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Feasibility of pre-operative mTOR inhibitor Sirolimus in children and young adults with desmoid tumor

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Background

- Desmoid tumor represents an intermediate grade neoplasm with a striking predilection for locally invasive growth and recurrence following resection
- More effective, well-tolerated non-surgical treatment options are needed
- **Current approaches**
  - If feasible, watchful waiting is the preferred approach
    - 20-30% spontaneous regression
  - In situations where treatment is indicated, the following approaches are utilized
    - Surgery is the primary approach if minimal morbidity is anticipated
    - Medical therapies
      - Cytotoxic drugs
      - Tyrosine kinase inhibitors
      - Hydroxyurea
      - Gamma secretase inhibitors
- **mTOR Inhibitor Rationale**
  - Desmoid tumor is well-known to be associated with deregulation of the APC/β-catenin pathway
  - Deregulation of the mTOR cell proliferation/survival pathway may play an important role in tumor biology when the APC/β-catenin pathway is disrupted
- The mTOR inhibitor **sirolimus** is attractive as a potential targeted therapy for desmoid tumor
  - Well-tolerated in children and young adults
  - Can be given orally in tablet or liquid formulation

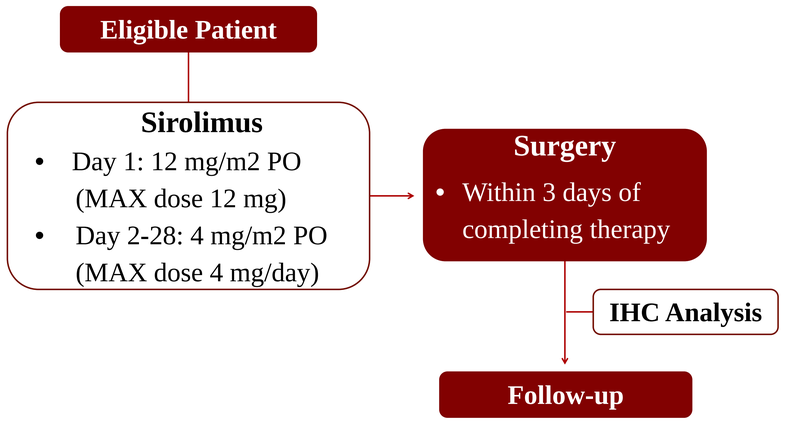
Objectives

- ***Primary***
  1. To determine whether mTOR pathway activation decreases in patients with surgically resectable desmoid tumor that is removed following pre-operative treatment with sirolimus
- ***Secondary***
  1. To assess whether sirolimus improves desmoid tumor-associated pain
  2. 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
  3. To assess the safety and tolerability of pre-operative sirolimus in patients with desmoid tumor

Methods

- Multi-institutional study open and actively accruing patients
- Eligibility criteria
  - <30 years of age
  - Surgery is planned to remove their desmoid tumor and either
    - (a) the desmoid tumor has already recurred after a prior surgery or
    - (b) the newly diagnosed or previously unresected disease is judged to be at high risk for recurrence due to its size (>5 cm) or location at an anatomic site making it unlikely to be resected with negative margins (e.g., adjacent to neurovascular structures)
  - Patients with germline APC causing FAP/Gardner's syndrome
- This is an IRB-approved study and patient consent is required

Figure 1. Experimental Design Schema



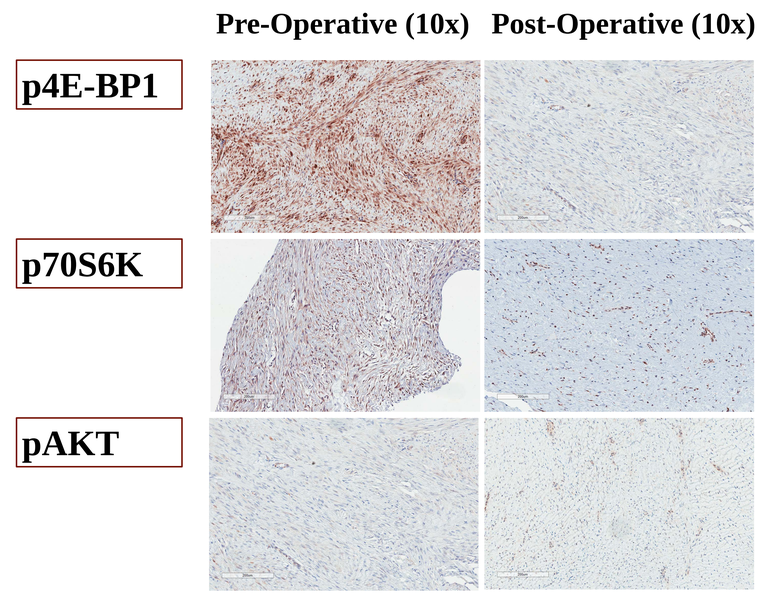
Results

- 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
- 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
- IHC staining is ongoing for p4E-BP1, p70S6K, and pAKT (Figure 2)
- Pain assessment measurements and anatomical imaging are being performed at designated surveillance intervals

Histologic Assessment

- Tissue
  - Pre-therapy biopsy
  - Post-therapy biopsy
  - Archived specimens (future analysis)
    - Paired, pre-treatment
    - Non-chemotherapy treatment

Figure 2. Representative pre- and post-operative IHC staining for mTOR pathway proteins p4E-BP1, p70S6K, and pAKT in desmoid tumor



Conclusion

- 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

Acknowledgements

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