Making Meaningful Medicines

Jefferies 2016 Healthcare Conference
Company Purpose

Tolero is committed to developing Meaningful Medicines to improve and extend the lives of patients with serious diseases.
What is a Meaningful Medicine?

A Meaningful Medicine…

• Makes a dramatic improvement in patient outcomes
• Targets a specific population that will most likely benefit from the drug
• Demonstrates activity linked directly to mechanism of action
## Tolero Pipeline

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Tolero’s Meaningful Medicine Approach Offers a Unique Opportunity for AML Treatment

- Rapidly progressing disease
- Heterogeneous cancer harboring multiple different mutations
- No single driver mutation has been identified for the majority of patients
- Patients are older (typically >60 years) and are very sick, limiting the use of toxic therapies
Alvocidib is a Meaningful Medicine

- Potential to dramatically improve the rate of complete remissions in patients with AML
  - Consistent and promising activity in both frontline and relapsed/refractory AML
  - Significant clinical experience in over 400 patients with AML
- Biomarker enables identification of patients likely to respond to alvocidib
- Potent inhibitor of CDK9 which regulates the transcription of many important proteins involved with cancer including, MCL-1
- Favorable regulatory feedback on registration study from FDA/EMA
Alvocidib Disrupts Super Enhancer Activity via CDK9 Inhibition

- Alvocidib is a potent inhibitor of CDK9.
- Alvocidib downregulates transcription of super enhancer-regulated genes, such as c-Myc and MCL-1.
Acute Myeloid Leukemia

AML remains a high unmet need

• Current standard of care, known as 7+3, is cytarabine and daunorubicin

• Majority of AML patients have high-risk features (75%) and respond poorly to 7+3

• Standard of care in AML leads to significant morbidity and treatment-related mortality in up to 20% of patients

• Patients achieving CR may be eligible to undergo a bone marrow transplant (BMT), considered to be the only curative treatment for AML

There is a significant opportunity in intermediate and high-risk AML to advance more patients to BMT by increasing CR rate

Alvocidib in AML

- AML is too complex to be effectively treated by single-agent therapy

- Investigators at the NCI identified Alvocidib as a promising novel agent to be used in combination AML therapy
  - Alvocidib targets key pathways involved with AML – differentiated from cytotoxic therapies
  - Synergistic when used in Timed Sequential Therapy (TST)

- Alvocidib has consistently shown promising activity in multiple AML studies as part of the regimen
  - Alvocidib, cytarabine, mitoxantrone (ACM)
Positive Randomized Phase II in Untreated AML Patients

ACM Demonstrated a Statistically Significant Improvement in CR Rate Over 7+3
Most Patients Had Secondary AML or Other Poor-Risk Features

CR Rate: ACM vs. 7+3

- ACM (n=109) 70%
- 7+3 (n=56) 46%

\[ p = 0.003 \]

ACM advantage was consistent across subgroups including adverse cytogenetics, FLT3, secondary AML

Survival Plateaued in a High Proportion of ACM-Treated Patients

Survival of ACM-Treated Patients
Phase I & II R/R AML Trials Overall Survival – Pooled Analysis

Relapse/Refractory (N = 79)

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95% confidence interval = 7.4, 16.8

38% (30/79) patients were refractory
Median duration of prior CR = 9 months

Combination of R/R patients from J06133 and J0254. Tolero, data on file.
Key Findings from Clinical Studies

• Significant improvement in the CR rate over standard of care (7+3) in a randomized, multicenter study with untreated intermediate or high-risk AML patients
• Consistently outperforms 7+3 across risk factors
• Frontline intermediate or high-risk AML patients and relapsed/refractory AML patients achieved consistent and high CR rates
  • 62-80% CR in newly diagnosed unfavorable-risk AML patients in three Phase II studies
  • 29-92% CR in patients with relapsed AML
  • 28-49% CR in combined trial populations of relapsed/refractory AML patients
• Promising survival (median, 11.6 months) in relapsed/refractory AML patients
• Toxicities are consistent with current treatments
Phase I & II R/R AML Trials Overall Survival – Pooled Analysis

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Exceptional Responders

Combination of R/R patients from J06133 and J0254. Tolero, data on file.
Predictive Biomarker Linked to Alvocidib Mechanism

- The activity of alvocidib can be enhanced by identifying patients likely to respond
- Alvocidib’s mechanism of action can be leveraged into an assay platform to identify sensitive patients
MCL-1 and NOXA Function Together to Regulate Apoptosis

MCL-1 is a key survival signal well documented in AML

NOXA priming is a functional measurement of MCL-1 dependence in AML
What is NOXA Priming?

- A simple functional assay to identify patients with a malignancy dependent on MCL-1

- The assay involves adding NOXA peptide to patient samples and measuring induction of apoptosis – readout is percentage of cells entering apoptosis

- Easy, scalable and provides quick turnaround

- In AML patients, the assay is run on standard bone marrow aspirates
Results from NOXA Priming Validation Set: High NOXA Priming is Predictive of Alvocidib Sensitivity in AML Patients

- NOXA % Priming
- NR (n=12)
- CR (n=12)

NOXA priming in CR and NR (No Response) pre-treatment bone marrow samples from AML patients treated with the ACM regimen.

NOXA priming did not predict response in patients treated with 7+3.
ACM-Treated AML Patients with NOXA Priming Greater than 40% Demonstrated Greater Survival

Overall Survival

Proportion Alive

Months

Above 40% NOXA Priming (n=7)
Below 40% NOXA Priming (n=17)

HR = 0.25
P = 0.023
Phase II Biomarker Protocol Design

R/R AML Patients with Demonstrated NOXA Priming Greater Than 40%

Single arm Lead in 23 Patients
If CR in 13 or More Patients
Proceed to Randomized Study

R

1:1
N=56

ACM

CM

Crossover Allowed

- Primary Endpoint: Rate of Complete Remission
- Secondary endpoints: EFS, OS, safety, CRi, CRp, duration of response
AML Market Positioned for Rapid Growth

- AML therapies have remained unchanged for decades
- As evidenced in other liquid tumors, therapies offering new mechanisms should experience rapid adoption
- Front-line AML and relapsed or refractory AML addresses 54,000 patients in the major markets
Expanding the Use of Alvocidib

**NHL**
MCL-1 Dependence: 53%

**CLL**
MCL-1 Dependence: 21%
J Clin Oncol 32:5s, 2014

**MDS**
MCL-1 Dependence: 60%
Tolero Data

**AML**
MCL-1 Dependence: 30-50%
Tolero Data

**NSCLC**
MCL-1 Dependence: 33%
Cell Death Differ. 2015 22(12):2098-106

**Advanced Prostate Cancer**
MCL-1 Dependence: 81%

**TNBC**
MCL-1 Dependence: 53%
Cell Death Differ. 2015 22(12):2098-106
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TP-1287 an Orally Available CDK9 Inhibitor

- TP-1287 is a pro-drug of alvocidib that can be delivered orally
- Oral delivery of alvocidib allows for more flexibility to expand into other CDK9-dependent indications
- Tolero is targeting a first in human trial with TP-1287 in 1H of 2017
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Axl Kinase in Cancer

• Axl kinase expression is an important pathway for resistance to EGFR and Her2 inhibitors
  • In the US 250K patients receive EGFR or Her2 inhibitors and most will fail treatment

• Axl signaling is also a resistance pathway for other targeted agents such as cKit, FLT3 and BTK inhibitors

• Inhibiting Axl kinase prevents cells from taking on a mesenchymal phenotype, which is a key feature for becoming resistant to many oncology treatments

• Axl inhibition provides a novel approach to addressing the unmet need in patients that progress or fail to respond to targeted agents
Cancer cells with an epithelial phenotype are less invasive and more sensitive to targeted agents, chemotherapy and lack the ability to metastasize.

Cancer cells undergo the transition to a mesenchymal phenotype leading to resistance to targeted agents, chemotherapy and metastasize to distant sites.

**Hallmarks of a Mesenchymal Phenotype**

- Drug Resistance
- Escape From Immune Surveillance
- Resist Endogenous Differentiation Signals

**TP-0903: Axl Inhibitor Blocks the Mesenchymal Phenotype in Cancer Cells**

Cancer cells with an epithelial phenotype undergo a transition to a mesenchymal phenotype due to Axl Kinase activity, leading to drug resistance and escape from immune surveillance. TP-0903 inhibits Axl kinase, blocking the mesenchymal phenotype and restoring sensitivity to targeted agents and chemotherapy.
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TP-0184: Oral Hepcidin Lowering Agent

TP-0184 reduces levels of hepcidin and restores normal levels of hemoglobin in animal models of inflammation-induced anemia.
TP-0184: Overview

- TP-0184 is a Potent and Selective Oral ALK2/3 Inhibitor
  - ALK2/3 regulates hepcidin expression, a master controller of iron levels and erythropoiesis
  - TP-0184 down-regulates liver and plasma hepcidin levels in relevant models of anemia

- TP-0184 normalizes hemoglobin levels in animal models of difficult to treat anemia

- Restores normal hemoglobin levels through a differentiated mechanism relative to ESAs

- Multiple Pathways for Development
  - Anemia of Chronic Inflammatory Diseases
  - Anemia of Cancer

- Capitalize on EPO-Sparing Strategy
Tolero Highlights

• Alvocidib pivotal study in relapsed/refractory AML – high probability approval path in an area of significant unmet medical need
  • Ongoing Phase II biomarker study may accelerate approval as well as optimize commercial opportunity and significantly extend exclusivity period

• Experienced management team with extensive record of successful drug approvals in hematologic malignancies
  • Campath, Clofarabine, Dacogen

• Pipeline of novel first-in-class agents targeting areas of high commercial opportunity
  • Axl kinase inhibitor addresses unmet medical need in many solid tumor and hematological indications including resistance to targeted therapies including EGFR and Her2 inhibitors through a novel mechanism
  • BMP signaling inhibitor targets a key pathway associated with anemia of chronic inflammation which is distinct from EPO