A phase I/II trial of BNC105P with everolimus in metastatic renal cell carcinoma (mRCC): Results of the randomized phase II DisrupTOR-1 trial

Sumanta Pal[1], Arun Azad[2], Sumeet Bhatia[3], Harry Drabkin[4], Brian Costello[5], John Sarantopoulos[6], Ravindran Kanesvaran[7], Richard Lauer[8], Christopher Sweeney[9], Noah Hahn[10], Guru Sonpavde[11], Stephen Richey[12], Timothy Breen[13], Gabriel Kremmidiotis[14], Annabell Leske[14], Elizabeth Doolin[14], David Bibby[15], Jeremy Simpson[14], Jose Iglesias[14] & Thomas Hutson[16]

[1]City of Hope Medical Center, Duarte, CA, [2]BC Cancer Agency, Vancouver, BC, [3]Univ. of Washington, Seattle, WA, [4]Medical College of South Carolina, Charleston, SC, [5]Mayo Clinic, Rochester, MN, [6]Univ.of Texas Health Science Center, San Antonio, TX, [7]Singapore National Cancer Center, [8]Univ. of New Mexico Cancer Ctr, Albuquerque, NM, [9]Dana Farber Cancer Center, Boston, MA, [10]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, [11]Deke-Slayton Cancer Ctr., Webster, TX, [12]Texas Oncology, Fort Worth, TX, [13]Hoosier Cancer Research Network, Indianapolis, IN, [14]Bionomics, Thebarton, SA, Australia, [15]bioCSL, Melbourne, Australia, [16]Charles A. Sammons Cancer Center, Baylor Univ.Medical Center, Dallas, TX

Background

- Agents targeting vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) represent a cornerstone of therapy for metastatic renal cell carcinoma (mRCC)
- Everolimus, an oral mTOR inhibitor, represents a standard treatment option in patients that have received prior VEGF-directed therapy for mRCC
- Clinical benefit with everolimus in this setting is modest, with an estimated progression free survival (PFS) of approximately 4 months in published phase III trials
- Trials combining VEGF-directed therapies with everolimus have been limited by toxicities
- In mRCC, few trials to date have combined other novel targeted agents with everolimus
- The novel vascular disrupting agent (VDA) BNC105P is a disodium phosphate ester prodrug of BNC105 [1]
- BNC105 is a tubulin polymerization inhibitor with a high degree of selectivity for tumor endothelial cells
- BNC105 displays >80-fold higher potency against endothelial cells that are actively proliferating or engaged in the formation of capillaries compared with non-proliferating endothelial cells or endothelium found in stable capillaries
- A phase I study of BNC105P monotherapy included 21 patients with advanced solid tumors, and identified an intravenous dose of 16 mg/m2 on days 1 and 8 of a 21-day cycle for further studies
- The phase I component of the current study has been previously reported, identifying BNC105P at 16 mg/m2 with everolimus at 10 mg daily as the recommended phase II dose [2]

Methods

Study Objectives

Primary

To determine if the addition of BNC105P to everolimus could lead to improvement in 6-month PFS as compared to everolimus monotherapy

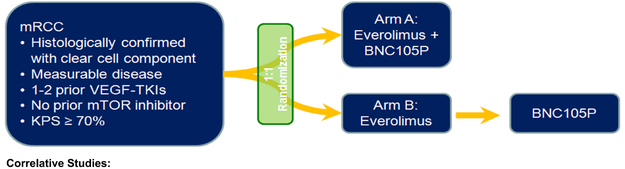
Secondary

To compare cumulative PFS with everolimus monotherapy versus everolimus with BNC105P
To compare overall survival (OS) with everolimus monotherapy versus everolimus with BNC105P
To determine if changes in serum biomarkers with BNC105P therapy can predict clinical outcome

Eligibility

- Histologically confirmed RCC with a clear cell component
- Documented metastatic disease
- Karnofsky performance status ≥ 70%
- Adequate organ function
- Measurable disease by RECIST 1.1
- Phase I eligibility based on prior treatment:
  - Patients may have received any prior number of VEGF-tyrosine kinase inhibitors (VEGF-TKIs)
  - Patients may have received prior therapy with an mTOR inhibitor
- Phase II eligibility based on prior treatment:
  - Patients may receive 1-2 prior VEGF-TKIs
  - Patients may not have received prior mTOR inhibitor therapy

Study Design



Correlative Studies:

- Everolimus with BNC105P: Blood draws on day 1 and 8 of therapy immediately prior to BNC105P, 1-3 hours following BNC105P and at progression.
- Everolimus alone: Blood draws at identical time points at the time of crossover onto BNC105P monotherapy
- All patients were given option to submit tissue

Statistical Consideration:

- With 61 patients per group, estimated to be 80% power to detect an improvement in 6MPFS from 36% on the control arm (everolimus alone) to 60% on the experimental arm using 1-sided Chi-square test with continuity correction (α=0.05)
- Stratification factors:
  - Memorial Sloan Kettering Cancer Center (MSKCC) risk group (good, intermediate and poor)
  - Number of prior regimens (VEGF-TKIs) (1 or >1)
- Assuming roughly 10% of patients would be inevaluable for the primary endpoint, a target total enrollment of 134 patients was set

Results

Patient Characteristics

	Total (%)	Arm A (%)	Arm B (%)	p-value
Sex	N=138	N=69	N=69	0.1624
Female	33 (23.91)	20 (28.99)	13 (18.84)	
Male	105 (76.09)	49 (71.01)	56 (81.16)	
Age (years)				0.4298
Mean (SD)	62.22 (9.34)	61.59 (9.26)	62.86 (9.44)	
Median	63	61	64	
Minimum	40	45	40	
Maximum	84	82	84	
Race				0.4561
White	120 (86.96)	61 (88.41)	59 (85.51)	
Black or African American	6 (4.35)	2 (2.90)	4 (5.80)	
Asian	10 (7.25)	5 (7.25)	5 (7.25	
American Indian or Alaska Native	1 (0.72)	0 (0.00)	1 (1.45)	
Unknown	1 (0.72)	1 (1.45)	0 (0.00)	

Table 1: Patient background

	Total (%)	Arm A (%)	Arm B (%)	p-value
MSKCC Risk Group				0.9274
Good	33 (23.91)	17 (24.64)	16 (23.19)	
Intermediate	92 (66.67)	45 (65.22)	47 (68.12)	
Poor	13 (9.42)	7 (10.14)	6 (8.70)	
Metastatic Site				
Lung	111 (80.43)	57 (82.61)	54 (78.26)	0.5197
Liver	26 (18.84)	13 (18.84)	13 (18.84)	>0.9999
Bone	45 (32.61)	21 (30.43)	24 (34.78)	0.5859
Brain	8 (5.80)	3 (4.35)	5 (7.25)	0.4663
Number of Prior Therapies				
1	27 (19.57)	14 (20.29)	13 (18.84)	
2	42 (30.43)	24 (34.78)	18 (26.09)	
3	25 (18.12)	10 (14.49)	15 (21.74)	
≥4	44 (31.88)	21 (30.43)	23 (33.33)	

Table 2: Patient clinical history

Survival Estimates

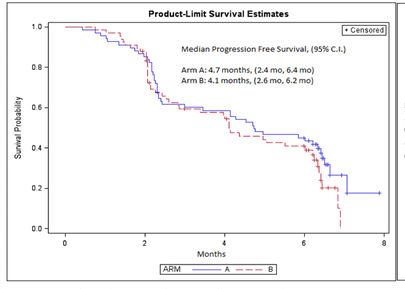


Figure 1. Cumulative PFS, 6MPFS was similar in the treatment arms (Arm A: 33.82% *v* Arm B: 30.30%, P=0.66)

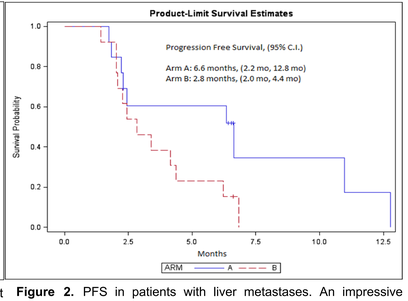


Figure 2. PFS in patients with liver metastases. An impressive preliminary signal seen amongst patients with liver metastases

Safety Results

	Arm A (n=69)					Arm B (n=67)					Total (n=136)	
	Grade1/2	Grade 3/4	Grade 5	Total	%	Grade1/2	Grade 3/4	Grade 5	Total	%	N	%
FATIGUE (ASTHENIA, LETHARGY, MALAISE)	28	3	0	31	44.9	24	6	0	30	44.8	61	44.9
HEMOGLOBIN	20	9	0	29	42.0	19	6	0	25	37.3	54	39.7
DYSPNEA (SHORTNESS OF BREATH)	18	4	0	22	31.9	17	4	0	21	31.3	43	31.6
CHOLESTEROL, SERUM-HIGH (HYPERCHOLESTREMIA)	17	0	0	17	24.6	19	0	0	19	28.4	36	26.5
COUGH	22	0	0	22	31.9	13	1	0	14	20.9	36	26.5
TRIGLYCERIDE, SERUM-HIGH (HYPERTRIGLYCERIDEMIA)	11	4	0	15	21.7	17	4	0	21	31.3	36	26.5
DIARRHEA	15	2	0	17	24.6	16	0	0	16	23.9	33	24.3
GLUCOSE, SERUM-HIGH (HYPERGLYCEMIA)	10	5	0	15	21.7	12	5	0	17	25.4	32	23.5
MUCOSITIS/STOMATITIS (CLINICAL EXAM) / ORAL CAVITY	13	0	0	13	18.8	13	6	0	19	28.4	32	23.5
NAUSEA	12	2	0	14	20.3	14	2	0	16	23.9	30	22.1
PLATELETS	19	1	0	20	29.0	8	2	0	10	14.9	30	22.1
EDEMA: LIMB	16	0	0	16	23.2	13	0	0	13	19.4	29	21.3
RASH/DESQUAMATION	13	1	0	14	20.3	15	0	0	15	22.4	29	21.3
PAIN / BACK	7	3	0	10	14.5	12	6	0	18	26.9	28	20.6
ANOREXIA	9	0	0	9	13.0	15	1	0	16	23.9	25	18.4
CONSTIPATION	10	0	0	10	14.5	15	0	0	15	22.4	25	18.4
DERMATOLOGY/SKIN - OTHER	9	0	0	9	13.0	11	3	0	14	20.9	23	16.9
MUCOSITIS/STOMATITIS (FUNCTIONAL/ SYMPTOMATIC) / ORAL CAVITY	11	0	0	11	15.9	10	0	0	10	14.9	21	15.4
PROTEINURIA	9	1	0	10	14.5	10	0	0	10	14.9	20	14.7

Table 3: Most frequently observed toxicities. Two deaths encountered with combination therapy were deemed potentially related to protocol-based therapy secondary to pneumonitis and infection, respectively. Given the lack of pneumonitis and infection seen in previous studies of BNC105P and the occurrence of these adverse events in previous studies of everolimus, they were presumably related to the latter.

Biomarker Results

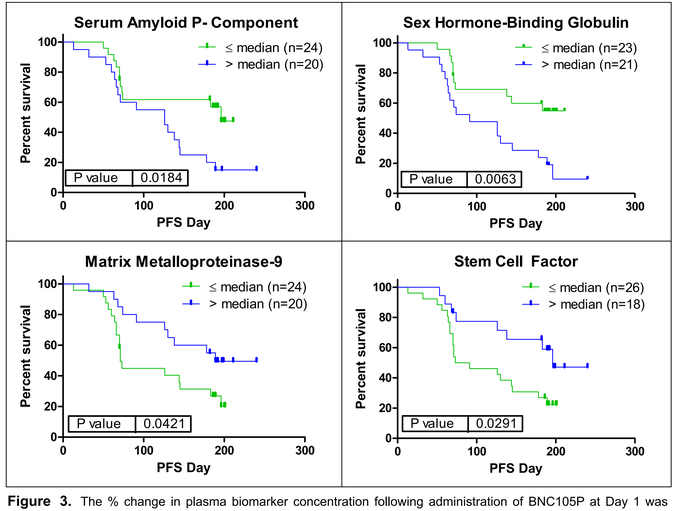


Figure 3. The % change in plasma biomarker concentration following administration of BNC105P at Day 1 was measured in 44 patients enrolled in the combination Arm. The median of % change distribution across these patients for each biomarker was used to stratify patients in 2 groups: (a) % change greater than the median and (b) % change lower or equal to the median. PFS Kaplan-Meier curves for each of these patient groups are shown for Matrix Metalloproteinase-9 (MMP9), Stem Cell Factor (SCF,) Sex Hormone Binding Globulin (SHGB) and Serum Amyloid-P Component (SAP).

Conclusions

- **The current study represents the first large-scale exploration of VDAs in mRCC**
- **In patients with mRCC and prior VEGF-directed treatment, the addition of BNC105P to everolimus did not improve 6MPFS as compared to everolimus alone**
- **The addition of BNC105P did not add substantially to the anticipated toxicity profile of everolimus**
- **Exploratory biomarker analyses identified associations between clinical outcome with combination therapy and MMP-9, SCF, SAP and SHBG**
- **A biomarker profile comprised of these four markers consistently identified patients who were progression free at 6 months**
- **Future studies of BNC105P in mRCC may be enriched for patients who possess a combined biomarker profile identified in the current study**

References

1. Kremmidiotis G *et al* Molecular Cancer Therapeutics. 2010;9(6):1562-73
2. Sarantopoulos J *et al* ASCO Meeting Abstracts. 2013;31(15_suppl):4563.

ESMO 2014