Fractionated Dosing of CLR 131 in Patients with Relapsed or Refractory Multiple Myeloma (RRMM)

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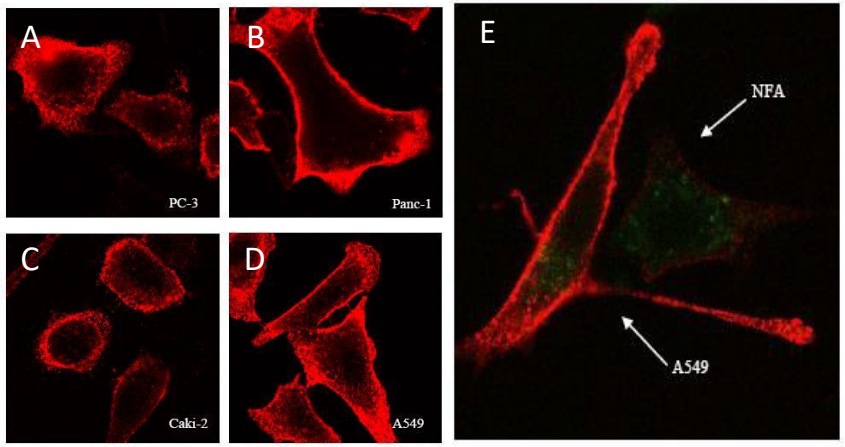
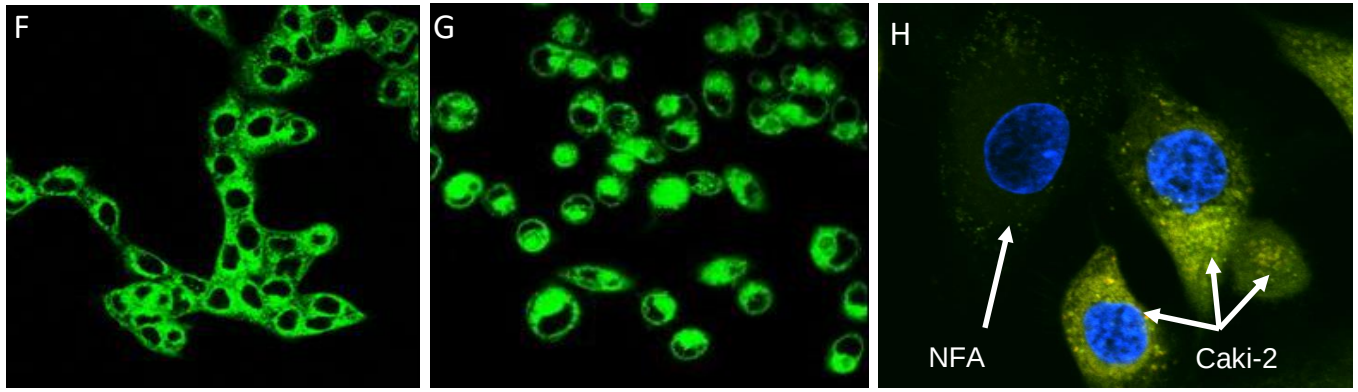
[6]Fred Hutchinson Cancer Research Center; [7]Cellectar Biosciences

Background

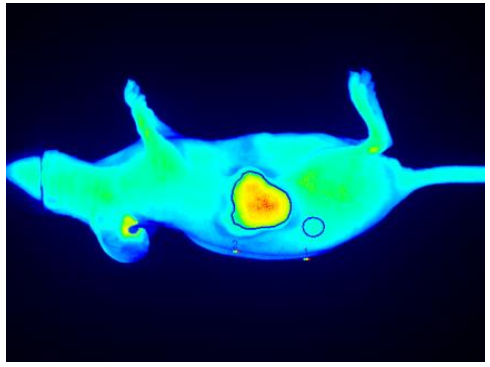
- Phospholipid ether (PLE) molecules are utilized to deliver cytotoxic molecules to tumors
- PLEs bind and enter tumor cells via lipid rafts; lipid rafts have been shown to be more prevalent and stabilized in tumor cells
- PLEs show preferential uptake in broad range of tumor cells; particularly hematologic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

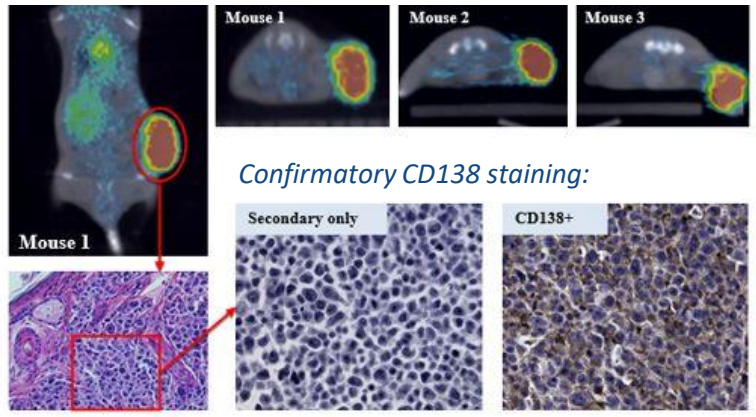


In vivo uptake in colorectal xenograft model. Image is 24 hours post infusion utilizing a near infra-red fluorescently labeled PLE.

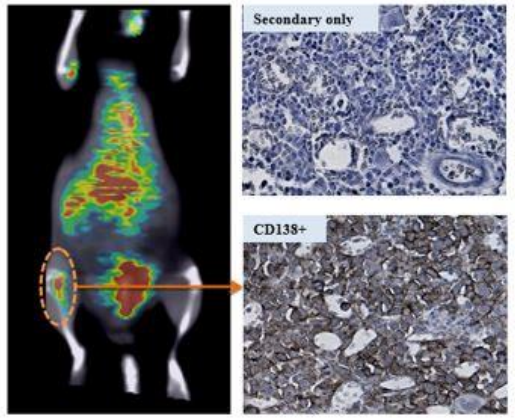
Rationale in RR Multiple Myeloma

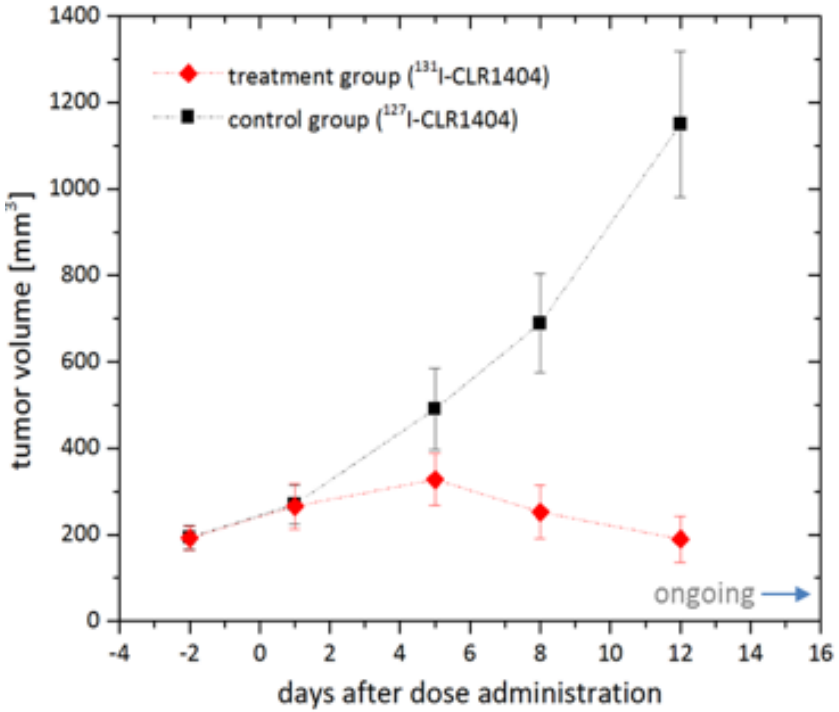
- CLR 131 is a targeted radiotherapeutic leveraging PLE molecules to provide targeting of an I-131 payload
- CLR 131 has been administered to over 80 patients (Phase 1/Phase 2 studies, hematologic and solid tumors)
- CLR 131 has demonstrated significant uptake and efficacy in preclinical multiple myeloma 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.



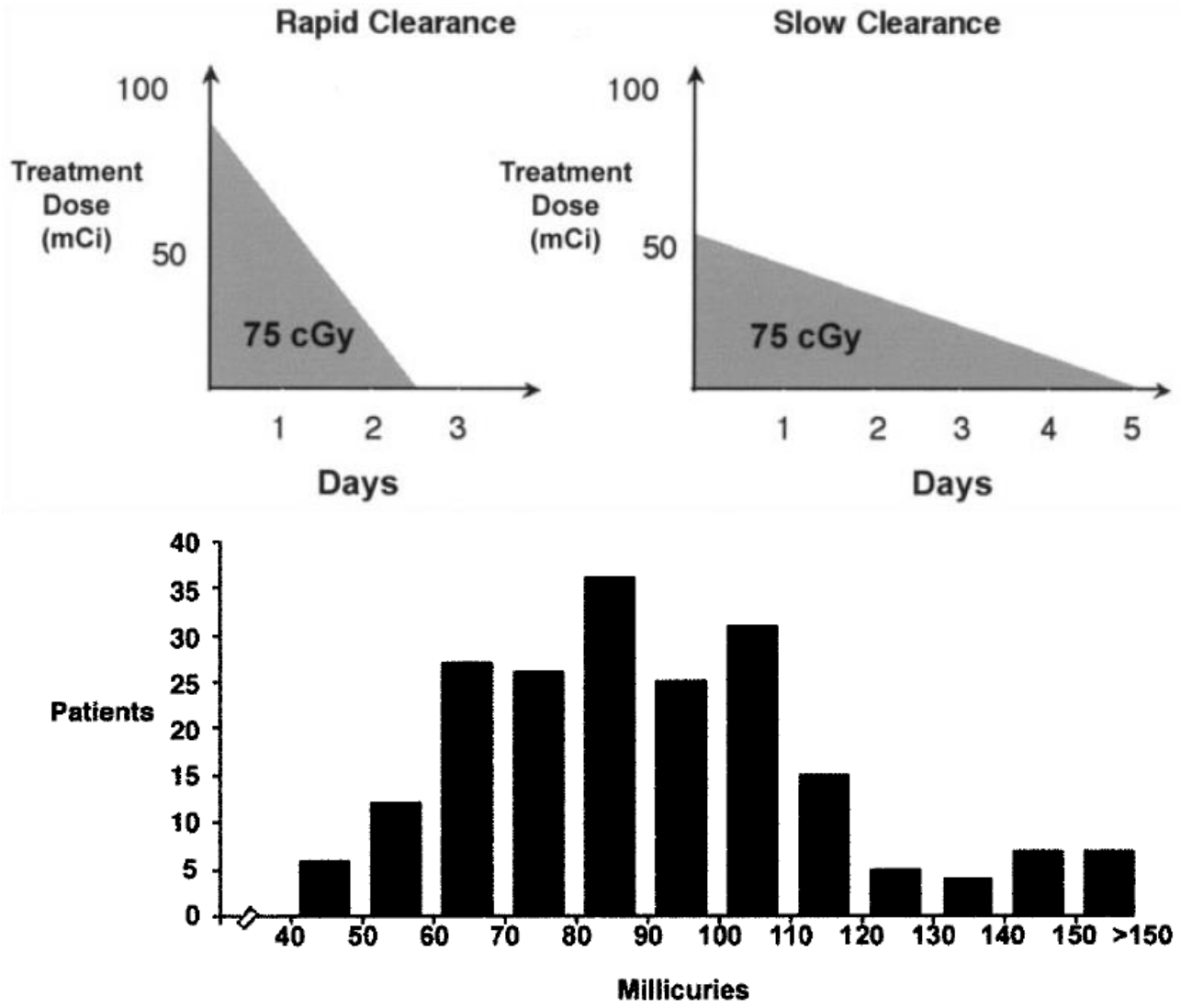
Selective uptake of radioiodinated CLR 124 in a disseminated MM model.





Dosing Regimen Rationale

Analysis of Bexxar and DeNardo Data

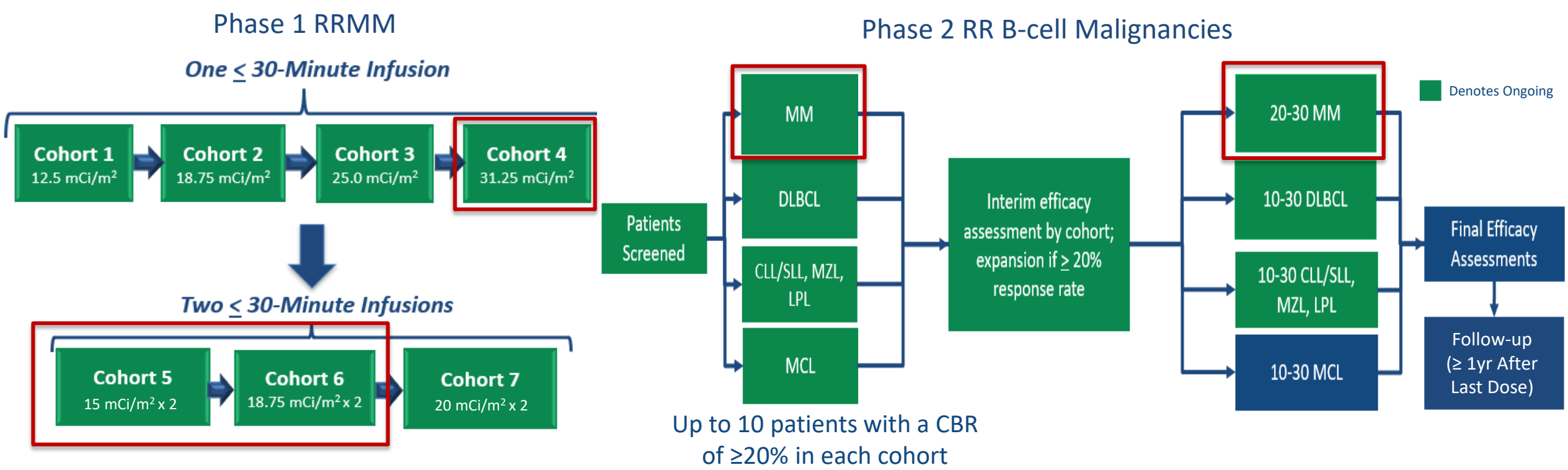


- It was demonstrated that 75cGy should be the target absorbed dose to be efficacious with I-131 (Bexxar)[1]
- Patients with rapid clearance will require higher doses to achieve the appropriate area under the curve to create the absorbed dose of 75cGy[1]
- The majority of patients require 90mCi or greater to achieve 75cGy absorbed dose [1]
  - 70% response rate when 75cGy achieved
- Fractionated dosing demonstrated an ability to increase the total body dose (and efficacy) without increasing the toxicity[2]
  - 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^2 or one of two fractionated doses (31.25mCi/m^2 split in 2 or 37.5mCi/m^2 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^2 n=3	Fractionated Dose 31.25mCi/m^2 n=10	Fractionated Dose 37.5mCi/m^2 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^2 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) ≥20%

All Grades

Event term	Bolus Dose 31.25mCi/m² n=3 (%)	Fractionated Dose 31.25mCi/m² n=10 (%)	Fractionated Dose 37.5mCi/m² 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)

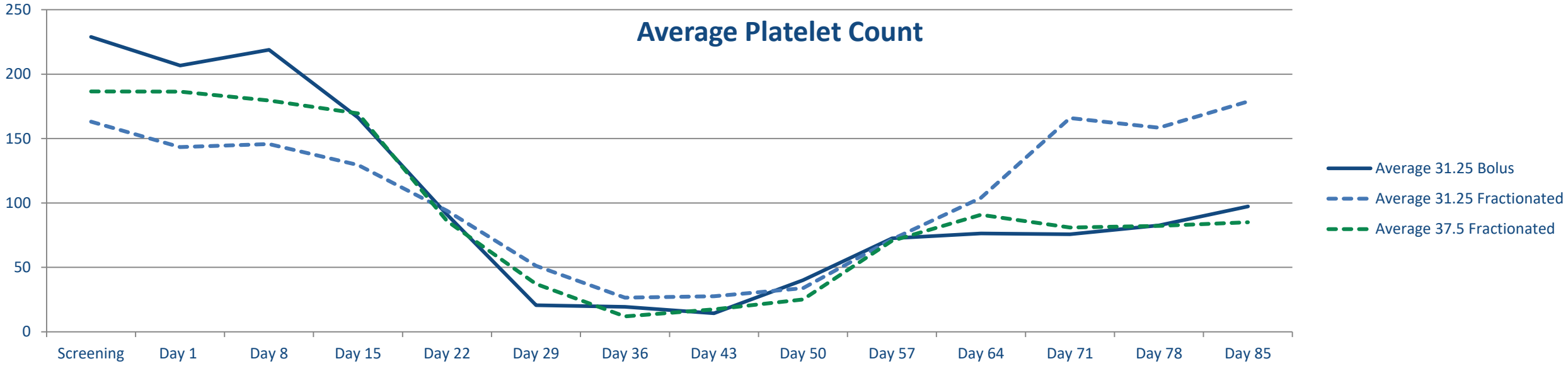
Grade 3/4 Only

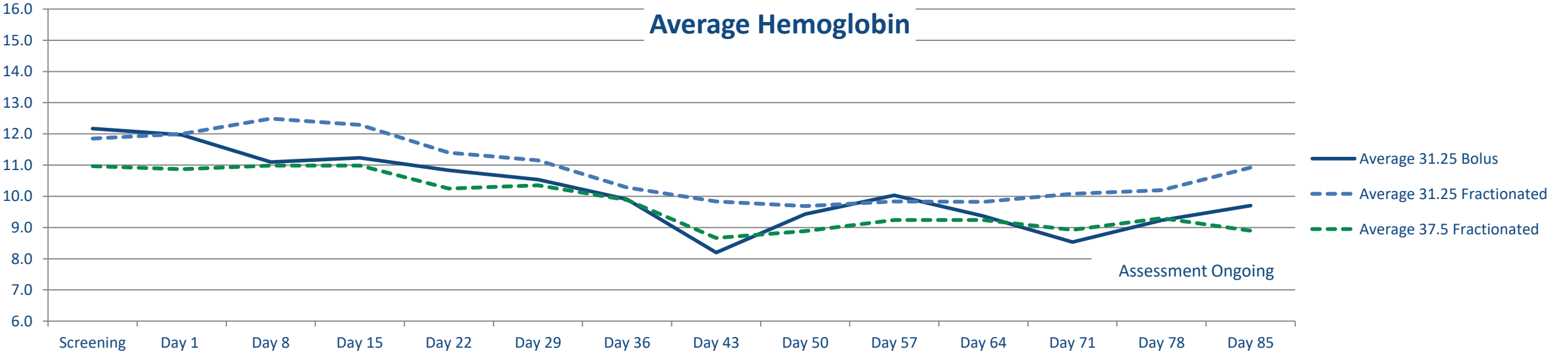
Bolus Dose 31.25mCi/m² n=3 (%)	Fractionated Dose 31.25mCi/m² n=10 (%)	Fractionated Dose 37.5mCi/m² n=6 (%)	All Fractionated Subjects n=16 (%)
3 (100)	7 (70)	4 (67)	**11 (69)**
2 (66.6)	1 (10)	0 (0)	**1 (6)**
3 (100)	3 (30)	2 (33)	**5 (42)**
3 (100)	5 (50)	2 (33)	**7 (44)**
3 (100)	6 (60)	1 (17)	**7 (44)**
3 (100)	5 (50)	1 (17)	**6 (37)**
1 (33)	2 (20)	0 (0)	**2 (12.5)**
0 (0)	0 (0)	0 (0)	**0 (0)**
0 (0)	0 (0)	0 (0)	**0 (0)**
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

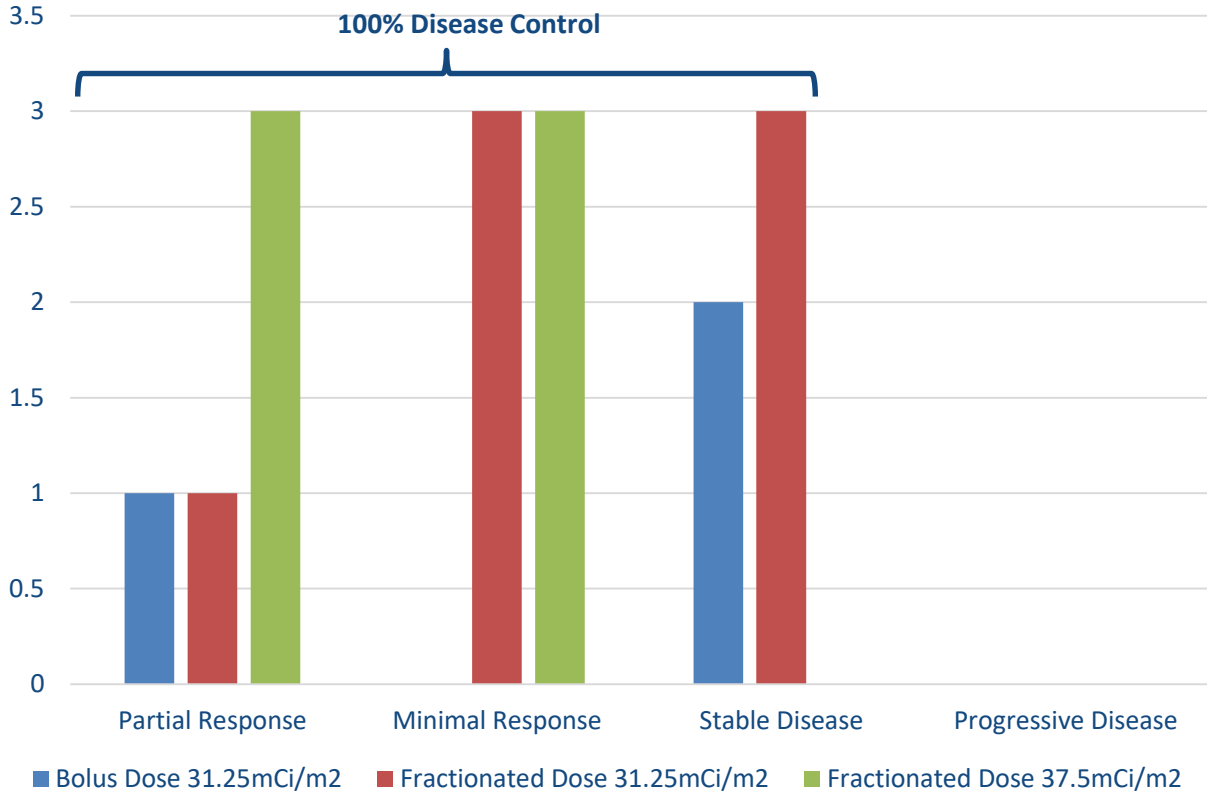




Tumor Assessment & Disease Control Rates (During 85 Day Study Assess. Period)

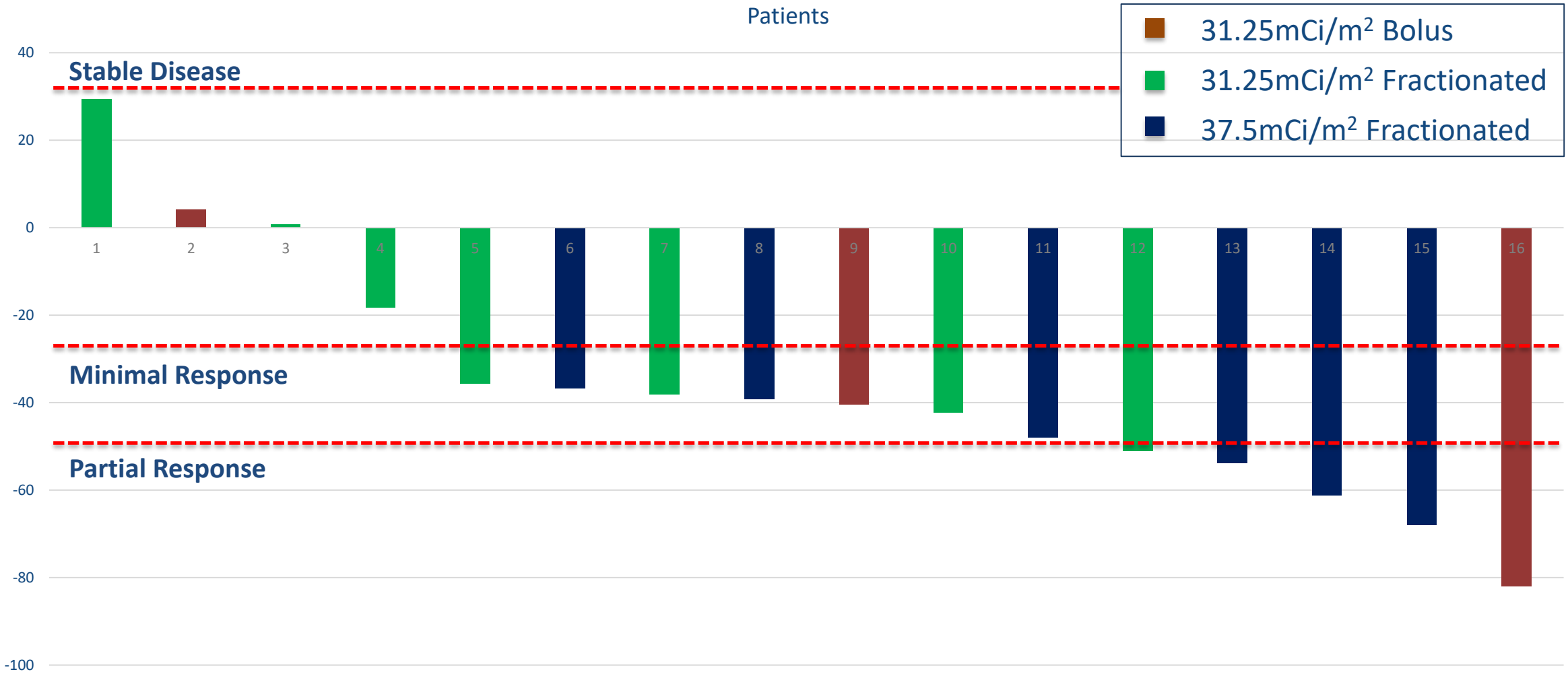
Tumor Response (n=16)				
	Bolus Dose 31.25mCi/m² n=3 (%)	**Fractionated Dose 31.25mCi/m² n=7 (%)**	**Fractionated Dose 37.5mCi/m² n=6 (%)**	**All Fractionated MM Subjects n=13 (%)**
Partial Response	1 (33)	1 (14.3)	3 (50)	5 (30.8)
Minimal Response	0	3 (42.9)	3 (50)	6 (46.1)
Stable Disease	2 (66)	3 (42.9)	0	3 (23.1%)
Progressive Disease	0	0	0	0

Data as of 30Jul2019



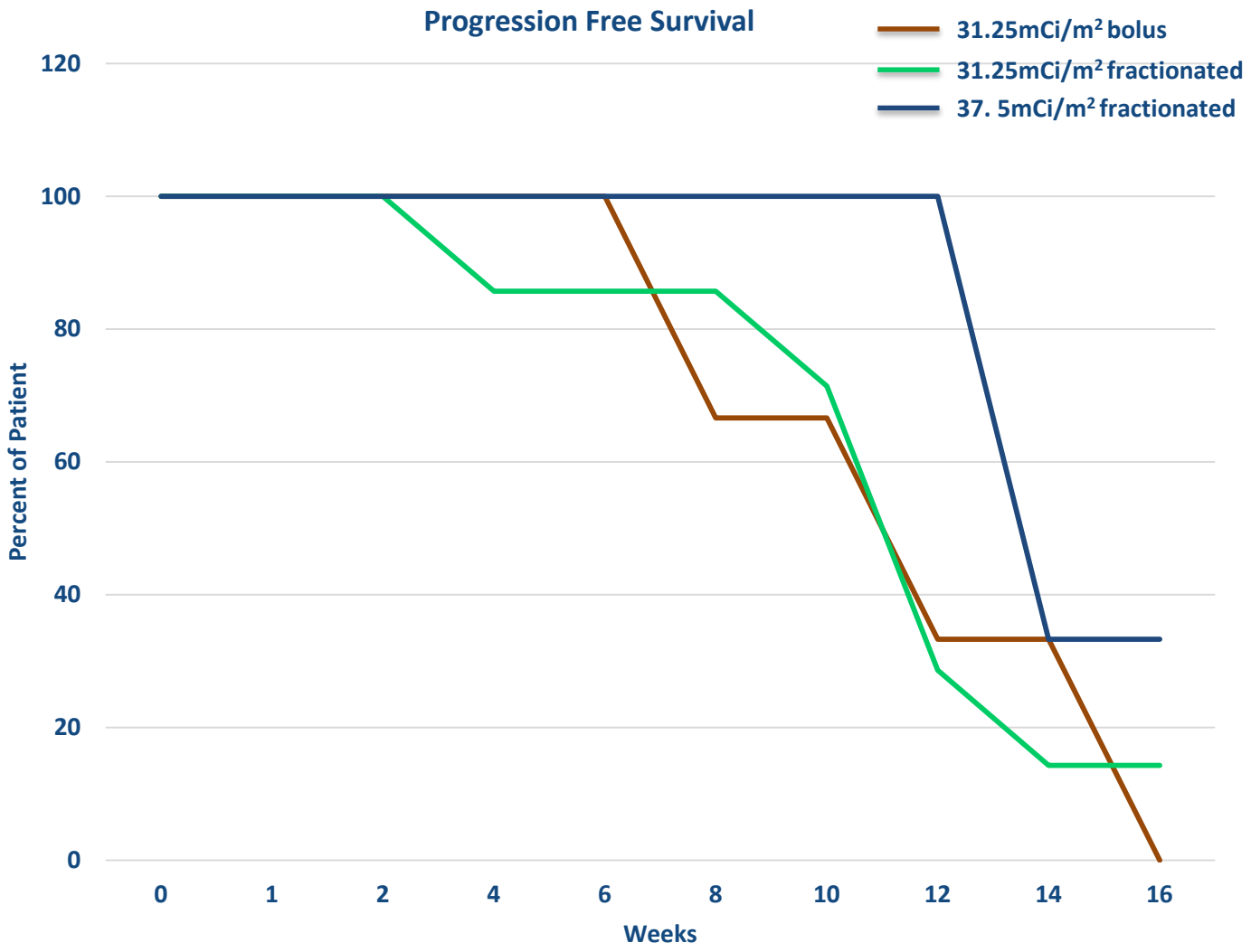
- Mean follow up of patients on fractionated dosing (n=13): 4.4 months
- Overall response rate (ORR):
  - All patients presented (n=16): 31.3%
  - Fractionated dosing (n=13): 30.8%
  - Fractionated dosing at 37.5mCi/m^2: 50%

Waterfall Plot of Best Patient Responses



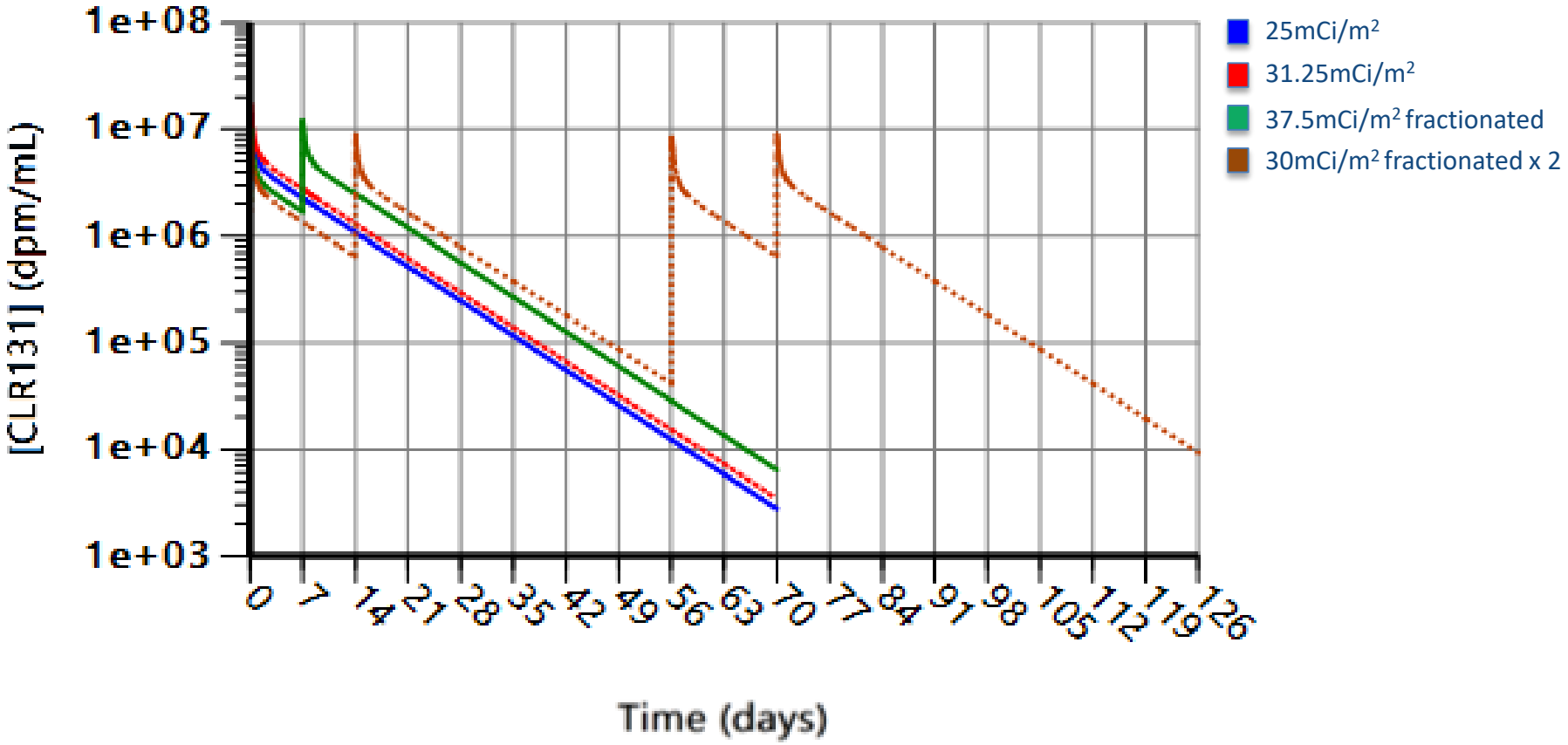
Fractionated dosing results in greater reduction in M-protein or FLC versus bolus dosing

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^2 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^2 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[1,2]

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University of Kansas[2]

Redlands Community Hospital[2]

University of Rochester[2]

Prism Health Cancer Center[2]

Ochsner Cancer Institute[2]

Northwestern - Warrenville[2]

[1]Phase 1 (NCT02278315); [2]Phase 2 CLOVER-1 (NCT02952508)

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