Pediatric Subcommittee of the Oncologic Drugs Advisory Committee

The MDM2 antagonist RO5503781

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MDM2 Antagonist RO5503781: Non-Genotoxic Activator of p53

- MDM2 - negative regulator of p53
- MDM2 antagonists - inhibitors of MDM2/p53 binding, causing:
  - Stabilization and activation of p53
  - Cell cycle arrest
  - Apoptosis
- Nutlins initially discovered at Roche
- RO5503781 - potent, oral MDM2 antagonist/Nutlin optimized for the clinic:
  - First-in-class MDM2 antagonist
  - Second generation in clinic
  - New chemical class with enhanced binding specificity and increased potency
Why Develop RO5503781 in Pediatrics?

- Evidence of efficacy in adult cancer patients
- Nonclinical evidence of efficacy of MDM2 antagonism in pediatric tumor subtypes (ALL, sarcomas, neuroblastoma)
- Strong scientific rationale for pediatric development
- Challenges:
  - Selection strategies for appropriate pediatric patient populations
  - Choosing the safest and most effective combination therapies given the “on-target” toxicities of RO5503781
  - Suitable administration forms for all pediatric patients
• Potently binds MDM2 in the p53 binding pocket inhibiting the protein:protein interaction

• Mean IC50 in p53 wild-type cell lines = 30 nM (MTT assay)

• Potently and selectively inhibits cancer cell growth
  ▶ 344-fold selective for p53wt vs. p53mut cells

• Blocks cell cycle progression in G1 and G2

• Induces p53-dependent apoptosis

Ding et al., J Med Chem 2013.
PPTP selected RO5045337 (previous clinical candidate) for nonclinical testing
- In vitro panel - 23 cell lines
- In vivo panel of p53 wild-type xenografts

RO5045337 induced tumor growth inhibition in ALL and 38% of solid tumor xenografts including:
- Medulloblastoma
- Rhabdomyosarcoma
- Ewing's sarcoma

ALL panel:
- 5 complete responses
- 1 partial response
- 1 maintained complete response

The novel MDM2 inhibitor RG7388 is highly effective against neuroblastoma in vitro and in vivo
Anna Lakoma¹, Eveline Barbieri², Matthew C McVay¹, Zaowen Chen², Saurabh Agarwal², Charitra Adhikari², Jason M Shohet², Eugene S Kim¹

¹ Division of Pediatric Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, ² Department of Pediatrics, Texas Children’s Cancer Center, Baylor College of Medicine, Houston, TX

Evaluation of targeted drugs in combination with the MDM2 antagonist RG7388 in neuroblastoma
Alan Van Goethem¹, Gwen Nichols², Frank Speleman¹, Jo Vandesompele¹, Tom Van Maerken¹

¹ Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium
² Roche-Genentech Inc, 1 DNA Way, South San Francisco, CA 94080, USA

Synergism of RG7388 with chemotherapy used for NB
Lindi Chen, David R. Newell, John Lunec and Deborah A. Tweddle¹

¹ Newcastle University
Northern Institute for Cancer Research
RO5503781 (RG7388) is Highly Effective Against Neuroblastoma In Vitro and In Vivo

The novel MDM2 inhibitor RG7388 is highly effective against neuroblastoma in vitro and in vivo

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**Cell Proliferation**

Marked decrease in NB cell proliferation with RG7388, with exception of the p53-silenced LAN5 si-p53.

**In Vivo Bioluminescence**

RG7388 treated NGP mice

**Tumor Weights**

RG7388 significantly inhibits tumor growth by 59% in NGP (p=0.003), 67% in SH-SY5Y (p=0.006), and 75% in LAN5 (p=0.0019) xenografts. RG7388 has no inhibitory effect on LAN5 si-p53 xenograft compared to vehicle treatment (p=0.57).
Combination of MDM2 and MEKi in AML and Colon cancer

MDM2 expression upregulated by Ras. MEK co-operates with MDM2 to target FOXO3a for degradation; inhibiting apoptosis and cell cycle arrest. Synergy data in colon lines/xenografts

Combination of MDM2 and radiation

RO5503781 plus BCL2i combo treatment: superior increase in life span in orthotopic AML models compared to single agent treatment

Combination of MDM2 and BCL2i in AML

RH18 Rhabdomyosarcoma xenografts

Peter Houghton/Arnab Chakravarty at NCH/OSU
RO5503781 Milestones:
Regulatory and Early Clinical Development

U.S. Food and Drug Administration

- IND clearance
- Orphan drug designation for treatment of AML

European Medicines Agency (EMA)

- Orphan drug designation for treatment of AML
- Agreed Paediatric Investigation Plan (PIP)

Adult Phase I Studies Ongoing
USA, France, Italy, Netherlands, UK, Australia, Canada, South Korea
**Adult Phase I Studies in Solid Tumors and AML: Early Evidence of Efficacy and Acceptable Benefit / Risk**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Study</th>
<th>Patients Enrolled</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP27872</td>
<td>Phase I Solid Tumors with “Biomarker Cohorts”</td>
<td>99</td>
<td>• <strong>Study complete</strong>. Best response stable disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• POM for p53 activation in tumor tissue post Tx (↑ apoptosis, ↓ proliferation)</td>
</tr>
<tr>
<td>NP28902</td>
<td>Relative Bioavailability / Drug-Drug Interaction Study (rBA/DDI)</td>
<td>50</td>
<td>• <strong>Ongoing study</strong>. Evaluation of optimized formulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• DDI analysis: no significant DDI potential</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Evaluated food effect</td>
</tr>
<tr>
<td>NP28679</td>
<td>Phase I/Ib AML monotherapy and combo with cytarabine</td>
<td>89</td>
<td>• <strong>Ongoing study</strong> to evaluate safety/activity in AML as single agent and in combination with Cytarabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Evaluate Benefit/Risk and PK of optimized formulation</td>
</tr>
</tbody>
</table>

Planned or ongoing investigations of RO5503781 in myeloproliferative neoplasms, metastatic castration-resistant prostate cancer, and multiple myeloma in collaboration with external groups.
Adult Safety: Diarrhea and On-Target Cytopenias

- **SOLID TUMORS**: Cytopenias limiting at higher exposures

<table>
<thead>
<tr>
<th>Solid Tumor Ph1 Monotherapy</th>
<th>TOTAL (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>74 (75)</td>
<td>7 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>71 (72)</td>
<td>11 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>51 (52)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>44 (44)</td>
<td>10 (10)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24 (24)</td>
<td>5 (5)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Anemia</td>
<td>26 (26)</td>
<td>20 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6 (6)</td>
<td>5 (5)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

- **ACUTE LEUKEMIA**: Diarrhea and infections

<table>
<thead>
<tr>
<th>AML Ph1 Monotherapy</th>
<th>TOTAL (%)</th>
<th>Grade 3-4 (%)</th>
<th>Grade 5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>42 (91)</td>
<td>11 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (74)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections/Infestations</td>
<td>30 (65)</td>
<td>17 (37)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (37)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>18 (39)</td>
<td>11 (24)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>14 (30)</td>
<td>12 (26)</td>
<td>0</td>
</tr>
</tbody>
</table>
Adult Clinical Pharmacokinetics:
Dose-Proportional Exposures and Well Distributed in Bone Marrow

- $t_{1/2}$: ~ 1 day
- Dose-proportional exposures in patients of both solid tumors (NP27872) and AML (NP28679)
- Inter-patient variability: ~ 50% in AML and solid tumor patients
- No variation with older age, body weight, Asian ethnicity, concomitant azoles, or cytarabine treatment
- Distribution: ~ 70% in bone marrow
- Elimination pathways: not excreted through urine

Target for AML Efficacy
$AUC_{24h} > 100 \mu g \cdot h/ml$
Exploratory Biomarker Assessments:
Proposed PD and Response Discrimination Strategies

Target/pathway-related biomarkers (potential predictive)
- TP53: Mutation analysis and RO5503781 response
- Evaluation of gene signatures for response prediction (qRT-PCR/RNASeq)

PD/pathway-related biomarkers
- MIC-1 in serum and MDM2 in tumor cells (AML only)
- MOA: apoptosis, cell proliferation, p21 and p53 expression

Solid tumor metrics
- Target/pathway/MoA-specific markers
- Tumor growth kinetics

Hematologic-specific metrics
- Assessing technologies for MRD analysis:
  - Flow panel
  - Fusion gene/mutation panel
  - WT-1 expression by RT-PCR
Core PD / Biomarkers of p53 Activation Assessed in the Clinic

Expression Levels → p53

↑ Expression Levels → p21

↑ Expression Levels → MDM2 ANTAGONIST

CDKs

↑ GENE TRANSCRIPTION

MDM2 mRNA and protein MIC-1 protein

↑ CELL CYCLE ARREST AND DECREASED CELL PROLIFERATION

Ki-67 ↓ FLT PET

↑ TUNEL

↑ NOXA — PUMA — BAX

MITOCHONDRIA

CYTOCHROME C RELEASE

CASPASE ACTIVATION

APOPTOSIS
Adult Efficacy:
Clinically Meaningful Change in Bone Marrow Blasts Observed in AML PhI/Ib Study

**Single Agent (N=32 evaluable)**

**Combo with Cytarabine (N=29 evaluable)**

*All bone marrow assessments performed at d28 or later except for one patient each in the single agent and combination therapy arms.*

**RESPONSE DEFINITIONS**

CR: < 5% marrow blasts with complete recovery of peripheral counts
CRi / MLFS: < 5% marrow blasts with incomplete / no recovery of peripheral counts
PR: > 50% decrease in marrow blasts

Yee et al., ASH Annual Meeting 2014 [Ab 69271]
Adult Efficacy:
Durable Responses in PhI/Ib Extension with Cytarabine in R/R AML

Yee et al., ASH Annual Meeting 2014 [Ab 69271]
Challenges for Pediatric Development: PK Variability and On-Target Cytopenias

- Cytopenias:
  - p53-related “on-target” toxicity
  - exposure-related

- Oral MDM2 antagonist: variability in exposure, not explained by food, weight or concomitant medications

- Narrow therapeutic window, particularly in solid tumor populations

- Limits combinations with cytotoxics in tumor types other than acute leukemias
### Challenges for Pediatric Development: Some p53 Mutant Patients Demonstrate Activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tumor</th>
<th>p53 Mutation</th>
<th>Evidence of Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO5045337</td>
<td>AML</td>
<td>S240G</td>
<td>↓ bone marrow blasts 33% → 0 on C2d28</td>
</tr>
<tr>
<td>RO5045337</td>
<td>AML</td>
<td>R175H</td>
<td>↓ peripheral blast plus tumor lysis syndrome</td>
</tr>
<tr>
<td>RO5045337</td>
<td>Lipo-sarcoma</td>
<td>R181L</td>
<td>↑ TUNEL 0 → 17.9 +density</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Ki67 84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ MDM2 mRNA 1.4-fold</td>
</tr>
<tr>
<td>RO5503781</td>
<td>Moderately Differentiated Carcinoma</td>
<td>Y236X (Stop)</td>
<td>↓ FLT-PET SUV 28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Ki67 31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ MDM2 mRNA 1.4-fold</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ TUNEL 19%</td>
</tr>
<tr>
<td>RO5503781</td>
<td>mDuod Cancer</td>
<td>C238Y</td>
<td>↑ TUNEL 215%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ FLT-PET SUV 32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ MDM2 mRNA 9.8-fold</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Ki67 57%</td>
</tr>
<tr>
<td>RO5503781</td>
<td>AML</td>
<td>H179R</td>
<td>↓ peripheral blasts</td>
</tr>
<tr>
<td>RO5503781</td>
<td>AML</td>
<td>M243R</td>
<td>↓ bone marrow blasts 15 → 1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complete Remission (recovery of peripheral counts)</td>
</tr>
</tbody>
</table>
Further Considerations for Pediatric Development: 
**p53 Mutations Infrequent in Pediatric Populations**

**Hematologic Malignancies:**
8 of 330 lymphoid malignancies, and 0 of 29 myeloid malignancies [2%]

**Solid Tumors:**
p53 mutation frequency in pediatric malignancies

<table>
<thead>
<tr>
<th>Tumor</th>
<th>p53 mutation frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>1</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>3</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>19</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>11</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>1.3%–5%</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>6</td>
</tr>
<tr>
<td>Pediatric leukemia</td>
<td>2</td>
</tr>
<tr>
<td>Relapsed leukemia</td>
<td>12.7%</td>
</tr>
<tr>
<td>Wilm’s tumor</td>
<td>10</td>
</tr>
<tr>
<td>Pediatric glioma</td>
<td>1</td>
</tr>
</tbody>
</table>

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Wada et al., Blood 1993; Van Maerken et al., Cancer Lett 2014.

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a Samples from adults and children analyzed. Zhu et al., Br J Cancer 1999.
Drug with poor solubility and limited absorption

- Large volume of drug to be administered in solid form

**Minimize tablet size**

- Disperse in liquid / food

- Still large total volume

- Closed handling with device

**Caregiver exposure to highly active drug**

**Drug not stable in liquid**

Prodrug for i.v. administration

- Soluble NME by coupling with polymer
- i.v. = no absorption limitation, less variability
- Conversion to RO5503781 by esterases

**Polymer chain providing solubility**

**RO5503781**

**Closed handling with device**
Proposed Studies:
**Development Plan in Pediatrics**

- **Technical:** Develop a pediatric formulation
- **Nonclinical:** Study in juvenile rats
- **Clinical:**
  - A pediatric study to evaluate the pharmacokinetics, toxicity, safety and any activity of RO5503781 in children with a solid tumor or acute leukemia
  - Pre-specify target treatment effect for each disease based on efficacy and safety criteria. Advance to pivotal trial when/where clinically meaningful improvement
European Medicines Agency:
Agreed Paediatric Investigation Plan (PIP)

• Procedure start September 12th 2013

• PDCO adopted an opinion agreeing to the RO5503781 PIP September 12th 2014

• For the treatment of acute myeloid leukemia, acute lymphoblastic leukemia and of all conditions included in the category of malignant neoplasms (except nervous system, hematopoietic and lymphoid tissue)

• Modifications anticipated
• Evidence of efficacy in adult cancer patients

• Nonclinical evidence of efficacy of MDM2 antagonism in pediatric tumor subtypes (ALL, sarcomas, neuroblastoma)

• Strong scientific rationale for pediatric development