AWARD NUMBER: W81XWH-22-1-1080

TITLE: Phase 1 Evaluation of the Safety and Pharmacokinetics of First-in-Class N-Myristoylation Inhibitor PCLX-001 in Patients with Relapsed/Refractory Acute Myeloid

PRINCIPAL INVESTIGATOR: Naveen Pemmaraju, MD

CONTRACTING ORGANIZATION: University of Texas MD Anderson Cancer Center
Houston, TX

REPORT DATE: October 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED	
		START DATE	END DATE
October 2023	Annual	30Sep2022	29Sep2023

4. TITLE AND SUBTITLE
Phase 1 Evaluation of the Safety and Pharmacokinetics of First-in-Class N-Myristoylation Inhibitor PCLX-001 in Patients with Relapsed/ Refractory Acute Myeloid

5a. CONTRACT NUMBER	5b. GRANT NUMBER	5c. PROGRAM ELEMENT NUMBER
W81XWH-22-1-1080	CA210175	
5d. PROJECT NUMBER	**5e. TASK NUMBER**	**5f. WORK UNIT NUMBER**

6. AUTHOR(S)
Naveen Pemmaraju

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX, 77030

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)	11. SPONSOR/MONITOR'S REPORT NUMBER(S)
U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012		

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
This is Phase 1 Study of Oral PCLX-001 in Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML) PCLX-001 is an oral small molecule N-myristoyltransferase (NMT) inhibitor that potently and selectively inhibits the growth of human Acute Myeloid Leukemia (AML) cells in vitro and in vivo models of human AM. Myristoylation, the N-terminal modification of proteins with the fatty acid myristate, is critical for targeting some proteins to the cell membrane and intracellular signaling. There is evidence of selective toxicity to malignant stem cell populations. An ongoing Phase 1 dose escalation study in lymphoma and solid tumor patients shows pharmacokinetic (PK) suitable for once daily oral dosing, achieving plasma concentrations continuously exceeding levels required to inhibit cultured AML cells. No dose limiting toxicities (DLT) have been identified in dose escalation up to 100 mg, and preliminary evidence of anti-cancer efficacy has been observed. PCXL-001 warrants further evaluation in adult AML. adult AML. Primary Objectives of our study are to determine the safety and tolerability of oral PCLX-001 in patients with R/R AML , the minimum safe and biologically-effective dose of daily oral PCLX and to evaluate the pharmacokinetics (PK) of PCLX-001 in patients with R/R AML when co-administered with azole antifungal drugs which are CYP3A inhibitors Secondary Objectives are to estimate PCLX-001 overall response rate (ORR), including best individual response including complete remission (CR), CR with incomplete platelet counts (CRp), CR with incomplete count recovery (CRi), CR with partial hematologic recovery (CRh), and partial remission (PR) in the dose expansion cohort and to describe response duration, time to progression, event free survival, and overall survival (OS) in the dose expansion cohort Exploratory Objectives include the evaluation the potential of pre-treatment variables, including NMT1 and NMT2 status, as biomarkers and clinical determinants of PCLX-001 treatment efficacy and disease outcome and the evaluation of the pharmacodynamic (PD) effects of PCLX-001 on blood cellular biomarkers including Lyn, Src, and HGAL.

15. SUBJECT TERMS

Relapsed/Refractory (R/R) Acute Myeloid Leukemia (AML), Oral medication PCLX-001, co-administration with azole antifungal drugs (CYP3A inhibitors), cellular biomarkers, pharmacokinetics (PK) and pharmacodynamic (PD) effects of PCLX-001.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES
a. REPORT	b. ABSTRACT	C. THIS PAGE		
unclassified	unclassified	unclassified	unclassified	15

19a. NAME OF RESPONSIBLE PERSON	19b. PHONE NUMBER *(Include area code)*
USAMRDC	

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and*

Myristoylation, the N-terminal modification of proteins with the fatty acid myristate, is critical for targeting some proteins to the cell membrane and intracellular signaling. PCLX-001 is an oral small molecule N-myristoyltransferase (NMT) inhibitor that potently and selectively inhibits the growth of human Acute Myeloid Leukemia (AML) cells in vitro and in vivo models of human AML; there is evidence of selective toxicity to malignant stem cell populations. Outcomes in relapsed/refractory AML, while improving slightly over the last few decades, remains quite dismal (Pemmaraju et al, 2015);Although there have been several recently approved therapies for patients with AML in the past year, many patients still die in the setting of relapsed/refractory AML. More effective and better tolerated therapies are still urgently needed. There remains no well-accepted standard second line and salvage therapy for relapsed AML; the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Version 1.2022/December 2, 2021 lists Clinical Trial as the strongly preferred treatment option. STUDY DESIGN This is a dose-finding study of oral PCLX-001 in patients with R/R AML. The primary efficacy endpoint is Best Response (BR) by cycle 3 of therapy, determined by bone marrow aspiration and or bone marrow biopsy in the context of peripheral blood counts. Responders are patients who obtain a CR, CRi, or PR, with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state as per the 2017 European LeukemiaNet (ELN) AML response assessment criteria.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

PCLX-001, zelenirstat, non-Hodgkin lymphoma, acute myeloid leukemia, Pacylex Pharmaceuticals, myristoylation, NMT, NMT inhibitor, N-myristoyltransferase inhibitor

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

OBJECTIVES Primary Objectives: • To determine the safety and tolerability of oral PCLX-001 in patients with R/R AML • To determine the minimum safe and biologically-effective dose of daily oral PCLX-001 in patients with R/R AML • To evaluate the pharmacokinetics (PK) of PCLX-001 in patients with R/R AML when coadministered with azole antifungal drugs which are CYP3A inhibitors Secondary Objectives: • To estimate PCLX-001 overall response rate (ORR), including best individual response including complete remission (CR), CR with incomplete platelet counts (CRp), CR with incomplete count recovery (CRi), CR with partial hematologic recovery (CRh), and partial remission (PR) in the dose expansion cohort • To describe response duration, time to progression, event free survival, and overall survival (OS) in the dose expansion cohort Exploratory Objectives: • To evaluate the potential of pre-treatment variables, including NMT1 and NMT2 status, as biomarkers and clinical determinants of PCLX-001 treatment efficacy and disease outcome • To evaluate the pharmacodynamic (PD) effects of PCLX-001 on blood cellular biomarkers including Lyn, Src, and HGAL

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Nothing to report. The study has not started.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report. The study has not started

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

The last patient has been enrolled in a separate Phase 1 study of the safety, tolerability and pharmacokinetics of PCLX-001 in patients with refractory/relapsed NHL and advanced solid malignancies. In this study, No Dose Limiting Toxicities (DLTs) were observed at doses of 210mg or less. Based on these data, the Phase 1 dose escalation protocol in patients with AML will therefore be amended to propose starting at a higher dose of 100mg instead of the 40mg dose in the current protocol approved by the FDA. The amended protocol will be submitted as an IND amendment. If authorized, the benefit of starting at a higher dose to patients will be starting at a potentially more biologically active dose and saving 4-6 months of time in the overall duration of the Ph 1 study in AML.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

As stated above, the Sponsor intends to amend the current approved protocol to start the study in patients with AML at a higher dose than the current protocol. This will potentially benefit patients because they won't receive subtherapeutic doses and also shorten the duration of the study. FDA approval of the protocol amendment is required.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

The AML study has not yet commenced but as described above, enrollment has been completed in a separate Phase 1 clinical study in solid tumor and NHL patients without any DLTs observed at doses of 210mg or less. Based on these data, the Phase 1 dose escalation protocol in patients with AML will therefore be amended to propose starting at a higher dose of 100mg instead of the 40mg dose in the current protocol approved by the FDA. The amended protocol will be submitted as an IND amendment. If authorized, the benefit of starting at a higher dose to patients will be starting at a potentially more biologically active dose and saving 4-6 months of time in the overall duration of the Ph 1 study in AML.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

If the FDA approves the protocol amendment, study costs could be less and will be recalculated at that time.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to Report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

No change

MDACC
Name: Naveen Pemmaraju MD
Project Role: Site PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked:
Contribution to Project: Dr. Pemmaraju works on designing and will supervise the execution of this project.

MDACC
Name: Gautam Borthakur MD
Project Role: Site Co-PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked:
Contribution to Project: Dr. Borthakur collaborates on designing and will assist on execution of the project.

MDACC
Name: Qiao Wei PhD
Project Role: Stat data analyst
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked:
Contribution to Project: Will perform biostatistical analysis for this project.

University of Alberta

Name: Luc Berthiaume PhD
Project Role: Co-PI(UA)
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked:
Contribution to Project: He will oversee the development, validation and execution of the pharmacodynamic assay in Aim #2, as well as the evaluation of NMT1 and NMT2 as potential predictive biomarkers for PCLX-001 treatment efficacy and clinical outcomes in Aim #3.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to Report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*

Nothing to Report. Study has not started yet.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*