

NKTR-102 Demonstrates Nonclinical and Phase 1 Clinical Anti-tumor Activity in Ovarian Cancer (Abstract 8015)

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NEKTAR

Abstract

Background: NKTR-102, a novel prodrug of irinotecan (IRI), is currently in phase 2 development in patients with platinum-resistant ovarian cancer. NKTR-102 uses Nektar's novel small-molecule advanced polymer conjugate technology to improve the pharmacokinetics and tumor distribution of IRI and its active metabolite SN38. **Objective:** To investigate the nonclinical and clinical anti-tumor activity of NKTR-102 in metastatic platinum resistant ovarian cancer. **Methods:** Mice bearing A2780 ovarian tumors that are minimally responsive to cisplatin, received NKTR-102 or IRI in 3 weekly doses of 50, 100, or 150 mg/kg. Anti-tumor efficacy was evaluated based on tumor growth delay (TGD) in mice and response rate in mice and humans. In the phase 1 study of NKTR-102, 5 patients with ovarian cancer were enrolled in weekly x 3 q4w, q14d and q21d regimens. Patients with measurable disease were assessed for tumor response using RECIST 1.0 every other cycle. **Results:** In mice, NKTR-102 and IRI were equally well tolerated. Control tumors grew rapidly and uniformly to the 2000 mm³ endpoint in a median of 14 days. IRI administered at 50, 100, and 150 mg/kg resulted in TGD of 12, 15, and 16 days, respectively, with one partial response (PR) at the highest dose. NKTR-102 at IRI-equivalent doses resulted in TGDs of 33, 32, and 34 days, respectively, with 100% regression response rate (PRs + CRs) in each group. Increasing NKTR-102 doses were associated with increased numbers of CR responses (5, 8, and 9 CRs, respectively). NKTR-102 was superior to the equivalent IRI dose at all doses tested and the lowest dose of NKTR-102 was superior to the highest IRI dose. In the phase 1 clinical study, tumor response could be assessed in 2 of 5 patients with ovarian cancer. Of these two patients, one patient receiving 145 mg/m² q14 (sixth line) had an unconfirmed partial response (37% reduction in target lesions) but terminated from the study prior to confirmation, and one patient on the weekly regimen receiving 172.5 mg/m² had a mixed response that included a 21% reduction in target lesions. **Conclusions:** NKTR-102 shows superior activity compared to IRI in the A2780 ovarian tumor model, inducing a 100% response rate at all doses and dose-related increases in CRs versus PRs. Anti-tumor activity was observed in heavily pre-treated patients with ovarian cancer. A phase 2 study in patients with platinum-resistant ovarian cancer is ongoing.

Background

Nektar's advanced polymer technology has been used to improve the pharmacokinetics and pharmacodynamics of several marketed therapeutic agents (e.g. Neulasta®, Cimzia®, PEG INTRON™, PEGASY®), etc. Nektar Therapeutics is developing NKTR-102, a 4-arm PEGylated prodrug of irinotecan, for the treatment of advanced tumors. Irinotecan belongs to the topoisomerase 1 inhibitor class and is widely used to treat colorectal cancer and other solid tumors. The active metabolite of irinotecan is SN38 which is responsible for its efficacy.

NKTR-102 has been specifically synthesized to provide a sustained release of irinotecan and SN38 with the aim of improving its efficacy, safety, and/or tolerability profile over marketed irinotecan. NKTR-102 has demonstrated the desired pharmacokinetic profile in nonclinical animal species and humans. The favorable changes in SN38 kinetics following NKTR-102 dosing correlated well with superior suppression of tumor growth compared with irinotecan in mouse xenograft models, where NKTR-102 showed superior activity in models of breast, colorectal, and non-small cell lung cancer.

Objective

To investigate the nonclinical and clinical anti-tumor activity of NKTR-102 in metastatic platinum resistant ovarian cancer.

Methods

Nonclinical Activity in A2780 Ovarian Carcinoma

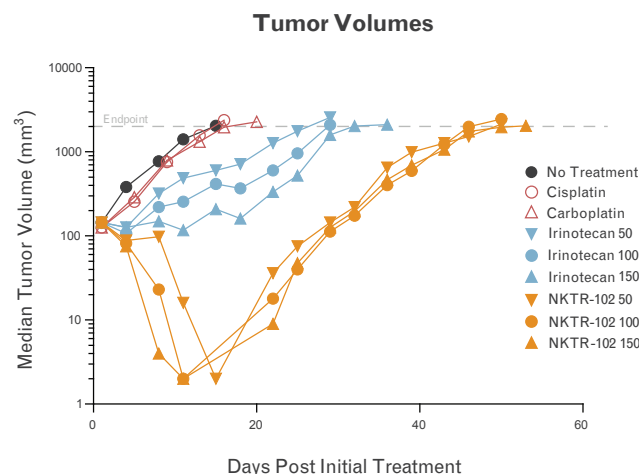
A2780 tumor cells were grown in vitro and implanted s.c. as a cell suspension in 9 to 10 weeks old female nude mice (nu/nu, Harlan) weighing 18-26 g. When the tumor volume reached an average of 146 mm³, mice (n=10/treatment) were randomized into the treatment groups and treated with 3 weekly intravenous injections of irinotecan or NKTR-102, or 3 weekly intra-peritoneal administrations of cisplatin or carboplatin. Animals were weighed and monitored twice weekly, and tumor volumes were measured until an endpoint was met (2000 mm³ or 60 days). Anti-tumor efficacy was evaluated based on tumor growth delay and response rate or partial or complete regression (PR or CR). In a PR, the tumor volume was 50% or less of its Day 1 volume for three consecutive measurements, and equal to or greater than 14 mm³ for one or more of these three measurements. In a CR, the tumor volume was less than 14 mm³ for three consecutive measurements. An animal with a CR response at termination was additionally classified as tumor-free survivor (TFS). A Student's T-test was performed to calculate statistical significance (p<0.05).

Clinical Activity in Ovarian Carcinoma

Study 06-IN-IR001, an open-label, dose-escalation, multicenter Phase 1 study, enrolled patients with advanced solid tumors whose tumors had failed prior treatments. The study enrolled a total of 76 patients, five of whom had ovarian cancer. Patients received 90-minute infusions of NKTR-102 on either a weekly x3 every 4 weeks (qwx3 q4w), every 14 days (q14d), or every 21 days (q21d) schedule. Patients were evaluated for safety, pharmacokinetics and evidence of anti-tumor activity (by RECIST 1.0 guidelines).

Results

NKTR-102 Shows Superior Activity Over Irinotecan in Platinum-Resistant 2780 Ovarian Cancer Model



Side Effects

- NKTR-102 was well tolerated
- Irinotecan resulted in acute effects immediately after dosing (tremors, hypo-activity, ataxia, pilo-erection, increased stool production)

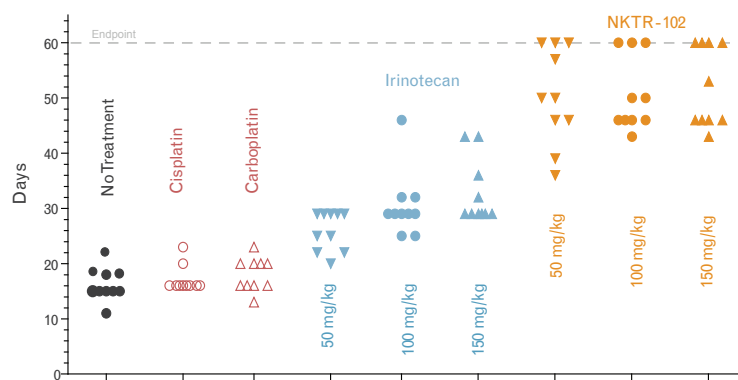
Tumor Growth Delay

- Control tumors grew to the 2000 mm³ endpoint in a median of 14 days, establishing a maximum possible TGD of 46 days (329%) for this 60-day study
- Cisplatin and carboplatin were inactive
- NKTR-102 was superior to the equivalent irinotecan dose
- The lowest dose of NKTR-102 had superior activity to the highest irinotecan dose

Response Rate

- Irinotecan**
 - 1/10 PR at the 150 mg/kg dose
 - All tumors reached 2000 mm³ by study end
- NKTR-102**
 - 10/10 PR or CR at all doses
 - Number of CR was dose-related and increased with higher doses
 - 10/30 mice did not reach 2000 mm³ by study end, with 7 animals remaining tumor free

Individual Times to Endpoint



Response Summary

Group	Treatment Regimen				Median TTE	T-C	TGD (%)	Regressions			Statistical Significance			
	Agent	mg/kg	Route	Schedule				PR	CR	TFS	vs G1	vs G2	vs G3	vs G4
1	NT	---	---	---	14	---	---	0	0	0	---	---	---	---
2	Irinotecan	50	IV	q7dx3	30	16	113	0	0	0	***	---	---	---
3	Irinotecan	100	IV	q7dx3	29	15	103	0	0	0	***	---	---	---
4	Irinotecan	150	IV	q7dx3	26	12	82	1	0	0	***	---	---	---
5	NKTR-102	50	IV	q7dx3	49	34	242	5	5	3	***	***	---	---
6	NKTR-102	100	IV	q7dx3	46	32	225	2	8	1	***	***	---	---
7	NKTR-102	150	IV	q7dx3	48	33	235	1	9	3	***	***	---	---
8	Cisplatin	10	IP	q7dx3	15	1	7	0	0	0	NS	---	---	---
9	Carboplatin	100	IP	q7dx3	17	3	21	0	0	0	NS	---	---	---

*** p<0.001
NS: not significant

NKTR-102 Anti-tumor Activity in Heavily Pre-treated Patients With Ovarian Cancer

In a Phase 1 dose-escalation study of single agent NKTR-102, patients received NKTR-102 weekly x3 every 4 weeks (qwx3 q4w), every 14 days (q14d), or every 21 days (q21d). Ten of 76 patients (13%) had partial responses to treatment, including 8 patients (11%) with confirmed partial responses. Five of 76 patients had ovarian cancer, of which two were evaluable for response. Both of these patients had previously progressed on prior platinum-based therapy and demonstrated anti-tumor responses with NKTR-102.

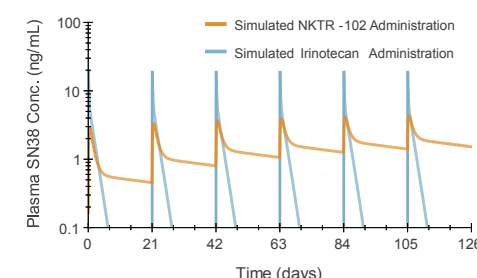
Dose Level (mg/m ²)	Schedule	Maximum Target Lesion Decrease	Maximum CA125 Decrease	Prior Chemotherapy Exposure
145	q14d	↓ 37%	N/A	carboplatin, cisplatin, docetaxel, paclitaxel, SNS-595 (experimental), tamoxifen
173	qwx3 q4w	↓ 21%	↓ 80%	carboplatin, cisplatin, gemcitabine, paclitaxel

NKTR-102 Phase 2 Study in Platinum-Resistant Ovarian Cancer

A phase 2 study evaluating two dose regimens (q14 and q21 days) of single-agent NKTR-102 in patients with platinum-resistant ovarian cancer patients is ongoing. Enrollment of the first stage of this Simon two-stage study is complete for both regimens (20 patients per regimen). Although many of these patients are still undergoing treatment and are not yet evaluable for response, the number of patients in both the q14 and q21 day regimens who have already achieved a confirmed response per RECIST 1.0 has enabled enrollment to begin for the second stage of each regimen.

SN38 Exposure is Sustained Following NKTR-102

Simulated SN38 concentrations based on NKTR-102 Phase 1 PK data demonstrate sustained SN38 exposure with every 3 week administration compared to simulated SN38 levels following repeat irinotecan administration.



Conclusion

- NKTR-102 demonstrates superior activity compared to irinotecan in a pre-clinical platinum-resistant A2780 ovarian carcinoma model.
- NKTR-102 Phase 1 data demonstrates a single agent response rate of 13% in heavily pre-treated patients with anti-tumor activity in a variety of tumor types including ovarian cancer
- The encouraging anti-tumor activity supports the ongoing NKTR-102 Phase 2 study in patients with platinum-resistant ovarian cancer