

ENHANCED ANTI-TUMOR ACTIVITY OF NKTR-102, A NOVEL PEGYLATED-IRINOTECAN, WHEN ADMINISTERED IN COMBINATION WITH BEVACIZUMAB IN A MOUSE MODEL OF HUMAN COLORECTAL TUMORS

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Abstract #766

Background:

- NKTR-102, a novel conjugate of irinotecan created using Nektar's small molecule PEGylation technology, is currently in clinical development as a second-line colorectal cancer therapy.
- At equivalent doses to irinotecan, NKTR-102 has demonstrated superior tumor growth inhibition in mouse xenograft models of lung, breast, and colorectal cancer (see Supplemental Figure in Appendix). This was associated with prolonged systemic and tumor SN38 exposure.^{1,2}
- The present study builds on these previous monotherapy studies to evaluate the anti-tumor activity of NKTR-102 when administered as combination therapy with bevacizumab in a mouse HT29 colorectal tumor model.

Objective:

- To examine the anti-tumor activity of the combination of NKTR-102 and bevacizumab in a mouse HT29 colorectal tumor model, which demonstrates moderate inherent resistance to irinotecan.

Methods:

- Tumor fragments comprised of HT29 cells, inherently resistant to irinotecan (see Supplemental Figure in Appendix), were implanted subcutaneously into female, athymic nude mice (CrI:NU-Foxn1tm).
- Tumors were measured and volumes were calculated using the following formula:
 - Volume (mm³) = (A) x (B²/2), where A is the largest diameter (mm) and B is the smallest diameter (mm).
 - Tumor volumes were converted into tumor weights assuming a tumor density of 1 mm³ = 1 mg.
- Sixty mice with tumor weights of 75 mg to 144 mg were randomly pair-matched into 6 groups of 10 each. NKTR-102 was administered at 23 mg/kg or 46 mg/kg (doses expressed as irinotecan-equivalent doses) on Days 1, 8, and 15. Bevacizumab was administered at 50 µg on Days 1 and 14 (Table 1). Doses were selected based upon the prior experience of the testing facility with this xenograft model.
- Tumor and body weight were measured at baseline and twice weekly during treatment. Mice were sacrificed when tumor weight reached approximately 2000 mg, or on Day 88 of the study.

Table 1: Study design.

Group	Treatment and Dose	
1	Vehicle Control	
2	Bevacizumab 50 µg	
3	NKTR-102 23 mg/kg	Monotherapy
4		+ Bevacizumab 50 µg
5	NKTR-102 46 mg/kg	Monotherapy
6		+ Bevacizumab 50 µg

NKTR-102 was administered IV on Days 1, 8, and 15. Bevacizumab was administered IP on Days 1 and 14. Vehicle control was phosphate-buffered saline administered at the same volume as NKTR-102.

- Tumor Growth Inhibition (TGI) was calculated as the differences in tumor weights in the active treatment groups at Day 25. Day 25 was the time point at which the first animal in the vehicle control treatment group reached the tumor weight endpoint of 2000 mg.
- Median Tumor Growth Delay (TGD) was defined as the difference in time (days) for actively treated animals to develop tumors weighing 1000 mg compared with animals treated with the vehicle control. (The mean tumor weight in the vehicle control animals was approximately 1000 mg at the point that the first vehicle control animal reached the endpoint 2000 mg). TGD was calculated by subtracting median time-to-endpoint (TTE) for control animals from median TTE of the various active treatment groups.
- Mean tumor growth inhibition (TGI) was calculated on Day 25 of treatment using the following formula:
 - TGI = $[1 - (\bar{X}^{\text{treated (final)}} - \bar{X}^{\text{treated (day1)}}) / (\bar{X}^{\text{control (final)}} - \bar{X}^{\text{control (day1)}})] \times 100\%$, where \bar{X} = mean tumor weight.
 - Tumors that regressed in weight as measured on Day 1 were excluded from this calculation.
- Differences in tumor weights at Day 25 were analyzed using analysis of variance (ANOVA) with Dunnett's multiple comparison posttest. Individual cohort comparisons were performed with Welch's *t*-test.
- Tumors that decreased in weight during treatment were assessed for partial or complete regression at the point in treatment when tumor weight was maximally reduced relative to the weight as measured on Day 1. A tumor whose weight was reduced compared with its weight on Day 1 was considered to be in partial regression. Complete regression was defined as sufficient reduction in mass so as to be not palpable.
- Tolerability was assessed by measuring changes in body weight and mortality during the treatment period.

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Poster presented at the 2008 AACR Annual Meeting, April 12-16, 2008, San Diego, CA, USA

Results:

Tumor Growth Delay

- NKTR-102 treatment was associated with a dose-dependent increase in TGD (Table 2).
- NKTR-102 in combination with bevacizumab demonstrated additive TGD compared with monotherapy (23 mg/kg and 46 mg/kg NKTR-102) (Table 2).

Table 2: Tumor regression and TGD with NKTR-102 is enhanced in combination with bevacizumab.

Treatment and Dose ^a	Median TTE (days) ^b	TGD ^c	%TGD ^d	Tumor Regression ^e		
				Partial	Complete	
Vehicle	25.5	—	—	0/10	0/10	
Bevacizumab 50 µg	43	17.5	68.6	0/10	0/10	
NKTR-102 23 mg/kg	Monotherapy	36	10.5	41.0	0/10	0/10
	+ Bevacizumab 50 µg	49	23.5	92.2	2/10	0/10
NKTR-102 46 mg/kg	Monotherapy	52	26.5	103.9	2/10	1/10
	+ Bevacizumab 50 µg	69	43.5	170.6	8/10	1/10

^a NKTR-102 doses reported as irinotecan equivalents.

^b Median time for tumor weight to reach 1000 mg.

^c Difference in median time to reach goal tumor weight for control and actively treated animals.

^d Calculated as median TTE_{treatment} - median TTE_{vehicle} / median TTE_{vehicle}.

^e Tumor regressions reported here are for the full duration of the study, not limited to those regressions noted at Day 25 (summarized in Table 3).

Tumor Regression

- At Day 25, regressions were observed in 2/10 animals administered NKTR-102 46 mg/kg monotherapy, 2/10 administered NKTR-102 23 mg/kg in combination with bevacizumab, and in 8/10 animals administered NKTR-102 at 46 mg/kg in combination with bevacizumab.
- NKTR-102 monotherapy resulted in 1/10 complete and 2/10 partial tumor regressions at 46 mg/kg. This was superior to bevacizumab monotherapy (0/10 complete and 0/10 partial tumor regressions).
- Combination therapy with NKTR-102 46 mg/kg and bevacizumab resulted in 1/10 complete and 8/10 partial tumor regressions.

Tumor Growth Inhibition

- NKTR-102 monotherapy resulted in TGI values of 52% and 92% on Day 25 of treatment in mice receiving 23 mg/kg or 46 mg/kg, respectively. TGI for bevacizumab 50 µg monotherapy was 52% (Table 3).
- NKTR-102 in combination with bevacizumab resulted in TGI values of 76% and 97% at NKTR-102 doses of 23 mg/kg and 46 mg/kg, respectively, which indicate an additive effect (Table 3).
- NKTR-102, both as monotherapy and in combination with bevacizumab, was well tolerated, with minimal (<5%) loss in mean body weight and no significant clinical observations.

Table 3: Tumor growth is inhibited at Day 25 in an additive manner with NKTR-102 and bevacizumab combination therapy.

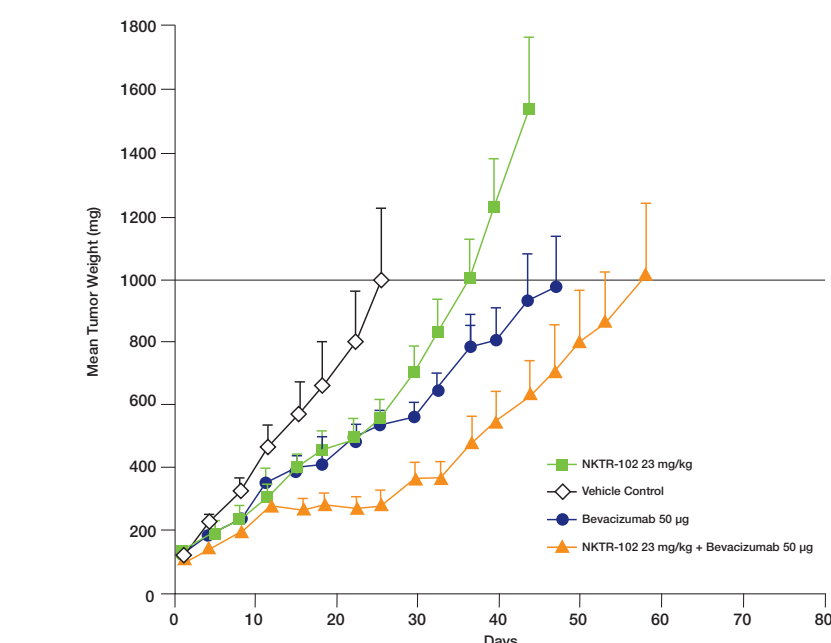
Treatment and Dose	TGI Observed	Predicted
Bevacizumab 50 µg	0.52	—
NKTR-102 23 mg/kg	Monotherapy	0.52
	+ Bevacizumab 50 µg	0.76
NKTR-102 46 mg/kg	Monotherapy	0.92
	+ Bevacizumab 50 µg	0.97

TGI calculation does not include animals for which regression is observed at Day 25.

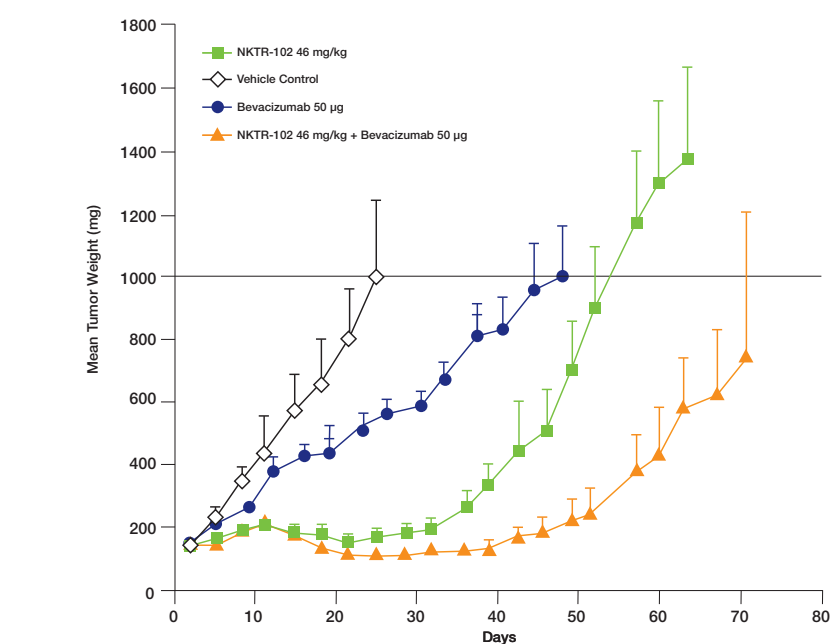
— = not applicable.

Figure 1: Combination therapy of NKTR-102 and bevacizumab inhibits tumor growth in a dose-related manner.

A NKTR-102 23 mg/kg



B NKTR-102 46 mg/kg



Body Weight

- Decrements in body weight were observed in the bevacizumab monotherapy and in both NKTR-102 + bevacizumab combination therapy groups.
- The maximum body weight loss observed during the study was 4% in the NKTR-102 46 mg/kg and bevacizumab combination therapy group at Day 8.

Conclusions:

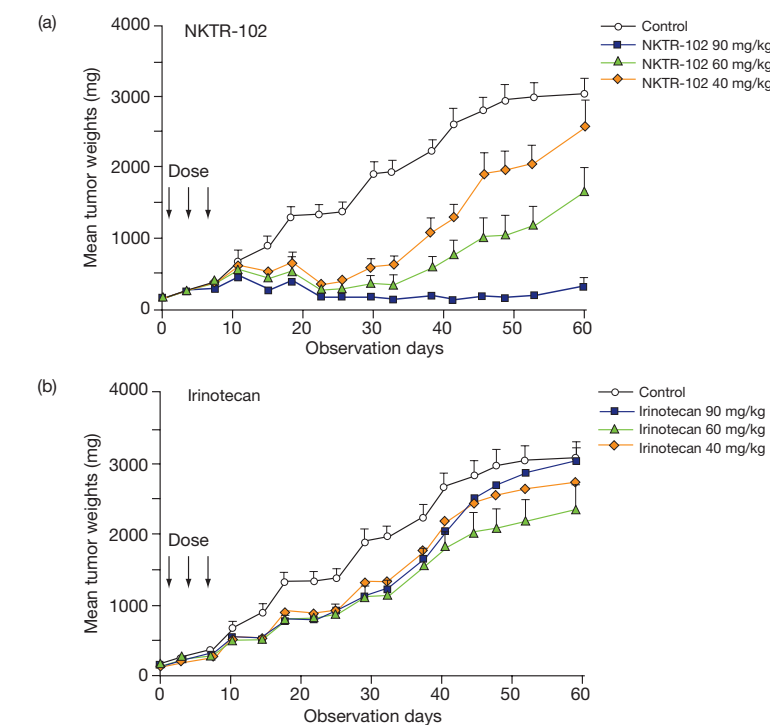
- NKTR-102 in combination with bevacizumab demonstrated an additive anti-tumor effect in a mouse xenograft model of colorectal cancer.
- NKTR-102 exhibited 52% and 92% tumor growth inhibition (TGI) relative to controls at 23 mg/kg and 46 mg/kg, respectively. NKTR-102 plus bevacizumab further increased TGI to 76% and 97%, respectively, suggesting an additive effect. Similarly, tumor growth delay was increased and showed the same additive effect.
- The combination of 46 mg/kg NKTR-102 with bevacizumab resulted in a 4-fold increase in partial tumor regressions versus NKTR-102 alone. No tumor regressions were observed with bevacizumab monotherapy.
- NKTR-102 alone and in combination with bevacizumab was well tolerated, with minimal weight loss and no significant clinical observations.

References:

- Persson H, Antonian L, Staschen C-M, et al. NKTR-102, a novel polyethylene glycol conjugate of irinotecan, has improved anti-tumor activity in three mouse xenograft models. Poster presented at the 2007 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Oct 22-26, 2007, San Francisco, CA, USA. Poster no. C10.
- Eldon MA, Staschen C-M, Viegas T, et al. NKTR-102, a novel PEGylated-irinotecan conjugate, results in sustained tumor growth inhibition in mouse models of human colorectal and lung tumors that is associated with increased and sustained tumor SN38 exposure. Poster presented at the 2007 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Oct 22-26, 2007, San Francisco, CA, USA. Poster no. C157.

Appendix:

Supplemental Figure: Effect of NKTR-102 versus irinotecan in HT-29 colorectal tumor-bearing mice.



Adapted with permission.¹

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