



Sumitomo Dainippon  
Pharma

Innovation today, healthier tomorrows

# Acquisition of Tolero Pharmaceuticals, Inc.

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December 21, 2016

Sumitomo Dainippon Pharma Co., Ltd.

# Acquisition of Tolero Pharmaceuticals, Inc.

## Significance of the Acquisition

- ✓ Acquire attractive compounds with potential to treat hematological disorders
- ✓ Obtain outstanding expertise in drug discovery capabilities for kinase inhibitors and other drug targets
- ✓ Contribute to business growth after LATUDA LOE

Reinforce pipeline in oncology area  
(Expand into hematologic malignancy area)

## ➤ Company profile

Name	Tolero Pharmaceuticals, Inc.
Established	June 2011
Headquarters	Lehi, UT, United States
Number of Employees	23 (As of October 31, 2016)



## ➤ Executive management

Name	Position	Name	Position
David J. Bearss, Ph.D.	Chief Executive Officer	Michael V. McCullar, Ph.D.	Chief Operating Officer
Dallin M. Anderson	Chairman and President	Steven L. Warner, Ph.D.	Vice President, Drug Discovery and Development
David W. Sampson	Chief Financial Officer	Michael A. Bernstein, M.P.H.	Vice President, Regulatory Affairs
Steven D. Weitman, M.D., Ph.D.	Chief Medical Officer		

# Tolero's Development Products and Discovery Capabilities

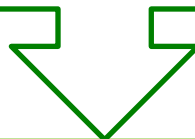
## ➤ Development products

Development code	Generic name	Mechanism of action	Target indication	Development location	Development stage
-	Alvocidib	CDK9 inhibitor	Acute myeloid leukemia	U.S.	Phase 2 (Completed)
			Acute myeloid leukemia (Biomarker)	U.S.	Phase 2
			Myelodysplastic syndromes	U.S.	Preclinical
TP-0903	TBD	AXL receptor tyrosine kinase inhibitor	Solid tumors, Hematologic malignancies	U.S.	Phase 1
TP-1287	TBD	CDK9 inhibitor	TBD	U.S.	Preclinical
TP-0184	TBD	ALK2 inhibitor	TBD	U.S.	Preclinical

\* In addition to the above list, Tolero possesses two compounds in the preclinical stage

## ➤ Drug discovery capabilities

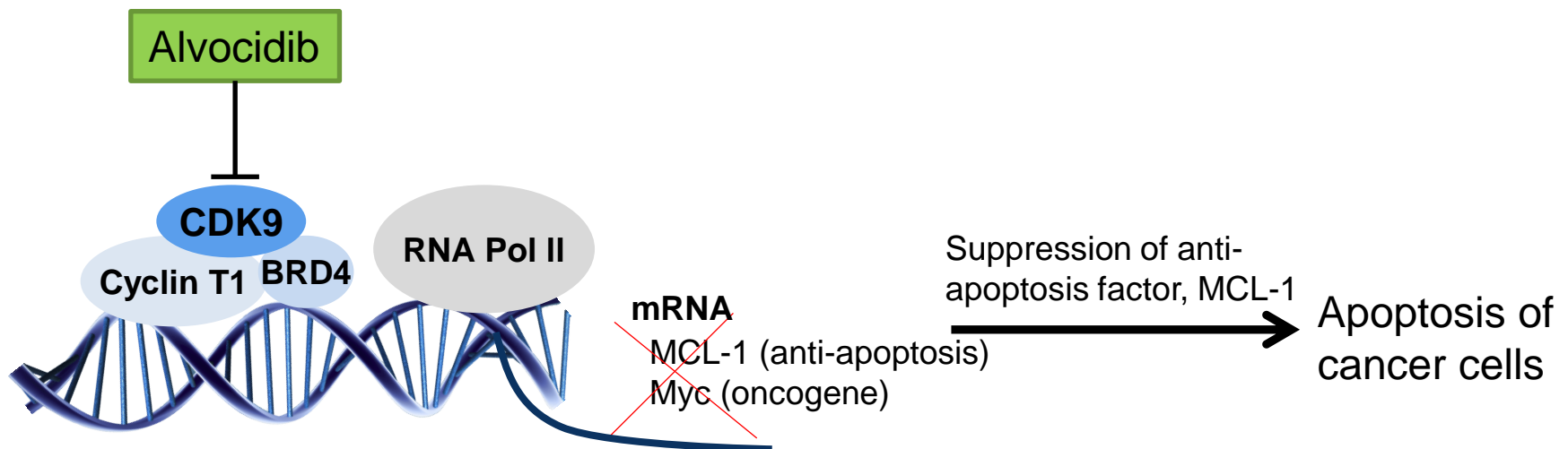
- Experienced personnel who have been involved in drug discovery and clinical development targeting kinases for more than 10 years.
- Unique evaluation system that assesses disease relevance and in-silico platform to discover disease-related kinases



**Select target indication, such as hematologic malignancies, most relevant to targeted kinase**

# Profile of Alvocidib

- **Mechanism of action:** Cyclin-dependent kinase 9 inhibitor (injection)
  - \* Cyclin-dependent kinase 9 (CDK9) : A member of the cyclin-dependent kinase family, which activates transcription of cancer-related genes
- **Target indications:** Acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), etc.
- **Development stage:**
  - Newly diagnosed AML (poor-risk patients): Phase 2 completed
  - Relapsed or refractory AML: Phase 2 completed
  - Relapsed or refractory AML (biomarker positive patients): Phase 2 ongoing
- **Expected Characteristics:**
  - Induce apoptosis in various types of cancer cells through suppressing MCL-1 expression by inhibiting CDK9

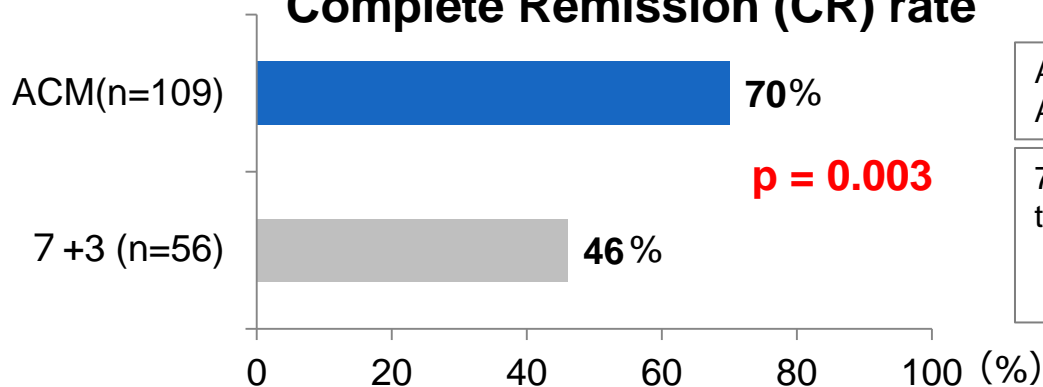


# Phase 2 Study Results of Alvocidib (efficacy) (Conducted by NCI)

- ACM regimen (alvocidib combination therapy) demonstrated a statistically significant improvement compared to control therapy

- **Newly diagnosed poor-risk AML patients**

## Complete Remission (CR) rate



ACM :  
Alvocidib + Cytarabine + Mitoxantrone

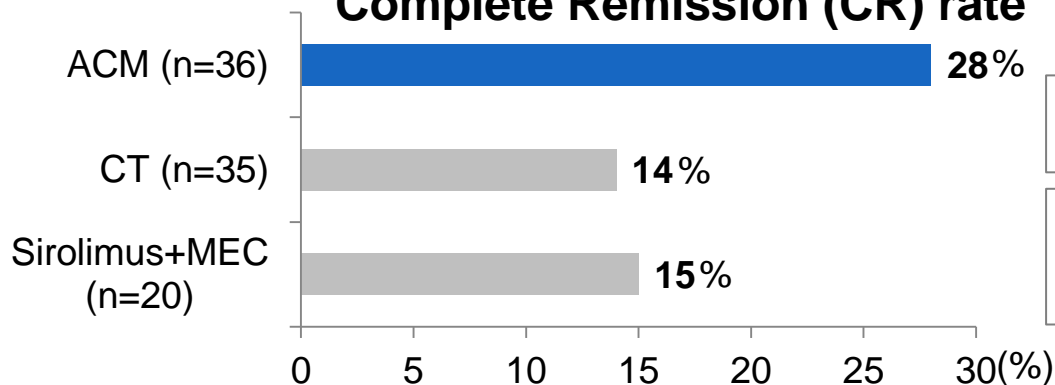
7+3 : Standard treatment regimen of induction therapy for newly diagnosed AML patients

- Cytarabine (day 1-7)
- Daunorubicin (day 1-3)

Joshua F. Zeidner, et al. *haematologica* 2015; 100: 1172.

- **Relapsed or refractory AML patients**

## Complete Remission (CR) rate



CT :  
Carboplatin + Topotecan

Sirolimus + MEC :

- Sirolimus
- Mitoxantrone + Etoposide + Cytarabine

Mark R. Litzow, et al. *Blood* 2014; 124: 3742.

# Phase 2 Study Results of Alvocidib (safety) (Conducted by NCI)

- ACM regimen (alvocidib combination therapy) demonstrated tolerability similar to that of the control therapy

- **Newly diagnosed poor-risk AML patients**

Grade $\geq 3$ toxicity	ACM (n=109)	7+3 (n=56)	p
Tumor lysis syndrome	9 (8%)	4 (8%)	>0.99
Myocardial dysfunction	8 (7%)	3 (8%)	0.75
GI toxicity	12 (11%)	5 (8%)	0.79
Hepatic dysfunction	23 (21%)	13 (23%)	0.84
Infection	38 (35%)	21 (38%)	0.74
Pulmonary toxicity	8 (7%)	4 (7%)	>0.99
Renal toxicity	3 (3%)	1 (2%)	>0.99
Thromboembolic events	3 (3%)	1 (2%)	>0.99
Febrile neutropenia events	52 (48%)	25 (45%)	0.74

Joshua F. Zeidner, et al. *haematologica* 2015; 100: 1172.

- **NCI completed 9 studies of Phase 1 and Phase 2 for AML  
(Total number of patients: about 600)**

# Clinical Development Plan of Alvocidib

## ➤ Development Strategy:

- Prioritize global studies with biomarker-positive population, aiming for early approval
- To be positioned as one of the standard regimens in induction therapy in AML
- Indication subsequently to be expanded to maintenance therapy by oral drug (TP-1287)

## ➤ Target Indication:

- Relapsed or refractory AML ⇒ Expand to newly diagnosed AML
- Additional indication for MDS

## ➤ Expected Peak Sales: About 50 billion yen

(Reference) Number of AML patients in the U.S.

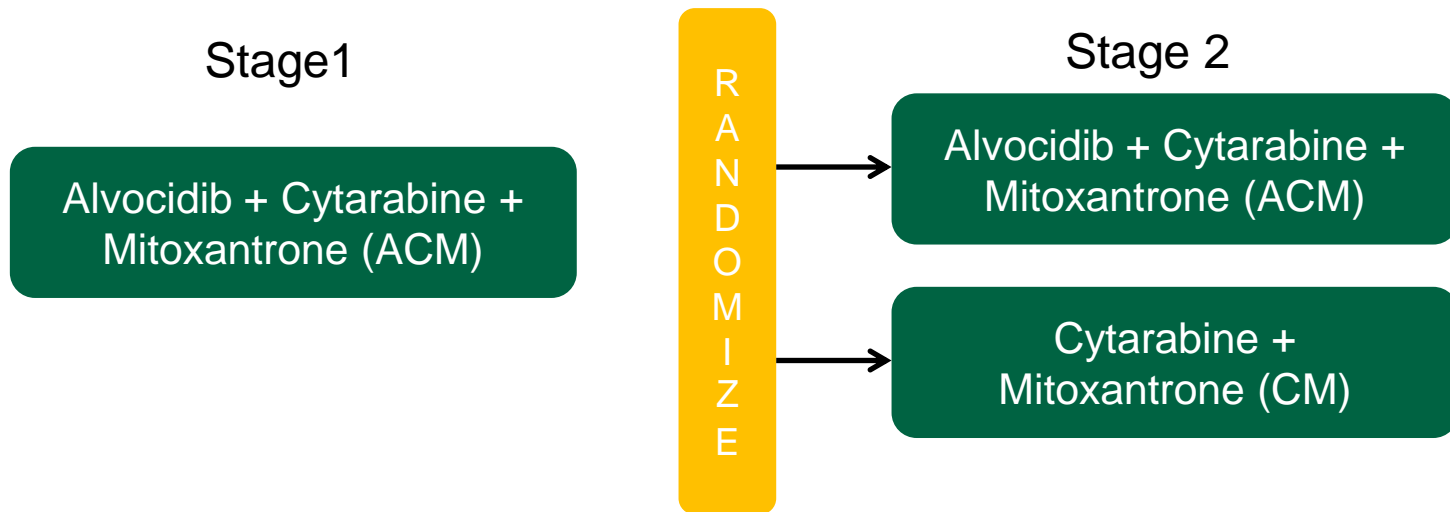
- Estimated New Cases in 2016: 19,950
- Estimated Deaths in 2016: 10,430
- Percent Surviving 5 Years (2006~2012): 26.6 %

*National Cancer Institute; SEET Stat Fact Sheets: Acute Myeloid Leukemia (AML) Created in 2016*

# Phase 2 Study Design of Alvocidib (Biomarker)

## ➤ Biomarker-driven Phase 2 AML Study:

- Two-stage Phase 2 study; Open-label, randomized study to assess the clinical response to ACM compared to AM treatment in relapsed or refractory AML patients (18-65 years) with patients with high MCL-1 expression
  - MCL-1 positive patients: Method of measuring using biomarker
- Primary endpoint: Complete remission rate
- Secondary endpoint: Overall Survival Rate, etc.
- Study Start Date : December 2015

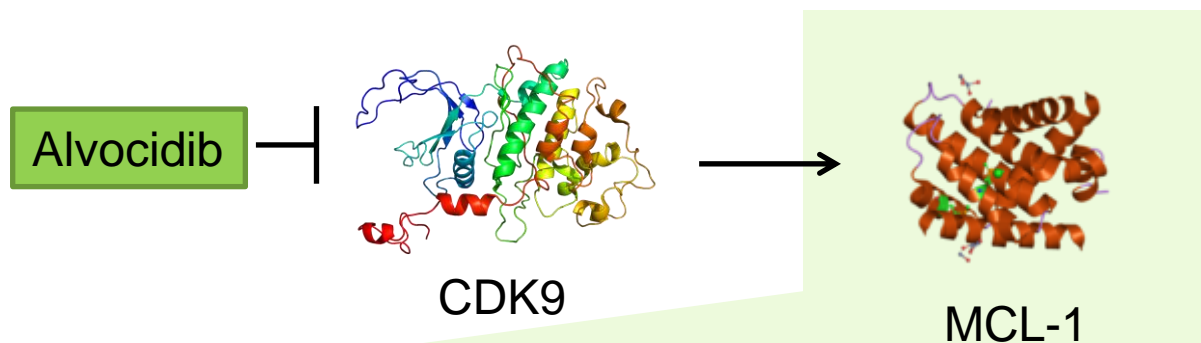


NDA to the FDA in FY2018 at the earliest (utilize accelerated approval\*)

\* Plan to consult with the FDA



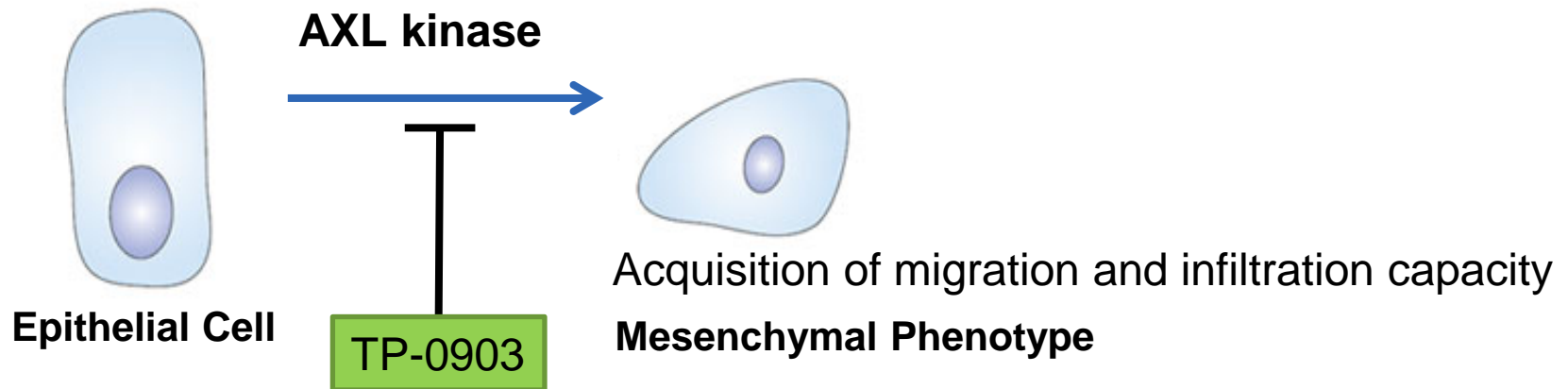
# Rate of Patients with High MCL-1 Expression



Type	Cancer type	Patients rate with high MCL-1 expression	Source
Hematologic malignancy	Acute myeloid leukemia	middle	Data of Tolero
	Myelodysplastic syndromes	high	Data of Tolero
	Chronic lymphocytic leukemia	21 %	J Clin Oncol 2014;32:5s
Solid tumors	Non small cell lung cancer	33 %	Cell Death Differ. 2015;22:2098
	Breast cancer (triple negative)	53 %	Cell Death Differ. 2015;22:2098
	Non-Hodgkin's lymphoma	53 %	Blood Cancer J. 2015;5:e368
	Prostate cancer	81 %	Am J Pathol. 1996;148:1567

# Profile of TP-0903

- **Mechanism of action** : AXL receptor tyrosine kinase inhibitor (oral)
  - \*AXL receptor tyrosine kinase: a member of the receptor tyrosine kinase family, involved in cell proliferation, migration, aggregation, and anti-inflammation
- **Target Indication** : Solid tumors and hematologic malignancies
- **Development Stage**: Phase 1 (US)
- **Expected Characteristics** :
  - Reduction of EMT
  - Synergistic effect with EGFR inhibitors
  - Suppression of metastasis and resensitization to drug resistance
    - \* EMT (Epithelial-Mesenchymal Transition) : Process by which epithelial cells lose their cell polarity and cellular adhesion function, and gain migratory and infiltrative properties to become mesenchymal stem cells



# Profile of TP-0184

## ➤ Mechanism of action : ALK2 inhibitor (oral)

\*ALK2 (activin receptor-like kinase-2) : a member of the bone morphogenetic protein (BMP) Receptor

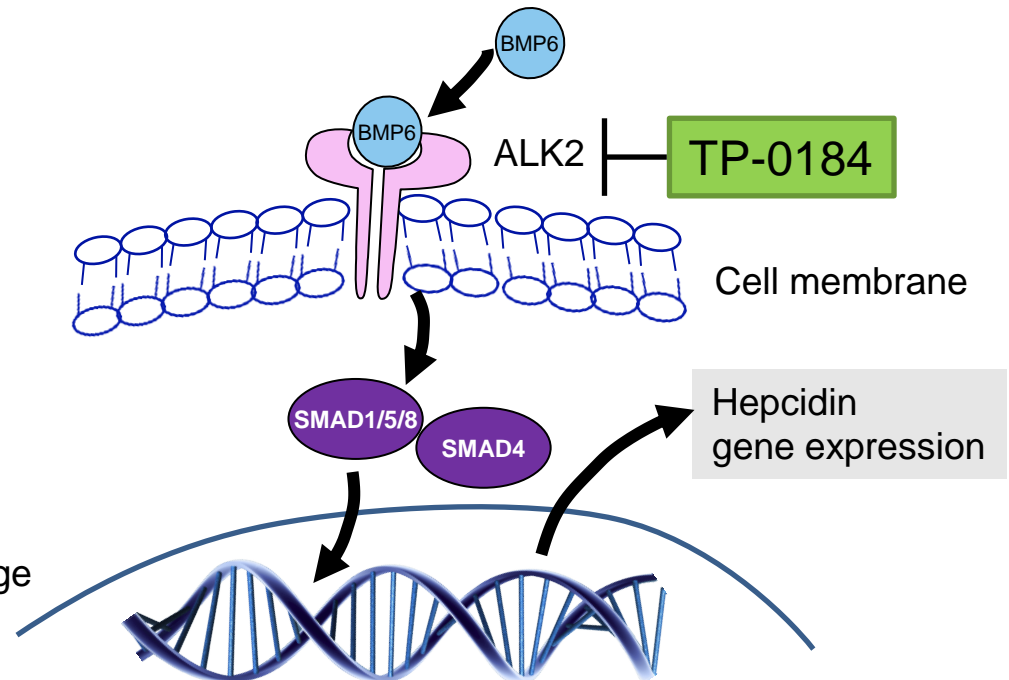
## ➤ Development Stage : Preclinical (Treated experience to patients)

## ➤ Expected Characteristics :

- ALK2 mutations in diffuse intrinsic pontine glioma (DIPG, one of pediatric brain tumors) are identified. TP-0184 is expected for a potential treatment to pediatric brain tumors
- Suppression of hepcidin (regulator of iron metabolism)
- Potential treatment to associated with chronic inflammation and cancer-related anemia

<Anemia associated with chronic inflammation>

- BMP6 production by inflammation
- Activation of BMPR signaling by BMP6
- Induction of hepcidin gene
- Suppression of iron metabolism by hepcidin
- Anemia caused by deficiency of iron, which is needed in hematopoietic lineage



# Transaction Summary and Financial Impact

## Transaction Summary

- **Form** : Implemented by way of a merger between Tolero and a special purpose company which has been established under Dainippon Sumitomo Pharma America Holdings, Inc. (Tolero will be the surviving company)
- **Consideration** : Upfront payment US\$200 million  
Development milestones up to US\$430 million  
Sales milestones up to US\$150 million
- **Closing (Planned)** : February 2017

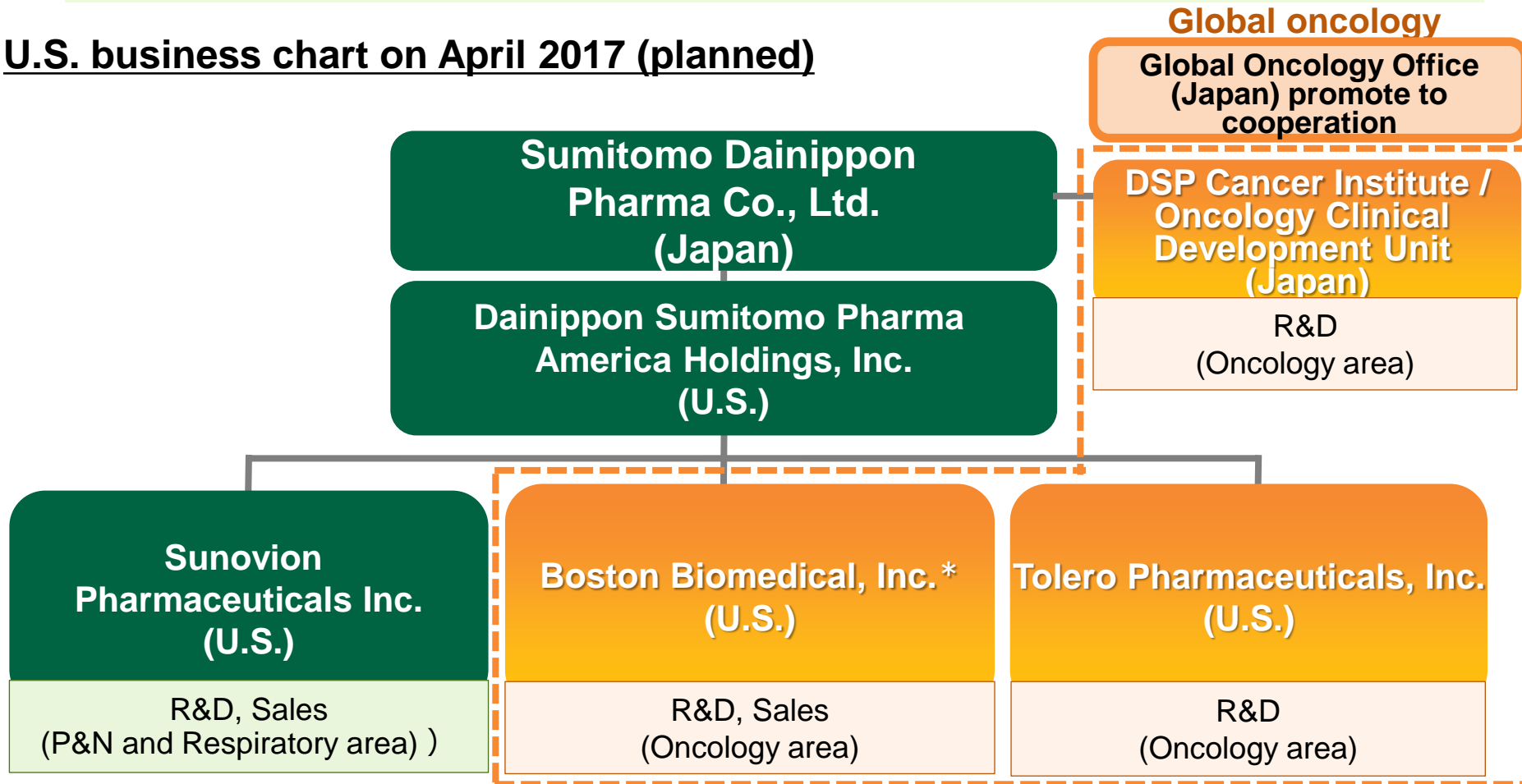
## Financial Impact

- **Accounting Treatment (USGAAP)**
  - The consideration will be allocated to assets and liabilities, and the difference between the net asset and total consideration will be recorded as goodwill.  
(Contingent consideration related to each milestone is recorded in liabilities by its fair value. Change of the fair value is recognized as expense.)
- **Impact to P/L**
  - Details of purchase price allocation and amortization of intangible assets / goodwill will be announced after the transaction completed.
- **Funding of Acquisition**
  - Own fund and debt loan

# R&D System of Oncology Area after Deal Closing

- Sumitomo Dainippon Pharma, Boston Biomedical and Tolero Pharmaceuticals to collaborate in drug discovery activities
- Continually create innovative products

## U.S. business chart on April 2017 (planned)



\* As of April 1, 2017, Boston Biomedical, Inc. planned to merge with Boston Biomedical Pharma, Inc.

# Results of Past Clinical Studies of alvocidib (AML)

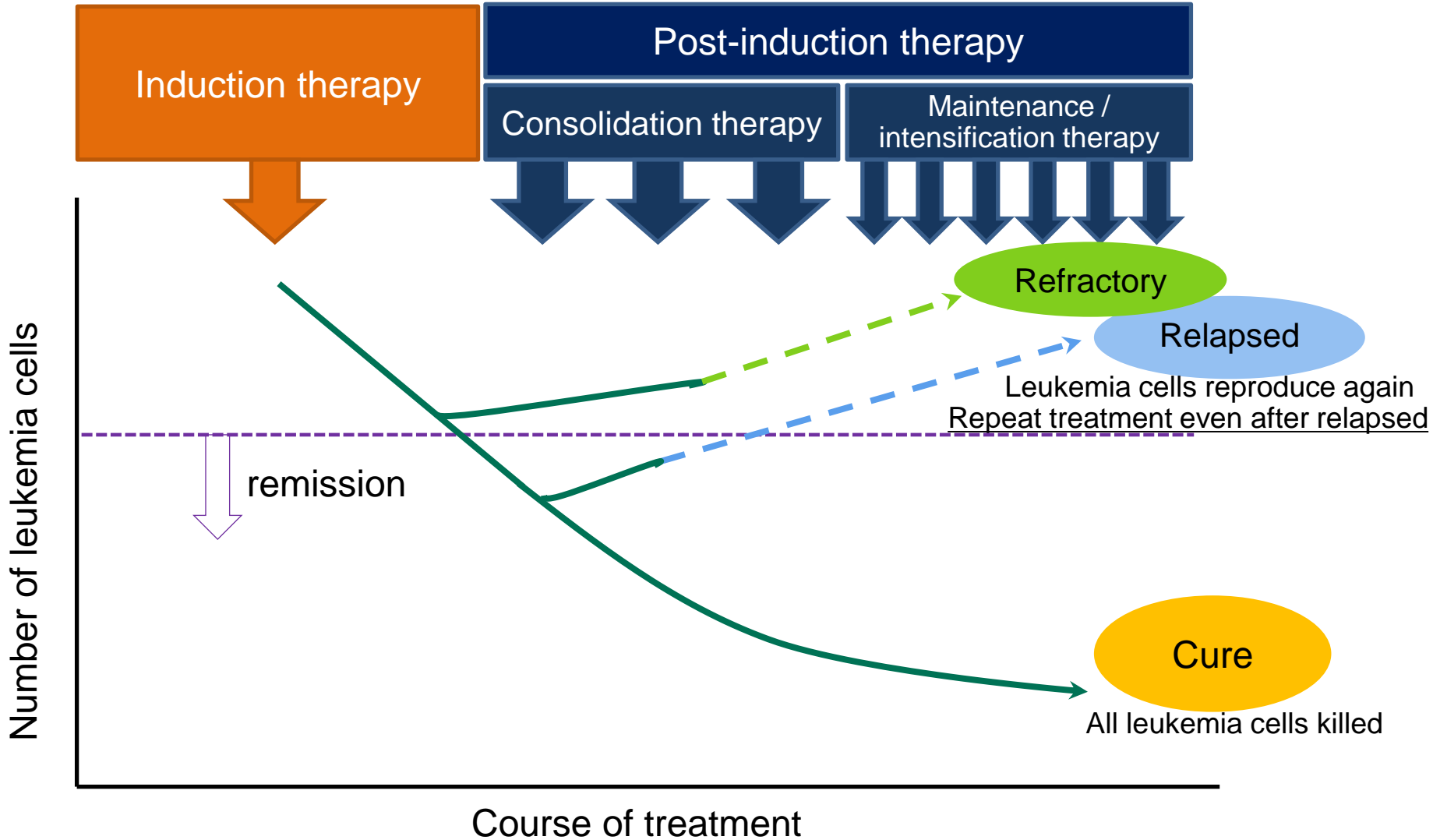
- **Clinical studies of ACM with newly diagnosed non-favorable risk AML (6 studies, 256 total patients)**

Type of Clinical study	CR rate
Phase 1 and pharmacokinetic study	50 %
Phase 1 and pharmacokinetic study	40 %
Phase 2 study	75 %
Phase 2 study	67 %
Phase 2 study	62 %
Phase 2 study	74 %
Phase 2 study	70 %
<b>Total</b>	<b>68 %</b>

- **Clinical studies of ACM with relapsed or refractory ATM (4 studies, 149 total patients)**

Type of Clinical study	CR rate
Phase 1 and pharmacokinetic study	18 %
Phase 1 and pharmacokinetic study	39 %
Phase 2 study	43 %
Phase 2 study	28 %
<b>Total</b>	<b>36 %</b>

# AML Treatment Methods



# Disclaimer Regarding Forward-looking Statements

The statements made in this presentation material are forward looking statements based on management's assumptions and beliefs in light of information available up to the day of announcement, and involve both known and unknown risks and uncertainties.

Actual financial results may differ materially from those presented in this document, being dependent on a number of factors.

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