Significant Efficacy in a Phase 2 Study of NKTR-102, a Novel Polymer Conjugate of Irinotecan, in Patients With Pre-Treated Metastatic Breast Cancer (MBC)

NEKTAR

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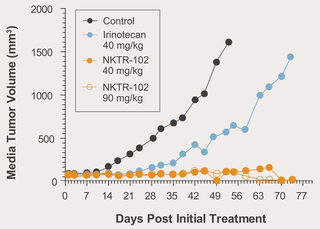
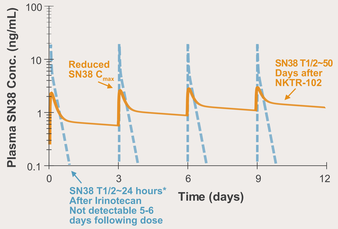
Background

- NKTR-102 is a topoisomerase 1 inhibitor-polymer conjugate of irinotecan with reduced peak concentrations, a continuous exposure profile, and a greater penetration into tumors.
- NKTR-102 has superior efficacy (measured both by tumor growth delay and regression rate) compared to irinotecan against a wide range of human xenograft tumors. (ENA 2007, abs C10)

MCF-7 Breast Tumor Model



Polymer Conjugation Improves Pharmacokinetics of Irinotecan

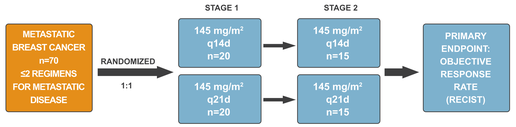


* Data from Xie R et al. 2002, J Clin Oncol 20:3293

- NKTR-102 demonstrated high anti-tumor activity in a range of tumors in phase 1 (11% confirmed PRs; ENA 2008, abs 595)
  - Of interest, 3 patients in the Phase 1 study with triple-negative breast cancer (TNBC) showed significant response to single-agent NKTR-102 (ENA 2008, abs 595)
- NKTR-102 showed a 22% confirmed response rate per RECIST in heavily pre-treated women with platinum resistant/refractory ovarian cancer (ASCO 2010, abs 5013)

Study Design & Objectives

Study Design: Randomized Simon Two-Stage



Statistical Hypotheses: H_0 ORR (RECIST version 1.0) ≤ 5% and H_a ORR ≥ 20%.
(Type 1 error = 0.029; type 2 error = 0.145)

Stage 1: If ≥ 1 patient responds, that treatment regimen proceeds to the next stage.
Stage 2: An additional 15 are patients enrolled

If > 4 patients respond out of 35 patients (Stage 1 + Stage 2 combined), the drug has met the efficacy threshold.

NKTR-102 Breast Cancer Study: Objectives

Primary Efficacy Objective:

- Determine the objective response rate (ORR) by RECIST v 1.0
- Determine the optimal schedule of NKTR-102 in breast cancer

Secondary Objectives:

- Estimate progression-free survival (PFS)
- Evaluate overall survival (OS) rates
- Characterize the safety profile

Key Eligibility Criteria

- Male or female patients with advanced breast cancer following taxane therapy (adjuvant or metastatic)
- Patients may also have received prior anthracycline or capecitabine
- No prior camptothecin therapy
- No more than two prior chemotherapy regimens given in the metastatic setting
- Measurable disease as defined by RECIST version 1.0
- ECOG PS: 0-1
- Adequate renal, hepatic and marrow function
- No known or suspected CNS metastases
- No significant pre-existing acute/chronic GI disorder

Study Demographics

		NKTR-102 145 mg/m² q14d N=35	NKTR-102 145 mg/m² q21d N=35
Age (years)	Median (Range)	53 (33-83)	56 (37-77)
ECOG PS	0 1	15 (43%) 20 (57%)	13 (37%) 22 (63%)
Receptor Status*	ER+ or PR+ ER-/PR-/HER-2 (triple negative) Her2+	22 (63%) 11 (31%) 6 (17%)	21 (60%) 10 (29%) 1 (3%)
Prior Systemic Treatments*	Neoadjuvant and/or Adjuvant therapy Taxane based regimen in metastatic setting Prior AT only (anthracycline/taxane) Prior AT only for metastatic disease Prior ATC (anthracycline/taxane/capecitabine) Median cytotoxic regimens (metastatic disease) Visceral (at least one lesion)	27 (77%) 31 (89%) 24 (69%) 6 (17%) 7 (20%) 1 28 (80%)	24 (69%) 30 (86%) 21 (60%) 8 (23%) 9 (26%) 2 33 (94%)
Time from primary diag. to metastatic	Median (years) (Range)	1.5 (0-7)	2 (0-12)

* Numbers may add up to more than 100% due to patients included in multiple rows

Results

Objective Tumor Response Rate by RECIST (Investigator Assessment)

Response by RECIST v 1.0	NKTR-102 145 mg/m² q14d ITT/Evaluable	NKTR-102 145 mg/m² q21d ITT/Evaluable	TOTAL ITT/Evaluable
N ORR (confirmed + unconfirmed) ORR (confirmed)	35/31* 11 (31%)/11(35%) 10 (29%)/10(32%)	35/35 11(31%) 9 (26%)	70/66 22 (31%)/22 (33%) 19 (27%)/19 (29%)
CR (confirmed) PR (confirmed) SD PD	2 (6%)/2 (7%) 8 (23%)/8 (26%) 17 (48%)/13 (42%) 8 (23%)/8 (26%)	0 9 (26%) 17 (48%) 9 (26%)	2 (3%)/2 (3%) 17 (24%)/17 (26%) 34 (49%)/30 (45%) 17 (24%)/17 (26%)
Clinical benefit (CR+PR+SD≥6 months)	12 (34%)/12 (39%)	15 (43%)	27 (38%)/27 (41%)

*4 patients in the Q14 day arm with no post-baseline scans but no evidence of progression were excluded from analysis in the evaluable population.

Response Rate By Prior Therapy

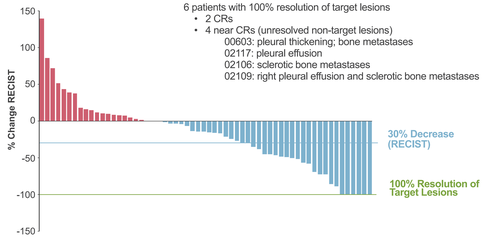
Prior Therapy Subgroup	Response by RECIST v 1.0 Evaluable Patients		
	NKTR-102 145 mg/m² q14d N=31	NKTR-102 145 mg/m² q21d N=35	TOTAL
Prior A/T only ORR (confirmed)	7/22 (32%)	5/21 (24%)	12/43(28%)
Prior A/T in MBC ORR (confirmed)	2/6 (33%)	2/8 (25%)	4/14 (29%)
Prior A/T/C ORR (confirmed)	2/6 (33%)	3/9 (33%)	5/15 (33%)

Response Rate By Tumor Characteristics

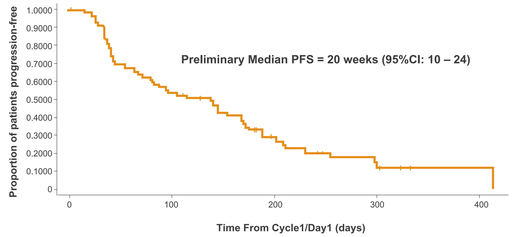
Disease Subgroup	Response by RECIST v 1.0 Evaluable Patients		
	NKTR-102 145 mg/m² q14d N=31	NKTR-102 145 mg/m² q21d N=35	TOTAL
ER+ and/or PR+ ORR (confirmed)	8/21 (38%)	4/21 (19%)	12/42 (29%)
TNBC ORR (confirmed)	2/8 (25%)	5/10 (50%)	7/18 (39%)
Visceral Disease ORR (confirmed)	8/25 (32%)	9/33 (27%)	17/58 (29%)

*TNBC: triple negative breast cancer

Maximum Decline in Tumor Measurements (All Patients)



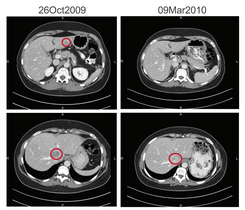
Phase 2 Breast Cancer Study: Progression-Free Survival (All Patients)



*Preliminary progression-free survival as of October 26, 2010. As of the data cutoff, approximately 60% of patients are still alive and being followed for survival. Because a majority of the patients are still alive and are therefore censored for any analysis of survival, it is not yet possible to report OS for this study.

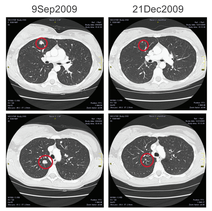
Patient 053802 Baseline / 4th On-study Scan

Prior A/T; PD on prior taxane. Shrinkage of visceral lesions (confirmed PR)



Patient 052103 Baseline / 3rd On-study Scan

TNBC: Prior A/T; PD on prior taxane. Shrinkage of visceral lesions (confirmed PR)



References

Von Hoff DD, Jameson GS, Borad MJ et al. First Phase 1 trial of NKTR-102 (Peg-Irinotecan) reveals early evidence of broad anti-tumor activity in three different schedules. Presented at the 20th EORTC-NCI-AACR Symposium on "Molecular Targets and Cancer Therapeutics" Meeting, Oct 21-24, 2008, Geneva, Switzerland.
Xie R, Mathijssen RHJ, Sparreboom A, et al. Clinical pharmacokinetics of irinotecan and its metabolites: A population analysis. J Clin Oncol 20 (15): 3293-3301, 2002
Vergote IB, Micha JP, Pippitt Jr. CH, Rao GG, Spitz DL, Reed N, Dark GG, Garcia A, Maslyar DJ, and Rustin GJ. Phase II study of NKTR-102 in women with platinum-resistant/refractory ovarian cancer. J Clin Oncol 28:15s, 2010 suppl; abstr 5013.

Safety

Safety: Summary of Drug Related AEs

Most Common Drug-related Grade 3 and 4 Adverse Events > 5% or event of interest N (%)	NKTR-102 145 mg/m² q14d N=35		NKTR-102 145 mg/m² q21d N=35	
	Grade 3	Grade 4	Grade 3	Grade 4
Diarrhea	6 (17%)	1 (3%)	8 (23%)	0
Neutropenia	2 (6%)	2 (6%)	3 (9%)	1 (3%)
Fatigue	4 (11%)	0	3 (9%)	0
Dehydration	2 (6%)	0	3 (9%)	0
Asthenia	2 (6%)	0	0	0
Lymphopenia	2 (6%)	0	0	0
Vomiting	2 (6%)	0	0	0
Neutropenic sepsis	0	0	1 (3%)	0
Febrile neutropenia	0	0	1 (3%)	0

*Grade 2 diarrhea occurred in 11% (q14d) and 11% (q21d) respectively
2 treatment-related deaths: sepsis (q21d) and acute renal failure following diarrhea (q14d)

Other Safety: Neuropathy and Alopecia

No grade 3 or 4 neuropathy was reported

	NKTR-102 145 mg/m² q14d N=35		NKTR-102 145 mg/m² q21d N=35	
	Grade 1	Grade 2	Grade 1	Grade 2
Alopecia	6 (17%)	0	3 (9%)	1 (3%)

Safety: Time Course of Diarrhea and Neutropenia

	NKTR-102 145 mg/m² q14d N=35	NKTR-102 145 mg/m² q21d N=35
Diarrhea (≥Grade 3) Dose 1 and/or 2 Dose 3 and/or 4 Onset Time, Median (Range) days	 9% 0% 88 (1-121)	 3% 14% 99 (8-131)
Neutropenia (≥Grade 3) Dose 1 and/or 2 Dose 3 and/or 4 Onset Time, Median (Range) days*	 3% 0% 98 (15-188)	 3% 6% 60 (28-140)

*Anti-diarrheals given therapeutically; no prophylactic anti-diarrheals administered

Conclusion

- High confirmed objective response rate (29% overall; 32% q14d; 26% q21d) with a preliminary PFS estimate of 20 weeks with single-agent NKTR-102 in 2nd/3rd line in patients with advanced breast cancer pre-treated with anthracycline and taxane +/- capecitabine
- Anti-tumor activity similar for both schedules
- The confirmed response rate is maintained in heavily pre-treated and poor prognosis subsets
  - A/T/C pre-treated: 33%
  - Triple negative: 39%
  - Visceral disease: 29%
- Side effects generally manageable with dose limiting toxicity consisting primarily of Grade 3 diarrhea (20-23%) typically occurring after 3 months of therapy for both schedules
- NKTR-102 is being evaluated in multiple cancer indications as a single and combination agent. Phase 3 planning is underway in ovarian and breast cancers.

33rd Annual CTRC-AACR San Antonio Breast Cancer Symposium, December 8 - 12, 2010, San Antonio, TX
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