

Actinium-225 Radioimmunotherapy in Delta-like Ligand 3 NEPC tumor model.

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Introduction:

We evaluated the anti-DLL3 monoclonal antibody TDI-Y-010 labeled with Actinium-225 for targeted alpha therapy in DLL3-expressing PDX models neuroendocrine prostate cancer (NEPC), using macropa-based chelators optimized for ^{225}Ac .

Methods:

Ex vivo biodistribution studies were conducted to evaluate the uptake of ^{225}Ac -mcp-TDI-Y-010 and to determine appropriate therapeutic dosing. Based on the dosimetry data, therapeutic efficacy study was conducted in male nude mice bearing NCI-H660 NEPC xenografts, with administered doses of 4.63, 9.25, and 18.5 kBq.

Results:

^{225}Ac -Macropa-TDI-Y-010 achieved radiochemical yields >98 %. Dosimetry analyses suggested that the bone marrow was at risk for toxicity from higher doses of ^{225}Ac -Macropa-TDI-Y-010. In the H660 NEPC model, complete responses were observed in the lowest dose, 4.63 kBq of ^{225}Ac -Macropa-PEG₄-TDI-Y-010, along with 9.25 kBq and 18.5 kBq doses. In addition, median survival was also significantly extended for the ^{225}Ac -mcp-TDI-Y-010 cohorts in the NEPC model compared to the 37-day median survival for ^{225}Ac -mcp-IgG4 (** $P = 0.002$ for the 4.63 kBq ^{225}Ac -mcp-TDI-Y-010 cohort, *** $P = 0.0001$ for the 9.25 kBq ^{225}Ac -mcp-TDI-Y-010 cohort, and *** $P = 0.0006$ for the 18.5 kBq ^{225}Ac -mcp-TDI-Y-010 cohort). Hematologic toxicity was transient and comparable across all cohorts. Histopathologic assessment of background organs demonstrated no kidney and mild ovary toxicity in the TDI-Y-010 cohort.

Conclusion:

^{225}Ac -Macropa-TDI-Y-010 induced complete responses at all tested doses in a DLL3-expressing NEPC model, supporting its potential for clinical translation in targeted alpha therapy.

Disclosures: ST, JSL, CMR, JSL, and MSKCC have patent on TDI-Y-010.

Funding Acknowledgements: PCF YIA Investigator Award 2024 (ST)

Figures:

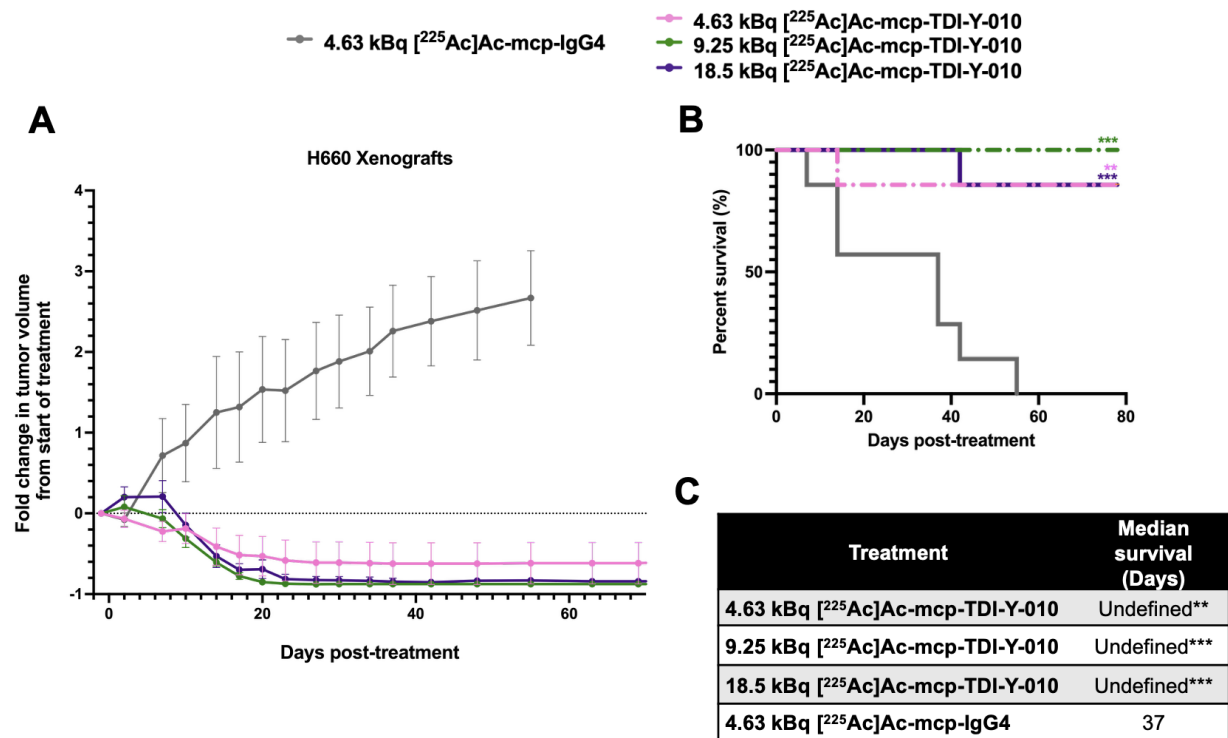


Figure 3. (A) The average fold change in tumor volumes of male mice bearing H660 xenografts after treatment (error bars indicate SD; n = 7 per cohort) **(B)** Percent survival of male mice bearing H660 xenografts following treatment. Log-rank tests were performed comparing each treatment to the [²²⁵Ac]Ac-mcp-IgG4 cohort (n = 7 per cohort; ** *P* = 0.002 for 4.63 kBq [²²⁵Ac]Ac-mcp-TDI-Y-010 cohort, *** *P* = 0.0001 for 9.25 kBq [²²⁵Ac]Ac-mcp-TDI-Y-010 cohort, *** *P* = 0.0006 for 18.5 kBq [²²⁵Ac]Ac-mcp-TDI-Y-010 cohort) **(C)** median survival of male mice bearing H660 xenografts following treatment. Log-rank tests were performed comparing each treatment to the [²²⁵Ac]Ac-mcp-IgG4 cohort (n = 7 per cohort; ** *P* = 0.002 for 4.63 kBq [²²⁵Ac]Ac-mcp-TDI-Y-010 cohort, *** *P* = 0.0001 for 9.25 kBq [²²⁵Ac]Ac-mcp-TDI-Y-010 cohort, *** *P* = 0.0006 for 18.5 kBq [²²⁵Ac]Ac-mcp-TDI-Y-010 cohort). SD, standard deviation.