

Interim Results of a Phase 2 Study of CT-322 (BMS-844203), a Targeted Biologic Inhibitor of VEGFR-2 Based on a Domain of Human Fibronectin, in Recurrent Glioblastoma (rGBM)

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INTRODUCTION

AdnectinTM are engineered versions of a fibronectin module with natural protein-binding characteristics

- Fibronectin protein designed by nature to bind integrins via RGD (arg-gly-asn) receptor recognition
- Natural high affinity, specific binding sites
- Well-tolerated protein
- Structurally amenable to antibody V_H domains
- Therapeutic use reduces binding loops to drug targets
- Rapidly accomplished through recombinant engineering techniques
- High molecular expression
- Stable in vivo
- CT-322 introduces 19 amino acid mutations to redress binding loops to extracellular domain of vascular endothelial growth factor receptor 2 (VEGFR-2)
- ~40 KD PEG attached to enhance plasma half-life
- Maximum tolerated dose (MTD) is weekly subcutaneous (SC) 2 mg/kg



CT-322 is a specific and potent blocker of VEGFR-2 with a distinct mechanism of action

- CT-322, a PEYated Adnectin, completely and specifically blocks VEGFR-2 signaling by all known VEGFR-2 activators (VEGF-A, C, and D)
- CT-322 specifically inhibits primary tumor angiogenesis pathway only

BACKGROUND

- Treatment of recurrent glioblastoma (rGBM) is an unmet medical need
- Historical 6-month progression-free survival (PFS-6) 9% to 15% in pooled studies^{1,2}; 18% to 21% with temozolomide³
- Overall survival, median, 5-6 months
- VEGF-A/VEGFR-2 signaling is a key for GBM angiogenesis⁴
- The US FDA recently approved bevacizumab, a VEGFR-2 monoclonal antibody, for the treatment of GBM⁵
- PFS-6 42%, median PFS 4.2 months, median overall survival 12.2 months (N = 85)⁶
- VEGFR-2 may also be upregulated in some GBM⁷ including GBM^{8,9}
- Completely blocking VEGFR-2 signaling by all its ligands (VEGF-A, C, and D) may be more efficacious than blocking only VEGF-A
- Alleviates synergistic effects and prevention of angiogenic escape mechanisms induced by VEGF-A inhibitor alone¹⁰
- Intensifies delays activity in GBM as monotherapy^{11,12} and when combined with temozolomide¹³
- Normalization of tumor vasculature by anti-VEGF agents may potentiate the action of cytotoxic chemotherapy agents¹⁴

METHODS

Study Objectives

Primary Objectives

- Part 1: Safety lead-in (4 subjects per cohort)
- Safety and tolerability of CT-322 either administered with and without irinotecan to patients with rGBM
- Part 2: Efficacy study
- Antitumor activity of CT-322 when administered with and without irinotecan

Secondary Objectives

- Pharmacokinetics of CT-322¹⁵ and irinotecan¹⁶
- Immunogenicity¹⁷
- Biological activity of CT-322 as assessed by plasma angiogenic¹⁸ and clinical biomarkers, and dynamic contrast-enhanced (DCE) imaging¹⁹

Exploratory Objective

- Disease-related patient-reported outcomes (FACT-FY)²⁰

These objectives will be the subjects of future reports.

Study Design

This is an open-label, randomized, noncomparative study of CT-322 monotherapy and combination with irinotecan (dose adjusted for weight or normal body surface area) in rGBM patients.

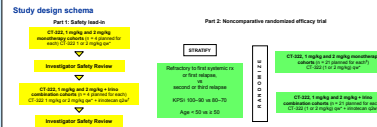
Starting dose of 1 mg/kg irinotecan (IV) every week (IV) based on initial pharmacokinetic biomarker data (plasma AUC₀₋₂₄) responses from a phase 1 study.

Additional data suggested that 2 mg/kg may be a more pharmacodynamically robust dose and therefore the protocol was amended after the first 21 patients to increase the dose from 1 to 2 mg/kg

2 mg/kg was the phase 1 MTD on the schedule.

All CT-322 monotherapy and irinotecan combination therapy dose groups were preceded by a 4-patient safety lead-in cohort

Patients testing positive for LUT1A/128 homozygosity are only enrolled into CT-322 monotherapy cohorts



¹Lee et al. J Clin Oncol. 2007;25:100-106. ²Lee et al. J Clin Oncol. 2007;25:100-106. ³Lee et al. J Clin Oncol. 2007;25:100-106. ⁴Lee et al. J Clin Oncol. 2007;25:100-106. ⁵Lee et al. J Clin Oncol. 2007;25:100-106. ⁶Lee et al. J Clin Oncol. 2007;25:100-106. ⁷Lee et al. J Clin Oncol. 2007;25:100-106. ⁸Lee et al. J Clin Oncol. 2007;25:100-106. ⁹Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁰Lee et al. J Clin Oncol. 2007;25:100-106. ¹¹Lee et al. J Clin Oncol. 2007;25:100-106. ¹²Lee et al. J Clin Oncol. 2007;25:100-106. ¹³Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁴Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁵Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁶Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁷Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁸Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁹Lee et al. J Clin Oncol. 2007;25:100-106. ²⁰Lee et al. J Clin Oncol. 2007;25:100-106.

METHODS (cont'd)

Key Eligibility Criteria

Inclusion Criteria

- Written informed consent
- Historically confirmed GBM in first, second, or third relapse
- Adequate organ function, including:
 - Absolute neutrophil count: >1000/mm³
 - Platelets: >100,000/mm³
 - Urea nitrogen: creatinine ratio < 1
- KPS ≥ 7
- At least 12 weeks from radiotherapy
- < 4 weeks from last systemic therapy (6 weeks if intrathecal)
- Stable corticosteroid dose for > 1 week prior to baseline magnetic resonance imaging (MRI)
- Measurable (RECIST) enhancing tumor

Exclusion Criteria

- Prior anti-VEGF or vascular targeting agents
- Prior grade 3 toxicity or failure of irinotecan
- Prior stereotactic radiotherapy, brachytherapy, or surgically created resection cavity for other localized therapies
- Progressive disease
- Central nervous system (CNS) hemorrhage on MRI unless grade 1 post-op and shown to be stable for 4 weeks
- Full therapeutic anticoagulation
- Myocardial infarction, unstable angina, congestive heart failure, thrombocytopenia within 12 months

Primary End Point and Analysis

- CT-322 monotherapy and irinotecan combination cohorts are noncomparative and analyzed independently
- Macrotumor criteria applied for response assessment
- Primary efficacy end point for each study cohort is PFS-6
- PFS-6 defined as the time from PFS-6 until the completion of 6 cycles (53 months = 168 days) in the intent-to-treat (ITT) population
- ITT population defined as all subjects who receive any dose or part of a dose of CT-322 with or without irinotecan
- Results of an independent radiological and clinical endpoint panel (IRC) constitute the primary analysis. Investigator-assessed results are secondary
- IRC consists of 3 independent neuro-radiologists (2 readers and 1 adjudicator when required plus 1 independent clinical oncologist) to apply the Macrotumor criteria for lesion measurements, corticosteroid dosage, and reported neurotoxicity
- IRC neuro-radiologists also make a visual assessment of serial changes in MRI T2FLAIR signal
- Macrotumor criteria: 10% reduction in total Macrotumor assessment

RESULTS

From October 29, 2007, through the analysis cut-off date of April 1, 2010

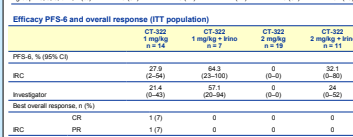
- 51 patients were enrolled and treated
- Of these, 44 (86%) enrolled prior to October 1, 2009, and had the opportunity to attain PFS-6 by the time of analysis

Patient demographics

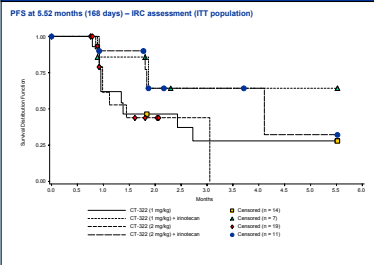
	CT-322 1 mg/kg	CT-322 2 mg/kg	CT-322 1 mg/kg + Irinotecan	CT-322 2 mg/kg + Irinotecan	Total
N	14	7	19	11	51
Male/Female, n (%)	9/5	6/1	11/8	7/4	33/18
Age, median (range)	54 (44-58)	54 (49-59)	59 (56-64)	56 (54-62)	56 (52-77)
Performance (KPS), n (%)					
White	12	7	18	9	46 (90%)
Black	0	0	1	1	2 (4%)
Asian	0	0	0	0	0 (0%)
Hispanic/Latin	0	0	0	0	0 (0%)
KPS	6/9 (80-100)	4/7 (57-100)	5/14 (36-100)	3/7 (43-100)	22/29 (43-100)
Stevens at baseline	8/9 (89%)	7/7 (100%)	8/11 (73%)	9/7 (100%)	32/39 (82%)
YIN (Y/N)	10/4 (100%/0%)	5/2 (100%/0%)	4/15 (27%/73%)	2/9 (22%/78%)	19/31 (61%/71%)
EMEA at baseline	1/19 (5%)	1/7 (14%)	4/19 (21%)	2/11 (18%)	8/49 (16%)
YIN (Y/N)	1/18 (6%)	1/6 (17%)	4/18 (22%)	2/11 (18%)	8/46 (17%)
UPT1A/128 homozygosity, n (%)	6/14 (43%)	3/7 (43%)	5/14 (36%)	4/11 (36%)	18/51 (35%)
Carson/NABTT rGBM RPA group ²¹ 3, 5, 6, 7, 8, 9, 10, 11	9/14 (64%)	5/7 (71%)	14/14 (100%)	9/11 (82%)	37/51 (73%)

Efficacy PFS-6 and overall response (ITT population)

	CT-322 1 mg/kg (n=14)	CT-322 2 mg/kg (n=7)	CT-322 1 mg/kg + Irinotecan (n=19)	CT-322 2 mg/kg + Irinotecan (n=11)
PFS-6 % (95% CI)	27.9 (0-51)	64.3 (23-100)	0 (0-0)	32.1 (0-60)
IRC	21.4 (0-43)	57.1 (20-94)	0 (0-0)	24 (0-52)
Best overall response, n (%)				
CR	1 (7)	0	0	0
CR PR	1 (7)	0	0	0
Investigator PR	0	0	0	0



RESULTS (cont'd)



PFS-6 by pooled groups

	Pooled CT-322 1 mg/kg (n=14)	Pooled CT-322 2 mg/kg (n=7)	Pooled CT-322 1 mg/kg + Irinotecan (n=19)	Pooled CT-322 2 mg/kg + Irinotecan (n=11)	Total (n=51)
IRC	22.7 (0-45)	48.3 (16-82)	37.2 (13-61)	19.3 (0-49)	32.8 (14-51)

PFS-6 % (95% CI)

- From October 29, 2007, through the analysis cut-off date of April 1, 2010
- 51 patients were enrolled and treated
- Of these, 44 (86%) enrolled prior to October 1, 2009, and had the opportunity to attain PFS-6 by the time of analysis

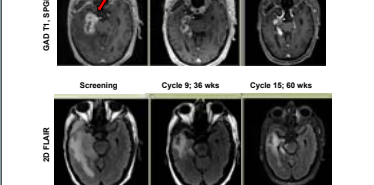
Investigator

Investigator	22.7 (0-45)	48.3 (16-82)	37.2 (13-61)	19.3 (0-49)	32.8 (14-51)
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* Including IRC's qualitative assessment of any increases in T2FLAIR signal abnormally would have shortened PFS for

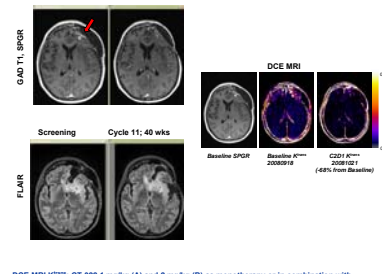
- 1 mg/kg CT-322 + irinotecan: 1 patient, 0 months shorter
- 2 mg/kg CT-322 + irinotecan: 2 patients, 0.8 and 1.7 months shorter
- None of these 3 patients achieved PFS-6 by Macrotumor criteria

Scans from a 54-year-old male; CT-322 1 mg/kg IV qw monotherapy; confirmed partial response by IRC (assessed at C13D1 and ongoing for 10+ months; Carson/NABTT rGBM RPA group 6)

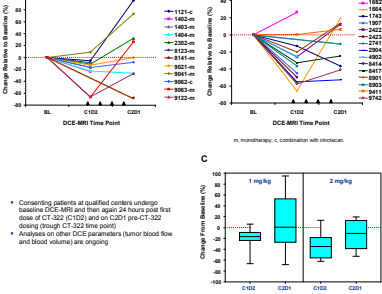


RESULTS (cont'd)

Scans from a 56-year-old female; CT-322 1 mg/kg IV qw; confirmed complete response by IRC (assessed CMI1 with duration 7 months; Carson/NABTT rGBM RPA group 1)



DCE-MRI K^{trans}, CT-322 3 mg/kg (A) and 2 mg/kg (B) as monotherapy or in combination with irinotecan. C_{max} summary plots (median, 29%–75%, 6%–95% percentiles) for specified time points c/w baseline



* Considering patients at qualified centers undergo baseline DCE-MRI and their scans 24 hours post first dose of CT-322 (C12D) and on C2D1 pre-CT-322 dosing through CT-322 monotherapy

- Analysis of other DCE parameters (tumor blood flow and blood volume) are ongoing

RESULTS (cont'd)

Adverse events*

Adverse Event	CT-322 1 mg/kg (n=14)	CT-322 2 mg/kg (n=7)	CT-322 2 mg/kg + Irinotecan (n=19)	CT-322 2 mg/kg + Irinotecan (n=11)	Total (n=51)
		14	7	17	11

Most common (> 10%) related, treatment-emergent AEs, all grades

	CT-322 1 mg/kg (n=14)	CT-322 2 mg/kg (n=7)	CT-322 2 mg/kg + Irinotecan (n=19)	CT-322 2 mg/kg + Irinotecan (n=11)	Total (n=51)
Fatigue, n (%)	5 (35.7)	4 (57.1)	3 (17.6)	3 (30.0)	15 (31.3)
Hypertension, n (%)	4 (28.6)	1 (14.3)	4 (23.5)	1 (10.0)	12 (25.0)
Diarrhea, n (%)	3 (21.4)	4 (57.1)	0	2 (20.0)	9 (18.8)
Nausea, n (%)	2 (14.3)	2 (28.6)	0	3 (30.0)	7 (14.6)

Most common (> 5%) treatment-emergent AEs grade 2 or regardless of causality

Grade	3	4	3	4	3	4	3	4
Nausea, n (%)	1 (7.1)	0	0	1 (5.9)	0	2 (20.0)	0	4 (9.3)
ALT increased, n (%)	1 (7.1)	0	0	1 (5.9)	0	1 (10.0)	0	3 (6.3)
Hypertension, n (%)	1 (7.1)	0	0	1 (5.9)	0	1 (10.0)	0	3 (6.3)
Hypophosphatemia, n (%)	1 (7.1)	0	1 (14.3)	1 (5.9)	0	0	0	3 (6.3)

All related grade 2-3 treatment-emergent AEs

Hypertension, n (%)	1 (7.1)	0	0	1 (5.9)	0	1 (10.0)	0	3 (6.3)
CNS hemorrhage, n (%)	0	0	0	1 (5.9)	1 (9.1)	0	1 (10.0)	2 (4.1)
Diarrhea, n (%)	1 (7.1)	0	1 (14.3)	0	0	0	0	2 (4.2)
Nausea, n (%)	0	0	0	2 (11.8)	0	0	0	2 (4.2)
Hypophosphatemia, n (%)	1 (7.1)	0	0	1 (5.9)	0	0	0	2 (4.2)
Elevated lipase, n (%)	0	0	1 (14.3)	0	0	0	0	1 (2.1)
Failure to thrive, n (%)	0	0	0	0	0	1 (10.0)	0	1 (2.1)
Lymphopenia, n (%)	1 (7.1)	0	0	0	0	0	0	1 (2.1)
Nausea, n (%)	0	0	0	0	0	1 (10.0)	0	1 (2.1)
Prothrombin, n (%)	1 (7.1)	0	0	0	0	0	0	1 (2.1)
Thrombocytopenia, n (%)	1 (7.1)	0	0	0	0	0	0	1 (2.1)

* All grade 5/6 AEs have been recorded as of the April 1, 2010, analysis date. 86.2% grade 1/2, 12.3% grade 3, 1.5% grade 4 or greater. Percentages are based on number of subjects with at least 1 treatment-emergent AE.

CONCLUSIONS

- CT-322, the first AdnectinTM class of clinical trials, demonstrates biological and clinical activity in rGBM
- CT-322 monotherapy (1 or 2 mg/kg qw) produced independently reviewed PFS-6 for 1 mg/kg (27%) vs 2 mg/kg (64%) (may be due to small patient numbers and/or prognostic imbalances)
- 1 mg/kg patients were younger, with fewer in secondarily first relapse, and fewer in the most adverse Carson/NABTT rGBM RPA groups
- While patients combined with irinotecan did not appear to benefit, the study is not powered to detect a difference between monotherapy and combination therapy. Preliminary efficacy data for CT-322 in combination with irinotecan indicates higher PFS-6 compared with CT-322 monotherapy
- The observation of numerically higher PFS-6 with CT-322/irinotecan combination therapy compared with CT-322 monotherapy is consistent with observations reported for bevacizumab and irinotecan
- DCE-MRI imaging indicates reductions in K^{trans} 24 hours following initial CT-322 dosing
- The reductions observed at C12D1 and on C2D1 pre-CT-322 dosing were not sustained on Day 29 DCE-MRI, possibly because the Day 29 DCE-MRI was performed at the trough of plasma VEGF-A pharmacodynamic biomarker levels is ongoing and may provide additional insights
- Analysis of other DCE parameters (tumor blood flow and blood volume) are ongoing
- Additional patients are accruing to the 2 mg/kg and pharmacokinetic analysis of CT-322, irinotecan, SN-38, plasma pharmacodynamic biomarkers, and immunogenicity
- CT-322 demonstrates suitable pharmacologic properties and provides additional clinical evidence supporting the Adnectin platform as a source for human therapeutics

REFERENCES

1. Schiff D et al. J Clin Oncol. 2008;26:100-106. ²Lee et al. J Clin Oncol. 2007;25:100-106. ³Lee et al. J Clin Oncol. 2007;25:100-106. ⁴Lee et al. J Clin Oncol. 2007;25:100-106. ⁵Lee et al. J Clin Oncol. 2007;25:100-106. ⁶Lee et al. J Clin Oncol. 2007;25:100-106. ⁷Lee et al. J Clin Oncol. 2007;25:100-106. ⁸Lee et al. J Clin Oncol. 2007;25:100-106. ⁹Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁰Lee et al. J Clin Oncol. 2007;25:100-106. ¹¹Lee et al. J Clin Oncol. 2007;25:100-106. ¹²Lee et al. J Clin Oncol. 2007;25:100-106. ¹³Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁴Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁵Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁶Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁷Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁸Lee et al. J Clin Oncol. 2007;25:100-106. ¹⁹Lee et al. J Clin Oncol. 2007;25:100-106. ²⁰Lee et al. J Clin Oncol. 2007;25:100-106. ²¹Lee et al. J Clin Oncol. 2007;25:100-106.

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