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

Abstract #112590

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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
- A pan-PLK inhibitor, volasertib in combination with LDAC, improved survival in a randomized Phase 2 trial in AML
- A 3rd generation PLK1 inhibitor, with increased specificity, potency and pharmacologic properties was needed to optimize features that hampered future development of volasertib

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 dose escalation trial in patients with solid tumors)[1]
- Currently in clinical trials for Acute Myeloid Leukemia (AML) – NCT03303339 and metastatic Castration-Resistant Prostate Cancer (mCRPC) – NCT03414034

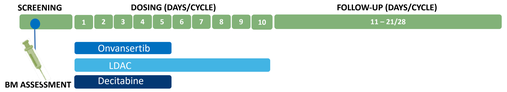
Phase 1b/2 Trial Design and Objectives

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

Study design:

- Dosing schedule:

Onvansertib x 5 days + either low-dose Cytarabine (LDAC – 20 mg/m^2 SC qd x 10d) or Decitabine (20 mg/m^2 IV qd x 5d) over 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

Study Objectives:

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

Key Eligibility Criteria:

- Patients with R/R AML who have received ≤3 (Phase 1) or ≤1 (Phase 2) previous therapies or treatment-naïve patients ineligible for induction therapy (Phase 1b and 2)
- Treatment-related AML or APL are excluded
- ECOG performance status ≤2

Patient Demographics

Patients (N=19)	N (%) or Median [range]
Age (years)	68 [33-88]
Male gender	14 (74%)
ECOG	1 [0-2]
Previous treatments	1 [0-2]
Cytogenetic Risk Status (N=19)	**N (%)**
Favorable	0 (0%)
Intermediate	4 (21%)
Adverse	14 (74%)
Unknown	1 (5%)

Mutation	Patients (N=17*)	Mutation	Patients (N=17*)
TP53	6	GATA2	1
ASXL1	4	TET2	1
SRSF2	3	SF3B1	1
RUNX1	2	PHF6	1
FLT3	2	CALR	1
NRAS	2	KRAS	1
STAG2	1	U2AF1	1

*Data of 2 patients are pending

Safety

- Primary endpoint of Phase 1b
- No trial therapy-related deaths
- No SAEs were considered related to study drug treatment
- AEs possibly related to Onvansertib were Grade 1 nausea in 4 patients
- All AEs reported are listed in the table below

All Non-Hematological Adverse Events Reported in ≥ 10% Patients (N=19)

	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Nausea	3	2			5
Constipation	4				4
Fatigue	1	3			4
Dizziness	3				3
Dyspnea	1	1	1		3
Febrile Neutropenia			3*		3
Lung infection			3*		3
ALK Phos. (ALP) Decrease	2				2
Edema	1		1*		2
Diarrhea	2				2
Headache	2				2
Hyponatremia			2		2
Nasal Congestion	2				2

*These were reported SAEs, but not related to study drug

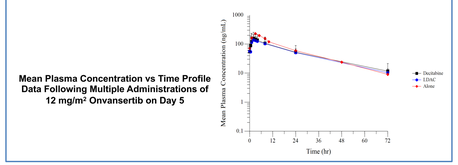
Treatment Summary

	N or Median [range]
Number of patients treated	19
Number of DLTs	0
Number of patients completing ≥1 cycle	15
Number of cycles	2 [1-7]

Pharmacokinetics

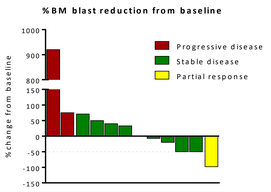
- The exposure (AUC) following Onvansertib administration was comparable in combination with either LDAC or Decitabine
- AUC on day 5 showed an accumulation of almost 2-fold between day 1 and 5
- The T_{max} values ranged between 2.3 and 3h for both groups
- PK data (table below) were very similar to the previous data obtained in a single agent Onvansertib Phase 1 trial in solid tumors[1]

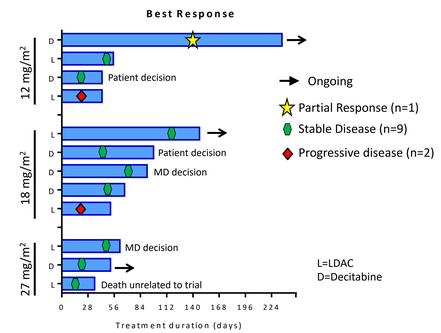
Dose (mg/m^2)	Combination Treatment	Day	# of Patients	T_{max}(h)	C_{max}(nM)	$AUC_{(0-24)}$ (nM.h)	$T_{1/2}$(h)
12	LDAC	1	3	2.33 ± 1.53	92.7 ± 5.28	1260 ± 270	NA
		5	3	2 ± 1	153 ± 83.5	2150 ± 833	32.2 ± 20.7
	Decitabine	1	4	3.25 ± 0.957	81.4 ± 15.8	1170 ± 286	NA
		5	4	2.5 ± 0.577	163 ± 89.7	2270 ± 1440	26.4 ± 16
18	LDAC	1	3	3 ± 1.73	71.4 ± 19.1	835 ± 201	NA
		5	3	3 ± 1	109 ± 38.6	1730 ± 847	32.6 ± 17.9
	Decitabine	1	3	2.67 ± 1.53	156 ± 106	2240 ± 1310	NA
		5	3	2.67 ± 0.577	230 ± 129	3380 ± 1740	20.9 ± 6.65
27	LDAC	1	2	2.5	367	2960	NA
		5	2	2.5	388	4590	34.4



Anti-Leukemic Activity

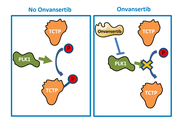
- Phase 1b objective is to assess the safety and tolerability of Onvansertib in combination with standard-of-care chemotherapy
- Of the 19 patients evaluable for safety, 12 patients had an evaluable bone marrow biopsy to assess anti-leukemic activity based on criteria from the 2017 ELN recommendations[2]
- Of the 12 patients evaluated for preliminary anti-leukemic activity, 1 patient had a PR, 9 patients had SD and 2 patients had PD





Biomarker Strategy and Analyses

PLK1 inhibition can be monitored in patients through pTCTP status

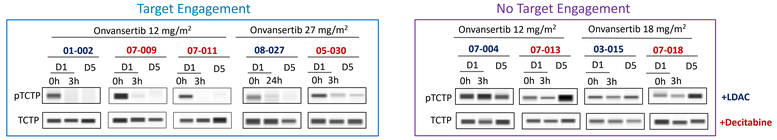


pTCTP as a marker of PLK1 activity:

- 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 of treatment (pre-dose and 3h post-dose) and on day 5 (4 doses of Onvansertib)
- pTCTP and TCTP were assessed by Western-Blot and %pTCTP (pTCTP/TCTP) was quantified
- 5 out of the 15 patients analyzed showed a decrease in %pTCTP at 3h post-dose compared to pre-dose (of at least 50%), and this decrease was sustained on day 5 of treatment
- PLK1 inhibition was not dependent on Onvansertib dose or PK, neither on the combination treatment



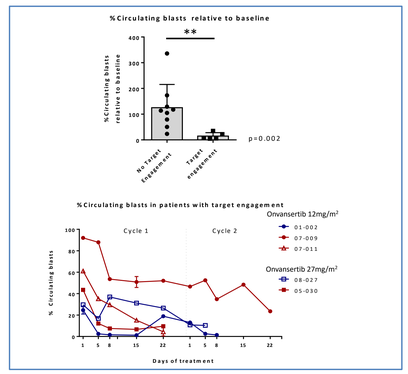
PLK1 inhibition by Onvansertib (Target Engagement) is correlated with higher response to treatment

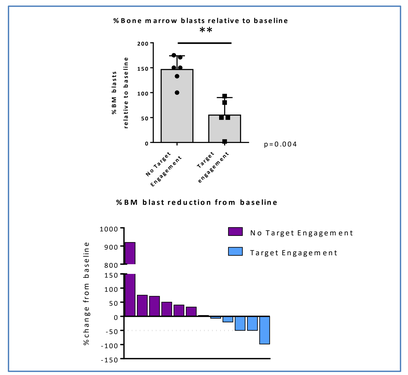
Methods:

- Blood samples collected on day 1 (pre-dose), 5, 8, 15, 22 of cycle and % of circulating blasts assessed by flow cytometry
- Bone marrow samples obtained at baseline and at end of cycles 1, 2, 4 and 7 and % blasts assessed by IHC by clinical site

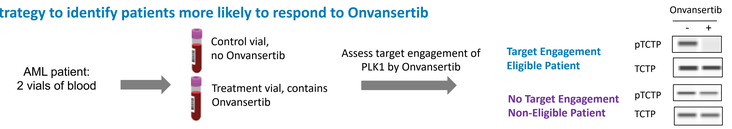
Results:

- The 5 patients with target engagement showed a decrease in circulating blasts of ≥50% on the last time point recorded compared to baseline
- 3 out of 5 patients with target engagement had a decrease of ≥ 50% in their last BM biopsy compared to baseline
- Decreases in circulating and bone marrow blasts were significantly higher in patients with target engagement compared to patients without target engagement





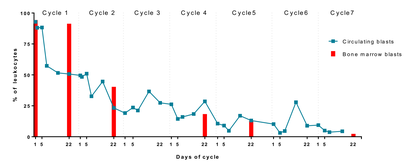
Strategy to identify patients more likely to respond to Onvansertib



Patient Case

Patient 07-009:

- 75 year-old male, diagnosed with AML in 2009 and treated with induction chemotherapy; relapsed in March 2018 and entered trial in April 2018 on Onvansertib + Decitabine
- Onvansertib entry dose of 12 mg/m^2 and was increased to 18 mg/m^2 at cycle 6
- Patient reached PR as of the end of cycle 4 / beginning of cycle 5 and is currently on cycle 8 of treatment
- % bone marrow blast decreased from 94% (at screening) to 2% (cycle 7) and circulating blasts decreased from 92% (C1D1) to 4% (C7D15)



Conclusions and Perspective

- Two dose-levels of Onvansertib (12 mg/m^2 and 18 mg/m^2) were completed, with 13 patients evaluable for safety
- 6 patients have been enrolled at the 27 mg/m^2 dose-level, 3 have finished cycle 1 without experiencing DLTs
- No drug-related deaths or SAEs have been reported to-date
- Preliminary efficacy in the evaluable population showed over 80% patient benefit (CR + PR + SD): 1 patient with PR, 9 patients with SD
- PLK1 inhibition by treatment was observed in 5 out of 15 patients and was associated with a higher response to treatment, measured by decreases in circulating and bone marrow blasts
- Implementation of a pTCTP biomarker strategy going forward will increase the opportunity to identify patients most likely to respond to Onvansertib

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REFERENCES:
[1] Weiss et al., Invest New Drugs, 2017
[2] Dohner et al., Blood, 2017
[3] Cucchi et al., Anticancer Res., 2010