A PHASE 2/3, MULTICENTER TRIAL OF LENZILUMAB AND AZACITIDINE IN CHRONIC MYELOMONOCYTIC LEUKEMIA: THE PREACH-M TRIAL

Authors: Devendra Hiwase [1,2], David Ross[1,2,3], Steven Lane[4], Kirsty Sharplin[1,2], Agnes Yong[1,5], David Yeung[1,2], Dale Chappell[6], Cameron Durrant[6], Timothy Hughes[1,2], Daniel Thomas[1,2]

Affiliations: [1]South Australian Health & Medical Research Institute, Adelaide Medical School, University of Adelaide, Australia [2]Central Adelaide Local Health Network, Australia [3]University of South Australia, Adelaide, Australia [4]Queensland Institute of Medical Research, Brisbane, Australia [5]Royal Perth Hospital, Perth, Australia [6]Humanigen, Short Hills, NJ, USA

Poster number CT085

Disclosures D. Ross, A. Yong and T. Hughes have received research funding and honoraria from Novartis and BMS/Celgene unrelated to the current work. C. Durrant and D. Chappell are employees and directors of Humanigen. All other authors have nothing to disclose.

INTRODUCTION

- Chronic myelomonocytic leukemia (CMML) is a rare, aggressive cancer and clonal stem cell disorder with limited targeted therapy and a propensity to develop into acute myeloid leukemia.
- Standard of care (SOC) includes azacitidine (AZA), with complete and partial response (CR and PR) rates ranging between 10-17%.
- The pro-inflammatory cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) plays a central role in leukemic monocyte proliferation.
- More than 90% of cases of CMML carry recurrent somatic mutations that are believed to drive leukemia.
  - *TET2* mutations occur in 46-60% of CMML cases.
  - *RAS* pathway mutations (*KRAS, NRAS,* or *CBL*) occur in 30-40% of cases.
- RAS pathway mutations
  - Associated with hyper-proliferative features and aggressive disease
  - Sensitive to GM-CSF blockade *in vitro* and in preclinical *in vivo* models
  - GM-CSF is central in promoting the survival and proliferation of CMML
- Lenzilumab (LENZ) is a proprietary Humaneered® first-in-class monoclonal antibody with best-in-class specificity and affinity that neutralizes GM-CSF to prevent signaling through its receptor.

AIMS / OBJECTIVES

The **PRE**cision **A**pproach to **CH**ronic **M**yelomonocytic Leukemia (PREACH-M) trial (ACTRN12621000223831p) assesses the efficacy of LENZ in addition to standard of care (SOC) in CMML subjects with specific molecular markers.

PRIMARY OBJECTIVES

- To assess response rates in participants with CMML through a precision medicine approach, using azacitidine combined with LENZ directed by the presence of somatic variants in the RAS pathway (*NRAS/KRAS/CBL*).

SECONDARY OBJECTIVES

- To compare clinical benefit, overall and progression free survival, toxicity and impact on frailty and quality of life in CMML patients managed through a precision medicine approach.

METHODS

- PREACH-M is a phase 2/3, non-randomized open-label study
- Number of participants: 72
- Duration: 2 years of active treatment, followed by 2 years of follow-up (Figure 1)
- Treatments:
  - Subjects exhibiting RAS pathway mutations (***high risk disease***)
    - 24 cycles
    - AZA (SC 75 mg/ m^2 ; d1-5, 8-9, or d1-7)
    - LENZ (IV; 552 mg; d1 & d15 of Cycle 1. d1 only for all subsequent cycles)
  - Subjects exhibiting only TET2 mutations (***low risk disease***)
    - 24 cycles
    - AZA (SC 75 mg/ m^2 ; d1-5, 8-9, or d1-7)
    - Sodium Ascorbate IV 30g d1-5, 8-9, or d107 (15g for 1st dose only, 30g thereafter if no evidence of Tumor Lysis Syndrome)
    - Sodium Ascorbate PO 1.1g on days where IV Sodium Ascorbate is not scheduled
- FOLLOW-UP
  - Subjects who complete 24 cycles of treatment are followed every 6 months for 24 months for survival, disease status, and CMML-related therapy

INCLUSION / EXCLUSION CRITERIA

KEY INCLUSION CRITERIA

- Confirmed diagnosis of CMML, satisfying WHO 2016 criteria
- Aged 18 or older
- Cytopenia
  - hemoglobin < 100 g/L
  - platelets < 100 x 10^9/L or absolute neutrophil count < 1.8 x 10^9/L
  - WBC count ≥ 13 x10^9/L (constitutional symptoms or proliferative CMML)
- Detection of TET2 and/or RAS pathway (NRAS/KRAS/CBL) mutations at a variant allele frequency of ≥3%

KEY EXCLUSION CRITERIA

- Prior treatment with investigational agents
- Radiotherapy within 28 days before treatment
- Treatment with G-CSF within 7 days of screening or GM-CSF within 28 days of screening
- Uncontrolled medical conditions
- Myocardial infarction or clinically significant pericardial effusion within the past month
- Another primary malignant disease that requires active treatment
- Prior allogeneic stem cell transplantation

ENDPOINTS

PRIMARY ENDPOINT

- The frequency of complete response (CR) and partial response (PR) at any point during the first 12 cycles of active therapy (Savona Criteria)

SAFETY ASSESSMENTS

- Hematological and non-hematological toxicity
- Incidence of adverse events and serious adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events, CTCAE)
- Regular physical exams, vital signs, and laboratory assessments

SECONDARY ENDPOINTS

- Proportion of subjects with clinical benefits at any point during the 24 cycles of active therapy according to Savona Criteria
- Overall survival and progression-free at 2 years
- Impact on physical and functional capacity
- Quality of Life (EORTC QLQ-C30 PGIC0)
- Social well-being by Multidimensional Geriatric Assessment (MGA)

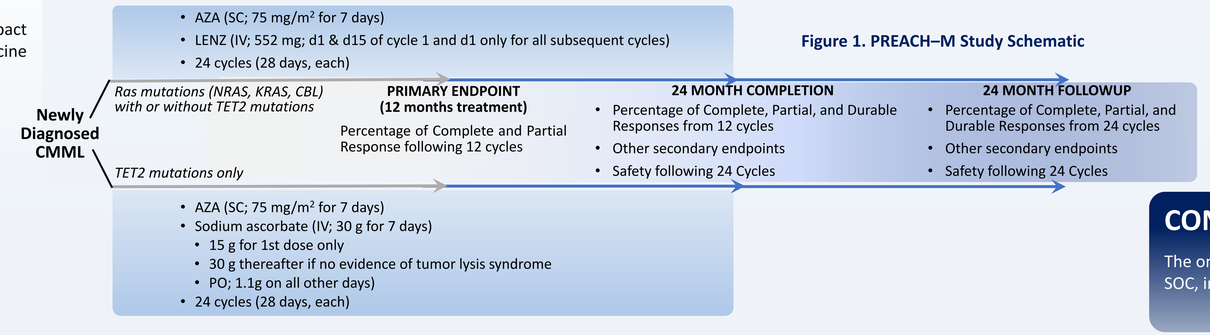


Figure 1. PREACH–M Study Schematic

RESULTS

- Baseline data for 11 subjects treated with AZA and LENZ are reported in Table 1
  - 5 males, 6 females,
  - mean age 68 years
- All subjects who began AZA and LENZ, remained on treatment at the census date of December 31, 2023
- *TET2* mutations were most common and most often associated *BCOR2* mutations (Figure 2)
- *RAS* pathway mutations *CBL* and *KRAS* were heterogeneously associated with other non-*RAS* mutations while the single *NRAS* mutation was singularly associated with PHF6 mutation (Figure 2)
- As of December 31, 2022, 6 subjects were evaluable based on at least 3 months of follow-up. Clinical responses including CR, PR and hematological responses were observed in all evaluable patients including 2 with high risk based on molecular profiling. Bone marrow remained hypercellular in some patients.
- Ten grade 3/4 Serious Adverse Events were observed of which 2 were assessed by the investigator as possibly related to LENZ.

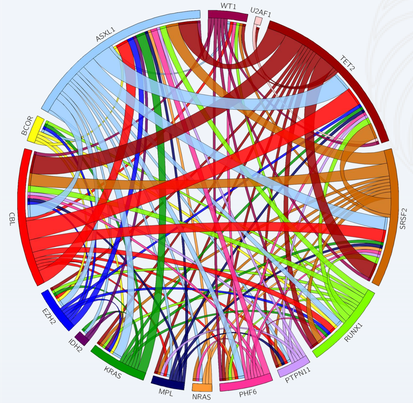
Table 1. Baseline demographics of 11 CMML subjects (5 males and 6 females) with mean age of 68 years

WBC ($x10^9$/L)	Monocytes ($x10^9$/L)	Bone Marrow Blasts (%)	Spleen Size (cm)	Hgb (g/L)
25.0 ± 5.7	5.8 ± 5.9	10.8 ± 1.1	14.3 ± 1.0	119.1 ± 5.9

Values represent mean ± sem

CPSS-Mol	Constitutional Symptoms
Intermediate 2 (n=6)	Fatigue (n=6)
Intermediate 3 (n=1)	Weight Loss (n=5)
High-Risk 4-6 (n=3)	Night Sweats (n=4)

Figure 2. CIRCOS plot of co-occurring somatic mutations detected at variant alleles with greater than 3% frequency, in all patients enrolled in the study to date.



CONCLUSION

The ongoing PREACH-M trial evaluates GM-CSF neutralization with lenzilumab in addition to SOC, in the treatment of CMML with RAS pathway mutations.