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Cancer nanomedicines: oversold or underappreciated?

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1 Introduction

Since the approval of liposomal doxorubicin (Doxil) and daunorubicin (DaunoXome) 20 years ago for the treatment of (HIV-related) Kaposi's sarcoma, significant investment and research efforts have been geared towards the development of nanomedicines for cancer treatment. The benefits of formulating cancer drugs in lipid- and polymer-based nanocarrier systems regarding drug solubility, circulation time, biodistribution and toxicity while maintaining (or even enhancing) therapeutic efficacy, have led to the approval of about a dozen cancer nanomedicines, including antibody-drug conjugates (ADCs) [1, 2].

Notwithstanding the advantages of tumor-targeted delivery systems over standard formulations of cancer drugs, some argue that cancer nanomedicines have not fully delivered on their promise, as the number of nanomedicines that have reached the clinic is considered to be rather low. The perceived poor clinical translation of cancer nanomedicines is mainly due to high expectations created by overgeneralizing drug targeting and delivery concepts, overselling pre-clinical results and further fueled by mixed results of recent clinical trials (Table 1). As the drug delivery field is maturing, advanced (imaging) techniques are improving our understanding of nanomedicine *in vivo* behavior and interactions with the

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Declaration of interest

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tumor microenvironment, resulting in a more realistic view on the potential and limitations of current nanomedicines.

At the same time, it can also be argued that cancer nanomedicines are underappreciated when taking into account recent clinical advancements including approval of the first generic cancer nanomedicine, delivery of two chemotherapeutic drugs in a therapeutically synergistic ratio by a single formulation and triggered-release strategies evaluated in phase III clinical trials.

With global sales of oncology therapeutics totaling $84 billion in 2015 (http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/global-oncology-trend-report-a-review-of-2015-and-outlook-to-2020), there is a big potential global market for successful cancer nanomedicines, exemplified by albumin-bound paclitaxel (Abraxane), of which the 2015 sales were reported to reach nearly $1 billion.

To describe the current status of cancer nanomedicines, we discuss factors that hamper their clinical translation and provide examples of recent clinical trial outcomes.

2 Overgeneralized concepts and oversold pre-clinical results

There are several underlying reasons for the limited clinical translation of cancer nanomedicines, which include poor understanding of the biological barriers that nanomaterials face inside the body, misinterpretation of drug delivery concepts [3], cost-effectiveness, manufacturing and scaling up, and regulatory issues. Most importantly, we must provide a more realistic representation of the potential (and limitations) of cancer nanomedicines by stopping the overgeneralization of targeting and delivery concepts as well as overselling pre-clinical results.

The seminal study by Matsumura and Maeda in which the enhanced permeability and retention (EPR) effect was first proposed [4], has made a huge contribution to the development of the drug delivery field and has considerably attributed to the “passive tumor targeting”-based design of current cancer nanomedicines. However, the EPR effect has been generalized to a point where all solid tumors (both murine and human) are considered to have the same characteristics and therefore all long-circulating nanoparticles ≤ 100 nm are presented as to preferentially accumulate in tumors. A recent meta-analysis of pre-clinical studies from the last 10 years, however, indicated that “only” 0.7% of the administered dose is actually delivered to tumors [5]. Although it can be debated if this (median) percentage is a fair representation, if it is low or not, and/or if it is important for patient benefit [6], it differs greatly from the perception of cancer nanomedicines’ preferential tumor accumulation that is often presented. Consequently, one might say that what has been achieved to date with cancer nanomedicines can be summarized as the mere development of carrier systems for improved drug solubility, stable encapsulation and prolonged circulation which accumulate somewhat more in tumors compared to free drug as a result of blood circulation and pathophysiology of the tumor, rather than true tumor-targeted delivery.

It seems that cancer nanomedicine development has focused on treatment of mice rather than humans by using fast-developing EPR-driven xenograft tumor models which are ideal

for demonstrating enhanced therapeutic efficacy of nanomedicine formulations vs. free drug but are less useful from a translational point of view. For example, a recent study demonstrated that there was a 13-fold variation in clearance of PEGylated liposomal doxorubicin (PLD) between 23 inbred mouse strains [7]. Generally, immunodeficient mice are subcutaneously implanted with tumor cells and treated when tumors are palpable (~100 mm^3) until the point that a pre-defined tumor volume (1000-1500 mm^3) is reached in control and/or treatment groups. For a 25 g mouse, an increase in tumor volume of 100 mm^3 to 1000 mm^3 corresponds to an increase of ~0.4% to 4% of its body weight (assuming a tissue density of 1 g/mL). For a human of 80 kg, 4% body weight would translate to a 3.2 kg tumor which obviously differs greatly from the situation of patients in clinical trials who often present with advanced, drug-resistant and/or metastatic disease. Although the EPR effect can clearly be present in humans [8], it is now recognized that the effect varies highly between types of cancer or even between different tumors of the same type. A meta-analysis of pre-clinical and clinical studies which compared liposomal and free doxorubicin indicated that while the overall survival (OS) rate in mice treated with PLD was significantly higher than those treated with free drug, this was not the case in 8 clinical trials where there was no statistical difference between treatments regarding objective response (OR) rates, progression-free survival (PFS) and OS [9].

The use of immunodeficient EPR-driven mouse models used in pre-clinical settings indeed hinders the clinical translation of cancer nanomedicines because they poorly represent the situation in a human patient. In recent years, however, more representative models are increasingly used, such as (drug-resistant) patient-derived xenografts and genetically engineered spontaneous tumor models. In addition, imaging techniques can be applied to evaluate of cancer nanomedicines in metastatic models [10], which may provide a more realistic prediction of therapeutic efficacy in human patients.

The focus of pre-clinical cancer nanomedicine research often appears to be on the development of novel materials and design of multifunctional capabilities such as targeting or imaging moieties and less so with treatment of patients in mind. With the exception of ADCs, no cancer nanomedicines equipped with targeting ligands have thus far been approved [11]. All approved cancer nanomedicines and most in late stage clinical evaluation can be considered as straightforward formulations from a technical point of view but are complex enough from a characterization point of view. It has been suggested that “simplified” systems have a better chance to eventually reach the patient [12].

3 Underappreciated clinical advancements

The claim that cancer nanomedicines have not delivered on their promise as indicated by the limited number of approved cancer nanomedicines is a misrepresentation of their current status, taking into account recent noteworthy clinical advancements.

In fact, over the last years a number of cancer nanomedicines have been approved including liposomal irinotecan (Onyvide, in combination with 5-FU and leucovorin) for treatment of patients with metastatic pancreatic cancer and liposomal vincristine (Marqibo) for treatment of Philadelphia chromosome negative acute lymphoblastic leukemia. In addition, albumin-

bound paclitaxel which was approved in 2005 for treatment of breast cancer, has also been approved for the treatment of non-small cell lung cancer (NSCLC) and metastatic adenocarcinoma of the pancreas. Genexol-PM/IG-001 (Cynviloq, micellar paclitaxel), has been approved in Korea in 2007 but not yet by the FDA. It is currently undergoing a phase III bioequivalence study vs. albumin-bound paclitaxel (NCT02064829, TRIBECA study) in patients with locally recurrent or metastatic breast cancer, with the aim to get approval via the FDA 505(b)(2) route which would allow to incorporate clinical date of free paclitaxel (Taxol) and albumin-bound paclitaxel in the case of a New Drug Application submission. Moreover, the first generic cancer nanomedicine was approved in 2013, namely Lipodox (liposomal doxorubicin), albeit after a priority review following a shortage of Doxil that was ongoing since 2011 because of manufacturing issues.

This year has so far has been both encouraging and disappointing in terms of cancer nanomedicine clinical trial outcomes (Table 1).

Mixed phase II trial results were announced lately for docetaxel polymeric nanoparticles equipped with targeting ligands directed at prostate-specific membrane antigen (BIND-014) (). Although docetaxel polymeric nanoparticles seemed to be (somewhat) effective in metastatic castration-resistant prostate cancer and NSCLC, no effect was observed in cervical and head and neck cancer. It is unsure whether the development of docetaxel polymeric nanoparticles will be continued following BIND Therapeutics' bankruptcy and subsequent acquisition by Pfizer. It was also announced that the phase III study of NK105 (micellar paclitaxel) for the treatment of metastatic or recurrent breast cancer failed to demonstrate statistical non-inferior PFS compared to paclitaxel. There are, however, plans for a phase I study for the treatment of solid tumors in combination with carboplatin according to manufacturer's website (http://www.nanocarrier.co.jp/en/research/pipeline/01.html). As NK105 is based on block copolymers with pendant aromatic groups for non-covalent π-π stacking interactions, it might be more beneficial to pursue methods that yield more stable nanoparticles such as Cristal Therapeutics' CriPec platform, of which CriPec docetaxel is currently evaluated in a phase I trial for the treatment of solid tumors (NCT02442531).

Excitingly, positive phase III results for treatment of acute myeloid leukemia (AML) were announced for CPX-351 (Vyxeos), a liposomal formulation of cytarabine and daunorubicin in a fixed molar ratio of 5:1 for synergistic therapeutic effects which was granted Fast Track designation. If Vyxeos gets approved, it will be the first therapy in 40 years to improve survival of patients with high risk, secondary AML. The clinical trial outcome led to the acquisition of Celator Pharmaceuticals by Jazz Pharmaceuticals for $1.5 billion. It will be interesting to see if the positive phase III results of CPX-351 and its expected approval will spark the development and clinical evaluation of subsequent two-in-one cancer nanomedicines. Celator have also conducted a phase II study in patients with advanced colorectal cancer with CPX-1, a liposomal formulation of irinotecan and floxuridine in a ratio of 1:1 which proved to be synergistic in pre-clinical studies. Although combination regimens of chemotherapy are standard for treatment of many types of cancers, physicians might be reluctant to make use of 2-in-1 nanomedicines as it does not allow them to alter the

dose of the individual components in case of adverse effects or toxicities but only to change the dose or regimen of the entire combination therapy.

Demonstrating the clinical potential of triggered-release formulations, Celsion announced positive final OS data from the phase III study in which patients with hepatocellular carcinoma (HCC) were treated with thermosensitive liposomal doxorubicin (Thermodox) plus radiofrequency ablation (RFA). Although the HEAT study initially did not meet its primary endpoint, it was demonstrated that in a subgroup of patients, treatment with thermosensitive liposomal doxorubicin plus RFA resulted in an improvement in OS which was confirmed by an independent NIH retrospective analysis. The same treatment will be used for HCC patients currently enrolling in the OPTIMA phase III study (NCT02112656).

Regarding ADCs, it was announced that in a phase III study brentuximab vedotin (Adcetris) significantly improved objective response rate (ORR) lasting at least for months when compared to methotrexate or bexarotene in patients with cutaneous T-cell lymphoma. It also demonstrated 75% ORR in a phase II study for treatment of patients with relapsed/refractory Hodgkin lymphoma (with 38% percent of patients achieving complete response, CR). Preliminary results from a phase II study with sacituzumab govitecan (IMMU-132) for the treatment of triple negative breast cancer indicated a 28% ORR. In a phase III trial of inotuzumab ozogamicin (CMC-544) for the treatment of acute lymphoblastic leukemia, the ADC demonstrated superior CR compared to chemotherapy but did not improve OS. While ado-trastuzumab emtansine (Kadcyla) combined with pertuzumab demonstrated improved pathologic CR (pCR) compared to trastuzumab and paclitaxel in a phase II trial for treatment of HER2-positive breast cancer, in a similar phase 3 trial the same combination demonstrated statistical inferior pCR when compared to trastuzumab plus pertuzumab.

4 Expert Opinion

So where do cancer nanomedicines stand 20 years after the first approval of its kind? It has certainly proven to be more challenging than expected to fulfill the high expectations of cancer nanomedicines regarding clinical translation that rose after the approval of liposomal doxorubicin and daunorubicin. The fact that these expectations were created by overgeneralization of drug targeting and delivery concepts as well as the exaggeration of the predictive value of pre-clinical results means that a more realistic view on the potential and limitations of cancer nanomedicines can be also created, which fortunately appears to be happening.

On one side, fundamental research should continue to explore new materials and possibilities to improve delivery vehicles for cancer drugs (and nucleic acids), possibly learning from nature’s own delivery systems [13], without overselling pre-clinical results. In addition, it is necessary to fundamentally understand the therapeutic window of cancer nanomedicines by studying their interactions in the body. For example, as we alter the circulation kinetics and shift the biodistribution of drugs by formulating them as nanomedicines, how does that affect the organs where the majority of the particles accumulate, i.e. the liver and the spleen, and how are nanomaterials eventually cleared by these organs [14]? What is the effect of using immunodeficient animal models on assessing

the role that the immune system plays in cancer and how does the interaction with nanomedicines influence their therapeutic efficacy? On the other side, to develop clinically relevant cancer nanomedicines that benefit patients, translational research should adopt a "disease-driven" approach rather than a "formulation-driven" approach [1].

There are delivery systems for the stable encapsulation of either hydrophilic or hydrophobic molecules and many drugs with poor characteristics (e.g. low solubility, high toxicity, suboptimal circulation kinetics and/or biodistribution) would profit from being formulated as nanomedicines. For example, it was demonstrated that two hydrophobic candidate drugs that failed in phase II clinical trials due to toxicity could be loaded into liposomes which significantly improved their therapeutic index [15]. There are several initiatives underway in the EU and the US to formulate drugs as nanomedicines from early stage development, rather than at a later stage because they have failed in (pre)clinical studies. In this context, it is exciting that the NCI's Frederick National Lab for Cancer Research announced collaborations with AstraZeneca, Amgen and Pfizer on formulating and analyzing nanomedicines (https://frederick.cancer.gov/News/NclPharma.aspx).

The majority of cancer types are treated with combinations of chemotherapeutic drugs, and as cancer nanomedicines have demonstrated to impact on patient benefit by ameliorating dose-limiting adverse effects, they are increasingly becoming part of combination treatment regimens or being evaluated as such. In addition to the first 2-in-1 combination cancer nanomedicine CPX-351, liposomal irinotecan is approved in combination with 5-fluorouracil and leucovorin and NC-6004 (Nanoplatin, micellar cisplatin derivatives) will be evaluated in a phase III study for treatment of locally advanced or metastatic pancreatic cancer in combination with gemcitabine vs. gemcitabine alone (NCT02043288). MM-302 (HER2-targeted liposomal doxorubicin) is undergoing phase a II/III clinical trial (NCT02213744, HERMIONE study) in combination with trastuzumab for treatment of breast cancer and CRLX101 (camptothecin-coupled cyclodextrin polymer nanoparticles) has been granted Fast Track designation by the FDA for treatment of platinum-resistant ovarian carcinoma, fallopian tube or primary peritoneal cancer in combination with paclitaxel (NCT02389985). Unfortunately, a phase II study evaluating CRLX101 plus bevacizumab for treatment of patients with metastatic renal cell carcinoma did not demonstrate an improvement in PFS when compared to standard of care. Patients with newly diagnosed, early stage unfavorable risk Hodgkin lymphoma that were treated with brentuximab vedotin combined with chemotherapy achieved 93% CR, while 100% of patients achieved CR when radiation therapy was added to the combination treatment. Of AML patients treated with vadastuximab talirine (SGN-CD33A) combined with hypomethylating agents in a phase I study (NCT01902329), 71% achieved CR prompting the start of a phase III trial (NCT02785900, CASCADE study).

Finally, as is now standard for molecularly targeted therapies, there is a need to develop companion diagnostic tests to stratify patients that are likely to benefit the most from treatment (and those who will not) and to be able to monitor therapeutic efficacy.

The key to improved clinical translation of cancer nanomedicines lies not only with researchers to increase their understanding of nanomedicine interactions in the body, adopt a

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more realistic view of nanomedicine potential and follow a “disease-driven” approach. There is also an important role for funding agencies (fundamental vs. translational funding), industry (adopting nanotechnology), physicians (incorporating nanomedicines in treatment regimens) and regulators (improving nanomedicine approval regulations).

In an era of technological developments that facilitate rapid and straightforward data sharing as well as improving cost-effective scale-up and manufacturing, we expect that cancer nanomedicines will increasingly deliver on their promise in the coming 20 years.

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Table 1

Recently announced clinical trial outcomes of selected cancer nanomedicines

Name / company	Formulation	Phase / Trial identifier	Condition	Primary outcome measure	Outcome
Ado-trastuzumab emtansine, T-DM1 (Kadcyla) / Roche (Genentech)	DM1 coupled to HER2-targeted antibody (+ pertuzumab)	Phase III / NCT01966471 (KRISTINE study)	HER2-positive primary invasive BC	Invasive DFS	Statistically significant inferior pCR of treatment (44%) vs. trastuzumab + pertuzumab (56%)
		Phase II / NCT01042379 (I-SPY 2 study)	HER2-positive BC	pCR	Statistically significant improved pCR of treatment (52%) vs. trastuzumab + paclitaxel (22%)
Brentuximab vedotin (Adcetris) / Seattle Genetics, Inc. (Takeda Pharmaceutical Co., Ltd.)	MMAE coupled to CD30-targeted antibody	Phase II / NCT00848926	Relapsed / refractory HL	ORR	ORR rate 75%
				Secondary outcomes: OS, PFS, CR	*OS rate 41%, PFS rate 22%, CR 38%*
		Phase III / NCT01578499 (ALCANZA study)	CTCL	ORR	Statistically significant improved ORR of treatment (56.3%) vs. methotrexate or bexarotene (12.5%)
	(+ AVD + ISRT)	Phase II / NCT01868451	Newly diagnosed early stage, unfavorable risk HL	CR	93% CR (+ AVD), 100% (+ AVD + ISRT)
CPX-351 (Vyxeos) / Jazz Pharmaceuticals (Celator Pharmaceuticals)	Liposomes containing cytarabine and daunorubicin in a 5:1 fixed ratio	Phase III / NCT01696084	high risk (secondary) AML	OS	Statistically significant improved median OS of treatment (9.56 mo) vs. SOC (5.95 mo)
CRLX101 / Cerulean Pharma, Inc.	Nanoparticle drug-conjugates containing camptothecin (+ bevacizumab)	Phase II / NCT02187302	Metastatic RCC	PFS	No statistically significant improved median PFS of treatment (3.7 mo) vs. SOC (3.9 mo)
Docetaxel polymeric nanoparticles (BIND-014) / Bind Therapeutics, Inc.	PSMA-targeted polymeric nanoparticles containing docetaxel	Phase II / NCT02283320 (iNSITE2 study)	NSCLC	DCR	70% DCR in per protocol population
		Phase II / NCT02479178 (iNSITE2 study)	CC	ORR	No ORR
			HNSCC	ORR	ORR rate 10%
		Phase II / NCT01812746	Metastatic CRPC	Radiographic PFS	71% of patients achieved PFS for 6 months
Inotuzumab ozogamicin, CMC-544 / Pfizer, Inc.	Calicheamicin coupled to CD22-targeted antibody	Phase III / NCT01564784 (INO-VATE ALL study)	ALL	CR	Statistically improved CR of treatment vs. chemotherapy (80.7% vs. 29.4%) in subgroup of 218 patients
				OS	No statistical improved OS of treatment vs. chemotherapy

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Name / company	Formulation	Phase / Trial identifier	Condition	Primary outcome measure	Outcome
Liposomal doxorubicin (ThermoDox) / Celsion, Inc.	Thermal-sensitive liposomal doxorubicin (+ RFA)	Phase III / NCT00617981 (HEAT study)	HCC	PFS	No statistically significant improved PFS of treatment (13.97 mo) vs. RFA (13.87 mo)
				Secondary outcome: OS	*Statistically significant risk improvement in OS of treatment (79 mo) vs. RFA (53.6 mo) in subgroup*
MM-398 (Onyvide) / Merrimack Pharmaceuticals, Inc.	Liposomes containing irinotecan (+ 5-FU/LEU)	Phase III / NCT01494506 (NAPOLI-1 study)	Metastatic PC	OS	Statistically significant improved OS of treatment (6.1 mo) vs. 5-FU/LEU (4.2 mo)
NK105 / Nippon Kayaku Co., Ltd. (NanoCarrier)	Polymeric micelles containing paclitaxel	Phase III / NCT01644890	Metastatic / recurrent BC	PFS	No statistically significant non-inferior PFS of treatment vs. paclitaxel
Sacituzumab govitecan (IMMU-132) / Immunomedics, Inc.	SN-38 coupled to TROP2 targeted antibody	Phase II / NCT01631552	Metastatic triple negative BC	*Secondary outcome: ORR*	*Confirmed ORR of 28% in 60 patients*

5-FU, 5-fluorouracil; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AVD, adriamycin, vinblastine, and dacarbazine; BC, breast cancer; CC, cervical cancer; CR, complete response; CRPC, castration-resistant prostate cancer; CTCL, cutaneous T-cell lymphoma; DCR, disease control rate; DFS, disease free survival; DM1, emtansine; HCC, hepatocellular carcinoma; HL, Hodgkin lymphoma; HMA, hypomethylating agents; HNSCC, head and neck squamous cell carcinoma; ISRT, involved site radiation therapy; LEU, leucovorin; MMAE, monomethyl auristatin E; mo, months; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PBD, pyrrolobenzodiazepine; PC, pancreatic cancer; pCR, pathologic complete response; PFS, progression free survival; PSMA, prostate specific membrane antigen; RCC, renal cell carcinoma; RFA, radiofrequency ablation; SOC, standard of care