Safety, Efficacy and Biomarker Analysis of a Phase 1 Study of Onvansertib, a Polo-like Kinase 1 (PLK1) Inhibitor, in Combination with Low-Dose Cytarabine or Decitabine in Patients with Relapsed/Refractory Acute Myeloid Leukemia

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Disclosures

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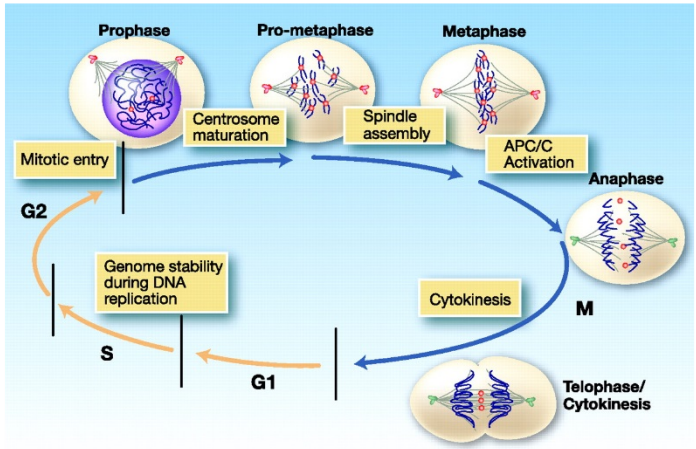
The Polo-like Kinase 1 (PLK1), a Target for AML

- **PLK1**
  - Serine/threonine kinase
  - Master regulator of the mitotic checkpoint and cell division[1]
  - Overexpressed in solid tumors and hematological malignancies, including AML[1]



- **PLK1 Inhibition**
  - Induces G2/M arrest and subsequent apoptosis
  - Inhibits tumor growth in AML mouse models[2]
  - Preferentially blocks proliferation of leukemic cells rather than normal hematopoietic progenitors[3]
- **Earlier generation PLK inhibitors in the clinic**
  - Volasertib: pan-PLK ATP-competitor inhibitor with a ~5 days half-life
  - Phase 2 randomized study of volasertib + LDAC showed a significant increase in overall survival in comparison to LDAC alone[4]. However, the Phase 3 study was negative[5].

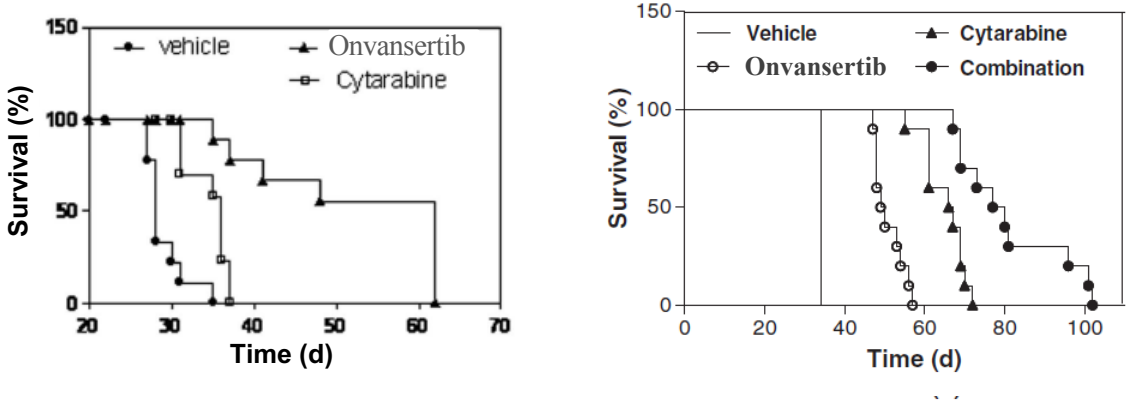
[1] Degenhardt and Lampkin, Clin Cancer Res. 2010 Jan 15;16(2):384–9; [2] Goroshchuk et al, Oncogene. 2019 Jan;38(1):1–16; [3]Renner et al, Blood. 2009 Jul 16;114(3):659–62; [4]Döhner et al, Blood 2014 Aug 28;124(9):1426-33; [5]Döhner et al, 21st Congress of EHA, Volume: Haematologica 101(suppl.1): 185-186, abstract S501

Onvansertib, a Highly Selective PLK1 Inhibitor with Anti-Tumor Activity in AML Preclinical Models

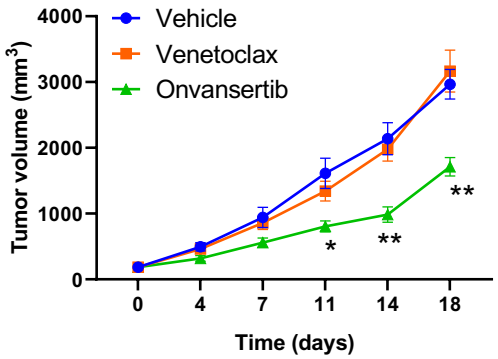
- **Onvansertib**
  - PLK1-selective ATP-competitive inhibitor
  - Orally-bioavailable
  - ~24-hour half-life
- Onvansertib in AML preclinical models
  - Inhibits cell line proliferation at nanomolar concentrations
  - Inhibits tumor growth in xenograft models as a single agent and in combination with cytarabine[6]
  - Inhibits cell proliferation and tumor growth in venetoclax-resistant models

[6] Valsasina et al., Mol Cancer Ther. 2012 Apr;11(4):1006-16

Survival in AML Disseminated Models



Tumor Growth in a Venetoclax-Resistant Subcutaneous Model (OCI-AML3)



* p<0.03, ** p<0.002

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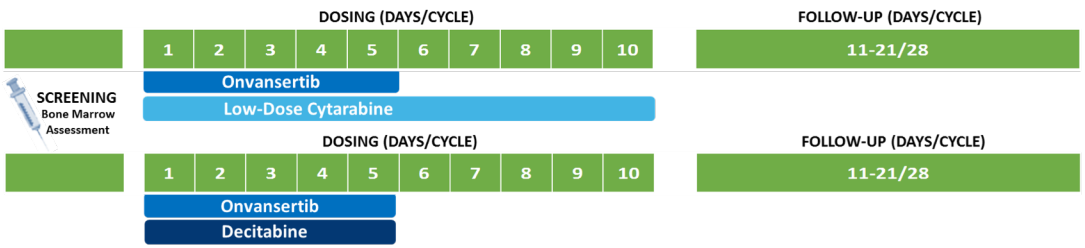
Onvansertib in AML: a Multicenter Phase 1b/2 Study (NCT03303339)

Main eligibility criteria

- Relapsed and refractory AML patients who have received ≤3 prior treatment regimens
- Treatment-related AML or APL excluded
- ECOG ≤2

Dosing schedule

- Onvansertib for 5 days + decitabine 20 mg/m^2 IV for 5 days OR low dose cytarabine (LDAC) 20 mg/m^2 SC for 10days
- 21-28-day cycles



Dose escalation (3 + 3 design)

- 50% incremental dose increase in successive cohorts of 3 patients
- Dose limiting toxicities (DLTs) evaluated during the 1st cycle

Primary and secondary objectives

- Assess safety (incidence and severity of AEs)
- Define dose-limiting toxicities (DLTs)
- Define MTD or RP2D
- Evaluate preliminary anti-leukemic activity

Exploratory objectives

- Assess PLK1 inhibition (target engagement) by measuring changes in the PLK1 substrate pTCTP
- Evaluate predictive biomarkers associated with response to treatment

Phase 1b Patient Characteristics and Treatment Summary

Data Cutoff: October 31st, 2019

Patient Baseline Characteristics	Value: n Median (range) or n (%)
Patients	40
Age	**68 (33-88)**
Male gender	28 (70)
ECOG performance status	1 (0-2)
Prior AML therapies	1 (0-3)
0	5 (13)
1	20 (50)
2+	15 (38)
Prior cytarabine treatment	24 (60)
Prior decitabine treatment	10 (25)
Cytogenetic risk	
Favorable	3 (8)
Intermediate	10 (25)
Adverse	**23 (58)**
Unknown	4 (10)
Bone marrow blasts	26 (5-95)

Treatment Summary	Decitabine	LDAC
Patients - n	23	17
First patient enrolled	April 2018	Feb 2018
Last patient enrolled	Aug 2019	Jun 2019
Cycles, median (range)	2 (0-18)	2 (0-8)
Time on study, median days (range)	63 (15-574)	44 (11-318)
Onvansertib maximum dose - mg/m^2	90	60
Patients at maximum dose - n	6	3
Number of DLTs - n	2	0
MTD or RP2D - mg/m^2	60	60

Mutation Profiling (n=40)

ASXL1	TP53	SRSF2	NRAS	NPM1	DNMT3A	FLT3 ITD	SF3B1	IDH2	RUNX1
20%	20%	18%	18%	10%	10%	8%	8%	8%	5%
SETBP1	**U2AF1**	**FLT3 TKD**	**CEBPA**	**KRAS**	**CBL**	**CSF3R**	**PHF6**	**GATA2**	**TET2**
5%	5%	5%	3%	3%	3%	3%	3%	3%	3%

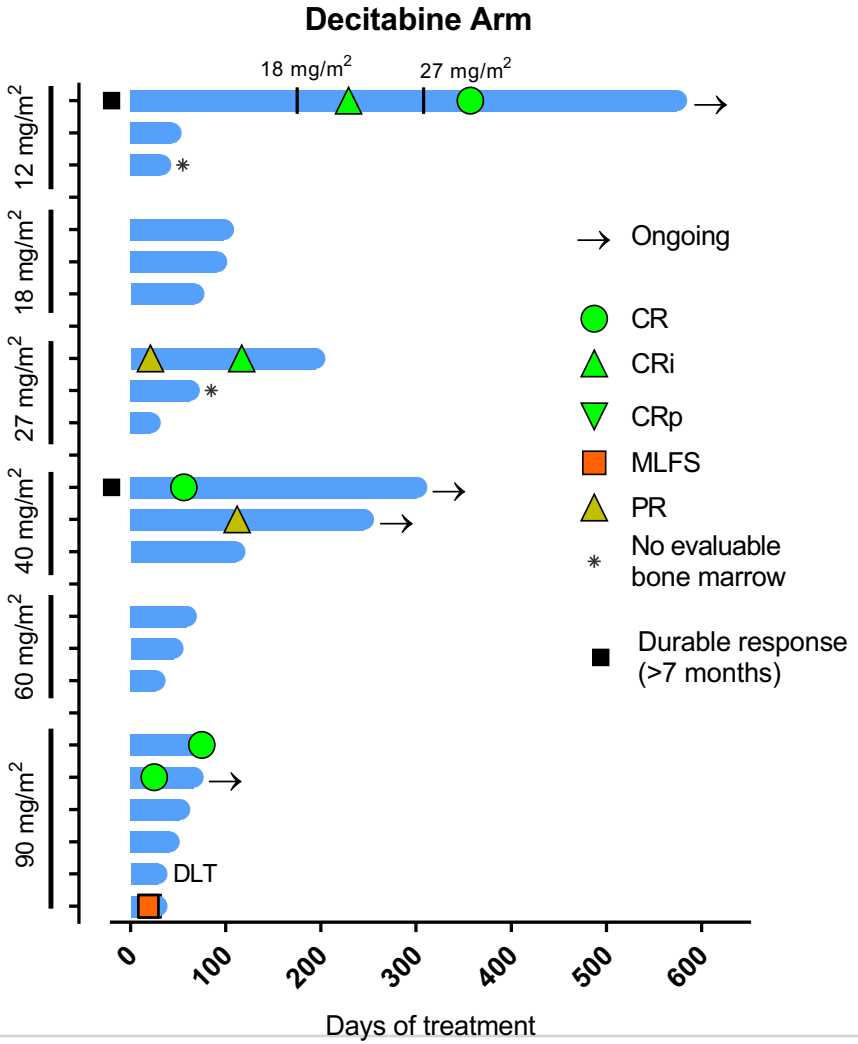
Safety Summary
Patients Treated with at Least 1 Dose (n=40)
Data Cutoff: October 31st , 2019

- Treatment was well tolerated through the 5 first dose levels: 12 – 60 mg/m^2
- 2 of the 6 patients treated with onvansertib 90 mg/m^2 + decitabine experienced a DLT: G3 mucositis and G4 skin lesion
- Subsequently, the MTD was established at 60 mg/m^2
- Grade 3/4 AEs possibly related to onvansertib were primarily on-target hematological events
- G3 stomatitis was the only non-hematological G3/G4 AE possibly related to onvansertib reported in more than 1 patient (1 at 60 mg/m^2 and 2 at 90 mg/m^2)
- 9 of the 71 SAEs (13%) were considered as possibly related to onvansertib and occurred at the higher dose levels: 40 mg/m^2 (1), 60 mg/m^2 (1) and 90 mg/m^2 (7)
- Five deaths occurred during study, however none were attributed to study treatment

Adverse Event	Grade 1-2	Grade 3-4	Total (%)
Anemia	1	14	15 (37.5)
Fatigue	14		14 (35)
Febrile neutropenia		12	12 (30)
Nausea/vomiting	12		12 (30)
Thrombocytopenia	2	10	12 (30)
Dyspnea	8	2	10 (25)
Neutropenia		10	10 (25)
Rash/Pruritus	9		9 (22.5)
Stomatitis	4	5	9 (22.5)
Diarrhea	8		8 (20)
Edema	6	2	8 (20)
Constipation	6		6 (15)
Cough	6		6 (15)
Decreased appetite	6		6 (15)
Epistaxis	6		6 (15)
Dizziness	5		5 (12.5)
Pyrexia	5		5 (12.5)
WBC decrease		5	5 (12.5)
Blood bilirubin increased	3	1	4 (10)
Headache	4		4 (10)
Lung infection		4	4 (10)
Oropharyngeal pain	4		4 (10)

Preliminary Efficacy
Patients Treated with ≥ 1 Cycle (n=36)
Data Cutoff: October 31st, 2019

- 6 (17%) patients had a complete response (CR, CRi); 9 (25%) had an ORR (CR, CRi, MLFS, PR) across LDAC and decitabine arms and doses
- At the 4 higher dose levels (27 to 90 mg/m^2), CR/CRi was observed in:
  - 5 (31%) of the 16 patients in the decitabine Arm
  - 1 (11%) of the 9 patients in the LDAC Arm
- Median time to achieve CR/CRi was 4 cycles (range 1-7)
- Median duration of response was 5 months (range 0-11.5)
- 4 of the 6 patients remain on treatment and in remission
  - Duration of CR/CRi is respectively: 1.5, 7, 8 and 11.5 months
- 2 of the 6 responders discontinued treatment:
  - 1 patient proceeded to transplant following CR
  - 1 patient progressed 2.5 months following CRi



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Characteristics of Responders

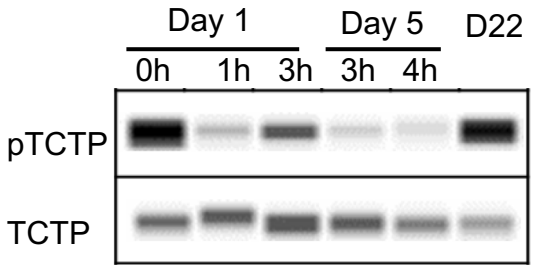
- Elderly population: median age 75 years (51– 83)
- Treatment naïve (but treated for prior MDS), relapsed and refractory patients:
  - 2 patients were treatment naïve for AML, but had received azacitidine for MDS
  - 4 patients had prior induction therapy (3 relapsed, 1 refractory)
- No specific mutation or karyotype was found to be associated with response to treatment
  - Different cytogenetic risk profiles: favorable (1), intermediate (2), adverse (2), unknown (1)
  - Mutations:

NRAS	SRSF2	ASXL1	DNMT3	NMP1	SF3B1	FLT3 TKD	FLT-ITD	IDH2
2	2	1	1	1	1	1	1	1

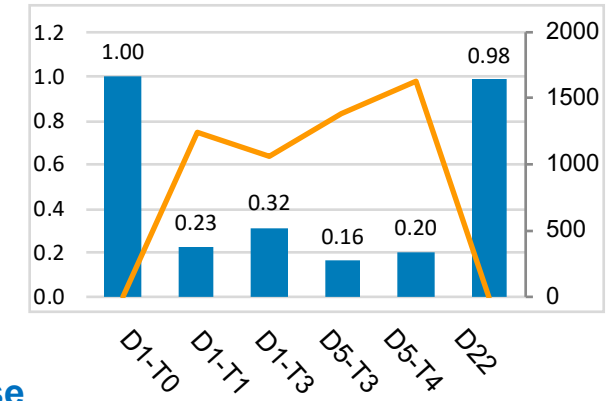
- Response was observed:
  - At a wide range of onvansertib doses: 27 mg/m^2 (2), 40 mg/m^2 (2), 90 mg/m^2 (2)
  - Primarily in combination with decitabine (n=5 in decitabine Arm vs n=1 in LDAC Arm)

Onvansertib Inhibits Phosphorylation of the PLK1 Target TCTP in a Plasma Inhibitory Activity Assay

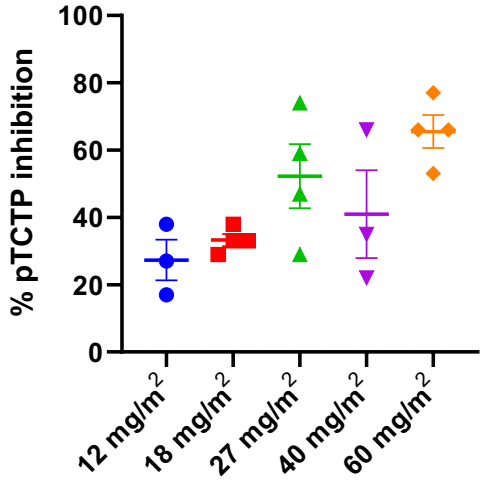
- The translational controlled tumor protein, TCTP is a direct target of PLK1[6,7]
- Plasma Inhibitory Activity (PIA) assay: an AML cell line was incubated with patient plasma collected pre- and post onvansertib treatment and changes in phosphorylated TCTP were assessed by Western-Blot
- pTCTP was downregulated by on-treatment plasma (Days 1 and 5), but not by plasma with undetectable onvansertib level (Day 22)
- pTCTP inhibition at post-dose (day 1) relative to pre-dose was observed for all doses
- Greater pTCTP inhibition was positively correlated with increasing dose levels



pTCTP/TCTP Relative to Day 1 Pre-Dose



pTCTP Inhibition at Post-Dose (Day 1) Relative to Pre-Dose



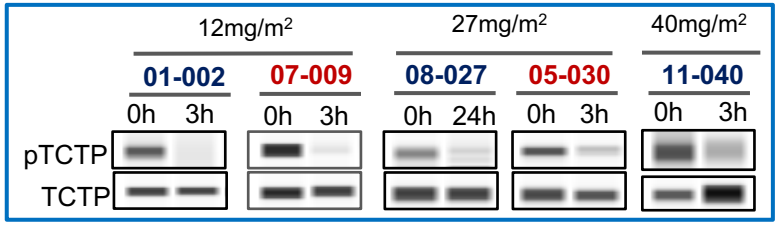
Samples from 3 to 4 patients were tested in each dose level

[6] Valsasina et al., Mol Cancer Ther. 2012 Apr;11(4):1006-16
[7] Cucchi et al., Anticancer Res. 2010 Dec;30(12):4973-85

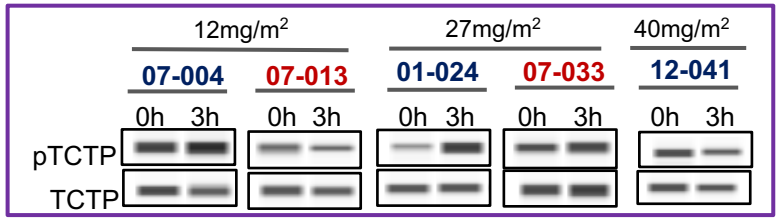
Target Engagement in Circulating Blasts is Associated with Response to Treatment with Onvansertib

- pTCTP/TCTP was assessed in PBMCs isolated from blood tubes collected on Day 1 at pre-dose and 3h post-dose
- Target engagement (TE) was evaluated in patients with ≥10% circulating blasts (n=24) and defined as a decrease of ≥50% in pTCTP/TCTP at 3h post-dose versus 0h
- 8 (33%) of the 24 evaluable patients showed target engagement
- TE was not dependent on onvansertib dose, pharmacokinetics or combination treatment (LDAC or decitabine)
- Among patients with at least 1 BM biopsy (n=17), TE was associated with higher response to treatment:
  - 67% TE patients (4/6) had a ≥20% decrease in blasts versus 18% in non-TE patients (1/11)
  - CR/CRi was achieved in 2 TE patients but in none of the non-TE patients

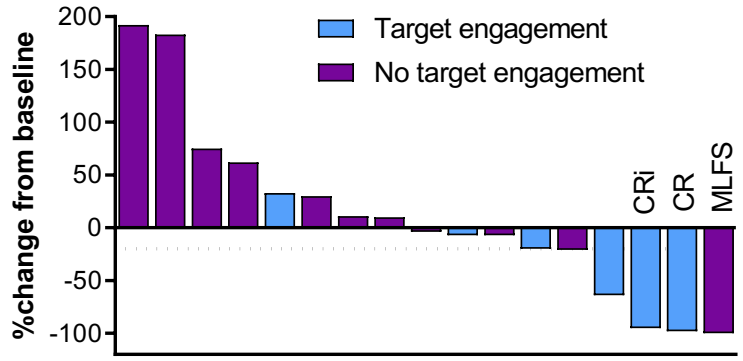
Target Engagement



No Target Engagement



Waterfall Plot of BM Blast Change From Baseline (Best Response)



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Conclusions
Phase 1b Study of Onvansertib in AML

- **Safety: onvansertib treatment was well tolerated**
  - MTD/RP2D was established at 60 mg/m^2 in both arms and no DLT was observed through this dose level
  - Onvansertib-related toxicities were primarily on-target hematological events, in accordance with its mechanism of action and prior Phase 1 clinical study
- **Efficacy: complete response (CR/CRi) was observed in 6 patients**
  - At a wide range of onvansertib doses: 27 mg/m^2 (2), 40 mg/m^2 (2), 90 mg/m^2 (2)
  - Primarily in combination with decitabine (n=5 in decitabine Arm vs n=1 in LDAC Arm)
  - CR/CRi rate was 31% (5/16) in patients treated with onvansertib 27-90 mg/m^2 in combination with decitabine
- **Pharmacodynamic and biomarker analysis:**
  - Onvansertib-plasma inhibitory activity was observed through all doses and positively correlated with increasing doses
  - Target engagement in circulating blasts was observed in a subset of patients and was associated with an increase in response to treatment as measured by decrease in BM blasts and rate of CR/CRi
- **Phase 2** has started enrolling and will include 32 patients to further assess the safety, efficacy, target engagement and correlation with response of onvansertib 60 mg/m^2 in combination with decitabine

Thank You!

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