

Radioimmunotherapy utilizing Actinium-225 in NEPC tumor model.

Authors:

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Introduction:

Neuroendocrine prostate cancer (NEPC) is an aggressive, treatment-resistant subtype with limited therapeutic options. Delta-like ligand 3 (DLL3) is highly expressed in NEPC and represents a promising target for radiopharmaceutical therapy. We evaluated the anti-DLL3 monoclonal antibody TDI-Y-010 conjugated to the MACROPA-derived chelator mcp and labeled with the α -emitting radionuclide ^{225}Ac (^{225}Ac]Ac-mcp-TDI-Y-010) as a targeted α -particle therapy for DLL3-expressing NEPC.

Methods:

TDI-Y-010 was conjugated to mcp-PEG4 and radiolabeled with ^{225}Ac . Radiochemical conversion, serum stability, and antibody binding were evaluated. Ex vivo biodistribution and dosimetry studies were performed in DLL3-expressing H660 NEPC xenografts to characterize tumor and normal-tissue uptake and estimate dose-limiting organs. Therapeutic efficacy was subsequently evaluated in male nude mice bearing H660 xenografts treated with 4.63, 9.25, or 18.5 kBq of ^{225}Ac]Ac-mcp-TDI-Y-010. Tumor response, survival, body weight, and hematologic toxicity were assessed.

Results:

DLL3-directed ^{225}Ac]Ac-mcp-TDI-Y-010 demonstrated high and sustained tumor uptake, potent antitumor activity, and durable complete responses across a range of doses in an NEPC xenograft model. The combination of efficient room-temperature-compatible radiolabeling, favorable tumor-to-normal tissue distribution, and limited hematologic toxicity supports further development of this targeted α -particle radioimmunotherapy as a potential therapeutic strategy for patients with DLL3-expressing NEPC.

Conclusion:

DLL3-directed ^{225}Ac]Ac-mcp-TDI-Y-010 demonstrated high and sustained tumor uptake, potent antitumor activity, and durable complete responses across a range of doses in an NEPC xenograft model. The combination of efficient room-temperature-compatible radiolabeling, favorable tumor-to-normal tissue distribution, and limited hematologic toxicity supports further development of this targeted α -particle radioimmunotherapy as a potential therapeutic strategy for patients with DLL3-expressing NEPC.

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

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Figures:

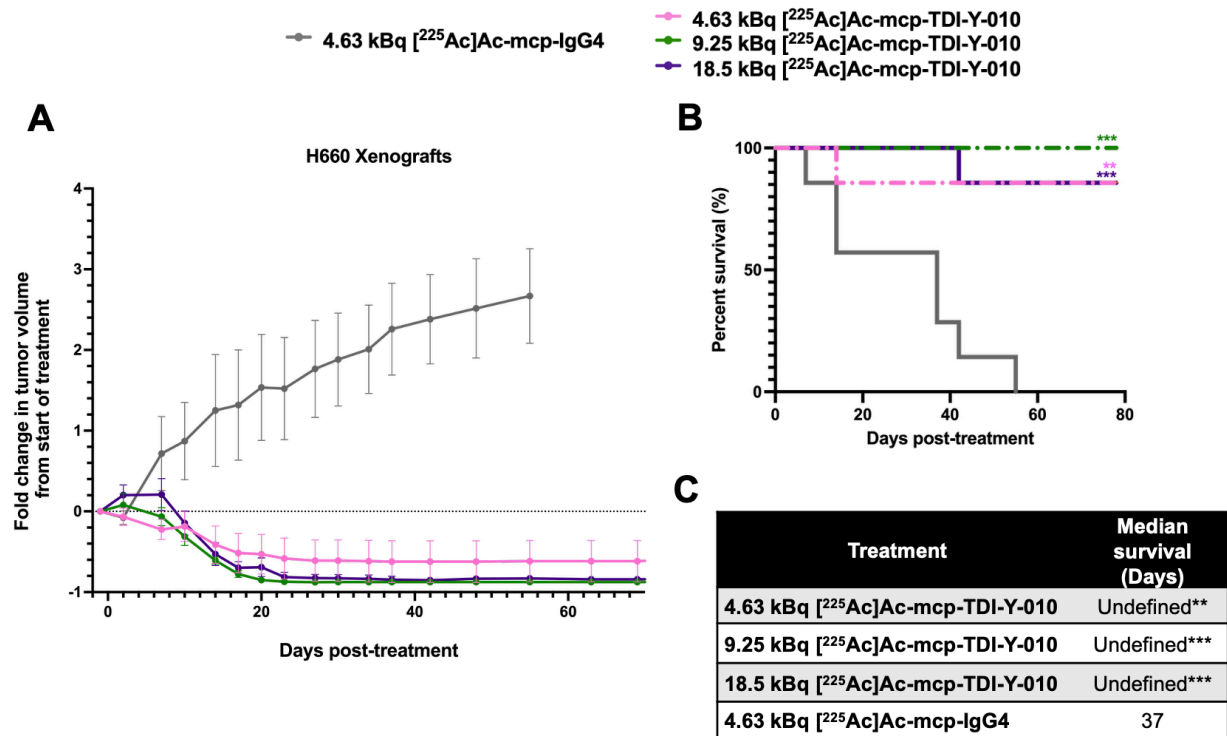


Figure 3. (A) The average fold change in tumor volumes of male mice bearing H660 xenografts after treatment (error bars indicate SD; n = 7 per cohort) **(B)** Percent survival of male mice bearing H660 xenografts following treatment. Log-rank tests were performed comparing each treatment to the [²²⁵Ac]Ac-mcp-IgG4 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.