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Enhanced anti-tumor effects of TP300, a novel camptothecin analogue, in combination with other anti-tumor agents in human tumor xenograft models

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Background: TP300 is a novel DNA topoisomerase I inhibitor currently in phase 1 clinical trial. It is a water-soluble prodrug administered by *iv* infusion. It is stable in an acidic formulation (ca. pH 3–4) but is rapidly converted to the lipophilic active form (CH0793076), at physiological pH. This pH dependent conversion could minimize individual variation in pharmacokinetics and toxicity derived from the efficiency of prodrug conversion. TP300 showed significantly greater anti-tumor activity than CPT-11 in both CPT-11-sensitive and -insensitive tumor xenograft models. The potency of TP300 in combination with six anticancer drugs, capecitabine, platinum agents (cisplatin, carboplatin, oxaliplatin), bevacizumab and cetuximab, was assessed in seven human cancer xenograft models.
Methods: The following tumors were transplanted into athymic nude mice: HCT116, WiDr, HT-29, HCT-8 and COL-16-JCK (colorectal); Calu-6 (lung); NCI-N87 (gastric). TP300 was administered *iv* bolus once per week for 6 weeks. Capecitabine was given orally for 2 cycles of daily dosing, each of 14 days followed by 7 days' rest. Platinum agents were administered *iv* bolus every other week (oxaliplatin) or every three weeks (cisplatin and carboplatin) for 6 weeks. Bevacizumab and cetuximab were administered by *ip* twice a week for 6 weeks.
Results: TP300 in combination with capecitabine produced synergistic and additive effects on the anti-tumor activity, including synergistic effects in the HCT116 and NCI-N87 xenograft models and an additive effect in the WiDr xenograft model, which is CPT-11-insensitive and BCRP-positive. Synergistic effects were more noticeable when TP300 was combined with platinum agents causing strong tumor remission in the COL-16-JCK and Calu-6 xenograft models. TP300 showed additive effects when combined with monoclonal antibodies such as bevacizumab (anti-VEGF) and cetuximab (anti-EGFR) in the HT-29 and HCT-8 xenograft models, respectively. For all these combinations, the effects were seen at doses which were not associated with any marked toxicity, there being no marked body weight loss during the dosing period.
Conclusion: TP300, a pH-activated water-soluble prodrug, displays additive to synergistic anti-tumor effects when combined with other anticancer drugs in human tumor xenograft models, at doses without any marked toxicity. The results support clinical investigation of TP300 with combination settings in indications such as colorectal, gastric and lung cancers.

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First Phase I trial of NKTR-102 (PEG-irinotecan) reveals early evidence of broad anti-tumor activity in three schedules

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Background: NKTR-102 is a novel PEGylated form of irinotecan. In xenograft studies, NKTR-102 has superior anti-tumor activity and significantly increased tumor levels of the active metabolite SN38 compared with irinotecan. Three single agent phase I schedules are being evaluated: weekly ×3 q4 weeks (w×3 q4w, complete), q14 days and q21 days (ongoing). For each schedule, the objectives were to establish the maximum tolerated dose (MTD)/recommended phase II dose (RP2D) and to characterize the safety and pharmacokinetic (pk) profile in patients (pts) with refractory solid tumors.
Materials and Methods: Pts with advanced solid tumors whose tumors had failed prior treatment options received 90 minute infusions of NKTR-102. Cohorts of 3 to 12 pts per dose cohort within each treatment schedule were treated. Serial plasma concentrations of NKTR-102, irinotecan, SN38 and SN38-glucuronide were quantified by LC-MS/MS.
Results: Drug-related toxicities for the 3 schedules, as observed in any course, are summarized in the table.

Table 1. Number of pts enrolled, and number of pts with diarrhea or neutropenia.

Dose level	Schedule: w×3 q4w					Schedule: q14 days					Schedule: q21 days				
(mg/m^2)	Enrolled	Diarrhea G3	Diarrhea G4	Neutropenia G3	Neutropenia G4	Enrolled	Diarrhea G3	Diarrhea G4	Neutropenia G3	Neutropenia G4	Enrolled	Diarrhea G3	Diarrhea G4	Neutropenia G3	Neutropenia G4
58	3	0	0	0	0	–	–	–	–	–	–	–	–	–	–
115	6	1	0	0	0	–	–	–	–	–	–	–	–	–	–
144	6	2	0	3	0	3	3	0	0	1	3	0	0	0	0
173	14	7	0	3	0	3	0	0	0	0	3	0	0	0	0
230	3	3	0	1	0	–	–	–	–	–	–	–	–	–	–

Thirteen pts had transient, self-limited visual disturbances (floaters) associated with dosing. One pt had G2 alopecia.
On the w×3 q4w schedule, the dose limiting toxicity is diarrhea. At 144 mg/m^2, 2 pts had coexistent G3 diarrhea and G3 neutropenia. Therefore, the MTD/RP2D was identified as 115 mg/m^2. Cumulative SN38 exposures (AUC $_{(0-tlast)}$) on the w×3 q4w schedule were approximately 3-fold higher than those predicted for irinotecan at equivalent doses and schedule. The other schedules are ongoing.
Significant anti-tumor activity was seen with a total of 7 PRs and 6 MRs in 44 patients:

- w×3 q4w: 3 PRs (SCLC, NSCLC, cervix), 4 MRs (esophageal, adrenocortical, Hodgkin's disease, ovarian)
- q14 days: 3 PRs (ovarian [uPR], maxillary sinus, bladder [transitional cell carcinoma with small cell infiltrates]), 2 MRs (breast ×2)
- q21 days: 1 PR (breast [uPR], ongoing)

Conclusions: NKTR-102 has an encouraging level of activity in a broad spectrum of tumors. On the w×3 q4w schedule, cumulative SN38 exposures were approximately 3-fold higher than those predicted for irinotecan at equivalent doses and treatment schedule. At the w×3 q4w schedule MTD/RP2D of 115 mg/m^2, toxicity is manageable. Diarrhea is dose limiting. The q14 and q21 day schedules are ongoing. Phase I and II studies of NKTR-102 are underway and planned.

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The topoisomerase I inhibitor gimatecan exhibits synergistic activity with temozolomide and tyrosine kinase inhibitors in malignant glioma xenografts

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Background: The novel oral lipophilic camptotecan gimatecan (ST1481; NVP-LBQ707) has shown to irinotecan and topotecan superior activity against several human cancer cell lines and xenografts.
Materials and Methods: We evaluated gimatecan in microemulsion in vivo against subcutaneous xenografts derived from primary malignant gliomas alone and combined with temozolomide, tyrosine kinase inhibitor imatinib mesylate, mTOR inhibitor everolimus and EGFR/VEGF tyrosine kinase inhibitor AEE788.
Results: Gimatecan 0.05–0.25 mg/kg/d administered orally q5 d/w x 4 weeks exhibited dose-dependent activity against all three gliomas. High sensitivity in the TP53 wild-type IGRG93 was associated with significant induction of apoptotic cell death and lack of p21 induction. Synergistic activity of gimatecan was observed with temozolomide 50 mg/kg/d q5 d without enhanced toxicity. Furthermore, gimatecan exhibited synergistic activity with imatinib 150 mg/kg/d q5 d/w x 4 weeks and everolimus 5 mg/kg/d q3 d/w in the PDGFRA gene amplified IGRG93 resulting in 100% tumor regression and more significant tumor growth delays (TGDs) (>66.0 and 57.8 days; $p < 0.001$, observed/estimated TGD ratio 1.75 and 1.31, respectively), compared to gimatecan alone (TGD 32.5 days; $p < 0.01$), although both agents were inactive alone (TGD 9.2 and TGD 6.6 days, respectively). Synergy with imatinib was also found in the TP53 wild-type, PDGFR non-amplified IGRG121 (100% tumor regression, TGD 49.6 days ($p < 0.001$), observed/estimated TGD ratio 1.30) compared to gimatecan alone (50% regression, TGD 46.6 days), but not with everolimus (1 PR of 6 tumors, TGD 42.6 days). Further evaluations are ongoing on synergy mechanisms.
Although gimatecan and AEE788 50 mg/kg/d q3 d/w x 4 weeks were both highly active against the TP53 mutant, EGFR gene amplified IGRG88