A phase I first-in-human study of Nesvacumab (REGN910), a fully-human anti-Angiopoietin-2 (Ang2) monoclonal antibody, in patients with advanced solid tumors.

Authors: Kyriakos P. Papadopoulos¹, Robin Kate Kelley², Anthony W. Tolcher¹, Albiruni Abdul Razak³, Katherine Van Loon², Amita Patnaik¹, Philippe L. Bedard³, Ariceli A. Alfaro², Muralidhar Beeram¹, Lieve Adriaens⁴, Carrie M. Brownstein⁴, Israel Lowy⁴, Ana Kostic⁴, Pamela A Trail⁴, Bo Gao⁴, A. Thomas DiCioccio⁴, Lillian L. Siu³

Authors’ Affiliations: South Texas Accelerated Research Therapeutics (START), San Antonio, TX¹; Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA²; Princess Margaret Cancer Centre, Toronto, ON³; Regeneron Pharmaceuticals, Inc., Tarrytown, NY⁴.

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Corresponding author: Kyriakos P Papadopoulos
South Texas Accelerated Research Therapeutics
4383 Medical Drive
San Antonio, TX 78229, USA

Email: Kyri.Papadopoulos@start.stoh.com

Tel: 210 593 5250

Fax: 210 615 1121

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Translational Relevance

Angiopoietin-2 (Ang2) expression is a key regulator of tumor angiogenesis and growth. Ang2, which functions as a ligand for vascular endothelial cell receptor tyrosine kinase Tie2, is upregulated in various cancers and associated with poor prognosis. Preclinically, Ang-2 inhibition results in decreased tumor vascularity and significant inhibition of human xenograft tumor growth. Furthermore, Ang2 inhibition potentiates the antitumor effects of anti-VEGF agents. Nesvacumab (REGN910) is a novel IgG1 fully human anti-Ang2 monoclonal antibody. This paper reports the first-in-human study of nesvacumab in patients with advanced tumors. The majority of analyzed tumors expressed Ang2, but none of several putative angiogenic biomarkers was informative for clinical efficacy. The manageable toxicity profile and preliminary evidence of antitumor activity support the further development of nesvacumab, particularly in combination with other targeted anti-angiogenic and cytotoxic therapies.
Abstract

Purpose: Nesvacumab (REGN910) is a fully human immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds and inactivates the Tie2 receptor ligand Ang2 with high affinity, but shows no binding to Ang1. The main objectives of this trial were to determine the safety, tolerability, dose-limiting toxicities (DLTs), and recommended phase 2 dose (RP2D) of nesvacumab.

Experimental Design: Nesvacumab was administered intravenously every two weeks (Q2W) with dose escalations from 1 to 20 mg/kg in patients with advanced solid tumors.

Results: A total of 47 patients were treated with nesvacumab. No patients in the dose escalation phase experienced DLTs, therefore a maximum tolerated dose (MTD) was not reached. The most common nesvacumab-related adverse events were fatigue (23.4%), peripheral edema (21.3%), decreased appetite and diarrhea (each 10.6%) (all grade ≤ 2). Nesvacumab was characterized by linear kinetics and had a terminal half-life of 6.35 to 9.66 days in a dose-independent manner. Best response by RECIST 1.1 in 43 evaluable patients included 1 partial response (adrenocortical carcinoma) of 24 weeks duration. Two patients with hepatocellular carcinoma had stable disease (SD) > 16 weeks, with tumor regression and >50% decrease in alpha-fetoprotein. Analyses of putative angiogenesis biomarkers in serum and tumor biopsies were uninformative for treatment duration.

Conclusion: Nesvacumab safety profile was acceptable at all dose levels tested. Preliminary antitumor activity was observed in patients with treatment-refractory advanced solid tumors. Based on cumulative safety, antitumor activity, PK and PD data, the 20 mg/kg dose was determined to be the RP2D.
INTRODUCTION

Inhibition of tumor angiogenesis, particularly with vascular endothelial growth factor (VEGF) /VEGF receptor antagonists, is a validated therapeutic approach for select oncologic indications (1-4). Angiopoietin-1 (Ang1) and angiopoietin-2 (Ang2), ligands for the vascular endothelial cell receptor tyrosine kinase Tie2 (5, 6), are proangiogenic factors selectively expressed during the angiogenesis process involved in tumor neovascularization (7, 8). Angiopoietin-1 appears to play a role in maturation and control of peripheral capillary permeability (9-11), while preclinical tumor models confirm that Ang2 is an important regulator of tumor angiogenesis and growth (12-16). Ang2 expression is upregulated in a range of human cancers (17-21), and high levels of circulating Ang2 are associated with a poor prognosis (22, 23).

Nesvacumab is a fully human immunoglobulin G1 (IgG1) VelocImmune® monoclonal antibody that selectively binds Ang2 with high affinity (24pM), blocks Ang2 binding to the Tie2 receptor; but does not bind to Ang1. In human tumor cell-line xenograft models, nesvacumab as a single agent demonstrated significant tumor growth inhibition in prostate adenocarcinoma (PC3), colorectal adenocarcinoma (Colo205), and epidermoid carcinoma (A431) (13). Non-human toxicology studies in Sprague Dawley rats and cynomolgus monkeys showed no direct, definitive adverse toxic insult to any organ of either species (data on file, Regeneron). The no-observed-adverse-effect levels (NOAEL) in rat and monkey dosed every other week were 50 mg/kg by the intravenous (IV) route and 10 mg/kg by the subcutaneous route, the highest nesvacumab doses evaluated for each route of administration in these studies.

Based on these data, the selected starting dose of nesvacumab for this phase 1 study was conservatively chosen as 1 mg/kg administered by IV infusion every 2 weeks. This first-in-
human phase 1 study (NCT01271972) reports the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) markers, preliminary antitumor efficacy, and recommended phase 2 dose for nesvacumab administered every 2 weeks (Q2W) in patients with advanced solid tumors.

PATIENTS AND METHODS

This multicenter, phase I, non-randomized, open-label study was conducted at two centers in the United States and one center in Canada. All patients provided written informed consent, and the study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and all applicable local regulatory requirements and laws.

Patient Eligibility

Eligible patients were ≥18 years, with histologically proven advanced solid malignancies, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, and adequate organ function. Exclusion criteria included uncontrolled hypertension (systolic blood pressure >150 mm Hg, diastolic blood pressure >95 mmHg), brain metastases, presence of any atypical T1 contrast enhancing brain lesions in brain MRI (protocol amendment implemented following an atypical brain MRI finding in an index patient with neurologic symptoms), serious non-healing wound or ulcer, active bleeding, significant cardiac event, and deep venous thrombosis or pulmonary embolism within 6 month prior to study enrollment. For patients with hepatocellular cancer (HCC), histologically proven disease was not required if classic tumor features were present on imaging consistent with accepted radiographic diagnostic criteria (24); HCC specific inclusion/exclusion criteria were also applicable (Supplementary Data).
Study Design and Treatments

Nesvacumab was administered as a 30-minute IV infusion every 2 weeks (Q2W) at planned doses of 1, 3, 6, 12, or 20 mg/kg in 28 day cycles. During the dose escalation phase to determine the MTD, enrollment was sequential and in a standard 3+3 design. Dose escalation was allowed if dose-limiting toxicity (DLT) occurred in 0/3 or \( \leq \frac{1}{6} \) patient in each cohort during cycle 1 (28 days). Patients not completing the first cycle for reasons other than DLT were considered non-evaluable and replaced. Expansion cohorts at candidate recommended phase 2 dose (RP2D) levels enrolled patients with advanced solid tumors (safety expansion cohorts) enriched for patients with HCC to further characterize safety and tolerability and assess preliminary antitumor activity. Enrichment for HCC in the expansion cohorts was a protocol amendment based on the observation of significant alpha-fetoprotein (AFP) decline and tumor regression in a patient with HCC treated in the dose escalation phase. Study treatment continued until disease progression, unacceptable toxicity (including DLT), or withdrawal of consent.

DLTs were defined during cycle 1, as any treatment-related grade 4 anorexia, nausea, vomiting, or diarrhea, or grade \( \geq 3 \) non-hematologic toxicities except inadequately treated grade 3 anorexia, nausea, vomiting or diarrhea. Hematologic toxicities defined as DLT were grade 3 or 4 neutropenia complicated by fever \( \geq 101.3^\circ \text{F} \) (38.5°C) or infection, grade 4 neutropenia \( \geq 7 \) days duration, grade 3 thrombocytopenia complicated by hemorrhage, or grade 4 thrombocytopenia.

Study Assessments

Safety assessments were performed weekly during the first cycle and Q2W throughout the study treatment period, followed by a post treatment study visit 30 days (±5 days) after the last dose. Assessments included vital sign measurements, physical examinations, clinical laboratory tests, urinalysis, brain MRIs (every 2 cycles, instituted following an index patient with
neurologic symptoms, found to have an atypical brain finding), and collection of adverse event (AE) information. The severity of an AE was graded by the investigator using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0.

Tumor response radiologic assessments were performed at baseline and approximately every 8 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Serum tumor markers as appropriate for tumor type were used to assess the effect of nesvacumab therapy.

**Pharmacokinetic Analysis**

Serum samples were collected on cycle 1 day 1 pre-dose, 0 (end of infusion), 1, 2, 4, 8, 24, 48 and 168 hours post dose, day 15 (predose and end of infusion) and on day 22. In cycle 2 serum samples were collected on day 1 predose, 0 (end of infusion), 1, 2, 4, and 8 hours post dose. In cycles ≥3, serum samples were collected on day 1 predose and end of infusion. Total nesvacumab concentration in serum was measured using a validated enzyme-linked immunosorbent assay (ELISA). (Regeneron, on file). In the assay, the lower limit of quantification (LLOQ) of total nesvacumab was 0.078 mg/L. Noncompartmental PK parameters were calculated using Phoenix WinNonlin (version 6.3, Certara, L.P.).

**Immunogenicity**

Serum samples collected during the treatment period and at follow-up were evaluated for anti-nesvacumab antibody (ADA) using an electrochemiluminescence bridging immunoassay.

**Biomarker Studies**

The pharmacodynamics (PD) effect of nesvacumab was explored in serum, and in mandated paired tumor biopsies obtained at baseline and after administration of 2 doses of
nesvacumab on cycle 1 day 22 (±2 days) in the solid tumor safety expansion cohorts. Biopsies were optional in HCC patients. Serum samples were collected at cycle 1 day 1 (pre-dose), cycle 1 day 2, day 3, day 8, day 15 (pre-dose) and day 22; and pre-dose on days 1 and 15 for all subsequent cycles. Exploratory analysis of serum levels of Ang2 and other potential PD markers, including endothelial cell-specific molecule 1 (ESM-1), stromal cell derived factor 1 (SDF-1), placental growth factor (PLGF) and soluble vascular cell adhesion molecule 1 (sVCAM-1) which may be affected by Ang2 inhibition, were performed by ELISA (R&D Systems, Minneapolis, MN, for total Ang2 (free and nesvacumab-bound) and SDF-1; Quest Diagnostics Clinical Trials Laboratory, Valencia, CA for PLGF and sVCAM-1; and Atila Biosystems, Mountain View, CA, for ESM-1). Archival tissue and paired tumor biopsies were processed for immunohistochemical analysis of Ang2, TIE-2 (Ang2 receptor), CD31, microvessel density (MVD), vascular endothelial growth factor A (VEGF-A), smooth muscle actin (SMA), Ki-67, and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL).

Statistical analysis

Categorical and continuous data were summarized with frequencies and percentages or descriptive statistics, respectively. The safety population included all patients who received at least one dose of study drug; the efficacy population included all patients in the safety population with a baseline assessment and at least one post-baseline tumor assessment.

RESULTS

Patient Characteristics and Disposition

A total of 47 patients were enrolled to the study between January 2011 and March 2013. Patient demographics and characteristics are listed in Table 1. The dose escalation phase initially
tested the 4 planned 1mg/kg to 12mg/kg dose levels [1mg/kg (n=4), 3mg/kg (n=4), 6mg/kg (n=3) and 12 mg/kg (n=6)]. One additional patient was enrolled concurrently in the 1mg/kg cohort, and one patient withdrew consent and was replaced in the 3mg/kg cohort. Following review of PK and safety data from the safety expansion cohort at 12 mg/kg (n=14), an additional 20 mg/kg cohort (n=6) was explored without defining an MTD, with a safety dose expansion cohort at 20mg/kg (n=10). Overall, 20 patients, including 6 with HCC were treated at 12mg/kg; and 16 patients, including 8 with HCC, were treated at 20mg/kg respectively.

At the time of the data cutoff in September 2013, forty-six patients (97.9%) had discontinued study treatment, including 38 patients (80.9%) because of progressive disease, 6 patients (12.8%) due to adverse events and 1 patient each, due to decision of the investigator and withdrawal of consent. There was one death within 30 days of completing treatment, which was assessed as unrelated to nesvacumab.

Patients received a median of 4 doses (range 1 to 32) leading to a median duration of nesvacumab exposure of 56 days (range 14 to 448 days).

**DLT and MTD**

There were no DLTs observed in any of the 22 patients evaluable for DLT in the dose escalation phase. One patient in the 3mg/kg dose level withdrew consent prior to completing the first treatment cycle and was not evaluable for DLT. As no MTD was determined, the maximum administered dose of 20mg/kg was designated the recommended phase 2 dose based on cumulative safety and PK data.

**Safety**
All 47 patients received at least one dose of nesvacumab and were evaluable for safety. All patients experienced at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs of any grade were fatigue (53.2%; n=25), diarrhea, nausea, and peripheral edema (each 25.5%; n=12) (Supplementary Table 1). Thirty-six patients (76.6%) experienced at least one adverse event assessed as being nesvacumab-related (Table 2). The most common treatment-related adverse events of any grade were fatigue (23.4%; n=11), peripheral edema (21.3%; n=10), decreased appetite and diarrhea (each 10.6%; n=5). The peripheral edema occurred in similar proportions of patients in the 12 mg/kg and 20 mg/kg cohorts and was mild to moderate (grade ≤2) in severity. Infusion-related reactions occurred in 3 patients (6.3%). Two patients, one each with grade 1 flushing and grade 3 back-pain, continued nesvacumab dosing without symptom recurrence; 1 patient (grade 2 bronchospasm) had dose interruption, and subsequently withdrew consent without resumption of dosing. Three patients, all in the 20 mg/kg dose group, each experienced at least possibly treatment-related AE assessed as grade ≥3 (transient infusion-related reaction, transient abdominal pain, and retinal detachment).

One patient receiving nesvacumab 6 mg/kg experienced a grade 1 cognitive disturbance during cycle 5, and dosing of nesvacumab was held as a precaution. Brain MRI showed atypical T2 white matter findings. At follow-up, both the symptoms and MRI findings resolved; the patient had disease progression and was off treatment at the time of resolution. This AE prompted a protocol amendment implementing screening and on-study brain MRIs in all active and subsequently enrolled patients. Two additional on-study patients were found to have atypical T2 white matter findings on brain MRI, but without associated neurologic symptoms. These finding respectively improved or resolved following discontinuation of dosing. No baseline brain MRIs were available for comparison for these 2 patients nor the index patient. A total of 26
additional patients had both baseline screening and follow-up brain MRIs, none of whom developed any changes from baseline.

Five patients (10.6%) had at least 1 study defined treatment-related SAE. These included the aforementioned 3 events of reversible central nervous system findings, with cognitive disturbance in 1 patient, and 1 event each of retinal detachment and vena cava thrombosis. The vena caval thrombosis occurred in the context of disease progression with retroperitoneal adenopathy and ureteric obstruction, but was considered possibly related to nesvacumab.

No dose reductions were required for nesvacumab-related AEs but five patients (10.6%) had nesvacumab dosing temporarily withheld due to a treatment-related AE, and 3 patients (6.4%) discontinued treatment permanently due to a treatment-related AE. One patient, an 82 year old male with a diagnosis of HCC in the 12 mg/kg group died 14 days after the last dose of nesvacumab due to unrelated respiratory failure, following worsening end-stage liver disease and chronic obstructive lung disease.

Pharmacokinetics

Following the first IV administration of nesvacumab, the mean concentration-time profiles of total nesvacumab were characterized by an initial distribution phase followed by a single linear beta elimination phase (Figure 1). A terminal target-mediated elimination phase was not observed within the scheduled Q2W dosing interval. With Q2W interval re-treatment of nesvacumab, a slight increase in \( C_{\text{max}} \) (1.2 to 1.8 fold) was observed over the first 3 or 4 dosing intervals (6 to 8 weeks); however, there was no clear evidence of continued accumulation with longer term dosing, suggesting steady-state was mostly achieved (Figure 1). At 20mg/kg, following the first and subsequent doses, \( C_{\text{min}} \) of \( \geq 122 \text{ mg/L} \) was approximately twice the
concentration associated with consistent antitumor activity in preclinical models (Figure 1). Mean $C_{\text{max}}$ and $AUC_{\text{last}}$ value increases were dose-proportional (Table 3).

Consistent with the dose proportionality observed, total body clearance (CL) and volume of distribution at steady-state ($V_{ss}$) appeared to be dose-independent. The mean observed elimination $t_{1/2}$ ranged from 6.35 to 9.66 days in a dose-independent manner.

**Immunogenicity**

One of the 47 patients, treated with nesvacumab at 3 mg/kg Q2W, tested positive on the 30-day post last dose follow-up visit sample with an ADA titer of 30 (the minimum titer for the assay). This patient had no associated infusion-related reaction and no sudden and/or persistent drop in total nesvacumab concentration, indicating the ADA detected did not affect exposure in this individual.

**Biomarker Studies**

Patients had a median baseline level of total serum Ang2 of 3.0 ng/ml (n=47, range: 1.1 – 49.6 ng/ml). Patients with HCC had higher baseline levels of Ang2 (HCC median of 7.2 ng/ml versus non-HCC median of 2.9 ng/ml). Increase in total Ang2 levels was observed after the first dose of nesvacumab, and further accumulation to plateau was detected upon extended exposure (Figure 2). When comparing the molar concentrations of total nesvacumab and total Ang2, and considering the ability of one nesvacumab molecule to bind two Ang2 molecules, Ang2 in serum was saturated by nesvacumab administered with the studied dose levels and dosing schedule. (Supplementary Figure 1). Serum levels of putative biomarkers of nesvacumab treatment (ESM-1, SDF-1, PLGF-1 and sVCAM-1) identified in preclinical studies were also determined. No
significant treatment-related changes in these biomarkers or correlations to treatment response or duration were observed (Supplementary Figures 2-4).

Archival tumor tissue (n=38) and paired tumor tissue biopsy samples (n=17) were available for analysis. In paired samples, expression of Ang2 was detected in most pre-treatment biopsies [86.7% of evaluable baseline biopsies (n=15) had Ang-2 positive vessel staining (H-score > 30)] and expression level in post-treatment biopsies was unaffected by nesvacumab treatment. Similar to Ang2, no nesvacumab-induced changes nor correlations to treatment response or duration were observed in tumor tissue for any of the other putative biomarkers (VEGF-A, TIE-2, SMA, MVD, TUNEL, Ki-67) (Supplementary Figures 5-9).

Antitumor Activity

Among the 47 patients enrolled, 43 patients were evaluable for tumor response. One patient with low-burden peritoneal adrenocortical carcinoma treated in the 1 mg/kg cohort achieved a confirmed PR by RECIST of 24 weeks duration, 23 patients (48.9%) achieved best response of stable disease and 19 patients (40.4%) had progressive disease as best response (Figure 3). Five HCC patients enrolled across dose levels, 3 of whom had progressive disease in the 3 months preceding study entry, had SD > 16 weeks. Two HCC patients with SD, treated at 1 mg/kg and 20 mg/kg, demonstrated significant decline in AFP at best response; 20506 ng/mL at baseline to 252 ng/mL and 42983 ng/mL at baseline to 14418 ng/mL, respectively.

DISCUSSION

In this first-in-human study, nesvacumab safety profile was acceptable at doses up to 20mg/kg Q2W in patients with advanced solid tumors. No patients in the dose escalation phase
experienced a protocol-defined DLT. Expansion cohorts at 12 and 20 mg/kg provided additional information on safety and preliminary antitumor activity in a population enriched for patients with HCC. The dose of 20 mg/kg was selected as the RP2D based on both clinical and preclinical data, including a $C_{\text{min}}$ of 122 mg/L, which was approximately twice the concentration associated with consistent antitumor activity in preclinical models.

The most common treatment-related AEs with nesvacumab, all grade ≤ 2, were fatigue, peripheral edema, diarrhea and decreased appetite. With the caveat of limitations of cross-trial comparisons, these data are similar to findings reported in clinical trials of other inhibitors of Ang1 and Ang2, where fatigue and peripheral edema were also the most common clinical toxicities (25,26). With the exception of fatigue, there were no obvious dose-related patterns in the occurrence or severity of treatment-related AEs. Nesvacumab–related peripheral edema (n=10, 21.3%) was mild in severity in the majority of patients, and all events but one resolved without any action taken to the study drug. Factors that might increase the risk of nesvacumab-associated edema are unknown and require further study.

The toxicity profile of nesvacumab was remarkable for the lack of AEs typically associated with inhibitors of angiogenesis (27, 28). In particular, no treatment-related hypertension, hemorrhage, arterial thromboembolic events or proteinuria were documented. Apart from the caveat of cross trial comparisons, a mechanistic explanation of selective inhibition of Ang2 without Ang1 inhibition may account for the lack of proteinuria seen with nesvacumab (29-31), unlike the proteinuria grade ≥ 3 reported with the Ang1/Ang2 inhibitors trebananib and AMG780 (25,26), Except for one patient with vena cava thrombosis, occurring in the context of progressive retroperitoneal disease, there were no other thrombotic events.
Reversible CNS abnormalities seen on MRI in 3 patients were atypical in their clinical and radiologic appearance from those seen with other anti-angiogenic agents (32, 33). The MRI findings suggest foci of restricted diffusion, distinct from the typical T2 weighted hyper-intensity signal generally seen in the population at large over the age of 50 (34, 35), and will require further elucidation. Infusion–related reactions were infrequent and easily managed, with patients receiving subsequent infusions without symptom recurrence. Anti-nesvacumab antibodies without clinical consequence were detected at a single timepoint in only 1 patient.

The PK profile of nesvacumab was dose-proportional, and serum concentration trough levels throughout the dosing interval at ≥12mg/kg were above the level that correlated with consistent antitumor activity in preclinical models. Ang2 levels increased and plateaued with repeat dosing, likely reflecting saturated antibody-target (nesvacumab-Ang2) complex formation. However, additional studies of mRNA Ang2 levels are required to rule out a possible change in target production rates. Elevations of similar magnitude in Ang2 levels have been observed following therapy with other Ang1/Ang2 inhibitors (36). Analyses of Ang2 and other putative angiogenesis biomarkers in serum and tumor biopsies did not show association with treatment response or duration, but were limited by small sample size and the heterogeneity of this population.

Evidence of antitumor effect included PR in 1 patient with adrenocortical carcinoma in the 1 mg/kg group and two HCC patients with tumor regression and >50% decrease in AFP.

In summary, the anti-Ang2 monoclonal antibody nesvacumab showed acceptable safety and evidence of objective treatment effects in 1 adrenocortical carcinoma patient and a few hepatocellular carcinoma patients when administered as monotherapy at intravenous doses up to 20mg/kg every 2 weeks. Preclinical combination studies (13) and the distinct safety profile of
nesvacumab suggest the feasibility and potential benefit of combination with anti-VEGF and other targeted or cytotoxic agents. Combination trials of nesvacumab with sorafenib and ziv-aflibercept/paclitaxel (37) have completed enrollment.
REFERENCES


Table 1: Baseline Demographics and Primary Cancer Diagnosis

<table>
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<th>Characteristic</th>
<th>Total (N=47)</th>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Mean (SD)</td>
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<tr>
<td>Min : max</td>
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<td>Gender, n (%)</td>
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<td>23 (48.9)</td>
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<tr>
<td>Race, n (%)</td>
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<td>Pancreatic cancer</td>
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*chordoma, placental site trophoblastic tumor (PSTT), thyroid carcinoma, sarcoma, malignant fibrohistiocyctoma, metastatic carcinoid, malignant neoplasm of floor of mouth, angiosarcoma, mucoepidermoid cancer, uterine carcinoma, uterine leiomyosarcoma, mesothelioma, lymphoepithelioma*
Table 2. Summary of Treatment-Related Adverse Events occurring in ≥ 2 patients or grade ≥ 3 (CTCAE, version 4.0.)

<table>
<thead>
<tr>
<th>Preferred Term a</th>
<th>1 mg/kg (N=4)*</th>
<th>3 mg/kg (N=4)</th>
<th>6 mg/kg (N=3)</th>
<th>12 mg/kg (N=20)</th>
<th>20 mg/kg (N=16)</th>
<th>Total (N=47)</th>
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<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
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<td>n (%)</td>
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<tr>
<td>Number of patients with any TRAE</td>
<td>3 (75.0)</td>
<td>0 (0.0)</td>
<td>1 (33.3)</td>
<td>16 (80.0)</td>
<td>13 (81.3)</td>
<td>36 (76.6)</td>
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<tr>
<td>Fatigue</td>
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<td>0 (0.0)</td>
<td>1 (25.0)</td>
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<td>11 (23.4)</td>
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<td>Edema peripheral</td>
<td>1 (25.0)</td>
<td>1 (25.0)</td>
<td>1 (33.3)</td>
<td>3 (15.0)</td>
<td>5 (10.6)</td>
<td>10 (21.3)</td>
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<tr>
<td>Decreased appetite</td>
<td>1 (25.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (15.0)</td>
<td>5 (10.6)</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (25.0)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
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<td>Infusion-related reaction</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (6.3)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (10.0)</td>
<td>0 (0.0)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (6.3)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (6.3)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (6.3)</td>
<td>2 (4.3)</td>
</tr>
</tbody>
</table>

Note: TRAE: Treatment-related Adverse Event. A TRAE was defined as an AE that occurred in the period from the first nesvacumab dose to end of study visit or 30 days post last dose, whichever was later. a All AEs were coded using the MedDRA, version 13.0. * Additional patient recruited concurrently at 2 sites.
Table 3: Summary Pharmacokinetic Parameters of Total Nesvacumab Following IV Infusion in Patients (Cycle 1 & Cycle 2)

<table>
<thead>
<tr>
<th>Parameter / Units</th>
<th>1 mg/kg (n=4)</th>
<th>3 mg/kg (n=4)</th>
<th>6 mg/kg (n=3)</th>
<th>12 mg/kg (n=20)</th>
<th>20 mg/kg (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>SD</td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>t1/2 Day</td>
<td>6.35</td>
<td>6.05</td>
<td>1.52</td>
<td>7.32</td>
<td>8.00</td>
</tr>
<tr>
<td>tmax Hour</td>
<td>3.04</td>
<td>3.08</td>
<td>1.68</td>
<td>3.54</td>
<td>2.58</td>
</tr>
<tr>
<td>CL mL/day/kg</td>
<td>6.27</td>
<td>6.30</td>
<td>1.15</td>
<td>5.40</td>
<td>5.47</td>
</tr>
<tr>
<td>Vss mL/kg</td>
<td>53.4</td>
<td>53.0</td>
<td>11.5</td>
<td>53.6</td>
<td>57.3</td>
</tr>
<tr>
<td>AUClast day*mg/L</td>
<td>130</td>
<td>124</td>
<td>22.1</td>
<td>415</td>
<td>407</td>
</tr>
<tr>
<td>AUClast/Dose day*kg/L</td>
<td>130</td>
<td>124</td>
<td>22.1</td>
<td>138</td>
<td>136</td>
</tr>
<tr>
<td>Cmax mg/L</td>
<td>22.1</td>
<td>22.3</td>
<td>2.53</td>
<td>74.8</td>
<td>75.7</td>
</tr>
<tr>
<td>Cmax/Dose kg/L</td>
<td>22.1</td>
<td>22.3</td>
<td>2.53</td>
<td>4.06</td>
<td>25.3</td>
</tr>
<tr>
<td>Clast mg/L</td>
<td>3.61</td>
<td>3.65</td>
<td>1.04</td>
<td>13.0</td>
<td>13.7</td>
</tr>
<tr>
<td>Clast/Dose kg/L</td>
<td>3.61</td>
<td>3.65</td>
<td>1.04</td>
<td>4.33</td>
<td>4.57</td>
</tr>
</tbody>
</table>

Cycle 1/Dose 2

<table>
<thead>
<tr>
<th>Parameter / Units</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax mg/L</td>
<td>24.6</td>
<td>25.9</td>
<td>3.15</td>
<td>86.3</td>
<td>83.2</td>
<td>13.5</td>
<td>184</td>
<td>204</td>
<td>39.9</td>
<td>353</td>
<td>350</td>
<td>149</td>
</tr>
<tr>
<td>Clast mg/L</td>
<td>6.00</td>
<td>6.31</td>
<td>2.28</td>
<td>26.1</td>
<td>35.5</td>
<td>27.1</td>
<td>45.8</td>
<td>47.4</td>
<td>8.81</td>
<td>123</td>
<td>136</td>
<td>38.9</td>
</tr>
<tr>
<td>Cmax a mg/L</td>
<td>23.6</td>
<td>4.53</td>
<td>25.0</td>
<td>84.5</td>
<td>90.0</td>
<td>10.4</td>
<td>183</td>
<td>170</td>
<td>26.1</td>
<td>399</td>
<td>412</td>
<td>87.8</td>
</tr>
<tr>
<td>Clast b mg/L</td>
<td>6.58</td>
<td>7.39</td>
<td>3.44</td>
<td>34.7</td>
<td>34.7</td>
<td>34.7</td>
<td>71.6</td>
<td>71.6</td>
<td>199</td>
<td>199</td>
<td>179</td>
<td>48.5</td>
</tr>
</tbody>
</table>

AUC = Area under the curve; CL = Clearance; C\text{max} = Maximum concentration; C\text{last} = Concentration at the end of the dosing interval; SD = Standard deviation; t\text{\textsubscript{1/2}} = half-life; t\text{max} = time to maximum concentration; V\text{ss} = Volume of distribution at steady-state; t\text{\textsubscript{1/2}} was estimated over the Q2W dosing interval.

a Mean concentration observed at the end of the first IV infusion of Cycle 2.
b Mean concentration observed at the end of the second dosing interval of Cycle 2.
c n=2
Figure Legends

Figure 1. Mean (±SD) log-scaled Concentrations of Total Nesvacumab versus Time in Patients Receiving IV Infusions of Nesvacumab every 2 weeks.

One standard deviation around the mean is presented. Horizontal dotted line = assay LLOQ (0.0870 mg/L). Horizontal dashed line = 122 mg/L.

Figure 2. Total median Angiopoietin-2 levels in serum versus Time (first cycle) in Patients Receiving Nesvacumab

Figure 3. Best Overall Percent Change in Target Lesions from Baseline.

Best percentage change from baseline in the sum of the diameter of measurable target lesions for patients with pre- and post-baseline tumor assessments. Interrupted line indicates RECIST 1.1. threshold for response (-30% for partial response). “Not-evaluable” patients had repeat CT performed < 6 weeks from baseline.
Figure 1
Figure 2.
Figure 3.
Clinical Cancer Research

A phase I first-in-human study of Nesvacumab (REGN910), a fully-human anti-Angiopoietin-2 (Ang2) monoclonal antibody, in patients with advanced solid tumors.


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