Celgene holds patents for Abraxane that expire in 2026 in the US and 2022 in Europe [127]. Nevertheless, in March 2016, Allergan launched a paragraph IV Abbreviated New Drug Application (ANDA) claiming that their generic Abraxane would not infringe on Celgene's patents and/or that their patents are unenforceable [128]. As expected, Celgene indicated that they intend to vigorously defend their IP and filed a lawsuit against Allergan [129]. Given that Celgene initiated litigation this triggered the 30-month stay in the FDA generic regulatory approval process. Thus, the earliest Allergan could receive approval for a generic version would be in 2018 [130]. As mentioned previously, there also remains the issue of the Citizen's petition filed by Celgene that put forward that safety and efficacy studies are necessary for formulations referencing Abraxane [50]. This would likely need to be addressed by the FDA prior to acting on the ANDA filed by Allergan. Allergan is the third largest generic drug manufacturer in the US and with a current market cap of $94 billion certainly has the resources for this pending legal battle [131,132]. In addition, Actavis acquired Allergan in March 2015 in a transaction valued at $70.5 billion [133], which may provide even more strength to the implementation of a generic form of Abraxane. As well in 2016, Glenmark Pharmaceuticals of India entered into a strategic agreement with the U.S. based company Particle Sciences Inc. (a Lubrizol company) for the development of a generic version of Abraxane. Glenmark Pharmaceuticals has obtained global exclusive marketing and distribution rights for this formulation and it is indicated that Glenmark intends to file an ANDA for this generic version of Abraxane in 2019 [134]. Importantly, Celgene was denied a patent on Abraxane in India in 2015 and thus a number of generic versions of the drug are under development and/or have entered the market in this country [135,136].

Table 2 summarizes key information on each of the PTX nano-formulations discussed in this review including the company that is developing the formulation, the nature and size of the nanotechnology that comprises the formulation and current stage of development.

1.3. A comparison

The ideal PTX formulation will have a high drug to material ratio, result in limited to no systemic toxicity or hypersensitivity reactions and yield specific and high accumulation of drugs in primary solid tumors and/or metastatic lesions. Table 3 summarizes several of the key performance related properties of the various PTX formulations. Of note, as shown, Cynviloq has the highest MTD [46,58,59] and NK105 has an AUC_{inf} that is at least 15-fold larger than that of any of the other formulations [137]. Thus, these two formulations were expected to represent the most serious threats to the current market leader, Abraxane. However, the recent outcome from a Phase III trial on NK105 has called this formulation's potential into question. Therefore, Cynviloq is the most advanced in terms of clinical development as it received regulatory approval in South Korea in 2007 and demonstrated BE to Abraxane, in the first eight patients enrolled, in the FDA registered TRIBECA clinical trial. However, Celgene's Citizens Petition to the FDA [50] regarding the need for stringent standards and demonstration of safety and efficacy for ANDAs or 505(b)(2) NDAs referencing Abraxane could delay and/or prevent FDA approval of Cynviloq and other nano-formulations of PTX. The FDA's response to this petition is of importance to our field. Generally it raises the question: is bioequivalence sufficient to justify approval of a nano-formulation? In the case of generic nano-formulations, which endeavor to be identical to the FDA-approved formulation in all aspects, it is reasonable to consider ANDAs and the requirement to demonstrate BE as a sufficient level of evidence for approval. Indeed, while a generic formulation of liposomal doxorubicin was originally approved on an urgent basis in 2013 in order to address market shortages of Doxil, a generic version has since been granted FDA approval as a result of an ANDA filing on behalf of Sun Pharma [138]. In addition, the FDA is currently reviewing an ANDA filed by Actavis LLC which has partnered with Merrimack on the clinical translation of a generic version of liposomal doxorubicin hydrochloride [139]. Of note, Merrimack's generic version of Doxil was part of a large pharmaceutical deal, potentially valued at up to $1.025 billion, between Merrimack and Ipsen for acquisition of Onivyde® (irinotecan liposome injection) and generic Doxil [140], demonstrating the technical level of expertise required in

Table 2
Paclitaxel nano-formulations in a nutshell.
A summary of key information on the various paclitaxel nanoformulations. *Completed Phase III study for NK105 resulted in failure of meeting endpoints.

Formulation	Company	Nanotechnology	Size	Status
Abraxane	Celgene	Albumin-based Nanoparticle	130 nm	Approved internationally
Cynviloq	NantPharma	Polymeric micelle	25 nm	Approved in South Korea
Paclical	Oasmia Pharmaceutical AB	Micelle	20–60 nm	Approved in Russian Federation
Lipusu	Luye Pharma Group	Liposome	400 nm	Approved in China
PICN	Sun Pharma	Polymeric-lipidic nanoparticle	100 nm	Approved in India
NK105	NanoCarrier	Polymeric micelle	85 nm	Completed phase II*
SB05	SynCore Biotechnology	Liposome	200 nm	Completed phase II
LEP-ETU	Insys Therapeutics	Liposome	150 nm	Completed phase II
DHP-107	Daehwa Pharmaceutical	Emulsion (oral administration)	10 μm	Approved in South Korea
Triolimus	Co-D Therapeutics	Polymeric micelle	40 nm	Preclinical phase

producing nanomedicines. In contrast, the 505(b)(2) regulatory pathway allows companies to use existing third party data, including safety and efficacy information, in partial fulfillment of FDA submission requirements, even when the composition of the drug formulations vary. While this may be a rational approach for formulations where absorption, distribution, and clearance are the main drivers of efficacy, the authors are not convinced that BE is the main determinant of efficacy for nanoformulations. Nanomedicine drug delivery vehicles can affect drug distribution not only at the whole body level, but also distribution within tissues and indeed within cells. Furthermore, following arrival within organs and cells, drug release kinetics can significantly impact efficacy. For example, SPARC (Secreted Protein Acidic and Rich in Cysteine) overexpression is correlated with treatment response to Abraxane both in PC and head and neck cancer due to albumin's affinity for SPARC [20,141]. In the case of Cynviloq's 505(b)(2) NDA the albumin-SPARC association may not be an issue, given the similar PK behaviour between Abraxane and Cynviloq and the high affinity of free PTX for binding to blood albumin that may enhance its affinity for SPARC in a similar way. Nevertheless, in future 505(b)(2) NDA comparisons between nano-formulations the differences in composition might influence the drug's distribution in the primary tumour and metastatic lesions both at the cellular and sub-cellular levels.

The nano-formulations outlined in Table 3 and currently in clinical development benefit from the absence of human serum albumin, thereby facilitating manufacture and reducing the risk of microbial growth and viral transmission relative to Abraxane. However, most of these formulations are reported to have similar PK profiles to Abraxane (i.e. Paclical, PICN) and therefore likely act more as solubilizers of PTX rather than stable drug carriers. As a result, these formulations are most likely to result in similar (and not superior) efficacy relative to Abraxane. Indeed, these companies often highlight the BE of their formulations relative to Abraxane. Thus, the success of these drugs will be contingent on

Table 3
Key performance indicators of paclitaxel formulations.
Summary of key performance indicators and the maximum tolerated dose (MTD), plasma area under the curve (AUC_{inf}), adverse reactions and dose limiting toxicities (DLTs) for the nine advanced drug delivery formulations of PTX that have reached clinical approval and/or development. Taxol® is included for comparison. *The MTD has been described up to 435 mg/m^2. **According to Oasmia's press release. ***A study to define the major PK parameters is in progress. ****PK parameters are not available from SynCore Bio.

	MTD (mg/m^2)	Common dose (mg/m^2)	AUC (h*μg/ml)	Adverse reactions and DLTs	Key performance indicators	Refs.
Taxol®	240	175	23 (at 210 mg/m^2 dose)	Neutropenia (grades 3 & 4) Neuropathy (grade 3) Hypotension (grades 3 & 4) Hypersensitivity	Hypersensitivity reactions due to Cremophor EL Premedication with corticosteroids is required	[8,142,143]
Abraxane®	300	260	16.7–19.1 (at 300 mg/m^2 dose)	Neutropenia (grades 3 and 4) Neuropathy (grade 3)	Absence of toxic excipient HSA donor is required Microbial growth	[8,44,60,61,145]
Cynviloq™	>300*	260	11.6 (at 300 mg/m^2 dose)	Neutropenia (grades 3 and 4) Pneumonia (grades 3 and 4)	>MTD than Abraxane Reduced neuropathy Similar PK to Abraxane® Premedication with corticosteroids is required	[44,46,52,58,59,146]
Paclical®	250	260	Similar to Abraxane**	Neuropathy	Readily metabolized vitamin A-based micelle carrier Similar PK to Abraxane®	[69,70,144,147]
Lipusu®	TBD***	175	TBD	Neutropenia (grades 3 & 4) Liver toxicity (grade 3)	Premedication with corticosteroids is recommended Limited PK data available	[78,79,148]
PICN	325	260, 295	15.6 (at 260 mg/m^2 dose) 14.2 (at 295 mg/m^2 dose)	Neutropenia (grades 3 & 4) Neuropathy (grades 3 & 4)	>MTD than Abraxane Similar effectiveness to Abraxane®	[82,86,149]
NK105	180	180	455 (at 180 mg/m^2 dose)	Neutropenia (grade 4)	Greatest AUC Potential to pursue active targeting Reduced neuropathy Low MTD	[88,137]
SB05	ns****	264 (44 × 6)	ns	ns	Vascular targeting Efficacy compared only to Taxol® Limited PK data available	[95,100,150,151]
LEP-ETU	325	175, 275	15.9 (at 175 mg/m^2 dose)	Neutropenia (grades 3 & 4) Neuropathy Dehydration (grade 3)	>MTD than Abraxane Bioequivalent to Taxol®	[103,107,108,152]
DHP107	600	200	–	Neutropenia (grade 3)	Oral administration >MTD than Abraxane Reduced adverse reactions Bioequivalent to Taxol®	[114–116,118]

the ability of the respective companies to offer lower drug prices in comparison to Abraxane, which could potentially be afforded by more straightforward manufacturing processes. In contrast to the other clinically evaluated formulations, NK105 is the only formulation that has demonstrated significantly increased PTX residence times in the blood compartment. An increased circulation lifetime can allow the nanocarrier to take advantage of the so-called enhanced permeability and retention effect thus resulting in significantly increased tumour accumulation, as shown in preclinical models, and providing the potential for future integration of an active targeting strategy. Yet, the recent Phase III data has raised questions regarding the future promise of this formulation. The major toxicities associated with PTX, neuropathy and neutropenia, were reported to some extent for all formulations [8,137,142–144]. Yet, each formulation results in an improvement in toxicity profile in comparison to Taxol, for which Cremophor EL is known to cause hypersensitivity reactions [143].

Table 4
Clinical indications for paclitaxel formulations.
The landscape of the various nano-formulations of PTX in terms of clinical approval (green), clinical development (yellow) and/or orphan drug designation (orange). *Indicates less common cancer types (i.e. angiosarcoma, liver cancer, billiary tract carcinoma, melanoma, etc.).

Formulation	Cancer Type						
	Breast	Pancreatic	NSCLC	Ovarian	Bladder	Gastric	Other*
Abraxane	+	+	+				
Cynviloq	+	+	+	+	+		
Paclical	+			+			
Lipusu	+		+	+			
PICN	+			+	+		+
DHP107						+	
NK105			+	+		+	
SB05	+	+					+
LEP-ETU	+			+		+	
Triolimus	+		+				+

2. The landscape in the near future

In the near future, we may see a number of advanced nano-formulations of PTX competing with Abraxane in the global PTX market. The PTX market can be divided into geographical regions and indications and expands when we consider the recognized 50% off-label use of drugs in oncology [153]. As shown in Fig. 3, many geographical regions are putting forward their own nanoformulation of PTX – yielding the question: will each formulation be strong enough to outperform the competition to such an extent that success is achieved beyond their own location? Furthermore, the various nanoformulations of PTX are being pursued for a wide range of indications, though with inevitable overlap. Table 4 summarizes the many indications for which each nano-formulation of PTX has been approved or for which clinical trials are currently underway. Given Abraxane's ability to largely overtake the Taxol market position and the billion dollar market at play, it is no wonder that so many companies are continuing to focus their efforts in this area.

3. Conclusion

Nanomedicine formulations of conventional antitumour agents endeavor to improve both the toxicity profile and therapeutic efficacy relative to the conventional drug formulation. Abraxane succeeded in both regards, allowing it to replace Taxol as the dominant PTX chemotherapeutic and thereby conquering the lucrative PTX market. Despite the higher cost of Abraxane, the life years gained and improved quality of life it affords relative to Taxol have resulted in adoption by healthcare funding agencies and healthcare insurance providers around the world. As such, Abraxane is viewed as one of the most significant nanomedicine success stories, both in terms of patient impact and financial gain. Unsurprisingly, this success has emboldened a new

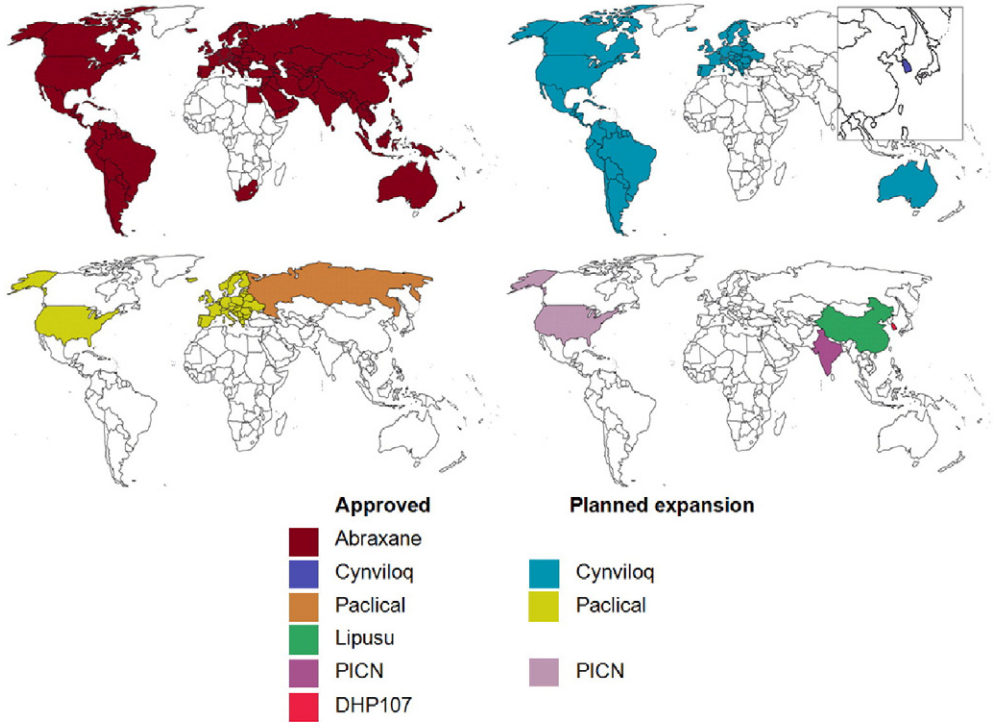

Fig. 3. Geographical landscape of approved and planned expansion of paclitaxel formulations. Abraxane (dark red) has been approved globally. Cynviloq (dark blue) has been approved in South Korea with Sorrento targeting approval in the western, Latin American, and Australian markets (light blue). Paclical (dark orange) is approved in the Russian federation with Oasmia seeking entry into Europe and the United States (light orange). Lipusu (green) and PICN (purple) are approved in China and India, respectively, and PICN is seeking entry into the US market (light purple). DHP107 (red) is approved in South Korea and seeking approval in other markets, possibly the United States and Europe. The competition in Northern America and Europe is fierce.

generation of competitors to develop their own nanomedicine formulations of PTX to compete with Abraxane for market share. These newer formulations have generally sought to enter the market by demonstrating BE to Abraxane, but in the future it is likely that they will attempt to distinguish themselves by demonstrating superior efficacy. If this cannot be achieved, improvements in toxicity and reductions in cost could also be appealing enough to patients and payers such that they might allow these new entrants to capture a substantial share of the PTX market. This is particularly true given the rapidly developing world market for PTX and the myriad of indications for which PTX therapies are likely effective, but for which Abraxane has not yet been approved. However, the increasing off-label use of Abraxane makes targeting these other indications a risky proposition. Despite the strides that each of these new formulations has taken to capture a distinct segment of the PTX market, as yet none have demonstrated clear superiority over Abraxane. Therefore, there remains an opportunity for one of these challengers to differentiate themselves or for a completely new formulation to surpass the current competitors and thus become the new dominant player in the PTX market.

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