Improved CXCR4-targeted radioligand therapy in neuroendocrine prostate cancer

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INTRODUCTION

Neuroendocrine prostate cancer (NEPC) is an aggressive subtype of prostate cancer and patients usually have a poor prognosis. Overexpression of c-x-c chemokine receptor 4 (CXCR4) has been reported in NEPC clinical samples and is a promising target for radiopharmaceutical therapy (RPT)[1]. To enhance therapeutic efficacy, we investigated the use of weak albumin-binding moieties to increase tumor uptake and increase the absorbed dose of beta-emitters[2].

AIM

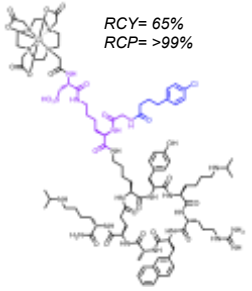
Evaluate the therapeutic efficacy of a CXCR4-targeting radiopharmaceutical with extended circulating half-life.

METHOD

[^{177}Lu]BL34T1 radiolabelling

2.4 GBq [^{177}Lu]LuCl$_3$ + 10 nmoles precursor in 0.5 mL of buffer pH 5 (0.1 M NaOAc pH 4.5, 7 mM gentisic acid + 4uM ascorbic acid + 47 uM methionine

RCY= 65%
RCP= >99%



NEPC PDX (LTL-331R) xenograft

Saline
N=20
(85.9 ± 41.2 mm^3)

9.5 ± 0.9 MBq
N=10
(96.8 ± 58.9 mm^3)

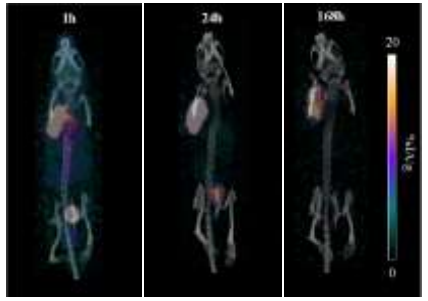
21.0 ± 2.3 MBq
N=8
(95.0 ± 57.4 mm^3)

44.8 ± 1.8 MBq
N=10
(108.9 ± 57.0 mm^3)

Preclinical dosimetry
Tumor growth
Survival
Blood cell counts

RESULTS

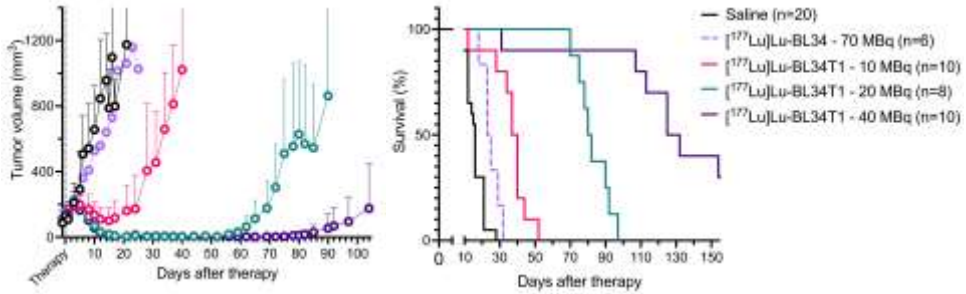
[^{177}Lu]BL34T1 SPECT/CT and preclinical Dosimetry.



Organ	%IA*h	Organ dose (mGy/MBq)
NEPC tumor[a]	1693.7	13,900
Blood	308.8	-
Heart	11.5	62.1
Kidneys	63.7	190
Liver	335.4	179

[a]Calculated using a sphere mass model of 100 mg

Tumor growth curves and survival curves of NEPC PDX tumor-bearing mice treated with different injected activities of [^{177}Lu]BL34T1.

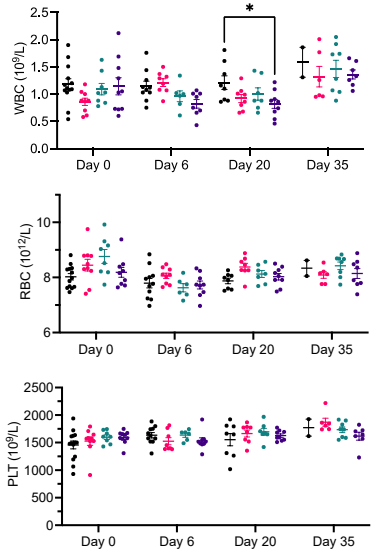


Therapy study design and evaluation of therapy efficacy.

Group	Injected activity	TGI% Day 8	TGI% Day 12	Median OS (Days)	CR Day 90
Saline[b]		-	-	16	0/20
[^{177}Lu]Lu-BL34[b]	70 MBq	33%	38%	24	0/6
[^{177}Lu]Lu-BL34T1	10 MBq	36%	84%	38.5	0/10
[^{177}Lu]Lu-BL34T1	20 MBq	43%	93%	81	0/8
[^{177}Lu]Lu-BL34T1	40 MBq	57%	95%	> 90	2/10

[b]Data obtained and pooled from a previous study.

Blood cell count analysis of NRG mice at days 0, 6, 20 and 35 after treatment



CONCLUSIONS

- [^{177}Lu]Lu-BL34T1 resulted in high tumor-to-normal organs absorbed doses optimal for RPT.
- Therapy studies resulted in improved therapy efficacy of [^{177}Lu]Lu-BL34T1 in comparison a non-albumin binding radiopharmaceutical ([^{177}Lu]Lu-BL34).
- No significant toxicities were observed.
- CXCR4 is a promising target for the treatment of advanced prostate cancers that do not respond to current therapies.

REFERENCES

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2. Kuo HT, Merkens H, Zhang Z, Uribe CF, Lau J, Zhang C, et al. Enhancing Treatment Efficacy of 177Lu-PSMA-617 with the Conjugation of an Albumin-Binding Motif: Preclinical Dosimetry and Endoradiotherapy Studies. Mol Pharmaceutics. 2018 Nov 5;15(11):5183–91.

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