

NKTR-102, a novel polyethylene glycol conjugate of irinotecan, has improved anti-tumor activity in three mouse xenograft models

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Background

- NKTR-102 is a novel PEGylated conjugate of irinotecan, an antineoplastic agent of the topoisomerase 1 inhibitor class that is widely used to treat colorectal cancer and other solid tumors.
- NKTR-102 was created using Nektar's small molecule PEGylation technology and is currently in Phase I clinical development.
- Adding a PEG moiety to anti-tumor drugs such as irinotecan is expected to lead to a decrease in drug clearance and an increase in exposure to active drug (see AACR-NCI-EORTC poster C157) causing greater inhibition of tumor growth.

Objective

- To evaluate the anti-tumor activity of NKTR-102 and irinotecan in colorectal (HT29), lung (NCI-H460), and mammary (MCF-7) mouse xenograft models.

Methods

- HT29, which is inherently resistant to irinotecan, NCI-H460 or MCF-7 tumor fragments were implanted subcutaneously into female, athymic (Ncr:Nu) nude mice.
- Tumors were allowed to reach a weight of 135 to 184 mg with HT29, 120 to 171 mg with NCI-H460, and a median of 75 mg with MCF-7 tumor cells.
- Mice bearing subcutaneously implanted HT29 and NCI-H460 tumors received either 40, 60, or 90 mg/kg irinotecan-equivalent doses of NKTR-102 or 40, 60 or 90 mg/kg irinotecan.
- Mice bearing subcutaneously implanted MCF-7 tumors received either 20, 40, 60 or 90 mg/kg irinotecan-equivalent doses of NKTR-102 or 20 or 40 mg/kg of irinotecan.
- Each treatment group (n=10) received a total of three intravenous doses administered every fourth day (q4d x3). Saline controls (n=20 in HT29 and NCI-H460 studies; n=10 in MCF-7 study) were dosed according to the same schedule.
- Animals were weighed and tumor volumes measured twice weekly after the first drug injection. Tumor volumes were converted to tumor weight assuming a tumor density of 1 mm³ = 1 mg.
- Animals exhibiting poor condition due to tumor progression were euthanized accordingly. Any remaining animals were sacrificed on Days 60, 53, or 72 for the HT29, NCI-H460, or MCF-7 studies, respectively.
- Anti-tumor activity was measured as changes in tumor weight, tumor growth inhibition, tumor regression and duration of regression.
- Tolerability was measured as body weight loss and deaths due to drug toxicity.
- Student's T test or life table analysis using the Mantel statistic was used to statistically compare growth between groups.

Results

- Significant anti-tumor activity was observed in each group receiving NKTR-102 compared to irinotecan in the three tumor models tested.

HT29

- NKTR-102 inhibited tumor growth compared to controls in a dose-dependent manner ($p < 0.0003$) (Figure 1a). Tumor growth inhibition due to irinotecan did not reach statistical significance (Figure 1b).
- Tumor growth delay (T-C value) was significantly longer for NKTR-102 compared with irinotecan at all three doses tested ($p < 0.001$, Table 1).
- NKTR-102 exhibited 94%, 64%, and 37% tumor growth inhibition relative to controls at 90, 60, and 40 mg/kg doses, respectively, as measured on Day 50. Tumor growth inhibition at 90 mg/kg persisted until termination on Day 60.

- Irinotecan exhibited 6%, 16%, and 16% tumor growth inhibition relative to controls at 90, 60, and 40 mg/kg doses, respectively, as measured on Day 50.
- NKTR-102 at the 90 mg/kg irinotecan-equivalent dose produced three complete regressions in contrast to none with irinotecan (Table 1).
- All doses of NKTR-102 and irinotecan were well tolerated with 5% and 11% loss in mean body weight at the 90 mg/kg irinotecan-equivalent dose, respectively. No deaths due to drug toxicity occurred with either compound.

Figure 1. Tumor growth delay curves following treatment with NKTR-102 (a) and irinotecan (b) to HT29 colorectal tumor-bearing mice.

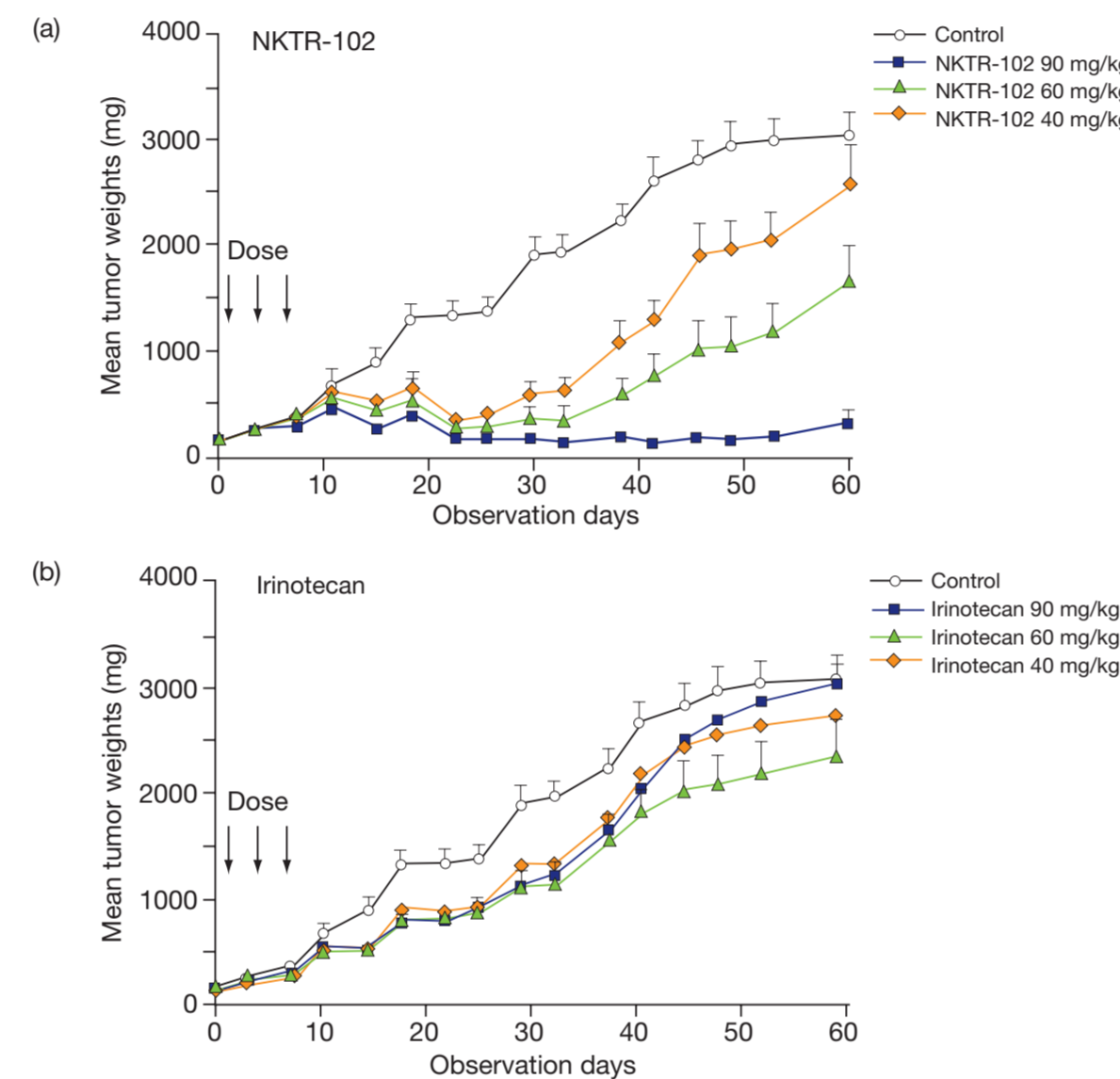


Table 1. Summary of tumor growth parameters for HT29 colorectal tumor-bearing mice following treatment with NKTR-102 or irinotecan

Test compound	Dose ^a (mg/kg)	Tumor regression ^{b,c}		Median duration of regression ^d (days)	Days to 2 tumor doublings ^e	T-C ^f (days)
		Partial	Complete			
Control	0	0/5	0/5	NA	11.8	NA
NKTR-102	90	1/10	3/10	12.4	>60	>48.2
NKTR-102	60	0/9	0/9	NA	38.1	26.3
NKTR-102	40	0/9	0/9	NA	32.7	20.9
Irinotecan	90	0/6	0/6	NA	12.1	0.3
Irinotecan	60	0/4	0/4	NA	16.1	4.3
Irinotecan	40	0/3	0/3	NA	13.4	1.6

^a Refers to amount of active compound administered in each dose. ^b Tumor regression: smallest tumor weight after the beginning of treatment relative to that observed on the first day of treatment. Partial: <50% of weight observed on Day 1; Complete: unpalpable. ^c Measured on Day 57. ^d Interval during which partial or complete regression was observed. ^e Median number of days for tumor to double in weight two times. ^f Difference in the median of times for tumors to attain an evaluation weight comparable to the median of the controls. NA = not applicable.

NCI-H460

- NKTR-102 caused a dose-dependent tumor growth inhibition compared to controls ($p < 0.0001$) (Figure 2a). Tumor growth inhibition due to irinotecan did not reach statistical significance (Figure 2b).
- Tumor growth delay (T-C value) was significantly longer for NKTR-102 compared to irinotecan at the three doses tested ($p < 0.026$) (Table 2).
- NKTR-102 exhibited 94%, 84%, and 59% tumor growth inhibition relative to controls at 90, 60, and 40 mg/kg doses, respectively, as measured on Day 28.
- Irinotecan exhibited 24%, 28%, and 28% tumor growth inhibition relative to controls at 90, 60, and 40 mg/kg doses, respectively, as measured on Day 28.

- NKTR-102 at doses of 60 and 90 mg/kg resulted in two complete tumor regressions but none with irinotecan at any dose level (Table 2)
- All doses of NKTR-102 and irinotecan were well tolerated with 10% and 16% loss in mean body weight at the 90 mg/kg irinotecan-equivalent dose, respectively. No deaths due to drug toxicity occurred with either compound.

Figure 2. Tumor growth delay curves following treatment with NKTR-102 (a) and irinotecan (b) to NCI-H460 lung tumor-bearing mice.

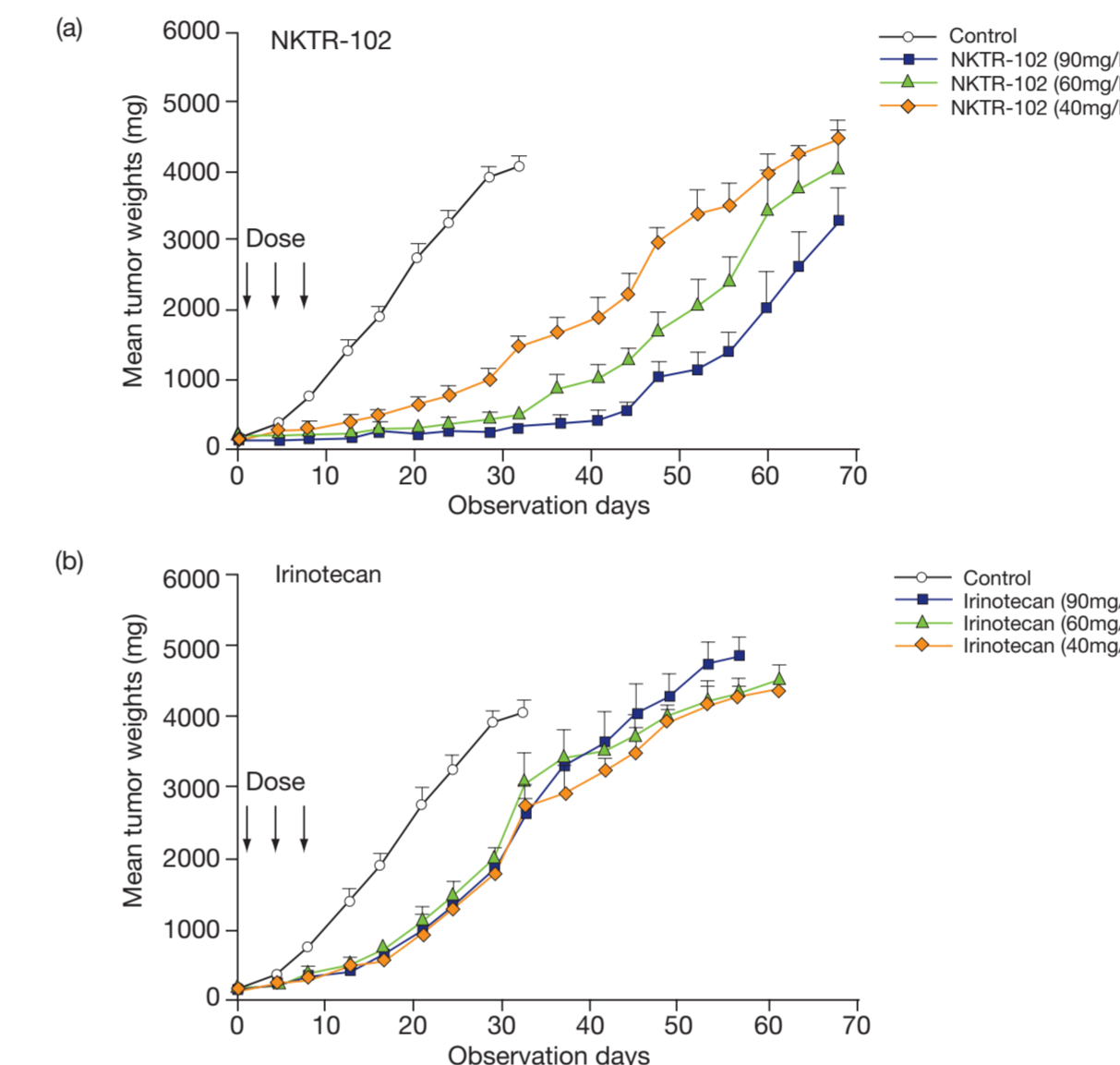


Table 2. Summary of tumor growth parameters for NCI-H460 lung tumor-bearing mice following treatment with NKTR-102 or irinotecan.

Test compound	Dose ^a (mg/kg)	Tumor regression ^{b,c}		Median duration of regression ^d (days)	Days to 3 tumor doublings ^e	T-C ^f (days)
		Partial	Complete			
Control	0	0/0	0/0	NA	9.9	NA
NKTR-102	90	0/9	1/9	34.1	41.1	31.2
NKTR-102	60	0/10	1/10	NA	38.4	28.5
NKTR-102	40	0/8	0/8	NA	26.8	16.9
Irinotecan	90	0/5	0/5	NA	21.0	11.1
Irinotecan	60	0/5	0/5	NA	19.3	9.4
Irinotecan	40	0/5	0/5	NA	20.2	10.3

^a Refers to amount of active compound administered in each dose. ^b Tumor regression: smallest tumor weight after the beginning of treatment relative to that observed on the first day of treatment. Partial: <50% of weight observed on Day 1; Complete: unpalpable. ^c Measured on Day 42. ^d Interval during which partial or complete regression was observed. ^e Median number of days for tumor to double in weight three times. ^f Difference in the median of times for tumors to attain an evaluation weight comparable to the median of the controls. NA = not applicable.

MCF-7

- NKTR-102 caused a marked tumor growth inhibition compared to controls ($p < 0.05$) at all four dose levels tested (Figure 3a). Irinotecan at 20 and 40 mg/kg did not result in significant tumor growth inhibition (Figure 3b).
- Tumor growth delay (T-C value) with all doses of NKTR-102 could not be calculated because the tumors did not achieve 4x the starting tumor weight.
- NKTR-102 inhibited tumor growth by approximately 92% relative to controls for all doses tested as measured on Day 52.
- Irinotecan exhibited 56% and 50% tumor growth inhibition relative to controls at 40 and 20 mg/kg doses, respectively, as measured on Day 52.
- All doses of NKTR-102 and irinotecan were well tolerated with $\leq 2\%$ loss in mean body weight. No deaths due to drug toxicity occurred with either compound.

Figure 3. Tumor growth delay curves following treatment with NKTR-102 (a) and irinotecan (b) to MCF-7 breast tumor-bearing mice.

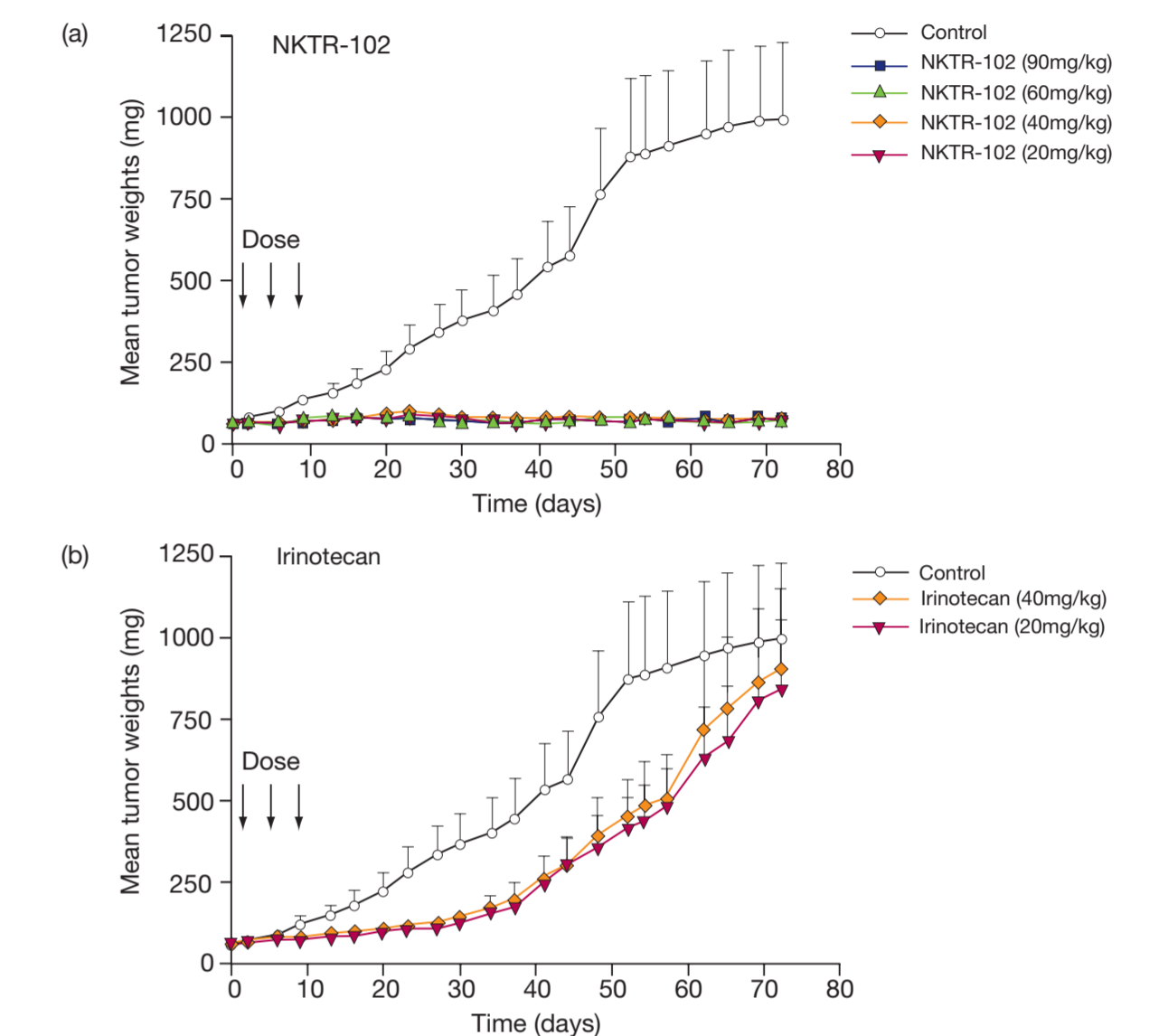


Table 3. Summary of tumor growth parameters for MCF-7 breast-tumor bearing mice following treatment with NKTR-102 or irinotecan.

Test compound	Dose ^a (mg/kg)	Tumor regression ^{b,c}		Median duration ^d of regression (days)	Days to 4 tumor doublings ^e	T-C ^f (days)
		Partial	Complete			
Control	0	0/4	0/4	NA	20.5	NA
NKTR-102	90	1/9	0/9	49.0	>72	>52
NKTR-102	60	0/9	0/9	NA	>72	>52
NKTR-102	40	1/8	0/8	22.0	>72	>52
NKTR-102	20	0/7	0/7	NA	>72	>52
Irinotecan	40	1/5	0/5	42.0	42.8	22.3
Irinotecan	20	0/7	0/7	NA	40.2	19.7

^a Refers to amount active compound administered in each dose. ^b Tumor regression: smallest tumor weight after the beginning of treatment relative to that observed on the first day of treatment. Partial: <50% of weight observed on Day 1; Complete: unpalpable. ^c Measured on Day 72. ^d Interval during which partial or complete regression was observed. ^e Median number of days for tumor to double in weight four times. ^f Difference in the median of times for tumors to attain an evaluation weight comparable to the median of the controls. NA = not applicable.

Conclusions

- NKTR-102 demonstrated superior tumor growth inhibition compared to irinotecan in colorectal (HT29), lung (NCI-H460), and breast (MCF-7) mouse xenograft models.
- NKTR-102 inhibited tumor growth by 94% relative to controls in colorectal and lung tumor xenograft models, respectively, at the appropriate time points. Irinotecan exhibited only modest tumor growth inhibition of 6% in colorectal and 24% in lung relative to controls at comparable doses.
- NKTR-102 inhibited tumor growth by 92% relative to controls for all doses tested in a breast tumor xenograft model. Irinotecan at comparable doses demonstrated tumor growth inhibition of 50 to 56% relative to controls.
- NKTR-102 was well tolerated with $\leq 10\%$ loss in mean body weight. The safety and tolerability of the molecule are now being evaluated further in ongoing clinical trials.
- Using Nektar's small molecule PEGylation technology, NKTR-102 was created to improve the concentration-time profile of irinotecan and metabolites. Superior anti-tumor efficacy compared with irinotecan is associated with prolonged systemic and tumor SN38 exposure secondary to extended disposition and metabolism of NKTR-102 (see poster C157).