ANG1005, a Brain-Penetrating Peptide–Drug Conjugate, Shows Activity in Patients with Breast Cancer with Leptomeningeal Carcinomatosis and Recurrent Brain Metastases

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ABSTRACT

Purpose: ANG1005, a novel taxane derivative, consists of three paclitaxel molecules covalently linked to Angiopep-2, designed to cross the blood–brain and blood–cerebrospinal barriers and to penetrate malignant cells via LRP1 transport system. Preclinical and clinical evidence of efficacy with ANG1005 has been previously shown.

Patients and Methods: A multicenter, open-label phase II study in adult patients with measurable recurrent brain metastases from breast cancer (BCBM), with or without leptomeningeal carcinomatosis was conducted ($n = 72$ BCBM; $n = 28$ leptomeningeal carcinomatosis subset). ANG1005 was administered intravenously at 600 mg/m^2 every 3 weeks. Tumor assessment was based on central nervous system (CNS) RECIST 1.1 for intracranial, and RECIST 1.1 for extracranial response. The primary endpoint was determination of intracranial objective response rate (iORR).

Results: Median age was 47.5 years. Safety profile was similar to that of paclitaxel with myelosuppression as the predominating toxicity. Average number of prior CNS-directed therapies was 2.8 and 94% of the patients had prior taxane treatment. Patient benefit (stable disease or better) was seen in 77% (intracranial) and 86% (extracranial) of the evaluable patients, with iORR of 15% (investigator) or 8% (independent radiology facility [IRF] review). In the leptomeningeal carcinomatosis subset, 79% of the patients had intracranial disease control and estimated median overall survival of 8.0 months (95% CI, 5.4–9.4).

Conclusions: Even though the study preset rule for iORR per IRF was not met in this heavily pretreated population, a notable CNS and systemic treatment effect was seen in all patients including symptom improvement and prolonged overall survival compared to historical control for the subset of patients with leptomeningeal carcinomatosis ($n = 28$).

Introduction

With targeted systemic therapies for metastatic breast cancer that prolong the overall survival (OS) of subpopulations of patients with breast cancer, the incidence of central nervous system (CNS) metastases including both brain parenchymal and leptomeningeal brain metastases has become an increasingly significant cause of morbidity and mortality because few treatment options effectively cross the blood–brain barrier (BBB) or blood–cerebrospinal fluid (CSF) barrier (BCB; refs. 1, 2). Even with good CNS penetration, many of these new therapies are targeted to specific subgroups of tumors having particular receptors or expression profiles, and therefore would only be able to effectively treat a proportion of patients with breast cancer with CNS involvement.

Brain metastases (BMs) are diagnosed in approximately 15% to 30% of patients with breast cancer, primarily in the later stages of their disease (3–6). In the modern era of improving systemic agents and immunotherapies, systemic disease is often better controlled; however, treatment options for BM remain limited, with median survival of 2.6 to 11 months despite therapy and 1- and 2-year survival rates are approximately 20% and 2%, respectively (7, 8).

Leptomeningeal carcinomatosis from breast cancer is a particularly disabling condition that may originate by direct seeding from circulating cancer cells, or from direct extension of a metastatic parenchymal brain lesion to the meninges. Reports that 4,000 patients are diagnosed annually with breast cancer leptomeningeal carcinomatosis in the United States probably underestimate the actual incidence, as autopsy studies suggest a substantial amount of underdiagnosis (9, 10). Leptomeningeal carcinomatosis treatment options are limited to radiation, and off-label intrathecal or systemic chemotherapies (11). The rapid and expansive tumor growth along the meningeal

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Translational Relevance

Leptomeningeal carcinomatosis from breast cancer is a disabling condition with few treatment options limited to local radiation, a few systemic chemotherapies and off label use of select intrathecal therapies. The rapid and expansive tumor growth along the meningeal membranes results in rapid clinical deterioration and short median survival of patients with leptomeningeal carcinomatosis, that is, 3 to 4 months when treated. The blood–brain barrier, blood–tumor barrier, and blood–CSF barrier limit the ability of systemic therapeutics to reach their intended target for treating leptomeningeal carcinomatosis. The phase II study provided evidence that by linking Angiopep-2 to paclitaxel, ANG1005 can cross the barriers and reach its target in the central nervous system (CNS) and meninges where paclitaxel is released to exhibit its antitumor activity. ANG1005 is a novel nontargeted therapeutic candidate for the treatment of all metastatic breast cancer with spread in the CNS and the meninges, due to its efficacy both in the CNS and systemically.

membranes results in rapid clinical deterioration (12), and no treatment has provided durable clinical benefits in breast cancer leptomeningeal carcinomatosis (13). In addition to physical barriers for drug delivery, most patients who develop leptomeningeal carcinomatosis have been treated extensively for their metastases and their disease may be resistant to traditional therapeutics. As a result, leptomeningeal carcinomatosis remains difficult to treat and the poor prognosis (median OS of 3–4 months) has not changed in 20 years of published research (14–18).

For decades, paclitaxel has been a mainstay therapy for HER2-positive and HER2-negative breast cancer (19), non–small and small cell lung cancer (20, 21) and ovarian cancer (22, 23) but has not been used to treat primary brain tumors, as early studies reported paclitaxel concentrations in brain substantially less than those in most other tissues (24, 25), indicating it does not cross the intact blood–CNS barriers (26, 27). More recent studies further confirmed that in a compromised BBB animal model, paclitaxel reaches cytotoxic concentrations in only a small percentage (~10%) of the most permeable brain metastases (28).

ANG1005 (paclitaxel trevatide) is a novel peptide–drug conjugate consisting of three paclitaxel molecules covalently linked to a proprietary 19-amino acid peptide (Angiopep-2). Angiopep-2 was designed to cross the CNS barriers via low-density lipoprotein receptor-related protein 1 (LRP1) mediated transcytosis (26, 29, 30) because of the high expression of LRP1 receptors on the surface of capillary endothelial cells at the BBB (31, 32) and in meningeal blood vessels and choroid plexus (BCB; refs. 33, 34).

Accumulation of Angiopep-2 in the meninges and parenchyma was demonstrated by intravital microscopy of fluorescently labeled Angiopep-2 after injection into a mouse brain (**Fig. 1**; unpublished data, courtesy of S. Rivest and P. Préfontaine, Laval University, 2014). Preclinical studies using *in situ* mouse and rat brain penetrating models demonstrated increased ANG1005 brain uptake compared with paclitaxel and proved that ANG1005 is not a substrate to the P-glycoprotein (P-gp) efflux pump (27, 29, 35).

Because LRP1 is also expressed on tumor cells in both CNS and systemic metastases, ANG1005 gains entry via LRP1 mediated endocytosis (29, 36, 37), where paclitaxel is cleaved from the peptide backbone by lysosomal esterases (35).

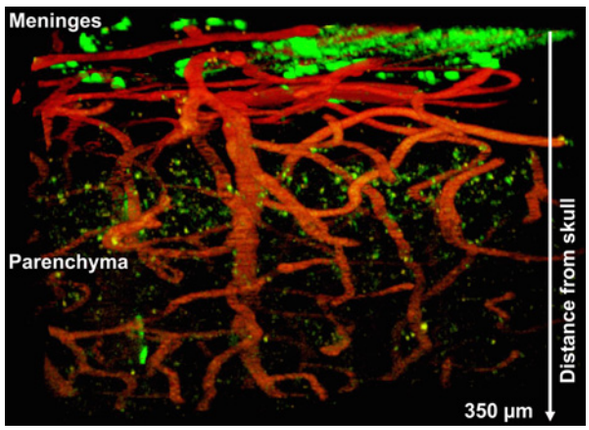

Figure 1.
Accumulation of Angiopep-2 in meninges and parenchyma of mouse brain. Demonstration of Angiopep-2 accumulation in meninges and parenchyma of living mouse brain (intravital imaging 5 days after intravenous administration). Red: vasculature depicted with Dextran Texas Red. Green: unconjugated Angiopep (S. Rivest and P. Préfontaine, 2014, Laval University, data on file).

In a phase I study, ANG1005 was detected at therapeutic concentrations in recurrent glioma tumors resected 3 to 6 hours after a single intravenous administration of ANG1005, providing evidence of transport across the BBB and tumor penetration (38).

Patients treated with ANG1005 in phase I studies of recurrent glioma and solid tumor BM had adverse events similar to those seen with paclitaxel, as neutropenia was the dose-limiting toxicity (38, 39). Evidence of ANG1005 antitumor activity was seen in both CNS and peripheral disease at doses ranging from 420 to 650 mg/m^2 in patients with BM (39, 40). Tumor responses with ANG1005 were seen in a phase II BCBM study with 15 of 61 (25%) patients with partial responses (PR). In addition, responses were seen in peripheral (non-CNS) metastases with one of 33 (3%) patients with complete response (CR) and eight of 33 (24%) patients with PR (40). On the basis of preclinical and early clinical data, this phase II study in patients with BCBM with or without leptomeningeal carcinomatosis was conducted to further evaluate ANG1005 antitumor activity at the recommended phase II dose (RP2D) of 600 mg/m^2.

Patients and Methods

Eligibility criteria

Eligibility criteria included the following: age ≥18 years, histologically or cytologically documented breast cancer, known HER2, ER, PgR status, unequivocal radiologic evidence of recurrent brain metastases with or without leptomeningeal carcinomatosis after CNS-targeted therapy, with ≥1 radiologically confirmed and measurable brain lesion per protocol-defined CNS RECIST criteria. A Karnofsky performance status (KPS) score ≥70, neurologically stable, adequate hematologic, hepatic, and renal function with ≥3 months of expected survival were also required. Relevant exclusion criteria included: whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) within 3 months of study entry, unstable or uncompensated organ system dysfunction, known severe hypersensitivity or allergy to paclitaxel or its components, evidence of uncontrolled diseases or infection, CNS disease requiring emergency neurosurgical intervention, peripheral neuropathy grade ≥2, inadequate bone marrow reserve, prior exposure to ANG1005, exposure to P450 CYP 3A4 and 2C8 enzyme-inducing

anticonvulsant drugs within 2 weeks, and other concomitant drugs to be adequately washed out prior to study entry based on specific therapeutic half-life.

Institutional Review Board approval and written informed consents were obtained from the subjects.

Study design

This open-label, multicenter phase II study was designed to evaluate efficacy, safety, and tolerability of ANG1005 in adult patients with breast cancer and recurrent BM and conducted in accordance with the Declaration of Helsinki. Patients were evaluated in a single cohort ($n = 72$) treated with ANG1005. Patients with HER2-positive breast cancer were allowed to continue trastuzumab or ado-trastuzumab emtansine (TDM-1; one patient only), while patients with ER/PgR-positive disease were allowed to continue hormonal therapy, in combination with ANG1005 for management of extracranial disease according to standard of care.

Although the study was originally planned to focus on HER2-positive breast cancer patient population due to the high incidence of BM in these patients, the protocol was amended shortly after study initiation to better represent and expand the available patient population to include patients with HER2-negative disease, triple-negative breast cancer (TNBC) disease and leptomeningeal carcinomatosis, and to better assess which patient population will benefit most from ANG1005. Patients with leptomeningeal carcinomatosis were initially excluded from this and earlier trials of ANG1005 because of the expected short survival of these patients, but due to unmet clinical need and preclinical evidence of ANG1005 crossing the BCB, this exclusion criterion was removed by amendment. Patients with leptomeningeal carcinomatosis only, without BM, did not meet the eligibility of the study.

ANG1005 was administered at the RP2D of 600 mg/m^2 by intravenous infusion every 3 weeks (one cycle), similar to paclitaxel dosing regimen. Patients remained on study treatment until documented disease progression or unacceptable toxicity. Dose reductions or delays were allowed at any dosing cycle if toxicity was observed. Patients were monitored during infusion and for a minimum of 1 hour following the infusion.

Patients were evaluated for intracranial and extracranial tumor responses by MRI and CT at baseline and after every two cycles (ie, every 6 $\pm$ 2 weeks) until disease progression. Intracranial disease assessment data was collected, as feasible, from patients who terminated treatment for reasons other than disease progression until documentation of CNS progression. Survival follow-up after treatment discontinuation was done at approximately 8-week intervals from the date of last dose.

Neurocognitive testing

Neurocognitive testing was performed at baseline and every 12 weeks until end of treatment. The battery included the following tests: Hopkins Verbal Learning Tests – Revised (HVLT-R; ref. 41), Trail Making Test (TMT; ref. 42), and Controlled Oral Word Association (43).

Evaluation of efficacy

The primary endpoint was determination of intracranial objective response rate (iORR) as evaluated by central IRF. Secondary endpoints included iORR per investigator, overall survival (OS), intracranial progression-free survival (PFS), intracranial clinical benefit rate (iCBR), defined as percentage of patients with best intracranial response of CR, PR, or stable disease (SD) (overall, and at 3 and 6 months), 6-month overall survival rate, and extracranial response rate. Efficacy evaluations were done locally at investigator sites for real-time patient management, and then sent for retrospective IRF reading.

Table 1. Determination of intracranial responses based on CNS RECIST v1.1 protocol-specific criteria.

Criterion	CR[a]	PR[a]	SD	PD
Target lesions—up to 5 measurable[b] lesions in the brain	None	≥30% ↓	<30% ↓ but <20% ↑	≥20% ↑[c]
Nontarget lesions in the brain	None	Stable or ↓	Stable or ↓	↑[c]
New lesion or clinical disease progression in the brain	None	none	none	Present[c]
Corticosteroids for CNS disease[d]	Please refer to the definitions below.			

Abbreviations: CNS, central nervous system; CR, complete response; PR, partial response.

[a]To confirm CR and PR, it is required that the response is sustained for at least 4 weeks.

[b]Measurable lesions were defined as lesions ≥10 mm in the longest diameter for slice thickness between 1.5 and 3 mm; or ≥5 mm in the longest diameter for slice thickness ≤1.5 mm; nonmeasurable lesions are <5 mm in the longest diameter.

[c]Progression occurs when this criterion is present only for intracranial disease.

[d]Corticosteroids consideration for CNS response: CR, no corticosteroids above physiologic levels (ie, equivalent of 20 mg of hydrocortisone per day); PR, corticosteroid dose at the time of the MRI must be no greater than the maximum dose used in the first 6 weeks from initiation of therapy; SD and PD, corticosteroid dose does not change determination of stable disease.

Intracranial evaluations were performed using protocol-specified CNS RECIST, v1.1 for 1-dimensional assessment. Extracranial tumor evaluations were performed according to RECIST v1.1 (44) in all organs in which disease was present, excluding brain. Evaluations were only made on clearly measurable extracranial disease (ie, with a minimum size of 10 mm in at least one dimension). Disease assessments were performed before treatment and every 6 weeks thereafter.

For intracranial disease assessment, all target and nontarget lesions (parenchymal brain metastases) per CNS RECIST v1.1 were documented at screening (≤14 days before the first dose of ANG1005), and reassessed at each subsequent tumor evaluation time point after every two cycles (ie, every 6 $\pm$ 2 weeks) during treatment up to end of treatment visit. CNS RECIST v1.1 criteria are provided in **Table 1**, otherwise RECIST v1.1 was followed. Scans for intracranial disease assessment were performed with Gd-MRI at a contiguous (no skip) ≤3 mm slice thickness. Target lesions were required to measure ≥5 mm in longest diameter when imaging slice thickness was up to 1.5 mm; this applied to 41 patients (IRF evaluation) and 24 patients (investigator evaluation). If the minimal slice thickness was >1.5 mm but ≤3 mm, the target lesions were required to measure ≥10 mm in longest diameter. Non-SRS–treated brain lesion(s) or progressing brain lesions previously treated with SRS ≥3 months prior to baseline were also allowed as target lesions.

Radiographic CNS responses were determined based on CNS RECIST v1.1 by comparing the sum of the longest diameters of target (enhancing) lesions obtained posttreatment to baseline or to the smallest tumor measurement (nadir) for determination of progression. Criteria for determination of tumor responses were as follows (all required): CR, if all target and nontarget CNS lesions disappeared, no new lesions and no corticosteroid dose above the physiologic levels (ie, equivalent of 20 mg of hydrocortisone per day); PR, if ≥30% decrease in the sum of the longest diameters of target lesions compared with baseline, stable or improved nontarget lesions, no new lesions and no change in the corticosteroid dose; SD, if <30% decrease and <20% increase in the sum of the longest diameters of target lesions, stable or improved nontarget lesions and no new lesions. To confirm CR or PR,

the response must be sustained for ≥4 weeks. PD was determined if any of the following criteria was present: ≥20% increase in the sum of the longest diameters of target lesions when compared with nadir (the sum should also demonstrate an absolute increase of ≥5 mm), increase in size of any nontarget lesion, appearance of a new lesion, or clinical deterioration based on CNS symptoms, as determined by the local investigator.

Patients with CNS SD or better (clinical benefit) would remain on ANG1005 treatment until intracranial disease progression is documented. Patients experiencing extracranial progression had to discontinue protocol therapy, unless there was evidence of clinical and radiographic improvement of BM, attributed to ANG1005 and the systemic progression is asymptomatic.

Statistical analysis

The primary efficacy analysis included estimation of iORR per CNS RECIST v1.1 criteria using a 95% confidence interval (95% CI) with statistical influence under the framework of Simon's Optimal 2-stage design. Sample size calculation yielded a total of 56 patients, 23 for the first stage. If ≤1 intracranial objective response is observed, then the alternative hypothesis that the true ORR is >15% would be rejected, indicating no further ANG1005 investigation. An additional 33 patients would enroll if stage one yielded ≥2 intracranial objective responses, looking for a total of >5 objective responses out of 56 patients, as determined by IRF.

Patients were considered evaluable per protocol if they had completed clinical evaluation and/or a postdose scan at ≥4 weeks from first dose of ANG1005.

Subgroup analysis of intracranial response rate based on HER2 status, presence or absence of prior cranial radiation (including WBRT and SRS), and taxane therapy was also performed.

Probabilities of intracranial PFS, OS, and distribution of duration of intracranial response were estimated using the Kaplan–Meier method. The OS rate at 6 months was determined as the percentage of patients who were alive at 6 months after first ANG1005 dose according to the Kaplan–Meier method.

Extracranial ORR was determined according to RECIST v1.1 criteria using a 95% CI. OS subgroup analysis for patients with leptomeningeal carcinomatosis and per HER2 status was performed.

Safety data including incidence of adverse events, related to ANG1005 treatment, were summarized by system organ class and preferred terms according to Medical Dictionary for Regulatory Activities (MedDRA) v.18, and severity per NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4.01 grade. Critical laboratory data are presented as changes from baseline to maximum posttreatment value based on local lab normal ranges.

Neurocognitive function test data were analyzed by descriptive statistics (mean, SD, and median) and change in neurocognitive function from baseline to each follow-up time point was categorized as improved, stable or declined based on the reliable change index (RCI) for each test (45, 46).

Results

Patient characteristics

Seventy-two (72) female patients with BCBM were enrolled in the study. The patient population was nearly equally divided into HER2-positive (31, 43%) and HER2-negative (41, 57%), the latter including 19 (26%) patients with TNBC.

Median age was 47.5 (range, 26–76) years. At the time of first study treatment, median time since initial diagnosis of breast cancer was 4.4 years and the median time from first BM diagnosis was 1.1 years. Sixty-eight (68, 94%) patients had previously received at least one course of taxane therapy (median, 1; range, 1–4). Sixty-one (61, 85%) patients had prior intracranial radiotherapies including intensity modulated radiotherapy, WBRT, or SRS (median, 1; range, 1–11). Furthermore, 18 (25%) patients had prior CNS-directed chemotherapies including intrathecal (ie, cytarabine, methotrexate, trastuzumab) or systemic therapies (ie, capecitabine alone or in combination with lapatinib, paclitaxel + bevacizumab + temsirolimus combination, doxorubicin, carboplatin, neratinib, temozolomide, vinorelbine; median, 1; range, 1–3), as shown in **Table 2**. Sixty-six (66, 92%) patients had at least one therapy targeting the CNS disease with average number of prior CNS-directed therapies per patient of 2.8 (SD, 2.4; median, 2; range, 1–13).

Twenty-eight (28, 39%) of the 72 patients with BCBM were diagnosed with leptomeningeal carcinomatosis including 16 (57%) HER2-positive and 12 (43%) HER2-negative patients. Median time from leptomeningeal carcinomatosis diagnosis to first dose of ANG1005 was 1 month. Twenty-seven (27, 96%) patients with leptomeningeal carcinomatosis previously received at least one course of taxane therapy (median, 1; range, 1–3). In addition, 25 (89%) patients received at least one therapy for CNS metastases. Detailed baseline patient characteristics and oncologic history are presented in **Table 2**.

ANG1005 administration

The median number of ANG1005 cycles, delivered every 3 weeks, received was 3 (range, 1–10).

Safety

Safety and tolerability of ANG1005 was consistent with expected taxane profile. Overall, 69 (96%) of the 72 patients, who received at least one cycle of ANG1005, experienced an adverse event considered related to ANG1005; however, only a small number of patients ($n = 5$, 7%) withdrew due to adverse events. Twenty-four (24, 33%) experienced any level of dose reduction. Of those 24 patients, the first dose reduction occurred at the following cycle: cycle 2 in 10 patients (10, 42%), cycle 3 (7, 29 %), cycle 4 (3, 13%), cycle 5 (1, 4%), cycle 8 (2, 8%), and cycle 9 (1, 4%). Twenty-two (22, 31%) patients required dose reductions from 600 to 550 mg/m^2, and one (1%) patient from 600 to 470 mg/m^2. Nine patients (9, 12%) had further reductions from 550 to 470 mg/m^2 and two (3%) patients had the dose reduced from 470 to 400 mg/m^2.

The most common toxicities were related to myelosuppression with several hematologic toxicities seen at grade ≥3, as follows: reduced white blood cell count documented in 45 (62%) patients, neutrophil count decreased (46, 64%), lymphocyte count decreased (31, 43%), platelet count decreased (11, 15%), and anemia (9, 13%). In addition, 13 (18%) patients experienced febrile neutropenia including 12 (17%) at grade ≥3. The most frequent nonhematologic ANG1005-related toxicities included fatigue and nausea in 37 (51%) and 28 (39%) patients, respectively. Peripheral neuropathy/peripheral sensory neuropathy was reported in 28 (39%) patients. Few patients experienced grade 3 nonhematologic toxicity, including eight (11%) with grade 3 fatigue, four (6%) with grade 3 nausea, and six (8%) with grade 3 peripheral neuropathy. None of these most common nonhematologic events were seen at grade 4.

Efficacy

All patients with BCBM

Of the 72 patients, 60 were considered evaluable per protocol for intracranial (parenchymal) response by completing clinical evaluation and/or a postdose scan at ≥4 weeks from first ANG1005 dose. The remaining 12 patients did not meet these criteria as they either did not

Table 2. Baseline patient characteristics – oncology history.

	All patients ($n = 72$)	LC patients ($n = 28$)
Histology of primary tumor, *n* (%)		
Infiltrating ductal carcinoma	51 (71%)	20 (71%)
Infiltrating lobular carcinoma	2 (3%)	2 (7%)
Inflammatory breast carcinoma	2 (3%)	0
Other	17 (24%)	6 (21%)
Stage at initial breast cancer diagnosis, *n* (%)		
0/I/IIA/IIB	36 (50%)	13 (46%)
IIIA/IIIB/IIIC/IV	36 (50%)	15 (54%)
Time from primary BC diagnosis to first dose, years		
Median (range)	4.4 (0.8–31.0)	3.6 (0.8–25.1)
Number of brain metastases		
Median (range)	3.0 (1–40)	3.0 (1–25)
Size of brain metastases		
At least one target lesion >1 cm, *n* (%)	57 (79%)	22 (79%)
All target lesions measuring 0.5–0.9 cm, *n* (%)	15 (21%)	6 (21%)
Time from brain metastases diagnosis to first dose, years		
Median (range)	1.1 (0.1–6.4)	1.0 (0.1–3.4)
Time from LC diagnosis to first dose, months		
Median (range)	NA	1.0 (0–12)
HER2 status		
Positive	31 (43%)	16 (57%)
Negative	41 (57%)	12 (43%)
Estrogen receptor status		
Positive	39 (54%)	17 (61%)
Negative	33 (46%)	11 (39%)
Progesterone receptor status		
Positive	29 (40%)	15 (54%)
Negative	43 (60%)	13 (46%)
Patients with triple-negative breast cancer, *n* (%)	19 (26%)	4 (14%)
Prior intracranial surgeries, *n* (%)	23 (32%)	11 (39%)
Mean (SD)	1.6 (0.8)	1.5 (0.7)
Median (range)	1.0 (1–4)	1.0 (1–3)
Prior intracranial radiotherapies[a], *n* (%)	61 (85%)	21 (75%)
Mean (SD)	2.0 (1.8)	1.8 (1.6)
Median (range)	1.0 (1–11)	1.0 (1–8)
Prior CNS-directed chemotherapies[b], *n* (%)	18 (25%)	10 (36%)
Mean (SD)	1.4 (0.7)	1.6 (0.8)
Median (range)	1.0 (1–3)	1.0 (1–3)
Prior taxane therapy, *n* (%)	68 (94%)	27 (96%)
Mean (SD)	1.6 (0.8)	1.4 (0.6)
Median (range)	1.0 (1–4)	1.0 (1–3)
Prior anti-HER2 therapy, *n* (%)	35 (49%)	18 (64%)
Mean (SD)	3.7 (2.9)	2.8 (1.3)
Median (range)	3.0 (1–17)	3.0 (1–5)
Prior steroid use, *n* (%)	69 (96%)	26 (93%)
Mean (SD)	1.5 (0.6)	1.6 (0.7)
Median (range)	1.0 (1–3)	1.5 (1–3)
KPS, *n* (%)		
60	2 (3%)	1 (4%)
70	11 (15%)	8 (29%)
80	23 (32%)	9 (32%)
90	31 (43%)	8 (29%)
100	5 (7%)	2 (7%)

Abbreviations: BC, breast cancer; CNS, central nervous system; LC, leptomeningeal carcinomatosis; *n*, number; NA, not applicable; SD, standard deviation; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.
[a]Including intensity-modulated radiotherapy (IMRT), SRS, and WBRT.
[b]CNS-directed chemotherapies include intrathecal or systemic therapies.

have a postdose disease evaluation or the evaluation was performed earlier than the minimal required period of 4 weeks after first ANG1005 dose. Interim analysis was conducted at the time when the first 23 patients were enrolled, showing two patients with documented intracranial objective response and thus, as per protocol, the study was continued.

On the basis of the CNS tumor response assessment, performed by local investigators, there were nine (15%) evaluable patients with PR including five (8%) confirmed PR (to confirm PR, it was required that the response was sustained for ≥4 weeks), and 32 (53%) evaluable patients with SD, resulting in an overall iORR of 15% and iCBR of 68%. These response rates are based on the 60 protocol-defined evaluable patients; therefore, only a slight difference could be expected if the 12 dosed, nonevaluable patients were also included. The majority of the evaluable patients had received at least one prior taxane therapy (n = 58, 97%; **Fig. 2A**), with iORR (95% CI) of 16% (7.3–27.4) and iCBR of 69% (55.5–80.5) in these patients who had previously progressed on taxane. Patients with no prior cranial radiation (n = 10, 17%) had higher iORR (95% CI) of 50% (18.7–81.3) compared with 8% (2.2–19.2) for the patients who were previously exposed to cranial radiation (n = 50, 83%). Investigator assessments resulted in median intracranial PFS of 2.8 months and the 3-month intracranial PFS rate was 52%. Median duration of response for the nine responding PR patients was 12.5 weeks (6.7–26.3).

Overall, intracranial response, as assessed by IRF was similar to the investigator assessment, with no complete responses, five (8%) patients with PR and 41 (68%) patients with SD as best response. The iORR was 8% and the overall iCBR was 77%. Better tumor response was achieved

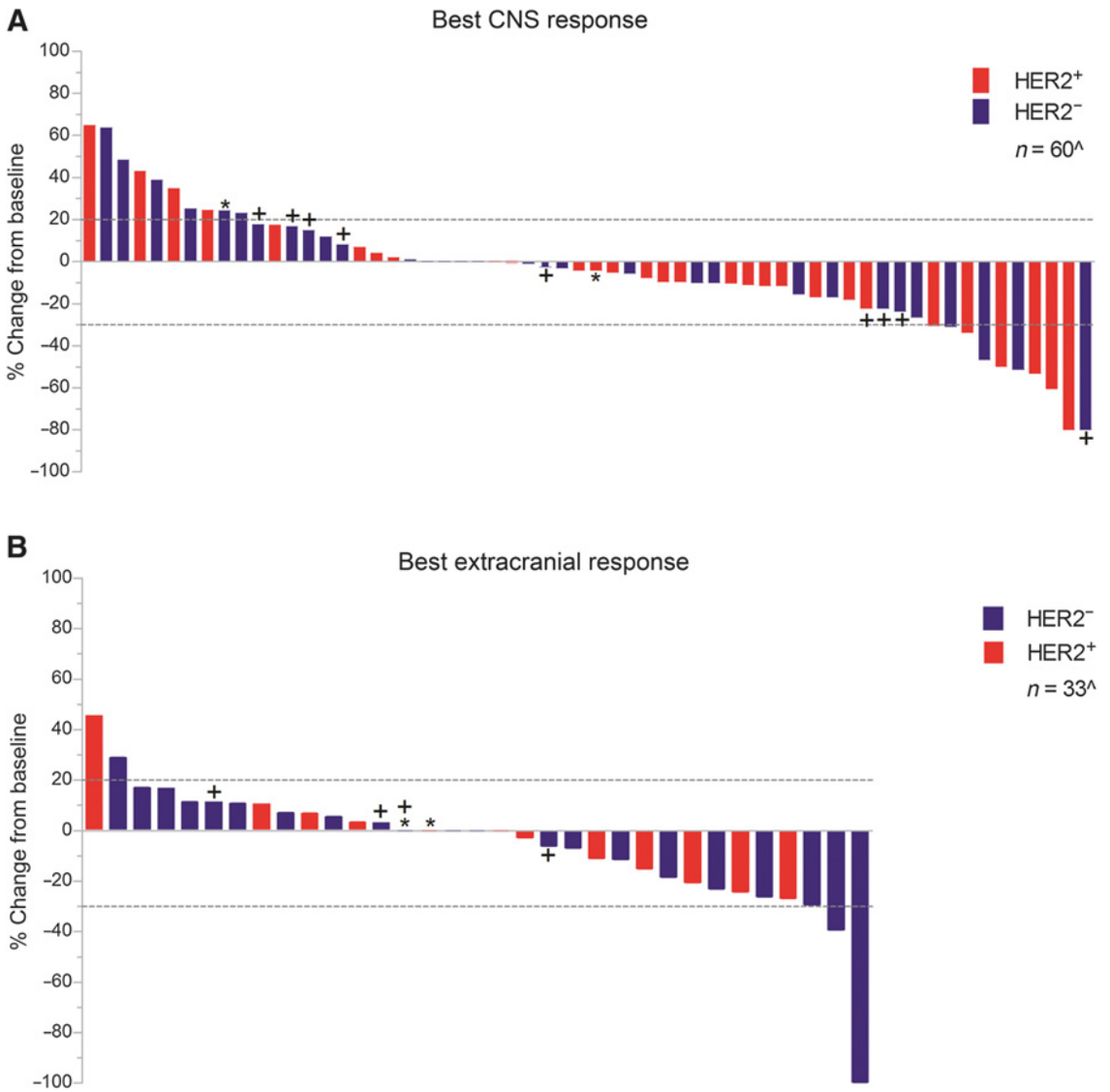

Figure 2.

Best CNS (**A**) and extracranial (**B**) response in BCBM-evaluable patients treated with ANG1005 as assessed by the investigators. *Taxane-naïve patients; all remaining patients had received prior taxane therapy. + PD determined due to progression in nontarget lesions or appearance of new lesions, or clinical progression. ^ Based on per-protocol efficacy population defined as patients with CNS disease evaluation ≥4 weeks from C1D1 with measurable lesions per CNS RECIST v1.1 (CNS response) or per RECIST v1.1 (extracranial response), as determined by investigator. An additional five patients (four $HER2^+$ and one $HER2^-$) were determined to have extracranial SD based on nontarget lesions only. One additional patient with $HER2^+$ disease was determined to have an extracranial PR; however, no measurements were provided. Data not graphed since no measurable lesions were noted.

Table 3. Intracranial tumor assessment by IRF and by investigator.

Assessment	All BCBM ($n = 60$)	HER2-positive ($n = 29$)	HER2-negative ($n = 31$)	TNBC ($n = 13$)[a]	LC ($n = 24$)
Investigator					
CNS RECIST 1.1 best response, *n* (%)					
CR	0	0	0	0	0
PR[g]	9 (15%)	6 (21%)	3 (10%)	1 (8%)	7 (29%)
Confirmed PR[b]	5 (8%)	3 (10%)	2 (6%)	0	4 (17%)
SD	32 (53%)	18 (62%)	14 (45%)	5 (38%)	9 (38%)
PD	19 (32%)	5 (17%)	14 (45%)	7 (54%)	8 (33%)
Intracranial ORR, *n* (%)	9 (15%)	6 (21%)	3 (10%)	1 (8%)	7 (29%)
(95% CI)[c]	(7.1–26.6)	(8.0–39.7)	(2.0–25.8)	(0.2–36.0)	(12.6–51.1)
Overall intracranial CBR, *n* (%)	41 (68%)	24 (83%)	17 (55%)	6 (46%)	16 (67%)
(95% CI)[c]	(55.0–79.7)	(64.2–94.2)	(36.0–72.7)	(19.2–74.9)	(44.7–84.4)
Intracranial PFS[d]					
Median PFS, weeks (95% CI)[e]	12.1 (9.3–18.3)	14.1 (11.1–23.4)	11.1 (6.0–16.6)	–	12.4 (7.0–23.4)
3-month PFS rate, % (95% CI)[f]	52% (38.6%–64.0%)	61% (40.6%–76.1%)	44% (26.2%–60.5%)	–	54% (32.7%–71.4%)
6-month PFS rate, % (95% CI)[f]	18.7% (9.5%–30.2%)	27.0% (12.0%–44.6%)	11.2% (2.9%–25.8%)	–	25.5% (9.5–45.2)
IRF					
CNS RECIST 1.1 best response, *n* (%)					
CR	0	0	0	0	0
PR[b]	5 (8%)	4 (14%)	1 (3%)	1 (8%)	4 (17%)
SD	41 (68%)	20 (69%)	21 (68%)	7 (54%)	15 (62%)
PD	12 (20%)	5 (17%)	7 (23%)	4 (31%)	4 (17%)
Missing	2 (3%)	0	2 (6%)	1 (8%)	1 (4%)
Intracranial ORR, *n* (%)	5 (8%)	4 (14%)	1 (3%)	1 (8%)	4 (17%)
(95% CI)[c]	(2.8–18.4)	(3.9–31.7)	(0.1–16.7)	(0.2–36.0)	(4.7–37.4)
Overall intracranial CBR, *n* (%)	46 (77%)	24 (83%)	22 (71%)	8 (62%)	19 (79%)
(95% CI)[c]	(64.0–86.6)	(64.2–94.2)	(52.0–85.8)	(31.6–86.1)	(57.8–92.9)
Intracranial PFS[d]					
Median PFS, weeks (95% CI)[e]	16.6 (12.7–20.6)	20.1 (11.9–25.0)	15.3 (11.1–18.3)	–	14.9 (12.7–23.4)
3-month PFS rate, % (95% CI)[f]	67% (52.5%–77.8%)	71% (49.9%–84.3%)	63% (41.3%–78.2%)	–	83% (60.3%–93.2%)
6-month PFS rate, % (95% CI)[f]	23% (10.5%–37.8%)	31% (12.6%–51.3%)	16% (3.2%–36.6%)	–	25% (6.7%–49.2%)

Abbreviations: CBR, clinical benefit rate (CR + PR + SD); LC, leptomeningeal carcinomatosis; ORR, objective response rate (CR + PR).
[a]Only ORR and iCBR analyses stratified for TNBC.
[b]To confirm PR, it is required that the response is sustained for at least 4 weeks. All PR reported by IRF were already confirmed.
[c]95% CI for the frequency distribution is Clopper–Pearson exact CI.
[d]Kaplan–Meier methodology is used to estimate PFS.
[e]95% CIs for median are computed using Brookmeyer and Crowley method.
[f]95% CIs for rate are computed using Greenwood's formula.
[g]Investigators reported PR and confirmed PR separately.
– analysis not done.

in the HER2-positive patients compared with HER2-negative with iORR of 14% and 3%, respectively (**Table 3**). Median intracranial PFS was 3.8 months and 3-month intracranial PFS rate was 67%. Median duration of response for the five responding PR patients was 9 weeks (6.7–19.4).

Systemic disease control was also documented in patients with BCBM, evaluable for extracranial tumor response. The extracranial responses were as follows: (i) as assessed by the investigators: $n = 39$, one CR (3%), three PR (8%), 29 SD (74%), and six PD (15%); (ii) as assessed by IRF: $n = 51$, three CR (6%), five PR (10%), 36 SD (71%), six PD (12%), and one missing (2%). The majority of patients evaluated for extracranial response had previously progressed on taxane therapy ($n = 37$; 95%; **Fig. 2B**).

The overall survival rate at 6 months (95% CI) in all enrolled patients ($n = 72$) was 56% (43%–66%). Survival analysis per HER2 status showed an OS rate at 6 months of 67% (47%–81%) and 47% (30%–62%) in HER2-positive and HER2-negative patients, respectively. The Kaplan–Meier estimated median OS (95% CI) was 7.8 (5.1–9.0) months for all, 9.9 (5.6–12.0) months for HER2-positive and 4.3 (3.4–8.0) months for HER2-negative patients from first ANG1005 dose.

Subset of patients with leptomeningeal carcinomatosis

In the absence of established diagnostic criteria for leptomeningeal carcinomatosis, the 28 patients with leptomeningeal carcinomatosis were identified based on imaging by craniospinal MRI in conjunction with symptoms. Parenchymal brain tumor responses (by MRI) were evaluable in 24 patients who met the protocol-specified criteria for evaluable patients, that is, with clinical evaluation and/or a postdose scan at ≥4 weeks from first dose of ANG1005. Investigator-based assessments of intracranial tumor response resulted in seven (29%) patients with PR, four (17%) of which were confirmed, and nine (38%) patients with SD. Investigator determined ORR was 29% and the iCBR was 67%. In terms of HER2-status stratification, more responses were seen in the HER2-positive patients with six (40%) PR versus one (11%) PR in the HER2-negative subset of patients with leptomeningeal carcinomatosis.

CNS assessment by IRF reported four (17%) patients with PR and 15 (62%) with SD as best response, resulting in 17% iORR and iCBR of

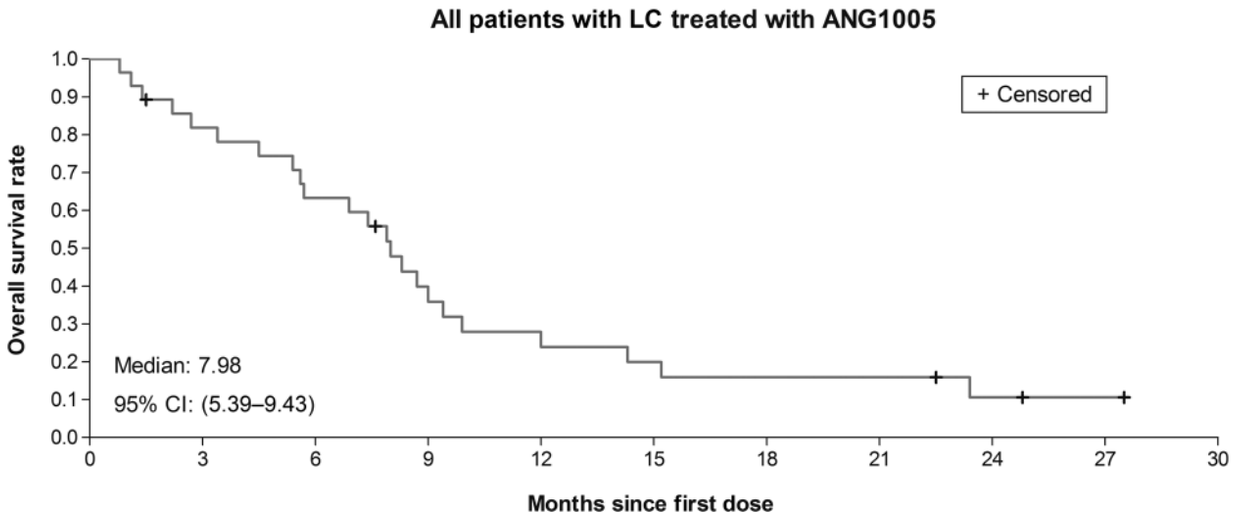

Figure 3.
Kaplan–Meier estimates of survival in patients with leptomeningeal carcinomatosis (LC) BCBM ($n = 28$) treated with ANG1005.

79% (**Table 3**). Parenchymal responses were accompanied by radiologic and/or clinical improvements of leptomeningeal metastases, as documented in three (75%) of the four patients with PR.

The investigator determined intracranial median PFS was 2.8 months and the 3-month PFS rate was 54% (**Table 3**). Median duration of response was 18 weeks (7.3–26.3). Median PFS for patients with leptomeningeal carcinomatosis per IRF was 3.4 months and the 3-month PFS rate was 83%. Median duration of response was 11 weeks (7.3–19.4).

Of the 28 patients with leptomeningeal carcinomatosis, 16 were evaluable for systemic disease per investigator. The extracranial ORR was 6% (0.2–30.2) based on one patient with PR. Systemic disease control was seen in the majority of evaluable patients with leptomeningeal carcinomatosis and included 14 (88%) patients with SD. The IRF review identified 23 patients who were evaluable for systemic disease. The extracranial ORR was 9% and the overall CBR was 87% per IRF based on two PR (9%) and 18 SD (78%).

Median OS for the patients with leptomeningeal carcinomatosis ($n = 28$) was estimated to be 8.0 (95% CI, 5.4–9.4) months (**Fig. 3**). On the basis of HER2 stratification, the median OS was 9.0 (5.4–15.2) months for the HER2-positive ($n = 16$) and 7.6 (1.4–9.4) months for the patients with HER2-negative leptomeningeal carcinomatosis ($n = 12$). The median OS was also evaluated in the subset of patients with TNBC leptomeningeal carcinomatosis ($n = 4$) and was estimated to be 2.8 (0.8–8.7) months. The OS rate at 6 months (95% CI) was 63% (42%–78%) in all patients with leptomeningeal carcinomatosis. The OS rate at 6 months was 60% (32%–80%), 67% (34%–86%), and 25% (1%–66%) in patients with HER2-positive, HER2-negative, and TNBC leptomeningeal carcinomatosis, respectively.

Neurocognitive function

Posttreatment test results were obtained from only 18 patients at week 12, because most of the remaining patients were already off study, due to progression, adverse events or other reasons for treatment discontinuation. The baseline KPS was similarly distributed across the 18 patients with 12-week neurocognitive testing compared with the entire safety population ($n = 72$); therefore, the results could be extrapolated to the trial population as whole.

RCI defined stable or improved performance was observed in ≥61% of these patients. Patients evaluated posttreatment improved most frequently (38%) on the TMT Part A. Declining function posttreatment was noted in 6% to 39% of patients across the battery of tests with the HVLT-R Total Recall identifying the highest number of declining patients (39%).

Discussion

Treatment with ANG1005 resulted in notable patient benefit both in CNS and systemic disease despite prior taxane therapy in almost all patients. Overall intracranial clinical benefit, defined as the percentage of patients with best intracranial response of CR, PR, or SD according to CNS RECIST v.1.1 per investigator, was seen in 68% of patients, regardless of HER2 status. As expected, the determination of true intracranial response was difficult in this heavily pretreated patient population with BCBM, which included 85% of patients with prior brain radiotherapy. This may have led to intracranial imaging ORR and PFS determinations that undervalued the full effect of ANG1005, as indicated by late responses in patients who remained on therapy due to investigator assessed response only, including a postsurgical pathologic CR (noted after treatment). At the time of study start in 2014, the RANO-BM criteria were not yet published and therefore, a protocol-specific CNS RECIST 1.1 criteria were used in the study, a response assessment criteria similar to the BM response criteria proposed by the RANO group (47), which in turn are still not considered to be completely validated tools for BM response. The current lack of such validated methods of CNS disease measurement may have resulted in differences in the reported iORR when done by different radiology facilities, explaining the variation in the results reported by the IRF versus the investigator.

Interestingly, even in the absence of validated tools, intracranial disease control was seen concurrently in both CNS compartments in patients with leptomeningeal carcinomatosis, that is, radiologic improvement of leptomeningeal disease was seen in five of the seven patients with a response in the parenchymal lesions; leptomeningeal lesions appeared stable in the two other responding patients.

This clinical trial did have a couple weaknesses worth noting. The first being that serial CSF was not collected from leptomeningeal carcinomatosis study patients. Although this was not done primarily to protect patients from having to undergo serial lumbar punctures, it is still important to collect CSF when evaluating for leptomeningeal carcinomatosis response. Another limitation was that we were evaluating response in a disease state where there is no validated measure for leptomeningeal carcinomatosis response.

Even though the predetermined study criteria for the primary endpoint of tumor response were not met, a subset of patients who benefitted from ANG1005 treatment was identified. Thus, the highest patient benefit of ANG1005 was noted for the subset of patients with leptomeningeal carcinomatosis. Because of an even higher heterogeneity in pretreatment and lack of a validated tool to measure disease progression, evaluation by OS is less disputed and more relevant for these heavily pretreated patients. The results from the survival analysis of the subset of patients with leptomeningeal carcinomatosis showed median OS of 8.0 (95% CI, 5.4–9.4) months from the first day of dosing, which surpassed the historical expectations of 2 to 4 months median survival from time of initial leptomeningeal carcinomatosis diagnosis (16–18, 48). Although it was not a predefined primary outcome for this study, a notable survival advantage to treatment with ANG1005 was seen in both HER2-positive and HER2-negative patients with leptomeningeal carcinomatosis and recurrent BCBM. The median survival in patients with HER2-positive leptomeningeal carcinomatosis of 9.0 (95% CI, 5.4–15.2) months is more than double the median OS of 4.4 (95% CI, 2.8–6.9) months reported by Abouharb and colleagues (17) based on a retrospective review of data from 56 patients with HER2-postive leptomeningeal carcinomatosis with breast cancer. Similarly, the median OS in patients with HER2-negative leptomeningeal carcinomatosis in the current study of 7.6 (95% CI, 1.4–9.4) months is greater than double the median OS of 3.7 (95% CI, 2.4–6.0) months reported by the same group based on a large retrospective review of data from 124 patients with HER2-negative leptomeningeal carcinomatosis with breast cancer. The median OS of 8.0 months seen in the ANG1005-treated patients with leptomeningeal carcinomatosis, regardless of HER2 status, is longer compared with patient subgroups receiving either intrathecal (5.0 months) or systemic therapy (6.4 months), as reported by Abouharb and colleagues (17). Although the prolonged survival noted in patients with leptomeningeal carcinomatosis is the most relevant endpoint suggesting treatment effect, CNS response was also noted and the iORR (29%) was higher in the leptomeningeal carcinomatosis subset as compared with all patients with BCBM. The documented improvement in the leptomeningeal carcinomatosis lesions in 3 (75%) of the four responding patients (both per IRF and investigator assessment) provided further evidence of an effect of ANG1005 treatment in the leptomeningeal carcinomatosis subset. Other systemic agents including high-dose methotrexate and pemetrexed have been evaluated in recent years for treatment of BM and/or leptomeningeal carcinomatosis from solid tumors with reported median OS of 4.6 months after high-dose methotrexate or 7.3 months following treatment with pemetrexed (49, 50). However, a direct comparison with our data (median OS of 8.0 months) remains difficult due to patient heterogeneity in these studies with leptomeningeal carcinomatosis origin from different primary tumors and lack of subset analyses for breast cancer patients with both BM and leptomeningeal carcinomatosis.

The prolonged survival seen in the current study is based on patients with leptomeningeal carcinomatosis who had been previously treated for their CNS metastases, including radiotherapy (75%), cranial resections (39%), and CNS-directed chemotherapy (36%) including intrathecal chemotherapy (14%). The patients were heavily pretreated with an average number of prior CNS-directed therapies per patient of 2.8 (SD, 2.5; median, 2; range, 1–11). There was no uniformity in the prior treatment for parenchymal or leptomeningeal carcinomatosis metastases. In addition, 96% were patients whose tumors had previously progressed on taxane, and yet there was a response to the taxane-derivative ANG1005. Certainly, due to the small sample size and patient heterogeneity, these results showing survival benefit in the heavily pretreated patients with BCBM with newly diagnosed leptomeningeal carcinomatosis need to be confirmed in a controlled randomized study. Subsequently, a randomized phase III study was designed to compare the OS of ANG1005 to a physician's best choice control. Despite the decades of studies indicating that paclitaxel is effective in HER2-positive, HER2-negative, TNBC, PR-positive, and ER-positive patient groups, and the subset analyses showing activity in HER2-postive, HER2-negative, TNBC, and leptomeningeal carcinomatosis breast cancer patients, the study will focus on patients with HER2-negative breast cancer with previously treated BM and newly diagnosed leptomeningeal carcinomatosis to ensure uniformity in the patient population.

In conclusion, ANG1005 resulted in notable CNS antitumor activity across multiple patient subgroups and demonstrated good efficacy systemically. To further evaluate the treatment effect seen in patients with leptomeningeal carcinomatosis who have poor prognosis, a randomized phase III study of ANG1005 compared with a physician's best choice control is underway.

Disclosure of Potential Conflicts of Interest

P. Kumthekar holds ownership interest (including patents) in Angiochem, and is an advisory board member/unpaid consultant for Elevate Bio. D.E. Piccioni is an employee/paid consultant for Tocagen. C.K. Anders is an employee/paid consultant for Genentech, Eisai, IPSEN, Seattle Genetics, and PUMA, reports receiving commercial research grants from PUMA, Lilly, Merck, Seattle Genetics, Nektar, and G1-Therapeutics, and is an advisory board member/unpaid consultant for Merck, Novartis, Merrimack, Lilly, Nektar, and Seattle Genetics, and reports receiving other remuneration from UpToDate and Jones and Bartlett. P. Chalasani is an advisory board member/unpaid consultant for Bayer, Amgen, Novartis, Heron Therapeutics, Nanostring Technologies, Eisai, and Asthenex. P. Kabos reports receiving commercial research grants (all to University of Colorado) from Pfizer, Radius Health, Eli Lilly, Angiochem, and Genentech. S.L. Puhalla is an employee/paid consultant for Abbvie, Medimmune, Celldex, Puma, Pfizer, AstraZeneca, Eisai, and Nanostring, reports receiving commercial research grants from AstraZeneca, Pfizer, and reports receiving other commercial research support from Abbvie and Lilly. M.S. Ahluwalia is an employee/paid consultant for Abbvie, AstraZeneca, BMS, Bayer, Kadmon, Karyopharm, Forma Therapeutics, VBI Vaccines, Flatrion, Varian Medical Systems, Tocagen, CBT Pharmaceuticals, and Monteris, reports receiving commercial research grants from AstraZeneca, Abbvie, Novocure, Novartis, Pharmacyclics, Incyte, BMS, Bayer, Merck, and Inspire, and holds ownership interest (including patents) in Mimivax and Doctible. J.S. Wefel is an employee/paid consultant for Angiochem, AbbVie, Bayer, Blueprint Medicines, Juno, Novocure, and Vanquish Oncology. N. Lakhani is an employee/paid consultant for Inovent Biologics. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.-C. Tang, S. Kesari, D.E. Piccioni, P. Chalasani, P. Kabos, J.S. Wefel, N. Ibrahim

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