Preclinical to clinical development of the novel camptothecin nanopharmaceutical CRLX101

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ABSTRACT

Camptothecin (CPT) is a potent broad-spectrum anticancer agent that acts through inhibition of topoisomerase 1. Clinical development of CPT was unsuccessful due to poor drug solubility, insufficient in vivo stability of the active form, and toxicity. In order to address these issues, a polymeric nanoparticle comprised of cyclodextrin-poly(ethylene glycol) copolymer (CDP) conjugated to CPT (CRLX101) has been developed and Phase 2 clinical studies are ongoing. Camptothecin is conjugated to the polymer in its active form at 10–12 wt.% loading. CRLX101 self-assembles in solution into nanoparticles with an apparent solubility increase of >1000-fold as compared to the parent drug camptothecin. Preclinical studies exhibited CRLX101 pharmacokinetics superior to the parent drug. Drug concentration in tumor relative to plasma and other major organs is consistent with the enhanced permeation and retention (EPR) anticipated from a nanoparticle. Significant anti-tumor activity was observed that is superior when compared to irinotecan across a broad range of xenograft models. Pharmacokinetic data are consistent with the prolonged half-life and increased AUC. The CRLX101 preclinical and clinical data confirm that CDP can address not only solubility, formulation, toxicity, and pharmacokinetic challenges associated with administration of CPT, but more importantly, can impart unique biological properties, that enhance pharmacodynamics and efficacy of camptothecin.

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1. Introduction

The total market for nanotechnology-enabled drug delivery is expected to rise to US$ 26 billion by 2012. Besides overcoming bioavailability hurdles for newly developed drugs, i.e., poor drug solubility or membrane permeability, nanoparticle drug delivery can enable reformulation of existing drug products to increase product lifecycle, and to discourage competition during a drug’s most valuable years. Nanometer-scale carriers may be constructed from a wide range of organic and inorganic materials such as emulsions, solid lipid nanoparticles (SLN), nanocapsules, nanospheres, micelles, liposomes, dendrimers, quantum dots (QD), and fullerenes and carbon nanotubes (CNT). These materials are being used to encapsulate or solubilize chemotherapeutic agents for improved in vivo drug delivery or to provide unique optical, magnetic and electrical properties for imaging and therapy. Several functional nanometer-scale carriers are being evaluated in preclinical and clinical studies and some have advanced status, including clinically approved liposome drug formulations and metallic imaging agents.

One of the best known examples for reformulated, nanometer-scale drug delivery is Doxil®. Doxil, approved in the U.S. in 1995, is the poly (ethylene glycol)-coated, liposome-encapsulated form of doxorubicin, a drug used in cancer chemotherapy. A more recent commercial product developed by Abraxis Bioscience, LLC, Abraxane®, consists of an albumin-based formulation of the anti-cancer drug paclitaxel. Abraxane was approved in the U.S. in 2005. Examples of lipid formulations in clinical trials include: CPX-1 (irinotecan-flouxuridine liposome; Phase 1) and CPX-351 (cytarabine-daunorubicin liposome; Phase 2), dual drug combinations from Celator Pharmaceuticals, Inc.; Brakiva™, a liposomal formulation of topotecan from Hana Biosciences; and LEP-ETU (liposomal paclitaxel) from Neopharm, Inc. Micelle-based drug formulations, i.e., formulations consisting of hydrophilic-hydrophobic block copolymers that self-assemble in aqueous solution into micellar particles with a hydrophobic core and a hydrophilic shell, are in clinical trials as well. NK012 and NK105 are micellar formulations of the camptothecin derivative SN38 and of paclitaxel, respectively. Both anti-cancer formulations from Nippon Kayaku Co., Ltd are in Phase 1 trials. Besides physical encapsulation, drugs have been chemically conjugated to polymers, forming produgs with improved solubility and reduced toxicity. These produgs release the drug based on pH or enzymatic activation at the desired therapeutic site. Examples are Opaxio™ from Cell Therapeutics, Inc. a paclitaxel conjugate of poly(glutamic acid). Inside tumor tissue the drug is released by the enzyme cathepsin B.
Opaxio is in Phase 3 clinical trials for the treatment of ovarian cancer and in combination with carboplatin for the treatment of non-small cell lung cancer. XMT-1001 from Mersana Therapeutics, Inc. is a camptothecin produg based on the carbohydrate-derived ‘Fleximer’ polysaccharide platform, which is currently evaluated in a Phase 1 study. Other companies are engaged in the development of poly(ethylene glycol) (PEG)-based produgs. NKTR-102 and NKTR-105 are PEG produgs of irinotecan and docetaxel from Nektar Therapeutics, currently in Phase 2 clinical trial for patients with solid tumor malignancies, including colorectal, breast, ovarian and cervical cancers (NKTR-102), and Phase 1 trial in patients with certain types of solid tumors including hormone-refractory prostate cancer (NKTR-105). EZN-2208 from Enzon Pharmaceuticals, Inc. is a PEG-prodrug of SN38. Enzon recently opened its first Phase 2 trial for EZN-2208 at multiple centers throughout the United States for patients diagnosed with metastatic colon cancer. These few examples clearly demonstrate the progression of nanotechnology-enabled drug delivery from basic research curiosities to viable business opportunities.

In contrast to these nanometer-scale carriers, the physical and chemical properties of polymeric nanoparticles can be designed to have defined size and surface properties to favor drug deposition and retention in tumors by extravasation through disorganized, leaky vasculature commonly found in tumors and inflamed tissues, described as the enhanced permeability and retention (EPR) effect [1,2]. Furthermore, the design can provide stealth behavior and physical integrity of polymeric nanoparticles, which can shield drug molecules from rapid systemic clearance, degradation, and metabolism while in circulation, and prevent broad, systemic drug dissemination and exposure in healthy tissues and organs. Polymeric nanoparticles can be engineered to incorporate drugs by covalent conjugation, which can provide control over drug-release kinetics that could have a significant impact on pharmacokinetics and a meaningful improvement in the drug’s pharmacodynamics and efficacy [3,4]. These design features can result in enhanced aqueous solubility, prolonged plasma half-life, and reduced systemic toxicity of chemotherapeutic agents in vivo [3,5]. Finally, the nanoparticle’s physical attributes can also be optimized to facilitate target tissue penetration and cellular uptake, thereby overcoming drug resistance by circumventing surface-pump mediated multi-drug resistance (e.g. P-glycoprotein-mediated) mechanisms [3].

CRLX101 (formerly IT-101) is a polymeric nanoparticle pharmaceutical, developed with the proprietary cyclodextrin polymeric nanoparticle (CDP) technology [6,7]. It is comprised of camptothecin (CPT) covalently conjugated to a linear, cyclodextrin-poly(ethylene glycol) copolymer, which self-assembles into nanoparticles (Fig. 1). The 20 S-isomer of camptothecin, a natural alkaloid isolated from the Chinese bush *Camptotheca acuminata*, was first identified in the National Cancer Institute (NCI) Anticancer Drug Screen as a promising cancer drug candidate with significant anti-tumor activity [8]. Its mechanism of action was later discovered to be potent inhibition of topoisomerase 1 (Topo 1), which is an important and validated drug target for cancer therapy today. Topo 1 remains a highly attractive drug target because it is essential for basic cellular processes including DNA replication, recombination, and transcription, which are particularly up-regulated in rapidly dividing tumor cells [9]. CPT has shown very high potency and promising anti-cancer activity at low nanomolar concentrations across a wide range of cancer cell types. However, development of CPT as a drug molecule was halted because of its challenging physicochemical and pharmaceutical properties. Firstly, CPT is poorly water-soluble (approx. 4 μg/mL) and is therefore not amenable to traditional pharmaceutical formulations. Secondly, the chemical structure of CPT includes an unstable lactone ring that is highly susceptible to spontaneous and reversible hydrolysis, which yields an inactive, but more water-soluble, carboxylate form that predominates at physiologic pH [10,11]. This inactive carboxylate form was also found to bind human serum albumin with 200-fold greater affinity than the active lactone form. In addition, the carboxylate form lead to bladder toxicity without showing efficacy when injected into humans [12].

In order to reduce these side effects, a significant medicinal chemistry effort has been devoted to developing CPT analogs. There are currently two FDA-approved small-molecule CPT analogs in the market, topotecan (Hycamtin®, GlaxoSmithKline) and irinotecan (Camptosar®, Pfizer) [13]. While their potency is similar to CPT, both drugs exhibit sub-optimal pharmacokinetics and still have significant dose-limiting toxicities, including bone marrow suppression and gastrointestinal disorders. A better tolerated CPT molecule with enhanced efficacy and improved pharmacokinetics, and with a longer half-life and prolonged bioavailability of the active lactone form, is a highly attractive cancer drug candidate that could have a significant and favorable clinical impact. Originally designed to address the challenges associated with CPT, CRLX101 is a nanophas-maceutical that has proven to augment CPT efficacy by (a) facilitating target tissue localization and retention, (b) increasing intracellular CPT deposition, (c) providing a sustained supply of active CPT, (d) maintaining intracellular CPT concentrations above therapeutic threshold, and (e) prolonging activity at the CPT target.

2. Results and discussion

2.1. Design of CRLX101

The chemical structure of CRLX101 is comprised of a linear copolymer backbone incorporating alternating repeat units of cyclodextrin (CD) and poly(ethylene glycol) (PEG) blocks with intervening chemical linkers for CPT conjugation. One of the key design features of the cyclodextrin-poly(ethylene glycol) copolymer (CDP) is that the CD blocks can form inclusion complexes with hydrophobic small molecule drugs, such as CPT, through both intra- and inter-molecular interactions [14]. Interactions between adjacent

**Fig. 1.** Schematic diagram of CRLX101, a nanophas-maceutical comprised of camptothecin conjugated to a linear, cyclodextrin-poly(ethylene glycol) (CD-PEG) copolymer and formulated into nanoparticles.
polymer strands likely catalyze the self-assembly of several CDP polymer strands into reproducible nanoparticles with diameters between 20 and 60 nm. The resulting drug-containing nanoparticles have neutral surface charge and the PEG blocks impart improved solubility and stealth properties, which together enable safe systemic administration, minimize immunogenicity, and help evade phagocytic uptake by the reticuloendothelial system [15]. As a result, CRLX101 exhibits extended plasma stability with prolonged circulation time, avoids rapid renal and systemic clearance, and accumulates in target tissues through the EPR effect.

Two other major design features of CDP as a drug carrier are the covalent linkage of CPT to the copolymer backbone and the physical integrity of the resulting self-assembled nanoparticles. To form CRLX101, CPT is derivatized at the 20-OH position with the natural amino acid glycine to form an ester linkage for covalent attachment to the CDP backbone. In vitro chemical characterization studies confirmed that this linker strategy successfully stabilizes the labile lactone ring of CPT in its closed, active form and prevents premature CPT inactivation by pH-mediated ring opening upon systemic administration [6]. In addition, the physical integrity of CRLX101 nanoparticles helps protect CPT from metabolic enzymes and premature hydrolysis. Consequently, only the active form of CPT is released in a controlled manner and over a sustained period of time.

Biocompatibility is another important design feature of CDP as a drug carrier technology. Preclinical animal study data demonstrated that the CDP polymer, in the absence of conjugated drug, is well tolerated, eliciting no observable side effects or immune responses, despite dosing up to 240 mg/kg in mice [6]. In CRLX101, the intermolecular interactions of CDP polymer strands that catalyze inclusion complex formation are lost upon CPT release, resulting in the disassembly of the nanoparticles into individual polymer strands with hydrodynamic diameters of <10 nm. Such individual polymer strands are then sufficiently small and inert for clearance through the kidneys. These preclinical findings are consistent with the clinical experience of patients tolerating multiple cycles of CRLX101 therapy without experiencing any unusual or unexpected non-drug related toxicity caused by the presence of CDP copolymer.

2.2. Pharmacokinetics and Biodistribution Studies with CRLX101

To demonstrate the controlled and sustained CPT release from CDP, the drug release kinetics and mechanism of CRLX101 were studied extensively in vitro. Cleavage of the glycine linker was found to be mediated through both enzymatic and base-catalyzed hydrolysis of the ester bond, with observed half-lives of 59 h and 41 h in PBS and human plasma, respectively [16]. Originally published data in reference [6] indicated a half-life of 1.7 hours in human plasma. However, subsequent repeat analysis indicated a corrected half-life of 41 hours in human plasma when the pH was adjusted to pH 7.4. Freshly reconstituted human plasma had a pH of approx. 9.5 prior to adjustment. While CPT release kinetics were observed to be relatively accelerated in plasma compared to PBS, the rate of drug release is slower than what is typically observed with polymeric prodrugs with an ester linkage [16]. The in vivo terminal half-life of CRLX101 in plasma after single-dose injection in rat and dog is similar (24 and 28 h, respectively), suggesting that hydrolysis of the glycine linker is not rate-limiting (Fig. 2). The observed slow and sustained CPT release from CRLX101 also illustrates the physical shielding effects of CDP, which form intact nanoparticles, and thereby protect the CPT payload and minimize the enzymatic and chemical hydrolytic degradation.

Drug concentrations in plasma and tumor were further assessed in tumor-bearing mice (Daudi B-cell lymphoma xenograft, single-dose pharmacokinetic study), comparing CRLX101 with the approved Topo 1 inhibitor irinotecan, a small-molecule prodrg of the active metabolite SN-38 [17]. In this experiment, drug levels were assessed in plasma samples and tumor biopsies harvested after administration of irinotecan and CRLX101 at their respective maximum tolerated dose (MTD). The results showed that, at 24 and 48 h post-administration, plasma and tumor concentrations of both CRLX101 and released CPT were more than four orders of magnitude higher than those of irinotecan and more than two orders of magnitude higher than those of SN-38 (Fig. 3). These findings correlate very well with the significantly enhanced efficacy observed with CRLX101 compared to irinotecan in several xenograft tumor models. Most remarkably, the enhanced efficacy and increased tumor drug concentrations were correlated with increased inhibition of Topo 1 enzymatic activity in two of the tumor models (Daudi and Karpas 299) at 48 h post-administration [17].

Key goals for the design of CRLX101 are increased efficacy and improved systemic tolerability through enhanced drug deposition in tumor tissue. Therefore, the biodistribution of CRLX101 was evaluated in xenograft tumor-bearing mice (LS174t colorectal xenograft, single-dose pharmacokinetic study) by assessing localized drug concentrations in target tissues (Table 1). In this study, tumors and other organs were

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**Fig. 2.** Plasma concentration of CPT (ng/mL) in (A) rat (dose 2.59 mg/kg) and (B) dog (0.58 mg/kg). CRLX101 shows favorable and consistent pharmacokinetic properties across species. Filled circles represent total CPT and open circles represent CPT that has been released from the polymer. The amount of released CPT is ~10% in both cases (6.8 and 2.9%, respectively). The fact that the two lines are parallel in each graph indicates that the drug is being released continuously.
measured at 24 and 48 h post-administration, compared to tumor CPT concentrations found in animals treated with CPT at its MTD [18]. Furthermore, the level of released CPT in tumor relative to plasma gradually increased from approximately a 2.5:1 tumor-to-plasma ratio at 24 h to 21:1 at 48 h post-administration. These observations are in sharp contrast with the data observed in animals administered with free CPT. In summary, findings from CRLX101 biodistribution studies provide substantive evidence that CDP nanopharmaceuticals can increase the efficacy of the active molecule by enhancing and sustaining higher localized drug concentrations in target tissues.

2.3. Efficacy and tolerability studies with CRLX101

A comprehensive evaluation of CRLX101 anti-tumor activity has been completed in multiple subcutaneous human cancer models, including LS174T and HT29 colorectal cancer, A2780 and SK-OV-3 ovarian cancer, H1299 non small-cell lung cancer, H69 small-cell lung cancer, Panc-1 pancreatic cancer, MDA-MB-231 breast cancer, along with four disseminated xenograft models, including Daudi, Karpas 299, and L540 lymphomas (Table 2). In every case, a single treatment cycle of three weekly doses of CRLX101 resulted in significant anti-tumor activity that was superior to commercial comparators including irinotecan and topotecan (Figs. 4 and 5). Most notably, complete tumor regression was observed in all animals bearing H1299 and A2780 tumors, and in the majority of animals with disseminated Daudi, and Karpas 299 lymphoma tumors.

CRLX101 was found to be highly effective in tumor models that respond poorly to treatment with irinotecan (MDA-MB-231, Panc-1, and HT29), suggesting the potential ability of CRLX101 to overcome the lack of drug response in these models. Overall, these findings provide compelling support that CDP as a nanopharmaceutical technology has (a) successfully overcome formulation, toxicity, and pharmacokinetic challenges of CPT, (b) maintained CPT in its active form resulting in potent anti-tumor activity, (c) increased intracellular CPT concentrations, (d) enhanced tumor drug localization and retention, and (e) produced a sustained therapeutic effect with superior efficacy over approved Topo 1 inhibitors.

2.4. Combination therapy with CRLX101

The increased therapeutic window of CRLX101 might offer the opportunity to combine this agent with other chemotherapeutic agents for synergistic activity. Studies were therefore conducted with CRLX101 in combination with the highly efficacious chemotherapeutic agents harvested from animals that were dosed with either CRLX101 or CPT, and assessed for localized drug concentrations. Remarkably, in tumor tissues harvested from animals treated with CRLX101 at its MTD, significantly higher intratumoral concentrations of released CPT were

Table 1
Biodistribution of CRLX101 in nude mice bearing subcutaneous, human LS174T colorectal cancer xenografts. Plasma and tissue collection at 24 and 48 h after single-dose administration at respective MTD (3 mg/kg intraperitoneally for CPT and 24 mg/kg CPT equivalent dose intravenously for CRLX101).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Level of released, active CPT (ng/mL or ng/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRLX101</td>
</tr>
<tr>
<td>Plasma</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>Tumor</td>
<td>183 ± 115</td>
</tr>
<tr>
<td>Liver</td>
<td>241 ± 132</td>
</tr>
<tr>
<td>Spleen</td>
<td>45 ± 42</td>
</tr>
<tr>
<td>Lung</td>
<td>57 ± 43</td>
</tr>
<tr>
<td>Heart</td>
<td>23 ± 21</td>
</tr>
</tbody>
</table>

Table 2
CRLX101 showed superior anti-tumor activity over commercial front-line drugs in multiple xenograft models.

<table>
<thead>
<tr>
<th>Xenograft model</th>
<th>Tumor type</th>
<th>Comparator drug</th>
<th>CRLX101 vs comparator fold improvement</th>
<th>Study duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1299</td>
<td>NSCLC</td>
<td>Topotecan</td>
<td>&gt;6.1</td>
<td>90</td>
</tr>
<tr>
<td>H69</td>
<td>SCLC</td>
<td>Irinotecan</td>
<td>&gt;2.0</td>
<td>95</td>
</tr>
<tr>
<td>Panc-1</td>
<td>Pancreatic</td>
<td>Irinotecan</td>
<td>&gt;3.3</td>
<td>91</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>Breast</td>
<td>Irinotecan</td>
<td>3.5</td>
<td>70</td>
</tr>
<tr>
<td>A2780</td>
<td>Ovarian</td>
<td>Irinotecan</td>
<td>&gt;6.3</td>
<td>60</td>
</tr>
<tr>
<td>SK-OV-3</td>
<td>Ovarian</td>
<td>Irinotecan</td>
<td>5.9</td>
<td>60</td>
</tr>
<tr>
<td>LS174T</td>
<td>Colorectal</td>
<td>Topotecan</td>
<td>4.5</td>
<td>71</td>
</tr>
<tr>
<td>HT-29</td>
<td>Colorectal</td>
<td>Topotecan</td>
<td>&gt;2.4</td>
<td>60</td>
</tr>
<tr>
<td>DAUDI (sc)</td>
<td>Lymphoma</td>
<td>Irinotecan</td>
<td>&gt;5.0</td>
<td>126</td>
</tr>
<tr>
<td>DAUDI (dissem)</td>
<td>Lymphoma</td>
<td>Irinotecan</td>
<td>&gt;4.8</td>
<td>126</td>
</tr>
<tr>
<td>Karpas 299 (sc)</td>
<td>Lymphoma</td>
<td>Irinotecan</td>
<td>3.0</td>
<td>126</td>
</tr>
<tr>
<td>Karpas 299 (dissem)</td>
<td>Lymphoma</td>
<td>Irinotecan</td>
<td>1.7</td>
<td>126</td>
</tr>
<tr>
<td>L540 Hodgkin (sc)</td>
<td>Lymphoma</td>
<td>Irinotecan</td>
<td>&gt;14</td>
<td>126</td>
</tr>
</tbody>
</table>

Medium Survival Fold improvement = CRLX101 MS/Vehicle MS/days/day.
cisplatin, carboplatin, paclitaxel, and gemcitabine (Fig. 6). Anti-tumor activity of such drug combinations was tested in xenograft tumor mouse models, including human A2780 and SK-OV-3 ovarian carcinoma [20]. In these studies, all CRLX101 drug combinations tested were found to exhibit greater than additive efficacy, compared to the single-agent activity observed with each of the individual chemotherapeutic agents. Furthermore, in the case of cisplatin, paclitaxel, and gemcitabine, the observed enhanced efficacy from combination therapy was achieved without additive toxicity. A key clinical implication from these findings is that CRLX101 can be developed as a highly versatile chemotherapeutic agent that has significant monotherapy activity, with the potential for combination with multiple widely-used oncology agents.

2.5. Clinical Phase 1 study with CRLX101

The preclinical studies of CRLX101 have confirmed that the CDP technology provides superior pharmacokinetics, improved tolerability, enhanced pharmacodynamics, and increased efficacy to CPT. Considering the original promise of CPT as an anti-tumor agent and the favorable pharmaceutical profile of its design and configuration, CRLX101 is a promising oncology agent, and clinical development was initiated. The primary objectives of the Phase 1 study were to determine the safety, pharmacokinetics, dose-limiting toxicities, maximum tolerated dose (MTD), as well as the recommended dose and dosing schedule. Secondary objectives of the study included the assessment of potential biomarkers, an estimation of clinical activity by RECIST, and an estimation of progression-free survival in patients receiving six or more monthly cycles of CRLX101 monotherapy. In this study, CRLX101 was administered intravenously to patients with advanced solid tumors and confirmed progressive disease that had relapsed or was refractory to standard therapy. The Phase 1 study of CRLX has been successfully completed, and detailed data will be published elsewhere. A randomized Phase 2 study is currently being initiated.

3. Conclusions

The application of polymeric nanoparticles addressing formulation and pharmacokinetic challenges has long been a hot topic in drug
delivery research and development. Advances in polymer chemistry and a better understanding of tumor microenvironment biology have supported the progress of nanopharmaceuticals as a new class of therapeutic agents. While other nanometer-scale drug carrier technologies and approaches have demonstrated an ability to overcome some of the formulation and pharmacokinetic hurdles, development of CRLX101 as a first-in-class nanopharmaceutical has established that cyclodextrin polymeric nanoparticle technology is a highly versatile platform technology that confers significant biological advantages to active pharmaceutical ingredients, including target-tissue localization, enhanced cellular uptake, and slow drug release kinetics, all resulting in sustained therapeutic drug concentrations in target cells. Together, these biological properties provide a strong potential to translate therapy into significant impact on clinical outcome.

References


Fig. 5. Efficacy study of CRLX101 compared to topotecan using xenograft tumor-bearing mice (A2780 ovarian xenograft). (A) Tumor growth delay and (B) survival graphs showing vehicle (circles), CRLX101 (diamonds, 12 mg/kg, weekly ×3), and topotecan (triangles, 12 mg/kg, every 4 days ×3). Arrows indicate the respective treatment days. CRLX101 shows superior survival compared to topotecan, both treated at optimized frequencies. (Adopted from reference [20]).

Fig. 6. (A) Tumor growth delay and (B) survival graphs in the A2780 ovarian xenograft model showing vehicle (circles), monotherapy efficacy of CRLX101 (filled squares, 5 mg/kg), cisplatin (filled diamonds, 7 mg/kg), and carboplatin (filled triangles, 100 mg/kg), and combination therapy efficacy of CRLX101+cisplatin (open diamonds, 5 +7 mg/kg) and CRLX101+carboplatin (open triangles, 5 +100 mg/kg). Both combination therapies are more efficacious than the respective monotherapies, with the combination CRLX101+cisplatin providing 100% survival up to day 70 after treatment, suggesting a mechanistic synergism between platinum drugs, which cause DNA damage, and CRLX101, which affects DNA repair. A sub-optimal dose of CRLX101 was used in this study because the MTD of CRLX101 alone causes complete tumor regression, as shown in Fig. 5. (Adapted from reference [20]).


