A Theranostic Approach: Therapy of Delta-Like Ligand 3 Expressing Neuroendocrine Prostate Cancer

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Objectives: Neuroendocrine prostate cancer (NEPC) is a highly aggressive subgroup of prostate cancer with selective cell surface expression of the inhibitory Notch ligand Delta-like ligand 3 (DLL3). The project aims to identify the next generation of DLL3-targeting radioimmunoconjugates to improve the clinical outcome for NEPC patients.

Methods: In collaboration with the Tri-Institutional Therapeutics Discovery Institute, we screened and evaluated >100 humanized antibodies for their binding affinities, internalization rates, and other pharmacological properties. Here, we present data for the leading candidate (9-N12) holding highest promise in both *in vitro* and *in vivo* imaging and biodistribution studies conducted in DLL3-expressing NEPC tumors. 9-N12 was was radiolabeled with β-emitting radionuclide Lutetium-177 for direct tissue penetration with minimal off-target radiation. The tumor-bearing mice were randomized into four cohorts: two experimental arms receiving 400 μCi and 600 μCi [^{177}Lu]Lu-DTPA-CHX-A"-9-N12, and IgG4 and SC16 controls. After dosing, subsequent tumor measurements and complete blood cell counts were assessed biweekly until the end of the study.

Results: The quality control of the 9-N12 *in vitro* included assessing radiolabeling properties, stability in human serum, and binding affinities to the selected DLL3-expressing human tumor cell lines. The constructs passed the *in vitro* assays, and was thereafrer tested *in vivo.* Dosimetry estimates suggested a high therapeutic index for the 9-N12, with the with the bone marrow being the dose-limiting organ. Treatment with [^{177}Lu]Lu-DTPA-CHX-A"-9-N12 400 μCi in the male athymic H660-bearing mice resulted in complete responses that were continuous in seven out of nine mice until the end of the study (D79). One mouse in this cohort was euthanized due to loss of ≥20% pretherapy weight (M2, D37), while the other was found dead in the cage due to an unidentified cause (M9, D37). Similar results were observed with the [^{177}Lu]Lu-DTPA-CHX-A"-9-N12 600 μCi cohort, with 7/8 mice demonstrating complete and durable responses until the end of the study, with one mouse being euthanized due to petechiae at D20 pi. (M7). The median OS was not reached for the 9-N12 and SC16 cohorts, with no statistical significance in OS between the two groups treated with 400 μCi (p-value 0.817). In addition, there was a statistically significant longer median OS favoring both 9-N12 and SC16 cohorts compared to the cohort treated with [^{177}Lu]Lu-DTPA-CHX-A"-IgG4 (Log-Rank p-value 0.0032, 0.0015, 0.012, respectively). Transient bone marrow toxicity was observed in all cohorts, with recovery observed at three weeks post-injection.

Conclusions:This study highlights the promise held by novel DLL3-direct radioimmunoconjugates as a therapeutic agent. The lead candidate 9-N12 appears promising for translation as an therapeutic agents for patients with NEPC.

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Conflict of Interest

ST Anti-DLL3 antibodies IP (Patent No. 63/240,237)

TH/DB/RD/AM/LC/ declare no COI.

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Dr. Lewis Anti-DLL3 antibodies IP (Patent No. 63/240,237)

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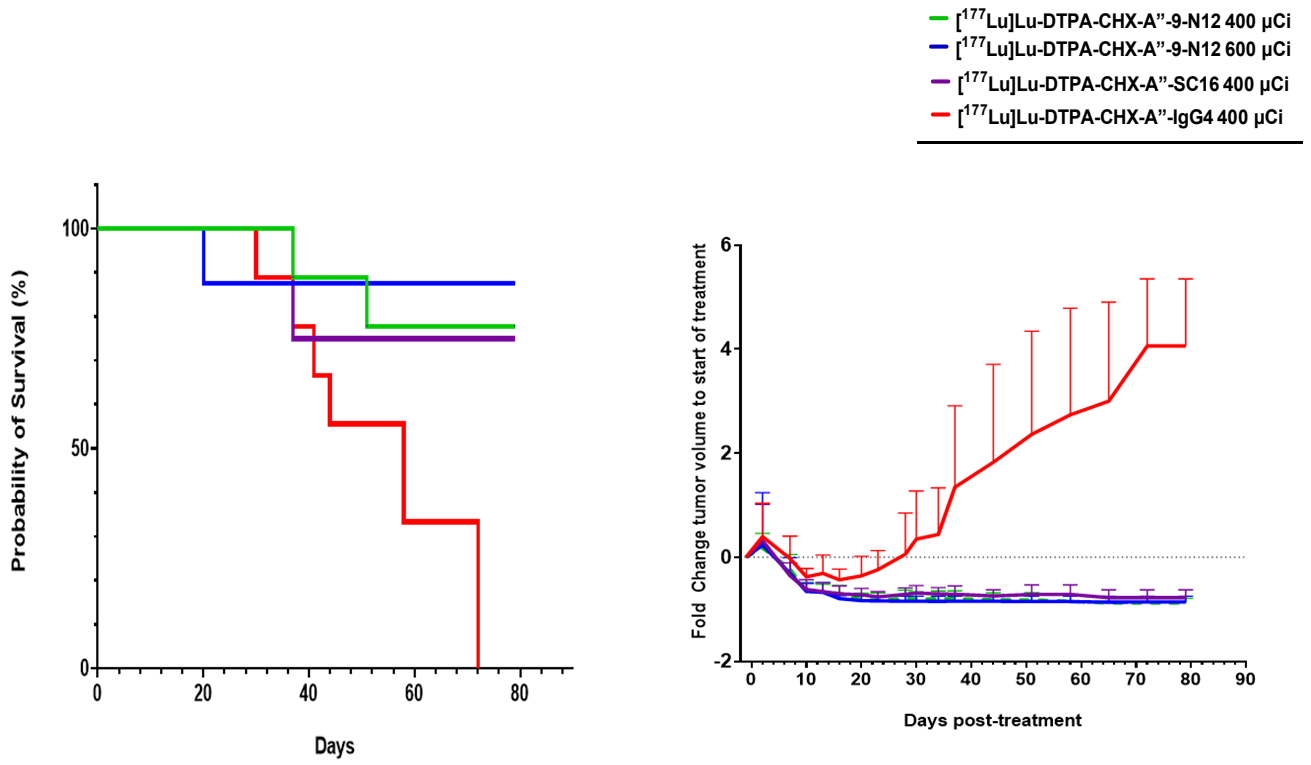

Figure 1.

[177Lu]Lu-CHX-A”-DTPA-9-N12 treatment improves overall survival and inhibits tumor growth in NEPC H660 tumor-bearing mice.