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An Open-Label, Multicenter, Phase 2 Study of CLR 131 in Patients with Relapsed or Refractory (R/R) Select B-Cell Malignancies (CLOVER-1) and Expansion Cohort in Patients with Waldenstrom Macroglobulinemia (CLOVER-WaM)

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BACKGROUND

Phospholipid ethers (PLE) provide an innovative approach to preferentially target cancer cells by capitalizing on their increased number/size of lipid rafts. PLE are designed to possess high affinity to lipid rafts which upon binding results in internalization and the ability to deliver an attached warhead to the cytosol. Iopofosine I 131 (formerly CLR 131) is a novel PLE conjugated to I-131, which was chosen due to its 8-day half-life and well-established efficacy in multiple cancer types. Preclinical/Phase I data has shown Iopofosine I 131 to be preferentially taken up by cancer cells and to cross the blood brain barrier.

A. B.

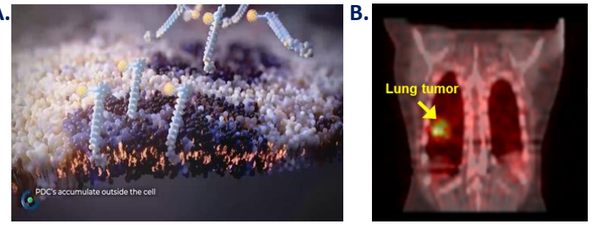


Figure 1: **A.** Schematic showing Iopofosine I 131 binding to lipid raft **B.** NSCLC SPECT scan showing Iopofosine I 131 uptake

WALDENSTROM'S MACROGLOBULINEMIA

Waldenstrom's Macroglobulinemia is an ultra-orphan rare disease

- 8-year survival post-initial diagnosis
- Median age of diagnosis - 65
- Annual incidence of ~6,500 globally

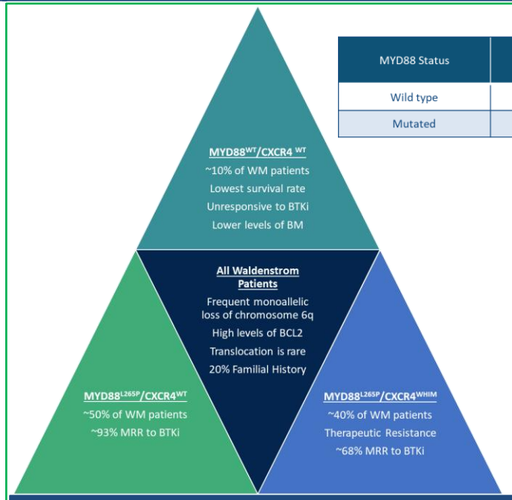
Incurable disease with significant sequelae

- Hyperviscosity syndrome
- Peripheral neuropathy
- Anemia/reduced iron levels
- Organomegaly – lymph nodes, liver, spleen
- Bing-Neel Syndrome (CNS Infiltration)

Annual Prevalence (~60k)[1]

Asia	Europe	USA
33%	33%	33%

CHALLENGING GENOTYPES

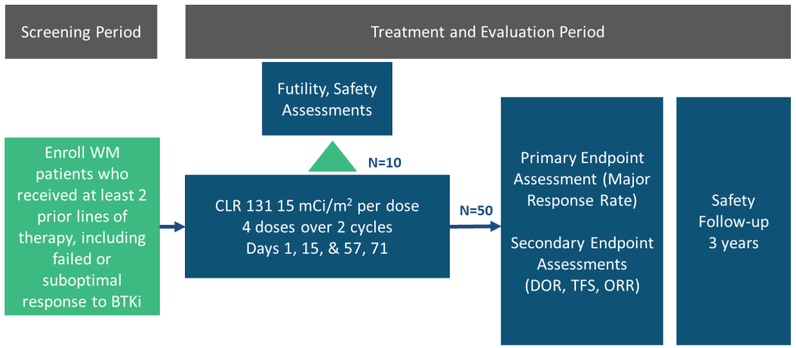


MYD88 Status	Median Time to Progression
Wild type	0.4 years
Mutated	4.5 years

ISSWM[8] Risk Group	Median Time to Progression
High Risk	1.9 years
Intermediate Risk	4.8 years
Low Risk	9.3 years

There is still significant unmet medical need for WM patients, particularly those that are WT for MYD88 or CXCR4 and patients who are high risk according to the International Prognostic Scoring System for Waldenstrom Macroglobulinemia (ISSWM). Patients in both groups have significantly faster median time to progression and have shown limited response to BTKi therapy[2,3].

CLOVER-WaM



CLOVER-WaM is a global, pivotal efficacy and safety expansion cohort evaluating Iopofosine I 131 in refractory patients with Waldenstrom Macroglobulinemia. Patients need to have received at least two prior lines of therapy (including those that have had a sub-optimal response or failed treatment with a BTK inhibitor). This study plans to enroll 50 WM patients who will receive a total of 4 (~20 minute) infusions of Iopofosine I 131 (15 mCi/m^2) over 2 cycles, each cycle lasting ~57 days. The primary efficacy endpoint is major response rate per criteria modified from VIth WM criteria for response assessment. Secondary endpoints include TFS, OS, PFS and safety, among others.

KEY INCLUSION/EXCLUSION CRITERIA

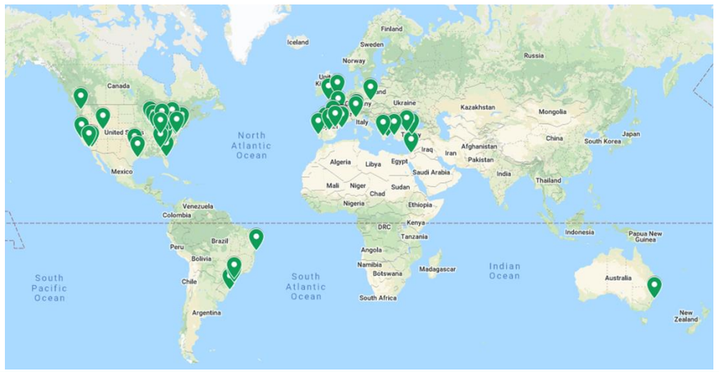
Inclusion

- Histologically or cytologically confirmed LPL/WM
- Patient has an ECOG performance status of 0-2
- Patient is 18 years of age or older
- Life expectancy of at least 6 months
- Patients that have undergone stem cell transplant must be at 3 years from transplant

Exclusion

- Ongoing Grade 2 or greater toxicities from previous therapies
- Prior external-bean RT resulting in greater than 20% of total bone marrow receiving greater than 20 Gy
- Prior total body or hemi-body irradiation
- Extradural tumor in contact with the spinal cord or tumor located where swelling in response to therapy might impinge upon the spinal cord

TRIAL SITES



This trial is in progress and sites are/will be actively enrolling in the United States, UK, EU, Israel, Turkey and Australia. Enrollment is expected to take 18 months.
Clinical Trial # NCT02952508

SUPPORT, DISCLOSURES & REFERENCES

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S. Ailawadhi is an employee/paid consultant for Celgene, Takeda, Janssen, and Amgen, and reports receiving commercial research grants from Pharmacyclics, Cellectar, BIVIS, Amgen, Medimmune, and Ascentage Pharmaceuticals

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3(Gavriatopoulou et al. The current role of BTK inhibitors in the treatment of Waldenstrom's Macroglobulinemia. Expert Review of Anticancer Therapy 2020.