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Efficacy of fractionated injections of CLR 131 in an OPM-2 mouse model

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BACKGROUND

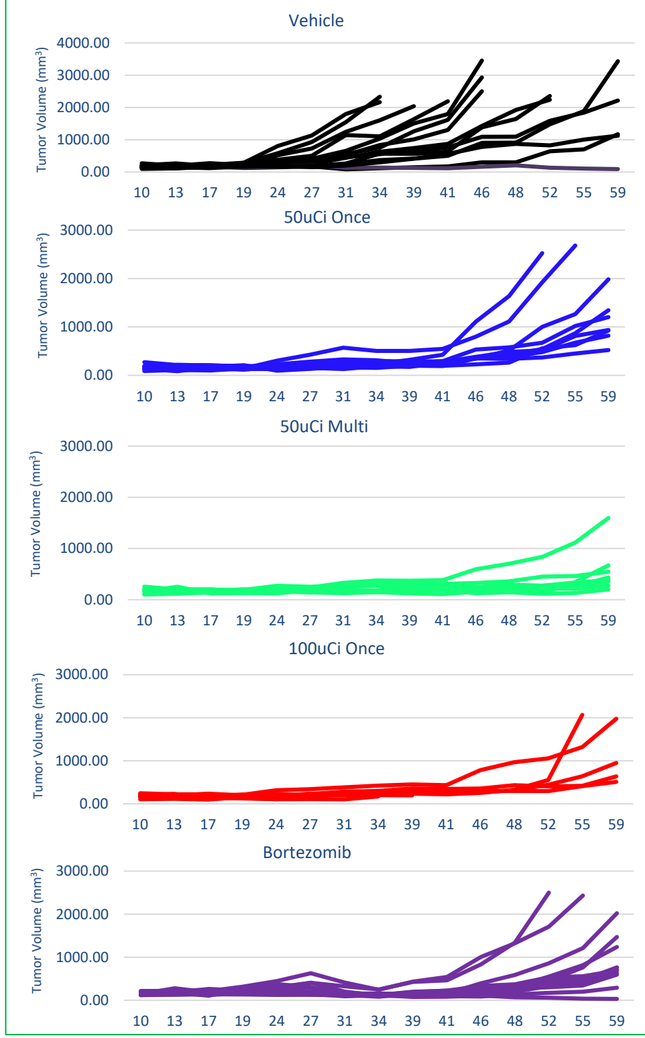
Multiple myeloma remains an incurable disease. Treatment with immunomodulators and proteasome inhibitors have provided significant benefits to patients. The introduction of new treatments like daratumumab have provided further benefit. However, patients continue to experience issues and relapse. CLR 131 is a novel radioiodinated therapeutic that exploits the selective uptake and retention of phospholipid ethers (PLEs) by malignant cells to provide targeted delivery of iodine-131 directly to tumor cells.[1-3] This study evaluates the effect of fractionated injections of CLR 131 in OPM-2 tumor bearing mice in comparison to equivalent doses of CLR 131 and the standard dosing of bortezomib.

STUDY DESIGN

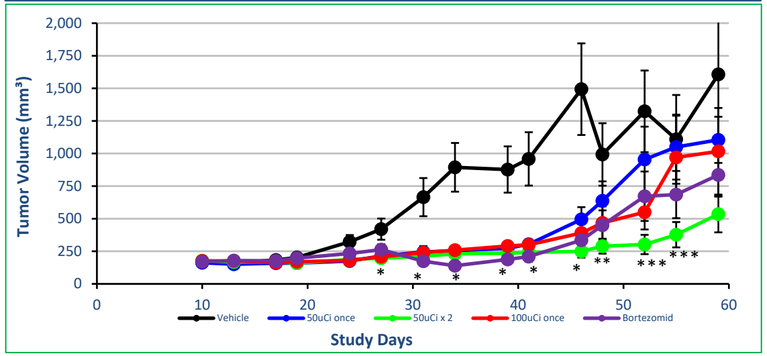
The OPM-2 cell line (human multiple myeloma) was purchased from American Type Culture Collection (ATCC, Rockville, MD) and maintained in McCoy's 5a media supplemented with 10% fetal bovine serum. Female CB17 SCID mice approximately 5-7 weeks of age were injected subcutaneously with 1x10^7 viable cells (in ~100 µL Dulbecco's PBS) into the right flank. The study was initiated when tumor size had reached a pre-determined size (approximately 150-200 mm^3). The mice were given potassium iodide at a concentration of 0.1% in their drinking water to block possible free iodide in the drug formulation three days prior to injection and continuing through two weeks post-injection. Mice were randomly assigned to dose groups. Tumor volume was measured with a caliper during the course of the study. Tumor doubling time calculation[4] TDT = D x log(2)/log(1+r/100), where D equals days between measurements and r=rate of growth; r/100=(V2-V1/V1)x100%. Statistical analysis: 1-way Anova, Dunnett's test.

	Dose	Dose Volume (uL)	Dosing Days
Vehicle (n=14)	0mg/kg	100	1 and 8
CLR 131 (n=9)	50uCi	100	1
CLR 131 (n=9)	50uCi	100	1 and 8
CLR 131 (n=9)	100uCi	100	1
Bortezomib (n=14)	0.6mg/kg	100	1, 4, 8, 11

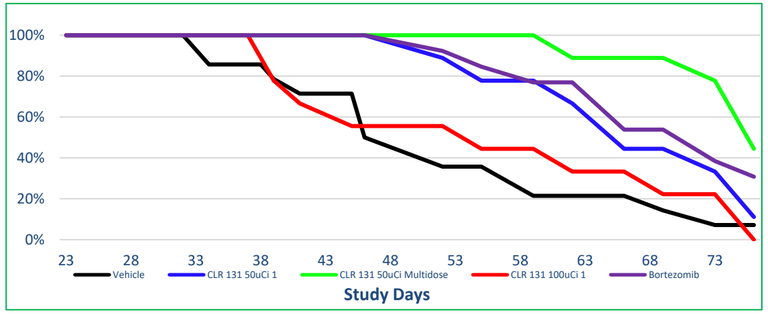
Individual Tumor Volume by Dose Group (mm^3)



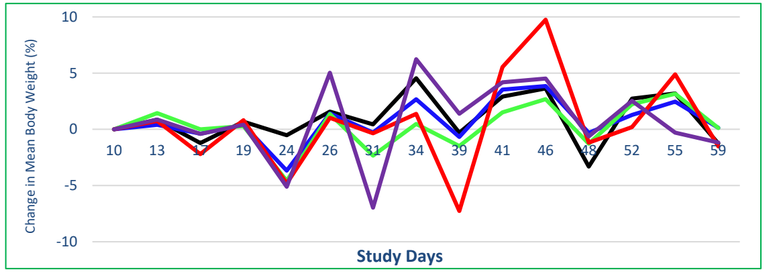
Mean Tumor Volume (mm^3)



Survival in OPM-2 Model of Multiple Myeloma (%)



Mean Body Weight Change (%)



Tumor Doubling Time

	Time to Reach 900mm^3	Tumor Volume Doubling Time
Control	35	8.24
CLR 131 50x1	51	18.50
CLR 131 50x2	74	58.02
CLR 131 100x1	54	28.21
Bortezomib	64	30.05

CONCLUSIONS

- Repeated/fractionated dosing of CLR 131 was well tolerated and better tolerated than the single equal dose
- All doses of CLR 131 showed marked antitumor activity in this model of multiple myeloma
  - Single dose infusions result in similar inhibition of MM similar to bortezomib
  - Fractionated dosing results in statistically significant reduction in tumor volume vs control after day 26
  - Fractionated dosing results in statistically significant reduction in tumor volume vs all other treatments at day 52 ($p<0.05$)
- Tumor doubling time was markedly increased for fractionated dosing versus all other treatments
- Fractionated dosing resulted in a statistically significant survival benefit
- These results support the exploration of fractionated doses of CLR 131 in clinical trials

References

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4. Gordon, A, *et al. Cancer Research* **69,** 5030-5030.