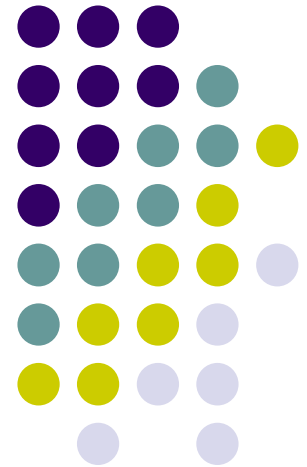


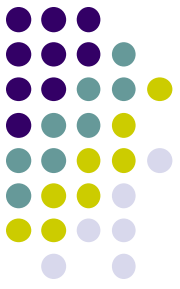
FEASIBILITY OF PRE- OPERATIVE mTOR INHIBITOR SIROLIMUS IN CHILDREN AND YOUNG ADULTS WITH DESMOID TUMOR

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Background



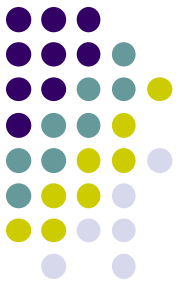
- Primary treatment modality in children
 - Surgery
 - High recurrence rate
 - Morbidity
- Second-line modalities in children
 - Radiation
 - Usually in residual or recurrent disease setting
 - May be more effective in adults than in children
 - Risk vs Benefit
 - post-radiation bone fractures, growth retardation, tissue fibrosis, lymphedema, secondary cancers, nerve pain, bowel blockage

Previous Desmoid Tumor COG Studies in Children



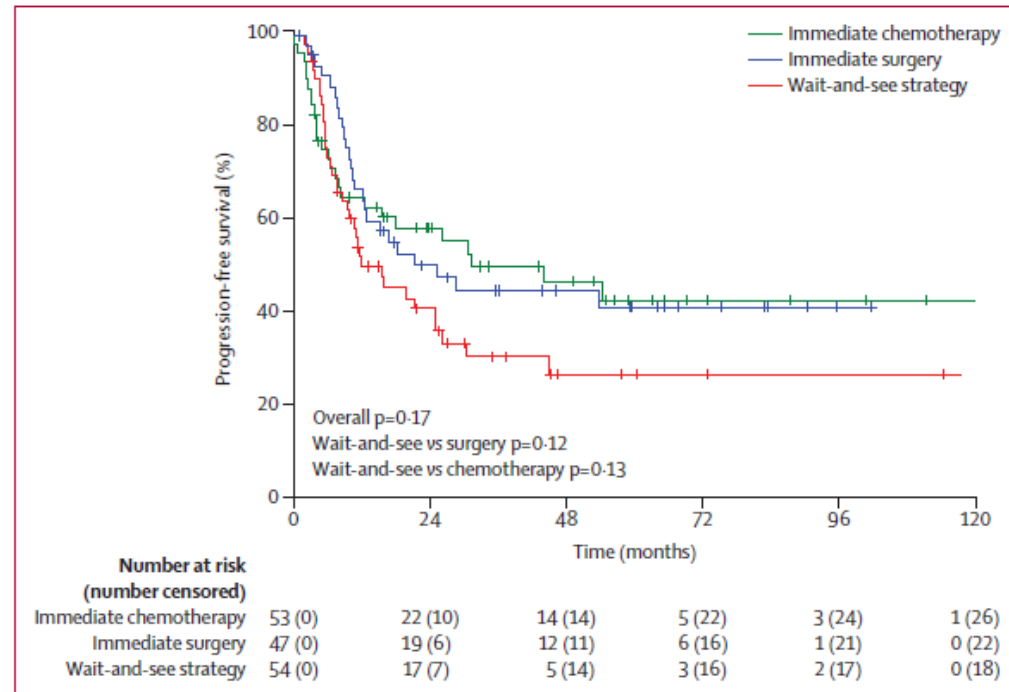
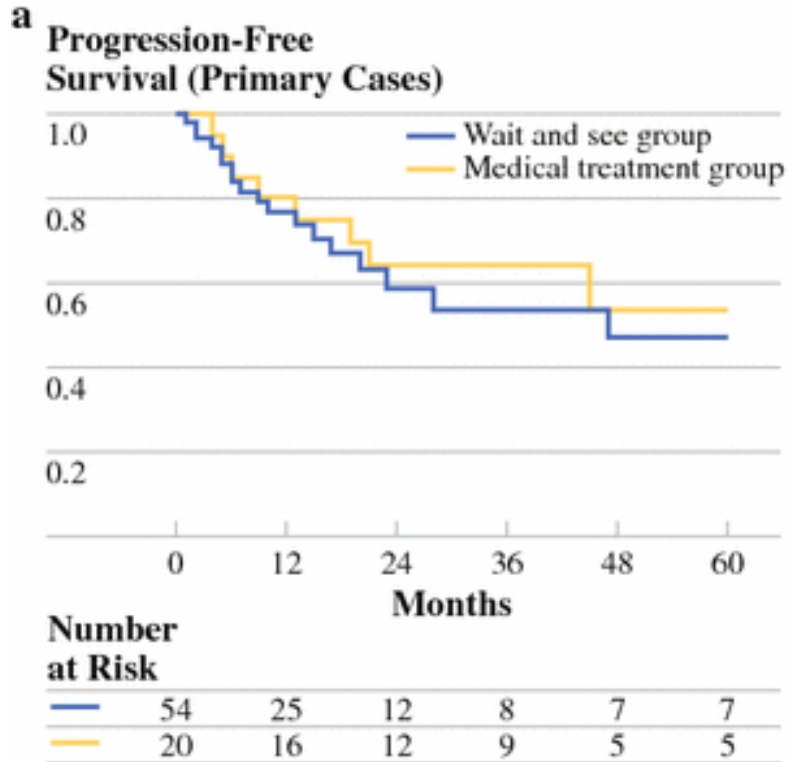
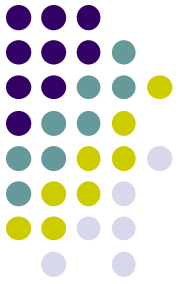
Study	Enrollment	Agents	Result
POG9650	August 1997 to February 2001	Vinblastine Methotrexate	40% 2-year PFS 66% with grade 3 or 4 toxicity
ARST0321	February 2004 to July 2009	Sulindac Tamoxifen	36% 2-year PFS 40% of females developed ovarian cysts

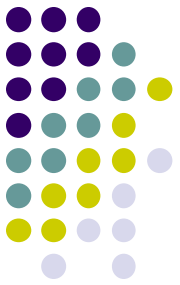
Other Approaches



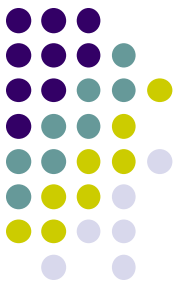
- Cytotoxics
 - VAC
 - Dacarbazine
 - Liposomal doxorubicin
- Tyrosine Kinase Inhibitors
 - Imatinib
 - Sorafenib
 - Pazopanib
- Hydroxyurea
- Gamma Secretase Inhibitors

Watchful Waiting



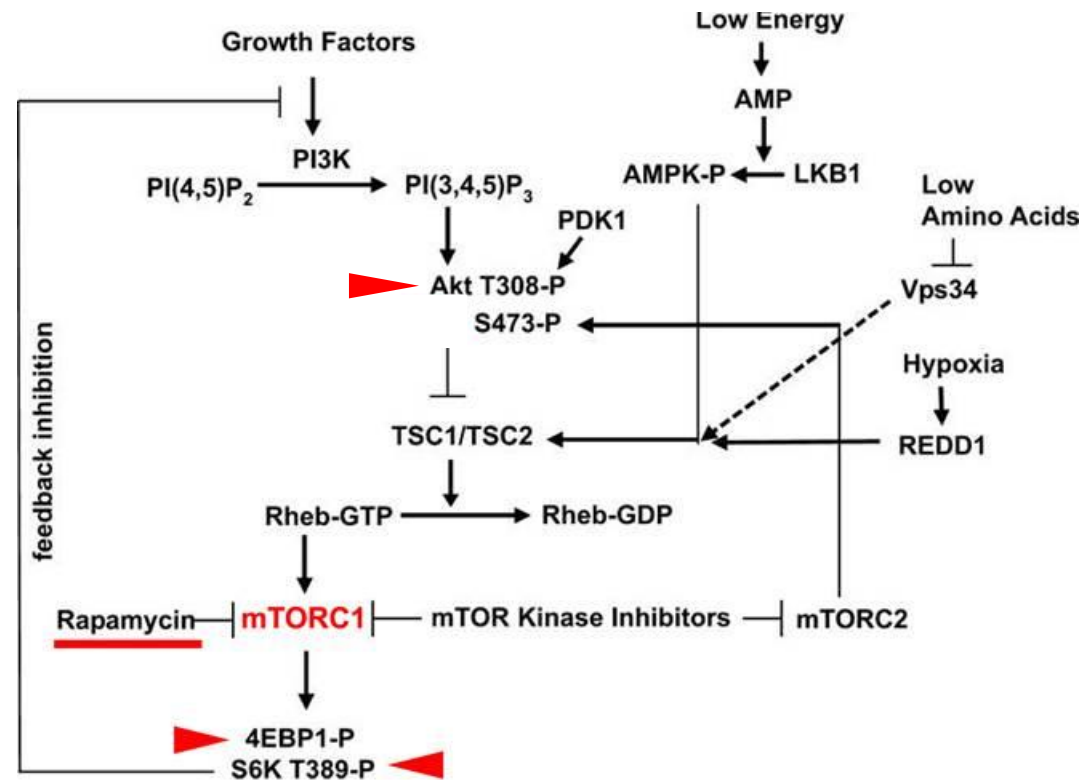


Targeted Therapy in Children with Desmoid Tumor

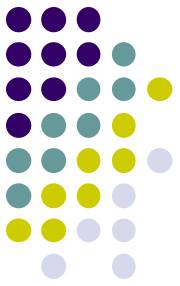


mTOR Pathway and Tumorigenesis

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

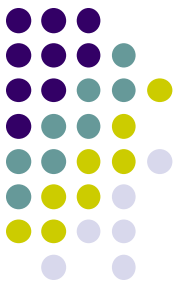


mTOR Inhibitor Rationale

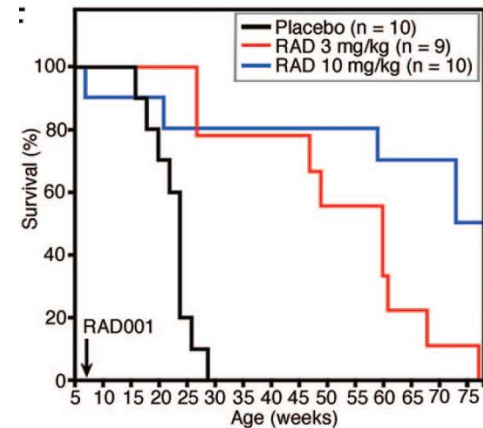
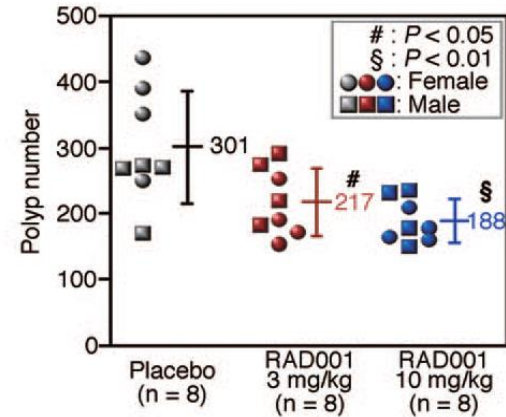


- Nearly all desmoid tumors display histologic or molecular evidence of APC/ β -catenin pathway activation
- Evidence suggests deregulation of mTOR cell proliferation/survival pathway plays important role in tumor biology when APC/ β -catenin pathway disrupted

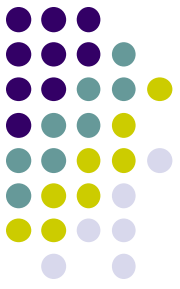
Genetic Evidence from Murine Models of mTOR Pathway Activation in Desmoid Tumor



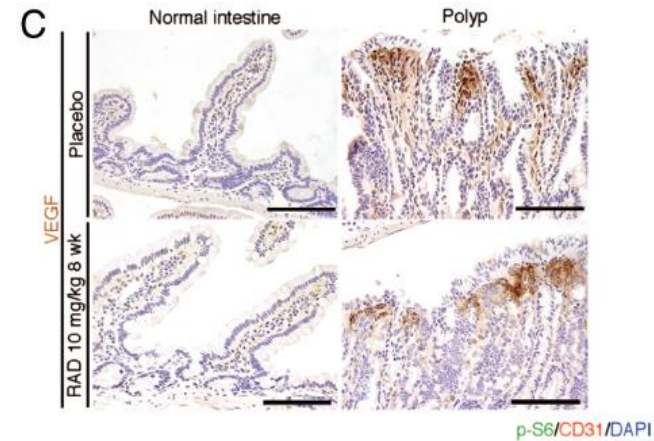
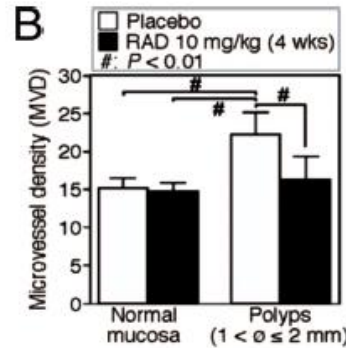
- *Apc*^{Δ716} mice
 - Murine model of FAP
- Treatment with everolimus (mTOR inhibitor)
 - Decrease in number and size of colonic polyps
 - Prolonged survival



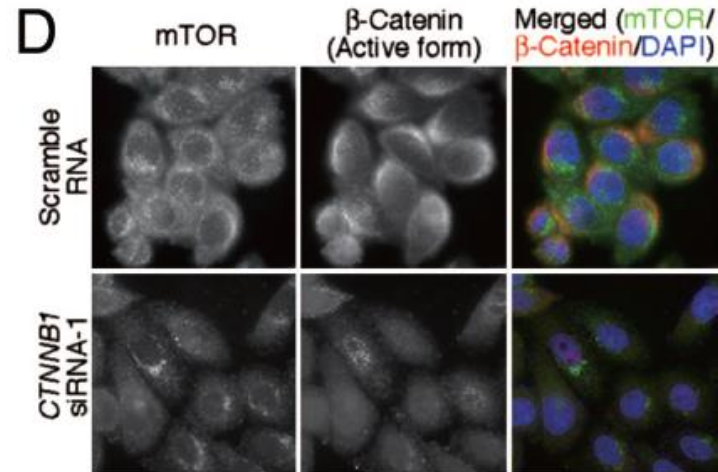
Genetic Evidence from Murine Models of mTOR Pathway Activation in Desmoid Tumor



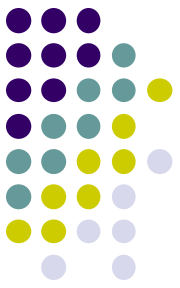
- Inhibition of tumor angiogenesis



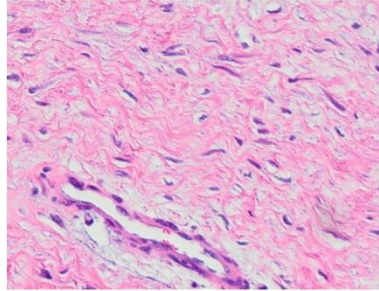
- β -catenin knockdown using siRNA decreased mTOR expression



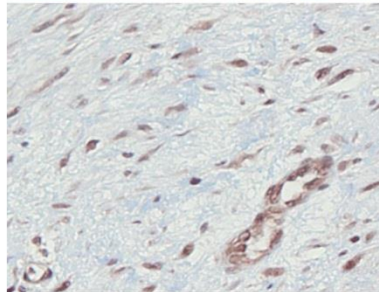
Immunohistochemical Evidence of mTOR Pathway Activation in Desmoid Tumor



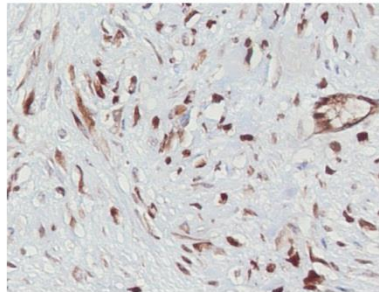
H&E



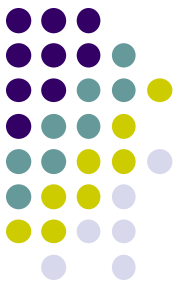
α -pAKT



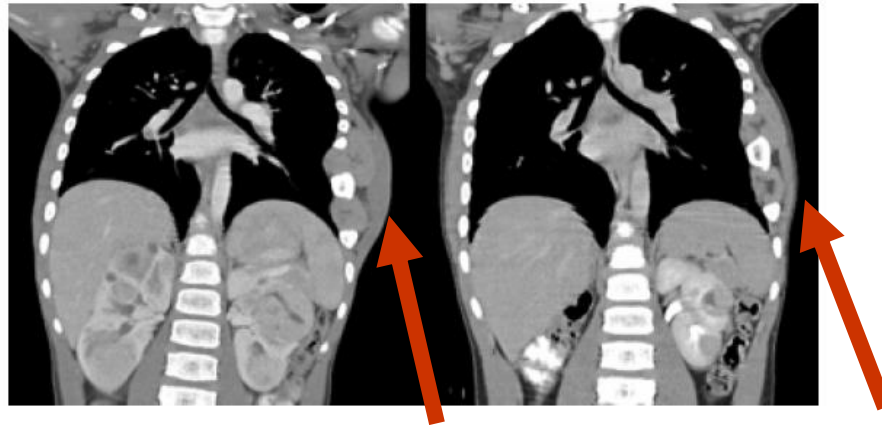
α -pS6K



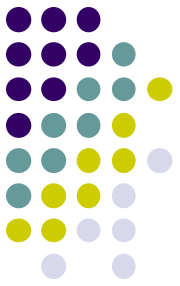
Clinical Evidence of mTOR Pathway Activation in Desmoid Tumor



- 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

A PILOT STUDY EVALUATING THE USE OF THE mTOR INHIBITOR SIROLIMUS IN CHILDREN AND YOUNG ADULTS WITH DESMOID-TYPE FIBROMATOSIS.

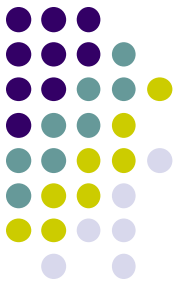
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- **Primary Objective:**
 - To determine whether mTOR pathway activation decreases in patients with surgically resectable desmoid tumor that is removed following pre-operative treatment with sirolimus

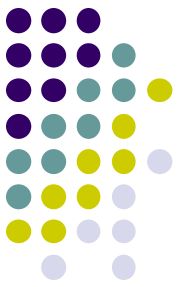
Desmoid Tumor Pilot Study



- **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

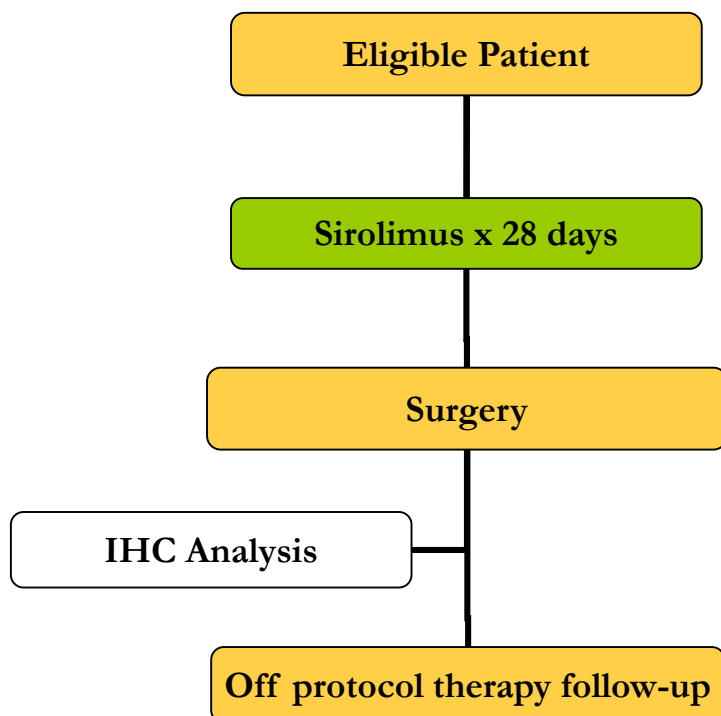


- Inclusion
 - < 30 years of age
 - Surgery is planned to remove the desmoid tumor and either
 - (a) the desmoid tumor has already recurred after a prior surgery or
 - (b) the newly diagnosed disease and/or previously unresected is judged to be at high risk for recurrence due to its size (> 5cm) or location 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

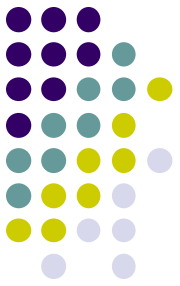


Enrollment goal: 15 patients

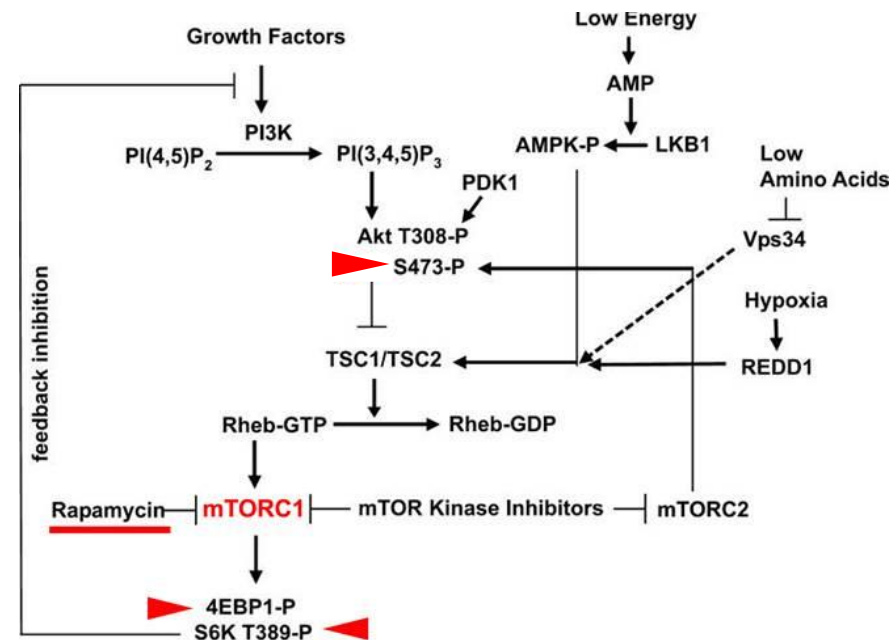


- Sirolimus:
 - Day 1: 12 mg/m² PO (**MAX dose 12 mg**)
 - Days 2-28: 4 mg/m² PO daily (**MAX dose 4 mg/day**)
- Surgery
 - Within 3 days of completing therapy

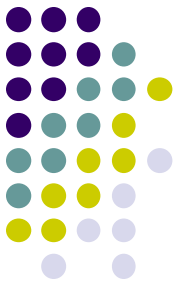
Histologic Assessment



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

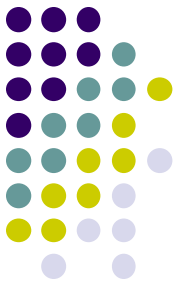


Current Status



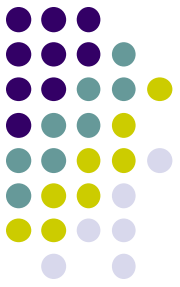
- Grant funding: Desmoid Tumor Research Foundation
- Drug supply: Pfizer
- Opened for enrollment: February 2014
- Study Sites:
 - Maine Children's Cancer Program (lead site)
 - UCLA (pathology)
 - Children's Mercy Hospitals and Clinics (Kansas City)
 - Seattle Children's Hospital
 - University of Minnesota
 - Children's Hospital of Wisconsin
 - Rady Children's Hospital – San Diego
 - University of Florida

Feasibility of Sirolimus



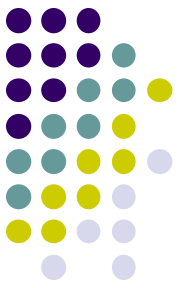
- Nine of an anticipated 15 total patients have enrolled to date
- Ages have ranged from 5 to 28 years.
- All patients have been able to take the pre-operative sirolimus as prescribed and undergone surgery within the protocol-directed time frame

Feasibility of Sirolimus

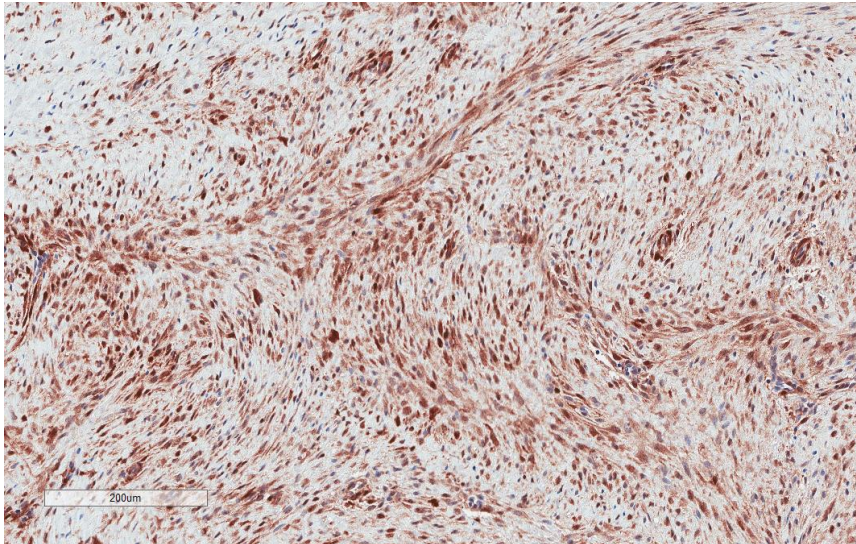


- All toxicities have been as expected and Common Terminology Criteria for Adverse Events grade 1 and 2 only except for one grade 3 neutropenia
- No post-operative complications have been reported

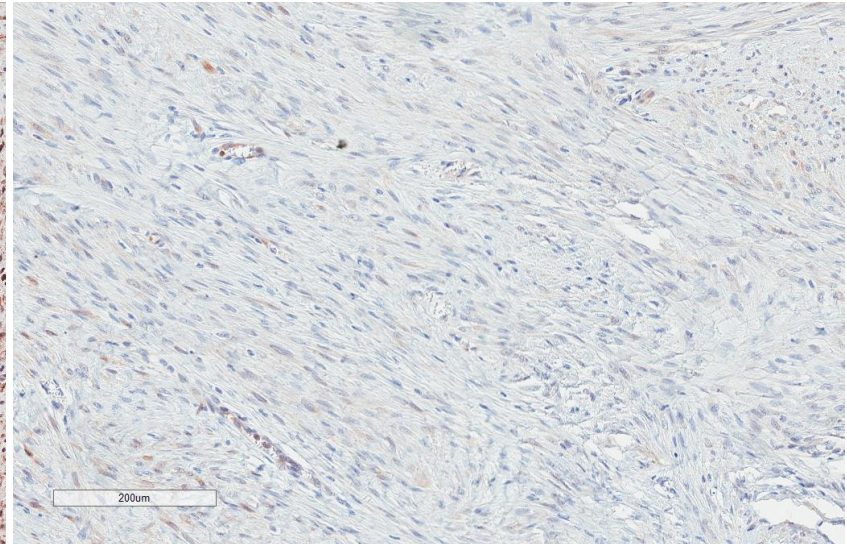
Representative pre- and post-operative IHC staining for mTOR pathway proteins in desmoid tumor



Pre-Operative (10x)

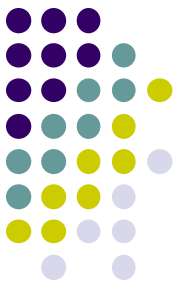


Post-Operative (10x)

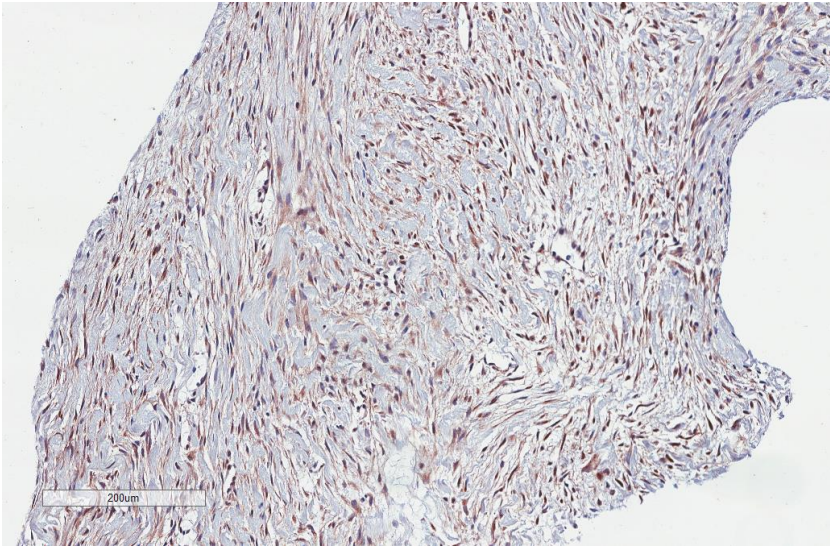


p4E-BP1

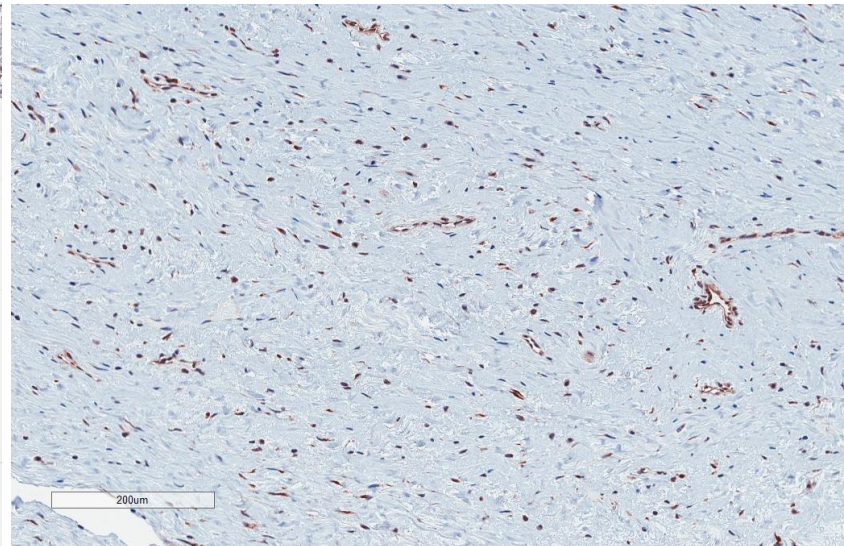
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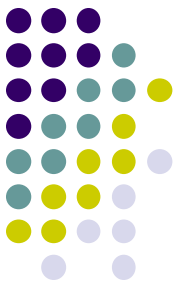


Post-Operative (10x)

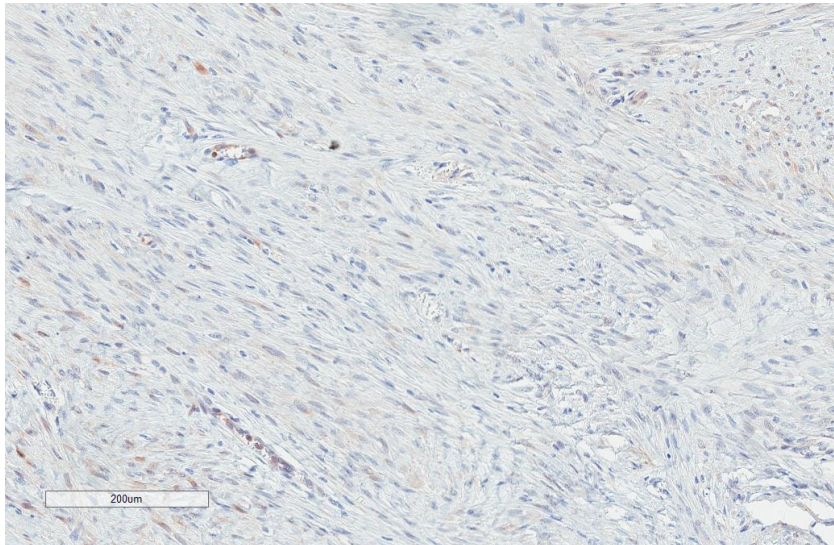


p70S6K

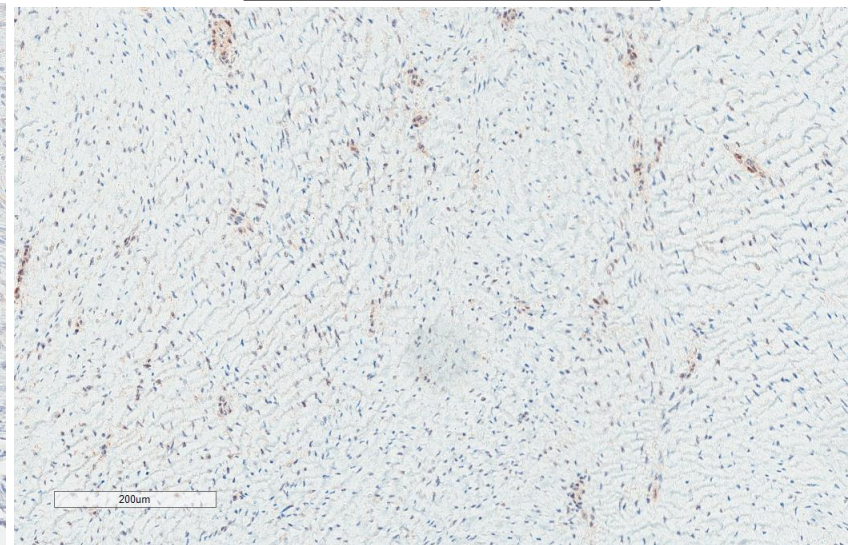
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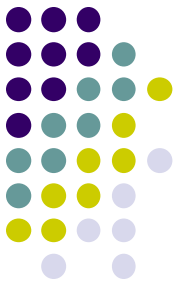
Post-Operative (10x)



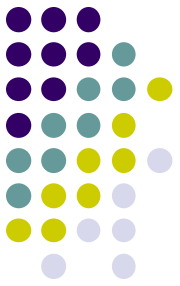
pAKT

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

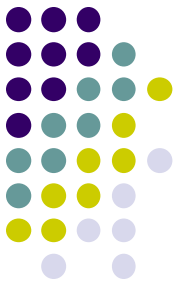


Future Directions



- 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

Acknowledgments



- DTRF
- Pfizer
- Clara Magyar (UCLA, pathology)
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- Noah Federman (UCLA)
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- Doug Hawkins (Seattle Children's)
- Katherine Chastain (Mercy Hospital)
- Joseph Khoury (MD Anderson)
- Sun Choo (Rady's Children's Hospital – SD)
- Meghen Browning (Children's Hospital of Wisconsin)
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- Brenda Weigel (University of Minnesota)