Clinical Evidence of Combining Radiopharmaceutical Therapy With Immune Checkpoint Inhibitors

Introduction

Radiopharmaceutical therapy (RPT) and immune checkpoint inhibitors (ICIs) represent transformative approaches to treating metastatic cancers. This review article discusses how RPT delivers targeted radiation to primary and metastatic tumors and the therapeutic advantages of combining RPT with ICIs while focusing on outcomes and challenges such as toxicity, immunosuppressive tumor microenvironment, and logistical barriers.

Learning Objectives

Upon completing this activity, the reader should be able to:

1. Distinguish the physical properties of α, β, and Auger-emitting radioisotopes to guide informed selection of radionuclides for RPT based on therapeutic goals and tumor characteristics.
2. Evaluate clinical trial data on RPT-ICI combinations and integrate evidence-based insights into patient selection, dosing strategies, and treatment sequencing for optimized therapeutic outcomes.

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Abstract

Radiopharmaceutical therapy (RPT) and immune checkpoint inhibitors (ICIs) represent transformative approaches in treating metastatic cancers. RPT uniquely delivers targeted radiation to primary and metastatic tumors, modulating the tumor microenvironment (TME) to enhance antitumor immunity. The therapeutic advantages of combining RPT with ICI have been shown preclinically. Clinical trials are now emerging, offering insights into the potential therapeutic synergy between RPT and ICI. This review highlights clinical trials of RPT combined with ICI, emphasizing their ability to improve metastatic cancer outcomes while addressing challenges such as toxicity, immunosuppressive TME, and logistical barriers, and underscores their promise to redefine cancer care.

Keywords: metastatic cancer, radiopharmaceutical therapy, β-particle emitters, α-particle emitters, immune checkpoint inhibitors

Introduction

Metastatic disease accounts for approximately 90% of cancer-related deaths.[1-6] Unfortunately, effective therapeutic strategies remain limited despite tremendous advances in cancer research.[7] Radiopharmaceutical therapy (RPT) represents a groundbreaking approach to treating metastatic disease by delivering targeted radiation to tumors throughout the body.[8,9] Leveraging pharmaceuticals that selectively bind to cancer cells or accumulate through physiological mechanisms, RPT provides a precise and effective treatment modality. Remarkably, RPT has demonstrated significant therapeutic efficacy with minimal toxicity in several cancer types.[8] As the role of RPT in metastatic disease management is on the rise, its combination with immune checkpoint inhibitors (ICIs) holds the potential to enhance clinical responses beyond that achievable by either monotherapy alone.

For over a century, radiation therapy, including external beam radiation therapy (EBRT) and RPT, has shown dual benefits: tumor eradication and immune activation.[10] Radiation triggers cancer cells to release damage-associated molecular patterns

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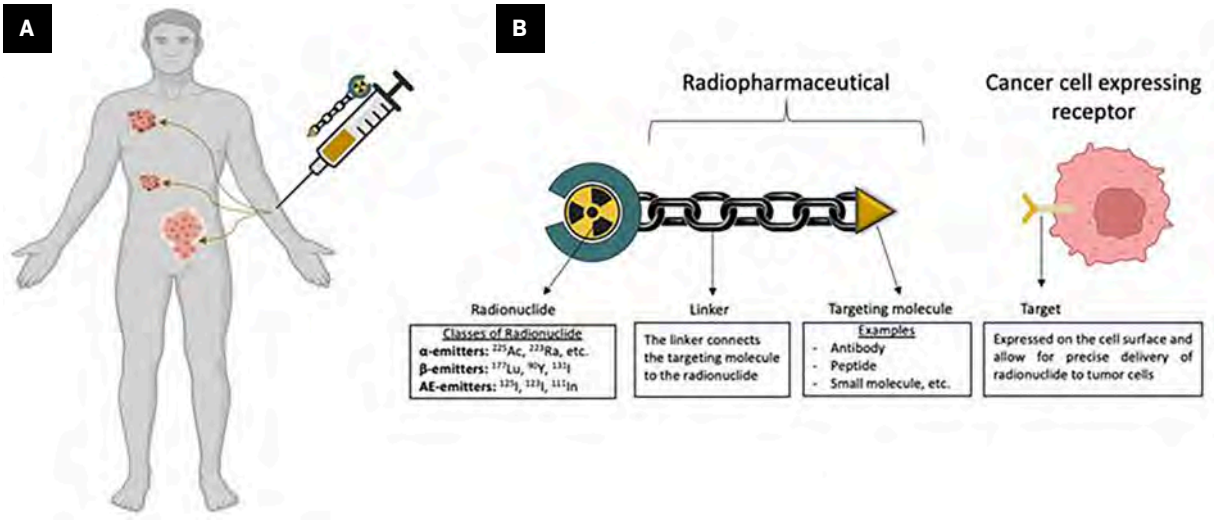
Figure 1. Radiopharmaceutical therapy delivers systemic radiation to tumor. (A) A radiolabeled, tumor-specific compound known as a "radiopharmaceutical" is administered intravenously, resulting in selective accumulation of radionuclide in the tumor microenvironment. (B) Pharmacophoric model of radiopharmaceutical agent. A targeting molecule is conjugated to a therapeutic radionuclide via a linker and chelator, forming a radiopharmaceutical that ensures precise delivery of radiation to tumor cells.



(DAMPs), activating the cGAS-STING pathway, which induces type I interferons and the release of cytokines that recruit immune cells.[11,12] The growing promise of RPT in treating metastatic cancer, coupled with emerging insights into the immunogenic effects of radiation, has spurred preclinical and clinical studies exploring the combination of RPT and immunotherapy, such as ICIs. This review explores clinical trials investigating the combination of RPT with ICI, highlighting key clinical findings, potential challenges, and future directions in this emerging field.

Radiopharmaceutical Therapy

RPT has emerged as a promising systemic therapy, enabling radiation delivery to both local and metastatic lesions while sparing healthy tissues (**Figure 1A**).[8,13] Unlike EBRT, which delivers radiation to all tissues in the radiation field, including malignant and adjacent normal tissues, RPT uses tumor-targeting biomolecules (eg, antibodies, peptides, or small molecules) linked to a radionuclide to form a "radiopharmaceutical" that preferentially targets cancer cells (**Figure 1**). The radiopharmaceutical binds selectively to receptors overexpressed on tumor cells, thus delivering radiation to the tumor while minimizing damage to surrounding tissues.[14] This molecularly targeted approach makes RPT particularly effective for treating metastatic and microscopic tumors,[8,15-17] where EBRT's utility is often limited. The efficacy of RPT depends on the targeting molecule's properties, the radionuclide's physical characteristics, and tumor characteristics such as receptor expression, size, and tumor type. Additional factors, such as the administrated activity, tumor uptake, and pharmacokinetics, also impact the treatment outcome.[18] Therefore, carefully considering these factors is crucial for RPT's clinical efficacy and safety. The approvals of several radiopharmaceuticals, such as [^{223}Ra]Ra-dichloride (Xofigo) and [^{177}Lu]Lu-PSMA-167 (Pluvicto) for metastatic castration-resistant prostate cancer (mCRPC) and [^{177}Lu]Lu-DOTATATE (Lutathera) for gastroenteropancreatic neuroendocrine tumors (GEP-NETs), have sparked a new excitement in the field.[19-21] RPT faces challenges like suboptimal targeting, radioresistance, and limited immune stimulation, hindering tumor eradication.[22-24] Combining RPT with systemic therapies like ICIs may overcome these limitations and improve outcomes.

Targeting Molecules

In RPT, antibodies, peptides, or small molecules are designed to bind selectively to tumor-specific receptors or antigens, ensuring precise delivery of radiation to cancer cells while sparing healthy tissues.[25]

Antibodies

Their high specificity and potentially strong binding affinity make antibodies ideal for targeting tumor-associated antigens and delivering radiation to cancer cells.[26,27] Effective antibodies target antigens that are highly expressed on tumors but minimally expressed or absent in healthy tissue.

However, antibody size can limit tumor microenvironment (TME) penetration[28] and prolong circulation,[29] increasing off-target toxicities. Smaller monoclonal antibody (mAb) fragments like single-chain variable fragments partially retain target binding capacity while improving TME penetration. The US Food and Drug Administration/European Medical Agency (FDA/EMA)-approved examples of antibody-based radiopharmaceuticals include Zevalin ([^{90}Y]Y-ibritumomab tiuxetan)[30] and Bexxar ([^{131}I]I-tositumomab),[31] which target the CD20 protein on the surface of B-cells expressed by non-Hodgkin lymphoma.

Peptides

Peptides are versatile for RPT owing to rapid TME penetration, high uptake, and quick clearance from nontarget tissues, offering optimized pharmacokinetics. Their relatively higher stability enables chemical modifications and radiolabeling, making them versatile agents in nuclear medicine. A notable example of a peptide-based FDA/EMA-approved radiopharmaceutical is Lutathera ([^{177}Lu]Lu-DOTA-TATE), indicated for the treatment of somatostatin receptor 2-positive gastroenteropancreatic neuroendocrine tumors.[32,33]

Small Molecules

Small molecule-based radioligands offer advantages as radiopharmaceuticals due to their efficient TME penetration and rapid clearance from systemic circulation, reducing off-target effects and toxicity. Although less specific than antibodies or peptides, small molecules effectively target cancer-associated antigens, such as the prostate-specific membrane antigen (PSMA) in prostate cancer. A notable example is the FDA-approved [^{177}Lu]Lu-PSMA-167 (Pluvicto) for mCRPC,[34] showcasing radioligand therapy's potential in precision oncology.

Each targeting molecule in RPT offers a unique balance of strengths and limitations, with selection guided by tumor traits, precision, clearance, and off-target risks. This enables personalized and effective cancer therapy.

Radionuclides

A wide range of radionuclides is available for RPT, and selecting the appropriate one is crucial, as it directly influences treatment safety and efficacy. This choice is guided by factors such as physical half-life, availability, cost, radiochemical methods, and radiation properties, including energy level, type (α, β, or Auger electrons), linear energy transfer (LET), and penetration range (**Figure 2** and **Table 1**).

Physical Half-Life

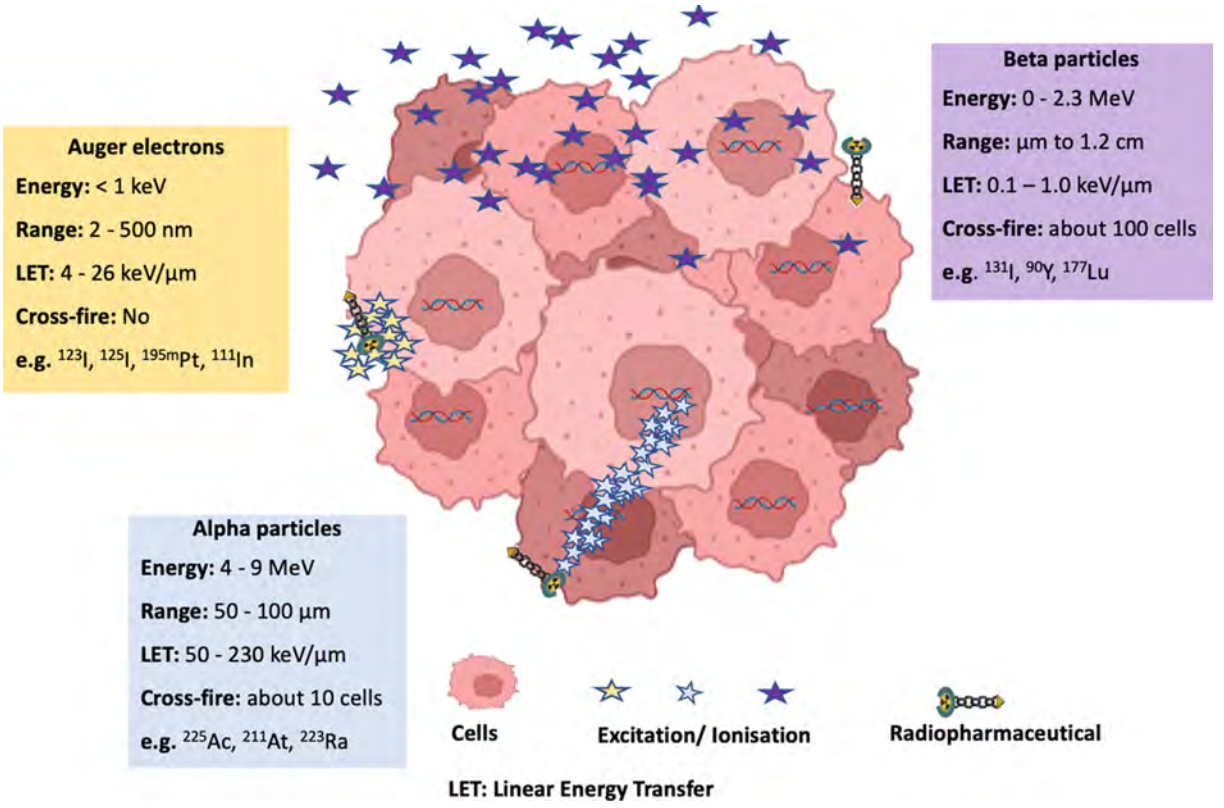
The time needed for half of an RPT's radioactive atoms to decay is critical. The half-life must be amenable to the radiolabelling process, the distribution logistics of the agent, and the targeting molecule's pharmacokinetics. While radionuclides with a short half-life, measured in hours, are preferred for imaging application, RPTs featuring short $T_{1/2}$ radionuclides may lead to a significant decay before the radiopharmaceutical reaches the TME, thus reducing treatment efficacy. Conversely, a long half-life can increase radiation exposure to healthy tissue, thus increasing treatment-related side effects. Ideally, RPT radionuclides should have a half-life of 1 to 7 days for optimal balance.[35]

Linear Energy Transfer

The linear energy deposited by ionizing radiation per unit distance in tissue (keV/μm) significantly influences its biological effect. High LET of radiation (eg, α-particles, 50-230 keV/μm) induces dense clusters of double-strand DNA breaks (DSBs), causing irreparable DNA damage and high cytotoxicity. Intermediate LET radiation (eg, Auger electrons, 4-26 keV/μm) generates localized single-strand DNA breaks (SSBs) and DSBs, with cytotoxicity dependent on nuclear proximity due to limited penetration. Low LET radiation (eg, β-particles, 0.2 keV/μm) primarily induces SSBs and indirect damage via free radicals, which are often repairable, though clustered SSBs may result in DSBs.[36,37] Radionuclides used in RPT are classified into 3 main categories based on their radiation type: β-particle emitters, α-particle emitters, and Auger/conversion electrons emitters.

- β-particle emitters such as lutetium-177 (^{177}Lu), yttrium-90 (^{90}Y), and iodine-131 (^{131}I), with a low LET (~0.2 keV/μm) and tissue penetration up to 12 mm, have been widely used in RPT. Owing to their deeper penetration range (several millimeters), low-LET β^--emitters can effectively treat heterogeneous (target expression) tumors,[38,39] resulting in more effective tumor coverage,[40,41] but may have lower lethal damage efficiency per unit dose.
- α-particle emitters such as radium-223 (^{223}Ra) and actinium-225 (^{225}Ac) deliver potent therapy with high LET (50-230 keV/μm) and a short tissue range (50-100 μm); thus, they are ideal for treating micrometastases.[39,40,42] Their high LET causes dense clusters of DSBs, which are difficult to repair,[39] making them highly cytotoxic.[43]
- Auger/conversion electron emitters such as iodine-123 (^{123}I), iodine-125 (^{125}I),

Figure 2. Characteristics of various radionuclides used for radiopharmaceutical therapy.



and indium-111 (^{111}In) have a very short tissue range (< 1 µm), making them effective near critical cell structures like nuclear DNA, and a medium-to-high LET (4-26 keV/µm) inducing a mix of SSBs and DSBs.[16,39,42]

Many β-particle and Auger emitters also emit γ rays, enabling their dual use for therapy and imaging.[44] For example, γ emissions from ^{177}Lu allow real-time visualization of radiopharmaceutical distribution, ensuring accurate targeting and dose optimization.[45,46]

Overall, radionuclide selection for RPT depends on properties like half-life, LET, radiation type, and tissue penetration. β-emitters appear to be better suited for larger tumors, while α-emitters target micrometastases with high cytotoxicity, and Auger emitters provide precise, localized radiation (< 1 µm) near critical structures like nuclear DNA.

Immunomodulatory Effects of RPT and Rationale for Combining RPT With ICI

The efficacy of RPT extends beyond direct cytotoxicity as it induces significant pro-inflammatory immune responses.[47,48] Ionizing radiation enhances tumor immunogenicity, modulates the TME, and promotes innate and adaptive immunity.[47,48] Irradiated tumor cells release DAMPs[49] and express immunomodulatory molecules, recruiting antigen-presenting cells to activate T cells and drive systemic antitumor immunity.[50] Potluri et al showed that [^{90}Y]Y-NM600 modified the TME by increasing CD8+ T cell infiltration and PD-L1 expression on myeloid cells.[51] In a murine study, Hernandez et al observed a reduction in immunosuppressive regulatory T cells and a notable increase in activated CD8+ T cells in EL4 murine tumors treated with [^{90}Y]Y-NM600 compared with controls.[52] Furthermore, upon rechallenging [^{90}Y]Y-NM600-treated complete responders with EL4 cells, none developed tumors,[52] suggesting the induction of a tumor-specific memory in RPT-treated mice. Emerging preclinical data suggest that targeted α-particle therapy (TAT) can also induce immunostimulatory effect.[53] Lejeune et al further demonstrated that TAT triggers transcriptional and

Table 1. Radionuclides Used in Radiopharmaceutical Therapy and Their Physical Properties

PARTICLE EMITTED	ENERGY	RANGE IN TISSUE	LET (keV/μm)	KEY DNA DAMAGE CHARACTERISTICS	EXAMPLE OF RADIONUCLIDES
β-particles	0-2.3 MeV	μm to1.2 cm	0.1-1.0	Most single-strand breaks and some double-strand breaks but is easily repairable. (lower lethal damage efficiency)	^{131}I, ^{90}Y, ^{177}Lu
α-particles	5-9 MeV	50-100 μm	50-230	Mostly clustered double-strand breaks, making them complex and difficult to repair. (higher lethal damage efficiency)	^{225}Ac, ^{211}At, ^{223}Ra
Auger and conversion electrons	<1 keV	<1 μm	4-26	Mix of clustered double-strand breaks and single-strand breaks (lethality dependent on nuclear DNA proximity)	^{123}I, ^{125}I, ^{195m}Pt, ^{111}In

Abbreviation: LET, linear energy transfer.

molecular signatures consistent with immunogenic cell death in preclinical syngeneic tumor models.[54] Despite the reported immunomodulatory effects of RPT, its efficacy as a monotherapy often lacks durability, underscoring the compelling rationale for combining RPT with immunotherapy.[55] Foundational studies have shown the synergism between RPT and immunotherapy, such as improved survival with [^{90}Y]-anti-CEA (carcinoembryonic antigen) antibodies in combination with a CEA/TRICOM (TRICOM: 3 T-cell costimulatory molecules B7-1, ICAM-1, and LFA-3) vaccine in colon cancer models.[56] This combination represents a promising strategy for achieving durable tumor control; thus, it may pave the way for enhancing patient outcomes through synergistic treatment strategies.

Clinical Trials Combining RPT With ICI

Building on preclinical evidence, several clinical trials have been initiated to evaluate the safety and efficacy of RPT-ICI combinations across cancers. Key outcomes are discussed here, underscoring the potential of these combination therapies to advance clinical treatment paradigms. **Table 2** concisely summarizes these clinical trials, categorized by disease type for clarity.

Prostate Cancer

A phase Ib study (NCT02814669) investigated the combination of [^{223}Ra]$RaCl_2$ with atezolizumab in mCRPC patients with bone, lymph node, or visceral metastases. This combination resulted in greater toxicity than either agent alone and failed to show clinical benefit.[57] Among the grade 3/4 adverse events, 34.1% were attributed to atezolizumab, while 27.3% were associated with [^{223}Ra]$RaCl_2$.

A randomized phase II study (NCT03093428) evaluated [^{223}Ra]$RaCl_2$ with pembrolizumab in patients with mCRPC. A recent report showed a median progression-free survival (PFS) of 6.1 months for [^{223}Ra]$RaCl_2$ + pembrolizumab versus 5.7 months for [^{223}Ra]$RaCl_2$ alone and a median overall survival (OS) of 16.9 months versus 16.0 months, respectively.[58] While the combination was well tolerated with no unexpected toxicity, it did not demonstrate improved efficacy.

PRINCE (NCT03658447), a phase I clinical trial, evaluated the safety and efficacy of [^{177}Lu]Lu-PSMA-617 in combination with pembrolizumab in patients with mCRPC. The prostate-specific antigen response rate (PSA-RR) was 76% compared with 46% with [^{177}Lu]Lu-PSMA-617 alone. The median radiographic PFS, PSA-PFS, and OS were 11.2 months, 8.2 months, and 17.8 months, respectively.[59] No additional safety concerns were identified with the addition of pembrolizumab, confirming the favorable safety profile of this combination.

Lung Cancer

Advanced lung cancer has also been the focus of clinical trials exploring the combination of RPT with immunotherapy. A phase I/II trial (NCT03325816) investigating nivolumab with Lutathera in patients with extensive-stage small cell

Table 2. Selected Clinical Trials Evaluating Radiopharmaceutical Therapy Combined With Immune Checkpoint Blockade in Cancer

DISEASE	TRIAL	PHASE	DISEASE STATUS	TARGET	RPT	ICI	COMBINATION SEQUENCE	TRIAL STATUS/ RESULT	REFERENCE
Prostate cancer	NCT02814669	Ib	mCRPC	Bone metastases	[^{223}Ra]Ra: 55 kBq/kg (IV) every 28 days, 6 administrations	Atezolizumab: 840 mg (IV) every 14 days	Concurrent or staggered	Combination: greater toxicity	57
	NCT03093428	II	mCRPC	Bone metastases	[^{223}Ra]Ra: every 4 weeks at a predetermined dose (IV)	Pembrolizumab: every 3 weeks at a predetermined dose (IV)	Concurrent	No improved efficacy	58
	NCT03658447 (PRINCE)	I	mCRPC	PSMA	[^{177}Lu]Lu-PSMA-617: 8.5 GBq (IV), every 6 weeks, up to 6 cycles	Pembrolizumab: 200 mg every 3 weeks (IV)	Concurrent	PSA-RR: 76% No safety concerns rPFS: 11.2 months PSA-PFS: 8.2 months OS: 17.8 months	59
Lung cancer	NCT03325816	I/II	Extensive stage SCLC	SSTR	[^{177}Lu]Lu -DOTA0-Tyr3-Octreotate: 3.7 or 7.4 GBq (IV), every 8 weeks, 4 cycles	Nivolumab: 240 mg every 2 weeks (IV)	Concurrent	Combination well tolerated PR: 1 out 7 patients	60
	NCT03996473	I	Metastatic NSCLC	Bone metastases	[^{223}Ra]Ra: 55 kBq/kg (IV), every 6 weeks, up to 6 cycles	Pembrolizumab: 200 mg every 3 weeks (IV) up to 35 doses	Concurrent	Study closed	
Renal cancer (ccRCC)	NCT05663710	Ib/II	Advanced ccRCC	CAIX	[^{177}Lu]Lu-girentuximab: 1.48 GBq/m^2 (IV), every 12 weeks, up to 3 cycles	Nivolumab (dose not available) Cabozantinib: given orally	Concurrent	Ongoing	61
	NCT05239533 (STARLITE 2)	II	Advanced ccRCC	CAIX	[^{177}Lu]Lu-girentuximab: 1.8 or 2.4 GBq/m^2 (IV), every 12-14 weeks, up to 3 cycles	Nivolumab: 200 mg every 2 weeks	Concurrent	Ongoing	62

Table 2. Continued

DISEASE	TRIAL	PHASE	DISEASE STATUS	TARGET	RPT	ICI	COMBINATION SEQUENCE	TRIAL STATUS/ RESULT	REFERENCE
Merkel cell cancer	NCT05583708	II	Metastatic	SSTR	[^{177}Lu]Lu-DOTATATE: 7.4 GBq (IV), every 2 months, up to 4 doses	Pembrolizumab: 400 mg every 6 weeks (IV)	Concurrent	Temporarily suspended	
	NCT04261855 (GoTHAM)	Ib/II	Metastatic	SSTR	[^{177}Lu]Lu -DOTATATE: 2 administrations separated by 8-10 weeks	Avelumab: 10 mg/kg every 2 weeks for 24 months (IV)	Concurrent	Ongoing	
Thyroid cancer	NCT03215095	I	Recurrent/ metastatic	rhTSH	[^{131}I]I : 100 mCi	Durvalumab: 1500 mg IV every 4 weeks	Concurrent	Active, not recruiting	
Refractory neuroblastoma	NCT02914405 (MiNivAN)	I	Relapsed or refractory High risk	Norepinephrine transporter	[^{131}I]I-meta-iodobenzylguanidine	Nivolumab: 3 mg/kg Dinutuximab (anti-GD2 monoclonal antibody): 50 or 100 mg/m^2	Concurrent	Recruiting	
NETs with liver metastases	NCT03457948	II	Metastatic	SSTR	[^{177}Lu]Lu-DOTA0-Tyr3-Octreotate	Pembrolizumab	Concurrent	Recruiting	

Abbreviations: CAIX, carbonic anhydrase IX; ccRCC, clear cell renal cell carcinoma; ICI, immune checkpoint inhibitor; IV, intravenous injection; mCRPC, metastatic castration-resistant prostate cancer; NET, neuroendocrine tumor; NSCLC, non-small cell lung cancer; OS, overall survival; PR, partial response; PSA-PFS, prostate-specific antigen progression-free survival; PSA-RR, PSA response rate (≥50% decrease in PSA level); PSMA: prostate-specific membrane antigen; rhTSH, recombinant human thyroid stimulating hormone; rPFS, radiographic progression-free survival; RPT, radiopharmaceutical therapy; SCLC, small cell lung cancer; SSTR, somatostatin receptor.

lung cancer (SCLC) demonstrated a tolerable toxicity profile. Lutathera, a β-emitting [^{177}Lu]Lu-labeled somatostatin analog approved for GEP-NETs,[63] targets somatostatin receptor-expressing cells. The combination therapy was well tolerated. Furthermore, 1 out of 7 patients achieved a partial response (PR), while 2 with pulmonary atypical carcinoid maintained stable disease (SD) for 6 months. Notably, the patient with PR exhibited the highest tumor uptake of ^{68}Ga-DOTATATE on PET/CT, underscoring the potential of this approach.[60]

A phase I study (NCT03996473) sought to evaluate the safety and efficacy of combining [^{223}Ra]$RaCl_2$ with pembrolizumab in metastatic non-SCLC. The trial included patients who were either treatment-naïve for advanced disease or had progressed after prior PD-1/PD-L1 checkpoint blockade. The primary objectives were assessing tumor shrinkage, duration, and treatment safety. However, the study was closed early due to insufficient accrual.

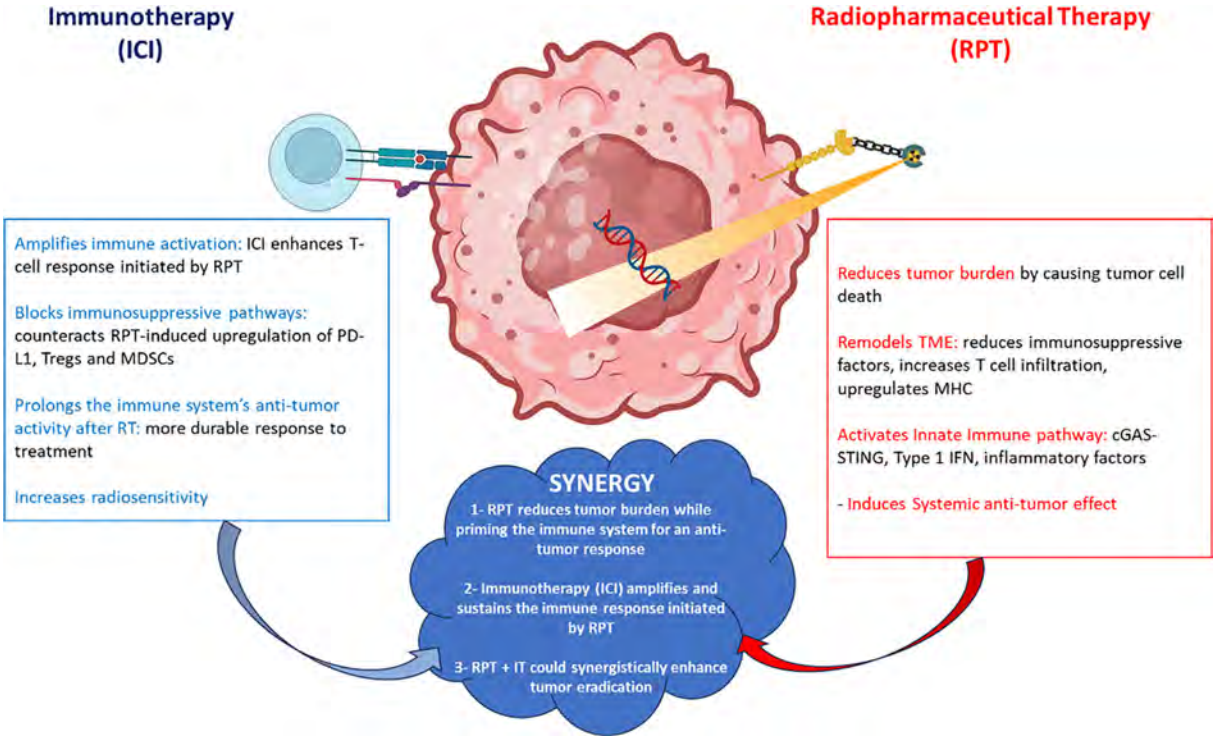
Renal Cancer

Clear cell renal cell carcinoma (ccRCC) is characterized by carbonic anhydrase IX expression resulting from von Hippel-Lindau loss, representing a compelling target for RPT-based therapies. The integration of RPT with immunotherapy in advanced ccRCC is gaining momentum, with 2 phase II clinical trials currently underway (NCT05239533; NCT05663710). These trials aim to evaluate the safety and efficacy of combining [^{177}Lu]Lu-girentuximab with nivolumab as a novel treatment strategy for advanced ccRCC.[61,62]

Merkel Cell Carcinoma

Two case reports underscore the significant therapeutic potential of combining RPT with ICI in metastatic Merkel cell carcinoma (MCC). These cases involved patients who had progressed on first-line avelumab or second-line therapies combining ipilimumab, nivolumab, and EBRT.[64,65] While up to half of patients with MCC either may not respond to or may develop resistance

Figure 3. Potential synergistic interactions between radiopharmaceutical therapy and immune checkpoint inhibitors (ICIs).



Abbreviations: MCH, melanin-concentrating hormone; MDSCs, myeloid-derived suppressor cells; TME, tumor microenvironment.

to ICIs,[65] the frequent expression of somatostatin receptors in MCC makes it a suitable target for [^{177}Lu]Lu-DOTATATE. In one case, a patient with extensive MCC metastases treated with [^{177}Lu]Lu-DOTATATE and anti-PD-L1 therapy demonstrated a rapid response, achieving a near-complete response within 1 month.[64] Another patient receiving [^{177}Lu]Lu-DOTATOC, along with ipilimumab and nivolumab, achieved and sustained a PR for 5 months.[65] Clinical trials (NCT05583708; NCT04261855) have been initiated to evaluate [^{177}Lu]Lu-DOTATATE combined with nivolumab or pembrolizumab in patients with metastatic MCC.

Other ongoing clinical trials are exploring RPT with ICI, including radioiodine (^{131}I) with durvalumab (NCT03215095) for thyroid cancer, ^{131}I-MIBG with nivolumab and dinutuximab (anti-GD2 monoclonal antibody) for refractory neuroblastoma (NCT02914405), and ^{177}Lu-DOTA0-Tyr3-Octreotate with pembrolizumab (NCT03457948) for NETs with liver metastases.

Challenges and Future Perspectives

Combining RPT with immunotherapy is a promising therapeutic option for metastatic cancers. With its targeted radiation delivery and ability to modulate the TME, RPT can complement the systemic antitumor effects of immunotherapy. Preclinical studies highlight the potential of RPT and ICI combination,[47-54] but robust clinical evidence remains limited. Nevertheless, few studies have shown promising results, including case reports with [^{177}Lu]Lu-DOTATATE or [^{177}Lu]Lu-DOTATOC plus ICI in MCC metastases,[64,65] and the phase I PRINCE trial with [^{177}Lu]Lu-PSMA-617 in combination with ICI in mCRPC.[59] Beyond these studies, we are awaiting results from ongoing clinical trials (**Table 2**). Nevertheless, challenges persist, including increased toxicities[57] with immune-related events and radiation-induced toxicities. The immunosuppressive TME, influenced by regulatory T cells and immune checkpoint expression, may further dampen treatment efficacy. Variability in patient responses, driven by tumor heterogeneity, highlights the need for predictive biomarkers for optimal patient selection. Economic and logistical barriers also hinder implementation.[66-70] The production and administration of RPT require specialized

infrastructure and expertise, while its high costs necessitate cost-benefit analyses for integration into clinical practice. Future research should optimize trial designs for sequencing, dosing, and timing of RPT-ICI combinations. Advances in imaging, dosimetry, and collaboration among specialists, along with efforts to reduce costs and improve access, are key to transforming metastatic cancer treatment. Moreover, most trials do not clearly differentiate whether observed toxicities stem from immune-related effects or radiation exposure. Gaining a deeper understanding of the predominant mechanism, whether immune-mediated or radiation-induced, is essential for optimizing toxicity management and improving the safety profile of these combinations.

Conclusion

The combination of RPT and immunotherapy offers a transformative approach to metastatic cancer, overcoming current treatment limitations. As shown in **Figure 3**, RPT synergizes with immunotherapy, including ICIs, by reducing tumor burden, releasing neo-antigens, enhancing MHC-I expression, and modifying the TME, while immunotherapy amplifies and sustains these effects, countering immune evasion and optimizing tumor control, especially in "cold" tumors. Despite challenges such as toxicity and logistical barriers, advances in radiopharmaceutical design, immune modulation, and personalized biomarkers driven by interdisciplinary collaboration could redefine cancer care for advanced, treatment-resistant, and metastatic malignancies.

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