Background

TNF-α has shown potent antitumoral and antitumor effects, but its clinical development has been hindered by severe toxicity.

NGR-TNF consists of TNFα fused with the tumor-homing peptide HGR(2)

NGR selectively binds CD33 overexpressed on tumor blood vessels.

In a previous phase I trial, the maximum tolerated dose (MTD) of HGR-TNF was established at 45 μg/m² when given as 1-hour intravenous infusion every 3 week (q3w).

Dose limiting toxicity (DLT) were grade 3 infusion related reactions.

In the present trial, further dose escalation was explored using:
- longer infusion time (2 hours)
- mid-premedication (paracetamol 1,000 mg hr)
- 4 patients enrolled at each of 11 dose levels (SI):
  - 60-80-100-120-130-150-170-200-250-300-350 μg/m²

Study design

Inclusion criteria:
- patients (≥ 18 years) with solid tumors refractory to standard therapies
- performance status (PS) 0-1
- ATD definition:
  - if ≥ 1/4 patients with DLT during 1st cycle: further dose escalation
  - if < 1/4 patients with DLT during 1st cycle: prior DL declared as ATD
- ATD definition:
  - grade 3-4 drug-related toxicity
  - exceptions: R/V, chills, and fever (quickly controlled with therapy)

Baseline characteristics

Sample size:
55 patients enrolled
Tumors:
50 colorectal (84%), 5 neuroendocrine (9%), 4 gastric (7%), 2 sarcomas (4%), 1 mesothelioma (2%)

Methods and results

PKs and kinetics of soluble TNF receptors (sTNF-α)

Baseline K
trans
= Volume transfer constant between plasma and extravascular space

IAUGC = Initial area under gadolinium concentration agent

Cmax and AUC of NGR-TNF increased proportionally with dose (p=0.0001 and p=0.0001, respectively).

Levels of TNF-α peaked significantly higher than those of TNF-α (median, 10.1 vs. 1.3 ng/mL; p=0.001, Mann-Whitney test).
Changes in TNF-α, however, did not differ across DLs

Conclusions

NGR-TNF can be safely delivered at doses higher than prior ATD using a mild premedication and a longer infusion time.

NGR-TNF at high doses induces low receptor shedding and early antitumoral effects.

The plateau at the shedding kinetics of receptors suggests that high doses can overcome this counterregulatory effect.

Antitumoral effects were observed in 60% of patients with an apparent dose relationship.

Further information on the nature of antitumoral effects and antitumoral mechanisms is ongoing.

Further dose escalations are ongoing at doses > 300 μg/m².