



Second International
Chordoma Research
Workshop

Therapeutic
Development

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Rational Therapeutics for Chordoma

- Currently not sufficient basis for “home run” strategies
- However, evidence supports PI3K, mTOR, CDKN2A
- Need additional pre-clinical data
 - Cell lines or other model system
 - Better understanding of biology
 - Why is PI3K pathway activated?
 - Mechanism of resistance to cytotoxic agents/radiation



Agents tested and being tested

- 9-NC
- Imatinib
- Sunitinib (n=8)
- Dasatinib (n=5)
- Imatinib + rapamycin



Humans as a model of human disease

- Even anecdotal responses to novel agents in humans would be powerful rationale for further clinical study
- Encourage participation in phase I clinical studies of novel agents, particularly combination studies



Clinical Settings for Trials

- Advanced stage (phase I or II trials)
 - Sequential therapies possible
 - Combination therapies
- Post-op with complete resection or minimal residual disease (vaccination)
- Window of opportunity (phase 0)
 - Targets
 - Drug delivery to drug



Clinical Efficacy Surrogate Endpoints

- Dimensional response (RECIST)
- Functional imaging (FDG-PET)
- Tumor perfusion imaging (CT, MRI)
- Progression or progression free survival
- Non-conventional
- Drug-specific endpoints



Recommendations for Clinical Trials

- Phase 2 studies (SARC, Italian NCI)
- Anecdotal reports of clinical activity
 - Phase I studies
 - Off-label treatments – registry
- Phase 0



Miscellany

- Consider alternate endpoints
- Tumor tissue penetration of small molecules, biologics
- Phase I trials of combinations



Suggested Discussion Topics

- Approaches – small molecules, radiation sensitization, combinations, immunotherapy
- Short term and long term strategies for getting drugs into the clinic
- Prioritizing clinical trials - What evidence is needed to justify clinical trial?