Phase 1b/2 Study of Onvansertib, a PLK1 Inhibitor, in Combination with Decitabine in Patients with Relapsed or Refractory Acute Myeloid Leukemia

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Background

New Treatment Options are Needed for Patients with Relapsed or Refractory (R/R) Acute Myeloid Leukemia (AML)

- R/R AML patients have limited therapeutic options, especially in the absence of targetable mutations such as FLT3 or IDH1/2[1]
- Outcomes are dismal for R/R AML patients; median overall survival is <6 months[2]

Onvansertib, an Oral and Highly-Selective Polo-like kinase 1 (PLK1) Inhibitor, Represents a Promising New Targeted Therapy for R/R AML

- PLK1 is a serine/threonine kinase, a master regulator of mitosis and overexpressed in AML
- Onvansertib is a third-generation PLK1 inhibitor with a half-life of ~24 hours
- In AML preclinical models, onvansertib demonstrated potent anti-tumor activity as a single agent and in combinations, including venetoclax-resistant models[3,4]

Phase 1b/2 Trial Design and Objectives

Study Design

- **Study population**:
  - R/R AML with up to 3 prior lines of therapy (phase 1b) and 1 line of prior therapy (phase 2) or treatment-naïve patients ineligible for intensive therapy
  - Treatment-related AML or APL are excluded
- **Dosing schedule**: Onvansertib (starting dose 12 mg/m^2, days 1 through 5) + decitabine (20 mg/m^2 IV, days 1 through 5) in a 28-day cycle
- **Phase 1b** dose escalation (3+3 design) to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D)
  - 50% incremental dose increase in successive cohorts of 3 patients
  - Dose limiting toxicities (DLTs) evaluated during the 1st cycle
- **Phase 2** expansion at the RP2D of onvansertib

Study Objectives

- **Primary Objectives:**
  - Phase 1b: Assess safety to identify DLTs and determine the MTD or RP2D
  - Phase 2: Assess safety, tolerability and anti-leukemic activity at the RP2D
- **Secondary Objectives (Phase 1b/2):**
  - Analyze pharmacokinetics
- **Exploratory Objectives (Phase 1b/2):**
  - Evaluate predictive biomarkers associated with response to treatment
  - Assess target engagement in circulating leukemic cells

Patient Enrollment and Baseline Characteristics

Enrollment as of February 19, 2020

Phase 1b	Treated patients
12 mg/m^2	4
18 mg/m^2	3
27 mg/m^2	3
40 mg/m^2	4
60 mg/m^2	3
90 mg/m^2	6
Phase 2	**Treated patients**
60 mg/m^2	13

N (%) or median [range]	Phase 1b (n=23)	Phase 2 (n=13)
Age, years	66 [33-77]	73 [23-85]
Male gender	15 (65)	8 (62)
ECOG	1 [0-2]	1 [0-2]
Prior treatment		
0	4 (17)	0
1	13 (57)	13 (100)
2+	6 (26)	0
Cytogenetic Risk		
Favorable	1 (4)	1 (8)
Intermediate	9 (39)	6 (46)
Adverse	13 (57)	6 (46)

Safety

Phase 1b: RP2D was established at 60 mg/m^2

- Treatment was well tolerated through the first 5 dose-levels (12 – 60 mg/m^2)
- 2 of the 6 patients treated at 90 mg/m^2 had a DLT (G3 mucositis and G4 rash)

Phase 1b/2 safety analysis:

- Most frequent Grade 3-5 adverse events (AEs) were
  - Hematological AEs (neutropenia, thrombocytopenia, WBC decrease)
  - Febrile neutropenia
  - Skin toxicities (rash, stomatitis) mostly at higher onvansertib doses (60 and 90 mg/m^2)
- 4 patients discontinued treatment due to AEs: G3 mucositis (n=2), G3 rash (n=1), G4 rash (n=1)
- 59 SAEs were reported in 25 patients and 14 (24%) were considered as possibility related to onvansertib
- 5 deaths occurred while on treatment, all of which were related to AML or its complications (progressive disease, pneumonia, septic shock, infection, sepsis)

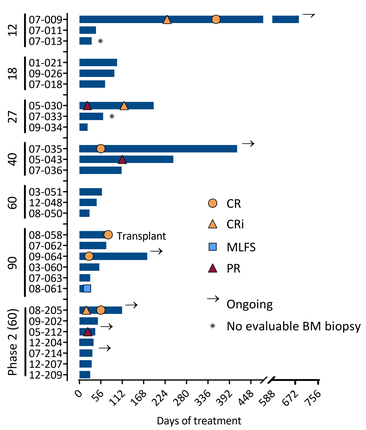
All-Causality Treatment-Related Adverse Events Reported in >10% patients (n=36)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All grades
Febrile neutropenia			13 (36)		1 (3)	14 (39)
Rash	4 (11)	3 (8)	5 (14)	1 (3)		13 (36)
Anaemia			11 (31)	1 (3)		12 (33)
Fatigue	3 (8)	6 (17)	1 (3)			10 (28)
Nausea	6 (17)	4 (11)				10 (28)
Stomatitis	1 (3)	2 (6)	6 (17)			9 (25)
Thrombocytopenia		2 (6)		7 (19)		9 (25)
Neutropenia			1 (3)	7 (19)		8 (22)
Cough	6 (17)	1 (3)				7 (19)
Diarrhoea	7 (19)					7 (19)
Epistaxis	5 (14)	2 (6)				7 (19)
Vomiting	4 (11)	3 (8)				7 (19)
Dyspnoea	2 (6)	3 (8)	1 (3)			6 (17)
Oedema peripheral	3 (8)	3 (8)				6 (17)
Oropharyngeal pain	5 (14)		1 (3)			6 (17)
Decreased appetite	2 (6)	2 (6)	1 (3)			5 (14)
Dizziness	3 (8)	2 (6)				5 (14)
Hypertension		4 (11)	1 (3)			5 (14)
Hypokalaemia	2 (6)	3 (8)				5 (14)
WBC decrease			1 (3)	4 (11)		5 (14)
Arthralgia		3 (8)	1 (3)			4 (11)
Blood creatinine increased	4 (11)					4 (11)
Constipation	3 (8)	1 (3)				4 (11)
Hypophosphataemia		3 (8)	1 (3)			4 (11)
Pruritus	1 (3)	3 (8)				4 (11)

Data are number of patients (%).
Patients with several occurrences of the same AE were counted only once by their worst grade

Anti-Leukemic Activity and Duration of Treatment

Clinical Course of Phase 1b/2 patients



Onvansertib doses (12- 90mg/m^2) and patient identifiers are indicated on graph. CR=complete remission, CRi=complete remission with incomplete hematopoietic count recovery, MLFS=morphological leukemia free-state, PR=partial response

Phase 1b: 21 patients completed 1 cycle of treatment

- 7 (33%) of patients achieved an objective response (CR, CRi, MLFS, PR)
- 5 (24%) of patients achieved CR/CRi:
  - Median time to achieve CR/CRi was 2.5 months [range 0.7-8]
  - 3 patients remain on treatment, time since response are 6, 12 and 15 months respectively
  - 1 patient proceeded to transplant after CR
  - 1 patient progressed 2.5 months after CR

Phase 2: 7 patients completed 1 cycle of treatment

- 2 (28%) of patients achieved an objective response
  - Patient 08-205: had a CRi at cycle 1 and CR at cycle 2; time since response is 3 months and patient remains on treatment
  - Patient 05-212 had a PR at cycle 1 and remains on treatment

Characteristics of CR/CRi patients (n=6)

- Median age 72 [51-76] years old
- Prior treatments:
  - 4 had relapsed, or were refractory, to intensive chemotherapy
  - 2 patients were treatment naïve for AML, but had HMA for MDS
  - Cytogenetic risk: intermediate (n=4) and adverse (n=2)
  - Mutations:

Gene	NRAS	SRSF2	FLT-ITD	SF3B1	FLT3-TKD	DNMT3A	IDH2
Patients	2	2	2	1	1	1	1

Biomarker Analyses

Decrease in Mutant ctDNA at First Cycle Predict Clinical Response

- Circulating tumor DNA (ctDNA) can be used as a noninvasive biomarker for monitoring tumor heterogeneity, treatment response, minimal residual disease (MRD), and disease progression in AML and MDS[5,6]
- For 17 patients, a driver mutation was identified by targeted-NGS and confirmed via ddPCR. The mutant allele frequency (MAF) of the selected variant was measured at baseline (C0) and end of cycle 1 (C1); changes in MAF were calculated as Log_2 (C1/C0)
- The 6 patients with CR/CRi showed a decrease in ctDNA MAF at cycle 1 (Log_2(C1/C0) < -0.05), while only 1 of the 11 non-responders showed a similar decrease
- Measuring the changes in plasma over the first cycle was highly predictive of patient clinical response: 100% sensitivity, 91% specificity, positive predictive value of 86% and negative predictive value of 100%

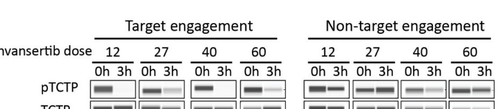
		Clinical Outcome			
		CR/CRi	Non CR/CRi		
Plasma ctDNA	Responder	6	1	PPV	86%
	Non-Responder	0	10	NPV	100%
		100%	91%		
		Sensitivity	Specificity		

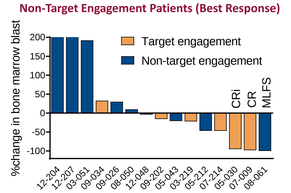
Patient	Target Gene	ctDNA MAF Log2(C1/C0)	Clinical Response
01-021	BCOR	0.22	Non-CR/CRi
05-030	NRAS	-0.43	CR/CRi
05-043	NRAS	-0.03	Non-CR/CRi
07-009	FLT3	-0.33	CR/CRi
07-013	PHF6	0.32	Non-CR/CRi
07-018	TP53	0	Non-CR/CRi
07-033	KRAS	-0.02	Non-CR/CRi
07-035	IDH2	-0.14	CR/CRi
07-036	TET2	0.29	Non-CR/CRi
08-058	NRAS	-1.44	CR/CRi
09-026	TP53	0.35	Non-CR/CRi
09-064	SF3B1	-1.69	CR/CRi
05-212	NRAS	0	Non-CR/CRi
07-214	KRAS	-0.03	Non-CR/CRi
08-205	DNMT3A	-1.21	CR/CRi
09-202	IDH1	-0.30	Non-CR/CRi
12-204	FLT3	0.54	Non-CR/CRi

Plasma ctDNA responders were defined as patients with Log2(C1/C0)< -0.05 (in yellow in the table).
PPV= positive predictive value; NPV= negative predictive value

Target Engagement in Circulating Blasts is Associated with Decrease in Bone Marrow Blasts

- Translational control tumor protein (TCTP) is a substrate of PLK1 and phosphorylated TCTP (pTCTP) was identified as a specific marker for PLK1 activity in vivo in preclinical models[7]
- pTCTP/TCTP was assessed by capillary Western-Blot in mononuclear cells isolated from blood samples collected on Day 1 at pre-dose and 3h post-dose in patients with ≥10% circulating blasts (n=15)
- Target engagement was defined as a decrease of ≥50% in pTCTP/TCTP at 3h post-dose versus 0h and was observed in 8 (33%) of the 24 evaluable patients
- Target engagement (TE) was not associated with the onvansertib dose, but was associated with higher bone marrow responses:
  - 4 (67%) of the 6 TE patients had a ≥20% decrease in blasts versus 3 (33%) of the 9 non-TE patients
  - 2 (33%) of the 6 TE patients had CR/CRi, vs 1 of the 9 non-TE had MLFS





Conclusions

- **Onvansertib in combination with decitabine was well tolerated**
  - MTD was established at 60 mg/m^2 with no DLT through this dose level
  - Treatment-related toxicities were primarily hematological; skin toxicities were observed at higher onvansertib doses
- **Anti-leukemic activity was observed**
  - At a wide range of onvansertib doses (27 to 90 mg/m^2)
  - Phase 1b CR/CRi rate was 24% through all doses and 31% at the 4 higher dose levels (27 – 90 mg/m^2)
- **Response biomarkers were identified**
  - Decreases in mutant ctDNA after 1 cycle of treatment were highly predictive of clinical response
  - Target engagement in circulating blasts was associated with greater decrease in bone marrow blasts
- **Phase 2 is enrolling 32 patients and ongoing**
  - To further assess safety, efficacy and biomarker strategies
  - 1 patient achieved CR and had a significant decrease in mutant ctDNA at first cycle of treatment

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