Background: NGR-hTNF is a VTA exploring a tumour-homing peptide (NGR) that selectively binds to aminopeptidase N/CD13 highly expressed on tumour blood vessels. NGR-hTNF combines activity on tumour vascular permeability and direct anticancer activity. In preclinical models, NGR-hTNF showed antitumour activity similar to that of the chemotherapeutic drug and at lower doses than standard treatments, including biological agents, were evaluated to enumerate a load of NGR-hTNF given at 0.8 µg/m² as 1-hour intravenous infusion every 3 weeks (q3w). This phase I trial had a 2-stage design with 16 and 27 pts to be enrolled in stage 1 and 2, respectively. Progression-free survival (PFS) was the primary and only point with tumour measurement performed q6w. Results: From January to May 2007, 32 pts with documented progressive disease after last therapy were enrolled. PFS characteristics were: 20 Pts (63%) ≥ median age 60 years, range 53-79; circulating tumour cells baseline value <3/7.5 mL, 12/38 %, 23-55; circulating tumour cells baseline value <3/7.5 mL, 12/38 %. Median time to progression was 2.3 months (range, 1.9-3.5). Median PFS was 2.6 months, 95% CI 1.9-3.5. Median PFS was 2.3 months and 0.8 months in pre-treated with <3 and ≥ median age, respectively. Objective response (tumour reassessment performed q6w) was achieved in 6/32 pts (18%). A significant increase of median PFS durations versus BSC were reported for ≥ median age (PFS) was the primary end point with tumour reassessment performed q6w. Conclusion: Inclusion: 16 M/16 F; PS 0/1 26/6; median age: 65 years, range 53-79; circulating tumour cells baseline value <3/7.5 mL, 12/38 %. Inclusion characteristics were: 16 M/16 F; PS 0/1 26/6; median age: 65 years, range 53-79; circulating tumour cells baseline value <3/7.5 mL, 12/38 %. Inclusion characteristics were: 16 M/16 F; PS 0/1 26/6; median age: 65 years, range 53-79; circulating tumour cells baseline value <3/7.5 mL, 12/38 %. A significant increase of median PFS durations versus BSC were reported for ≥ median age (PFS) was the primary end point with tumour reassessment performed q6w. Conclusion: Inclusion: 16 M/16 F; PS 0/1 26/6; median age: 65 years, range 53-79; circulating tumour cells baseline value <3/7.5 mL, 12/38 %. Inclusion characteristics were: 16 M/16 F; PS 0/1 26/6; median age: 65 years, range 53-79; circulating tumour cells baseline value <3/7.5 mL, 12/38 %. A significant increase of median PFS durations versus BSC were reported for ≥ median age (PFS) was the primary end point with tumour reassessment performed q6w. Conclusion: A significant increase of median PFS durations versus BSC were reported for ≥ median age. Although a 2-stage design was planned, a total of 111 cycles of therapy were administered with a median of 2 (range, 1 to 10) cycles per patient. Neither grade 3-4 treatment-related adverse events nor toxicity-related deaths were observed in the study population. The most common treatment-related adverse events were grade 1-2 nausea, vomiting, fatigue, constipation and disorders of taste. In the Kaplan-Meier plots for PFS and OS are depicted in Figures 4-5.

Efficacy

In the 1st stage of the study (n=16), one patient achieved after 4 cycles a PR lasting 5 months and 9/16 pts (56%) had SD as best response. Median and 3-month PFS in this cohort of patients were 2.9 months and 47%, respectively. Preliminary efficacy results after the 2nd stage (n=32) are reported in Tables 3-4.

Conclusions

InGBR-hTNF administered at low dose is safe and shows preliminary evidence of activity in heavily pretreated patients with advanced colorectal cancer. Noteworthy, the toxicity profile is limited to reversible and easily manageable constitutional symptoms, such as chills, generally occurring during the administration of the first infusion. NGR-hTNF is currently developed both as single agent, exploring a weekly schedule of administration, and in combination with a standard capcitabine and oxaliplatin regimen.