A four-arm randomized phase II trial with NGR-hTNF given at low or high dose with or without doxorubicin in soft tissue sarcomas (STS)

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Background

- NGR-hTNF (asparginyl-glycine-arginine human tumor necrosis factor) is a tumor-targeting antivascular agent, selectively binds to CD13-expressing tumor vessels, and displays a low-dose-response curve, with antitumor activity shown at very low dose (LD) or high dose (HD) with very low toxicity.
- Antitumor effects of NGR-hTNF at LD are mainly driven through induction of necrosis, while at HD, stabilization was observed that included both intratumoral desvascularization and T-cell infiltration.
- Two previous phase I studies established the optimal biological dose (OBD) and the maximum tolerated dose (MTD) of NGR-hTNF at 0.8 μg/m² and 45 μg/m², respectively.

Study design

- Open-label, 4-arms randomized phase II trial evaluating OBD and MTD of NGR-hTNF either alone or in combination with doxorubicin standard-dose (D).
- Study target population: STS patients previously untreated or pretreated with one or more systemic regimens.
- ECOG performance status of 0 to 2.
- Primary endpoint: progression-free survival (PFS).
- Secondary endpoints: overall survival (OS), disease control rate, tumor atrophy, and overall response, as assessed by RECIST criteria.
- Stratification factors: prior cumulative D dose (≤ 150 mg/m²), histology (vascular or nonvascular sarcoma).
- Treatment arms:
  - Arm A: NGR-hTNF 0.8 μg/m² ≤ prior disease progression (D) (B) NGR-hTNF 45 μg/m² ≤ prior disease progression (D).
  - Arm B: NGR-hTNF 0.8 μg/m² > prior disease progression (D) (B) NGR-hTNF 45 μg/m² > prior disease progression (D).
- Hypothesis testing:
  - Stages 1 and 2: minimum design, with each regimen rejected if ≤ 2/5-2/6 patients (for stage I) or ≤ 2/5-2/6 patients (for stage II).
  - Stages 3 and 4: progression-free of 3 months.

Changes in SUVmax by PET imaging

PFS for all patients

PFS for pretreated patients

OS for all patients

OS for pretreated patients

Results and Conclusions

- After the first study stage (n=55), the primary endpoint was met only for NGR-hTNF 5 μg/m² doxorubicin (arm C), with 7 of 10 patients (70%) being PFS for 12 months.
- At the end of second stage study (n=69), median PFS was a combination of NGR-hTNF 0.8 μg/m² doxorubicin, while it was 1.4 for the other pooled arms (p=0.04 for trend).
- For arm C (n=28), median PFS and OS were 4.8 and 5.5 months, respectively, at the 5 months previously in untreated patients (n=17), respectively.
- Per RECIST criteria, SD was 57% for arm C and 29% for the other pooled arms (p=0.03 for trend), while no confirmed responses were reported among patients measurable by clinical criteria (n=24), 55% (p=0.05) had decreased or unchanged SUVmax, with 10 (21%) having a median response by ECOG-NPRG criteria, while 19 (44%) had increased SUVmax.
- The treatment with NGR-hTNF 0.8 μg/m² plus doxorubicin showed good tolerability profile and demonstrated a meaningful trend in PFS and overall survival rates, especially in pretreated patients that deserves further investigation in histology-driven trials.