TARGETING BETA CATENIN AS A TREATMENT FOR DESMOID TUMORS

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β Catenin Implicated in Numerous Cancers, Affecting Many

% of Cancer with β Catenin Activation/Mutation

<table>
<thead>
<tr>
<th>TYPE</th>
<th>Colon</th>
<th>Breast</th>
<th>Lung</th>
<th>Prostate</th>
<th>Melanoma</th>
<th>Ovarian</th>
<th>Liver</th>
<th>Gastric</th>
<th>AML</th>
<th>CML</th>
<th>MM</th>
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</thead>
<tbody>
<tr>
<td># AFFECTED*</td>
<td>100K</td>
<td>90K</td>
<td>85K</td>
<td>55K</td>
<td>20K</td>
<td>30%</td>
<td>50%</td>
<td>30%</td>
<td>25%</td>
<td>30%</td>
<td>30%+</td>
</tr>
</tbody>
</table>

~ 400,000 ANNUAL US INCIDENCE

* Annual New Patients (US Only)
β-Catenin mutations predominate in Desmoid tumors

-Three Mutations in β-Catenin have been identified in sporadic desmoid tumors Exon 3 (T41A, S45F, S45P)

-Mutations are at sites on β-Catenin that are usually marked for phosphorylation and proteasomal degradation by APC

-Mutations lead to impaired degradation of β-Catenin and its retention in the nucleus

-Thus β-Catenin becomes the oncogenic driver in Desmoid Tumors
A Fundamental Pathway that Cancers Use in Later Stages of Development
Understanding the Beta-Catenin/TBL1 Interaction and Our Novel Approach

**NORMAL CELL**

- **Beta Catenin Destruction Complex**
  - GSK3
  - APC
  - AXIN
  - Ubiquitin-mediated proteolysis

- **Beta Catenin**

- **SMRT/NCOR Repressor Proteins**
  - Bind and Prevent TBL1/TBLR1 Activation

- **TBL1/TBLR1 Tetramer**
  - Hydrophobic Pockets: Binding Sites for Proteins
  - Transcription Turned “Off”

**CANCER CELL**

1. **TBL1-Sumoylates and Pockets Change**
2. **Repressor Proteins Drift Away**
3. **Beta Catenins Dock into Pockets**
4. **Sumoylated TBL1/β-cat Moves to Nucleus**
5. **β-cat Hooks to TCF**
6. **Transcription Turned “On”**

- **SMRT/NCOR Repressor Proteins**
- **TBL1/TBLR1 Tetramer**
- **TCF**
- **Targets**

**Cytoplasm**

**Nucleus**

- **Transcription Turned “Off”**
- **Transcription Turned “On”**

- **sFRP**
- **WNT**
- **Frizzled**
- **DKK**
- **LRP5/6**
- **TBL1/TBLR1**

**Notes:**

- Beta Catenins
- DNA
- Smurf
- Wnt
- Axin
- Frizzled
- DKK
- LRP5/6
- sFRP
Tegatrabetan helps to stop the β-Catenin Cascade

Tegatrabetan – TREATED CELL

1. Tegatrabetan Binds in Pocket
2. Kicks Out Beta Catenin, SMRT and NCOR Re-attach
3. ‘Free’ Beta Catenin Proteolyzed
4. Transcription Turned “OFF”

ADVANTAGES

- Biologically elegant – sumoylated TBL1 goes back to acting like regular TBL1
- Apoptotic to cancer cells
- Potent and highly specific
- No effect on membrane bound beta catenin
- No effect on normal stem cells repopulating the GI tract

TBL1 Tetramer

Hydrophobic Pockets Allow Our Inhibitor to Bind Directly to TBL1 and Displace Beta Catenin;

Free Beta Catenin is Immediately Proteolyzed
Tegatrabetan (BC-2059): Significant Activity in Mice Human Xenograft Disease Models

**Acute Myeloid Leukemia (AML)**

- **Graphs showing survival rates**
- **Comparison of different treatments**

**Myelodysplastic Syndromes**

- **Graphs showing survival rates**
- **Comparison of different treatments**

**AML: In Combination with Novartis’s Panabinostat**

- **Graphs showing survival rates**
- **Comparison of different treatments**

**Multiple Myeloma**

- **Graphs showing survival rates**
- **Comparison of different treatments**

*Treatment 2x Per Week, for 3 Weeks – 6 Doses, Then Watch (No Intent to Cure)*
Path Forward: Registration in Orphan, Accelerated Approval Disease

Initial Focus: Orphan Indications

- Single Agent Trials
  - Desmoid tumors
  - Germinal center B cell lymphomas
  - Osteosarcoma

- Combo Trials
  - AML

Wnt / Beta Catenin Pathway Inhibition

A Fundamental Cancer Pathway
Uniquely driving select Orphan cancers

Advantages

- Orphan designation
- High unmet medical need
- Potential breakthrough therapy
- Potential accelerated approval
Broad Potential: Many Cancers and Fibrotic Disease

Commercialization Focus: Major Tumors & Fibrosis

Combo Potential - Cancer
- Colon Cancers
- Breast Cancers
- Lung Cancers
- Melanoma
- Multiple Myeloma

Additional Indications
- Pulmonary Fibrosis
- Dupuytren’s Contracture

Potential

Other Cancers

Wnt Important in Scar Healing (e.g. Dupuytren’s Contracture, Pulmonary Fibrosis)

Wnt / Beta Catenin Pathway Inhibition
Phase I/II Trial of Tegatrabetan in Advanced Non Resectable Desmoid tumors

- Phase 1/2 Trial being planned
- Likely starts Q4 this year
- Will be a first in man safety/efficacy trial
- Aims to bring a promising drug into clinical trials for desmoid patients