Interim Evaluation of a Targeted Radiotherapeutic, CLR 131, in Relapsed/Refractory Diffuse Large B-Cell Lymphoma Patients (R/R DLBCL)

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Disclosures

- **J. Longcor,** K. Oliver, J. Friend**:** Cellectar Bioscience employee/s, or former employee/s
- N. Callander: Research funding from Cellectar Biosciences,
- Ongoing study: Presentation contains preliminary data that are partially monitored and validated

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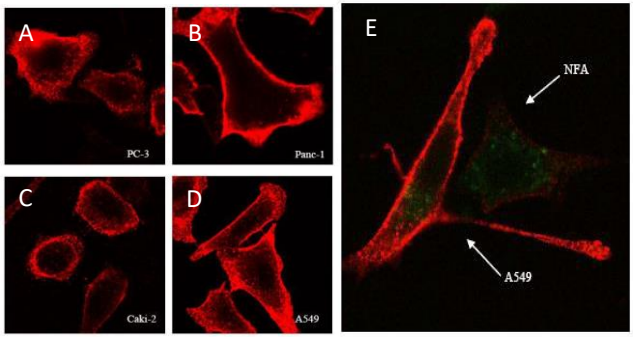
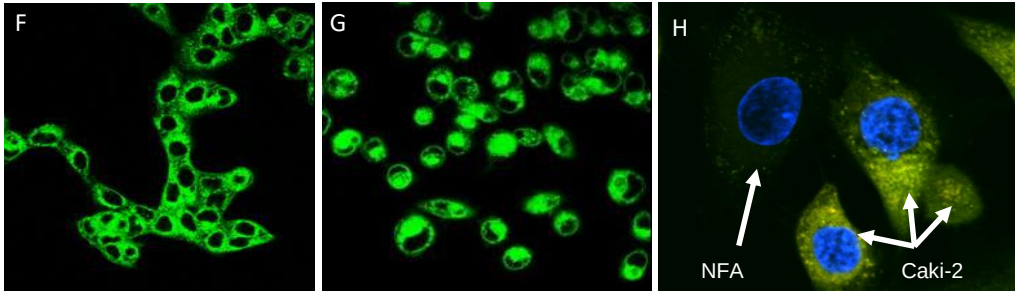
Background

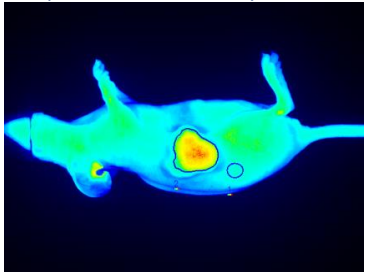
- Phospholipid ether (PLE) molecules are being utilized to deliver cytotoxic molecules to tumors
- PLEs bind and enter tumor cells via lipid rafts; lipid rafts have been shown to be more prevalent and stabilized in tumor cells
- PLEs show preferential uptake in broad range of tumor cells; particularly hematologic cancers
- Targeted in vivo delivery has been demonstrated
- Preclinical studies demonstrate that the PLEs provide delivery of the I-131 to a wide range of tumors, including lymphoma



A, B, C, D, E demonstrates presence of lipid rafts on various tumors . A=prostate; B=pancreatic; C=renal; D=lung; E is co-culture of lung tumor and normal fibroblasts and treated or 24 hours. Staining is with cholera toxin B.



F, G and H show in vitro uptake of fluorescently labeled PLE. F=colorectal; G=glioma; H is co-culture

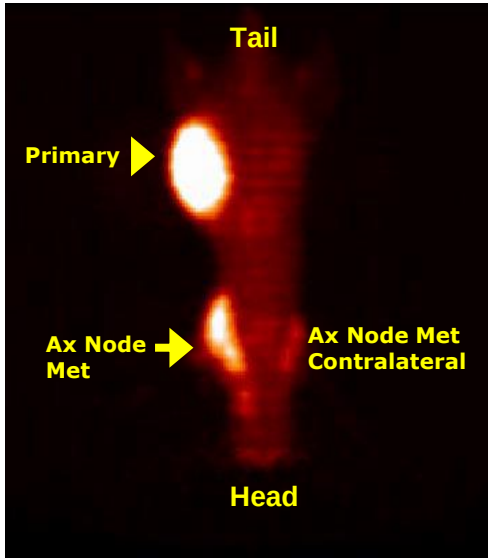


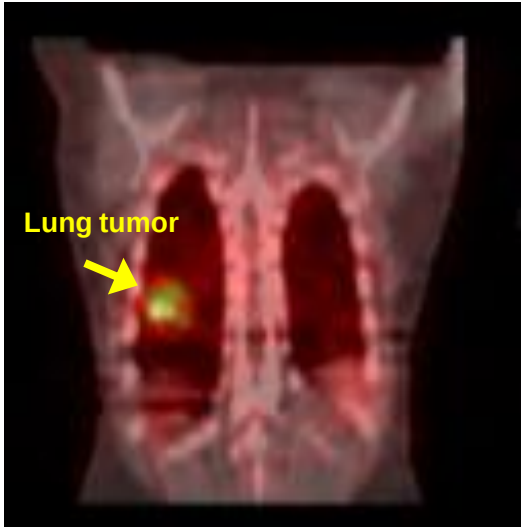
In vivo uptake in colorectal xenograft model. Image is 24 hours post infusion utilizing a near infra-red fluorescently labeled PLE.

Rationale for CLR 131 in DLBCL

- CLR 131 is a targeted radiotherapeutic leveraging PLE molecules to provide targeting of iodine-131 payload
- CLR 131 has been dosed in over 80 patients
  - Phase 1 and Phase 2 studies
  - Hematologic and solid tumor
- Here we provide initial data on the safety and efficacy of CLR 131 in relapsed or refractory diffuse large B-cell (DLBCL) patients including patients with progressive disease post CAR-T therapy

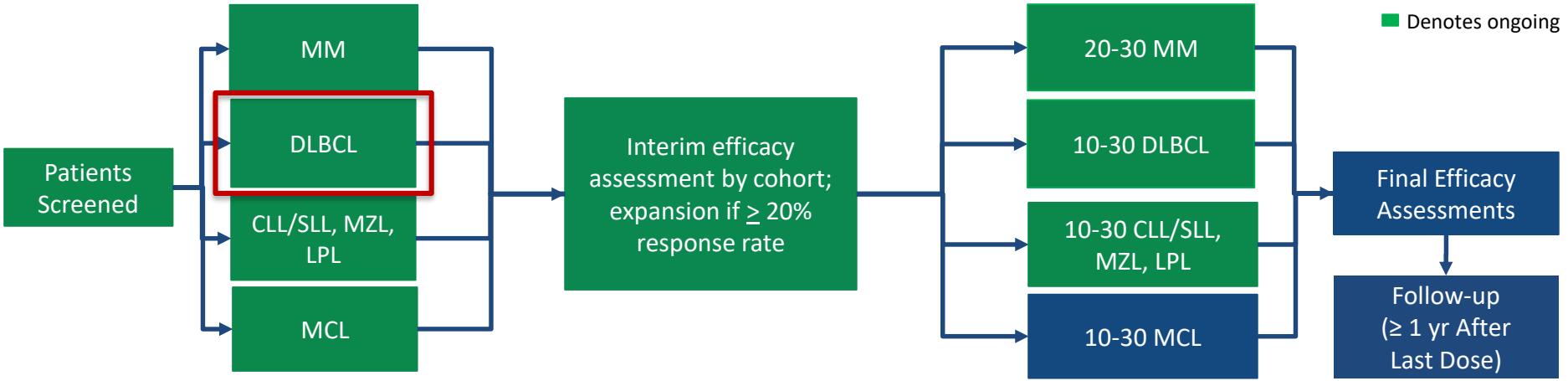
CLR 131 targeting in metastatic xenograft model





CLR 131 targeting in adult male with lung tumor

CLR 131: R/R Hematologic Phase 2 Study Overview
(Clover-1: NCT02952508)



- Dose finding study evaluating either single bolus or fractionated IV doses with max of 2 cycles
- Primary endpoint is efficacy as determined by response rates (IMWG or Lugano)
- Initial patients received a single 25mCi/m^2 bolus dose on day 1
- Patients now receive a fractionated 37.5mCi/m^2 dose
- Major eligibility requirements for DLBCL patients
  - Relapsed or refractory to at least 2 prior combination lines of treatment (must include rituximab)
  - ECOG 0 – 2: expected survival no less than 6 months
  - Treatment with CLR 131 would not exceed life-time maximum exposure to radiation

CLR 131 DLBCL Patient Characteristics

- Median age: 73 years (range 52 – 79)
- ECOG PS:
  - 0: 1/6 (15%)
  - 1: 4/6 (66.6%)
  - 2: 1/6 (15%)
- Subtype:
  - GCB: 3/6 (50%)
  - ABC: 3/6 (50%)
  - Cytogenic*
    - c-Myc: 1/3 (33.3%)
    - BCL-2: 0/3 (0.0%)
    - Dual: 1/3 (33.3%)
- Mean prior number of agents 3.3 (median = 3; range 1 – 9)
  - R-CHOP: 6/6 (100%)
  - RICE: 4/6 (66.6%)
  - ASCT: 2/6 (33.3%)
  - Other: 4/6 (66.6%)
- Refractory** 5/6 (83.3%)

* Data only available on 3 patients. ** Defined as disease progression within 60 days of treatment or post best response.

CLR 131 Safety Population – Summary of TEAEs (All Ph 2 Patients)

(Treatment Emergent AE / Regardless of Causality) ≥15% (N=20)

Event Term	Total Events	Grade 1/2	Grade 3/4
Anaemia	17 (85)	7 (35)	10 (50)
Neutropenia	13 (65)	2 (10)	11 (55)
Thrombocytopenia	18 (90)	1 (5)	17 (85)
Lymphocyte count decreased	9 (45)	3 (15)	6 (30)
White blood cell count decreased	15 (75)	4 (20)	11 (55)
Abdominal pain	3 (15)	3 (15)	0
Constipation	3 (15)	3 (15)	0
Diarrhea	5 (25)	5 (25)	0
Dry mouth	3 (15)	3 (15)	0
Nausea	6 (30)	6 (30)	0
Fatigue	11 (55)	7 (35)	4 (20)
Contusion	5 (25)	5 (25)	0
Decreased appetite	5 (25)	5 (25)	0
Hypoalbuminaemia	5 (25)	5 (25)	0
Hyponatraemia	3 (15)	3 (15)	0
Hypophosphataemia	5 (25)	3 (15)	2 (10)
Back pain	7 (35)	7 (35)	0
Pain in extremity	3 (15)	1 (5)	2 (10)
Dizziness	4 (20)	4 (20)	0
Headache	6 (30)	6 (30)	0
Anxiety	3 (15)	3 (15)	0
Dyspnoea	6 (30)	5 (25)	1 (5)
Hypotension	3 (15)	2 (10)	1 (5)

DLBCL Patients Only

Event Term	Total Events (%)	G1/2	G3/4
Anaemia	4 (67)	3	1
Neutropenia	2 (20)	1	1
Thrombocytopenia	4 (67)	1	3
Lymphocyte count decreased	2 (20)	0	2
White blood cell count decreased	4 (67)	2	2
Abdominal pain	2 (20)	2	0
Diarrhea	2 (20)	2	0
Fatigue	3 (50)	2	1
Non-cardiac chest pain	2 (20)	1	1
Contusion	2 (20)	2	0
Decreased appetite	3 (50)	3	0
Dizziness	2 (20)	2	0
Anxiety	2 (20)	2	0
Dyspnoea	2 (20)	1	1

Treatment Exposure

	Single Infusion
Dose	25mCi/m^2
Body surface area, median (range)	2.1m^2 (1.78 – 2.38m^2)
Average dose, mean (range)	52.68mCi (44.72 – 59.57mCi)
Tumor volume, median (range)	3471mm^3 (825 – 5285mm^3)
Infused dose to tumor ratio, median (range)	1.45% (0.9 – 7%)

Tumor Assessment and Disease Control Rates

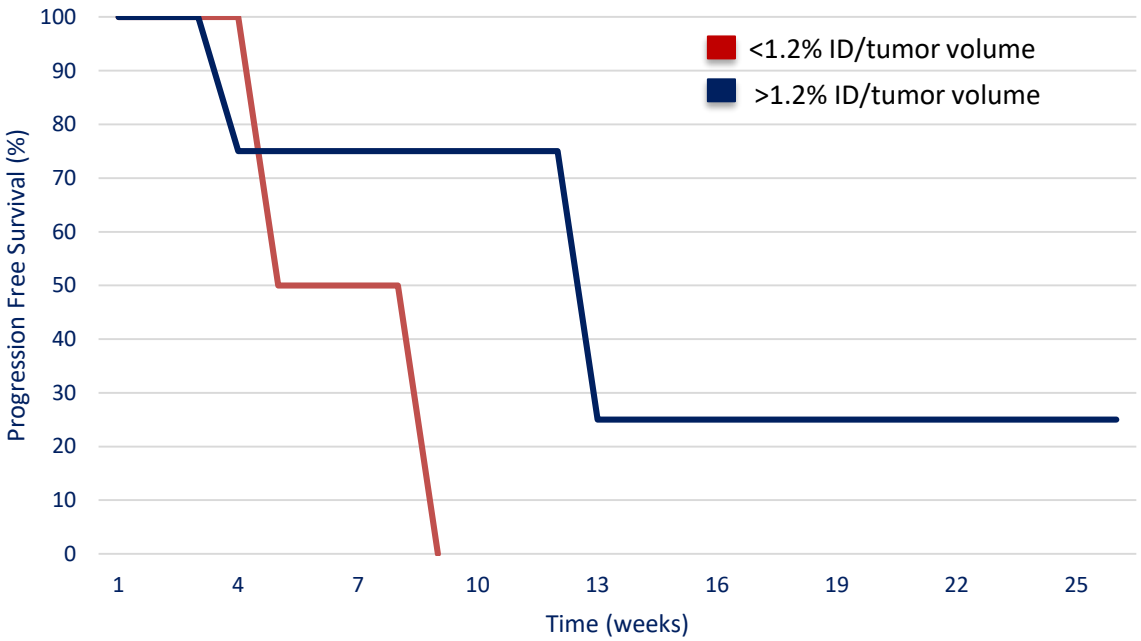
Disease Control Rate (DCR) (dose > 1.2% infused dose to tumor volume)
75% (3/4) at 12 weeks
25% (1/4) at 52 weeks
*CR + PR + SD per Lugano Criteria

Tumor Response (N=6)				
	Complete Response	Partial Response	Stable Disease	Progressive Disease
<50mCi (N=2)	0 (0%)	1/2 (50%)	1/2 (50%)	0 (0%)
50-55mCi (N=2)	0 (0%)	0 (0%)	0 (0%)	2/2 (100%)
>55mCi (N=2)	1/2 (50%)	0 (0%)	0 (0%)	1/2 (50%)

- Currently dose is driven by body surface area, however, this does not correlate to tumor size/volume
  - Does not discriminate responses by dose
- Ratio of millicurie dosed to tumor volume does discriminate
  - 3 of 4 highest dose to tumor volume correlated with stable disease or better
  - 1 of 4 had 9 prior therapies and was refractory to RCHOP, RICE, R-DHAP, BR, nivolumab + IDO inhibitor as well as another clinical stage compound
- Activity demonstrated in both GCB and ABC patients
- Unable to determine if expression of c-MYC and BCL-2 impacts activity

CLR 131 Progression-Free Survival

Patients treated with a ratio of dose to tumor volume >1.1 compared to ≤1.1



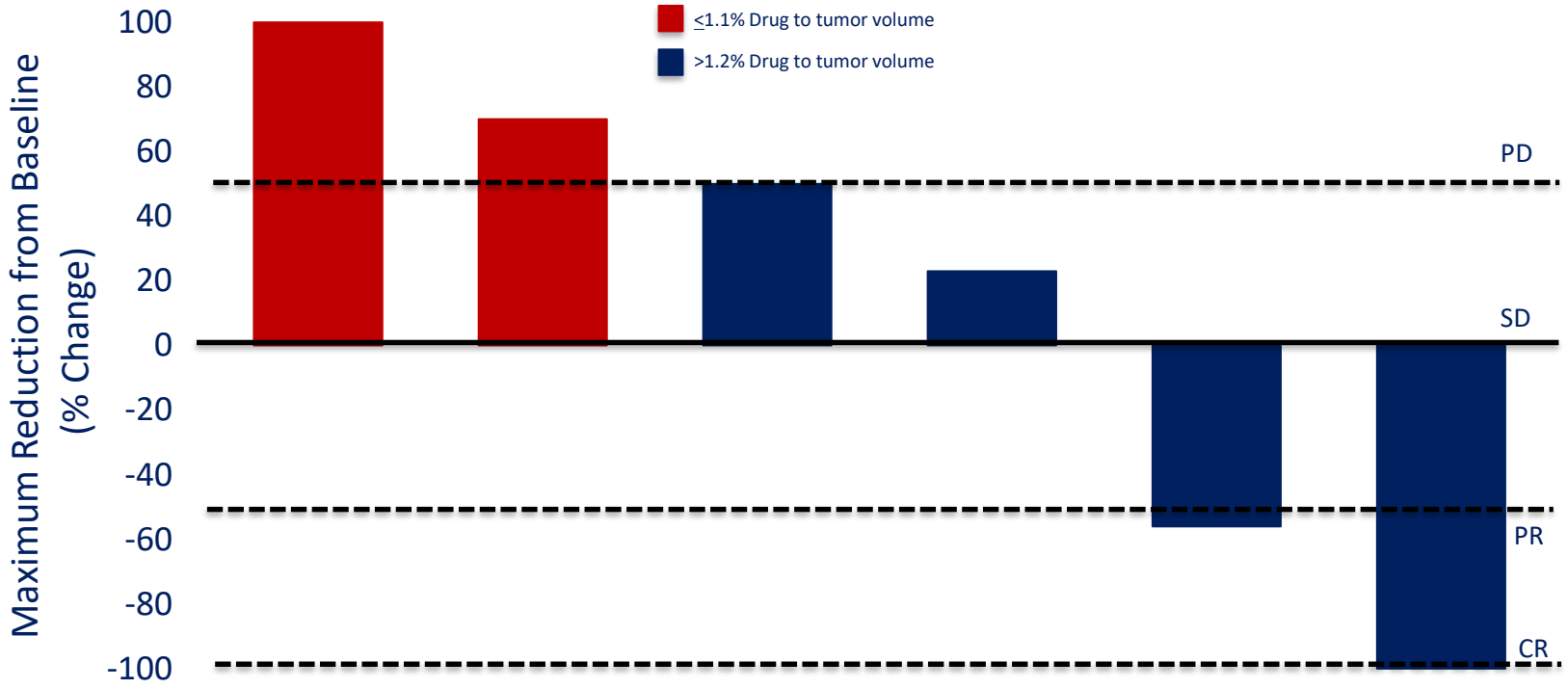
Number at risk

>1.1	4	3	3	3	1	1	1	1	1
≤1.1	**2**	1	1	0	0	0	0	0	0

- Despite small sample size, results suggest that infused dose to tumor volume ratio of less than 1.2 are insufficient
- Ratios of greater than 1.2 or greater are supported by the number of responses and duration of response post 7 weeks

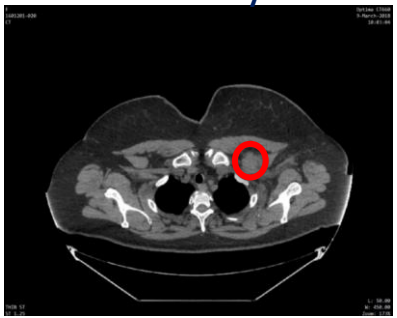
Waterfall Plot of DLBCL Patients

(Best Response per Lugano Criteria)

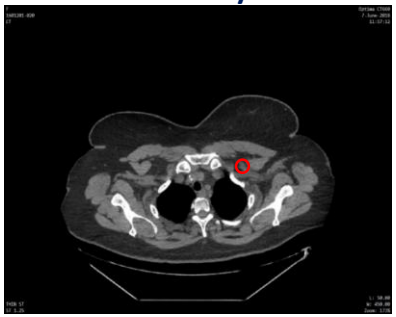


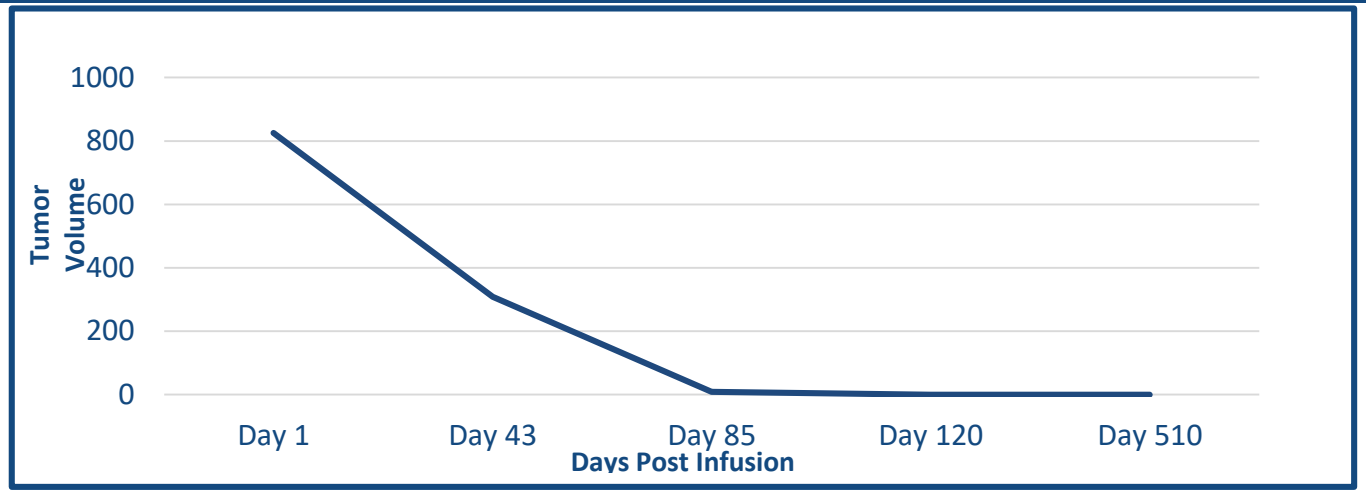
Evaluation of Complete Responder

Scan Day 1



Scan Day 85





- Female, 52 years old with subpectoral lymph node mass
  - Germinal cell
  - MYC positive; BCL-2 negative
- 3 prior lines of treatment (R-CHOP, RICE and chemo-soup)
- Relapse within 10 months of 1st line, determined to be refractory to 2nd and 3rd line treatments
- Patient continues to be complete response; 510+ days post treatment

Conclusions

- CLR 131 is well tolerated with cytopenic events being the dominate TEAE reported
  - Rate and severity of cytopenia reduced significantly when disease is extra-medullary
- CLR 131 is showing encouraging disease control in heavily pretreated DLBCL patients
  - Activity against both GCB and ABC variations
  - Activity against dual hit
- Dosing based upon tumor volume versus patient BSA may result in improved outcomes
  - Patients receiving higher ratio of infused drug to tumor volume experienced increased disease control and extended durability
- While early, the encouraging results strongly support testing of CLR 131 in a larger DLBCL patient population at the new higher dose of 37.5 mCi/m^2

Acknowledgements

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