Activity of NKTR-102 in Nonclinical Models of Gastrointestinal Cancers (Abstract # P-0025)

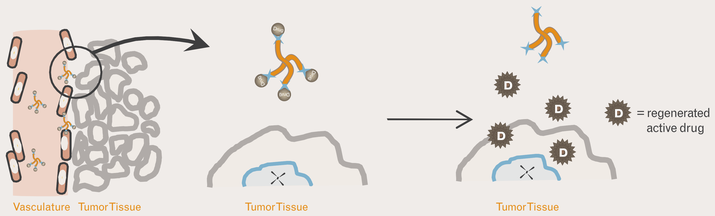
Ute Hoch and Michael A. Eldon, Nektar Therapeutics, San Carlos, CA

Abstract

Background: NKTR-102, a topoisomerase I inhibitor-polymer conjugate with reduced peak concentrations and a continuous concentration profile of its active metabolite SN38, is currently in Phase 2 development in ovarian, breast, and colorectal cancers. NKTR-102 demonstrated superior activity over irinotecan (IRN) in mouse models of lung, breast, and ovarian cancers. In the current study we compare the activity of NKTR-102 and IRN alone or in combination with 5-FU in nonclinical models of gastrointestinal cancers. **Methods:** Mice bearing established HT29 colorectal or NCI-H87 gastric tumors, received NKTR-102 or IRN in 3 weekly doses alone (HT29 and NCI-H87 studies) and in combination with 5-FU (HT29 study). Doses ranged from 60-150 mg/kg in the NCI-H87 study. In the HT29 study, IRN and 5-FU were administered at maximum tolerated dose (MTD) (100 mg/kg) and ½ MTD (50 mg/kg), and NKTR-102 was administered at IRN equivalent dose levels. NKTR-102 and IRN were combined with MTD and ½ MTD doses of 5-FU. Anti-tumor activity was evaluated based on tumor growth delay (TGD) and regression response rate. **Results:** NKTR-102 and IRN were equally well tolerated. In the NCI-N87 gastric tumor model, control tumors grew rapidly and uniformly to the 800 mm^3 endpoint in a median of 18 days. NKTR-102 administered at doses of 60, 100, and 150 mg/kg resulted in maximum TGDs of 362% at all three dose levels. Regression response rate (partial regressions [PRs] and complete regressions [CRs]) was dose-related and increased from 30-100% with 8 animals remaining tumor fee at the end-of-study at the 150 mg/kg dose level. In contrast to NKTR-102, IRN was minimally active, yielding slight TGDs of 64%, with no regressions and no end-of-study survivors at its MTD of 60 mg/kg. In the HT29 colorectal tumor model, control tumors grew rapidly and uniformly to the 1000 mm^3 endpoint in a median of 25 days. The 50 mg/kg IRN monotherapy was not active and the 100 mg/kg monotherapy resulted in a TGD of 42%. The 50 and 100 mg/kg 5-FU monotherapy regimens resulted in dose-related TGDs of 55% and 70%, respectively. The 50 mg/kg NKTR-102 monotherapy resulted in a TGD of 118%, and the 100 mg/kg NKTR-102 resulted in a maximum TGD of 232% with 80% regression response rate. NKTR-102 monotherapy was superior to IRN and 5-FU monotherapy. Moreover, the combination of 100 mg/kg NKTR-102 and 50 mg/kg 5-FU was the most active regimen in the study, yielding the maximum TGD of 232% and a 100% regression response rate. This combination had superior activity to all four IRN/5-FU combinations. **Conclusions:** NKTR-102 shows superior activity compared to IRN in mouse models of gastrointestinal tumors when administered alone or in combination with 5-FU. A Phase 2 study of NKTR-102 in patients with metastatic colorectal cancer and a Phase 1 study of NKTR-102 in combination with 5-FU are currently ongoing.

Introduction

Nektar's advanced polymer conjugate technology can be used to improve the pharmacokinetics (PK) and pharmacodynamics of both large and small molecule therapeutics. Nektar's technology has enabled the development of several marketed therapeutic products including CIMZIA®, PEGASYS®, NEULASTA® and SOMAVERT®. PEG (polyethylene glycol) is a water soluble, non-toxic, non-immunogenic compound that is safely cleared from the body, thus offering a versatile technology for improving the PK characteristics of many drugs. Multi-arm polymer scaffolds using PEG are ideal as cores for engineering long acting nanoparticle prodrugs of chemotherapeutic agents. Variation in core size and drug-to-core linker release characteristics allows engineering of new chemotherapeutic drugs that have favorable in vivo distribution and metabolism characteristics, such as taking advantage of the "Enhanced Permeability and Retention" (EPR) effect that predicts that polymer conjugates can traverse leaky tumor blood vessels into tumor tissue, where they are retained due to a lack of effective tumor lymphatic drainage. Once present in the tumor, the degradable linker of the drug-polymer conjugate is hydrolyzed, releasing the active drug or metabolite for action on tumor cells:



NKTR-102 has been synthesized to provide a sustained release of IRN and SN38 with the aim of improving its efficacy, safety, and/or tolerability profile over marketed IRN. NKTR-102 has demonstrated the desired PK 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 IRN in mouse xenograft models, where NKTR-102 showed superior activity in models of breast, colorectal, and non-small cell lung cancer.

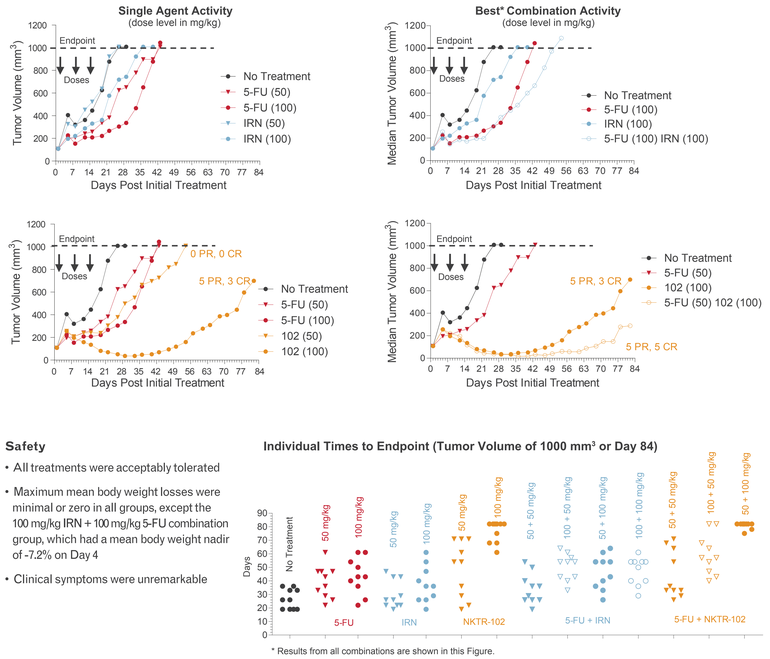
Objective

To investigate the nonclinical anti-tumor activity of NKTR-102 alone and in combination with 5-FU in two models of gastrointestinal cancers (HT29 colorectal and NCI-N87 gastric).

Results

NKTR-102 Shows Superior Single Agent and Superior Combination Activity with 5-FU Over Irinotecan in HT29 Colon Tumor Model

Tumors were grown in vivo and implanted subcutaneously in 8-9 week old female athymic nude mice as tumor fragments. Animals were randomized into treatment groups (n=10/group) when their tumors reached 75-144 mm^3 and subsequently received either no treatment (NT), NKTR-102, IRN, 5-FU, or combinations of 5-FU with IRN or NKTR-102. Irinotecan/NKTR-102 and 5-FU were administered q7dx3, intravenously and intraperitoneally, respectively. Animals were weighed and monitored twice weekly, and tumor volumes were measured until an endpoint (1000 mm^3 or Day 84) was met. Antitumor activity was determined by tumor growth delay and regression response rate.



Safety

- All treatments were acceptably tolerated
- Maximum mean body weight losses were minimal or zero in all groups, except the 100 mg/kg IRN + 100 mg/kg 5-FU combination group, which had a mean body weight nadir of -7.2% on Day 4
- Clinical symptoms were unremarkable

Individual Times to Endpoint (Tumor Volume of 1000 mm^3 or Day 84)

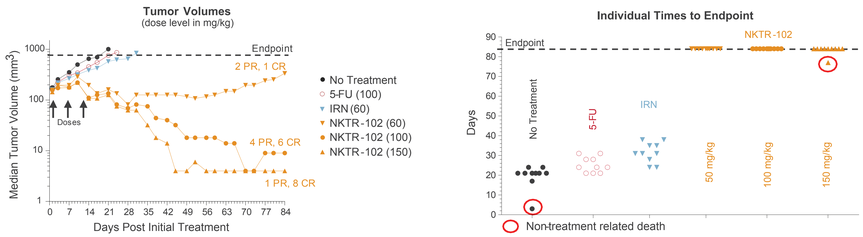
* Results from all combinations are shown in this Figure.

Response Summary

Treatment Regimen		Median TTE	T-C (days)	TGD (%)	Regressions			Statistical Results For Groups Tested
Agent	mg/kg				PR	CR	TFS	
NT	—	25	—	—	0	0	0	
IRN	50	24	-1	-2	0	0	0	Not significant against NT
IRN	100	35	10	42	0	0	0	Significant against NT (p<0.05)
5-FU	50	38	14	55	0	0	0	Significant against NT (p<0.05)
5-FU	100	42	17	70	0	0	0	Significant against NT (p<0.001)
102	50	54	29	118	0	0	0	Significant against NT (p<0.01), and IRN 50 mg/kg (p<0.01)
102	**100**	**42**	**17**	**70**	**5**	**3**	**2**	**Significant against NT (p<0.001), and IRN 100 mg/kg (p<0.001)**
5-FU+IRN	50+50	29	4	17	0	0	0	Not significant against NT
5-FU+IRN	100+50	53	28	115	0	0	0	Significant against NT (p<0.001)
5-FU+IRN	50+100	46	21	86	0	0	0	Not significant against NT
5-FU+IRN	**100+100**	**50**	**26**	**104**	**0**	**0**	**0**	**Significant against NT (p<0.001)**
5-FU+102	50+50	34	9	36	0	0	0	Significant against NT (p<0.05), not significant against IRN 50 + 5-FU 50 mg/kg
5-FU+102	100+50	55	31	124	1	0	0	Significant against NT (p<0.001), not significant against IRN 50 + 5-FU 100 mg/kg
5-FU+102	**50+100**	**82**	**57**	**232**	**5**	**5**	**4**	**Significant against NT (p<0.001), IRN 100 + 5-FU 50 mg/kg (p<0.001), and IRN 100 + 5-FU 100 mg/kg (p<0.001)**

NKTR-102 Shows Superior Activity Over Irinotecan in NCI-N87 Gastric Tumor Model

Tumor cells were grown in vitro and implanted subcutaneously in 7-8 week old female severe combined immunodeficient (SCID) mice as cell suspension in Matrigel matrix. Animals were randomized into treatment groups (n=9 or 10/group) when their tumors reached 100-200 mm^3 and subsequently received either NKTR-102 or IRN by intravenous injection q7dx3. Animals were weighed and monitored twice weekly, and tumor volumes were measured until an endpoint (800 mm^3 or Day 84) was met. Antitumor activity was determined by tumor growth delay and regression response rate.



Safety

- NKTR-102 and 5-FU were well tolerated, with mean body weight nadirs ranging from -3.3 to -7.7%
- Irinotecan resulted in acute effects immediately after dosing (tremors, hypo-activity), with a mean body weight nadir of -11.1%

Response Rate

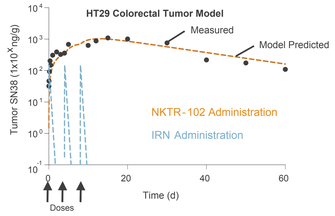
- 5-FU / IRN
  - 0/10 partial response (PR) at the IRN or 5-FU MTD
  - All tumors reached 800 mm^3 by study end
- NKTR-102
  - 2 PR and 1 complete response (CR) at IRN equivalent dose level
  - 1 PR and 8 CR at NKTR-102 MTD
  - Number of CR was dose-related and increased with higher doses
  - 29/29 mice did not reach 800 mm^3 by study end, with 13 animals remaining tumor free

Response Summary

Treatment Regimen		Median TTE	T-C	TGD (%)	Regressions			Statistical Significance		
Agent	mg/kg				PR	CR	TFS	vs NT	vs 5-FU 100	vs IRN 60
NT	---	18	—	—	0	0	0	---	---	---
5-FU	100	22	4	21	0	0	0	p<0.01	---	p<0.01
IRN	60	30	12	64	0	0	0	p<0.001	---	---
102	60	84	66	362	2	1	0	p<0.001	p<0.001	p<0.001
102	100	84	32	362	4	6	5	p<0.001	p<0.001	p<0.001
102	150	84	66	362	1	8	8	p<0.001	p<0.001	p<0.001

NKTR-102 Leads to Greater and Sustained SN38 Tumor Concentrations

HT29 tumors were grown as described above. When tumor sizes reached 100-172 mm^3, animals were dosed by intravenous injection of IRN (q4dx3, 40mg/kg) or NKTR-102 (q4dx3, 40mg/kg). Blood and tumor samples (n=4/time point) were collected from 0-60 days post initial dose. Plasma and tumor samples were analyzed for SN38 using qualified methods based on LC-MS/MS.



Conclusion

- NKTR-102 demonstrates superior activity compared to IRN in nonclinical models of gastrointestinal cancers.
- NKTR-102 can be safely combined with 5-FU. The combination of NKTR-102 and 5-FU shows greatly improved activity over either single agent and over combination of IRN and 5-FU.
- The encouraging antitumor activity supports the ongoing NKTR-102 Phase 2 study in metastatic colorectal cancer (www.clinicaltrials.gov reference no. NCT00856375) and the Phase 1 study of NKTR-102 in combination with 5-FU.

Poster P-0025, ESMO Conference: 12th World Congress on Gastrointestinal Cancer, 30 June to 03 July 2010, Barcelona, Spain
To download a copy of this poster, please visit http://www.nektar.com/product_pipeline/oncology_nktr-102.html

Acknowledgment:
We would like to thank Piedmont Research Center for conducting the xenograft studies.