Recurrent, Refractory and/or Metastatic Rhabdomyosarcoma in Children: A K30 Case Presentation

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Case

• 3 yo boy presented in January 2008 with an enlarging buttock mass

• Excisional biopsy of mass consistent with alveolar rhabdomyosarcoma (RMS) of gluteus medius

• Staging showed localized (non-metastatic) disease

• Tx: surgery, chemotherapy (VAC) x 40 wks, and radiation therapy (45Gy)
Case: 1st recurrence

- 1 month off therapy (Feb 2009) surveillance CT scan showed 2-3cm para-aortic LN
- Excisional biopsy performed
- Path consistent with Alveolar RMS
- Patient treated with Irinotecan + Temozololamide and concurrent regional XRT (45Gy) to retroperitoneal LNs
- Plan for 12 cycles (about 9mos – 1yr)
What are the options now?

- No therapy, end of life comfort care/hospice
- Palliative oral low dose chemotherapy + hospice
- Another chemotherapeutic salvage regimen
- Enrollment onto a clinical trial for new therapeutic agent
Rhabdomyosarcoma: Background

- Most common STS of childhood (5% of pediatric cancer)
- 350 cases/yr in US (4.3 cases/million <20 yo)
- ½ of all soft tissue sarcomas (in children)
- 2/3 pts < 6yrs
- Slight male predilection [M:F=1.4:1]

The Good News…

- Pre-IRS: 21%
- IRS-I (1972-78): 55%
- IRS-II (1978-84): 63%
- IRS-IV (1991-97): 73%

Overall Survival (%)

Pre-IRS: 21%
IRS-I (1972-78): 55%
IRS-II (1978-84): 63%
IRS-III (1984-1991): 71%
IRS-IV (1991-97): 73%
The Bad News...

- Survival from 2\textsuperscript{nd} recurrence of Alveolar RMS is anecdotal
Family opted for Phase I trial

- A Phase I trial of the anti-IGFRmAb (SCH717454) in combination with chemotherapy in children with recurrent solid tumors
- Industry sponsored (Schering now Merck)
- Collaborative
  - UCLA Site investigator (Noah Federman)
  - CHOC (Violet Shen)
Insulin-like Growth Factors & Cancer

- Cell proliferation stimulated
- Anti-apoptotic activity (AKT)
- Angiogenesis promoted
- IGF expression linked to cancer risk
- Many cancers have IGF-1R expression & overexpression
SCH 717454: Anti-IGF-1R mAb

High Affinity Fully Human IgG1

IGF-1R Specific
Insulin Receptor Not Recognized

Potential Antitumor Effect Properties
- Inhibits ligand binding & signaling
- Downregulation of IGF-1R protein
- Antibody-dependent cellular cytotoxicity
- Enhances other anti-tumor agents

Growth inhibition in a variety of mouse tumor models

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>TGI Range</th>
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<tbody>
<tr>
<td>Breast</td>
<td>19-68%</td>
</tr>
<tr>
<td>NSCLC</td>
<td>24-83%</td>
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<tr>
<td>Neuroblastoma</td>
<td>82-103%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>40-60%</td>
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<tr>
<td>Osteosarcoma</td>
<td>88%</td>
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</tbody>
</table>
SCH717454: Preclinical Activity

- Inhibits osteosarcoma, Ewing’s sarcoma & neuroblastoma xenografts
- PPTP/NCI: complete responses in 2 of 6 osteosarcoma (OS1, OS9) & 1 Ewing’s sarcoma model (EW5). Improved Event Free survival in 4/6 osteosarcoma & 2/5 Ewing’s models.
SCH 717454 with Cyclophosphamide Further Inhibits SK-N-AS (Neuroblastoma)
Enhancement of activity in combination

- IGFRmAb SCH 717454 additive in combination including:
  - Irinotecan,
  - Alkylating agents
  - Anthracyclines,
  - other chemotherapy and targeted agents

- Evidence suggests that pathway inhibition can lead to resistance reversal
### IGFRmAb Most Common Adverse Events (144 subjects)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence [# of Subjects (%)]</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (6%)</td>
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<tr>
<td>Fatigue</td>
<td>4 (3%)</td>
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<tr>
<td>Hyperglycemia</td>
<td>3 (2%)</td>
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<tr>
<td>Hemoglobin Decreased</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (1%)</td>
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Primary Objectives

• Determine safety, tolerability, and well-tolerated dose of SCH 717454 in combination with:
  – A: temozolomide and irinotecan
  – B: CAV (cyclophosphamide, doxorubicin, & vincristine)
  – C: IE (ifosfamide and etoposide)

…in pediatric subjects (≤21 years of age) with advanced solid tumors.
Key Secondary Objectives (To be Evaluated)

• Pharmacokinetics (PK)
• Anti-SCH 717454 antibodies incidence
• Peripheral blood biomarkers:
  – IGF-I, IGF-II,
  – IGFBP-2, IGFBP-3,
• Potential pharmacogenetic markers/Patient selection biomarkers
• Tumor responses
### Treatment Arms

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<thead>
<tr>
<th>SCH 717454 (10 or 20 mg/kg IV Day 1) and</th>
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<tbody>
<tr>
<td><strong>A:</strong> Temozolomide &amp;Irinotecan &amp; 100 mg/m²/day orally Days 1-5 &amp; (10 mg/m²/day IV Days 1-5 &amp; Days 8-12)</td>
</tr>
<tr>
<td><strong>B:</strong> (CAV) &amp; Vincristine &amp; Doxorubicin &amp; Cyclophosphamide &amp; (2 mg/m²/day IV Day 1) &amp; (75 mg/m²/day IV Day 1-2) &amp; (1200 mg/m²/day IV Day 1)</td>
</tr>
<tr>
<td><strong>C:</strong> (IE) &amp; Ifosfamide &amp; Etoposide &amp; (1800 mg/m²/day IV Days 1-5) &amp; (100 mg/m²/day IV Days 1-5)</td>
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</tbody>
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All Arms: One cycle is defined as 3 weeks of treatment.
3x3 Factorial DESIGN DIAGRAM

Dose Level

Dose Limiting Toxicity (DLT) Evaluation

1 Subject with DLT in 3 to 4 subjects

Enroll 2 to 3 additional subjects in the current dose level

0 Subjects with DLT in 3 to 4 subjects; or 1 Subject with DLT in 6 subjects

Next Dose Level

2 Subjects with DLT

Stop Enrollment. Additional subjects may be enrolled at the previous dose level

Previous dose level is the Maximum Tolerated Dose

Subjects Enrolled
Key Inclusion Criteria

• Subject ≤ 21 years of age
  – older subjects may be considered

• Histologic confirmation of the advanced solid tumor
  – except brainstem tumors
  – leptomeningeal or metastatic CNS lesion may be considered

• Performance score:
  – Karnofsky ≥50 (>16 years-old)
  – Lansky ≥50 (≤ 16 years-old)

• Adequate organ function (lab values)
  – No minimum ANC or platelet count if bone marrow involved (may be considered). Must not be transfusion refractory
Back to our patient with multiply recurrent, heavily pretreated alveolar RMS with widely metastatic disease

- Enrolled 12/3/09
- Now started 3rd cycle of ARM C-- Ifosfamide/Etoposide in combination with SCH717454 IGFRmAb
- DLTs: Grade IV neutropenia, Grade III anemia, Grade IV thrombocytopenia
Thank you!