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Clinical Cancer Research

Title: A Review of Study Designs and Outcomes of Phase I Clinical Studies of Nanoparticle Agents Compared with Small Molecule Anticancer Agents

Authors: Whitney P. Caron**, Katherine P. Morgan**, Beth A. Zamboni, William C. Zamboni

Affiliations: *These authors contributed equally to this work. 1. Division of Pharmacotherapy and Experimental Therapeutics, University of North Carolina (UNC) Eshelman School of Pharmacy, 2. Department of Mathematics, Carlow University, Pittsburgh, Pennsylvania, 3. UNC Lineberger Comprehensive Cancer Center, 4. UNC Institute for Pharmacogenomics and Individualized Therapy, 5. Carolina Center of Cancer Nanotechnology Excellence, 6. North Carolina Biomedical Innovation Network

Correspondence to: William C. Zamboni, PharmD, PhD
Division of Pharmacotherapy and Experimental Therapeutics
Eshelman School of Pharmacy
University of North Carolina at Chapel Hill
120 Mason Farm Road, Suite 1013, CB 7361
Chapel Hill, NC 27599-7361
Office Phone: 919.843.6665
Office Fax: 919.966.5863
Email: zamboni@email.unc.edu

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**Translational Impact Statement:** The degree of dose escalation from starting dose to MTD is significantly greater for nanoparticle (NP) compared to small molecule (SM) anticancer drugs. This is associated with a significantly greater number of dose levels, time required to complete phase I studies, and costs to conduct phase I studies of NP. These findings necessitate the need to optimize the design of phase I studies of NP agents, particularly the identification of the most appropriate preclinical animal model to use when evaluating NP toxicity.
ABSTRACT

Background: Nanoparticles (NP) or carrier-mediated agents have been designed to prolong drug circulation time, increase tumor delivery, and improve therapeutic index compared to their small molecule (SM) counterparts. The starting dose for phase I studies of SM and NP anticancer agents is based on the toxicity profile of the most sensitive species (e.g., rat or canine), but the optimal animal model for these studies of NP is unclear. The objective of this study was to evaluate the design, progression, and outcomes of phase I studies of NP compared to SM anticancer agents. Methods: In preclinical studies, the maximum tolerated dose (MTD) in rats and dogs was evaluated for NP and their respective SM. In phase I clinical trials in patients with advanced solid tumors, the basis for starting dose, the number of dose escalations, number of patients enrolled, and the ratio of MTD to starting dose was determined for NP and SM. Results: The mean ratio of MTD to starting dose in clinical phase I studies was significantly greater for NP (13.9 ± 10.8) compared with SM (2.1 ± 1.1) (P = 0.005). The number of dose levels in a clinical phase I study was also significantly greater for NP (7.3 ± 2.9) compared with SM (4.1 ± 1.5) (P = 0.008). Conclusions: The degree of dose escalation from starting dose to MTD was significantly greater for NP compared to SM anticancer drugs. These findings necessitate the need to identify the most appropriate preclinical animal model to use when evaluating NP toxicity.
INTRODUCTION

Nanoparticles or carrier-mediated agents (NP) used to deliver anticancer therapies have many unique advantages over their traditional small molecule (SM) counterparts, including improved solubility, longer circulation time, greater plasma exposure (AUC), tumor-selective delivery, increased antitumor response and reduced toxicity (1, 2). The pharmacokinetics (PK) of NPs is dependent upon the carrier and not the drug encapsulated within the carrier until the drug gets released from the carrier (2-5). The drug that remains encapsulated within NPs, (generally >95%) or linked to a conjugate or polymer is an inactive prodrug, and thus the drug must be released from the carrier in order to be active. After the drug is released from the carrier, the PK disposition of the drug will be the same as that following administration of the non-carrier form of the drug (3, 4, 6). There is significant interpatient variability seen in the PK of NPs, such as PEGylated liposomes, and the observed differences between patients could be attributed to heterogeneity in the mononuclear phagocyte system (MPS) (7, 8). The MPS is comprised of circulating monocytes and dendritic cells, as well as phagocytic cells in the liver and spleen (8).

The relationship between MPS and NP clearance (CL) was demonstrated in a clinical phase I study using S-CKD602, a PEGylated liposomal camptothecin analogue, in patients with refractory solid tumors (9). After administration of S-CKD602 there was a greater % decrease in monocytes (58 ± 34) versus ANC (42 ± 30) on 1 cycle of treatment (P= 0.001) (9). There was also a linear relationship between % decrease in monocytes and the CL of encapsulated drug (R²= 0.75) and release of drug from the liposome (R²= 0.51) (9). This relationship was not observed with the small molecule formulation CKD-602. Therefore, unlike SMs, there is a bi-directional interaction between NP and cells of the MPS where the MPS cells are involved in the uptake and clearance of NP, which results in pharmacologic effects of NP on MPS cells. Conversely, SM are cleared from circulation by more traditional mechanisms such as liver metabolism and renal excretion (10).
Preclinical trials of anticancer drugs require a rodent and non-rodent model for toxicokinetic (TK) and toxicologic studies (11). The non-rodent model most commonly selected is a canine (11). The toxicologic and TK data is used to determine the starting dose in phase I trials based on one-tenth of the rodent LD$_{10}$ (lethal dose for 10% of population tested) or one-third of the dose associated with the dose-limiting toxicity (DLT; side effects of a drug or other treatment are serious enough to prevent an increase in dose or level of that treatment) in dogs (11, 12). The starting dose in the first inhuman phase I study of anticancer agents is then based on dose in the most sensitive species (11).

The most predictive animal model for toxicology and pharmacology studies of NPs is unclear (13)(14). The CL of PEGylated liposomes in preclinical species has been assessed through allometric scaling (15). PK studies were performed at the maximum tolerated dose (MTD) of PEGylated liposomal doxorubicin (Doxil; PLD), CKD-602 (S-CKD602 and cisplatin (SPI-077) in mice, rats, and dogs, and as part of phase I studies in patients with refractory solid tumors (12, 15). Dogs had the fastest CL of the three different PEGylated liposomes evaluated when compared to mice, rats, and humans (15). As these studies were performed at the MTD, dogs also had the lowest exposure associated with toxicity, which suggests that dogs may not be appropriate models for NP toxicology or pharmacology studies (15).

It has been observed that the starting doses in phase I trials for NPs are considerably lower and more dose escalations are required to reach the first signs of toxicity and eventually DLT compared with SM (10, 15). When developing therapeutic agents that are associated with potential high costs and adverse events it is critical to optimize the preclinical and clinical study designs of these drugs. Therefore, the objective of the current study was to conduct a review of clinical phase I trials of NPs and equivalent SM to evaluate whether significant differences existed in study design, progression, and outcomes between NPs and SM. NPs comprises carrier-mediated platforms of
anticancer agents, including liposomes and conjugates which contain an active SM, while SM includes cytotoxics and any non-nano anticancer agent excluding targeted therapies.

METHODS

Study Design

We evaluated differences in how phase I studies of NP and SM were designed and performed. We evaluated the following factors related to phase I study designs for NP and SM: 1) ratio of MTD to starting dose; 2) the number of dose escalations; 3) the number of patients enrolled; 4) time required to complete the study; and 4) total estimated cost of the study.

Using databases such as PubMed, Medline, and ASCO Proceedings, searches for peer reviewed phase I studies of NP and SM were conducted using the search terms: MTD, preclinical, phase I, pharmacokinetics, and toxicity. Data was collected for 9 NPs and matching SM anticancer agents. The NPs were Abraxane (albumin bound paclitaxel), NKTR-102 (PEGylated irinotecan), liposomal vincristine, OSI-211 (liposomal lurotecan), liposomal vinorelbine, NK-105 (PEGylated paclitaxel), S-CKD602 (PEGylated liposomal CKD-602), IHL-305 (PEGylated liposomal irinotecan), MBP-426 (PEGylated liposomal oxaliplatin) (16-24). The SM were paclitaxel, irinotecan, lurtotecan, vinorelbine, CKD-602, and oxaliplatin (25-28). The NP and SM preclinical toxicology data was collected when available to determine the animal model used in defining starting dose in phase I clinical trials.

For preclinical studies, the MTD found in rats and dogs were recorded. For phase I studies in patients with advanced solid tumors, the starting dose, the number of dose escalations from starting dose to MTD, number of patients, and the ratio of MTD to starting dose were recorded for each NP and SM. The MTD reported in all studies was defined as 1 dose below the dose associated with the DLT. The DLT was defined as a grade 4 hematologic or grade 3/4 non-hematologic toxicity in all studies. The dose escalation strategy for all of the
reviewed phase I studies were performed using the conventional 3+3 modified Fibonacci design (29). The methods used to determine the starting dose in the phase I study of the NP and SM were the same. As per standard methods, toxicology studies were performed in rats and dogs. If rats were the most sensitive species the starting dose in the phase I study was equal to 1/10 of the dose that was severely toxic to 10% of the animals on a mg/m^2 basis. If dogs were the most sensitive species, the starting dose in the phase I trial was equal to 1/6 of the highest nontoxic dose in the dog on a mg/m^2 basis.”

A cost estimation analysis was conducted in order to appraise the costs associated with a NP compared with a SM phase I study. Cost estimates were obtained from the literature and were based on the class (NP or SM) of agent, number of treatment levels, and patients (30).

**Statistics**

The null hypothesis was that there was no difference in the ratio of MTD to starting dose, dose escalations, and patients enrolled in a phase I clinical study between NP and SM. This was tested using a student’s t-test with alpha set at 0.05.

**RESULTS**

**Ratio of MTD to Starting Dose.** The starting doses, MTD, and ratios of MTD to starting dose for each SM are shown in Table 1. For SM, the mean ± SD (range) of the ratio of MTD to starting dose was 2.1 ± 1.1 (1.3 to 4.0). The starting doses, MTD, and ratios of MTD to starting dose for each NP are shown in Table 2. For NP, the mean ± SD (range) of the ratio of MTD to starting dose was 13.9 ± 10.8 (2.2 to 37.7). The ratio of MTD to starting dose of NP was approximately 7-fold higher than SM (P= 0.005). For the NP, including NKTR-102 (PEGylated irinotecan), liposomal vincristine (Marqibo), liposomal vinorelbine, NK-105 (PEGylated paclitaxel), S-CKD602 (liposomal CKD-602), and IHL-305 (PEGylated liposomal irinotecan), it
was confirmed that the starting doses in clinical phase I studies were based on toxicology studies in dog (18-20, 22-24).

**Dose Escalations and Number of Patients.** The dose escalation strategy for all of the reviewed phase I studies were performed using the conventional 3+3 modified Fibonacci design (29). There was an increase in the number of dose escalations and patients enrolled on phase I studies of NP compared with SM. The total number of dose escalations and patients enrolled in a clinical phase I study for SM and NP are listed in Tables 1 and 2, respectively. The mean ± SD (range) number of dose levels in a phase I clinical study for NP and SM were 7.8 ± 2.9 (4-13) and 4.1 ± 1.5 (3-7), respectively (P = 0.008). A summary of mean ± SD (range) of MTD to starting dose, number of dose levels, and number of patients enrolled is provided in Table 3. There was a higher but not statistically different number of patients enrolled in a clinical phase I study of NP and SM (31.0 ± 9.3 and 25.1 ± 11.2, respectively), (P= 0.16.)

**Cost Estimation.** The average cost per patient to complete a phase I clinical trial is approximately $35,000 (30). Assuming 3 patients per dose level based on the conventional 3+3 modified Fibonacci design, the cost of a SM or NP phase I clinical study would be $430,500 and $819,000, respectively. Excluding the NP agents that did not require an increased number of dose levels compared to their SM counterpart brings the cost of a clinical phase I study of a NP to approximately $966,000. The rationale and justification of the removal is detailed within the Discussion section. Thus, a phase I clinical study of two identical chemical entities administered as a standard SM or within a NP formulation results in an approximately two-fold difference in the overall costs.

**DISCUSSION**

This is the first study or review highlighting major differences between NP and SM phase I clinical study design and outcomes. There was a significantly greater number of dose levels,
time required to complete phase I studies, patient related resources and costs to conduct phase I studies of NP compared with SM. These results indicate the inefficiency in which phase I studies of NP are designed and/or carried out relative to SM. The cause of observed differences in clinical phase I studies may be due to differences in the PK and PD of NPs, preclinical animal models used for toxicities of NP, or study design issues of NP compared to SM.

The PK of NP is more variable than SM. A meta-analysis compared differences in AUC CV% as a measure of variability between liposomal and non-liposomal anticancer agents (31). For liposomal agents, the mean ± SD of CV% of AUC was 65.6 ± 18.6. For non-liposomal agents, the mean ± SD of CV% of AUC was 30.7 ± 16.0. The ratio of liposomal to non-liposomal CV% of AUC for each pair was 2.7 (P<0.001) (Eq 1). Similarly, the mean ± SD ratio of AUC<sub>max</sub> to AUC<sub>min</sub> at the MTD was 34.1 ± 41.9 for liposomes and 3.6 ± 1.8 for non-liposomal drugs. The ratio of liposomal to non-liposomal ratio of AUC<sub>max</sub> to AUC<sub>min</sub> for each pair was 16.7 (P<0.13). The significantly higher and clinically relevant PK variability of NP compared to SM may be affecting the design and progression of phase I studies of NP agents. Thus, studies need to be performed and methods developed to evaluate and predict the factors inducing the high PK and PD variability of NP (32-34, 34).

A potential reason for the discrepancy between NP and SM in human phase I studies could be model selection in preclinical studies. When allometric scaling was used to compare the PK disposition of three different PEGylated liposomes (S-CKD602, Doxil, SPI-077) across species (mice, rats, dogs, and humans) at the MTD, the PK disposition in dogs was a consistent outlier from other animal models (15). Additionally, when a Dedrick Time Equivalent model was used, dogs had the highest CL and thus the lowest exposure of all three liposomal agents at the MTD (15). This suggests that dogs clear PEGylated liposomes faster than other species which results in a lower plasma exposure but are the more sensitive to NP toxicity at this lower
exposure. Thus, using dogs to determine starting dose in man results in a dose that is lower than needed and consequently creates exposures that have a low probability of achieving response and/or inducing toxicity. This results in an increase in the number of dose levels, number of patients, and ratio of MTD to starting dose for NP compared with SM. Physiologically-based pharmacokinetic modeling and allometric scaling have been previously used for many small molecule agents to predict human PK from animal data. Mahmood reported on the MTD of 25 small molecule anticancer drugs that could be used to predict the proper starting dose in humans (35). He concluded that the approach saves time and avoids many unnecessary steps in attaining the MTD in humans. This information is in contrast to NPs, which are not extensively metabolized, have greater PK variability compared with SM and the PK in animal models is not directly extrapolated to humans. (15). Although animal models have successfully predicted SM PK in humans in prior studies, the ability to predict NP PK in humans based on results in animal models appears to be more problematic. The inability to extrapolate NP PK to patients from animal models is most likely due to differences in the MPS across species. Thus, the standard models and methods used for SM cannot be used for NP. Future studies are needed to determine the most appropriate animal model and scaling methods for NP.

Another potential reason for an increased number of dose levels could be that NP have a lower toxicity than SM and therefore the dose of NP can be escalated to higher levels than SM. *In vitro* and preclinical studies have demonstrated that toxicity of PEGylated liposomal agents and other non-targeted NP carriers is less than the comparative SM (3, 36, 37). For example, the cytotoxicity of mitomycin C was drastically reduced when prepared in PEGylated liposomes (38). It also has been clinically noted that the biodistribution pattern of liposomes can lead to a relative reduction of drug concentrations in tissues that are known to be sensitive to the drug (39). The biodistribution pattern is due to the unique PK profile that is obtained after administration of NP, such as increased plasma exposure (AUC) and reduced CL of the
inactive-encapsulated drug (3, 22). Generally, stable NP carriers have minimal drug release in the circulation which reduces toxicities in normal organs (3, 22).

Of the NP 9 agents reviewed 4 studies stated that the starting dose was based on dogs within the clinical phase I study. One study (Abraxane) stated that dogs had a hypersensitivity reaction to the NP and the in the remaining 4 studies, no information was provided on the starting dose. There were three NPs that did not follow the trend of greater resources and time to complete the phase I study (e.g. greater ratio of MTD to starting dose) compared with SM. Those were NP were liposomal vincristine, albumin bound paclitaxel (Abraxane), and liposomal irinotecan. These agents all exhibit “non-classical” NP properties and interesting aspects of their preclinical and clinical results provide rationale for why they can be removed from the analysis.

A study conducted by Zhigaltsev, et al., compared drug loading and retention among liposome-encapsulated vinca alkaloids: vincristine, vinblastine, and vinorelbine (40). While vincristine had the greatest % drug retention after a single dose of the three tested vinca alkaloids, it had only approximately 56% or 78% drug retention after 24 hours for the 0.1 w/wt and 0.3 wt/wt drug-to-lipid ratio formulations, respectively. This finding is in contrast to preclinical and clinical in vivo data of other liposomal anticancer agents which have a much greater % (i.e. 90-95%) drug retention during the first 24 hours and beyond (22, 41). One of the most compelling examples of low vincristine retention in liposomes comes from a study conducted by Sapra, et al., whose objective was to find an effective strategy for treating B-cell malignancies in a murine model of human B-cell lymphoma (42). Long-circulating sterically stabilized immunoliposome formulations of vincristine and doxorubicin were given to these mice. The liposomal vincristine formulation had a much faster drug release rate from the liposomes than liposomal doxorubicin. Additionally, after normalization of drug load to lipid amount, the drug to lipid ratio was several fold higher for liposomal doxorubicin than for liposomal vincristine over a 48-hour period (42). Thus, the liposomal vincristine included in this review appears to
have rapid CL and release of drug from the carrier and thus does not exhibit classic NP properties of prolonged circulation of encapsulated drug that is cleared by the MPS. Instead, the vincristine is rapidly released from the liposome and cleared via hepatic metabolism and thus acts more like a SM agent than the other NP included in this review.

The PK and PD of IHL-305 were also different than other NPs. IHL-305 is a PEGylated liposome formulation of CPT-11. CPT-11 is a prodrug that must be converted to the active moiety SN-38 by carboxylesterase enzymes \textit{in vivo} (43). The complexity of CPT-11 metabolism goes further, to include active lactone and inactive carboxylate forms of both the CPT-11 and SN-38, which exist at an equilibrium dependent upon pH and binding proteins (44). The complexity of metabolism increases with the involvement of genetic polymorphisms in uridine diphosphate glucuronosyltransferases (UGT) isoform 1A1, (UGT1A1), which is responsible for glucuronidation of SN-38 (45). Therefore, it is unclear whether differences in phase I outcomes are observed due to IHL-305 formulation, or due to the dosing of a pro-drug that is dependent upon many factors for metabolism.

The phase I starting dose of albumin bound paclitaxel was not based on the dog toxicology studies because dogs had a hypersensitivity reaction to human albumin which lead to an early termination of toxicologic studies in dogs (46). Therefore, the starting dose of albumin bound paclitaxel was based on toxicology studies in non-human primates. Dogs appear to be inherently sensitive to the toxicologic effects of NPs, as evidenced through toxicology studies as well as allometric scaling (15). The starting dose of albumin bound paclitaxel based on toxicity studies in non-human primates was most likely higher than would have been determined based on toxicology studies in dogs. Thus, the number of dose levels from the higher starting dose to the MTD of albumin bound paclitaxel was less than other NP in the review. This highlights the potential benefits of performing toxicologic and pharmacologic studies of NP in non-human primates instead of dogs as the non-rodent species of choice.
There are major differences between the design and performance of phase I studies of NP compared with SM. There is a significant difference in the number of dose levels and ratio of MTD to starting dose as well as increased number of patients enrolled and overall costs associated with studies of NP versus SM. These findings indicate that patients are being treated at doses that are very low and unlikely to produce toxicity and/or response. This undoubtedly leads to an inefficient use of patient resources, time, and funding. The potential primary cause of these issues in phase I studies of NP is that the low starting dose results from the use of an inappropriate toxicology model, which appears to be dogs or the ability to escalate the dose of NP higher. An alternative non-rodent model such as non-human primates may be more suitable.

There is preliminary evidence that suggests that factors associated with the MPS may contribute to NP PK and PD variability. Thus, there is a compelling need to identify the factors associated with MPS function in order to improve the preclinical and clinical studies of NP. It will be essential to further test whether the PK of NP can be scaled across species using various measurements and surrogates of the MPS, such as monocyte and macrophage activity or function, genetics, complement, or cytokines. In addition, the most appropriate animal models for GLP toxicology studies must be identified. Identification of the correct animal model may drastically decrease the number of dose levels, patients, and costs associated with phase I clinical studies. Additionally, there must be exploration into new study designs for phase I studies of NP, as the unique pharmacology of NP agents may not be amenable to trial designs established for SM.
Author Contributions:

Conception and design: W.C. Zamboni
Data Collection: W.P. Caron, K.P. Morgan
Statistical methods: B.A. Zamboni
Analysis and interpretation of data: W. P. Caron, K.P. Morgan, W.C. Zamboni

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Conflict of Interest: The authors have no conflicts of interest to disclose.
### Table 1. Summary of starting dose, MTD, and ratio of MTD to starting dose in patients with refractory solid tumors in phase I clinical trials of small molecule anticancer agents.

<table>
<thead>
<tr>
<th>Small Molecule (SM)</th>
<th>Starting dose (mg/m²)</th>
<th>MTD (mg/m²)</th>
<th>Ratio of MTD to starting dose</th>
<th>Total number of dose levels</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>vincristine</td>
<td>0.5</td>
<td>0.75</td>
<td>1.5</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>irinotecan</td>
<td>240</td>
<td>320</td>
<td>1.3</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td>CKD-602</td>
<td>0.5</td>
<td>0.7</td>
<td>1.4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>paclitaxel</td>
<td>70</td>
<td>100</td>
<td>1.4</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>vinorelbine</td>
<td>35</td>
<td>40</td>
<td>1.1</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>oxaliplatin</td>
<td>45</td>
<td>135</td>
<td>3.0</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>lurtotecan</td>
<td>0.3</td>
<td>1.2</td>
<td>4.0</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td><strong>Mean ± SD (range)</strong></td>
<td></td>
<td><strong>2.0 ± 1.1 (1.1-4)</strong></td>
<td><strong>4.1 ± 1.5 (3-7)</strong></td>
<td><strong>25.1 ± 11.2 (13-44)</strong></td>
<td></td>
</tr>
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Table 2. Summary of starting dose, MTD, and ratio of MTD to starting dose in patients with refractory solid tumors in phase I clinical trials of nanoparticle anticancer agents

<table>
<thead>
<tr>
<th>Carrier Mediated Agent (NP)</th>
<th>Starting dose (mg/m²)</th>
<th>MTD (mg/m²)</th>
<th>Ratio of MTD to starting dose</th>
<th>Total number of dose levels</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>albumin bound paclitaxel</td>
<td>135</td>
<td>300</td>
<td>2.2</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>*NKTR-102 (PEGylated irinotecan)</td>
<td>58</td>
<td>144</td>
<td>2.5</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>*liposomal vincristine</td>
<td>0.5</td>
<td>2.4</td>
<td>4.8</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>OSI-211 (liposomal lurtotecan)</td>
<td>0.15</td>
<td>1.8</td>
<td>12.0</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>*liposomal vinorelbine</td>
<td>2</td>
<td>28</td>
<td>14.0</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>*NK-105 (PEGylated paclitaxel)</td>
<td>10</td>
<td>180</td>
<td>18.0</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>*S-CKD602 (PEGylated liposomal CKD-602)</td>
<td>0.1</td>
<td>2.1</td>
<td>21.0</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td>*IHL-305 (PEGylated liposomal irinotecan)</td>
<td>7</td>
<td>160</td>
<td>22.9</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>MBP-426 (PEGylated liposomal oxaliplatin)</td>
<td>6</td>
<td>226</td>
<td>37.7</td>
<td>11</td>
<td>39</td>
</tr>
</tbody>
</table>

Mean ± SD (range)

13.9 ± 10.8 (2.2-37.7) 7.8 ± 2.9 (4-13) 31.8 ± 9.5 (19-45)

*Confirmed starting doses in clinical phase I studies were based on toxicology studies in dog.
Table 3. Comparison of ratio of MTD to starting dose, number of dose levels, and number of patients enrolled on study for clinical phase I studies of nanoparticle and small molecule anticancer agents.

<table>
<thead>
<tr>
<th></th>
<th>Ratio of MTD to starting dose</th>
<th>Number of dose levels</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP Mean ± SD (range)</td>
<td>13.9 ± 10.8</td>
<td>7.3 ± 2.9</td>
<td>31.0 ± 9.3</td>
</tr>
<tr>
<td>SM Mean ± SD (range)</td>
<td>2.0 ± 1.1</td>
<td>4.1 ± 1.5</td>
<td>25.1 ± 11.2</td>
</tr>
<tr>
<td>Comparison of NP vs. SM; two sample t-test</td>
<td><strong>P= 0.005</strong></td>
<td><strong>P= 0.008</strong></td>
<td><strong>P= 0.16</strong></td>
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