

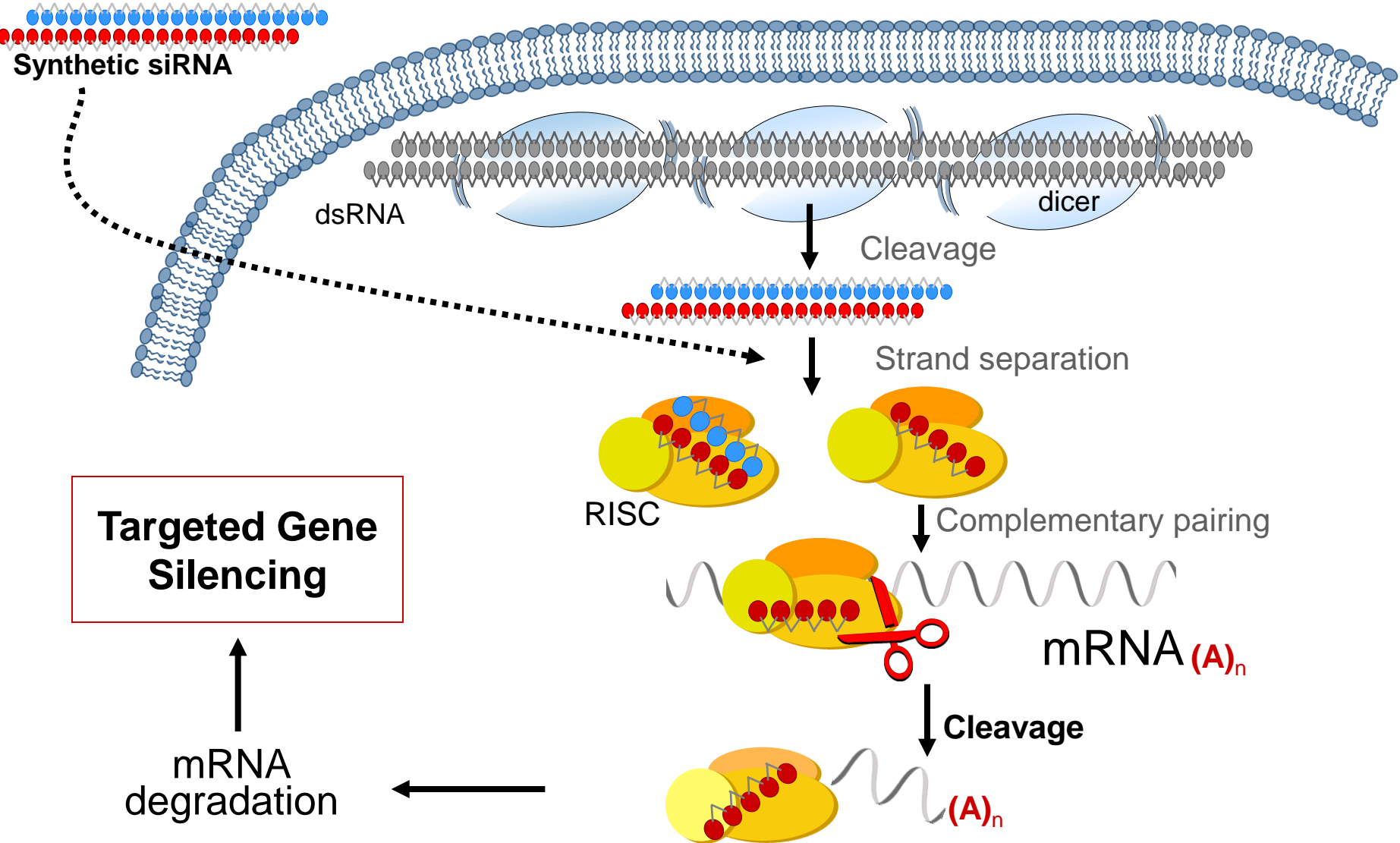
ASCO June 2011

Phase I Dose Escalation Study of ALN-VSP02

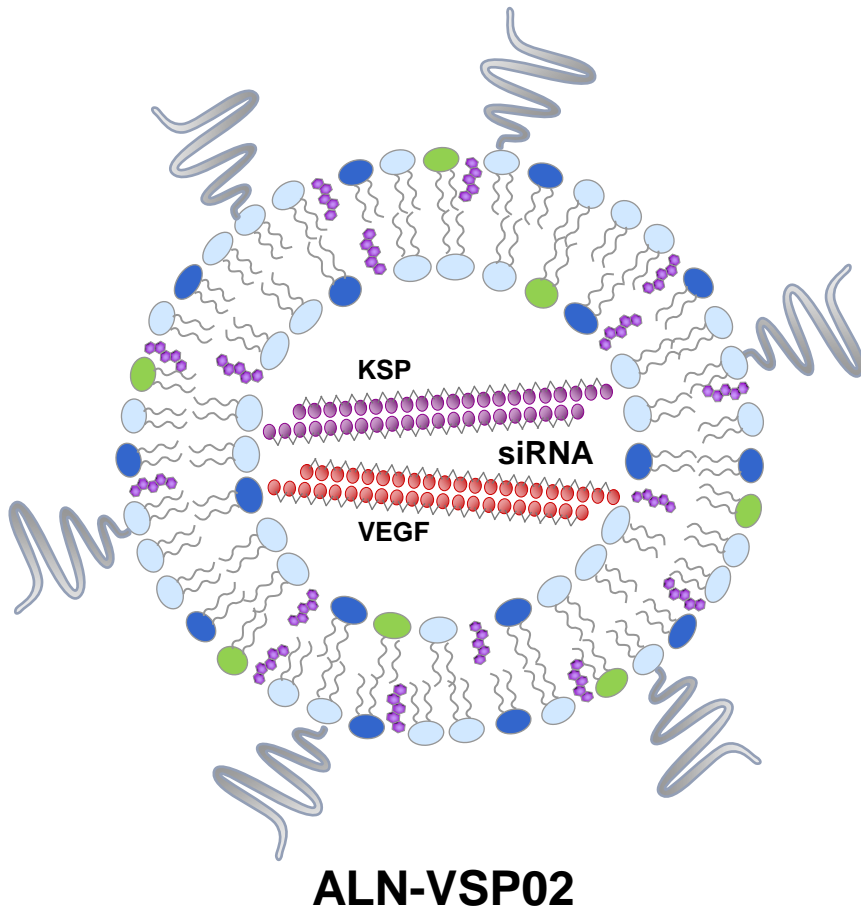
A Novel RNAi Therapeutic for Solid Tumors with Liver Involvement

June 4, 2011

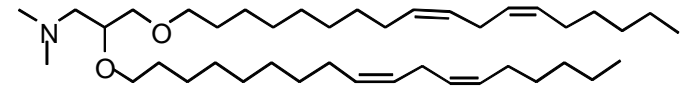
Mechanism for RNA Interference (RNAi)



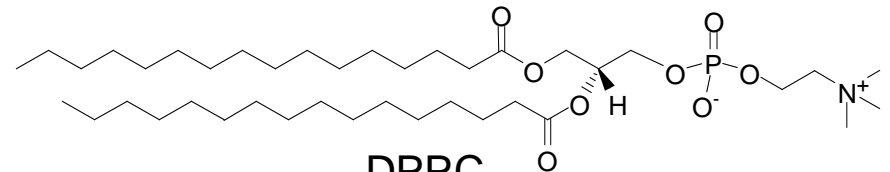
ALN-VSP02 Scheme



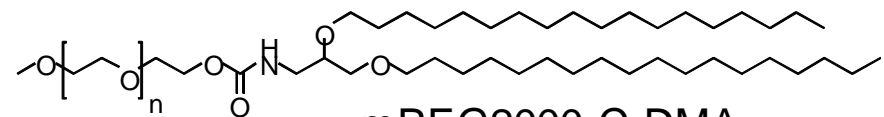
Lipid nanoparticle* (LNP) components:



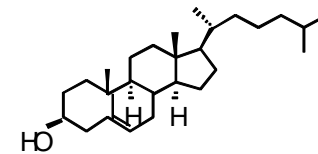
DLinDMA



DPPC



mPEG2000-C-DMA



Cholesterol

*Lipid nanoparticle formulation from Tekmira Pharmaceuticals

ALN-VSP02 Phase I Study Objectives

Primary

- Evaluate the safety and tolerability of ALN-VSP02

Secondary

- Characterize PK
- Assess for evidence of antitumor/antiangiogenic activity
 - » Tumor response rate, change in tumor blood flow on DCE-MRI

Exploratory

- Analyze voluntary tumor biopsies for drug levels and for evidence of RNA interference using 5' RACE assay

Key Inclusion and Exclusion Criteria

ALN-VSP02 Phase I

Key Inclusion Criteria

Each patient must meet the following criteria within 14 days of C1W1D1 to be enrolled in the study

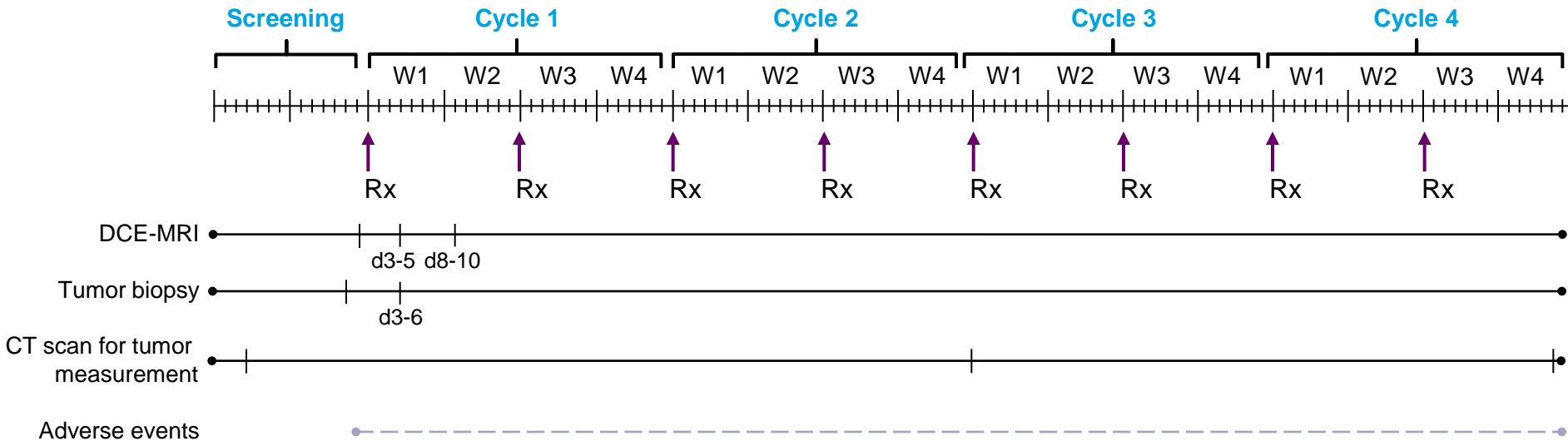
- Patients must have histologically or cytologically confirmed advanced solid tumors that have recurred or progressed following standard therapy, or that have not responded to standard therapy, or for which there is no standard therapy, or who are not candidates for standard therapy.
- Patient has measurable tumor in the liver (≥ 1 cm by spiral CT or ≥ 2 cm by standard CT).
- Patient has an Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1.
- Patient has adequate liver function, demonstrated by an aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN), total bilirubin within normal limits, albumin > 3.0 g/dL, international normalized ratio (INR) ≤ 1.2 , and Child-Pugh Class A (for hepatocellular carcinoma [HCC] patients).
- Patient has adequate renal function: serum creatinine $\leq 1.5 \times$ ULN.

Key Exclusion Criteria

Patients meeting any of the following criteria within 14 days of C1W1D1 will be excluded from the study:

- Patient has brain or leptomeningeal metastases. (Note: Patients with completely resected brain metastases and no evidence of residual disease on CT or MRI scan of the brain will be considered eligible).
- Patient has known HBV, HCV, or human immunodeficiency virus (HIV) infection.
- Patient has $>50\%$ involvement of the liver by tumor.
- Patient has undergone splenectomy.

ALN-VSP02 Phase I Study Design



Dose levels and dosing schedule

- 0.1, 0.2, 0.4, 0.7, 1.0, 1.25, 1.5, 1.7 mg/kg
- 3 + 3 cohort design, expansion phase of 10 pts at MTD
- 15-min IV infusion q2 wks; premed with steroids, H1 and H2 blockers, acetaminophen
- Cycle = 2 doses (1 month), tumor measurements after every 2 cycles, treat until disease progression
 - » ALN-VSP02-002 extension study for pts remaining on study beyond 4 cycles (8 doses)

Demographics and Dosing

- N=41
 - » Dose escalation (0.1-1.5 mg/kg): N=31
 - » Expansion phase at 1.0 and 1.25 mg/kg: N=10 (5 per dose level)
- Median age 57 (range 34-78)
- Male: Female = 17:24
- ECOG performance status 0/ 1 (%): 44 / 56
- Average # of prior regimens for metastatic disease: 4.3 (range 1-13)
- Prior chemotherapy/anti-VEGF therapy (%): 88 / 61
- Liver/Extrahepatic metastases (%): 98 / 88
- Tumor types
 - » GI (N=24)
 - » GYN (N=9)
 - » GU (N=3)
 - » Sarcoma (N=2)
 - » Other (N=3)
- Total of 182 doses administered to date
- Average # of doses/patient: 4.4 (range 1-24)
 - » One patient continues on study after full year of dosing

Treatment Emergent Adverse Events

Number of Patients with Grades 1, 2, 3, 4

Toxicity**	% of Patients (n=41)	ALN-VSP02 Dose Level (mg/kg)						
		0.10 (n=3)	0.20 (n=3)	0.40 (n=6)	0.70 (n=7†)	1.00 (n=9)	1.25 (n=11‡)	1.50 (n=2)
Fatigue	24%	1, 0, 0, 0	0, 0, 0, 0	0, 2, 0, 0	2, 1, 0, 0	1, 0, 0, 0	1, 1, 0, 0	1, 0, 0, 0
Nausea	17%	1, 0, 0, 0	0, 1, 0, 0	1, 1, 0, 0	1, 0, 0, 0	1, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0
Fever	15%	0, 0, 0, 0	0, 0, 0, 0	1, 0, 0, 0	1, 0, 0, 0	2, 0, 0, 0	2, 0, 0, 0	0, 0, 0, 0
Infusion-Related Reaction	15%	0, 0, 0, 0	0, 0, 0, 0	0, 1, 0, 0	0, 1, 0, 0	0, 3, 0, 0	0, 1, 0, 0	0, 0, 0, 0
Vomiting	12%	2, 0, 0, 0	1, 1, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0
AST Elevation	12%	0, 1, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 1*, 0	2, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0
Rash/Flushing	12%	1, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0	1, 0, 0, 0	1, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0
Thrombocytopenia	12%	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 1*, 0	2, 0, 0, 0	0, 0, 2, 0	0, 0, 0, 0
Chills/Rigors	10%	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	1, 0, 0, 0	1, 2, 0, 0	0, 0, 0, 0
Diarrhea	7%	0, 0, 0, 0	0, 1, 0, 0	1, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0
Abdominal Pain	7%	1, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0	0, 1, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0
Headache	7%	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	1, 0, 0, 0	1, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0
Hypertension	5%	0, 0, 0, 0	0, 0, 0, 0	0, 1, 0, 0	0, 1, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0
ALT Elevation	5%	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 1*, 0, 0	1, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0
Dizziness	5%	1, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0
Anorexia	5%	1, 0, 0, 0	0, 0, 0, 0	1, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0	0, 0, 0, 0

**Includes only those toxicities deemed related or possibly related to study drug in 5% or more pts

*Patient with extensive liver metastases died from liver failure, possibly related to study drug

†1 patient reduced to 0.40 mg/kg after dose 1

‡2 patients reduced to 1.00 mg/kg after dose 1

Serious Adverse Events

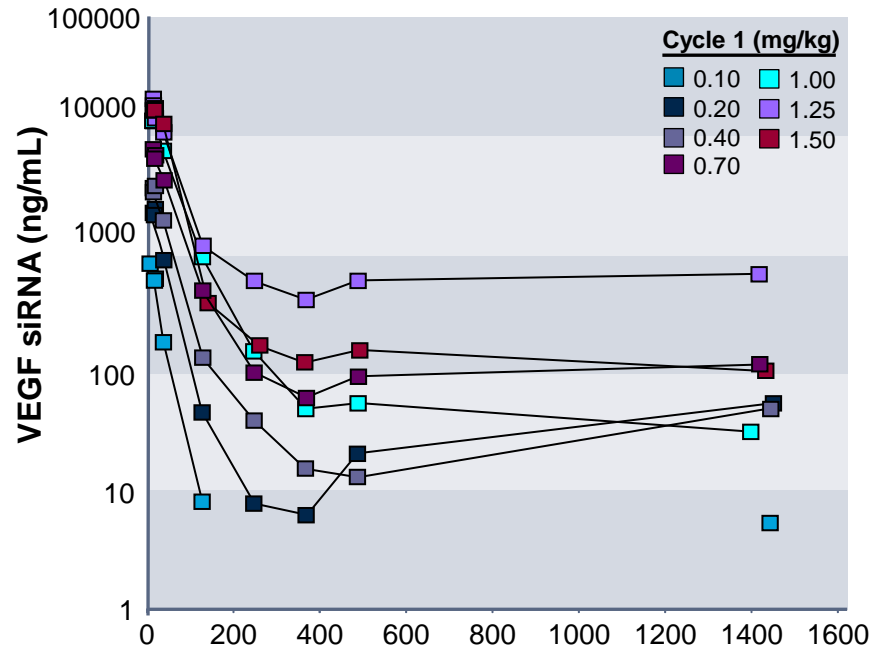
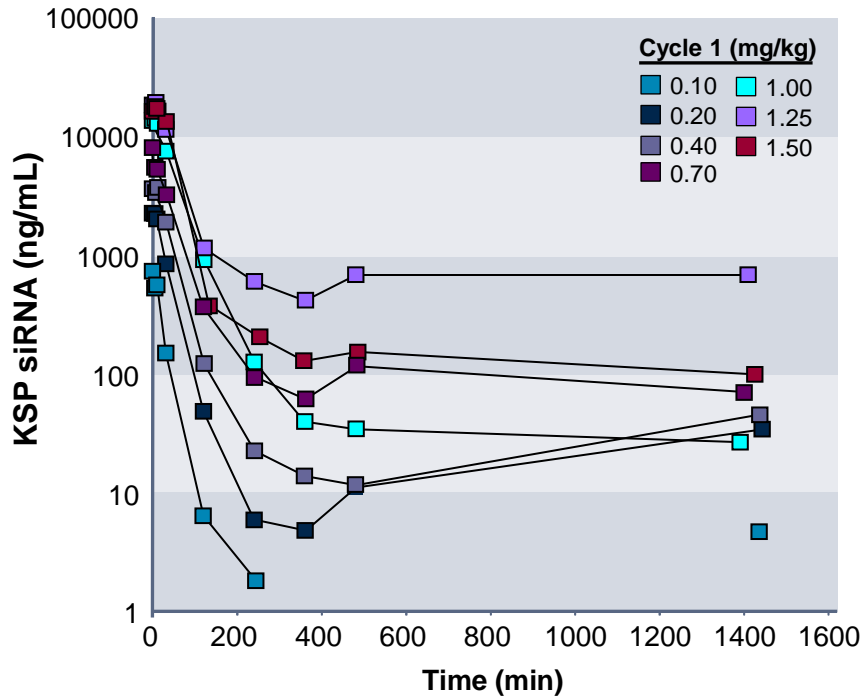
Patient #	Tumor Type	Dose Level (mg/kg)	Event(s)	Relatedness
003-012	Pancreatic neuroendocrine	0.70	<ol style="list-style-type: none"> 1. Liver failure 2. Hepatic encephalopathy <p>Both arising 5 days post-dose 2, resulting in death</p>	Possibly related
001-021	Endometrial	0.70	<ol style="list-style-type: none"> 1. Elevated WBC 2. Fever <p>Both occurred post-dose 23. Hospitalized to rule out infection and then resumed dosing on study.</p>	Possibly related
001-030	Endometrial	1.25	<p>Elevated WBC post-dose 3. Hospitalized to rule out infection and then resumed dosing on study.</p>	Possibly related

- 5 possibly related SAEs in 3 patients
- 23 unrelated SAEs in 10 patients



Plasma PK Data Summary

VEGF and KSP siRNAs



KSP siRNA

ALN-VSP Cycle 1 (mg/kg)	0.10 (n=3)	0.20 (n=3)	0.40 (n=5)	0.70 (n=7)	1.00 (n=4)	1.25 (n=5)	1.50 (n=2)
C_{max} ($\mu\text{g/mL}$)	0.76 \pm 0.36	2.26 \pm 0.54	3.92 \pm 1.12	7.99 \pm 3.39	15.31 \pm 5.35	21.94 \pm 7.64	18.04
AUC_{0-last} ($\text{min} \cdot \mu\text{g/mL}$)	30.83 \pm 20.86	133.02 \pm 46.66	252.38 \pm 97.9	523.18 \pm 206.18	923.59 \pm 360.13	2035.74 \pm 1100.08	1491.03

VEGF siRNA

ALN-VSP Cycle 1 (mg/kg)	0.10 (n=3)	0.20 (n=3)	0.40 (n=5)	0.70 (n=7)	1.00 (n=4)	1.25 (n=5)	1.50 (n=2)
C_{max} ($\mu\text{g/mL}$)	0.86 \pm 0.42	2.51 \pm 0.56	4.31 \pm 1.10	8.81 \pm 2.75	15.84 \pm 7.01	21.58 \pm 6.80	18.19 \pm 1.09
AUC_{0-last} ($\text{min} \cdot \mu\text{g/mL}$)	68.95 \pm 66.12	143.11 \pm 58.58	272.21 \pm 98.16	626.37 \pm 272.66	984.26 \pm 436.81	2006.58 \pm 1113.54	1514.63 \pm 150.24

- AUC and C_{max} dose proportional
- Same PK profile for Cycles 1 and 2 with no evidence of drug accumulation

Safety Summary

- ALN-VSP02 was generally well-tolerated
 - » 1 patient has so far received 24 doses over 1 year
- No dose-dependent changes in liver function tests
- Grade 1-2 fatigue (24%), nausea (17%) and fever (15%) most common AEs with no clear dose dependence
- Grade 2 infusion-related reactions seen in 15% of patients or 3% of doses administered
 - » Responded to slowing of infusion
 - » No patients discontinued from study because of infusion reaction
- Grade 1-2 chills/rigors seen at 1.25 mg/kg dose level
 - » Occurred after completion of dosing in 3 of 11 patients and associated with higher levels of transient IL-6 induction (peak at 6 hrs post-dose, resolution by 24 hrs)
 - In 2 patients, symptoms re-occurred after dose reduction to 1.0 mg/kg
- Dose-limiting toxicities included:
 - » Liver failure and death in patient with extensive hepatic metastases and prior splenectomy/partial hepatectomy at 0.7 mg/kg (possibly related),
 - » Transient grade 3 thrombocytopenia in 2 patients at 1.25 mg/kg,
 - » Grade 3 hypokalemia in 1 patients at 1.5 mg/kg
- Recommended Phase II dose is 1.0 mg/kg IV q2 weeks

Tumor Response Summary

Dose Level (mg/kg)	N (evaluable for response)	Avg # of Doses Received (range)	# Pts with Stable Disease or Better for ≥ 2 mos	# Pts Who Went on to Extension Study (>8 doses) to Date
0.10	3	3 (2-4)	0	0
0.20	3	4 (4-4)	0	0
0.40	7*	4.6 (2-11)	1	1
0.70	5	9.6 (3-23)	3 (includes 1 PR with ~70% tumor reduction)	2
1.00	11†	4.8 (2-8)	7	1
1.25	7	2.4 (1-6)	2	0
1.50	1	4	0	0

PR: partial response

*Includes 1 patient whose first dose was given at 0.7 mg/kg

†Includes 2 patients whose first dose was given at 1.25 mg/kg

Stable disease or better in:

- 1/13 pts (8%) at ≤ 0.4 mg/kg
- 12/24 pts (50%) at ≥ 0.7 mg/kg

Characteristics of Patients with SD or PR

Patient #	Dose Level (mg/kg)	Tumor Type	Best Response	# of Doses
016	0.40	Squamous Cell Head and Neck	SD	11
019	0.70	Colorectal	SD	8
020	0.70	Angiosarcoma	SD	10
021	0.70	Endometrial	PR	24 (ongoing)
022	1.00	Colorectal	SD	8
025	1.00	Synovial Sarcoma	SD	7
037	1.00	Renal Cell	SD	8 (ongoing)
040	1.00	Pancreatic Neuroendocrine	SD	5 (ongoing)
041	1.00	Renal Cell	SD	4 (ongoing)
042	1.00	Uveal Melanoma	SD	4 (ongoing)
044	1.00	Pancreatic Neuroendocrine	SD	4 (ongoing)
028	1.25	Esophageal Adenocarcinoma	SD	6
030	1.25	Endometrial	SD	4

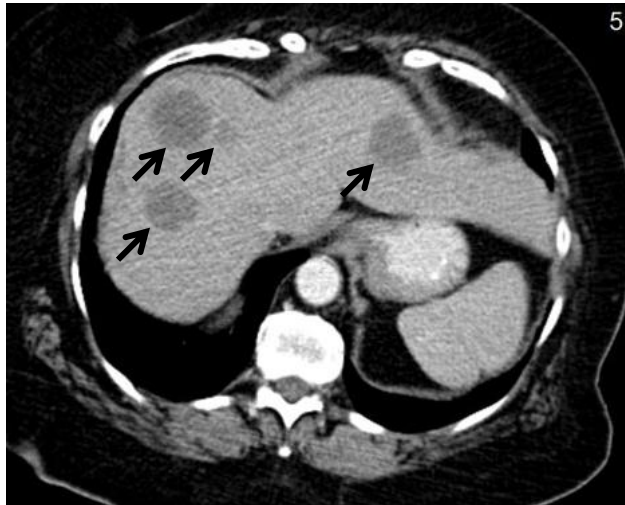
SD: stable disease

PR: partial response

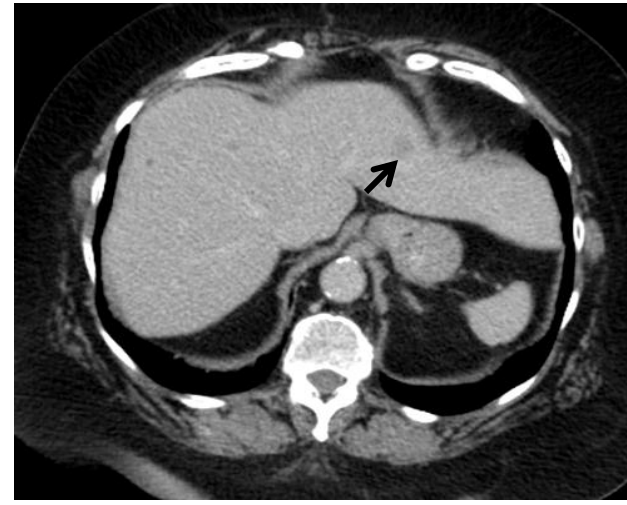
Major Response in Endometrial Cancer

Patient 021, 70% Regression of Liver Metastases

Pre-Treatment

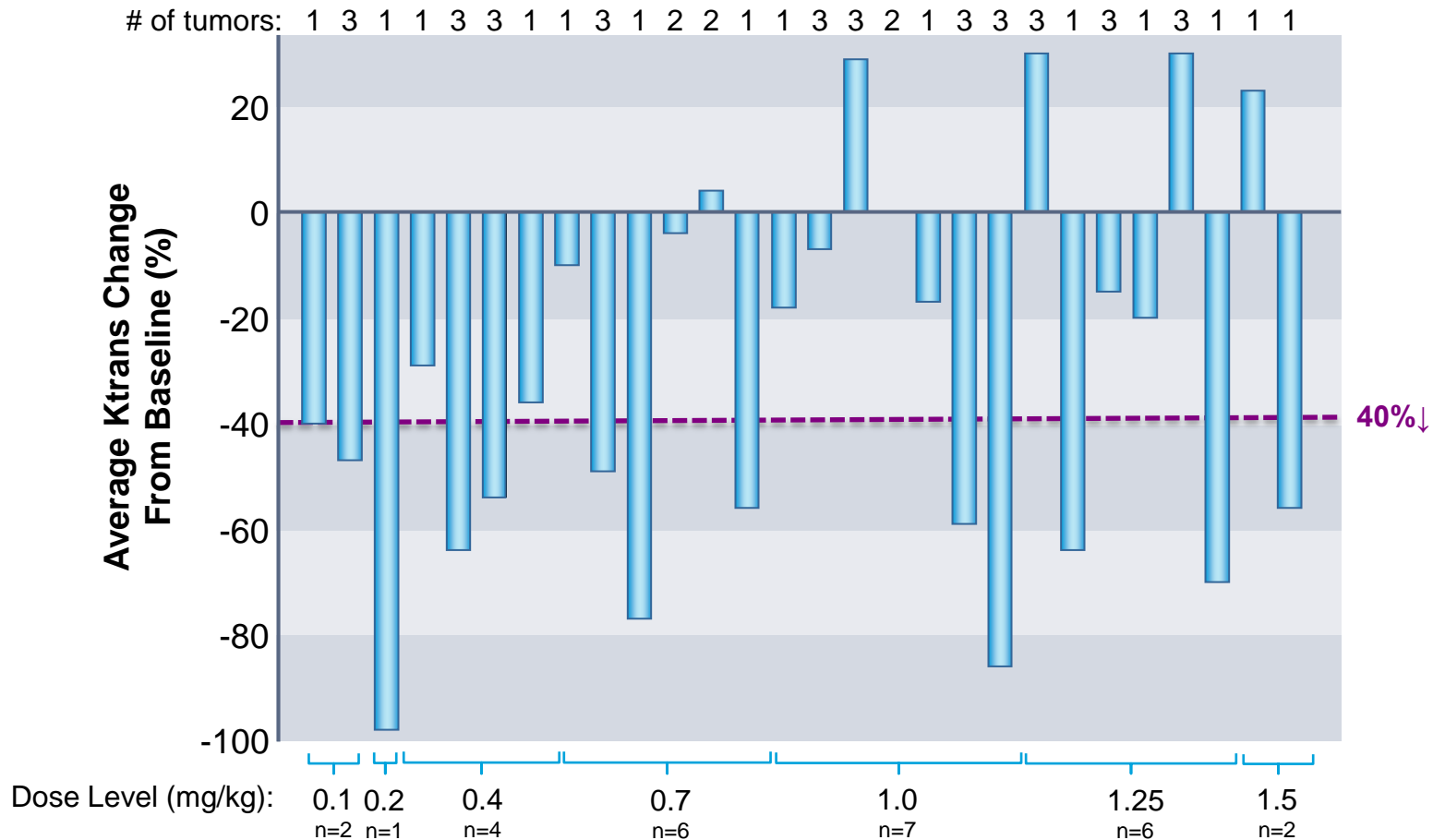


After 12 Doses ALN-VSP02*



*Response ongoing after 24 doses

DCE-MRI Results on Evaluable Patients



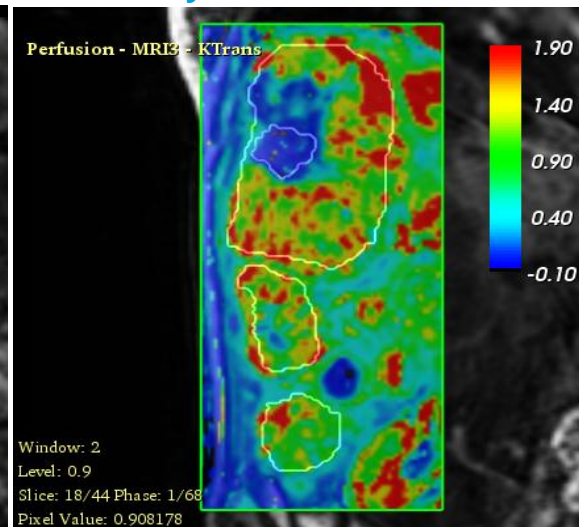
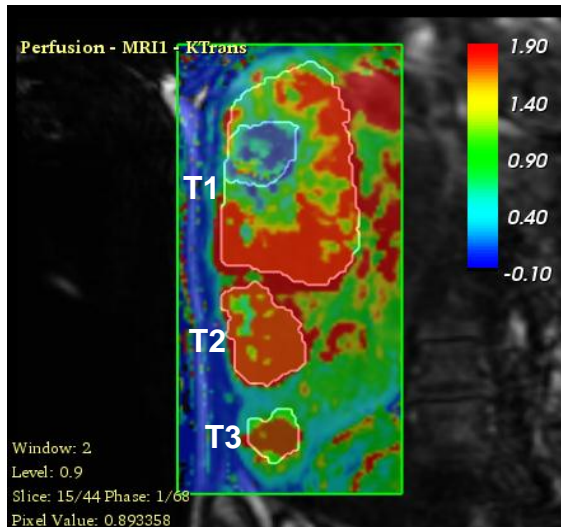
- 46% (13/28) of patients with average Ktrans ↓ of ≥40%

DCE-MRI in PNET Patients with Liver Metastases

Pre-Treatment

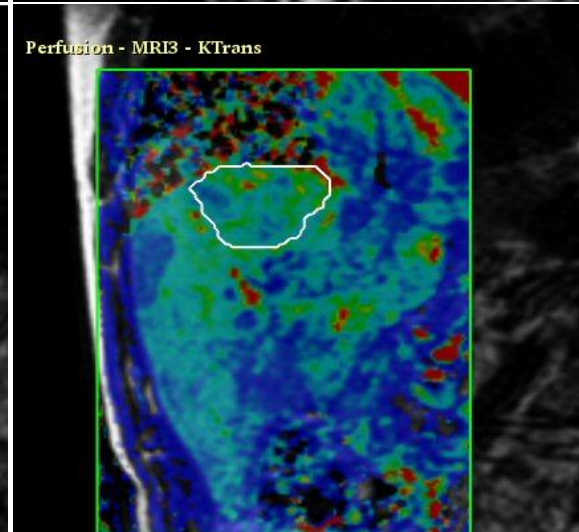
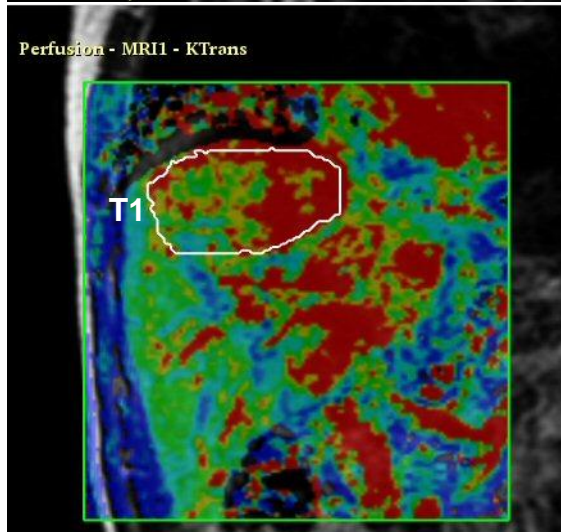
Day 7 Post-Dose 1

Pt 012
(0.7 mg/kg)



Avg Ktrans↓=49%
(n=3 tumors, T1-T3)

Pt 044
(1.0 mg/kg)



Avg Ktrans↓=86%
(n=3 tumors, only T1 shown)

T: liver tumor
PNET: pancreatic neuroendocrine tumor

Voluntary Tumor Biopsies

- CT-guided core needle biopsies obtained pre- and post-dose 1 in patients on voluntary basis
 - » Analyses:
 - Drug levels
 - 5' RACE
 - qPCR
- 29 Tumor biopsies obtained from 15 patients across multiple dose levels
 - » 0.4 mg/kg (n=3), 0.7 mg/kg (n=2), 1.0 mg/kg (n=6), 1.25 mg/kg (n=3), 1.5 mg/kg (n=1)
 - » Liver tumor biopsies in 11 patients
 - » Extrahepatic tumor biopsies in 4 patients
- Histological exam reveals high degree of variability in proportion of tumor, fibrotic/necrotic tissue, and normal tissue in biopsy samples
 - » Impacts certain quantitative interpretations of molecular results

Drug Levels in Tumor Biopsies Post-Dose 1

Pt #	Dose mg/kg	Tumor Type (Biopsy Site, Day of Post-Dose Biopsy)	Post-Dose Biopsy (%)			Drug Levels** (ng/g tissue)	
			Viable Tumor	Liver	Fibrosis/ Necrosis	VEGF siRNA	KSP siRNA
007	0.40	Colorectal (liver, d7)	17	80	3	25.7	12.5
017	0.40	Ovarian (liver, d2)	0	95	5	28.9	17.2
019	0.70	Colorectal (liver, d2)	20	5	75	142	73.3
022	1.00	Colorectal (adrenal, d2)	10	0	78*	9.8	3.8
025	1.00	Sarcoma (muscle, d2)	96	0	4	0.45	0.40
033	1.00	Colorectal (liver, d3)	56	0	35†	5.4	2.2
041	1.00	RCC (liver, d2)	70	15	15	6.0	6.8
042	1.00	Uveal mel (liver, d2)	100	0	0	7.0	5.8
026	1.25	Colorectal (liver, d6)	14	0	71‡	0.32	<LLOQ
031	1.25	Ovarian (abdomen, d4)	30	0	70	4.9	3.6
035	1.25	Ovarian (L. node, d5)	40	0	60	20.4	20.3
032	1.50	Small bowel (liver, d6)	42	0	58	4.9	3.6

**Measured by qPCR, LLOQ (lower limit of quantitation)=0.14 ng/g tissue. All pre-treatment biopsy samples were <LLOQ.

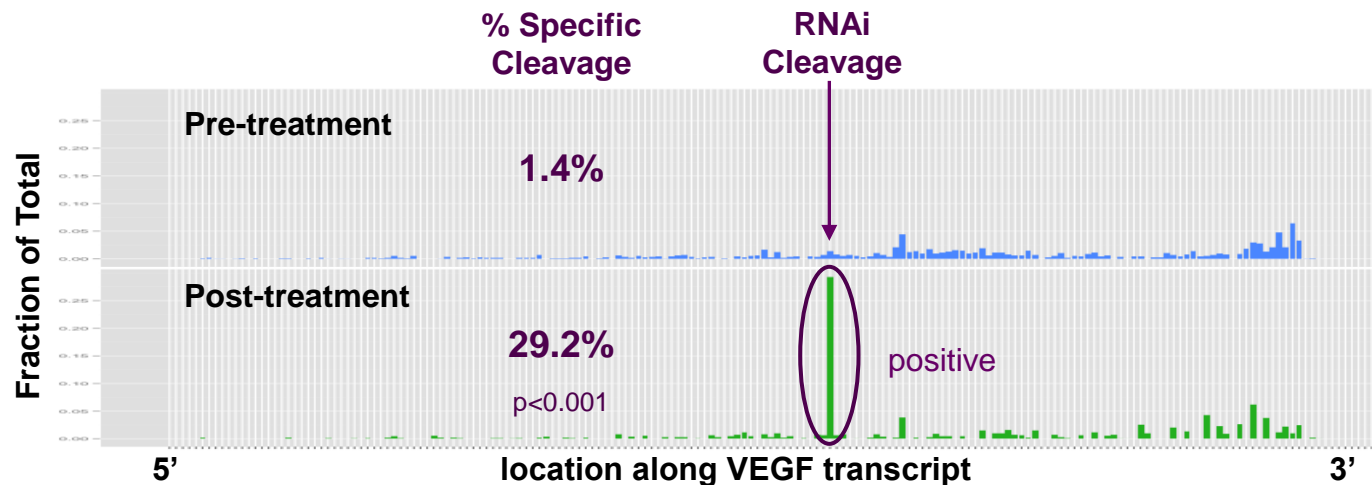
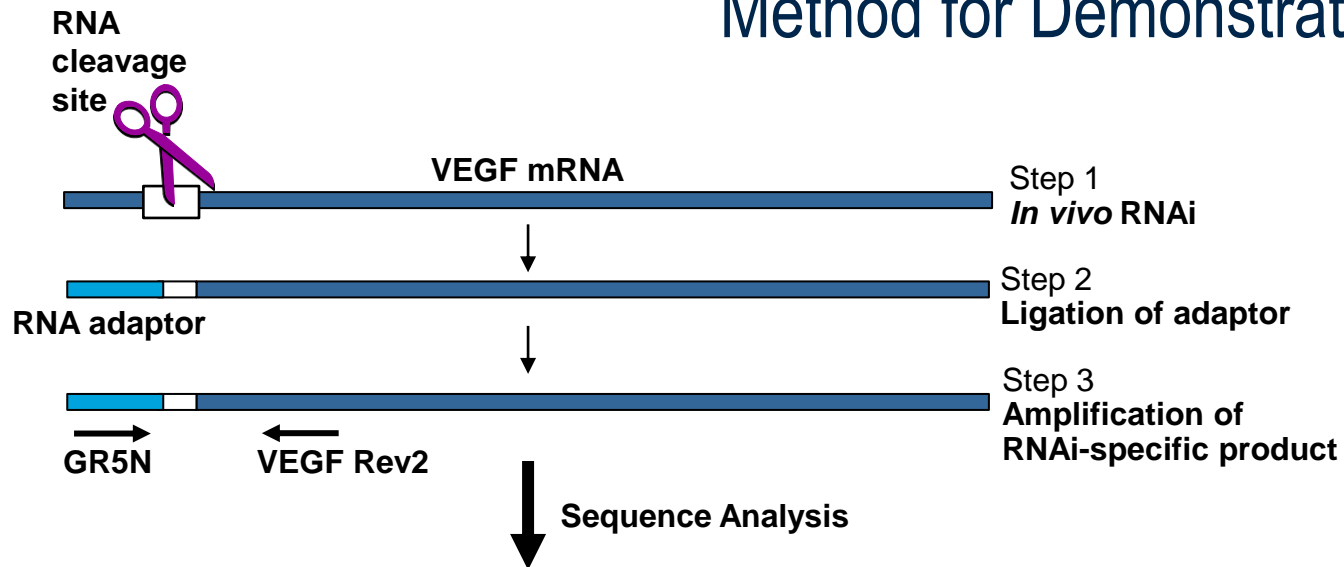
*Remaining 12% was normal adrenal (6%) and fat (6%)

†Remaining 9% was skeletal muscle

‡Remaining 15% was skeletal muscle

VEGF 5' RACE Assay

Method for Demonstrating RNAi



Illustrative
Example:
Patient 016

Tumor Biopsies Positive By VEGF 5' RACE

Pt #	Dose mg/kg	Tumor Type (Biopsy Site, Day of Post-Dose Biopsy)	Pre-Dose Biopsy (%)			Post-Dose Biopsy (%)			VEGF 5' RACE
			Viable Tumor	Liver	Fibrosis/Necrosis	Viable Tumor	Liver	Fibrosis/Necrosis	
016	0.40	SCC H&N (liver, d2)	10	0	90	0	100	0	Pos*
017	0.40	Ovarian (liver, d2)	N/A	N/A	N/A	0	95	5	Pos*
031	1.25	Ovarian (abdomen, d4)	25	0	75	30	0	70	Pos*

SCC H&N: Squamous cell cancer of head and neck
 N/A: No sample for analysis

*p<0.001

- 15 patients with post-treatment biopsy evaluable by 5' RACE :
 - » 0.4 mg/kg (n=3), 0.7 (n=2), 1.0 (n=6), 1.25 (n=3), 1.5 (n=1)
- 3 of 15 positive for VEGF 5' RACE
 - » 2 liver tumor biopsies at 0.4 mg/kg
 - » 1 extrahepatic tumor biopsy at 1.25 mg/kg
- Assay development in progress for KSP 5' RACE
 - » Required due to low KSP mRNA levels

Clinical Activity/PD Summary

Evidence of antitumor activity in heavily pre-treated patients at doses ≥ 0.7 mg/kg

- Major ongoing response (PR with $\sim 70\%$ tumor reduction) in patient with endometrial cancer and multiple liver metastases treated at 0.7 mg/kg
 - » Patient treatment continuing after one full year
- 64% (7 of 11) of patients with stable disease ≥ 2 months at recommended Phase II dose of 1.0 mg/kg
 - » 45% (5 of 11) of patients continue receiving drug on study

DCE-MRI results suggestive of anti-VEGF effect

- $\sim 50\%$ of pts showing $\geq 40\%$ drop in Ktrans in liver tumors, including endometrial cancer patient with major response (PR) and two PNET pts

siRNA delivery and RNAi proof of mechanism shown in tumor biopsies

- Pharmacologically relevant concentrations of VEGF and KSP siRNAs in hepatic and extrahepatic tumors
- Molecular evidence of RNAi-mediated VEGF mRNA cleavage in biopsies of hepatic and extrahepatic tumors by 5' RACE