

# FRACTIONATED DOSING OF CLR 131 IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM)

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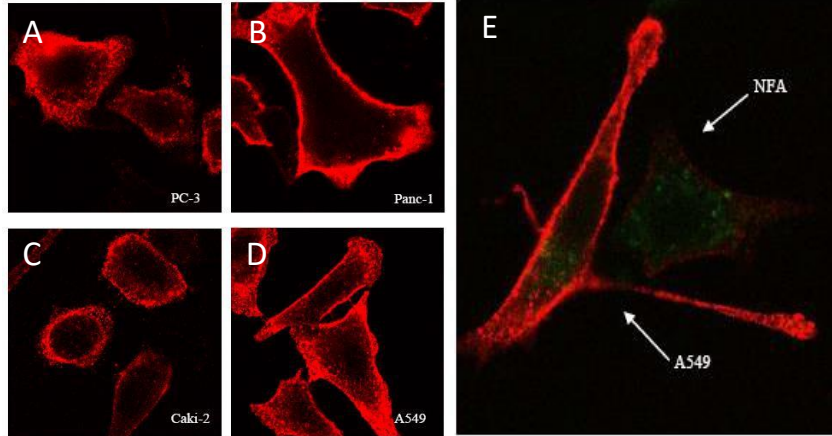
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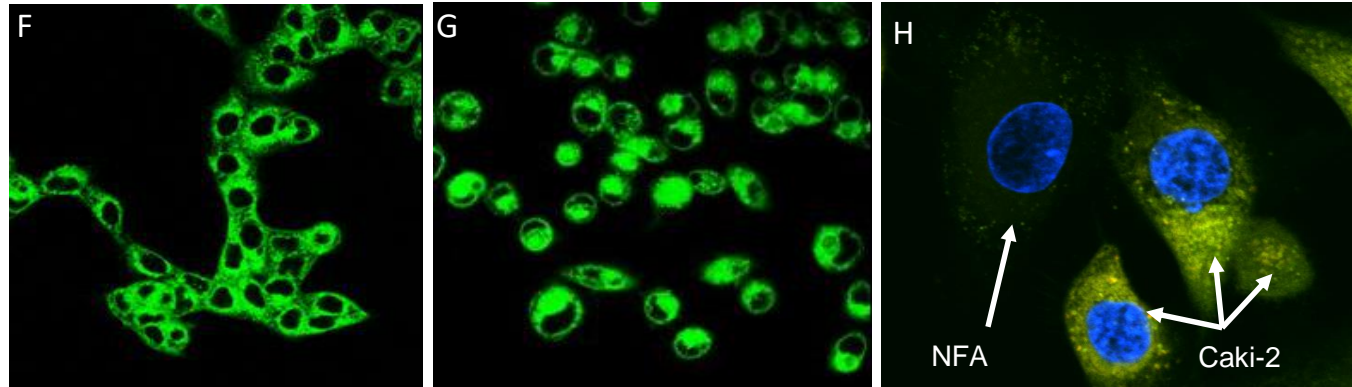
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# Background

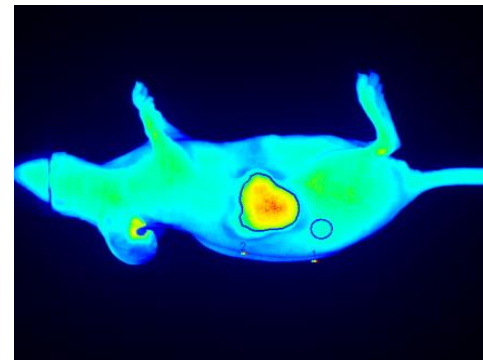
- Phospholipid ether (PLE) molecules are utilized to deliver cytotoxic molecules to tumors
- PLEs bind and enter tumor cells via lipid rafts; lipid rafts have been shown to be more prevalent and stabilized in tumor cells
- PLEs show preferential uptake in broad range of tumor cells; particularly hematologic 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 for 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

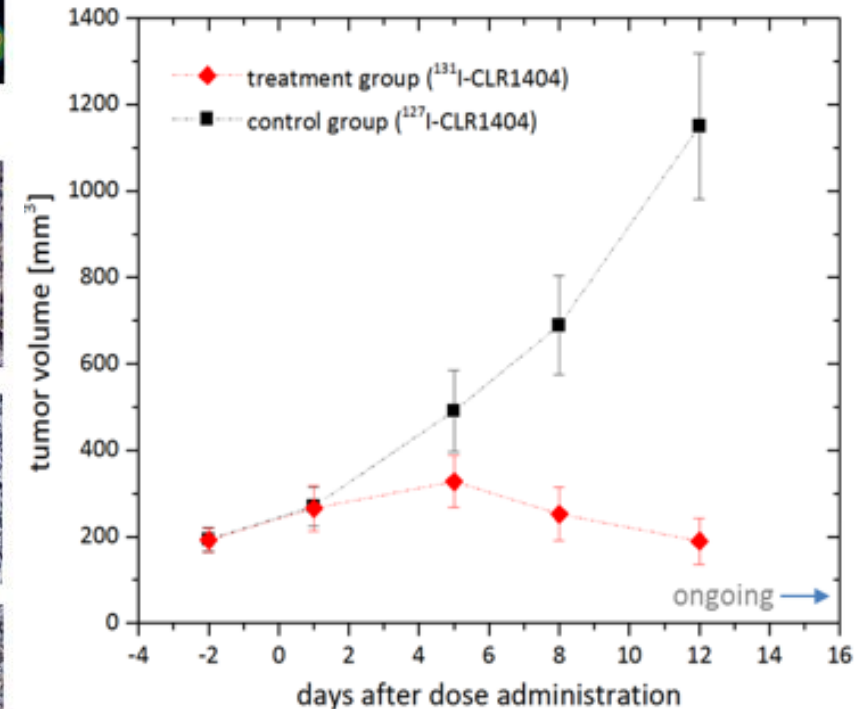
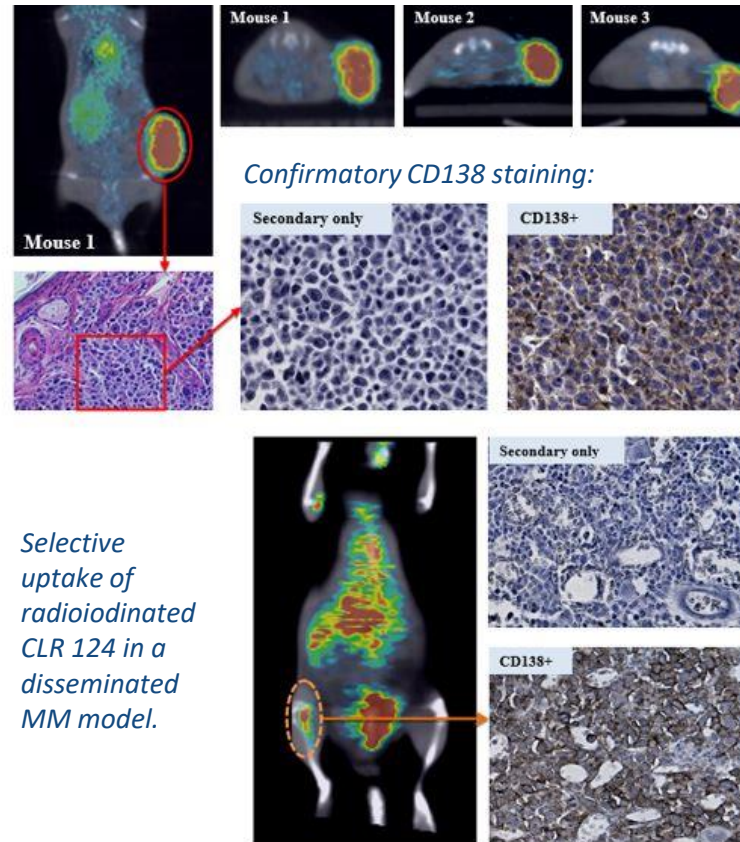


In vivo uptake in colorectal xenograft model. Image is 24 hours post infusion utilizing a near infra-red fluorescently labeled PLE.

# Rationale in RR Multiple Myeloma

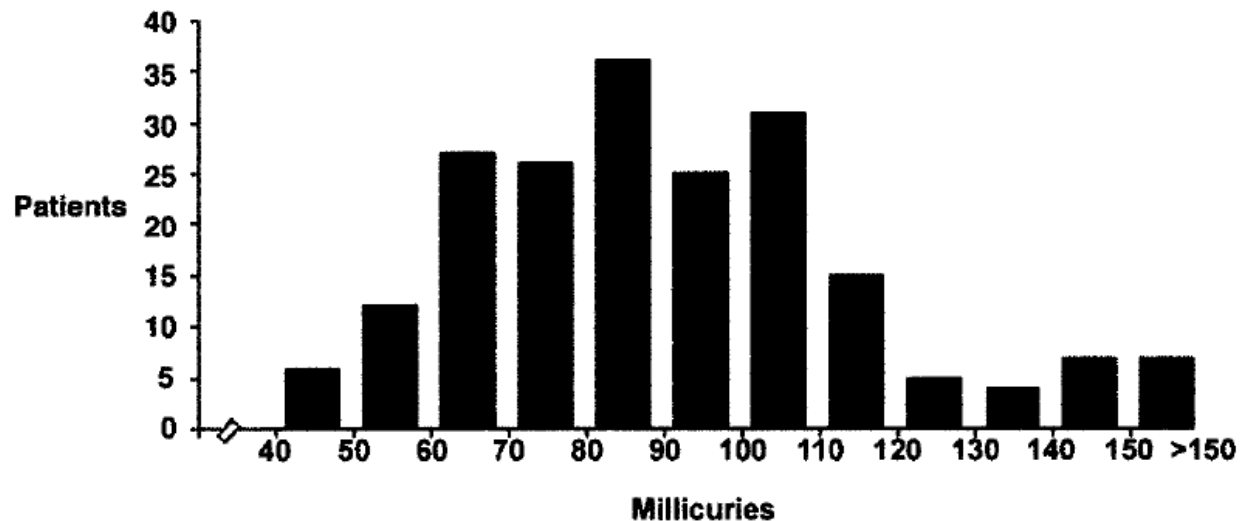
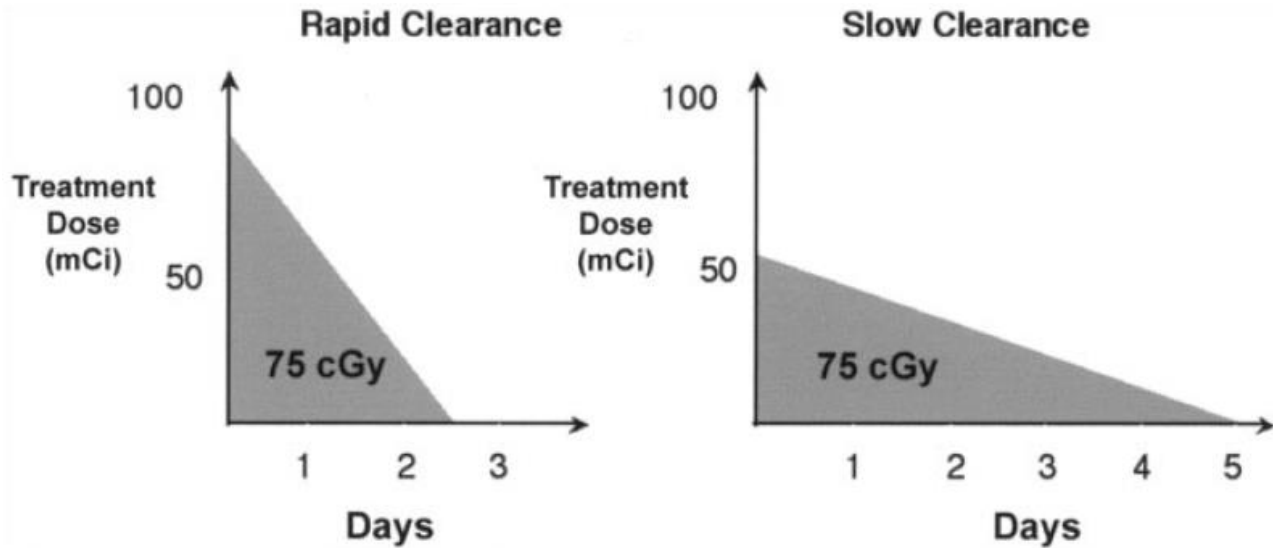
- CLR 131 is a targeted radiotherapeutic leveraging PLE molecules to provide targeting of an I-131 payload
- CLR 131 has been administered to over 80 patients (Phase 1/Phase 2 studies, hematologic and solid tumors)
- CLR 131 has demonstrated significant uptake and efficacy in preclinical multiple myeloma models with a single dose
- Here we provide initial clinical trial data on the benefits of fractionated dosing

Selective uptake of radioiodinated CLR 124 in MM flank xenograph tumors.



# Dosing Regimen Rationale

## Analysis of Bexxar and DeNardo Data



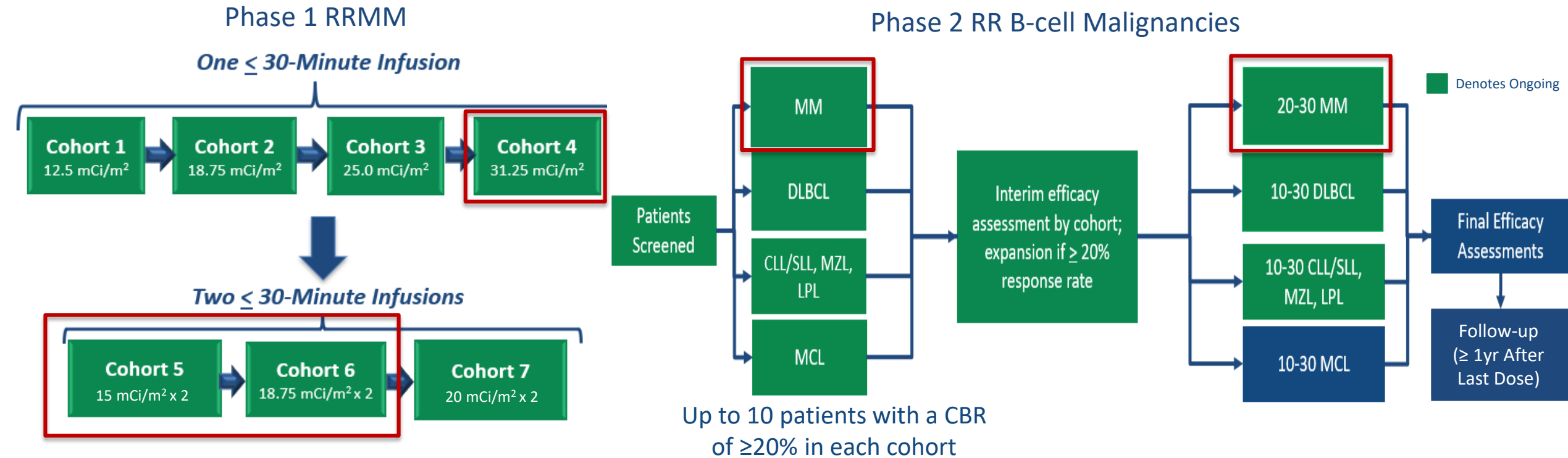
- It was demonstrated that 75cGy should be the target absorbed dose to be efficacious with I-131 (Bexxar)<sup>1</sup>
- Patients with rapid clearance will require higher doses to achieve the appropriate area under the curve to create the absorbed dose of 75cGy<sup>1</sup>
- The majority of patients require 90mCi or greater to achieve 75cGy absorbed dose<sup>1</sup>
  - 70% response rate when 75cGy achieved
- Fractionated dosing demonstrated an ability to increase the total body dose (and efficacy) without increasing the toxicity<sup>2</sup>
  - Tumor absorbed dose was increased
  - Bone marrow absorbed dose was decreased
  - Strategy allowed for treatment of patients with greater bone marrow involvement

1. Seldin, DW. Techniques for Using Bexxar for the Treatment of Non-Hodgkin's Lymphoma. *J Nuc Med Tech*. 2002; 30(3): 109-114.

2. DeNardo, GL., et al. Rationale, Evidence and Design Considerations for Fractionated Radioimmunotherapy. *Cancer*. 2002; 94(4): 1332 - 1347

# CLR 131 RR Hematologic Studies Overview

(Phase 1: NCT02278315; CLOVER-1: NCT02952508)



Data presented focuses on relapsed or refractory multiple myeloma patients receiving CLR 131 either as a single bolus dose at 31.25mCi/m<sup>2</sup> or one of two fractionated doses (31.25mCi/m<sup>2</sup> split in 2 or 37.5mCi/m<sup>2</sup> split in 2) + **low dose dexamethasone (40mg/week for 12 weeks).**

- ECOG 0-2; expected survival no less than 6 months
- No limit to number of prior therapies
- Designated study period: 85 days. Patients received weekly labs and AE assessments. Could be done locally.



# RRMM Fractionated Dose Patient Characteristics

	Bolus dose 31.25mCi/m <sup>2</sup> n=3	Fractionated Dose 31.25mCi/m <sup>2</sup> n=10	Fractionated Dose 37.5mCi/m <sup>2</sup> n=6	All Fractionated MM Subjects n=16
Median Age	67	69	74	71
Min	59	51	59	51
Max	70	75	83	83
Female	2	4	2	6
Male	1	6	4	10
Median Prior Therapies	5	5	4	4
Min	3	2	2	2
Max	8	13	6	13
Quad-refractory or greater (%)	66%	43%	80%	58%
Cytogenetics at Diagnosis				
High Risk	1	3	3	6
Not High Risk	2	4	2	6
Unknown	0	3	1	4

Data as of 30Jul2019

## Fractionated Cohorts Together:

- Median age: 71 years
- Average bone marrow plasma cell involvement: 23% (Range 1%-60%)
- Majority of patients are quad refractory or greater
  - 37.5mCi/m<sup>2</sup> cohort at 80%
- Quad- or more refractory: Refractory to 4 or more out of lenalidomide, bortezomib, pomalidomide, carfilzomib or daratumumab
- Cytogenetics shows even split between high risk and not high risk

# Safety Population - Summary of TEAEs

(Treatment Emergent AE / Regardless of Causality)  $\geq 20\%$

## All Grades

Event term	Bolus Dose 31.25mCi/m <sup>2</sup> n=3 (%)	Fractionated Dose 31.25mCi/m <sup>2</sup> n=10 (%)	Fractionated Dose 37.5mCi/m <sup>2</sup> n=6 (%)	All Fractionated Subjects n=16 (%)
Thrombocytopenia	3 (100)	7 (70)	4 (67)	11 (69)
Fatigue	3 (100)	6 (60)	4 (67)	10 (63)
Anemia	3 (100)	5 (50)	2 (33)	7 (44)
Neutropenia	3 (100)	5 (50)	2 (33)	7 (44)
Lymphocyte count decreased	3 (100)	6 (60)	1 (17)	7 (44)
White blood cell count decreased	3 (100)	6 (60)	1 (17)	7 (44)
Dyspnea	1 (33)	5 (50)	2 (33)	7 (44)
Nausea	3 (100)	2 (20)	2 (33)	4 (25)
Weight decreased	1 (33)	3 (30)	1 (17)	4 (25)
Headache	0	3 (30)	1 (17)	4 (25)

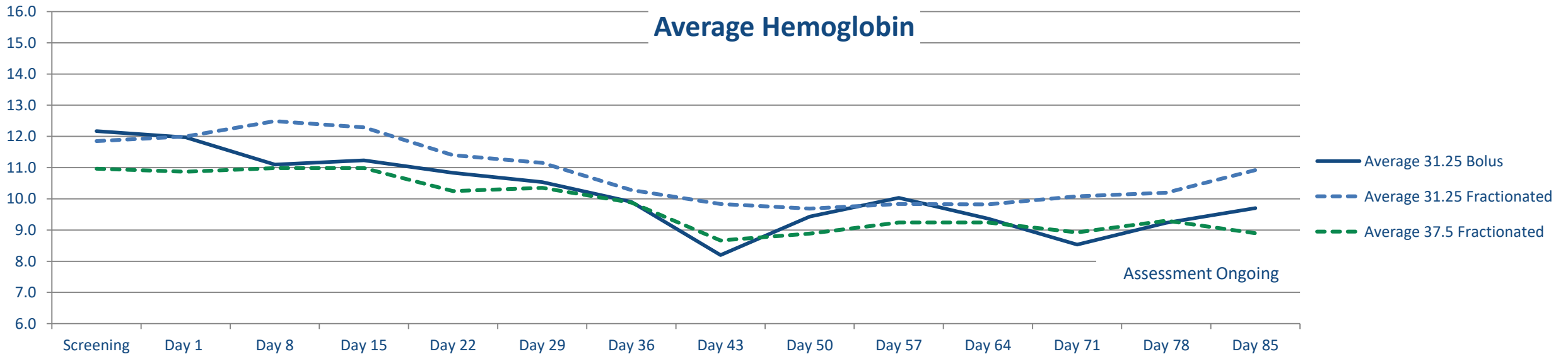
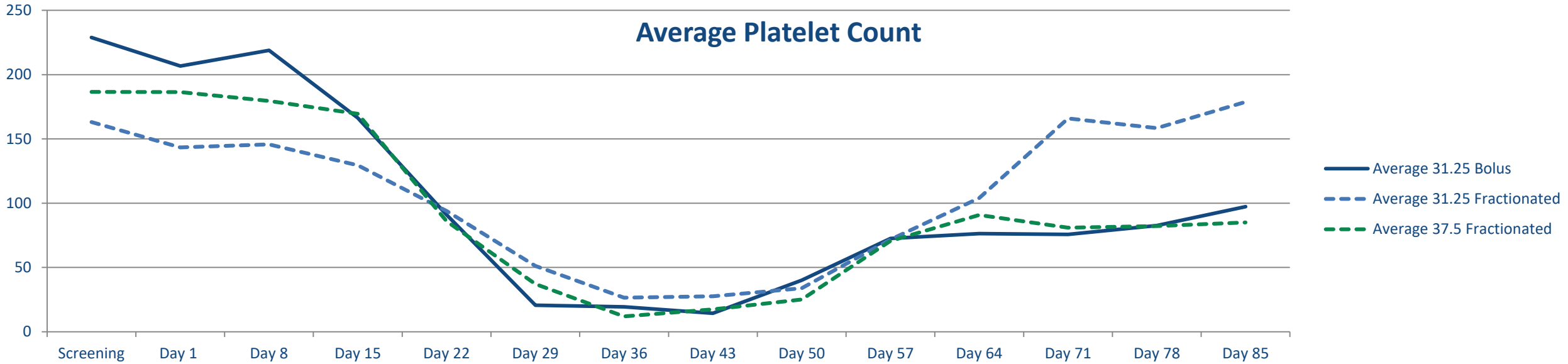
## Grade 3/4 Only

Event term	Bolus Dose 31.25mCi/m <sup>2</sup> n=3 (%)	Fractionated Dose 31.25mCi/m <sup>2</sup> n=10 (%)	Fractionated Dose 37.5mCi/m <sup>2</sup> n=6 (%)	All Fractionated Subjects n=16 (%)
Thrombocytopenia	3 (100)	7 (70)	4 (67)	11 (69)
Fatigue	2 (66.6)	1 (10)	0 (0)	1 (6)
Anemia	3 (100)	3 (30)	2 (33)	5 (42)
Neutropenia	3 (100)	5 (50)	2 (33)	7 (44)
Lymphocyte count decreased	3 (100)	6 (60)	1 (17)	7 (44)
White blood cell count decreased	3 (100)	5 (50)	1 (17)	6 (37)
Dyspnea	1 (33)	2 (20)	0 (0)	2 (12.5)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)
Weight decreased	0 (0)	0 (0)	0 (0)	0 (0)
Headache	0 (0)	0 (0)	0 (0)	0 (0)

Data as of 30Jul2019

- CLR 131 demonstrates limited “off-target” effects
  - No peripheral neuropathy, no changes in liver enzyme, and no renal toxicities
  - Cytopenias are the most common AE (Growth factor and transfusion support was as per institutional guidelines)
- Fractionated dosing demonstrates improved tolerability as compared to bolus dosing
  - Reduction in cytopenias

# CLR 131 Safety Population - Cytopenia Trends

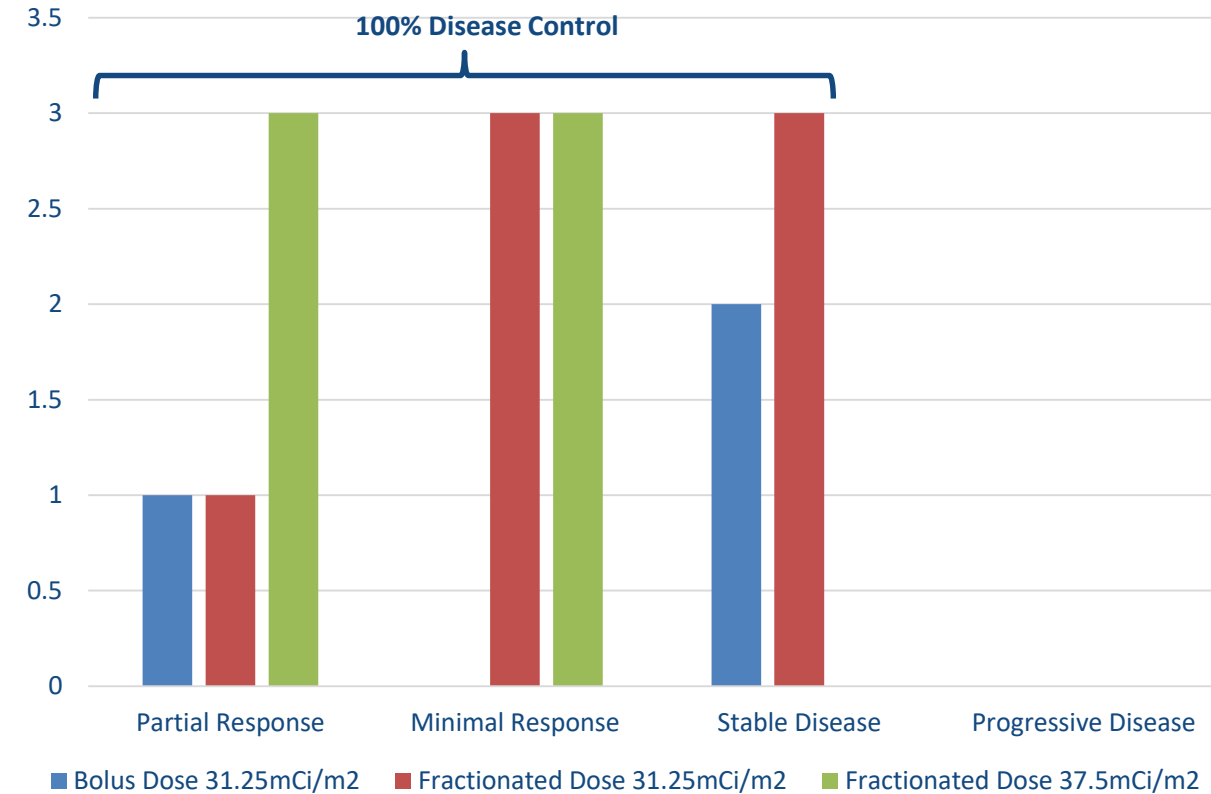




# Tumor Assessment & Disease Control Rates (During 85 Day Study Assess. Period)

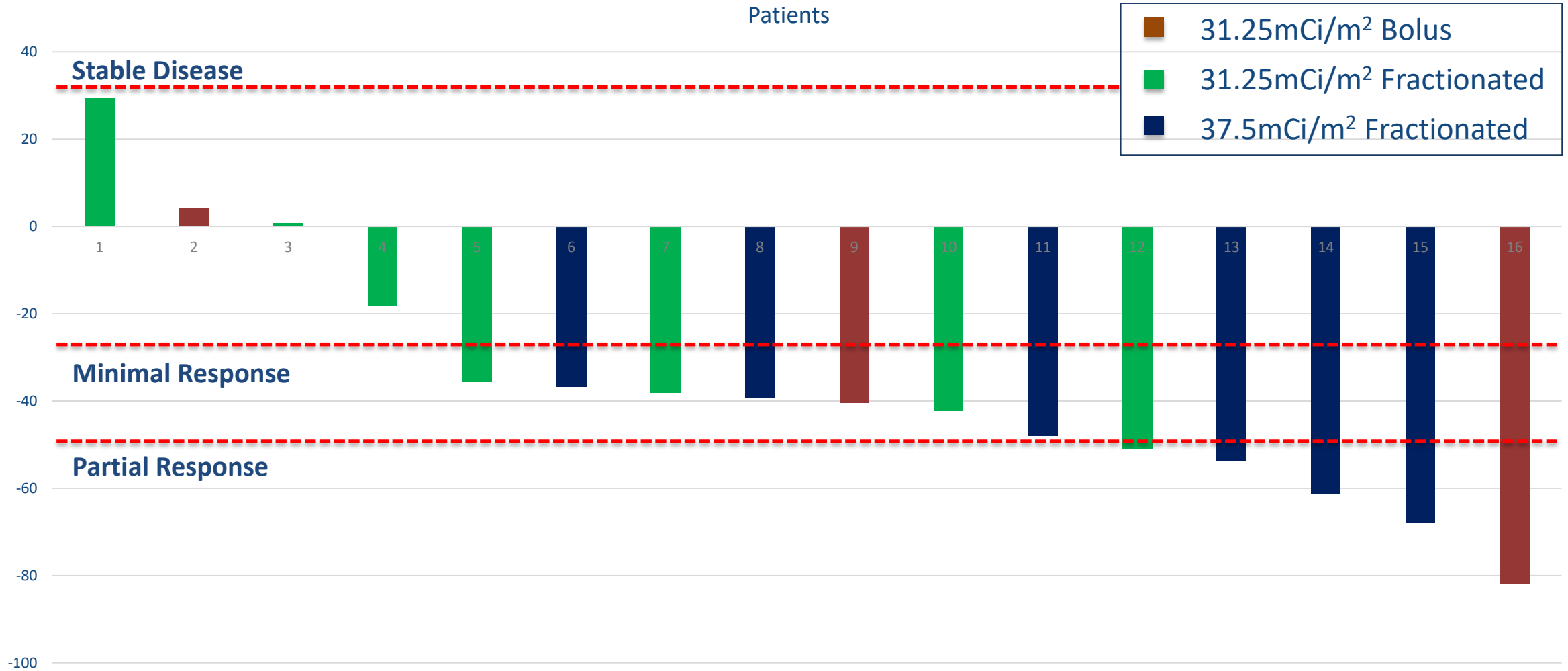
Tumor Response (n=16)				
	Bolus Dose 31.25mCi/m <sup>2</sup> n=3 (%)	Fractionated Dose 31.25mCi/m <sup>2</sup> n=7 (%)	Fractionated Dose 37.5mCi/m <sup>2</sup> n=6 (%)	All Fractionated MM Subjects n=13 (%)
Partial Response	1 (33)	1 (14.3)	3 (50)	5 (30.8)
Minimal Response	0	3 (42.9)	3 (50)	6 (46.1)
Stable Disease	2 (66)	3 (42.9)	0	3 (23.1%)
Progressive Disease	0	0	0	0

Data as of 30Jul2019



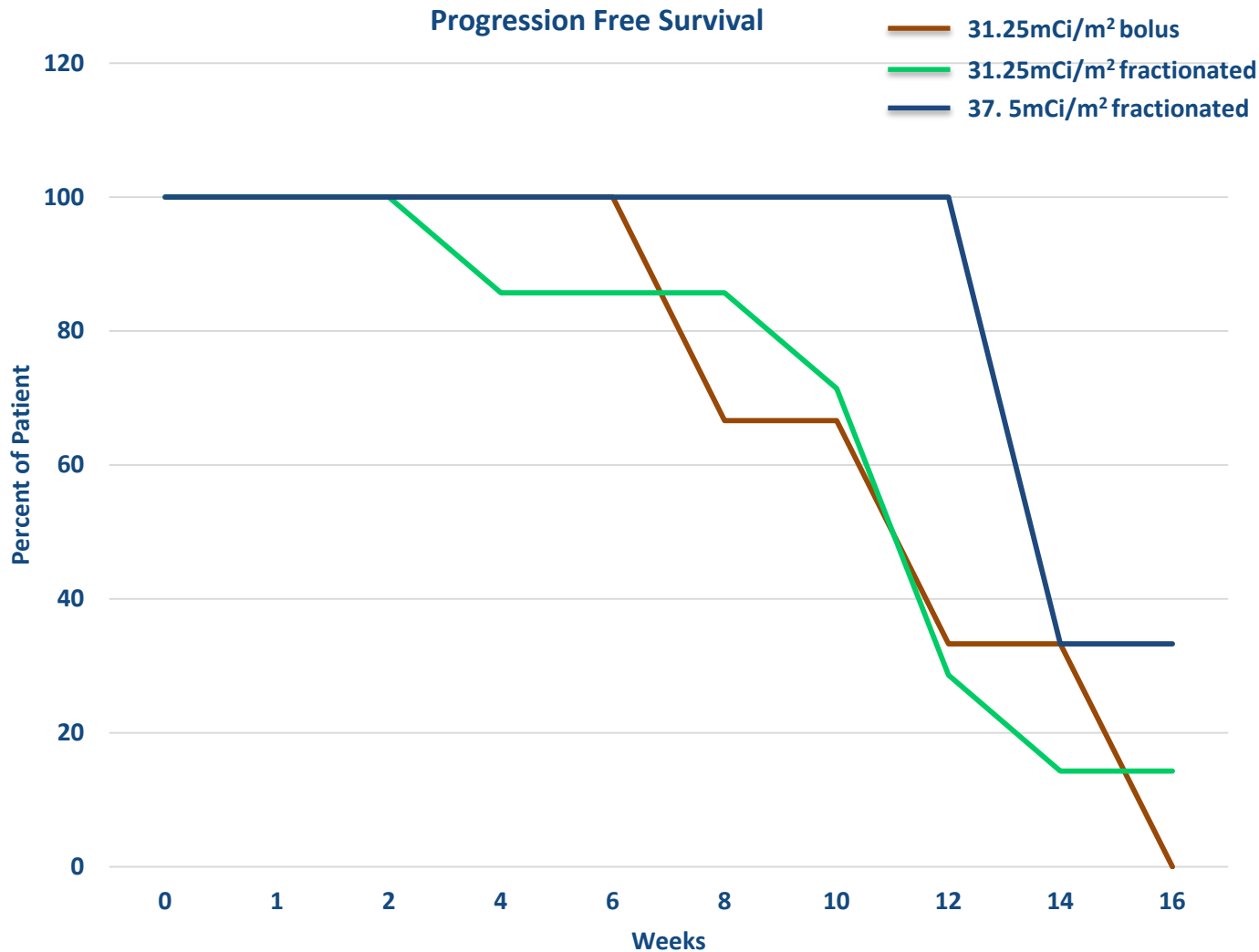
- Mean follow up of patients on fractionated dosing (n=13): 4.4 months
- Overall response rate (ORR):
  - All patients presented (n=16): 31.3%
  - Fractionated dosing (n=13): 30.8%
  - Fractionated dosing at 37.5mCi/m<sup>2</sup>: 50%

# Waterfall Plot of Best Patient Responses



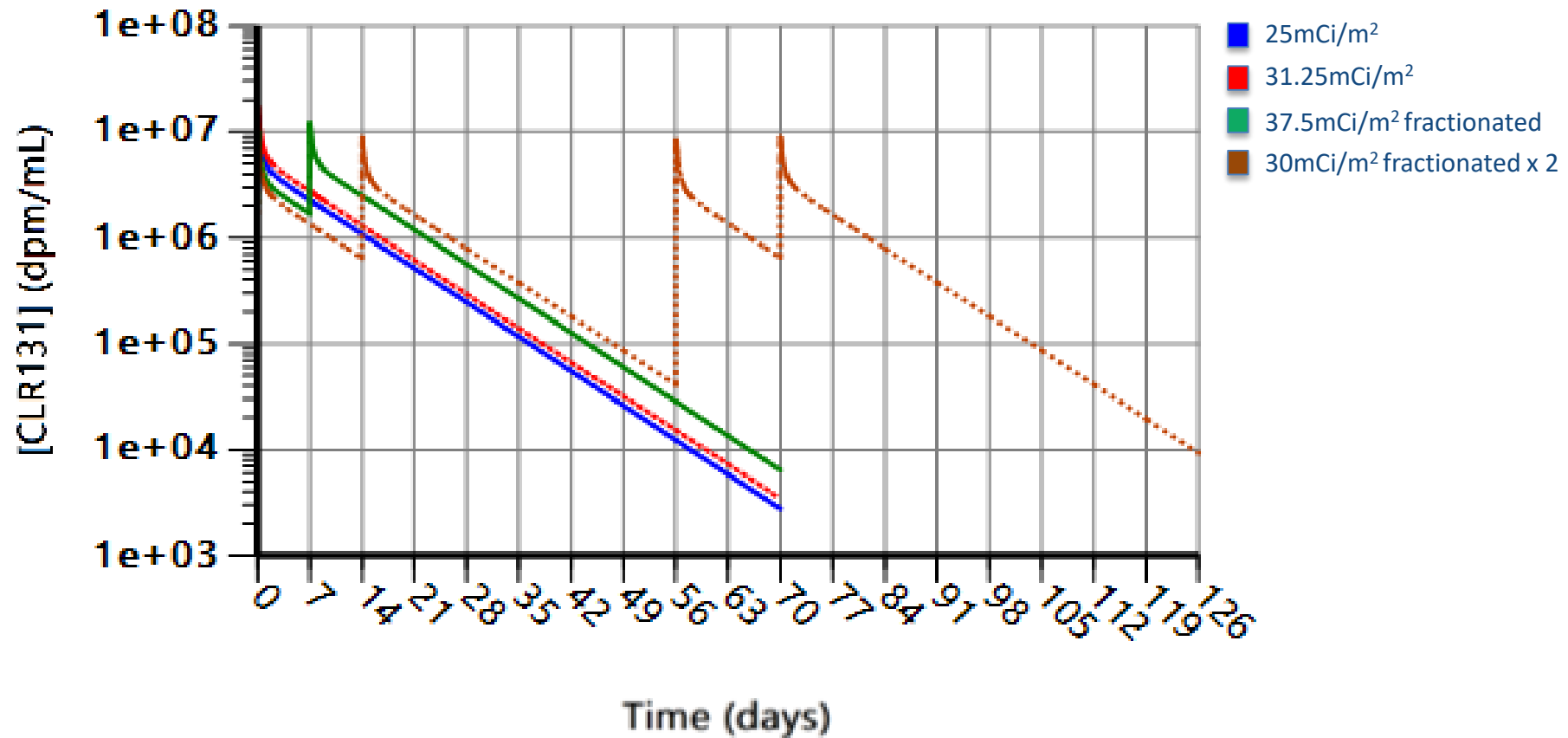
Fractionated dosing results in greater reduction in M-protein or FLC versus bolus dosing

# Kaplan Meier Curve of Progression Free Survival



- All 3 dosing regimens show CLR 131 progression free survival (PFS) is consistent with other RRMM drugs
  - To date, median PFS approximately 3-4 months in all three doses
- Fractionated dosing appears to improve progression free survival
  - Both fractionated doses have patients exceeding 6 months of PFS
- Majority of patients are quad refractory or greater
  - 37.5mCi/m<sup>2</sup> cohort: 80%
- Patients alive at the time of data cut off: 13

# Pharmacokinetics By Dosing Regime of CLR 131



- Increased plasma exposure has demonstrated increased tumor uptake and increased responses
- Cycle two could more than double the plasma exposure further increasing tumor uptake and potentially increasing overall responses, durability of responses, progression free survival and overall survival

# Conclusions

- CLR 131 is well tolerated with cytopenic events being the majority of TEAE reported
  - Fractionated dosing improves tolerability over bolus dosing
- CLR 131 demonstrates efficacy in late line, heavily pretreated and multiple-agent refractory multiple myeloma patients
  - Approximately 30% ORR observed across all doses
  - 50% ORR with 37.5mCi/m<sup>2</sup> fractionated dose
  - 100% disease control rate across all doses (over the study period)
- Fractionated dosing demonstrates increasing response rates vs. bolus dose
- The efficacy data is comparable to certain other novel agents in combination with dexamethasone, with the advantage of non-continuous dosing and predictable AEs.
- This data warrants further clinical development of CLR I 131. Ongoing clinical trials will pave the way for future studies including combination therapies, and repeat dosing.

# Acknowledgements

**Mayo Clinic Florida<sup>1,2</sup>**

**University of Wisconsin Carbone Cancer Center<sup>1,2</sup>**

**Cardinal Bernardin Cancer Center, Loyola University<sup>1,2</sup>**

**Fred Hutchinson Cancer Research Center<sup>2</sup>**

**University of Kansas<sup>2</sup>**

**Redlands Community Hospital<sup>2</sup>**

**University of Rochester<sup>2</sup>**

**Prism Health Cancer Center<sup>2</sup>**

**Ochsner Cancer Institute<sup>2</sup>**

**Northwestern - Warrenville<sup>2</sup>**

<sup>1</sup>Phase 1 (NCT02278315); <sup>2</sup>Phase 2 CLOVER-1 (NCT02952508)

*Additionally, we would like to thank all of the patients and their families for their participation and support of clinical trials*