Pharmacokinetic and Pharmacodynamic Analysis of Circulating Biomarkers of Anti-NRP1, a Novel Antiangiogenesis Agent, in Two Phase I Trials in Patients with Advanced Solid Tumors

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Abstract

Purpose: MNRP1685A is a monoclonal antibody to neuropilin-1 (NRP1). We evaluated blood-based pharmacodynamic biomarkers of MNRP1685A in two phase I studies to assess exposure/response relationships to inform target dose and regimen selection.

Experimental Design: The phase I studies evaluated escalating doses of MNRP1685A as a single agent or in combination with bevacizumab. Plasma placental growth factor (PlGF), VEGF, and circulating NRP1 (cNRP1) were evaluated at multiple time points using meso-scale discovery (MSD) assays and ELISA, respectively. Plasma PlGF was also measured in a phase I/II trial of bevacizumab in metastatic breast cancer (AVF0776). The association between PlGF and MNRP1685A dose was described by a sigmoid $E_{\text{max}}$ model. cNRP1 and MNRP1685A PK profiles were described using a two-target quasi-steady state (QSS) model.

Results: A dose- and time-dependent increase in plasma PlGF and cNRP1 was observed in all patients treated with MNRP1685A. PK/PD analysis showed that bevacizumab and MNRP1685A had an additive effect in elevating PlGF. Predictions based on the two-target QSS model showed that the free drug concentration to maintain greater than 90% saturation of membrane NRP1 (mNRP1) and cNRP1 is about 8 µg/mL.

Conclusion: These data show that MNRP1685A inhibits the VEGF pathway in humans as assessed by an increase in plasma PlGF. MNRP1685A seems to enhance bevacizumab-mediated VEGF pathway blockade, as showed by an increase in the magnitude of PlGF elevation when combined with bevacizumab. PK/PD analysis of biomarkers in the phase I population allowed identification of doses at which apparent maximal pathway modulation was observed.

Introduction

The neuropilins, NRP1 and NRP2, are nontyrosine kinase receptors for class 3 semaphorins and VEGF. NRP1 was first characterized as a semaphorin receptor–mediating axonal guidance (1, 2). Shortly after this discovery, it was shown that NRP1 is also a receptor for VEGF$_{165}$ (3). It was then shown in genetic studies that NRP1 is required for vascular endothelial sprouting and remodeling during embryonic development (4). The mechanism by which NRP1 mediates its effects on endothelial function is complex. As the cytoplasmic domain of NRP1 is short, it is generally believed that coupling with other receptors is required for signal transduction, therefore, NRP1 is proposed to act as a coreceptor for VEGF$_{165}$ (3). VEGFR2–NRP1 complexes are formed due to bridging when VEGF$_{165}$ binds to both receptors simultaneously, resulting in increased VEGFR2 signaling (3). VEGF$_{121}$ also binds to the b1b2 domain of NRP1 and promotes endothelial cell migration and sprouting (6).

MNRP1685A is a fully human monoclonal antibody directed to the b1b2 domain of NRP1 (7). This antibody blocks the binding of VEGF$_{165}$ and VEGF$_{121}$ to NRP1 (6, 7). In preclinical xenograft models, administration of a function-blocking antibody anti-NRP1b, a precursor of MNRP1685A, designed specifically to block VEGF binding to NRP1, shows marginal tumor growth delay as a single agent. However, an additive effect in reducing tumor growth...
Translational Relevance

Blockade of VEGF signaling with monoclonal antibodies or small-molecule inhibitors to the receptors (VEGFR1, VEGFR2) results in an increase in systemic plasma placental growth factor (PIGF). We have shown for the first time that blocking neuropilin-1 (NRP1), a coreceptor for VEGFR2, results in an increase in plasma PIGF, total circulating soluble NRP1, and VEGF in humans. Furthermore, MNRP1685A, a function-blocking antibody to NRP1, enhances pharmacodynamic (PD) response to bevacizumab-mediated VEGF pathway blockade, as shown by an increase in the magnitude of PIGF elevation when combined with bevacizumab. Pharmacokinetic (PK) and PD analysis of biomarkers in the phase I population allowed for identification of doses at which maximal sustained biomarker modulation was observed. These results are pertinent as they show an integrated PK/PD approach to guiding dose and schedule selection in humans.

and tumor vascular density is observed when anti-NRP1b is combined with murine anti-VEGF (8). It is proposed that anti-NRP1b enhances anti-VEGF activity by inhibiting vascular remodeling, as evident by a reduction of pericyte association with vessels, thereby rendering vessels more susceptible to anti-VEGF therapy (8). Given the promising preclinical antiangiogenesis profile, MNRP1685A has been evaluated in first in human phase I studies as a single agent (IA) and in combination with bevacizumab (IB) to investigate safety, tolerability, and pharmacokinetic (PK) with the goal to further improve therapeutic benefit of bevacizumab by combining with MNRP1685A in humans with advanced solid malignancies (9, 10).

Biomarkers were included in the phase I studies of MNRP1685A to evaluate doses at which target modulation was observed. These included circulating biomarkers for antiangiogenesis agents such as VEGF, plasma placental growth factor (PIGF), and fibroblast growth factor-2 (bFGF) among others (11–13). We also assessed the levels of total cNRP1 as a surrogate marker for receptor occupancy (14). The objectives of these analyses were to explore the relationship between drug exposure and biomarker response to inform target dose and regimen selection for MNRP1685A.

Materials and Methods

Exploratory biomarker analyses in cynomolgus monkeys

Cynomolgus monkeys received a single intravenous dose of MNRP1685A at 0, 0.5, 3, 15, or 50 mg/kg and were monitored for a period of 50 days. Plasma samples were collected at predose (baseline) and various time points after the dose to evaluate the effect of NRP1 pathway inhibition on circulating levels of VEGF pathway markers including PIGF, VEGF, bFGF, and soluble VEGFr1, using a four-plex assay (Meso Scale Discovery).

Biomarker evaluation in MNRP1685A phase I studies

The phase I study (NCI study #ANP4509) consisted of a standard 3 + 3 dose escalating trial design with i.v. MNRP1685A administered every 3 weeks (q3w) at 2, 5, 10, 15, 20, 30, or 40 mg/kg. All patients enrolled provided written informed consents for exploratory biomarker analysis. Serum for MNRP1685A PK and plasma (EDTA-plasma) for exploratory biomarkers were collected at predose (baseline), and 1, 3, 7, 14, and 21 days after the first dose of MNRP1685A from 32 patients.

Arm A of the phase IB trial (NCI study #ANP4667) consisted of escalating doses of MNRP1685A at 7.5, 15, or 24 mg/kg administered along with a standard dose of 15 mg/kg bevacizumab (both IV, q3w). All patients enrolled provided written informed consents for biomarker analysis. Serum for PK and plasma (EDTA-plasma) for exploratory biomarkers were collected at predose (baseline), and 1, 7, and 14 days after the first dose of MNRP1685A from 10 patients. Premedications such as dexmethasone were allowed in both studies to manage infusion-related symptoms after drug administration. To avoid confounding the biomarker assessment by the premedications, the earliest time point chosen to evaluate plasma biomarkers was 8 days after drug administration to allow for washout of the premedications from patients (dexmethasone has a half-life of 36–54 hours).

PIGF modulation by bevacizumab

In a phase I/II trial (AVF0776), 75 patients with metastatic breast cancer were treated with escalating doses of bevacizumab ranging from 3 to 20 mg/kg administered intravenously every other week (15). Plasma samples were available at predose (baseline) and 14 and 28 days after the first dose from 66 patients. Plasma PIGF was measured from...
15 patients in the 20 mg/kg cohort using a four-plex assay (Meso Scale Discovery).

**MNRP1685A/PlGF PK/PD analysis**

The PK/PD relationship between plasma PlGF level (normalized to baseline) and MNRP1685A dose, with (Arm A of phase IB) or without (phase IA) coadministration of bevacizumab was evaluated. Various analyses were explored to correlate the MNRP1685A and PlGF exposure parameters, including dose of MNRP1685A, concentration at specified time point, or area under concentration–time curve (AUC). The dose of MNRP1685A and PlGF AUC (AUCPlGF) showed more pronounced relationship, which is well described by a sigmoid $E_{\text{max}}$ model (equation 1).

$$E = E_0 + \left(\frac{E_{\text{max}}}{C_0} - E_0\right) \times \frac{\text{Dose}}{\text{Dose} + ED_{50}} \quad (1)$$

where $E$ is the drug (MNRP1685A) effect on PlGF, $E_0$ the baseline PlGF level, $E_{\text{max}}$ the maximum drug effect on PlGF level, and $E_{\text{max}} - E_0$ is the change in PlGF level. Dose is the MNRP1685A dose level (mg/kg), and $ED_{50}$ represents the dose of MNRP1685A that leads to 50% maximum drug effect. Note that instead of using the PlGF level at a specific time point, the area under PlGF concentration (baseline-normalized)–time curve (AUCPlGF) from 0 to 14 days after MNRP1685A administration was used to reflect PlGF level change over the time. The analysis was done in S-PLUS (version 8.2; TIBCO Software Inc.).

**MNRP1685A/cNRP1 PK/PD analysis**

Because MNRP1685A binds to both mNRP1 and cNRP1, the 2-target quasi–steady-state (QSS) model (16) has been shown to adequately describe the free drug MNRP1685A and total cNRP1 concentration–time profiles in cynomolgus monkeys (17). In this model, MNRP1685A distributes to both central and peripheral compartments, with parallel linear and nonlinear clearance of free drug, and binds to free cNRP1 in the central compartment. To understand the target occupancy after MNRP1685A administration, free cNRP1 and mNRP1 profiles were simulated using the parameters obtained from the 2-target QSS model to predict free receptor levels, at the studied dose regimens.

**Results**

**PlGF: a biomarker of systemic pathway inhibition for anti-NRP1**

Plasma biomarkers related to angiogenesis were evaluated in cynomolgus monkeys administered with a single dose of MNRP1685A with the aim of identifying a systemic marker of pathway inhibition. Of the 4 markers tested, namely VEGF, PlGF, bFGF, and FLT1, plasma PlGF was the only biomarker that showed an immediate 1.5- to 2-fold elevation at 24 hours, the earliest time point evaluated (Fig. 1). Doses of 15 mg/kg and higher showed sustained elevation in PlGF for the duration of the study (28 days). At day 28, quantifiable circulating drug concentrations (110 ± 50.1 μg/mL) were present only at the 50 mg/kg dose that may explain the sustained increase in PlGF at this dose level.

PlGF was also evaluated in the cynomolgus monkeys as a biomarker reflecting drug binding to target (14). A dose- and time-dependent elevation in total cNRP1 was observed, again more pronounced at the 3 mg/kg and higher dose levels (14).

Given the effect of MNRP1685A on systemic PlGF in nonclinical models, plasma PlGF evaluation was included in the phase I study as a marker of target modulation (Table 1). As shown in Fig. 2A, patients on the phase I study had 6 times higher baseline levels of plasma PlGF compared with healthy donors. As expected from preclinical studies, single-agent MNRP1685A administration resulted in a 2-fold elevation in systemic plasma PlGF at doses of 10 mg/kg and higher. Sustained elevation in PlGF through the day 28 after a single dose of MNRP1685A. Ratios to baseline levels for each animal were generated at each time point. Each dose level included $n = 3$ animals. Data represent mean ± SEM ($P < 0.05$; paired $t$ test).

![Figure 1](https://cancerres.aacrjournals.org/content/18/21/6042/F1.large.jpg)
duration of the dosing cycle was observed at doses of 20 mg/kg and higher (Fig. 2B). In arm A of the phase IB study, when combined with bevacizumab, PlGF levels increased to 2.4-fold at day 8 and reached 1.8-fold by the end of the dosing cycle at the first dose (7.5 mg/kg) administered (Fig. 2C). Drug concentration for this dose cohort at day 7 was 13.2 ± 3.75 μg/mL and undetectable at day 21. This observed effect on PlGF is greater than equivalent doses with single-agent MNRP1685A based on phase IA study. Consistently, increasing the dose of MNRP1685A to 15 and 24 mg/kg showed up to 3.7-fold increase in PlGF levels at day 21 (end of cycle 1). The day 21 drug concentrations for the 15 and 24 mg/kg dose cohorts were 1.63 ± 1.32 μg/mL and 7.69 ± 9.64 μg/mL, respectively.

Because arm A of the phase IB trial included coadministration of MNRP1685A with bevacizumab, PlGF modulation by bevacizumab alone was also evaluated to better understand the combination effect of bevacizumab and MNRP1685A. Plasma samples from baseline and days 14 and 28 from the 20 mg/kg dose cohort of AVF0776, a single-agent trial of bevacizumab in breast cancer were used to evaluate the degree of PlGF elevation by single-agent bevacizumab (15). Patients enrolled on this trial had equivalent levels of PlGF at baseline as those evaluated in the phase I study (Supplementary Fig. S1). Treatment with bevacizumab alone resulted in a consistent approx. 1.8- to 2-fold elevation in plasma PlGF that was sustained through the duration of treatment cycle in all patients (Fig. 2D). These observations are similar to those previously reported for bevacizumab (18, 19).

Because bevacizumab does not show greater than 2-fold increase in PlGF, and MNRP1685A as a single agent did not
increase PlGF levels at 7.5 mg/kg (based on single agent results from phase IA), the sustained and enhanced (15 and 24 mg/kg) PlGF elevation observed in arm A of the phase IB study suggests a potential readout of enhanced pathway inhibition for the 2 antiangiogenesis agents.

PK/PD modeling further indicates the additive effect between bevacizumab and MNRP1685A on PlGF elevation. Either as a single agent or in combination with bevacizumab, the profile of AUClPlGF versus MNRP1685A dose was well described by a sigmoid $E_{\text{max}}$ model (Eq. 1), as shown in Fig. 3. For single-agent MNRP1685A (phase IA), the estimated parameter value is 9.2-fold-day (90% CI, 1.1–12%) for $E_0$, 43-fold-day (90% CI, 29–60%) for $E_{\text{max}}$, and 23.5 mg/kg (90% CI, 4.5–40%) for ED$_{50}$. These results suggest that the potential pharmacologically active dose is about 20 mg/kg or higher. For the combination of MNRP1685A and bevacizumab, the $E_0$ value is consistent with that in the bevacizumab alone study (AVF0766). After subtracting the 1.8- to 2-fold elevation of PlGF by bevacizumab alone, the estimated model parameters for AUClPlGF versus MNRP1685A dose were similar to those in phase IA, with $E_0$ at 9.1 (fold-day), $E_{\text{max}}$ at 42.4 (fold-day), and ED$_{50}$ at 21.7 mg/kg. The results suggest an additive effect of combination of MNRP1685A and bevacizumab on PlGF elevation.

In addition to PlGF, a dose-independent elevation in plasma VEGF was observed in a subset of patients in the phase IA study (Fig. 4A). This elevation was dependent on baseline values at start of treatment, where patients with baseline levels of 250 pg/mL or less showed a rise in plasma VEGF with drug administration (Fig. 4B). Notably, subjects who showed an increase in plasma VEGF also seemed to
exhibit sustained elevation through the dosing period, independent of the dose administered, which is contrary to the observed effects with plasma PI GF. No correlation was observed between elevation of plasma VEGF and duration of therapy.

cNRP1: a surrogate marker for receptor occupancy

cNRP1 is abundantly found in plasma from healthy donors with a mean level of 200 ng/mL (Fig. 5A). The phase IA patients showed a broader dynamic range in baseline expression with a mean level of 400 ng/mL. We next evaluated vendor procured cancer blood samples to determine the levels of cNRP1 in 3 major disease indications. Despite being abundantly expressed in healthy donors, circulating levels of cNRP1 seem to be further elevated in cancer blood samples, with higher levels observed in colorectal and non–small cell lung cancer (NSCLC; median level 400 ng/mL) compared with breast cancer (median level 330 pg/mL; Fig. 5A).

MNRP1685A administration resulted in elevation of total cNRP1 at doses of 10 mg/kg and higher (Fig. 5B). By day 14, doses of 15 mg/kg and higher showed a approximately 2-fold elevation in total cNRP1. The increase of total cNRP1 was sustained through the end of the cycle at doses of 30 and 40 mg/kg, suggesting a plateau for total cNRP1 at these dose levels.

Although total cNRP1 correlates well with the MNRP1685A dose (Fig. 5B), in cynomolgus monkey studies, the increase of total cNRP1 seems to be driven by the accumulation of drug–cNRP1 complex (17). To better use total cNRP1 as a surrogate marker for receptor occupancy in humans, a mechanistic PK/PD model (2-target QSS model) was applied to predict the profiles of free receptors both the membrane mNRP1 and cNRP1. Totally 414 data points for MNRP1685A (from 44 patients in both phase IA and phase IB studies) and 275 data points for total cNRP1 (from 30 patients in phase IA study) were included in the analysis using NONMEM version VI, level 1.0 (LLC; Globomax). As shown in Fig. 6, the receptor occupancy profiles of both mNRP1 and cNRP1 changed in a concentration-dependent manner after MNRP1685A administration. Both free mNRP1 and free cNRP1 levels were maintained at greater than 90% target saturation at concentrations above 8 μg/mL. Therefore, the higher the dose, or the more frequent the dose, the longer the duration of full target occupancy. At q3wk doses of 25 mg/kg, both free targets can be maintained at lower than 10% baseline (i.e., greater than 90% saturation) during the dosing intervals at steady state.

Discussion

Phase I trials for anticancer agents are traditionally designed to primarily evaluate safety and pharmacokinetics of novel drugs, with exploratory efforts focused on (PD activity. Phase II dose estimates are typically identified using integrated preclinical and clinical PK/PD and safety in humans. As monoclonal antibodies inhibiting angiogenesis pathways generally have favorable safety profiles and the maximum-tolerated dose (MTD) may not be possible...
to determine in the phase I dose-escalation studies, identification of a recommended phase II dose relies on the strength of preclinical PK/PD and clinical PK data. In conditions where preclinical models are not representative of disease or molecule biology, the use of preclinical data to identify a recommended phase II dose is limited. This results in dose finding being extended to a largely underpowered phase II study, or costly phase III studies, which in the past have not been definitively informative in selecting dose. Examples include dose-seeking phase III trials conducted for bevacizumab in NSCLC (AVAIL) and breast cancer (AVADO), where both the lower dose of 7.5 mg/kg q3wk and higher doses of 15 mg/kg q3wk were evaluated (20, 21). Although tumor-based biomarkers of efficacy are most informative in confirming target modulation at the site of action, circulating biomarkers have the potential to inform the lowest doses at which target inhibition is observed. Given the ease of frequent sampling, these biomarkers are also informative in determining the duration of target inhibition through the cycle of therapy. We used exploratory circulating biomarkers in the phase I study of MNRP1685A to confirm target modulation and conduct PK/PD analysis with the goal of using the results to contribute to decisions on recommended phase II dose and schedule.

PIGF is a systemic biomarker of VEGFR2 pathway blockade and has been clinically evaluated as a biomarker of antiangiogenesis activity for both large molecules, including bevacizumab, and small-molecule tyrosine kinase inhibitors (TKI), including sunitinib (19, 22, 23). Treatment of HUVECs in 2-dimensional cultures in vitro with bevacizumab or MNRP1685A does not lead to increase in PIGF in the media (data not shown). Yet, administration of these agents in vivo results in a time-dependent, and in the case of MNRP1685A, a dose-dependent rise in plasma PIGF, potentially as a physiologic response not reflected by healthy endothelial cells in vitro. PIGF is a ligand for NRPI. Using BIACore assays to assess ligand–receptor interactions, we observed that MNRP1685A is only partially able to block the binding of PIGF to NRPI (Supplementary Fig. S2). Thus, ligand displacement from the receptor may not entirely explain the rise in PIGF. As anti-NRPI treatment also results in a rise in cNRPI, stabilization of PIGF bound to cNRPI may explain yet another mode by which plasma PIGF is elevated. We did not, however, observe a high degree of concordance in cNRPI compared with PIGF after the drug administration (Supplementary Fig. S3). Thus, it is likely that plasma PIGF elevation may indeed be reflective of pathway inhibition. Apart from expression on endothelial cells, NRPI is expressed on smooth muscle cells, pericytes, and plasmacytoid dendritic cells (24, 25). These cell types may contribute as likely sources of PIGF upon receptor blockade. In the single-agent trial, PIGF elevation was useful to estimate the dose and duration of pathway inhibition, albeit in a surrogate tissue compartment. Assessing the biomarker in arm A in combination with bevacizumab needed additional PK/PD modeling to confirm the additive nature of the combination therapy and identify the dose at which surrogate biomarker modulation occurs.

In addition to PIGF, we observed a sustained increase in plasma VEGF with single-agent MNRP1685A in patients with low baseline levels. Similar observations have been reported with small-molecule TKIs like sunitinib where all patients treated with these agents show an increase in systemic plasma VEGF, most likely because of increased release of VEGF from intracellular stores (i.e., platelets; ref. 26). The fact that the effect with MNRP1685A is seen only in patients with low baseline levels may simply be due to loss of dynamic range in patients with higher levels where the ability to detect a 2- to 3-fold change may be difficult to ascertain. Interestingly, the kinetics of plasma VEGF elevation seem distinct from plasma PIGF or drug exposure where sustained elevations through the duration of the treatment cycle are observed even at doses where drug clearance is nonlinear. This suggests that displacement of ligand from the receptor may not be the driver for elevated VEGF levels. It is unlikely a systemic marker given that plasma from nontumor bearing cynomolgus monkeys dosed with MNRP1685A did not show an effect on circulating VEGF (Supplementary Fig. S4). As to the role of these ligands as potential resistance mechanisms of angiogenic escape for the combination therapy, the rise in VEGF is unlikely to provide a potential mechanism for escape as bevacizumab is administered far in excess of the released VEGF, thus neutralizing the bioactivity of the ligand. Without clear evidence, it is premature to comment on the rise of PIGF and its contribution to angiogenic escape, as larger, adequately sized studies would be needed to further explore this hypothesis.

NRPI is abundantly expressed in endothelial cells and can be detected in circulation (cNRPI) in mice, rats, monkeys, and humans in 2 forms: the naturally occurring human soluble NRPI isoforms (sNRPI) that contain a1a2 and b1b2 domains of the extracellular domain (ECD; refs. 27–29) and the complete NRPI ECD shed from the membrane-bound NRPI (14). Total cNRPI comprising both the soluble and membrane bound isoforms is expressed at moderately high levels in healthy donors, reflective of the abundant expression of the receptor on endothelial cells. Despite high baseline expression, cancer patients have 2- to 3-fold higher levels of cNRPI (fig. 5A). It would be interesting to determine if baseline cNRPI may serve as a prognostic marker of disease or predictive marker of anti-NRPI efficacy. As an on-treatment measure of receptor occupancy, what is truly pharmacologically important is the free receptor level, including both the membrane-associated mNRPI and cNRPI. As measurement of mNRPI level is difficult and quantitation of free cNRPI is technically challenging, this study showed an example where circulating receptors can be used as a surrogate marker to assess receptor occupancy for molecules with membrane-bound targets, with the assistance of PK/PD modeling. Optimal dose/regimen can then be selected to achieve maximal drug effect by maintaining the free target as low and as long as possible. This offers great clinical use, as soluble target is
easily accessible. The MNRP1685A/cNRP1 PK/PD relationship is driven by the drug-cNRP1 interaction, thus the results from current analysis are not expected to be impacted by the lack of cNRP1 data from the arm containing the combination regimen with bevacizumab.

In conclusion, in this study, intravenous infusion of MNRP1685A resulted in a dose- and time-dependent elevation in plasma PlGF. PK/PD modeling support the use of this biomarker as a means to assess combination activity with bevacizumab. Using PK/PD modeling via monitoring cNRP1 as a surrogate marker for receptor occupancy measurement in the periphery, we were also able to identify a target drug concentration (i.e., 8 μg/mL) and a target dose (i.e., 25 mg/kg q3w) at which maximum target occupancy is achieved. This target dose is also potentially pharmacologically active by elevating the systemic PlGF level greater than 50% of the maximum effect by MNRP1685A. This study shows the incorporation of exploratory systemic biomarkers of pathway inhibition in a phase I study to guide phase II dose selection.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References

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