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Phase I study of NGR-hTNF, a vascular targeting agent (VTA), in combination withcisplatin in refractory patients (pts) with solid tumours

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Background: NGR-hTNF is a VTA consisting of TNF-a fused to the tumour-homing peptide (NGR) able to selectively binds an aminopeptidase N overexpressed on tumour blood vessels. Low-dose NGR-hTNF displayed significant preclinical synergism with cisplatin.
Methods: Pts with resistant/refractory solid tumours received NGR-hTNF given with a low-dose, doubling-dose scheme (0.2−0.4−0.8−1.6 μg/sqm) as 1-hour intravenous infusion, in combination with a fixed-dose of cisplatin 80 mg/sqm. Both drugs were given every 3 weeks. A 3+3 design was followed. Any grade 3−4 toxicity related to NGR-hTNF was defined dose-limiting toxicity (DLT). Sampling for pharmacokinetics (PK) and pharmacodynamics (soluble TNF-receptors, sTNF-R1 and 2) was done during the first 3 cycles.
Results: 22 pts (median age, 60 years; M/F 14/8; PS 0/1 12/10) with various solid tumors were evaluated over 77 cycles (range, 1−10). The median number of prior regimens was 3 (range, 1−6) and 12 pts (55%) were platinum-pretreated. NGR-hTNF C_{max} and AUC increased dose-proportionally ($r^2 = 0.91$, $p = 0.0001$ and $r^2 = 0.67$, $p = 0.001$, respectively). No shedding of sTNF-Rs was noted up to 0.8 μg/sqm. Higher and faster peaks of sTNF-R1 ($p = 0.001$) and sTNF-R2 ($p = 0.0001$) were observed at 1.6 μg/sqm than at lower doses. A correlation was detected between first-cycle NGR-hTNF exposure and sTNF-R2 AUC ($r = 0.64$, $p = 0.005$), while no relationship was noted for sTNF-R1. The combination was safely administered without PK interaction or worsening of platinum toxicity. Consistently with the low doses tested, MTD was not reached. No DLTs were recorded at 0.2 μg/sqm (n = 4), 0.4 μg/sqm (n = 3) and 1.6 μg/sqm (n = 3). At 0.8 μg/sqm, a transient grade 3 infusion reaction was registered. This cohort was expanded to 6 pts for safety check with no further DLT, and to 12 pts for activity assessment. At this dose, 2 lung cancer pts, both platinum-pretreated, achieved a partial response (−79%) and a significant tumor shrinkage (−28%), lasting 7.2 and 6.7 months, respectively. An additional 4 pts had stable disease for a median time of 6.4 months. The median progression-free survival for all pts (n = 22), for pts enrolled at 0.8 μg/sqm (n = 12), and for platinum-pretreated pts (n = 9) were 2.7, 4.7, and 4.3 months, respectively.
Conclusion: The combination of NGR-hTNF 0.8 μg/sqm with cisplatin is well-tolerated and shows promising activity.

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A phase I study of continuous and intermittent schedules of lapatinib in combination with vinorelbine in solid tumors

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Background: A phase I trial (UCD #171) of combination vinorelbine (VIN) and lapatinib was conducted to evaluate two schedules of EGFR inhibition, based on in vitro data.
Methods: Patients with advanced solid tumors and ⩽2 prior chemotherapeutic regimens were eligible. No prior VIN, lapatinib, or EGFR1-targeted agent was allowed. Prior trastuzumab was allowed. Patients were accrued in cohorts of 3 to alternating arms (see table).
Dose limiting toxicity (DLT) was defined as: grade 4 platelets, grade 3 platelets with bleeding or transfusion, febrile neutropenia, or any ⩾grade 3 non-hematologic toxicity related to study drugs.
Results: 51 patients with advanced solid tumors were treated, 33 on Arm A and 18 on Arm B. The most common cancer types included breast cancer (18), prostate (8), and non-small cell lung cancer (5). Median number of prior chemotherapy regimens was 2. Median age was 61 years (range 29−85), 63% were female, and median ECOG PS was 0 (range 0−2). Patients received a median of 2 cycles (range 1−17) of protocol therapy with 3 patients still receiving active treatment (range 5−17 cycles), 2 on ARM A and 1 on ARM B. 41 patients were evaluable for DLT, which included: 1 each grade 3 infection, diarrhea and febrile neutropenia on Arm A and 1 each grade 3 bone pain and fatigue on Arm B. The most common grade 3/4 hematologic toxicity was neutropenia, seen in 42% of patients in Arm A and 72% in Arm B. The most common 3/4 non-hematologic toxicity was diarrhea in 3 patients and rash in 1 patient. The maximum tolerated dose (MTD) for Arm A was VIN 20 mg/m^2 and lapatinib 1500 mg; for Arm B, VIN 25 mg/m^2 and lapatinib 1500 mg. Of the 41 patients evaluable for response, 2 had a complete response (CR) (1 each Arm), 3 had partial response (1 Arm A, 2 Arm B), 19 had stable disease (11 Arm A, 8 Arm B), and 17 had PD. Both patients with CR had HER2/neu positive breast cancer.

Dose level	Lapatinib (mg)	Vinorelbine (mg/m^2)
ARM A (continuous)	daily × 28 days	D1, 8 and 15
1	250	20
2	500	20
3	1000	20
4	1250	20
5	1500	20
6	1500	25
ARM B (intermittent)	days 2−5, 9−12, and 16−25 q 28 days	D1, 8 and 15
1	1250	20
2	1500	20
3	1500	25
4	1750	25

Conclusions: We report the first completed phase I trial testing the combination of lapatinib and VIN. The combination is feasible and well-tolerated on both schedules. A phase II trial for second-line metastatic HER2/neu positive breast cancer at ARM A MTD is ongoing.
The co-authors were responsible for the concept and design and all data analysis and interpretation for this study. Glaxo-Smith-Kline supplied lapatinib.

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Cediranib (an oral, highly potent VEGF signalling inhibitor) in combination with saracatinib (AZD0530; a potent, selective Src inhibitor): a phase I open-label study in patients with advanced solid tumours

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Background: Combining targeted agents with different mechanisms of action may be a useful approach to develop more effective cancer treatments. Initial results of the present study (study codes NCT00475956; 2171IL/0014) indicated cediranib (RECENTIN™) 45 mg/day as the maximum-tolerated dose (MTD) in combination with saracatinib (Trarbach T *et al. J Clin Oncol* 2008:26(15S):abst 3592). The primary objective was to evaluate the safety and tolerability of combination treatment with cediranib and saracatinib. Secondary assessments included pharmacokinetics (PK) and preliminary efficacy (RECIST).
Materials and Methods: Patients with advanced solid tumours refractory to standard therapies received cediranib 20, 30 or 45 mg/day for 7 days followed by daily treatment with cediranib at the same dose in combination with saracatinib 175 mg/day. The PK profiles of cediranib and saracatinib were investigated in the cohort expansion at the MTD.
Results: Thirty-nine patients were treated with cediranib (20 mg, n = 6; 30 mg, n = 6; 45 mg, n = 27), including 20 patients in the cohort expansion at the MTD (cediranib 45 mg/day with saracatinib 175 mg/day). The most common primary tumour type was colorectal cancer (n = 12). All three dosing regimens met the protocolled criteria for being tolerated, however cediranib 45 mg was found to be less sustainable on chronic dosing; 59% of patients required a dose reduction or pause with a median time to dose reduction or pause of approximately 50 days. This level of dose reductions and pauses was not seen with cediranib 20 or 30 mg. Overall, the most common adverse events (AEs) were hypertension (67%), diarrhoea (62%), dysphonia (41%) and fatigue (39%). Diarrhoea and fatigue were also the most common CTC grade ⩾3 AEs (both 13%). There was no evidence of a clinically significant effect of saracatinib on cediranib PK and vice versa. Efficacy data showed 22/35 evaluable patients had a best overall response of stable disease (cediranib 20 mg, n = 6 [100%]; cediranib 30 mg, n = 3 [50%]; cediranib 45 mg, n = 13 [48%]).
Conclusions: All doses met the protocolled criteria for being tolerated; cediranib 20 and 30 mg/day in combination with saracatinib were more sustainable and have been identified for future studies. When used in combination cediranib and saracatinib PK data were comparable with historical monotherapy data, and there was evidence of antitumour activity.