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POLO-LIKE KINASE 1 (PLK1) INHIBITOR, ONVANSERTIB, IN COMBINATION WITH LOW-DOSE CYTARABINE OR DECITABINE IN PATIENTS WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

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Presentation Number 10660

Lecture Time: 14:57 – 15:09

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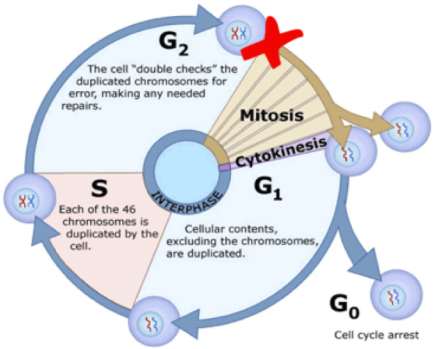
DISCLOSURE SLIDE

- A.M.Z. received research funding (institutional) from Trovagene, Celgene, Abbvie, Astex, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Incyte, Takeda, Novartis, Aprea, and ADC Therapeutics.
- A.M.Z had a consultancy with and received honoraria from Trovagene, AbbVie, Otsuka, Pfizer, Celgene, Jazz, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Taiho, Seattle Genetics, BeyondSpring, Takeda, Ionis, and Epizyme.
- A.M.Z received travel support for meetings from Pfizer, Novartis, and Trovagene.

BACKGROUND

POLO-LIKE KINASE 1 (PLK1)



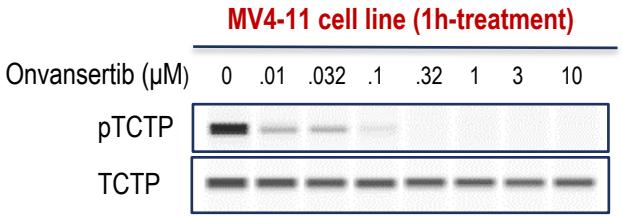
- Serine/threonine kinase, master regulator of cell-cycle progression[1]
- Operates at G2/M checkpoint[1]
- Inhibition of PLK1 causes mitotic arrest and subsequent cell death[1]
- Over-expressed in blasts cells from AML patients[2]
- The pan-PLK inhibitor, volasertib, showed some efficacy in combination with LDAC in AML
  - In a phase 2 randomized study volasertib + LDAC showed a significant increase in overall survival in comparison to LDAC alone[3]. However, the Phase 3 study was negative[4]
  - Unfavorable features of volasertib may have contributed to this outcome: a long half-life (~5 days), the lack of specificity, the dosing regimen and the absence of biomarker strategy

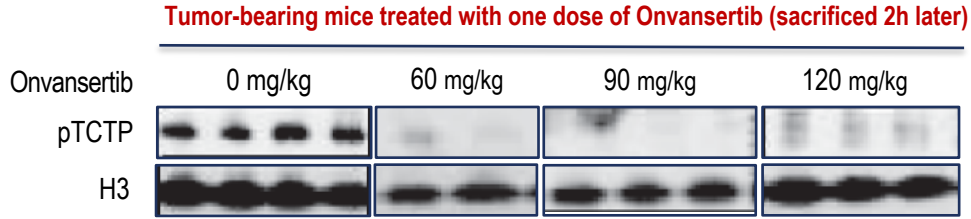
[1]Zitouni et al., Nat Rev Mol Cell Biol. 2014 Jul;15(7):433-52
[2]Renner et al, Blood 2009 Jul 16;114(3):659-62
[3]Döhner et al, Blood 2014 Aug 28;124(9):1426-33
[4]Döhner et al, 21st Congress of EHA, Volume: Haematologica 101(suppl.1): 185-186, abstract S501

BACKGROUND

ONVANSERTIB

- Orally-bioavailable, highly-selective PLK1 inhibitor, with ~24-hour half-life
- Potent anti-tumor activity in AML preclinical models
  - Induces G2/M arrest and apoptosis in the nanomolar range in leukemic cells
  - Induces tumor growth inhibition in mouse models as a single agent and in combination with LDAC
- PLK1 inhibition by onvansertib can be monitored in-vitro and in-vivo through changes in the phosphorylation of its direct substrate, the translational controlled tumor protein, TCTP [5,6]





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

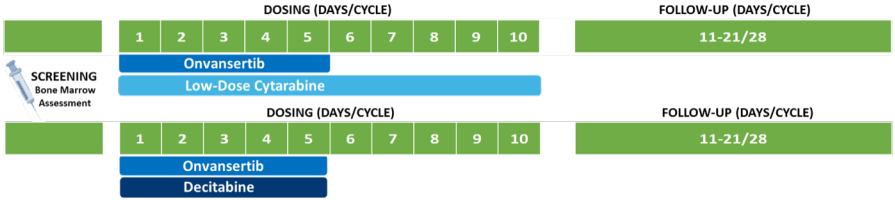
PHASE 1B TRIAL DESIGN

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 20mg/m^2 IV for 5days OR low dose cytarabine (LDAC) 20mg/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

- Evaluate predictive biomarkers associated with response to treatment
- Assess PLK1 inhibition in circulating leukemic cells by measuring pTCTP levels

TREATMENT SUMMARY

Data Cutoff: June 1st, 2019

	N or Median [range]
Number of patients treated	33
Cleared doses in Decitabine arm	12, 18, 27, 40 and 60mg/m^2
Cleared doses in LDAC arm	12, 18, 27 and 40mg/m^2
Number of DLTs	0
Number of patients completing ≥1 cycle	27
Number of cycles	2 [1-13]

Patients (N=33)	N (%) or Median [range]
Age (years)	68 [33-88]
Male gender	25 (76%)
ECOG	1 [0-2]
Previous treatments	**2 [0-3]**
Cytogenetic Risk Status (N=33)	**N (%)**
Favorable	3 (9%)
Intermediate	4 (12%)
Adverse	**23 (70%)**
Unknown	3 (9%)

SAFETY SUMMARY

For patients who received ≥ 1 dose

Data Cutoff: June 1st, 2019

- Treatment was well tolerated; no unexpected toxicities were reported
- No DLTs, SAEs or trial-related deaths attributed to onvansertib
- 3 deaths on trial were not attributed to onvansertib (2 due to progression; 1 intracranial hemorrhage due to fall)
- MTD not reached through 60mg/m^2 dose level
- Grade 3/4 AEs possibly related to onvansertib: hematological AEs (n=10; 30%); non-hematological (n=1; 3%)

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Table of All Adverse Events Reported in ≥ 10% of Patients (N=33)					
	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Fatigue	3	8			11 (33%)
Thrombocytopenia		2	1	7	10 (30%)
Febrile Neutropenia			9*		9 (27%)
Anemia	1		7	1*	9 (27%)
Neutropenia			1	7	8 (24%)
Dyspnea	3	3	1		7 (21%)
Nausea	4	3			7 (21%)
Constipation	6				6 (18%)
Rash	2	3	1		6 (18%)
Cough	3	2			5 (15%)
Diarrhea	5				5 (15%)
Dizziness	4				4 (12%)
Epistaxis	3	1			4 (12%)
Headache	4				4 (12%)
Stomatitis	1	2	1		4 (12%)
WBC Decrease			1	3	4 (12%)

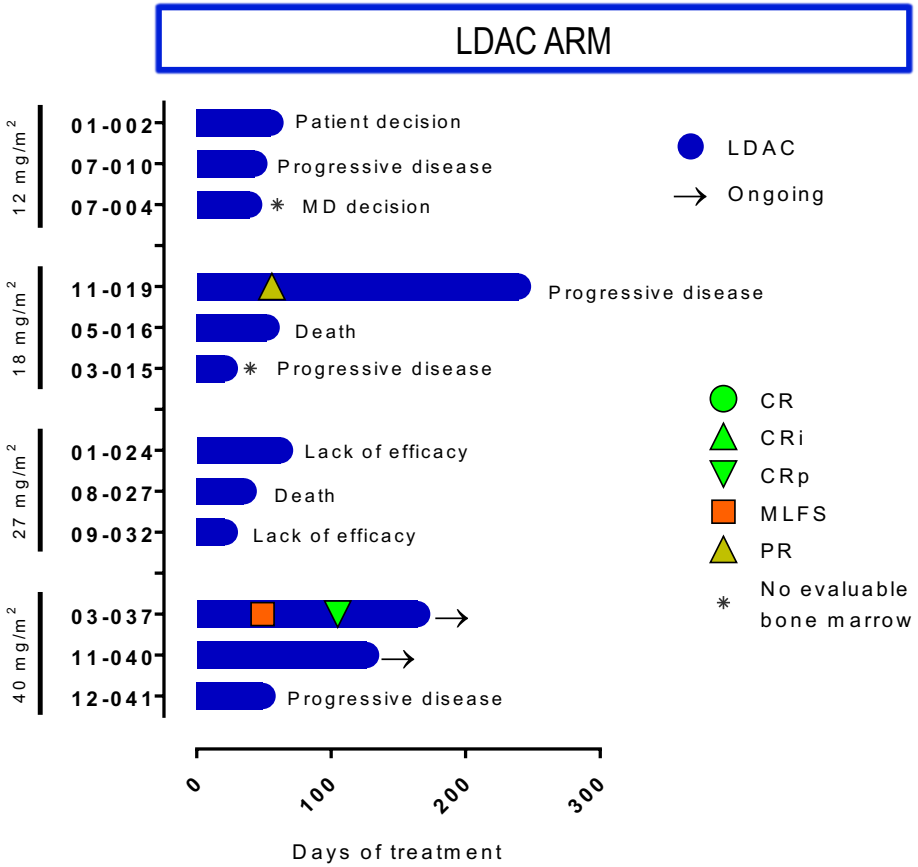
*reported as SAE

PRELIMINARY EFFICACY LDAC ARM

For patients who completed ≥ 1 cycle

Data Cutoff: June 1st, 2019

- 12 patients evaluable for efficacy (treated for ≥1 cycle) at **onvansertib 12 – 40mg/m^2 plus LDAC**
- 1 patient achieved objective response
  1 CRi at onvanserib 40mg/m^2
- LDAC arm discontinued following completion of onvansertib 60mg/m^2 cohort



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PRELIMINARY EFFICACY DECITABINE ARM

For patients who completed ≥ 1 cycle

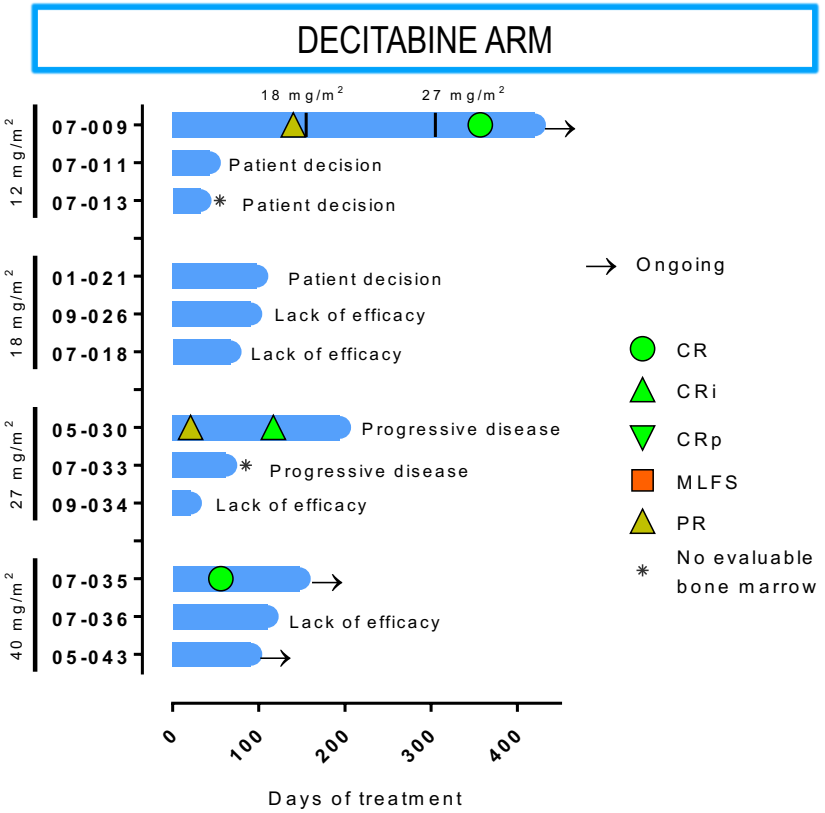
Data Cutoff: June 1st, 2019

- 12 patients evaluable for efficacy (treated for ≥1 cycle) who received **onvansertib 12 – 40mg/m^2 plus decitabine**

- 3 patients achieved objective responses

  2 CR: 1 at onvansertib 27mg/m^2 and 1 at onvansertib 40mg/m^2

  1 CRi at onvansertib 27mg/m^2



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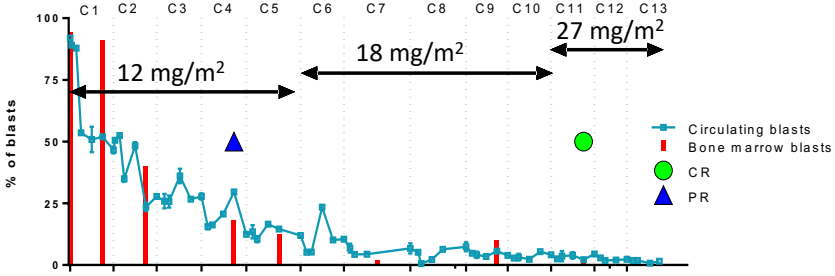
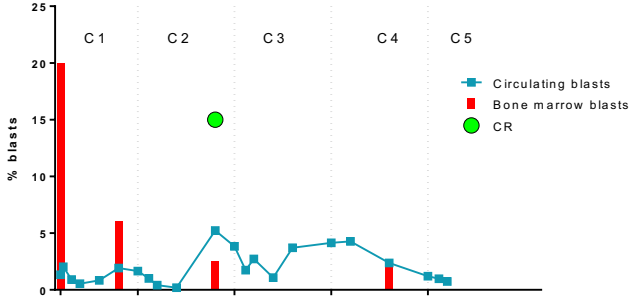
PRELIMINARY EFFICACY

Onvansertib + Decitabine Patient Cases of Complete Response

- 75 year-old male, diagnosed with AML in 2009; treated with induction chemotherapy followed by alloBMT; relapsed in March 2018
- Mutations: RUNX1, GATA2, SF3B1, FLT3-TKD
- Entered trial April 2018 on onvansertib 12mg/m^2 + decitabine
- Onvansertib dose increased to 18mg/m^2 cycle 6; 27mg/m^2 cycle 11
- Patient reached PR at end of cycle 4 and CR at end of cycle 11
- Patient is currently on cycle 14 (as of 01 June 2019)
- % BM blasts decreased from 94% (at screening) to <5% (cycle 11)



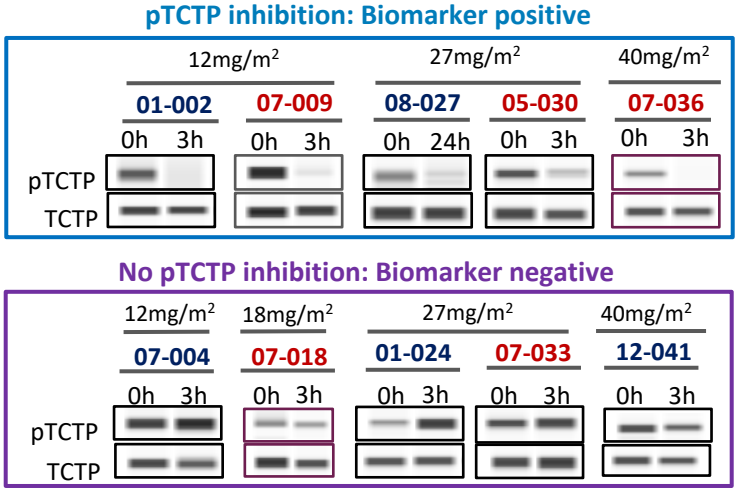
- 82 year-old male, diagnosed with AML in 2015; treated with induction and consolidation chemotherapy; relapsed in December 2018
- Mutations: ASXL1, SRSF2, IDH2
- Entered trial in January 2019 on onvansertib 40mg/m^2 + decitabine
- Patient reached CR as of the end of cycle 2. Patient was in cycle 5 (as of 01June 2019) with ongoing CR
- % BM blasts decreased from 22% (at screening) to less than 5% at the end of cycles 2 and 4

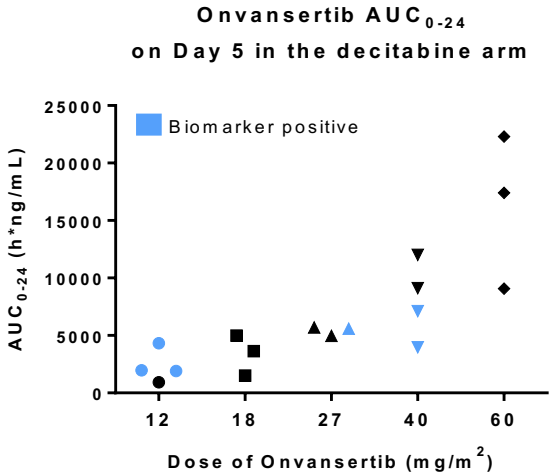


BIOMARKER STRATEGY

Assessing inhibition of PLK1 in patients

- Blood samples collected on day 1hr pre (0h) and 3hr post (3h) dose (corresponding to onvansertib ~Cmax)
- pTCTP and TCTP assessed by capillary Western-Blot in isolated peripheral mononuclear cells
- Biomarker+ defined as ≥ 50% decrease in pTCTP/TCTP at 3h versus 0h
- Nine of 24 evaluable patients (38%) were biomarker positive for both arms
- Biomarker positivity was not correlated with onvansertib blood concentration (PK), dose level, % blasts, or combination (onvansertib plus LDAC or decitabine)





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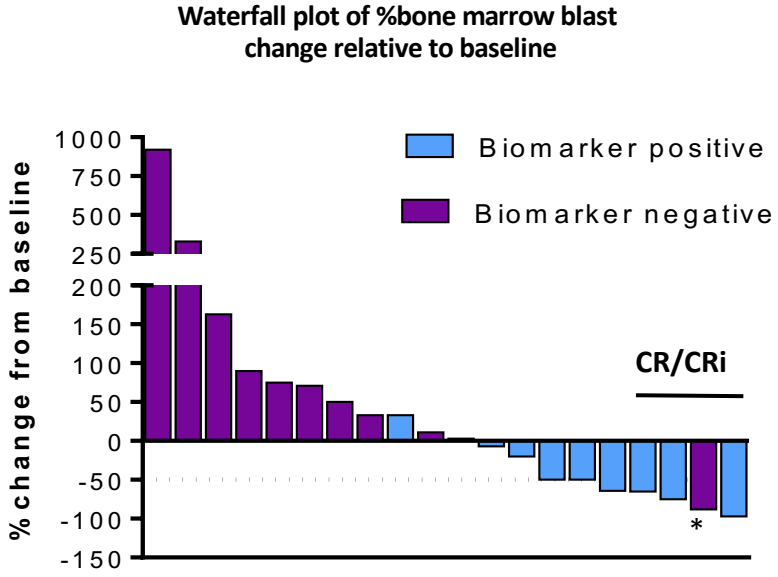
BIOMARKER STRATEGY

Biomarker positivity is associated with response to treatment

- 20 patients evaluable for anti-leukemic efficacy and biomarker+ (defined as ≥ 50% decrease[1] in pTCTP/TCTP at 3h versus 0h)
- 6 of 9 biomarker positive patients had a decrease in BM blasts ≥ 50%, versus 1 of 11 in the biomarker negative patients
- Among the 4 patients with OR (CR+CRi), 3 were biomarker positive and 1 was borderline biomarker positive (40% decrease in pTCTP)
- Further biomarker validation is ongoing; development of a more sensitive and quantitative assay



* Patient sample showed a 40% reduction in pTCTP

[1]The ability to observe two-fold differences by methodology has been analytically validated

CONCLUSIONS

Onvansertib Treatment of Relapsed/Refractory AML

- Dose escalation as of 01June 2019 demonstrated safety of onvansertib up to 60mg/m^2
- Anti-leukemic activity was observed at the 2 highest evaluable doses: 27 and 40mg/m^2
  - 2 patients reached a CR (at 27 and 40mg/m^2) and 2 patients a CRi (at 27 and 40mg/m^2)
- Biomarker positivity was defined as a ≥ 50% decrease in pTCTP (PLK1 substrate) 3h post first dose of onvansertib
  - 40% of patients were biomarker positive
  - Biomarker positivity was associated with an increase in response to treatment, as measured by decrease in BM blasts and rate of OR (CR+CRi)
- Phase 2 will enroll 32 patients to further assess the safety, efficacy, biomarker positivity and correlation with response of onvansertib plus decitabine

ACKNOWLEDGMENTS

We would also like to extend a special thanks to our patients and their families for participating in this trial

Happy to answer any questions
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