ABSTRACT C41 A Phase I, Open-Label, Multiple Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of Oral Aneustat™ (OMN54) Administered on a Daily Oral Regimen in Patients With Advanced Cancer and Lymphomas

Daniel Renouf[1], Christian Kollmannsberger[1], Kim Chi[1], Stephen Chia[1], Anna Tinker[1], Teresa Mitchell[1], Stephen Lam[1], Teresa Joshi[2], David Kwok[3], John Ostrem[2], Simon Sutcliffe[2], Karen A. Gelmon[1]

[1]BC Cancer Agency, Vancouver, BC, Canada; [2]Omnitura Therapeutics, Burlingame, CA; [3]BRI Biopharmaceutical Research, Vancouver, BC, Canada;

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ABSTRACT

Purpose: With the increasing interest in natural products as therapeutics, we performed a Phase I open label study of OMN54 in patients with advanced malignancies to determine toxicity, maximum tolerated dose (MTD), dose limiting toxicities (DLT), and pharmacokinetics (PK). OMN54 is a multitargeted agent prepared from three Chinese botanical sources: Ganoderma lucidum, Salvia miltiorrhiza, and Scutellaria barbata, each with long histories of use as single agents. **Methods:** Eligible patients (pts) were ≥ 18 years with advanced solid tumor malignancies, able to swallow oral capsules, ECOG performance status ≤2, measurable disease as defined by RECIST 1.0, and adequate organ function. **Results**: 22 pts were enrolled in 6 dose levels, 2 at daily and 4 with twice daily dosing ranging from 1 to 5 gm orally per day; all evaluable for toxicity and 20 for response. Most common cancers included colorectal (13 pts), non small cell lung (3 pts), and ovarian (2 pts). 5 pts patients completed Cycle 1, 9 pts Cycle 2, 3 pts Cycle 3 and 1 pt each completed Cycles 4, 5, and 8. 2 pt had < 1 cycle. Only 7 AEs in 5 pts were reported as possibly related to study drug; 6 were gastrointestinal disorders, 1 a skin disorder. One GR 2 AE of vomiting was probably related to study drug. All other AEs were Grade 1. There were no treatment-related SAEs or DLTs. A recommended phase II dose (RP2D) is 2.5 g orally twice daily. PK data revealed evidence of detectable plasma total OMN54 in cohorts 1 to 6 with all 4 parent drug chemical markers with plasma half-lives of 1- 2 hours and no evidence of accumulation. Preliminary evidence of biological activity was seen with stable disease for 8 months in 1 pt and 4 pts with dose responsive reductions in TGF-β, EGF & Rantes, biomarkers of immune suppression. Significant TGF-β decreases were seen for 4 pts at doses of 2gm daily to 2.5 gm bid including an ovarian, colorectal, fallopian tube and esophageal cancer. **Conclusion**: OMN54 was well tolerated with no DLTs observed. Further studies at RP2D of 2.5 g bid orally should be done to assess activity.

Chemical Markers for Qualified Compounds and Aneustat™ (OMN54) Drug Substance

Qualified Compounds and Aneustat™ (OMN54)	Botanical Material	Chemical Marker Compounds
Qualified Compound 9	Extract of *Ganoderma lucidum* (Leyss. Ex Fr) Karst	Ganoderic Acid A, Apigenin
Qualified Compound 14	Extract of *Salvia miltiorrhiza* Bge.	Tanshinone IIA
Qualified Compound 15	Extract of *Scutellaria barbata* D.Don	Scutellarein, Apigenin
Aneustat™ (OMN54) drug substance	Mixture of 9, 14, and 15 in specified ratio	Ganoderic Acid A, Apigenin Tanshinone IIA, Scutellarein

Study Formulation OMN54 (Aneustat™) 100 mg soft gelatin capsules;

Route of Administration and Regimen

Oral, once daily or twice daily; approximately 30 minutes before meal at the same time each day

OBJECTIVES

Primary Objectives

a. Assessment of safety and tolerability of Aneustat™ (OMN54) in patients with advanced cancer and lymphomas

b. Determination of maximum tolerated dose (MTD) of two dosing regimens (once daily [QD] and twice daily [BID]) of Aneustat™ (OMN54)

c. Determination of dose limiting toxicity (DLT) of two dosing regimens (once daily [QD] and twice daily [BID]) of Aneustat™ (OMN54)

d. Evaluate the pharmacokinetic profile of Aneustat™ (OMN54) in cancer patients

Secondary Objectives

a. Preliminary assessment of anti-tumor activity using standard response evaluation criteria and tumor markers

b. Evaluation of potential surrogate pathway biomarkers: EGF, eotaxin, G-CSF, HGF, IFN-α, IL-1b, IL-2, IL-2ra, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, IL-18, IL-RA, IP-10, MCP-1, MIG, MIP-1α, MIP-1ß, TNFα, IFN-gamma, VEGF, FGF, TGF-ß, GM-CSF, and RANTES to help characterize Aneustat™ (OMN54) activity

METHODS and STUDY DESIGN

Study Design

Open label, dose escalation phase I design

3-4 Patients/Cohort until DLT and then expansion to 6 patients

DOSE ESCALATION COHORTS AND REGIMEN				
Dose Cohort	Single Dose Phase (Day 1 only)* Daily Dose (g)	Repeat Dose Phase (Starts on Day 3)		
		g/dose	g/day	Regimen
1	1	1	1	QD
2	2	2	2	QD
3	2	1	2	BID
4	3	1.5	3	BID
5	4	2	4	BID
6	5	2.5	5	BID

PATIENT CHARACTERISTICS

Number		men =11	Women= 11		
Age (years)	Range 43-80	Men median= 63.7	Women median = 60.3		
Race	Caucasian = 14	Asian = 7	American Indian= 1		
ECOG	0 = 6	1 = 14	2 = 2		
Colon Ca = 13	Lung = 3	Ovary/ fallopian = 3	Tonsil = 1	Esophageal= 1	Vulvar = 1

Number of Cycles	Number of Patients Completing Each Cycle N (%)
< 1	2 (9)
≥ 1 but < 2	5 (9)
2	9 (41)
3 to 5	5 (23)
8	1 (4)

15 patients came off study for progressive disease according to RECIST criteria

6 patients came off for clinical progression

1 patient came off at day 22 as his medical condition rendered him ineligible for further treatment

One patient died of acute dyspnea not related to study drug while on treatment

One patient had stable disease from cycle 2 to 8 prior to developing progressive disease

Overall Treatment-Emergent Adverse Events

Number of Subjects:	All (N=22)	Cohort 1 1 g QD (N=4)	Cohort 2 2 g QD (N=4)	Cohort 3 1 g BID (N=3)	Cohort 4 1.5 g BID (N=3)	Cohort 5 2 g BID (N=4)	Cohort 6 2.5 g BID (N=4)
# One TEAE	22 (100.0%)	4 (100.0%)	4 (100.0%)	3 (100.0%)	3 (100.0%)	4 (100.0%)	4 (100.0%)
# One Treatment-related TEAE	5 (22.7%)	0 (0.0%)	1 (25.0%)	1 (33.3%)	2 (66.7%)	0 (0.0%)	1 (25.0%)
# One Serious TEAE	7 (31.8%)	3 (75.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	1 (25.0%)
# One Serious Treatment-related TEAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
# One TEAE Leading to Treatment Inuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

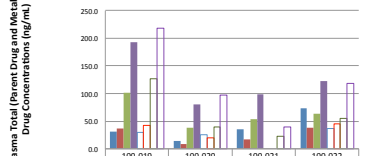
Treatment-Related Adverse Events

Cohort	Patient ID	AE Term	AE CTCAE Grade	Relationship to Study Drug
Cohort 2: 2g QD	100-006	Nausea	1	Possibly
		Vomiting	1	Probably*
Cohort 3: 1g BID	100-010	Gastroesophageal reflux	2	Possibly
		Gastroesophageal reflux	1	Possibly
Cohort 4 1.5g BID	100-012	Dry cracked hands	1	Possibly
		Vomiting	1	Possibly
Cohort 6 2.5g BID	100-022	Bloating	1	Possibly
		Constipation	1	Possibly

Patients Dosed for More Than Three Cycles of Aneustat™ (OMN54)

Cohort	Patient Number	Tumor Type/Stage	Cycle/Date of Last Stable Tumor Evaluation	Total Cycles/Days Dosed	Study Exit Date/ Comments
Cohort 1 *1 g QD*	100-001	AC colon/T3	Cycle 2 Day28 10/18/2012	3+/108	12/04/2012 PD; Progression of target lesions
	100-004	AC colon/ Stage 3	Cycle 2, 4/Day 28 11/01/2012	4+/139	02/06/2013 Discretion of PI; CEA at 4400 and clinical condition
Cohort 5 *2 g BID*	100-016	Vulvar cancer/Stage 4	Cycle 2,4,6/Day 28 01/13/2014	8/223.5	01/16/2014 PD; new hepatic lesions
Cohort 6 *2.5 g BID*	100-019	AC lung/ Stage 4	Cycle 2 Day28 09/24/2013	3+/94	11/13/2013 Death; respiratory failure secondary to lung cancer
	100-020	AC esophagus Stage 4	Cycle 2 Day28 09/24/2013	3+/94.5	PD; target lesion progression

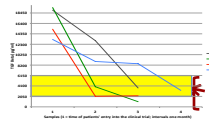
Plasma Cmax of Total Chemical Markers in Cohort 6 Patients (OMN54 2.5 g Twice Daily) on Day-1 and Day-22



	100-019	100-020	100-021	100-022
Day-1 GAA Total Cmax	31.6	14.8	35.3	72.7
Day-1 TIIA Total Cmax	37.0	8.8	16.5	37.9
Day-1 APG Total Cmax	102.0	38.6	53.0	63.0
Day-1 SCT Total Cmax	193.0	80.6	99.3	122.0
Day-22 GAA Total Cmax	29.0	25.7	0.0	36.6
Day-22 TIIA Total Cmax	42.8	19.5	0.0	44.6
Day-22 APG Total Cmax	127.0	39.1	22.4	55.4
Day-22 SCT Total Cmax	218.0	97.8	39.4	119.0

Immune Signaling Biomarker Study Patient Response in TGF-β Study

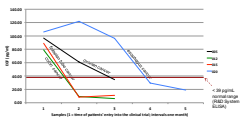
Most Abnormal TGF-β Values at Study Entry



TGFβ range (+/- 1 Standard Deviation) in healthy people[1]

Immune Signaling Biomarker Study Patient Response in EGF Study

- **Most Abnormal EGF Values at Study Entry**



CONCLUSIONS

Aneustat™ was well tolerated with no dose related toxicities noted in this Phase I study

22 patients had 1,451 total days of dosing

AE Severity[1]

- 99 (44%) grade 1 (mild)
- 87 (39%) grade 2 (moderate)
- 35 (16%) grade 3 (severe)
- 4 (<2%) grade 4 (life threatening)
- 4 deaths—none of which were treatment related

No MTD was reached but there was evidence of biological activity with the doses delivered

- Stable disease for upto 8 months (based on radiological imaging)
- Suggestion of dose responsive reduction in TGF-β, EGF & Rantes, biomarkers of immune suppression and cancer promoting activity

Further trials of this agent in specific tumor types are planned

Trial Support was from Omnitura