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Landscape analysis of Phase 2/3 clinical trials for Targeted Radionuclide Therapy

Erik Mittra[1], Amanda Abbott[2], and Lisa Bodei[3]

Affiliations

1. Division of Nuclear Medicine & Molecular Imaging, Oregon Health & Science University, Portland, OR

2. Clinical Trials Network, Society of Nuclear Medicine & Molecular Imaging, Reston, VA

3. Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY

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Text

Within Nuclear Medicine, theranostics has revitalized the field of Targeted Radionuclide Therapy (TRT) and there is a growing number of investigator-initiated and industry-sponsored clinical trials of TRT. This article summarizes the current trials available in the NIH database, the largest trial repository, to provide both an overview of the current landscape and a glimpse towards an undeniably exciting future of theranostics.

This landscape analysis was completed by searching the terms “radionuclide therapy”, “radioisotope therapy”, “radiopharmaceutical therapy” and “radioligand therapy” on ClinicalTrials.gov in November 2020. Other terms may provide different results. Phase 1/2, 2, and 3 trials that are currently recruiting and those not yet recruiting were included.

Studies. Overall, the results showed 42 clinical trials including 13 Phase 1/2, 26 Phase 2, and three Phase 3. Given this range of phases, the planned enrollment varies widely from 10-813, with an average of 147 participants. Five different radioisotopes, 12 ligands or targets, and 11 different cancer types are represented (Figure 1). These include 22 single and 20 multi-institution studies. Of the 42 total trials, 21 are single-group, 15 are randomized, and six are non-randomized.

Molecules & targets. Of the five different radioisotopes represented, the vast majority (28) use Lutetium-177. The next most common are Iodine-131 (7) and Radium-223 (6). Others included three trials with Yttrium-90, and one with Copper-67. The ligands or targets are also skewed, with 20 trials on somatostatin receptors (SSTRs). Of these, 16 are focused on DOTATATE/oxodotreotide, four on DOTATOC/edotreotide, and one on SARTATE. Expectedly, the next most common are the PSMA-ligands (617, I&T, 1095, and R2) with eight trials, followed by six for bone metastases with Ra-223, and four for ^{131}I-MIBG. Diverse trials include ligands for human epidermal growth-factor receptor-2 (HER2), gastrin-

releasing peptide receptor (GRPR or bombesin), neurotensin receptor-1 (NR-1), B-cell CD37, and phospholipid ethers with the compound CLR-131. The 11 cancer types of interest include gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs, 15 trials), prostate cancer (11), and four trials each for pheochromocytoma/paraganglioma, neuroblastoma, or a variety of solid tumors. Less common are meningioma (3), lymphoma (2), and one trial each for Merkel Cell carcinoma (1), breast cancer, renal cell cancer, and salivary gland carcinomas.

Developmental phase. For Phase 3, there are only three trials. The largest is a multicenter (US and Canada) trial sponsored by the Children's Oncology Group, with an enrollment of up to 813 participants, comparing ^{131}I-iobenguane versus Crizotinib plus standard therapy for younger patients with newly diagnosed high-risk neuroblastoma or ganglioneuroblastoma. The second is a single-site randomized trial (the ESCALATE trial at the Carolina Urologic Research Center) of 499 participants comparing Radium-223 plus enzalutamide or darolutamide versus enzalutamide or darolutamide alone for patients with metastatic castrate-resistant prostate cancer (mCRPC). The last is the worldwide (US, Europe, South Africa, and Australia) COMPETE trial sponsored by Isotopen Technologien Munchen AG (ITM). This a multisite, randomized trial of 300 participants with GEP NETs. The primary goal is comparison of ^{177}Lu-edotreotide to everolimus.

Phase 2 include the largest number of trials (26) and spectrum of design. These include novel agents in expected indications, novel/off-label indications for approved agents, and questions of combining or sequencing approved therapies. Examples of novel agents include ^{177}Lu-PSMA-I&T and ^{131}I-PSMA-1095 for prostate cancer or CLR-131 for lymphoma. Examples of novel/off-label indications include ^{177}Lu-PSMA for salivary gland carcinomas, and PRRT for non-GEP-NETs (e.g. pheochromocytoma / paraganglioma, and thymic NETs) or meningioma. Examples of combining or sequencing existing therapies include neoadjuvant PRRT for pancreatic NETs, Ra223 plus paclitaxel for breast cancer or in addition to cabozantinib for renal cell cancer, capecitabine and/or temozolomide plus PRRT for GEP-NETs, and PRRT versus sunitinib for pancreatic NETs. There are also several studies on dosimetry-based personalization of PRRT.

Phase 1/2 has 13 studies with a focus on novel radiopharmaceuticals. These include ^{177}Lu-lilotimab satetraxetan targeting CD37 for follicular lymphoma, ^{131}I-CAM-H2 for breast, gastric, and gastro-esophageal junction cancers, ^{67}Cu-SARTATE for neuroblastoma, ^{177}Lu-PSMA-R2 for mCRPC, and ^{177}Lu-neobombesin and ^{177}Lu-3BP-227 (a neurotensin receptor-1 agonist) in a variety of solid cancers. Similar to Phase 2, other trials investigate novel indications for approved agents and questions of combining or sequencing approved therapies such as the evaluation of combining ^{177}Lu-DOTATATE and ^{131}I-MIBG for midgut NETs, the role of ^{177}Lu-PSMA-617 prior to prostatectomy, combining ^{177}Lu-PSMA and immunotherapy in prostate cancer, and combining olaparib and Ra-223 Dichloride for prostate cancer. There are also additional studies on dosimetry-guided PRRT.

Coda. This landscape analysis, while not exhaustive and only a snapshot of the current time, provides an overview of Phase 1/2, 2, and 3 studies of targeted radioisotope therapies. As seen, PRRT, radioligand therapy and their variations are predominant. Additionally, there are multiple new targets/ligands and, as a result, cancer types being evaluated with a variety of agents using the theranostics approach. Furthermore, for already (and soon to be) approved agents, there is considerable work being done to expand the indications, and improve their efficacy using combination therapies, better understanding sequencing of therapies, and enhancing the personalized approach using dosimetry. It should be noted

that the vast majority of the multicenter trials and some of the single center studies are sponsored by pharmaceutical companies, a critical factor to bring these trials to fruition and advance the field. This analysis highlights the concentration of studies and ideas around the concept of theranostics, while these trials continue to grow and the field further matures.

Figures

Figure 1 Title: Clinical trials for Targeted Radionuclide Therapy. The majority involve PRRT (15 studies) or PRRT combinations (5) predominantly for neuroendocrine neoplasms, mainly (16 studies) with ^{177}Lu-DOTATATE. Radioligand therapy (RLT) with PSMA agents, alone (5 studies) or in combination (3 studies) and Ra-223 Dichloride, mainly in combinations (5 studies), account for most of the remaining studies, mainly directed at prostate cancer.

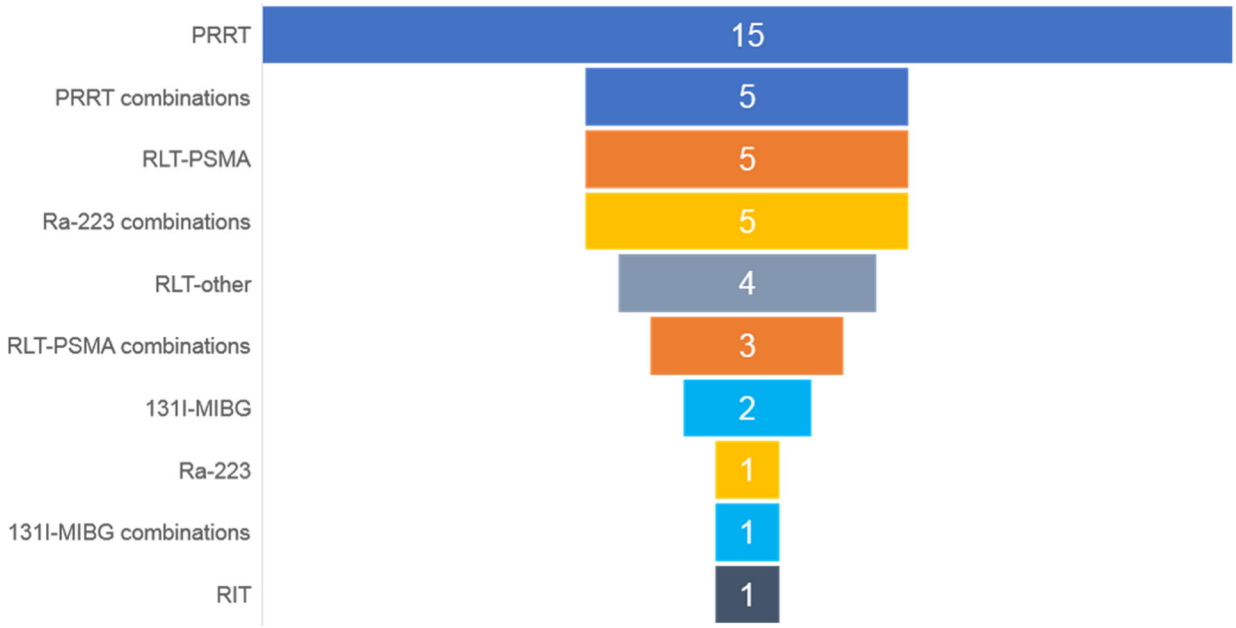

Figure 1 Legend: Legend: PRRT, peptide receptor radionuclide therapy; RLT, radioligand therapy; PSMA, prostate specific membrane antigen; Ra-223, Ra-223 Dichloride; 131I-MIBG, Iodine-131-meta-iodo-benzyl-guanidine; RLT-other: radiolabeled bombesin, neurotensin, phospholipid ester and HER2 ligands, anti-CD37 antibodies; RIT, radioimmunotherapy.