MC210807: Phase 1 clinical trial assessing the safety and efficacy of Onvansertib, a novel, oral, PLK1 inhibitor in relapsed/refractory myeloproliferative chronic myelomonocytic leukemia (CMML)

Abhishek A. Mangaonkar[1], Kristen B. McCullough[1], Susan Geyer[2], Ashya R. Burgess[1], Kimberly Rice[1], Eric Asmus[2], Patricia Koenig[1], Terra Lasho[1], Christy Finke[1], Rachel Reither[1], Ryan Carr[3], Jenna Fernandez[4], Antoine N. Saliba[1], Aref Al-Kali[1], Martin E. Fernandez-Zapico[3], Mrinal M. Patnaik[1]

[1]Division of Hematology, Department of Medicine, [2]Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, [3]Department of Medical Oncology, [4]Center for Individualized Medicine
Mayo Clinic, Rochester, MN

BACKGROUND

DNA methyltransferase inhibition offers palliative benefit but does not alter disease biology in CMML[1]. This was conclusively demonstrated in the phase 3 DACOTA study, where decitabine did not improve event-free survival in comparison to hydroxyurea (median 12.1 versus 10.3 months, *P*=0.27) in advanced myeloproliferative CMML (MP-CMML)[2].

We and others have demonstrated a role for *RAS* mutations in MP-CMML through the activation of the *KMT2A-PLK1* axis. Targeting of this axis using onvansertib, an inhibitor of PLK1, has demonstrated its pre-clinical efficacy in MP-CMML patient-derived organoid and xenograft models[3].

OBJECTIVES

PRIMARY: Characterization of adverse events

SECONDARY

- Efficacy: Complete response (CR) rate according to 2015 MDS/MPN IWG criteria[4]
- Response: Overall response rate (ORR) [CR, complete cytogenetic response (CCR), partial response (PR)]
- Spleen: Volumetric spleen response by ultrasound
- Symptoms: Constitutional symptoms by MPN-SAF TSS

EXPLORATORY

- Onvansertib activity in *RAS*m MP-CMML
- Monocyte subset analysis by flow cytometry
- Relation of genomic backgrounds and changes, as assessed by NGS, to response
- Relation between changes in mutant ctDNA and CR, ORR, spleen response rate
- Assessment of target engagement
- Expression levels of PLK1 and KMT2A

PATIENT CRITERIA

INCLUSION

- Histologically confirmed MP-CMML, relapsed/refractory to hydroxyurea; or at least 4 cycles of hypomethylating agent; or intolerant to treatment
- Baseline platelets ≥ 20,000/mm^3
- Estimated eGFR ≥ 50 mL/min/m^2

EXCLUSION

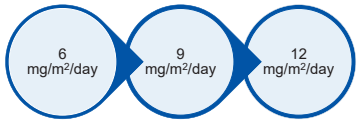
- Prior allogeneic HSCT
- Active central nervous system disease
- Strong CYP3A4 inhibitors/inducers
- QTc > 480 msec

Please review NCT05549661 clinical trial for a full list of inclusion & exclusion criteria.

METHODS

Onvansertib is administered orally, once daily on Days 1 through 21 of a 28-day cycle. Hydroxyurea may continue in Cycle 1 per investigator discretion.

- Three planned dose levels for Phase 1.
- Bayesian optimal interval (BOIN) design for determination of Dose Expansion.
- Completion of at least 80% of intended dose in cycle 1 to qualify for dose limiting toxicity (DLT) evaluation.



Bone marrow assessment after Cycle 3. Patients in CR, CCR, or PR may continue treatment. Follow up reported through November 1, 2025.

PATIENT COHORT

Table 1. All patients enrolled and receiving at least one dose of study medication.

	All Patients N (%)
Number of Patients	10 (100)
Male	5 (50)
Median age at diagnosis (range)	71 (60 – 83)
White	10 (100)
Diagnosis	
CMML-1	10 (100)
Normal karyotype	8 (80)
Previous Therapy	
Hydroxyurea	9 (90%)
Decitabine	1 (10%)
Median Baseline Labs (Range)	
Hemoglobin (g/dL)	9.9 (7.1 – 13.2)
Platelets (x 10^9/L)	36 (20 – 494)
WBC (x 10^9/L)	13.3 (3.1 – 72.7)
Absolute monocyte count (x 10^9/L)	2.22 (0.19 – 19.63)
Bone marrow blasts (%)	5 (0 – 9)
Mutation Profile	
TET2	9 (90)
SRSF2	8 (80)
ASXL1	6 (60)
NRAS/KRAS	3 (30)
CBL	3 (20)
RUNX1	2 (20)

RESULTS

Figure 1. Swimmers' plot showing patients who received at least 1 cycle (n=8) with 3 (38%) patients meeting criteria for either hematological or optimal marrow response. One patient (not pictured here) was also PF but did not complete the assessable DLT

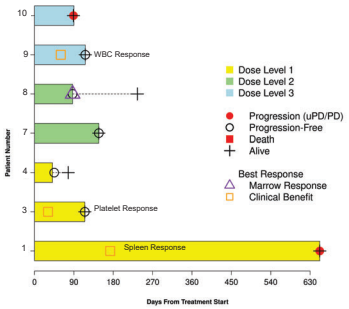


Table 2. Adverse events by dose level and patient

Patient	Dose Level	DLT	Grade 3 or 4 AEs‡
1	6 mg/m^2	None	Sinusitis, Sepsis, AKI
2	6 mg/m^2	Pericardial effusion*	Pericardial effusion, atrial fibrillation with RVR, hypertension, headache, dyspnea, dyspepsia, hiatal hernia
3	6 mg/m^2	None	None
4	6 mg/m^2	None	None
5	9 mg/m^2	None§	Cellulitis
6	9 mg/m^2	None†	None
7	9 mg/m^2	None	None
8	9 mg/m^2	None	None
9	12 mg/m^2	None	None
10	12 mg/m^2	None	Anemia, thrombocytopenia, neutropenia, lymphocytopenia

DLT = Dose limiting toxicity; AE = Adverse events; AKI = Acute kidney injury; RVR = Rapid ventricular response
*Per BOIN design, the presence of a DLT necessitated the addition of two more patients at the 6 mg/m^2 dose level. Pericardial effusion has never been seen with onvansertib and may have been CMML related.
§Did not complete the DLT period due to a Grade 3 cellulitis
†Did not complete the DLT period due to progressive disease
‡Last follow up 11/1/2025

Figure 2. Inhibitory activity on HL-60 from onvansertib-containing patient plasma samples Targeting efficacy was assessed by measuring phosphorylation of TCTP (a PLK1 substrate), specifically pTCTP/TCTP ratios by immunoblotting in peripheral blood mononuclear cell (PBMC) samples pre and post cycle 1 (Days 1, 7, 21) and end of cycle 3. Both cases represent the examples from the 6 mg/m^2 cohort.

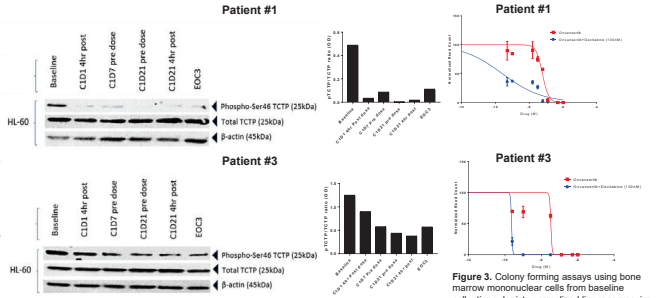
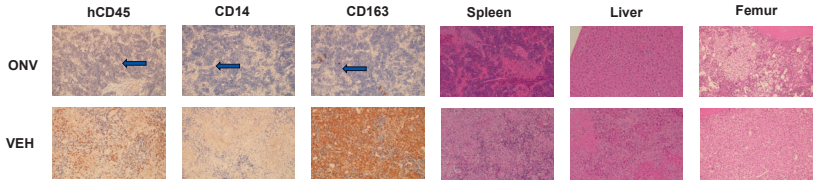


Figure 3. Colony forming assays using bone marrow mononuclear cells from baseline collections depicts normalized linear regression derived from these assays for onvansertib only (red) and onvansertib + decitabine (blue).

Figure 4. NSGS mice xenografts treated with onvansertib or vehicle
Mice were xenografted 24 hours after irradiation. Engraftment was confirmed with hCD45. Vehicle or Onvansertib was dosed at 60 mg/kg for 2 cycles (5 days on/2 days off for 28-days per cycle) and were euthanized two weeks after the last cycle. Cells from the spleen, liver, femur are represented below showing efficacy of the drug in clearing malignant cells.



DISCUSSION

- Follow up now extends through November 1, 2025, with median duration of therapy 124 days (15-654).
- Dose escalation was complete without evidence of a DLT after expansion of the first dose level. Pericardial effusion has never been seen with onvansertib and may have been related to the CMML itself.
- The responses have included three clinical benefits (38%) with one each of the following: a 100% platelet response, normalization of WBC (baseline WBC count > 50 x 10^9/L), and spleen response. There has also been one (12.5%) optimal marrow response with bone marrow blast reduction from 8% to 2% facilitating for allogeneic hematopoietic stem transplant and 3 patients with stable disease (38%).
- No new safety signals were identified though anecdotally patients seem to have hyperphosphatemia and low-grade clinical tumor lysis which may necessitate close monitoring of electrolytes and renal insufficiency in the setting of potential pre-existing lysozyme nephropathy.
- Preliminary target engagement evaluations confirmed adequate suppression via pTCTP/TCTP ratios and further dose level evaluations are ongoing.
- Preliminary data suggestions the IC50 of onvansertib is improved with concomitant decitabine and evaluation in patient derived colony forming assays appears reflective. Further evaluation is required for confirmation.

CONCLUSIONS

- In MP-CMML, PLK1 inhibition with onvansertib appears relatively well tolerated with preliminary efficacy in approximately 40% of patients.
- One patient achieved optimal marrow response at 9 mg/m^2, 3 patients achieved clinical benefit (6 mg/m^2 and 12 mg/m^2), one of which also achieved MPN-SAF TSS reduction of 50%.
- Dose expansion is currently open and recruiting at Mayo Clinic in Rochester, Minnesota, at the 12 mg/m^2/day dose.

FUNDING

Funded through NIH/NCI R01 CA272496, Mayo Clinic Comprehensive Cancer Center
Onvansertib supplied by Cardiff Oncology

REFERENCES

1. Merlevede J, et al. Nat Commun. 2016; 7: 10767.
2. Itzykson R, et al. J Clin Oncol 2023; 41(10: 1888-97.
3. Carr RM, et al. Nat Commun. 2021; 12: 2901.
4. Savona MR, et al. Blood. 2015; 125(12): 1857-65.

©2025 Mayo Foundation for Medical Education and Research