#7561

Treatment Free Remission (TFR) and Overall Response Rate (ORR) Results in Patients with Relapsed/Refractory Waldenstrom's Macroglobulinemia (WM) Treated with CLR 131

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BACKGROUND

Phospholipid ethers (PLE) provide a novel mechanism to specifically target tumor cells leveraging high lipid raft content in their cell membranes. PLE/phospholipid drug conjugates are specifically designed to have high affinity to lipid rafts which upon binding results internalization into the tumor cell delivery and release of the attached warhead directly to the cytosol. CLR 131 (I-131-CLR1404) is a novel targeted radiotherapeutic PLE molecule armed with the isotope I-131, which has been validated in multiple tumor types (figure 1).

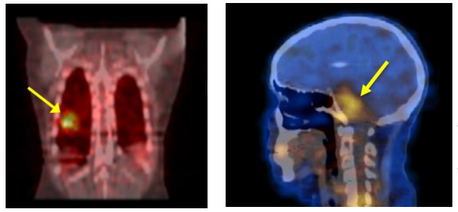


Figure 1: Uptake of CLR 131 in a lung tumor (left) and DIPG tumor (right)

WM is an ultra rare subset of Lymphoplasmacytic lymphoma with a detectible IgM and bone marrow involvement. While there have been recent advances in WM therapies, certain genotypic subsets (MYD88 WT and CXCR4 WT) have proven difficult to treat with median progression occurring in 0.4 years or 4.8 months (Treon 2021). There is still a high unmet medical need for these patients as well as those ineligible for SOC. CLR 131 was examined in relapsed or refractory WM through an open-label, Phase 2 trial, CLOVER-1 (NCT02952508).

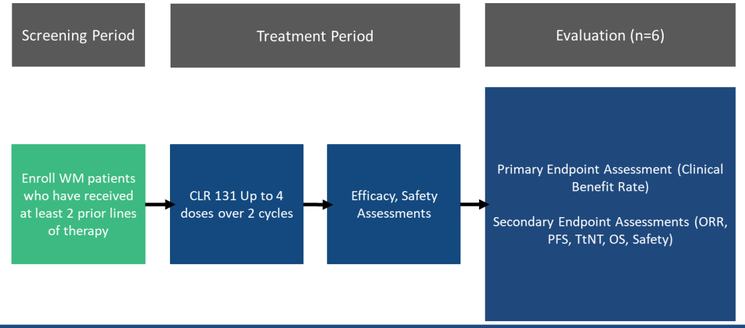
METHODS

The primary objective of this study is to determine the efficacy and safety of CLR 131 in WM patients. Eligibility criteria for pts include:

- Measurable disease, i.e. IgM or extramedullary disease
- Received at least 2 prior treatment regimens or ineligible to receive standard therapies

CLR 131 is administered in up to 4 IV infusions (15-20 min) over 3 months. Adverse events (AEs) are graded by NCI-CTCAE v4.03; responses are assessed by the VIth WM Criteria for Response Assessment [Owen 2013].

TREATMENT SCHEMATIC



RESULTS

6 pts with r/r WM were enrolled in the study with data current as of 8 Jan 2021. 3 of 6 patients were MYD88 wild type (WT) of which 2 were dual WT (MYD88 WT & CXCR4 WT). The overall response rate (ORR) was 100% and the major response rate (MRR) was 83%, including 1 pt with a CR, 4 PR, and 1 MR. For those pts who were MYD88 WT or dual WT, the MRR was 100% with the 1 pt who was MYD88 WT (CXCR4 is unknown) having a complete response. The median time to initial response was 25 days. Median duration of response (DOR) and treatment free remission (TFR) have not been reached; ongoing mean DOR is 335 days and mean TFR is 384 days. 100% of MYD88 WT patients have exceeded 8.5 months of follow up with average TFR of 18.1 months. Median PFS was not reached after 18 months for MYD88 WT patients. This compares to a recent study by Treon, et al. (2021), where the PFS in MYD88 WT patients treated with ibrutinib was 4.8 months. Patients treated with CLR 131 who were refractory to 2 or more therapies had a median PFS of 11 months. MYD88 WT and multi-drug refractory patients treated with CLR 131 had a >70% reduction in serum IgM from baseline.

Criteria	Total Body Dose ≥60 mCi (n=6)
Median Age (Min-Max)	69 (54-81)
Male (%)	33.3
Median Prior Lines of Therapy (Min-Max)	2 (1-5)
Risk Level at Diagnosis	
High Risk [n (%)]	4 (66.6)
Intermediate Risk [n (%)]	1 (16.7)
Low Risk [n(%)]	1 (16.7)

Table 1: Patient demographics

TEAEs in WM subjects (at least possibly related)			
Adverse Event	All Grades N (%)	Grade 1-2 N (%)	Grade 3-4 N (%)
Anemia	4 (67)	0	4 (67)
Neutropenia	5 (83)	0	5 (83)
Pancytopenia	2 (33)	0	2 (33)
Thrombocytopenia	6 (100)	0	6 (100)
Fatigue	5 (83)	3 (50)	2 (33)
Lymphocyte count decreased	2 (33)	1 (17)	1 (17)
White blood cell count decreased	2 (33)	1 (17)	2 (33)

Table 2: Related TEAE occurring in at least one patient

PATIENT RESPONSE

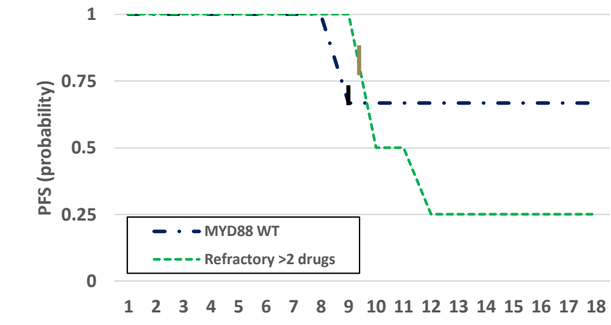


Figure 3: Progression Free Survival (Censored patients are still in follow-up: censored at time of last visit)

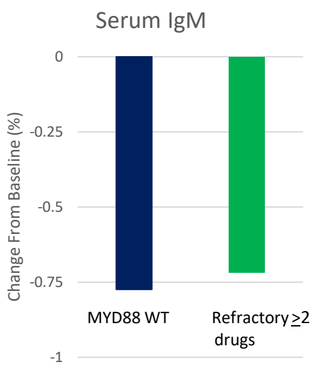


Figure 4: Change in Serum IgM

ADVERSE EVENTS

The primary treatment emergent AEs (TEAE's) in pts with WM included fatigue and cytopenias, in line with prior experience with CLR 131 in other B-cell malignancies. The most commonly observed cytopenias (All Grades) included transient thrombocytopenia (100%), neutropenia (83%), anaemia (66%) and decreased white blood cell count (33%). Of note, no cases of bleeding or febrile neutropenia were observed and all patients recovered from their cytopenias with a median time to recovery of 21 days post nadir.

CONCLUSIONS

Initial results with CLR 131 demonstrate robust efficacy and durable responses, irrespective of patient genotypes and in multi-drug refractory patients. In all patients DOR is ~1 year and ongoing and TFR is ~1.1 years after 2 to 4 infusions. CLR 131 represents a novel and promising approach to the treatment of WM patients and specifically MYD88 WT and multi-drug refractory patients who have a historical median PFS of 0.4 years/4.8 months (CLR 131: ongoing DOR of 18.1). These encouraging data led to the initiation of a global CLOVER-WaM trial (N=50) in relapsed or refractory WM patients including those who have failed or had a suboptimal response to a Bruton Tyrosine Kinase inhibitor. CLOVER-WaM is currently enrolling.

Funding

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