

PROTOCOL ABSTRACT

0C-04-8

A Phase I Study of VEGF-Antisense Oligonucleotide (VEGF-AS) Given as a Daily Fixed Dose Subcutaneous Injection in the Treatment of Patients with Relapsed or Refractory Malignancies

ELIGIBILITY CRITERIA

INCLUSION CRITERIA:

- Histologically or cytologically confirmed malignancy for which standard therapeutic measures do not exist or are no longer effective
- Age ≥ 18 years old
- ECOG PS ≤ 2 (KPS $\geq 50\%$)
- Estimated survival ≥ 3 months
- AGC ≥ 1.5 ; platelets $\geq 75,000$ (AGC and platelets waived for patients with proven metastatic or primary disease in BM)
- Total bilirubin $\leq 1.5 \times \text{uln}$; SGOT/SGPT $\leq 2.5 \times \text{uln}$
- Creatinine ≤ 1.5
- HIV-infected patients eligible (provided that all other eligibility criteria are met)
- Patients with history of prior malignancy eligible (provided that all other eligibility criteria are met)
- Patients who have had prior VEGF-AS may be entered (provided that all other eligibility criteria are met)
- Signed informed consent (including HIPAA authorization)

EXCLUSION CRITERIA:

- Prior chemotherapy, immunotherapy, or RT within 4 weeks prior to study entry (6 weeks for nitrosourea-containing chemotherapy). Must have recovered from toxicities of prior therapy.
- Receiving therapy with other investigational agents at the time of study enrollment
- Cancer involving the brain or brain metastases
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (excluding HIV in patients known to be HIV-seropositive)
- History of symptomatic CHF, unstable angina pectoris, or clinically significant cardiac arrhythmia
- History of DVT or PE
- Pregnant or nursing women. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating MD immediately.
- Any prior major surgery within 2 weeks of study entry

TREATMENT

VEGF-AS as subcutaneous injection given once daily for 28 days (1 cycle).

Patients/family member/support person to administer drug; diary will be given to record each injection, as well as any symptom or side effect. Patients to return all used drug vials on a weekly basis.

Dose Level	VEGF-AS (mg) SC daily x 28 days
1	50
2	100
3	150
4	200

3 patients will be treated at initial cohort and the 3rd patient on the cohort will be followed for at least 28 days from the first dose for evaluation of side effects. If no DLT, then the next dose level will be opened. If DLT is observed in 1 patient, 3 additional patients will be accrued to that dose level and observed for a minimum of 21 days from the first dose of therapy. A minimum of 3 patients will be evaluated at each dose level. The next cohort of patients will be treated at a higher dose level if no DLT is encountered in these first 3. There will be no dose escalations within the same patient. If 2 DLTs are observed in an expanded cohort of 6 patients, that level will be declared as the DLT level and the preceding dose will be declared MTD. At least 6 evaluable patients must be treated at MTD level.

If patient does not experience any DLT and does not have PD, they may receive additional treatment cycles. A maximum of 6 cycles will be permitted. There will be no intra-patient dose escalation.

8. STUDY CALENDAR

Except where specified, baseline/pre-therapy evaluations will be performed within 14 days of first study drug administration. Diagnostic tests, x-rays, and diagnostic biopsies (ie bone marrow) may be done within 30 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours. If the day 1 occurs within 48 hours of baseline, the same day 1 evaluations do not need to be repeated.

Course	Pre-Therapy						1						2	3	4	5	6	Off Study /25
	1	2	3	4	5-8	9-12	13-16	17-20	21-24									
Week of therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
VEGF-AS injections ¹																		25
Week of Test, Day 1	1	2	3	4	5	9	13	17	21									
Medical history	X				X	X	X	X	X									X
Physical exam	X				X	X	X	X	X									X
Vital signs ^b	X				X	X	X	X	X									X
Height	X				X	X	X	X	X									X
Weight	X				X	X	X	X	X									X
Perform. Status	X				X	X	X	X	X									X
CBC w/diff, plts ^a	X				X	X	X	X	X									X
Serum chemistry ^{a,c}	X				X	X	X	X	X									X
PT/PTT/Fibrinogen	X				X	X	X	X	X									X
β-HCG ^e	X				X	X	X	X	X									X
EKG	X				X	X	X	X	X									X
LVEF by MUGA or Echo	X				X	X	X	X	X									X
Tumor measurements (appropriate scans, etc) ^c	X				X	X	X	X	X									X
Bone Marrow Biopsy ^f	X				X	X	X	X	X									X
Toxicity	X				X	X	X	X	X									X
Pharmacokinetics ^g	X				X	X	X	X	X									X
Plasma for VEGF Levels ^h	X				X	X	X	X	X									X
Tumor donation ⁱ	X				X	X	X	X	X									X ⁱ

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1. Once a day subcutaneous injection, each day, for every 28-day course
 - a. On day 8, 15 and 22 of course 1 and day 1 of subsequent courses, repeat CBC with differential, and serum chemistry
 - b. Vital signs: At all visits indicated take blood pressure, heart rate, temperature, respirations. On the first treatment day, additional monitoring will consist of blood pressure and pulse rate within 1 hour prior to administration of the dose and every hour for up to 4 hours post injection.
 - c. Including alkaline phosphatase, total bilirubin, SGOT[AST], electrolytes, protein, creatinine
 - d. Serum pregnancy test (women of childbearing potential)
 - e. For responding patients (SD, PR, or CR) response must be confirmed 3 to 4 weeks after first observation of response, using the same diagnostic technique. Tumor measurements positive by radiologic scans at baseline to be repeated between days 21 and day 28 of course 1. Repeat tumor evaluations will be performed between days 21 and 28 of course 2, course 4, and then again at off study, or a at post course 6.
 - f. In patients with malignancies primary to bone marrow (i.e., AML, or ALL): Bone marrow biopsy to be repeated between days 21 and day 28 of course 1. Patients receiving additional courses of therapy should have a repeat bone marrow performed between days 21 and 28 of courses 2, 4 or 6, or at off-study, if progressive disease has not already been documented.
 - g. Pharmacokinetics to be performed on day 1 of treatment. (within 30 min pre-injection, and at 0, 30 minutes, 1, 2, and 6 hours after injection. Also on days 2 and 8 pre-injection, and at off study. Blood specimen handling instructions are provided in Section 7.1
 - h. Plasma for VEGF levels to be performed at the following time points: pre study, 24 hours after VEGF-AS injection on day 1 (pre-injection on day 2), and pre-injection on days 8, 15, and 21 of the first course, then preinjection day one of each subsequent course, and at off study. See Appendix E for processing instructions.
 - i. Readily accessible tumor samples (skin punch biopsies, bone marrow, or peripheral blood in patients with circulating malignant cells in the peripheral blood) will be obtained prior to study entry, on day 5, and again on day 28 of courses 1 and 6, if the separate consent for same is provided by the patient. See Appendix F for processing instructions. These samples will be used to study changes in tumor levels of VEGF and VEGF family members.