FEASIBILITY OF PRE-OPERATIVE mTOR INHIBITOR SIROLIMUS IN CHILDREN AND YOUNG ADULTS WITH DESMOID TUMOR

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Background

- Primary treatment modality in children
  - Surgery
    - High recurrence rate
    - Morbidity

- Second-line modalities in children
  - Radiation
    - Usually in residual or recurrent disease setting
    - May be more effective in adults than in children
    - Risk vs Benefit
      - post-radiation bone fractures, growth retardation, tissue fibrosis, lymphedema, secondary cancers, nerve pain, bowel blockage
## Previous Desmoid Tumor COG Studies in Children

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment</th>
<th>Agents</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>POG9650</td>
<td>August 1997 to February 2001</td>
<td>Vinblastine Methotrexate</td>
<td>40% 2-year PFS 66% with grade 3 or 4 toxicity</td>
</tr>
<tr>
<td>ARST0321</td>
<td>February 2004 to July 2009</td>
<td>Sulindac Tamoxifen</td>
<td>36% 2-year PFS 40% of females developed ovarian cysts</td>
</tr>
</tbody>
</table>
Other Approaches

- Cytotoxics
  - VAC
  - Dacarbazine
  - Liposomal doxorubicin

- Tyrosine Kinase Inhibitors
  - Imatinib
  - Sorafenib
  - Pazopanib

- Hydroxyurea

- Gamma Secretase Inhibitors
Watchful Waiting

Progression-Free Survival (Primary Cases)

- Wait and see group
- Medical treatment group

Number at Risk

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>25</td>
<td>12</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>7</td>
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<tr>
<td>20</td>
<td>16</td>
<td>12</td>
<td>9</td>
<td>5</td>
<td>5</td>
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</tr>
</tbody>
</table>

- Immediate chemotherapy
- Immediate surgery
- Wait-and-see strategy

Number at risk (number censored)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate chemotherapy</td>
<td>53 (0)</td>
<td>22 (10)</td>
<td>14 (14)</td>
<td>5 (22)</td>
<td>3 (24)</td>
<td>1 (26)</td>
</tr>
<tr>
<td>Immediate surgery</td>
<td>47 (0)</td>
<td>19 (6)</td>
<td>12 (11)</td>
<td>6 (16)</td>
<td>1 (21)</td>
<td>0 (22)</td>
</tr>
<tr>
<td>Wait-and-see strategy</td>
<td>54 (0)</td>
<td>17 (7)</td>
<td>5 (14)</td>
<td>3 (16)</td>
<td>2 (17)</td>
<td>0 (18)</td>
</tr>
</tbody>
</table>

Overall p=0.17
Wait-and-see vs surgery p=0.12
Wait and see vs chemotherapy p=0.13

Fiore Ann Surg Oncol 2009
Orbach Lancet Child Adolesc Health 2017
Targeted Therapy in Children with Desmoid Tumor
mTOR Pathway and Tumorigenesis

- mTOR complexes with RAPTOR to form *mTORC1 complex*
  - Critical pathway for tumorigenesis
  - Promotes:
    - Cell growth
    - Proliferation
    - Cell motility
    - Angiogenesis

Adapted from Ballou and Lin, Journal of Chemical Biology 2008
mTOR Inhibitor Rationale

- Nearly all desmoid tumors display histologic or molecular evidence of APC/β-catenin pathway activation

- Evidence suggests deregulation of mTOR cell proliferation/survival pathway plays important role in tumor biology when APC/β-catenin pathway disrupted
Genetic Evidence from Murine Models of mTOR Pathway Activation in Desmoid Tumor

- $Apc^{Δ716}$ mice
  - Murine model of FAP

- Treatment with everolimus (mTOR inhibitor)
  - Decrease in number and size of colonic polyps
  - Prolonged survival

Fujishita PNAS 2008
Genetic Evidence from Murine Models of mTOR Pathway Activation in Desmoid Tumor

- Inhibition of tumor angiogenesis

- β-catenin knockdown using siRNA decreased mTOR expression

Fujishita PNAS 2008
Immunohistochemical Evidence of mTOR Pathway Activation in Desmoid Tumor

H&E

α-pAKT

α-pS6K
Clinical Evidence of mTOR Pathway Activation in Desmoid Tumor

- 7 year old male with tuberous sclerosis
- Recurrent chest wall desmoid tumor
- Treated with sirolimus
  - Significant tumor regression within 6 months
  - Prolonged disease stabilization
Sirolimus

- mTOR inhibitor

- Can be given orally
  - Tablet or liquid formulations

- Favorable safety profile, particularly in children and young adults
Primary Objective:

- To determine whether mTOR pathway activation decreases in patients with surgically resectable desmoid tumor that is removed following pre-operative treatment with sirolimus.
Desmoid Tumor Pilot Study

- **Secondary Objectives:**
  - To assess whether sirolimus improves desmoid tumor-associated pain
  - To begin to explore whether pre-operative sirolimus decreases tumor recurrence following surgical removal of desmoid tumor felt to be at high-risk for recurrence because of size and/or anatomic site
  - To assess the safety and tolerability of pre-operative sirolimus in patients with desmoid tumor
Eligibility

**Inclusion**
- < 30 years of age
- Surgery is planned to remove the desmoid tumor **and either**
  - (a) the desmoid tumor has already recurred after a prior surgery **or**
  - (b) the newly diagnosed disease and/or previously unresected is judged to be at high risk for recurrence due to its size (> 5cm) or location at an anatomic site making it unlikely to be resected with negative margins (**e.g.**, adjacent to neurovascular structures).
- Patients with germ-line APC mutations causing FAP/Gardner’s syndrome
Experimental Design Schema

Enrollment goal: 15 patients

- **Sirolimus:**
  - Day 1: 12 mg/m² PO (MAX dose 12 mg)
  - Days 2-28: 4 mg/m² PO daily (MAX dose 4 mg/day)

- **Surgery**
  - Within 3 days of completing therapy

Diagram:
- Eligible Patient
- Sirolimus x 28 days
- Surgery
- IHC Analysis
- Off protocol therapy follow-up
Histologic Assessment

- Tissue
  - Archived specimens (~50)
  - Pre-therapy biopsy
  - Post-therapy resection
- Immunohistochemical targets:
  - p-4E-BP1
  - p-p70S6K
  - p-AKT

Adapted from Ballou and Lin, Journal of Chemical Biology 2008
Current Status

- Grant funding: Desmoid Tumor Research Foundation
- Drug supply: Pfizer
- Opened for enrollment: February 2014

Study Sites:
- Maine Children’s Cancer Program (lead site)
- UCLA (pathology)
- Children’s Mercy Hospitals and Clinics (Kansas City)
- Seattle Children’s Hospital
- University of Minnesota
- Children’s Hospital of Wisconsin
- Rady Children’s Hospital – San Diego
- University of Florida
Feasibility of Sirolimus

- Nine of an anticipated 15 total patients have enrolled to date
- Ages have ranged from 5 to 28 years.
- All patients have been able to take the pre-operative sirolimus as prescribed and undergone surgery within the protocol-directed time frame
Feasibility of Sirolimus

• All toxicities have been as expected and Common Terminology Criteria for Adverse Events grade 1 and 2 only except for one grade 3 neutropenia

• No post-operative complications have been reported
Representative pre- and post-operative IHC staining for mTOR pathway proteins in desmoid tumor

Pre-Operative (10x)  Post-Operative (10x)

p4E-BP1
Representative pre- and post-operative IHC staining for mTOR pathway proteins in desmoid tumor

Pre-Operative (10x)  
Post-Operative (10x)

p70S6K
Representative pre- and post-operative IHC staining for mTOR pathway proteins in desmoid tumor

Pre-Operative (10x)  Post-Operative (10x)

pAKT
Conclusions

- Sirolimus appears to be well-tolerated when administered in the pre-operative setting to children and young adults with desmoid tumor
- Surgery is feasible and safe immediately after completing therapy
- Formal assessment of the mTOR pathway by IHC analysis will take place at study completion
- The study continues to actively accrue
Future Directions

- Consider use for progressive/symptomatic disease with or without planned surgery
- Expand to use in adjuvant setting
- Foundation for future cooperative group pediatric desmoid tumor study
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