Taking a Precision Cancer Medicine Approach to Develop Oncology Drugs That Target Mitosis
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  – Associate Director Adult Oncology and Co-Leader Gastrointestinal Cancers
Strategy for Oncology Drug Development

- Taking a precision cancer medicine approach to develop Onvansertib, a first-in-class, 3rd generation PLK1 inhibitor
- Leveraging a proven cancer target, PLK1
- Incorporating predictive clinical biomarkers
- Combining Onvansertib with already approved drugs
  - Phase 1b/2 trial of Onvansertib + cytarabine or decitabine in Acute Myeloid Leukemia (AML)
  - Phase 2 trial of Onvansertib + abiraterone acetate (Zytiga®)/prednisone in metastatic Castration-Resistant Prostate Cancer (mCRPC)
  - Phase 1b/2 trial of Onvansertib + FOLFIRI and bevacizumab in metastatic Colorectal Cancer (mCRC)
## Onvansertib – Pipeline Within a Molecule
Opportunities in Leukemias/Lymphomas and Solid Tumors

<table>
<thead>
<tr>
<th></th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<tbody>
<tr>
<td>**Leukemias &amp; **</td>
<td>Acute Myeloid Leukemia – Orphan Drug Designation in the U.S. and Europe</td>
<td><strong>Phase 1b/2 trial in combination with low-dose cytarabine (LDAC) or decitabine</strong></td>
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<td><strong>Lymphomas</strong></td>
<td><strong>Metastatic Castration-Resistant Prostate</strong></td>
<td></td>
<td><strong>Phase 2 trial in combination with Zytiga® (abiraterone acetate)/prednisone</strong></td>
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<td></td>
<td>Colorectal (CRC)</td>
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<td></td>
<td>Lung</td>
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<td></td>
<td>Ovarian</td>
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<tr>
<td></td>
<td>Others (adrenocortical, sarcomas, head and neck, skin, liver, pancreatic, ampullary)</td>
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<tr>
<td><strong>Solid Tumor</strong></td>
<td><strong>Triple Negative Breast</strong></td>
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<tr>
<td><strong>Cancers</strong></td>
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</table>
Licensed Drug Candidate from NMS
Onvansertib – Polo-like Kinase 1 (PLK1) Inhibitor

- Largest oncology research and development company in Italy
- Developed anthracycline class of drugs (doxorubicin)
- Leader in protein kinase drug development (Polo-like Kinase Inhibitors)
- Identification and validation of molecular targets focused on driver oncogenes
- Excellent track record licensing innovative drugs to pharma/biotech companies including: Genentech (Roche), Ignyta (Roche), Novartis

Oncology Drug Discovery

- Licensed global development and commercialization rights for Onvansertib
- Nerviano will continue manufacturing GMP API and finished drug
- Two active INDs in place with the FDA
- Financing in place to advance clinical programs into mid-2019

IND = Investigational New Drug
Nerviano Oncology Portfolio Success

- Excellent track record licensing innovative drugs to pharma/biotech companies that have subsequently received FDA breakthrough status and priority review designation

<table>
<thead>
<tr>
<th>Licensed</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Registered</th>
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<tbody>
<tr>
<td>ARRAY</td>
<td>Encorafenib (B-RAF IP)</td>
<td>Melanoma Braf mutation in combination with binimetinib</td>
<td></td>
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<tr>
<td>Roche Ignyta</td>
<td>Entrectinib (TRK, ROS, ALK)</td>
<td>Non-Small Cell Lung</td>
<td></td>
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<tr>
<td>tiziana LIFE SCIENCES</td>
<td>Milciclib (CDK, other kinases)</td>
<td>Thymic Cancer</td>
<td></td>
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<tr>
<td>trovagene</td>
<td>Onvansertib (PLK1 inhibitor)</td>
<td>AML and mCRPC</td>
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<tr>
<td>Servier Oncology</td>
<td>MPS1 Inhibitor</td>
<td>Solid Tumors</td>
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<tr>
<td>Genentech</td>
<td>ADC (PNU-652)</td>
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<tr>
<td>OXFORD BioTherapeutics</td>
<td>ADC (NMS-P945)</td>
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</tbody>
</table>
Leveraging a Proven Cancer Target
PLK1 – Established Target for Cancer Therapy

PLK1 Plays a Critical Role in Initiation, Maintenance and Completion of Mitosis

▶ Polo-like Kinase 1 (PLK1)

- Belongs to a family of kinases (PLK1,2,3,4,5)
- Dysfunction leads to cancer formation and progression
- Over-expressed in dividing cancer cells
- Inhibition leads to cancer cell death

1Liu et al- PLK1, A Potential Target for Cancer Therapy; Translational Oncology – Vol. 10 – pp. 22-32; February 2017
# PLK1 – Over-Expressed in Multiple Cancers

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>PLK1 Fold Change Over-Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>13.0</td>
</tr>
<tr>
<td>B-cell Lymphoma</td>
<td>56.3</td>
</tr>
<tr>
<td>Prostate</td>
<td>3.3</td>
</tr>
<tr>
<td>Adrenocortical</td>
<td>4.5</td>
</tr>
<tr>
<td>Lung Adeno</td>
<td>9.7</td>
</tr>
<tr>
<td>Lung Squamous</td>
<td>20.8</td>
</tr>
<tr>
<td>Breast</td>
<td>11.3</td>
</tr>
<tr>
<td>Esophageal</td>
<td>10.2</td>
</tr>
<tr>
<td>Stomach</td>
<td>4.8</td>
</tr>
<tr>
<td>Colon</td>
<td>2.5</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>4.2</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2.2</td>
</tr>
<tr>
<td>Ovarian</td>
<td>31.7</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>12.4</td>
</tr>
<tr>
<td>Kidney</td>
<td>4.7</td>
</tr>
<tr>
<td>Liver</td>
<td>11.7</td>
</tr>
<tr>
<td>Uterine</td>
<td>21.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>9.1</td>
</tr>
</tbody>
</table>

1Liu et al- PLK1, A Potential Target for Cancer Therapy; Translational Oncology – Vol. 10 – pp. 22-32; February 2017
Developing Onvansertib
First-in-Class
3\textsuperscript{rd} Generation PLK1
Onvansertib First-in-Class 3\textsuperscript{rd} Generation PLK1 Best-in-Class Attributes
Onvansertib Intellectual Property

- Four worldwide patent families
  - Genus, Compound, Combinations, Salt
- Mature portfolio
  - Granted in most major jurisdictions
- Patent term 2030 plus up to 5 years extension
Onvansertib – Highly-Selective Only for PLK1

Selective PLK1 Inhibitor

► Tested against >260 kinases
► PLK1 was the only active target (IC$_{50}$ of 2nM)

Causes cancer cell death by G$_2$M arrest

► Onvansertib blocks cell division (mitosis)

<table>
<thead>
<tr>
<th>PLK Member</th>
<th>Onvansertib IC$_{50}$* (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLK1</td>
<td>0.002</td>
</tr>
<tr>
<td>PLK2</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>PLK3</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

Data on File, Trovagene, Inc.

AML-NS8 Patient-Derived Cells Treated with 200 nM Onvansertib for 24 Hrs$^1$

$^1$Data on File, Trovagene, Inc.
Onvansertib Phase 1 Safety Trial \(^1\)
Favorable First-in-Human Data

**Phase 1 Dose Escalation Trial in Patients with Advanced or Metastatic Solid Tumors**

**Trial Design**

- Open-label dose escalation to assess safety and identify Phase 2 dose
- 19 patients administered Onvansertib orally, once daily for 5 consecutive days, every 21-days
- Solid Tumors: colorectal, pancreatic, lung, sarcomas, hepatocellular, ampullary, prostate, ovarian, skin

**Trial Results**

1. Established safety and identified Phase 2 dose of 24 mg/m\(^2\)/day
2. 16 patients evaluable with 30% stable disease
3. Only mild to moderate side effects
4. No GI disorders, mucositis, or hair loss

\(^1\)Weiss G et al., Phase I dose escalation study of NMS-1286937, an orally available Polo-like Kinase 1 inhibitor, in patients with advanced or metastatic solid tumors – Invest. New Drugs DOI 10.1007/s10637-017-0491-7
Benefiting From Drug Class Experience
Drawbacks Associated with 1st and 2nd Generation PLK Inhibitors

Prior PLK inhibitors in development demonstrated significant clinical activity in combination with standard-of-care chemotherapy in AML.

Major drawbacks, unrelated to efficacy of the drug class, resulted in discontinuation of development.

- **Non-Selective**
  - panPLK inhibitors targeting both normal and tumor cells
- **Significant Toxicities**
  - Serious adverse effects that are non-mechanism based
- **Sub-Optimal PK**
  - Intravenous formulation; relatively long half-life
- **No Dosing/Schedule Flexibility**
  - Fixed dose; no option to increase time between treatment
- **Lethal Infections**
  - No mandated anti-infective prophylaxis
- **No Biomarker Strategy**
  - Inability to identify patients most likely to respond
Onvansertib – First-in-Class, 3rd Generation PLK1 Addresses Drawbacks of 1st and 2nd Generation

- Onvansertib product profile and clinical development program effectively addresses drawbacks associated with 1st and 2nd generation PLK inhibitors

<table>
<thead>
<tr>
<th>Feature</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly-Selective</td>
<td>Selective only for PLK1 which is overexpressed in tumor cells</td>
</tr>
<tr>
<td>Safe and Well Tolerated</td>
<td>Only mild to moderate side effects reported</td>
</tr>
<tr>
<td>Ideal PK Properties</td>
<td>Orally administered and relatively short half-life of ~24 hours</td>
</tr>
<tr>
<td>Dosing and Treatment Schedule Flexibility</td>
<td>Dose individualized to patients based on weight and body surface area; flexibility to increase time between treatment</td>
</tr>
<tr>
<td>Proactive Infection Management</td>
<td>Protocol mandated prophylactic anti-infectives for all patients</td>
</tr>
<tr>
<td>Biomarker Strategy</td>
<td>Ability to identify patients most likely to respond to therapy</td>
</tr>
</tbody>
</table>
Combination Therapy Approach
Onvansertib Combination Therapy Strategy

- Cornerstone of precision cancer medicine
- Onvansertib has demonstrated synergy with chemotherapies and targeted therapeutics
- Enhances efficacy (targets key pathways by synergy or additive effect)
- Reduces drug resistance, while providing therapeutic benefits

Onvansertib – Synergistic in Combination

- High PLK1 expression is associated with the most aggressive cancers
- Synergistic activity may enhance efficacy of standard-of-care therapies

<table>
<thead>
<tr>
<th>Potentially Synergistic Drugs(^1,2)</th>
<th>Associated Cancers(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate</td>
<td>Leukemias/Lymphomas:</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>- Acute Myeloid Leukemia</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>- Acute Lymphocytic Leukemia</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>- Non-Hodgkin Leukemia</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>- Multiple Myeloma</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Solid Tumor Cancers:</td>
</tr>
<tr>
<td>FLT3 Inhibitors (Quizartinib)</td>
<td>- Castration-Resistant Prostate</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>- Adrenocortical Carcinoma</td>
</tr>
<tr>
<td>HDAC Inhibitors (Belinostat)</td>
<td>- Triple Negative Breast</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>- Sarcomas</td>
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<td></td>
<td>- Small Cell Lung</td>
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<td></td>
<td>- Colon</td>
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</tbody>
</table>

\(^1\) Alphabetical order. \(^2\) Preclinical data on file with PCM-075 and these combined therapeutics
Onvansertib Rationale for Combination with DNA Damaging Agents\textsuperscript{1,2}

DNA Damage Response (DDR) arrests cells at G2/M checkpoint

Mitosis
1. Checkpoint adaptation
2. PLK1 inhibits DDR, induces mitotic entry for tumor cells & cell division

G2/M Arrest

DNA Damaging Agents
- Cytarabine
- Doxorubicin
- Cisplatin

Cell Death
1. Keeps tumor cells in G2/M arrest leading to apoptosis
2. For cells that escape, mitosis is blocked, also leading to apoptosis

\textsuperscript{1}van Vugt & Yaffe, Cell Cycle 2010 9:2097-2101; \textsuperscript{2}van Vugt et al., 2010, PLoS 8:1-19
Onvansertib (PCM-075) + FLT3 Inhibitor  
Acute Myeloid Leukemia (AML)

► 30% of AML patients have a FLT3 mutation¹

► Quizartinib in Phase 3 clinical development²

► Combination of PCM-075 + quizartinib demonstrated:
  – 97% tumor growth inhibition
  – Regression in FLT3 AML xenograft model³

Onvansertib (PCM-075) + Abiraterone
Metastatic Castration-Resistant Prostate Cancer

► PCM-075 + abiraterone demonstrated synergy¹

► Combination enhances PCM-075 mechanism of action¹

► Medical need to increase duration of response to anti-androgen drugs

¹Yaffe, Michael, MD and Trovagene, 2017

*C4-2 Castration-Resistant Prostate Cancer Cells Increased Sensitivity to Abiraterone in the Presence of PCM-075*

*Expected = the calculated value of the effect of the addition of each drug as calculated by Michael Yaffe, MD - MIT*
Onvansertib (PCM-075)
Clinical Development

Phase 1b/2 Acute Myeloid Leukemia (AML)

Phase 2 metastatic Castration-Resistant Prostate Cancer (mCRPC)

Phase 2 metastatic Colorectal Cancer (mCRC)
Clinical Development Roadmap

Acute Myeloid Leukemia

Prostate Cancer

Colorectal Cancer
Acute Myeloid Leukemia\(^1\)  
Significant Need for New Treatment Options

- Aggressive hematologic malignancy of immature blood cells
- 20,000 new cases, 10,400 deaths annually, and 5 year survival rate of 25%
- Treatment options vary based on patient condition / age, but can include:
  - Chemotherapy / Radiation / Stem Cell Transplant
- Preclinical *in-vitro* and *in-vivo* data demonstrate efficacy of Onvansertib\(^*\) as single agent and in combination with drugs used to treat AML

\(^*\)Orphan Drug Designation granted for Onvansertib by the FDA September, 2017 and by the EMA in July, 2018;\(^1\)National Cancer Institute SEER 2016;\(^2\)Valsasina et al., Mol Cancer Ther; 11(4) April 2012
AML Clinical Development Landscape\(^1\)

Medical Need for New Therapeutic Options

- The majority of therapeutic advances for AML have not come from the introduction of novel therapeutics but instead from optimizing use of older drugs\(^2\)

- With increased understanding of the molecular pathogenesis of AML in recent years there is a significant opportunity to introduce new targeted therapeutics\(^2\)

**Significant Opportunity for New Therapeutic Options**

<table>
<thead>
<tr>
<th>Company</th>
<th>Market Cap</th>
<th>Drug</th>
<th>Combination</th>
<th>Development</th>
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<tbody>
<tr>
<td>trovagene</td>
<td>$15M</td>
<td>Onvansertib (PLK1 inhibitor)</td>
<td>Cytarabine / Decitabine</td>
<td>Phase 1b/2</td>
</tr>
<tr>
<td>cti Biopharma</td>
<td>$104M</td>
<td>Tosedosat (aminopeptidase activity inhibitor)</td>
<td>Cytarabine / 5-Azacytadine</td>
<td>Phase 1/2</td>
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<tr>
<td>AVEO Oncology</td>
<td>$288M</td>
<td>Ficlatuzumab (antibody targeting HGF)</td>
<td>Cytarabine</td>
<td>Phase 1</td>
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<tr>
<td>agios</td>
<td>$4.5B</td>
<td>Tibsovo (IDH1 Inhibitor)</td>
<td>Single Agent</td>
<td>FDA Approved</td>
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<tr>
<td></td>
<td></td>
<td>AG-221 (IDH2 Inhibitor)</td>
<td>Single Agent</td>
<td>Phase 1/2</td>
</tr>
</tbody>
</table>

\(^1\)www.clinicaltrials.gov; \(^2\)www.hematology.org/TheHematologist/Years-Best/8155.aspx
Onvansertib (PCM-075) Scientific Rationale
Clinical Development in AML

► in-vitro studies¹
  – High sensitivity of hematological tumor cell lines to PCM-075

► in-vitro and in-vivo mode of action (MoA) studies²
  – Xenograft model demonstrates dose dependent inhibition of PLK1 activity and G2/M arrest

► in-vivo efficacy in AML xenograft models²
  – Dose dependent efficacy of PCM-075 in
    • HL60 promyelocytic leukemia xenograft
    • Disseminated AML patient derived xenografts (AML-PS)
  – Combination of PCM-075 + cytarabine has greater survival than either agent alone (AML-PS)

¹Source: Report No. N-0018670 Antiproliferative activity of NMS-1286937 in a panel of cell lines;²Valsasina et al., Mol Cancer Ther; 11(4) April 2012; ³ClinicalTrials.gov, NCT03303339: PCM-075 in Combination With Either Low-dose Cytarabine or Decitabine in Adult Patients With Acute Myeloid Leukemia (AML) - Data-on-file, Trovagene 2018
Orphan Drug Designation (ODD) in AML

In the U.S. and Europe

Regulatory and Financial Incentives

Extended Market Exclusivity
Onvansertib Comparative and Combination with Cytarabine in AML Models$^1,2$

In Vivo Disseminated Leukemia Models

- Onvansertib 60 mg/kg BID (Days 1-2 with 5-day rest) + cytarabine 75 mg/kg IP Injection (Days 1-5 with 5-day rest)
- Onvansertib 120 mg/kg for 2 days repeated for 4 cycles with a 10-day rest
- Cytarabine IP at 75mg/kg for 5 cycles of 5 consecutive days with 7-day rest
- The combination was given at the same schedule, doses, and routes of the single agents

Onvansertib + cytarabine in combination showed increased survival compared to either agent alone

$^1$Casolaro et al. (2013) PLOS One 8(3); $^2$Valsasina et al. (2012), Mol Cancer Ther 11(4)
Onvansertib Positioning in AML Patient Selection Algorithm

- AML Diagnosis: 18,376 cases/year
- Eligible for Induction Treatment: ~11,000
- Ineligible for Induction Treatment: ~7,400
- Relapsed & Refractory: 30-50%
  - 3,300 to 5,500
- Responders: 50-70%
- Consolidation Treatment

Onvansertib in combination with standard-of-care chemotherapy and/or targeted therapeutics

1 Visser et al. (2012), Eur J Cancer (48). Estimated cases in EU27 per year; 2 e.g. Midostaurin for FLT3 mutation
Ongoing Phase 1b/2 Clinical Trial in AML

Onvansertib in Combination with Either Low-Dose Cytarabine or Decitabine in Patients with Acute Myeloid Leukemia (AML)

**Phase 1b:** Dose escalation to assess safety and identify recommended Phase 2 dose

- **12 mg/m²**
- **18 mg/m²**
- **27 mg/m²**
- **40 mg/m²**

► Administered orally, once daily on days 1-5 of each cycle (21-28 days)

**Phase 2:** Assess safety and preliminary antitumor activity

► **Efficacy Endpoints:** Rate of complete response (CR + CRi) defined as morphologic leukemia-free state (MLF)

► **Exploratory Endpoints:** Evaluation of pharmacodynamic and correlative biomarkers
Biomarker Strategy in AML

- Biomarkers will be measured and correlated with pharmacokinetic drug levels to assess:
  - Treatment effects by measuring % blast cells in blood and bone marrow
  - Inhibition of PLK1 by Onvansertib (Target Engagement)
  - Correlating underlying tumor genetics with treatment response

### Genomic Profiling:
- Tumor Mutations

### Immuno-Profiling

### PLK1 Target Engagement
- pTCTP/TCTP

### Procedural Flow
- Cell Isolation
- DNA Isolation
- Flow Cytometry
- Protein Extraction
- Cell Isolation
Immuno-Profiling: Monitoring Leukemic Blast Cells in Response to Treatment

% of Leukemic Cells in Blood

%Leukemic Cells in Bone Marrow (Trovagene analysis)

%Leukemic Cells in Bone Marrow (Clinical site analysis)

1NCT03303339, ClinicalTrials.gov; *Onvansertib in Combination With Either Low-dose Cytarabine or Decitabine in Adult Patients With Acute Myeloid Leukemia (AML)
Onvansertib inhibits PLK1 kinase activity resulting in reduction in PLK1 substrates phosphorylation; Translational Control Tumor Protein (TCTP) is phosphorylated by PLK1.

PLK1 inhibition was assessed 3-hours following administration of Onvansertib at peak concentration ($C_{\text{max}}$).

1Cusshi U. et al, Phosphorylation of TCTP as a Marker for Polo-like Kinase 1 Activity In Vivo – Anticancer Research December 2010 vol. 30 no. 12 pp. 4973-4985
Correlation of Target Engagement and Treatment Response

% of Leukemic Cells in Blood

Cycle 1  Cycle 2
Onvansertib + LDAC
- 01-002
- 07-004
- 07-010

Days of cycle

Onvansertib 12mg/m² + LDAC

01-002
- D1 0h 3h 0h
- D5

07-004
- D1 0h 3h 0h
- D5

07-010
- D1 0h 3h 0h
- D5

pTCTP status as a surrogate for PLK1 inhibition

% of Leukemic Cells in Blood

Cycle 1  Cycle 2
Onvansertib + Decitabine
- 07-009
- 07-011
- 07-013

Days of cycle

Onvansertib 12mg/m² + Decitabine

07-009
- D1 0h 3h 0h
- D5

07-011
- D1 0h 3h 0h
- D5

07-013
- D1 0h 3h 0h
- D5

pTCTP status as a surrogate for PLK1 inhibition

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Summary of Target Engagement and Correlation to Treatment Response

Onvansertib 12mg/m² + Cytarabine

Onvansertib 12mg/m² + Decitabine

- D1 predose (0h)
- D1 post dose (3h)
- D5

- pTCTP/TCTP relative to D1 predose

- % Blasts

- Response

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Predictive Response Strategy

Evaluating Patient Responsiveness to Onvansertib

AML Patient

Patient receives single dose Onvansertib

Assess target engagement of PLK1 by Onvansertib

Target Engagement Eligible Patient

NO Target Engagement Non-Eligible Patient

1Trovagene Patent Pending – PLK1 Target Phosphorylation Status and Treatment of Cancer with PLK1 Inhibitors
<table>
<thead>
<tr>
<th>AML Genomic Subgroup</th>
<th>Frequency of Patients</th>
<th>Most Frequently Mutated Genes (%)</th>
<th>DNA Panel</th>
<th>RNA Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM1 mutation</td>
<td>27%</td>
<td>NPM1(100), DNMT3A(54), FLT3(39), NRAS(19), TET2(16), PTPN11(15)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mutated chromatin, RNA-splicing genes, or both</td>
<td>18%</td>
<td>RUNX1(39), MLLPTD(25), SRSF2(22), DNMT3A(20), ASXL1(17), STAG2(16), NRAS(16), TET2(15), FLT3ITD(15)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>TP53 mutations, chromosomal aneuploidy, or both</td>
<td>13%</td>
<td>Complex karyotype(68), -5/5q(47), -7/7q(44), TP53(44), -17/17p(31), +8/8q(16)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11</td>
<td>5%</td>
<td>inv(16) (100), NRAS(53), +8/8q(16), KIT(15), FLT3TKD(15)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>biallelic CEBPA mutations</td>
<td>4%</td>
<td>CEBPAbiallelic(100), NRAS(30), WT1(21), GATA2(20)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>t(15;17)(q22;q12); PML-RARA</td>
<td>4%</td>
<td>t(15;17) (100), FLT3 ITD(35), WT1(17)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>t(8;21)(q22;q22); RUNX1-RUNX1T1</td>
<td>4%</td>
<td>t(8;21) (100), KIT(38), -Y(33), -9q(18)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MLL fusion genes; t(x;11)(x;q23)</td>
<td>3%</td>
<td>t(x;11q23) (100), NRAS(23)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2,MECOM(EVI1)</td>
<td>1%</td>
<td>inv(3) (100), -7(85), KRAS(30), NRAS(30), PTPN11(30), ETV6(15), PHF6(15), SF3B1(15)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IDH2R172 mutations and no other class-defining lesions</td>
<td>1%</td>
<td>IDH2R172(100), DNMT3A(67), +8/8q(17)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>t(6;9)(p23;q34); DEK-NUP214</td>
<td>1%</td>
<td>t(6;9) (100), FLT3ITD(80), KRAS(20)</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1Papaemmanuil et al. Genomic classification and prognosis in acute myeloid leukemia; NEJM 2016;374:2209-2221
Genomic Profiling: Correlation of Mutation Detected in Blood and % Leukemic Cells

- Genomic analysis was performed on bone marrow and blood samples
- Mutations detected in bone marrow and blood were identical for all patients examined
- The mutation allelic frequencies detected in blood correlates with % of circulating leukemic cells

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutations detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>07-004</td>
<td>TP53  c.955 A&gt;T p.Lys319Ter</td>
</tr>
<tr>
<td>07-011</td>
<td>TP53  c.773A&gt;C p.Glu258Ala</td>
</tr>
</tbody>
</table>
25,000 men die from metastatic prostate cancer annually and the five-year survival rate is 37%.

Treatments
- Zytiga® (Johnson & Johnson)/prednisone
- Xtandi® (Astellas/Pfizer)

Ongoing need to increase duration of response to treatment
- Patients develop resistance within 9-15 months and do not respond well to subsequent therapies

Preclinical studies demonstrate synergy between Onvansertib and Zytiga®
- PLK1 inhibition improves abiraterone efficacy by repressing the androgen signaling pathway.

PLK1 and Abiraterone Acetate (Zytiga®)
Metastatic Castration-Resistant Prostate Cancer (mCRPC)

► All metastatic prostate cancer patients become castration-resistant

► PLK1 dependent microtubule dynamics promotes androgen receptor (AR) signaling¹,²

► PLK1 inhibition improves abiraterone efficacy³

► Inhibition of PLK1 represses androgen signaling pathway⁴

► PLK1 inhibitors may add important therapeutic benefit for the treatment of castration-resistant prostate cancer patients⁵

**Ongoing Phase 2 Clinical Trial in mCRPC**

### Onvansertib in Combination with Zytiga® and Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC)

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Duration</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onvansertib – 24 mg/m² Days 1-5 (21-Day Cycle) + Zytiga®/prednisone daily</td>
<td>4 Cycles = 12 Weeks</td>
<td>Disease Control based on PSA level</td>
</tr>
</tbody>
</table>

### Efficacy Endpoints

Effect of Onvansertib in combination with Zytiga®/prednisone on disease control assessed by prostate-specific antigen (PSA) decline or stabilization pre- and post-treatment

### Safety Endpoint

Safety of Onvansertib in combination with Zytiga®/prednisone

### Exploratory Endpoint

Target inhibition of PLK1, evaluation of relevant biomarkers and correlation with patient response and genomic profile
Biomarker Strategy in mCRPC

- PSA: Assessment of Disease Control
- ctDNA: Dynamic Changes Associated with Treatment
- CTCs: Baseline Genomic Correlations with Response
- PBMC’s: Assess PLK1 Target Inhibition
- Tissue: Baseline Tumor Profiling for Predicting Synergy
PSA: NCCN Recommended Biomarker Trial Eligibility and Efficacy for mCRPC

► PSA is a validated biomarker assessing disease stability or progression

► Prostate Cancer Clinical Trials Working Group (PCWG)\(^1\) has set criteria for the use of blood PSA levels:
  – Trial eligibility (defining progression)
  – Initial assessment of efficacy

\(^1\)PCWG2: Sher et al, JCO, 2008, PCWG3: Sher et al, JCO, 2016
Biomarker Assessment Schedule

Week:

- Cycle 1: Week 1
- Cycle 2: Week 3
- Cycle 3: Week 6
- Cycle 4: Week 9
- Cycle 5: Week 12

Primary Endpoint: Proportion of patients achieving disease control after 12 weeks of study treatment, as defined by lack of PSA progression
140K new cases of CRC in 2018 with 64.5% 5 year survival
- ~51K deaths per year from mCRC

Tumor biomarkers drive therapy decisions for 1st line mCRC therapy
- ~50% mCRC is RAS mutant (KRAS): FOLFOX/FOLFIRI/FOLFOXIRI

Large unmet need in RAS mutant CRC
- No targeted therapies are available for RAS mutant CRC
- 2nd line therapies have ~5% response rate in metastatic CRC (mCRC)

Onvansertib in Pre-Clinical CRC Synergy with Irinotecan

**In vitro:**
- CRC cell lines are sensitive to Onvansertib:
  
  25/27 cell lines tested had an IC50<1uM and 10 had an IC50<0.1uM

- Onvansertib is synergistic with paclitaxel, cisplatin, SN-38 and irinotecan

**In-vivo:**
- Onvansertib inhibits tumor growth of CRC xenograft models
  
  3 independent models were tested and Onvansertib induces maximal tumor regression of ~84% compared to vehicle

- The combination of Onvansertib with Irinotecan significantly reduces tumor growth compared with vehicle or either single agent treatment

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1Data on File at Trovagene, Inc.
KRAS Mutation: Multiple *in-vitro* Studies Indicate Mutation is Biomarker for Onvansertib Sensitivity

- In a genome-wide RNAi screen there was found a synthetic lethal interactions (profound mitotic block/death) with KRAS oncogene and PLK1; Tested in 2 mutant & isogenic cell lines

- KRAS-mutant cancer cell lines are more sensitive to PLK1 inhibition (BI2536)

- KRAS mutated NIH3T3 cells showed higher sensitivity to onvansertib compare to KRAS wild-type (WT) cells

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Value Creating Milestones

Q4’18

✓ AML – ASH Presentation
✓ Efficacy and Safety Data Readouts (AML, mCRPC)
✓ mCRC IND & Protocol Filed to FDA

Q2’19

✓ Initiate mCRC Phase 1b/2 Trial
✓ Efficacy and Safety Data Readouts (AML, mCRPC)
✓ AACR Presentation (AML, mCRPC)
✓ Complete Enrollment of AML Phase 2
✓ Complete Enrollment of mCRPC Phase 2
✓ AML Companion Diagnostic

Q4’19

✓ Data Readouts (AML, mCRPC, mCRC)
✓ Begin Enrolling Phase 2 mCRC
✓ AML – ASH Presentation

Q1’19

✓ AML – Reach MTD and RP2D
✓ Begin Enrolling AML Phase 2 trial
✓ mCRPC – ASCO GU Presentation
✓ Efficacy and Safety Data Readouts (AML and mCRPC)
✓ Evaluate Expanding Clinical Program to Europe
✓ Formalize Japan Partnering

Q3’19

✓ Efficacy and Safety Data Readouts (AML and mCRPC)
✓ Assess Dose Escalation – Phase 1b mCRC Trial – Identify Phase 2 Dose
✓ Begin Enrolling mCRC Phase 2
Summary

► Precision Cancer Medicine, predictive biomarker approach

► Leveraging a proven cancer target, PLK1

► Onvansertib – first-in-class, 3rd generation, oral PLK1 inhibitor

► Synergy strategy – Onvansertib in combination with approved drugs
For additional information or questions please contact: ir@trovagene.com