Phase I Trial of a Combination of the VEGFR Kinase Inhibitor Cediranib (AZD2171) and Bevacizumab in Advanced Malignancies (NCI Protocol#7534)

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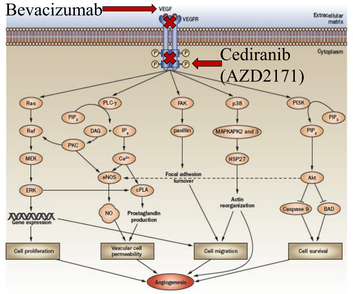
Introduction

Targeted therapeutics are increasingly playing an important role in the management of cancer patients. A rational strategy is to combine multiple targeted therapies to inhibit multiple pathways or inhibit multiple points in one pathway to bring about additive or synergistic effects. As a first step, this study explored a rational combination of two targeted agents targeting tumor vasculature: 1) Bevacizumab (Avastin™), and 2) a kinase insert domain-containing receptor (KDR) inhibitor, cediranib (AZD2171).

Our central hypothesis is that by inhibiting two components of the angiogenesis pathway in cancer, synergistic or additive activity can be obtained in tumors and their vasculature and that biological correlates can be identified to correlate with this synergistic activity.

Targeting the VEGF Angiogenesis Pathway

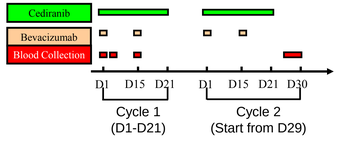


Objectives

- To determine the phase II recommended dose of the combination
- To determine the pharmacokinetics of cediranib combined with bevacizumab
- To determine the preliminary efficacy of the combination
- To determine Pharmacodynamics associated with the combination (CECs, CTCs, DCE-MRI, and NO levels)

Study Design

- Conventional 3+3 design
- Expansion phases (25 pts) to better evaluate anti-tumor activity and PD markers.
- Each cycle-cediranib (21 days) and bevacizumab (days 1 &15)
- PDs drawn at pre, days 1,2, 15 and end of cycle 2
- Biopsy pre and after cycle 1 required after first PR observed
- DCE-MRI optional



Key Eligibility Criteria

- Advanced malignancies refractory to standard therapy or no standard therapy increasing survival > 3 months
- Age >16 years allowed
- ECOG PS ≤2
- Adequate hematologic, renal, and hepatic function
- Stable brain metastasis allowed and primary brain malignancies allowed

Demographics

Results

Dose Level	Bevacizumab	Cedarinib	Pts (n)	DLTs
-1	3 mg/kg/2 weeks	15 mg/day	0	0
1	3 mg/kg/2 weeks	20 mg/day	3	0
2	5 mg/kg/2 weeks	20 mg/day	7	1
3	5 mg/kg/2 weeks	30 mg/day	14	2
4	5 mg/kg/2 weeks	45 mg/day	4	2
5	10 mg/kg/2 weeks	45 mg/day	0	0

- The recommended phase II dose of combination is cediranib (30 mg/day) and bevacizumab (5mg/kg)
- The DLTs were grade 3 fatigue, hypertension, chest pain, and thrombocytopenia

Safety and Tolerability

Most Common Toxicities-Any Grade

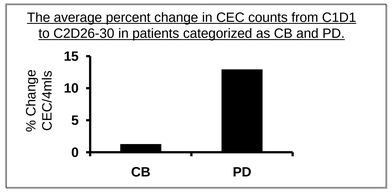
Total patients (N=28)		Grade 1-2	Grade 3-4
Most common drug-related toxicities		n(%)	n(%)
Hypertension		18(64)	2(7)
Anorexia		15 (48)	0 (0)
Fatigue		13(46)	1 (4)
Diarrhea		10 (36)	2(7)
Nausea		8 (29)	3 (11)
Headache		7 (25)	0 (0)
Proteinuria		7 (25)	2 (7)
Elevated AST/ALT		7(25)	0 (0)
Neuropathy		5 (18)	0 (0)
Hypothyroidism		4 (14)	0 (0)

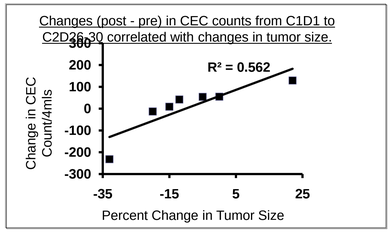
- Most common toxicities of the combination were hypertension, anorexia, and fatigue

Pharmacodynamics

CEC Enumeration

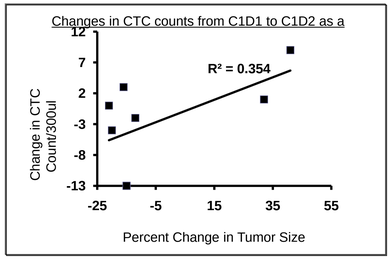
- Bevacizumab and cediranib combination significantly decreased the number of CD105+ Circulating Endothelial Cells (CEC) in patients from the Clinical Benefit (CB) group compared to Progressive Disease (PD) group at C2D26-30, and this observation correlated with changes in tumor size.





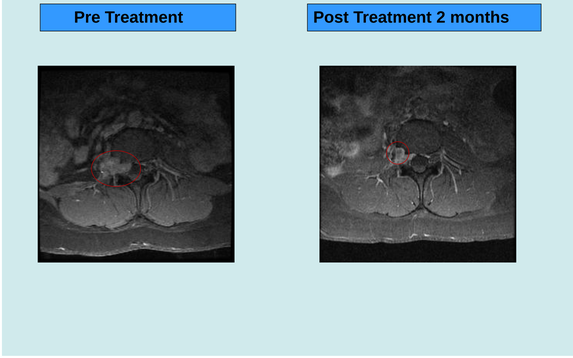
CTC Enumeration

- Circulating Tumor Cell (CTC) isolation using CellSearch™ Profile kit followed by LSC detection demonstrated significantly higher rate of CTC recovery as compared to CellSearch™ kit.
- B + C treatment significantly (p<0.001) decreased Circulating Tumor Cells in patients with CB (avg. -95%; pre=5 to post=0.25) compared to patients with PD (avg. 1,000%; pre=0.5 to post=5.5) at 24 hrs post-treatment, and this observation correlated with changes in tumor size.

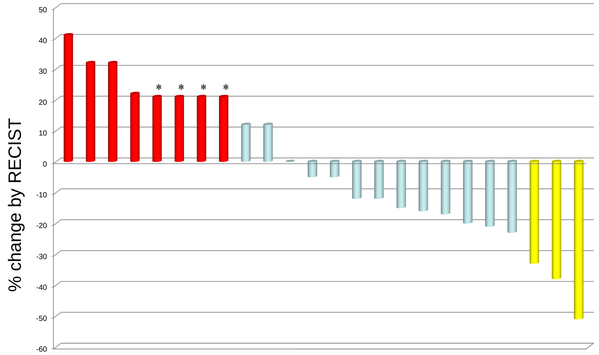


Tumor Response

Partial Response in Aveolar Soft Part Sarcoma Patient



Best Response



- 24/28 pts evaluable; 2 pts withdrew consent, 2 pts too early
- 2 confirmed PRs: ASPS (-38%),Basal cell (-33%)
- 1 unconfirmed PR:IBC (-51%)
- Prolonged SD (>4 months) seen in patients with H&N,ASPS endometrial, and basal cell ca
- *clinical progression

Conclusions

- **The recommended phase II dose of combination is cediranib (30 mg/day) and bevacizumab (5mg/kg)**
- **The DLTs was grade 3 fatigue, hypertension, CP, thrombocytopenia**
- **Most common toxicities were hypertension, anorexia, fatigue**
- **Combination may have clinical activity in ASPS**
- **CEC and CTC correlate with clinical benefit and may provide an early measure of metastatic tumor burden**
- **DCE-MRI,PKs pending**
- **Prolonged SD (>4 months) seen in patients with H&N, ASPS, endometrial, and basal cell cancers**

References

1)

Acknowledgements

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