Abstract #CT102

Phase 1b Safety, Preliminary Anti-Leukemic Activity and Biomarker Analyses of the Polo-like Kinase 1 (PLK1) Inhibitor, Onvansertib, in Combination with Low-Dose Cytarabine or Decitabine in Patients with Relapsed/Refractory Acute Myeloid Leukemia

Amer Zeidan, MBBS, MHS[1]; Alexander Spira, MD[2]; Pamela Becker, MD[3]; Prapti Patel, MD[4]; Gary Schiller, MD[5]; Michaela Tsai, MD[6]; Tara Lin, MD[7]; Eunice Wang, MD[8]; Maya Ridinger, PhD[9]; Peter Croucher, PhD[9]; Sandra Silberman, MD, PhD[10]; Mark Erlander, PhD[9]; Jorge Cortes, MD[11]

[1]Yale University Hospital, New Haven, CT; [2]Virginia Cancer Specialists Research Institute, Fairfax, VA; [3]Seattle Cancer Care Alliance, Seattle, WA; [4]University of Texas Southwestern, Dallas, TX; [5]Division of Hematology-Oncology, David Geffen School of Medicine, Los Angeles, CA; [6]Minnesota Oncology, Minneapolis, MN; [7]University of Kansas Cancer Center, Kansas, KS; [8]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [9]Trovagene, Inc., San Diego, CA; [10]SLS Oncology LLC, Durham, NC; [11]MD Anderson Cancer Center, Houston, TX

trovagene ONCOLOGY

Background

Polo-like Kinase 1 (PLK1):

- Serine/threonine kinase, master regulator of cell-cycle progression
- Inhibition of PLK1 causes mitotic arrest in prometaphase and subsequent cell death
- Over-expressed in numerous cancer types, including AML, and associated with poor prognosis
- Onvansertib is a 3rd generation PLK1 inhibitor, with increased specificity, potency and pharmacologic properties compared to prior PLK inhibitors

Onvansertib (also known as PCM-075 and NMS-1286937):

- Orally-bioavailable, highly-selective PLK1 inhibitor
- ~24-hour half-life
- Induces G2/M arrest and apoptosis in cancer cells, including leukemic cells
- Inhibits tumor growth alone and in combination with cytarabine in AML mouse models
- Safe and well tolerated (Phase 1 safety trial in patients with solid tumors)[1]
- Currently in clinical development in three indications:
  - Acute Myeloid Leukemia (AML) – NCT03303339
  - Metastatic Castration-Resistant Prostate Cancer (mCRPC) – NCT03414034
  - Metastatic Colorectal Cancer (mCRC) – NCT03829410

Patient Demographics

Patients (N=26)	N (%) or Median [range]
Age (years)	68 [33-88]
Male gender	20 (77%)
ECOG	1 [0-2]
Previous treatments	1 [0-3]
Cytogenetic Risk Status (N=26)	**N (%)**
Favorable	1 (4%)
Intermediate	3 (12%)
Adverse	19 (73%)
Unknown	3 (12%)

[4]Molecular subgroups (N=26)	N (%)
Mutated chromatin/RNA splicing genes	14 (54%)
TP53 mutations/aneuploidy	8 (31%)
CEBPA Biallelic	1 (4%)
Unknown	3 (12%)

Treatment Summary

	N or Median [range]
Number of patients treated	26
Number of DLTs	0
Number of patients completing ≥1 cycle	24
Number of cycles	2 [1-10]

Safety

- Primary endpoint of Phase 1b
- No trial therapy-related deaths
- No SAEs were considered related to study drug treatment
- Non-hematological AEs possibly related to Onvansertib were G1 nausea (3pts), G1 diarrhea (4pts), G1 headache (3pts)
- All non-hematological AEs reported are listed in the table below

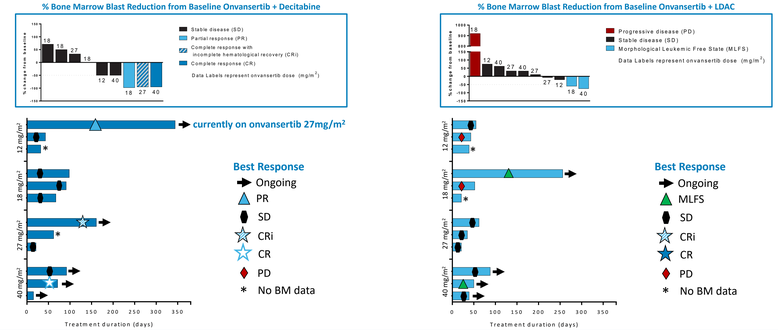
All Non-Hematological Adverse Events Reported in ≥ 10% Patients (N=26)

	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Fatigue	3	5			8
Constipation	6				6
Nausea	3	3			6
Dyspnea	2	2	1		5
Cough	3	1			4
Diarrhea	4				4
Epistaxis	3	1			4
Febrile Neutropenia			4*		4
Asthenia	2	1			3
Decreased appetite	1	2			3
Dizziness	3				3
Headache	3				3
Nasal Congestion	2	1			3
Lung infection			3*		3

*Reported SAEs, but not related to study drug, onvansertib

Anti-Leukemic Activity

- Of 26 patients evaluable for safety, 19 patients had a bone marrow biopsy to assess anti-leukemic activity based on criteria from the 2017 ELN recommendations[2]
- Anti-leukemic activity was observed in 17 of the 19 evaluable patients: CR (1), CRi (1), MLF (2), PR (1), SD (12)



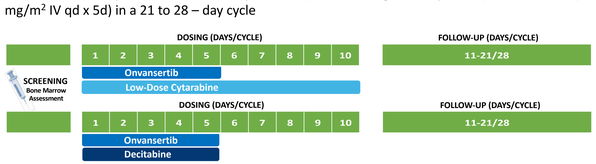
Phase 1b/2 Trial Design and Objectives

Phase 1b/2 Trial of Onvansertib in Combination with Either Low-Dose Cytarabine or Decitabine in Patients with Relapsed/Refractory Acute Myeloid Leukemia

Study design:

- Dosing schedule:

Onvansertib x 5 days + either low-dose Cytarabine (LDAC – 20 mg/m² SC qd x 10d) or Decitabine (20 mg/m² IV qd x 5d) in a 21 to 28 – day cycle



- Dose escalation in Phase 1b (3+3 design) with expansion cohort at MTD or RP2D for Phase 2
  - 50% incremental dose increase in successive cohorts of 3 patients
  - Dose limiting toxicities (DLTs) evaluated during the 1st cycle

Arm A: Onvansertib + LDAC	Completed 12 mg/m²	Completed 18 mg/m²	Completed 27 mg/m²	Completed 40 mg/m²	Enrolling 60 mg/m²
Arm B: Onvansertib + Decitabine	Completed 12 mg/m²	Completed 18 mg/m²	Completed 27 mg/m²	Completed 40mg/m²	Enrolling 60mg/m²

Study Objectives:

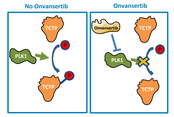
- Primary objectives:
  - Phase 1b: Assess safety, define dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) and evaluate preliminary anti-leukemic activity
  - Phase 2: Assess safety, tolerability and anti-leukemic activity at the RP2D
- Secondary objectives (Phase 1b/2):
  - Assess the incidence and severity of adverse events
  - Analyze pharmacokinetics
- Exploratory objectives (Phase 1b/2):
  - Evaluate predictive biomarkers associated with response to treatment
  - Assess PLK1 inhibition in circulating leukemic cells by measuring pTCTP levels (PLK1 substrate)

Key Eligibility Criteria:

- Patients with relapsed/refractory AML who have received ≤3 prior treatment regimens
- Treatment-related AML or APL are excluded
- ECOG performance status ≤2

Biomarker Strategy and Analyses

PLK1 inhibition can be monitored in patients through pTCTP status



pTCTP as a marker of PLK1 activity:

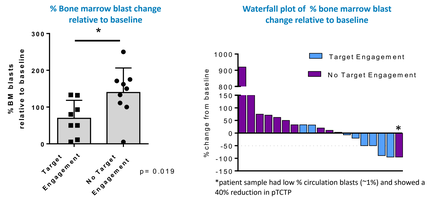
- PLK1 phosphorylates the translational control tumor protein (TCTP) on serine 46[3]
- pTCTP was identified as a specific marker for PLK1 activity in vivo in preclinical models[3]

Assessment of PLK1 activity in patients through pTCTP:

- Blood samples were collected from patients enrolled in the trial on day 1 before (0h) and 3h after (3h) treatment
- pTCTP and TCTP were assessed by Western-Blot and % pTCTP (pTCTP/TCTP) was quantified
- 8 out of the 22 evaluable patients (36%) showed a decrease of ≥50% in % pTCTP at 3h post-dose compared to pre-dose
- PLK1 inhibition was not dependent on onvansertib dose, PK, nor single-agent effects of LDAC or decitabine regarding % blasts

PLK1 inhibition by onvansertib (target engagement) is correlated with higher response to treatment

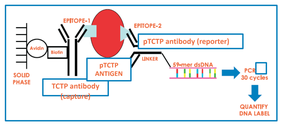
- Patients with target-engagement had a significantly greater decrease in BM blasts compared to patients with no target-engagement
- Four out of the 8 patients with target-engagement had a decrease in BM blasts ≥50%



Biomarker strategy to identify patients most likely to respond to onvansertib

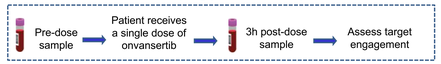
Development of a second-generation in-vitro assay to assess target engagement

- Immuno-PCR based technology: designed to identify low-abundance proteins
- Highly sensitive, specific and quantitative method



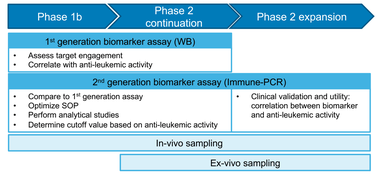
In-vivo and ex-vivo sampling to test target-engagement in patients

In-vivo sampling (current method)

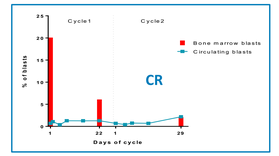


Ex-vivo sampling (in development)

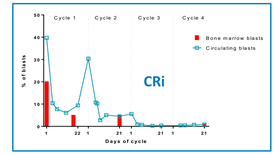
Biomarker assay clinical development and validation plan



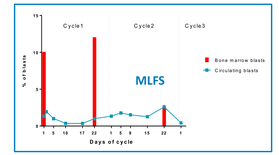
Patient Cases



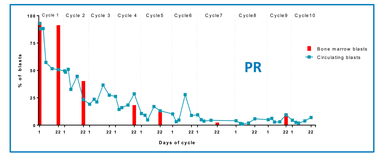
- 76 year-old male, diagnosed with AML in 2015; treated with induction chemotherapy; relapsed in December 2018; entered trial in January 2019 on onvansertib 40mg/m²+ decitabine
- Patient reached CR as of the end of cycle 2 and is currently in cycle 3
- % bone marrow blasts decreased from 22% (at screening) to less than 5% at the end of cycle 2; circulating blasts remained low during the entire treatment (0.2 to 2.2%)



- 68 year-old female with MDS progressed after 6 cycles of azacytidine; diagnosed with AML in September 2018; entered trial in October 2018 on onvansertib 27mg/m² + decitabine
- Onvansertib dose was reduced to 18mg/m² at cycle 5
- Patient reached CRi at then end of cycle 4 and is in cycle 6
- % bone marrow blasts decreased from 20% (at screening) to 1% (cycle 4) and circulating blasts decreased from 43% (C1D1) to 1% (C4D21)



- 83 year-old male, diagnosed with AML in January 2017; treated with induction chemotherapy and decitabine; relapsed in November 2018; entered trial in December 2018 on onvansertib 40mg/m² + LDAC
- Patient reached MLFS as of the end of cycle 2 and is currently on cycle 4 of treatment
- % bone marrow blasts decreased from 9% (at screening) to 5% (cycle 2) and circulating blasts remained low during the entire treatment (0.4 to 2.6%)



- 75 year-old male, diagnosed with AML in 2009; treated with induction chemotherapy; relapsed March 2018; entered trial April 2018 on onvansertib 12mg/m² + decitabine
- Onvansertib dose increased to 18mg/m² cycle 6; 27mg/m² cycle 11
- Patient reached PR at end of cycle 4 and is currently in cycle 11
- % bone marrow blasts decreased from 94% (at screening) to 10% (cycle 10) and circulating blasts decreased from 92% (C1D1) to 7% (C10D22)

Conclusions

- Anti-leukemic activity was observed in 17 of the 19 evaluable patients: CR (1), CRi (1), MLF (2), PR (1), SD (12)
- The greatest anti-leukemic activity has been observed in the onvansertib + decitabine arm with 2 of 4 (50%) evaluable patients from the two highest dose levels (27mg/m² and 40mg/m²) achieving a complete response (CR and CRi)
- Early indication of safety, tolerability and durability of response has been demonstrated by 16 of 24 patients having completed ≥2 cycles and 2 patients having been on treatment for 344 days (PR) and 161 days (CRi), respectively
- Positive biomarker status (pTCTP) to-date has been observed in 8 out of 22 patients (36%) and has been associated with a significantly higher response to treatment (p = 0.019)
- Preliminary efficacy data is encouraging, given the previously demonstrated low response rates (CR) of 7.9% (LDAC) and 15.7% (decitabine) in the treatment-naïve, elderly patient population that is ineligible for induction therapy[5]

Contact:
Mark Erlander, PhD - (Trovagene, Inc.)
merlander@trovagene.com

REFERENCES:
[1] Weiss et al., Invest New Drugs, 2017
[2] Dohner et al., Blood, 2017
[3] Cucchi et al., Anticancer Res., 2010
[4] Papaemmanuil et al,. N Engl J Med., 2016
[5] Kantarjian et al., JCO, 2012