ESMO 2008 - Abstract 483P

MOLMED

Phase Ib study to define the optimal low dose of NGR-hTNF, a novel vascular targeting agent (VTA), in combination with cisplatin in patients with solid tumours

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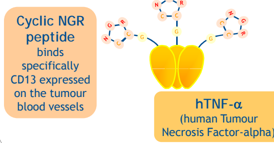
ABSTRACT

Background: NGR-hTNF is a VTA exploiting a tumour-homing peptide (NGR) that selectively binds to aminopeptidase N/CD13 highly expressed on tumour blood vessels. At low doses, NGR-hTNF combines activity on tumour vascular permeability and direct anticancer activity. Consistently, preclinical data indicate significant synergy between low doses of NGR-hTNF and cisplatin. **Methods**: Pts with refractory solid tumours were treated with low doses (20-200 fold lower than MTD) of NGR-hTNF given with a doubling-dose scheme (0.2-0.4-0.8-1.6 μg/m²) as 1-hour intravenous infusion, in combination with cisplatin 80 mg/m2, both given every 3 weeks. A 3+3 escalation/de-escalation design was followed. Blood samples for PK analysis were collected after the first 3 cycles. Definition of DLT: any severe (G3-4) toxicity clearly related to NGR-hTNF. **Results**: 19 pts (median age: 59 years [range, 47-73]; 13M/6F; ECOG PS 0/1 10/9) were enrolled. Tumour types were: colorectal (6 pts), NSCLC (5), mesothelioma (4), sarcoma (2), and melanoma (2). Median number of prior regimens was 3 (range, 1-6), with 9 and 6 pts pre-treated with platinum- and oxaliplatin-based regimens, respectively. Both NGR-hTNF Cmax and AUC increased linearly with dose. The combination was safe without PK interaction or exacerbation of platinum-associated toxicity profile. As expected for the low doses explored, MTD was not reached and no DLTs were registered at 0.2 μg/m² (n=4), 0.4 μg/m² (n=3) and 1.6 μg/m² (n=3). At 0.8 μg/m² (n=8), a pt experienced a G3 transient acute infusion reaction, not surely dose-related. Nevertheless, this cohort was expanded up to 6 pts for safety reasons, with no DLTs registered, and subsequently up to 12 pts, for preliminary anti-tumour activity evaluation. At this DL, two NSCLC pts, with documented PD after platinum-based regimens, achieved a confirmed PR and a significant tumour shrinkage (-28%), and two pts with rectal cancer and sarcoma had SD lasting 20+ and 12+ weeks, respectively. **Conclusion**: The combination of NGR-hTNF 0.8 μg/m² with cisplatin 80 mg/m2 shows a manageable toxicity profile and promising preliminary antitumour activity.

Background

- A large body of preclinical evidences have shown that tumour necrosis factor-alpha (TNF-α) has potent antitumour activity. However, its clinical use has been hampered by severe systemic toxicity, with MTD significantly lower than ED in humans[1]
- The antivascular effects of TNF-α provided the rationale for developing a vascular targeting strategy aimed at increasing the local antitumour activity
- NGR-hTNF is a novel vascular targeting agent (VTA) that has been genetically engineered by coupling the N-terminus of human TNF-α with the C-terminus of the tumour-homing peptide Cys-Asn-Gly-Arg-Cys (NGR) (Figure 1)
- The cell surface receptor for the NGR-containing peptide is a CD13/aminopeptidase N (APN) isoform selectively expressed by endothelial cells of newly formed human tumour vessels[2-4]

Figure 1. Recombinant fusion protein consisting of NGR peptide and human Tumour Necrosis Factor-alpha (hTNF-α)



- NGR-mTNF was found to have antitumour activity also at doses in the picogram range (equivalent to a dose of 0.2 μg/m² in humans) in preclinical model[4], without induction of circulating TNF receptors shedding (Figure 2)
- Additionally, low doses of NGR-mTNF significantly increased the antitumour activity of cisplatin, with maximal synergism being observed with a 2-hour delay between NGR-TNF and cisplatin administration[5](Figure 3)

Figure 2. Low doses of NGR-TNF do not induce sTNF-R2 shedding while triggering antitumour effects

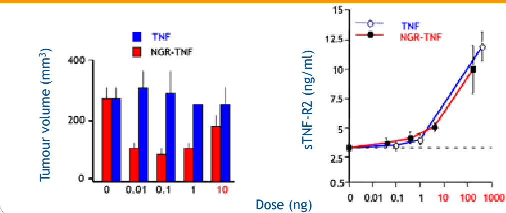
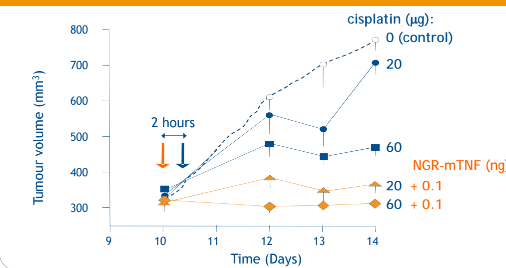


Figure 3. Synergistic antitumour activity of NGR-TNF mTNF with cisplatin

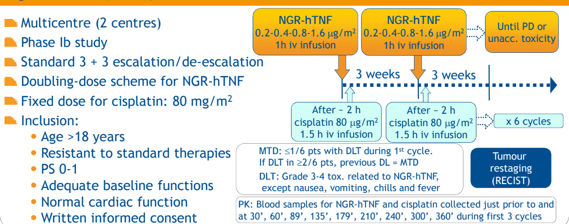


Phase I trials

- In a phase I study evaluating a dose-interval ranging from 0.2 to 60 μg/m² the MTD of NGR-hTNF was established at 45 μg/m² when given as single agent once every 3 weeks[6]
- Conversely, a further phase I trial exploring the low-dose range of NGR-hTNF from 0.2 to 1.6 μg/m², selected the dose of 0.8 μg/m² as the optimal biological dose, based on dynamic imaging changes and preliminary antitumour activity[7]

Methods

Figure 4. Study design, dose and assessment



Results

- From July 2007 to April 2008, 22 patients resistant or refractory to standard treatments were enrolled
- Baseline characteristics were: Male/Female 14/8; ECOG PS 0/1 12/10; median age 60 years (range 47-75)
- Median number of prior regimens was 3 (range 1-6), with 9 patients (41%) pre-treated with ≥4 regimens
- 12 patients (55%) had previously received a platinum-based regimen, and 7 additional patients (32%) an oxaliplatin-based regimen

Safety

- A total of 73 cycles were administered (median 2, range 1-10). Eight patients (36%) have received ≥4 cycles
- Overall, 205 treatment-emergent adverse events (AEs) were reported and the majority were of grade 1 (58%) or grade 2 (30%) severity. 25 grade 3 (12%) and 1 grade 4 were noted. Most common were nausea, vomiting, chills and fatigue
- Only 21 AEs (10%) were considered NGR-hTNF-related, and the most frequent was chills, with 15 events (7%) experienced by 8 patients (36%) (Table 1). This event generally occurred approx 30' after the start of 1st infusion and lasted about 20'
- Neither grade 4 treatment-related AEs nor toxicity-related deaths were observed in the study population
- At 0.8 μg/m2, a grade 3 acute infusion reaction (dyspnea and hypoxia) was noted. Though this AE was not surely dose-related, the cohort was expanded up to 6 patients for safety reasons, with no subsequent DLT observed
- Considering that dose level 0.8 μg/m² was previously selected for phase II development as single-agent in the low-dose range, the cohort has been further expanded up to 12 patients, for preliminary antitumour activity evaluation

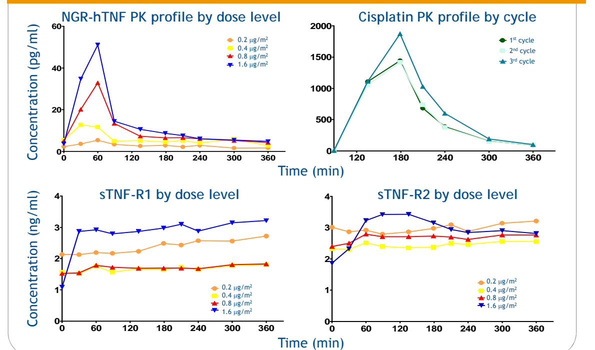
Table 1. Adverse events related to NGR-hTNF by number of patients

Event	Grade 1	Grade 2	Grade 3	Grade 4
Chills	6 (27%)	2 (9%)	-	-
Vomiting	2 (9%)	-	-	-
Dyspnea	-	-	1 (4%)	-
Headache	-	1 (4%)	-	-

Pharmacokinetics

- Both NGR-hTNF Cmax and AUC increased in a dose-proportional manner and there was no apparent interaction with cisplatin PK parameter (Figure 5)
- At 0.2-0.4-0.8 μg/m², the levels of both TNF receptors were scattered around baseline values, indicating neither stimulation nor inhibition of NGR-hTNF on the receptor concentrations
- Stimulation of both receptors was only observed after 1.6 μg/m²

Figure 5. Pharmacokinetic profile of NGR-hTNF, cisplatin and soluble TNF receptors R1 and R2



Antitumour activity

- 16 patients had at least a tumour restaging after 2 cycles and were assessable for response (Table 2)
- At DL 0.8 μg/m², a confirmed PR was observed in a 73-year-old male patient with NSCLC previously treated with cisplatin. At this DL, an additional lung cancer patient pretreated with 6 regimens had a significant tumour shrinkage (-28%) lasting 6.7 months
- Six patients had SD with a median duration of 4.5 months (range 4.0-6.7 months)
- 6-month PFS rate for the ITT population was 37%

Table 2. Patient characteristics and preliminary antitumour activity by DL

DL (μg/m²)	Pt #	tumour type	Age	PS	N° prior regimens	Prior regimen based on platinum/oxaliplatin	BOR to last regimen/ TTP (months)	Cycles	BOR	SD/PR duration (months)
0.2	1	MPM	59	1	2	platinum	PD/1.5	1	NA	-
	2	Colorectal	56	0	5	oxaliplatin	SD/11.6	2	PD	-
	3	Melanoma	47	0	1	platinum	SD/8.0	2	PD	-
	4	Melanoma	58	1	1	platinum	SD/5.6	1	NA	-
0.4	5	Lung	52	1	3	platinum	PD/3.1	1	NA	-
	6	Sarcoma	49	0	1	-	SD/10.6	2	PD	-
	7	MPM	55	1	3	platinum	PD/0.5	2	PD	-
0.8	8	Colorectal	60	1	6	oxaliplatin	PD/4.5	5	SD	4.6
	9	MPM	65	1	3	platinum	PD/1.2	1	NA	-
	10	Sarcoma	48	0	2	-	NA/4.9	4	SD	4.0
	11	NSCLC	60	0	6	platinum	PD/2.5	8	SD	6.7
	12	Colorectal	69	0	4	platinum	PD/3.7	2	PD	-
	13	NSCLC	73	0	1	platinum	PR/8.9	9	PR	5.8+
	17	Colorectal	65	1	5	platinum	PD/2.7	2	PD	-
	18	Colorectal	70	1	5	platinum	PD/2.3	1	NA	-
	19	Colorectal	58	1	5	-	PD/2.6	2	PD	-
	20	Pancreas	75	0	3	oxaliplatin	SD/5.2	6	SD	5.2+
	21	Hepatic duct	60	0	2	platinum	SD/4.2	1	NA	-
	22	Gastric	57	0	4	platinum	PD/2.4	6	SD	4.1+
1.6	14	Carcinoid	67	1	1	platinum	SD/9.8	5	SD	4.1
	15	SFTP	51	0	4	oxaliplatin	SD/12.6	7	SD	5.2
	16	NSCLC	62	0	2	platinum	PD/1.1	2	PD	-

DL=dose level; PS=performance status; BOR=best overall response; TTP=time to progression; SD=stable disease;PR=partial response; PD=progressive disease;NA=not assessed; SFTP=solitary fibrous tumour of the pleura; NSCLC=non-small cell lung; MPM=malignant pleural mesothelioma

Conclusions

- NGR-hTNF administered at low doses in association with cispatin was safe without apparent PK interaction or exacerbation of platinum-associated toxicity
- As expected for using a low-dose range of NGR-hTNF, MTD was not reached
- Combination of NGR-hTNF 0.8 μg/m² with cisplatin 80 mg/m² showed promising preliminary antitumour activity also in platinum-pretreated patients and will be further developed in selected tumour types

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Acknowledgements

- Istituto Scientifico San Raffaele: G. Donadoni, G. Rossoni, A. Zanoni
- Istituto Europeo di Oncologia: L. Ariu
- MolMed: C. Ammannati, S. Colombi, A. Troysi