Interim safety, pharmacokinetic and pharmacodynamic results for ALN-VSP02, a novel RNAi therapeutic targeting VEGF and KSP for the treatment of solid tumors with liver involvement

Chemotherapy Foundation Symposium
November 10, 2010
Therapeutic Approach to Harnessing RNAi

Natural Process of RNAi

Targeted Gene Silencing

mRNA degradation

mRNA

(A)_n

(dsRNA)

dicer

Cleavage

Strand separation

Complementary pairing

RISC

Cleavage

mRNA (A)_n
Lipid Nanoparticles (LNP) for Systemic siRNA Delivery

Liver: Targeting ApoB

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cholesterol</th>
<th>LDL</th>
<th>HDL</th>
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<tbody>
<tr>
<td>2 day</td>
<td>31.7</td>
<td>9.2</td>
<td>8.9</td>
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<tr>
<td>11 day</td>
<td>60.5</td>
<td>23.2</td>
<td>11.7</td>
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</table>

>65% Inhibition

Tumor: Targeting VEGF and KSP

Control siRNA

ALN-VSP

Keynote RNA, Feb 2009

Nature, 441, 111-114, Apr 2006
## Systemic Delivery siRNA Programs

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Program (Stage of Development)</th>
<th>Status</th>
<th>Target</th>
<th>Mode of Delivery</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Alnylam</td>
<td>ALN-VSP (Phase 1)</td>
<td>Ongoing</td>
<td>VEGF, KSP</td>
<td>LNP</td>
<td>1° and 2° liver cancer</td>
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<tr>
<td>Calando</td>
<td>CALAA-01 (Phase 1)</td>
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<td>RRM2</td>
<td>Targeted cyclodextrin-based nanoparticle</td>
<td>Cancer</td>
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<tr>
<td>Silence</td>
<td>Atu-027 (Phase 1)</td>
<td>Ongoing</td>
<td>PKN3</td>
<td>Lipoplex-siRNA</td>
<td>Cancer</td>
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<tr>
<td>Tekmira</td>
<td>SNALP PLK-1 (Phase 1)</td>
<td>IND approved</td>
<td>PLK-1</td>
<td>LNP</td>
<td>Cancer</td>
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<td>Tekmira</td>
<td>ApoB SNALP (Phase 1)</td>
<td>Completed</td>
<td>ApoB</td>
<td>LNP</td>
<td>Hypercholesterolemia</td>
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<tr>
<td>Alnylam</td>
<td>ALN-TTR (Phase 1)</td>
<td>Ongoing</td>
<td>Transthyretin (TTR)</td>
<td>LNP</td>
<td>TTR amyloidosis</td>
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<tr>
<td>Alnylam</td>
<td>ALN-PCS</td>
<td>Preclinical</td>
<td>PCSK9</td>
<td>LNP</td>
<td>Hypercholesterolemia</td>
</tr>
</tbody>
</table>
RNAi to treat primary and secondary liver cancers

- Prevalent solid tumor and common site of metastatic disease
  - ~700,000/yr: Incidence of HCC worldwide
  - ~500,000/yr: Patients with liver metastasis

- ALN-VSP is first dual-targeted RNAi drug
  - Targeting 2 pathways with 2 different siRNAs increases potential therapeutic impact
    - Proliferation: Kinesin Spindle Protein (KSP)
    - Angiogenesis: VEGF
  - Lipid nanoparticle (LNP) formulation
    - From Tekmira Pharmaceuticals

- Preferential biodistribution of LNPs to liver, spleen, tumors
  - May be able to avoid dose-limiting on-target toxicities associated with systemic delivery of small molecules and antibodies:
    - KSP: myelosuppression, gastro-intestinal toxicity
    - VEGF: Hypertension, bleeding, thrombosis, proteinuria, bowel perforation
**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, planned expansion phase of up to 20 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
ALN-VSP02 Phase I Study Current Status
Cohorts 1-6

- N=28 Enrolled to date
- Total of 127 ALN-VSP02 doses administered
  - Range of doses per patient: 2-13
- Dose escalation ongoing
  - Current dose 1.25 mg/kg
  - MTD not yet reached
- Key demographics
  - Median age 56 yrs (range 34-78)
  - 13 males, 15 females
  - Tumor types
    - Colorectal cancer (N=16)
    - Pancreatic neuroendocrine tumor (N=1)
    - Papillary renal cell cancer (N=1)
    - Squamous cell cancer of head and neck (N=1)
    - Pancreatic cancer (N=1)
    - Esophageal cancer (N=1)
    - Endometrial cancer (N=2)
    - Angiosarcoma (N=1)
    - Ovarian cancer (N=2)
    - Synovial sarcoma (N=1)
    - Mullerian stromal tumor (N=1)
- All patients treated with multiple prior anti-angiogenic and/or chemotherapy regimens
ALN-VSP02 Phase I Safety Summary

- ALN-VSP02 generally well tolerated to date
  - 127 doses administered to 28 patients across 6 dose levels
  - Up to 13 doses given to single patient
- No dose-dependent trends in clinical or laboratory adverse events
- No dose-dependent changes in LFTs
- Human plasma PK showed dose-proportional Cmax and AUC with no evidence of drug accumulation
  - Animal PK studies accurately predicted for human
- Two dose-limiting toxicities
  - 0.7 mg/kg: Liver failure and death after 2 doses (possibly related to study drug) in patient with near complete replacement of liver by tumor and prior partial hepatectomy and splenectomy
  - 1.25 mg/kg: Grade 3 thrombocytopenia after dose 1 (related to study drug), resolved within 5 days
- Three grade 2 infusion reactions (one each at 0.4, 0.7 and 1.25 mg/kg), all 3 tolerated further treatment with prolongation of infusion duration
- MTD not yet reached, dose escalation continuing
DCE-MRI Results: Patient 003-012

0.7 mg/kg

Baseline MRI, coronal view

Patient 003-012

Ktrans and IAUGC Change from Baseline (%)

T1
T2
T3

Ktrans2
IAUGC2
Ktrans3
IAUGC3

T: liver tumor number
Ktrans2/IAUGC2: Δ DCE-MRI #1 (BL) to DCE-MRI #2 (Day 4)
Ktrans3/IAUGC3: Δ DCE-MRI #1 (BL) to DCE-MRI #3 (Day 7)

KTrans

Baseline (BL) Pre-Dose

Day 4 Post-Dose 1

Day 7 Post-Dose 1

ASCO, June 2010
DCE-MRI Results
Summary of Cohorts 1-4

- 21 evaluable liver tumors in 12 patients
- 19/21 tumors (90%) showed decline in Ktrans
- 13 of 21 tumors (62%) had ↓Ktrans of ≥40%
- 8 of 12 patients (67%) had average ↓Ktrans of ≥40%

ASC0, June 2010
### Clinical Responses Across Dose Levels

<table>
<thead>
<tr>
<th>Dose Level (mg/kg)</th>
<th>N</th>
<th>Avg # of Doses Received (range)</th>
<th># Pts with Stable Disease for ≥ 2 mos</th>
<th># Pts Who Went Onto Extension Study (8+ doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>3</td>
<td>3 (2-4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
<td>3</td>
<td>4 (4-4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.4</td>
<td>6</td>
<td>4.5 (2-11)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.7</td>
<td>7</td>
<td>5.7 (2-10)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1.0</td>
<td>3</td>
<td>5.7 (4-8)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1.25</td>
<td>6</td>
<td>Pending</td>
<td>Pending</td>
<td>Pending</td>
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</table>
Voluntary Tumor Biopsies
Summary of Samples Obtained to Date

• 17 Tumor biopsies obtained from 9 patients
  » 3 at 0.4 mg/kg
  » 2 each at 0.7, 1.0 and 1.25 mg/kg
  » Liver tumor biopsies in 6 patients
  » Extrahepatic tumor biopsies in 3 patients

• 3 CT-guided core needle biopsies per timepoint (pre- and post-dose 1)
  » Analyses ongoing:
    – H&E for monoasters (anti-KSP), IHC for phosphohistone-H3 and Ki67 (anti-KSP), IHC for CD31 and VEGF (anti-VEGF)
    – 5’ RACE for VEGF and KSP
    – qPCR for VEGF and KSP
    – Drug levels (VEGF and KSP siRNAs) by qPCR
• Safety data in 28 patients receiving doses up to 1.25 mg/kg show ALN-VSP02 is generally well-tolerated
  » MTD not yet reached
  » Dose escalation continuing

• PD data preliminary but encouraging
  » Serial DCE-MRI results at 0.1-0.7 mg/kg suggestive of anti-VEGF effect in majority of treated patients
  » Trend towards more stable disease at higher doses

• Paired tumor biopsies obtained in multiple patients at all dose levels starting at 0.4 mg/kg
  » Histopathological and molecular analyses ongoing to assess drug delivery and target engagement
  » Anticipate multiple additional biopsies as study progresses

• Next Steps
  » Continued accrual to determine MTD
  » Further assessment of safety and activity at MTD expansion
  » Expect to update results at ASCO 2011
Acknowledgements

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- Hospital Universitario Virgen del Rocio (Seville)
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