

TUMOR CELL/VASCULAR CELL INTERACTIONS

FROM DESIGN TO CLINICAL PHASE 3 IN ONCOLOGY: CD13-TARGETED TISSUE FACTOR TTF-NGR AND TUMOR INFARCTION

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Introduction and Aim. This overview summarizes the development of CD13-targeted tissue factor (tTF-NGR) from its original design to clinical phase 3 in oncology.

Materials and Methods. A series of targeted tissue factors (TFs) were cloned and biotechnologically produced with various tumor endothelial cell and pericyte targets. They were tested in vitro and in vivo for pro-coagulatory activity, specific binding, tumor accumulation, vascular occlusion, inhibition of blood flow, therapeutic antitumor effects, toxicology in rodents and non-rodents, and in clinical studies.

Results. The lead compound tTF-NGR showed strong in vitro and in vivo activity, factor X activation, inducing tumor infarction, tumor growth inhibition and regression. Its preclinical efficacy was independent of tumor histology (melanoma, lung, breast, sarcoma, glioblastoma). Combination with cytotoxics such as doxorubicin or trabectedin (T) yielded combinatorial effects. A phase 1 trial in end-stage cancer patients defined the Maximum Tolerated Dose (MTD) at 3 mg/m² IV daily for 5 days, q day 22. Dose-limiting toxicities (DLT, grade 3 CTCAE) at higher doses were observed as troponin T hs elevation (early myocardial hypoxia) and reversible thromboembolic events. No grade 4 or 5 events occurred. In

a dose-finding cohort of 19 advanced soft-tissue sarcoma patients treated with T plus tTF-NGR, MTD was T 1.5 mg/m² over 24 h (day 1) plus tTF-NGR 1.0 mg/m² IV (days 2-3), q day 22. The recommended starting dose for phase 3 is tTF-NGR 0.5 mg/m² (days 2-3). At this dose, none of six patients had DLTs. Number of cycles per patient (RECIST result) were: 2 (PD, progressive disease), 3 (PD), 6 (PD), 12 (SD, stable disease), 14 (PR, partial response), 14 (SD). All SD patients had tumor shrinkage. Higher tTF-NGR doses or extended schedules led to grade 3 DLTs (troponin T hs rise, N-STEMI, thromboembolic events), all reversible upon anti-coagulation. Again, no grade 4 or 5 toxicities were seen. Pharmacokinetics show more and longer tTF-NGR in the plasma after T which explains MTD differences between monotherapy and combination therapy. Among 11 L-sarcoma patients completing at least one cycle, the Disease Control Rate (PR plus SD) was 63.6%.

Conclusions. CD13-targeted tTF-NGR demonstrates strong preclinical antitumor efficacy and a manageable safety profile with clinical anti-sarcoma activity when combined with T. A randomized phase 3 trial (1:1, T vs T plus tTF-NGR) is actively recruiting patients.