Review

Discovery Medicine 2026; 38(209): 1693–1705
https://doi.org/10.24976/Discov.Med.202638209.132

PARP Inhibitor-Sensitized Radionuclide Therapy Combined With Immune Checkpoint Inhibitors: A Review of Mechanistic Synergy, Tumor Microenvironment Remodeling, and Systemic Immune Effects

Jinfeng Rong[1], Yan Xu[1], Hongjia Zhu[1], Xue Zhou[1], Yan Chen[1], Linquan Mu[2,*]

[1]Department of Oncology, The Second People's Hospital of Yibin, 644000 Yibin, Sichuan, China
[2]Department of Cardiothoracic Surgery, The Second People's Hospital of Yibin, 644000 Yibin, Sichuan, China
*Correspondence: mr2026168@163.com (Linquan Mu)
Submitted: 21 April 2026 Revised: 7 May 2026 Accepted: 1 June 2026 Published: 20 June 2026

Radionuclide therapy has garnered significant attention for its ability to be precisely delivered to tumor sites, particularly in metastatic cancers not effectively controlled by conventional external beam radiation. However, the efficacy of radionuclide therapy alone is often suboptimal, making the exploration of radionuclide-based combination regimens critically important. The "triple therapy" strategy of PARP inhibitor (PARPi)-sensitized radionuclide therapy (RNT) combined with immune checkpoint inhibitors (ICI) aims to overcome the limitations of monotherapies through multi-mechanistic synergy, thereby enhancing antitumor efficacy. This review summarizes the synergistic mechanisms underlying this combination strategy, focusing on the DNA damage and replication stress induced by the synergy between PARPi and RNT, as well as the consequent remodeling of the tumor microenvironment (TME), including the induction of immunogenic cell death (ICD), alterations in immune cell infiltration, and the weakening of immunosuppressive barriers. These local effects ultimately synergize with ICI, potentially activating a robust systemic antitumor immune response. We systematically summarize the preclinical evidence for this strategy, review the progress of ongoing clinical trials, and discuss its challenges and future directions, aiming to provide a theoretical basis for optimizing combination cancer therapies.

Keywords: PARP inhibitor; radionuclide therapy; immune checkpoint inhibitor; DNA damage repair; immunogenic cell death; tumor microenvironment; combination therapy

Introduction

Radionuclide therapy (RNT) is a precise therapeutic approach that delivers radionuclides to tumor sites, utilizing emitted particles (e.g., alpha or beta particles) to induce DNA damage in tumor cells [1,2]. However, radionuclide therapy alone often fails to achieve satisfactory therapeutic outcomes [3]. Furthermore, despite the approval of drugs like ^{177}Lu-PSMA-617, primary resistance remains a clinical challenge [4]. Therefore, the current research focus has shifted towards combination therapies, exploring strategies combining RNT with radiosensitizers (e.g., PARP inhibitors) [5,6], targeted drugs [7], or other radionuclides [8], aiming to overcome the limitations of monotherapy and improve efficacy.

Poly(ADP-ribose) polymerase inhibitors (PARPi), a class of drugs targeting DNA damage repair, inhibit the repair of DNA single-strand breaks (SSBs) [9]. In tumor cells with homologous recombination repair (HRR) deficiency (e.g., BRCA1/2 mutations), PARPi-induced replication fork stalling blocks SSB repair and ultimately converts them into lethal double-strand breaks (DSBs), a process known as synthetic lethality [9,10]. Data have shown that PARPi can enhance tumor sensitivity to radiation [11]. RNT directly induces DSBs, while PARPi indirectly leads to DSB accumulation by inhibiting SSB repair. Together, the two agents exhibit significant synergistic lethal effects in inducing DNA damage, thereby providing a solid molecular foundation for combination therapy.

Moreover, PARPi can trigger immunogenic cell death (ICD) [12,13], characterized by dying tumor cells releasing a series of damage-associated molecular patterns (DAMPs) in a spatiotemporally coordinated manner [14]. These DAMPs act as "danger signals", attracting and activating antigen-presenting cells (e.g., dendritic cells), promoting the cross-presentation of tumor-associated antigens (TAAs), and thereby initiating adaptive immune responses against the tumor [15]. Studies have shown that various chemotherapeutic agents and radiotherapy (RT) are effective ICD inducers [16,17]. RNT, as a form of internal radi-

ation therapy, can also induce ICD. Therefore, the "PARPi + RNT" combination strategy is expected to enhance tumor immunogenicity through synergistic ICD induction, creating favorable conditions for subsequent immunotherapy.

However, the immunosuppressive state prevalent in the tumor microenvironment (TME) often limits the effectiveness of this ICD-initiated antitumor immune response [18]. The TME is enriched with various immunosuppressive cells that suppress the function and infiltration of effector T cells through various mechanisms, including secreting immunosuppressive cytokines (e.g., TGF-β, IL-10), depleting essential nutrients, and expressing immune checkpoint molecules (e.g., PD-L1), thereby aiding tumor immune escape [19,20]. For example, in various tumors such as lung cancer, renal cell carcinoma, and melanoma, high levels of MDSCs and Tregs are associated with poor prognosis and resistance to immune checkpoint inhibitors (ICI) [20,21]. The upregulation of PD-L1 on tumor cells and immune cells, by binding to PD-1 on T cells, further inhibits T cell activation and is one of the key immunosuppressive mechanisms [18,22]. Therefore, even if "PARPi + RNT" successfully induces ICD and releases tumor antigens, these "braking" mechanisms in the TME may prevent the immune response from effectively initiating or sustaining.

Immune checkpoint inhibitors (ICI), such as anti-PD-1/PD-L1 antibodies, can relieve the inhibition on T cells and restore their antitumor cytotoxic activity [20]. However, the efficacy of ICI is highly dependent on the pre-existing infiltration of effector T cells in the TME, i.e., so-called "hot tumors" [23,24]. For "cold tumors" lacking T cell infiltration, ICI monotherapy often has limited efficacy [23,25]. Therefore, converting "cold tumors" into "hot tumors" is a key strategy to improve ICI efficacy. Studies indicate that both PARPi and RNT can activate the cGAS-STING pathway through DNA damage, inducing type I interferon (IFN) production, thereby promoting dendritic cell maturation and T cell recruitment, and remodeling the TME [26,27]. Thus, the "PARPi + RNT" combination therapy is expected to create a more favorable environment for ICI and may significantly enhance its efficacy [23].

Synergistic DNA Damage Mechanisms of PARP Inhibitors and Radionuclide Therapy

The PARP enzyme family, particularly PARP1 and PARP2, plays a crucial role in maintaining genomic stability, with its key function being to recognize DNA single-strand breaks and initiate the base excision repair pathway [28,29]. When DNA suffers single-strand damage, PARP1/2 rapidly recognizes and binds to the damage sites through its DNA-binding domain and catalyzes the synthesis of substrate NAD+ into poly(ADP-ribose) chains, a process called PARylation. This process recruits and activates downstream repair proteins, enabling efficient damage repair [30]. PARP inhibitors work by competitively binding to the catalytic active site of PARP enzymes, mimicking the structure of NAD+, thereby inhibiting their enzymatic activity [28]. However, the action of PARPi extends beyond simple catalytic inhibition. More critically, they can "trap" PARP enzymes at DNA damage sites, forming stable and toxic PARP-DNA complexes. This "trapping" effect physically impedes the progress of DNA repair mechanisms, allowing SSBs that should be rapidly repaired to persist [31]. These "trapped" PARP-DNA complexes interfere with the normal progression of replication forks, leading to fork stalling and ultimately converting the original SSBs into more cytotoxic DSBs [32]. Meanwhile, radionuclide therapy, for example, using alpha- or beta-particle emitting nuclides like actinium-225 or lutetium-177, releases high-LET radiation that directly induces high-density, complex DSBs within tumor cells [2,33]. Therefore, the combination of PARPi and RNT constitutes a multi-layered DNA damage attack strategy: on one hand, PARPi induces DSBs by inhibiting SSB repair and utilizing the "trapping" mechanism; on the other hand, RNT triggers a large number of DSBs through ionizing radiation. Acting together, they facilitate uncontrolled accumulation of DSBs within tumor cells, exceeding the cell's own repair capacity and leading to cell death (Fig. 1). This excessive DNA damage load is a significant challenge even for cells with intact HR function, but for HR-deficient tumor cells, such as those carrying BRCA1/2 mutations, it produces a strong "synthetic lethal" effect, leading to apoptosis [34,35]. Multiple studies have shown that, regardless of the HR status of tumor cells, the combination of PARPi and RNT can significantly increase tumor cell mortality, demonstrating clear synergistic efficacy [6,36]. Thus, the combination of PARPi and RNT can effectively broaden the applicable population for PARPi, enabling some tumors with partially retained HR function to respond to treatment, providing a solid theoretical basis for combination therapy [37].

Tumor Microenvironment Remodeling Triggered by DNA Damage

Immunogenic Cell Death (ICD) and Antigen Release

The combined application of PARP inhibitors and radionuclide therapy, by inducing intense DNA damage and cell death, triggers typical immunogenic cell death. This is a non-"silent" form of death characterized by the exposure of calreticulin (CRT) on the surface of dying cells and the release of high mobility group box 1 (HMGB1), ATP, and a large number of tumor-associated antigens (TAAs) and neoantigens [38]. CRT acts as a key "eat me" signal, promoting the phagocytosis of dead tumor cells by dendritic cells (DCs) [39]. Simultaneously, released HMGB1 binds to Toll-like receptor 4 (TLR4) on DCs, while ATP binds to the purinergic receptor P2RX7. These signals collectively promote the maturation and activation of DCs [40]. Furthermore, the TAAs and neoantigens released during the

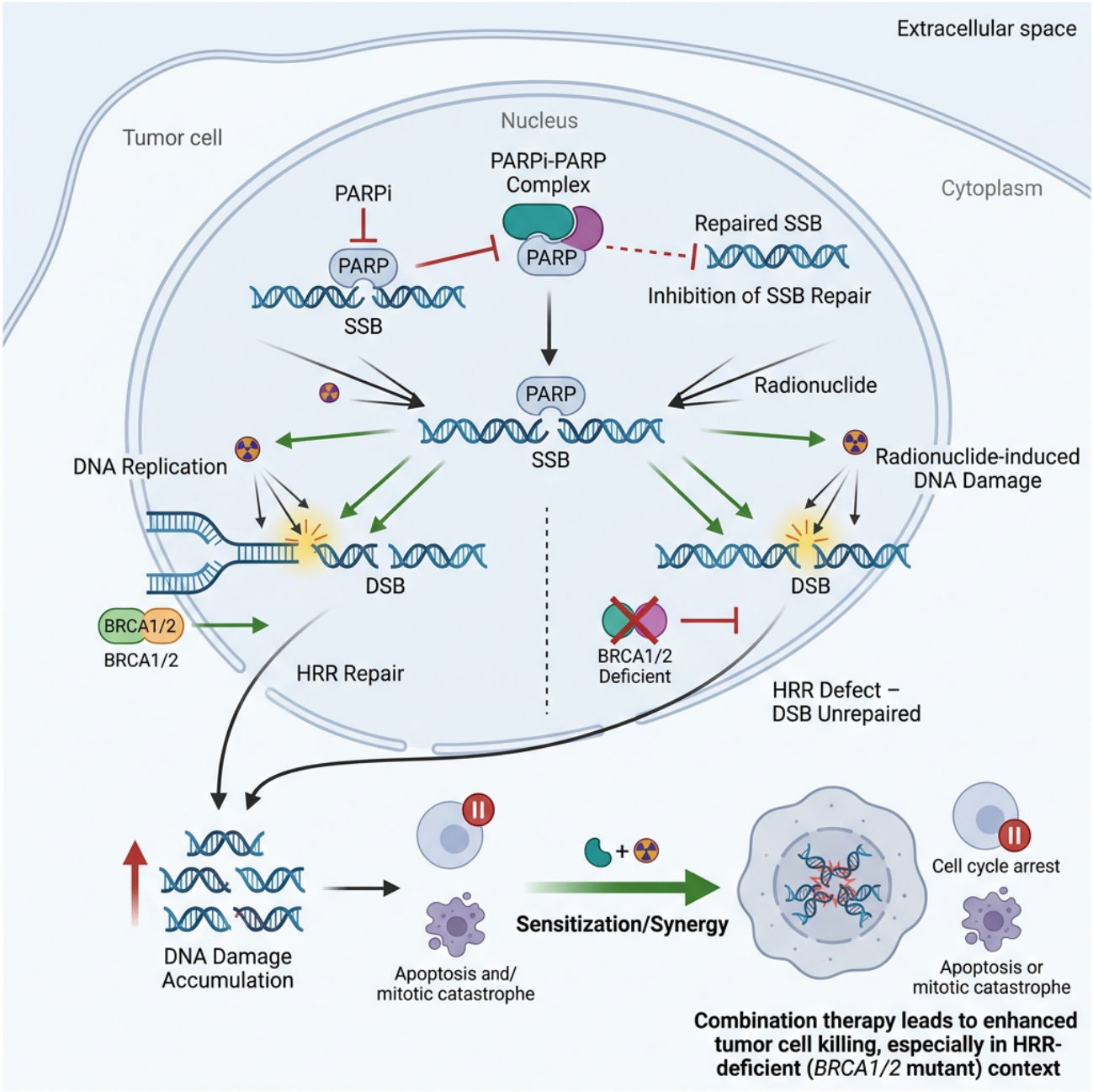

Fig. 1. Synergistic DNA damage mechanisms of PARP inhibitors and radionuclide therapy. PARPi induces DSBs by inhibiting SSBs repair and utilizing the "trapping" mechanism; RNT triggers DSBs through ionizing radiation. Combination therapy facilitates uncontrolled accumulation of DNA damage within tumor cells, leading to cell death. Drawn with jova.ai (https://jova.ai/). PARPi, poly (ADP-ribose) polymerase inhibitor; SSB, single-strand break; DSB, double-strand break; HRR, homologous recombination repair; BRCA1/2, breast cancer 1/2; RNT, radionuclide therapy.

cell death process provide a rich source of antigens for presentation by DCs [41]. This series of events transforms the death of tumor cells into a "vaccine"-like effect, thereby initiating the first step of the adaptive immune response: antigen presentation and T cell priming [42]. Research has shown that cytotoxicity mediated by cytotoxic T lymphocytes (CTL) or natural killer (NK) cells is itself a form of ICD, effectively promoting cross-presentation of tumor antigens [39]. In preclinical models, PARPi such as olaparib combined with radiotherapy have been confirmed to induce ICD, characterized by CRT exposure and HMGB1 release, thereby remodeling the tumor immune microenvironment [43]. Similarly, radionuclide therapies such as iodine-131 have also been shown to induce ICD and enhance tumor immunogenicity [44]. Therefore, the synergistic effect of PARPi and RNT, by inducing ICD, lays a crucial antigen and adjuvant foundation for subsequently activating a robust antitumor immune response.

Activation of the Type I Interferon Signaling Pathway

The combined action of PARP inhibitors and radionuclide therapy can lead to abnormal accumulation of DNA double-strand breaks. Cytosolic DNA fragments abnormally accumulated in the cytoplasm can serve as endogenous danger signals, recognized by cytosolic DNA sensors such as cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) [13,45]. cGAS catalyzes the generation of the second messenger cGAMP, which then activates STING protein, driving the transcription and expression of type I interferons (IFN-α/β) and various inflammatory cytokines through the TANK-binding kinase 1-interferon regulatory factor 3 (TBK1-IRF3) signaling axis [46]. Type I interferon is crucial for antitumor immunity; it can directly enhance the antigen-presenting capacity of tumor cells, for example, by upregulating major histocompatibility complex class I (MHC-I) molecules, while powerfully recruiting and activating dendritic cells, CD8+ T cells, and natural killer cells, and inhibiting the function of regulatory T cells [47]. Therefore, activating the cGAS-STING pathway is one of the key mechanisms by which PARPi, combined with radiation, shifts tumors from an "immune-ignorant" state to an "immune-inflammatory" state. Research has confirmed that in hepatocellular carcinoma models, DSBs induced by olaparib combined with radiotherapy can activate the cGAS-STING pathway, initiate immunogenic cell death in distant (abscopal) tumors, and trigger the release of type I interferons and chemokines, thereby amplifying T cell priming against tumor neoantigens [46]. In pancreatic cancer models, ^{125}I combined with olaparib can also activate the cGAS-STING pathway, promoting antitumor immune responses [48]. Additionally, low-dose radiotherapy combined with nano-sensitizers and PARPi (e.g., olaparib) can synergistically trigger the cGAS-STING pathway and remodel the tumor microenvironment [47]. These findings indicate that activating the type I interferon response via the cGAS-STING pathway is a key molecular bridge through which the PARPi + RNT combination exerts systemic antitumor immune effects.

Modulation of Immunosuppressive Cellular Components

While activating immune effector cells, the combination of PARP inhibitors and radionuclide therapy also significantly affects the immunosuppressive components of the tumor microenvironment. Evidence shows that PARP inhibitors can reduce the recruitment and function of tumor-associated myeloid-derived suppressor cells by modulating chemokine expression or through direct effects [49]. Furthermore, the activation of the DNA damage response is closely associated with the upregulation of programmed death-ligand 1 (PD-L1) expression on tumor cells, which is often viewed as an immune escape mechanism, where tumor cells inhibit infiltrating T cell function by upregulating PD-L1 [43,50]. However, this upregulation precisely provides a clear target and "window of opportunity" for subsequent combination with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1 antibodies), converting the upregulation of PD-L1 from an immune escape signal into a vulnerability that can be therapeutically exploited [12]. In preclinical studies, PARPi (e.g., niraparib) combined with radiotherapy has been confirmed to upregulate PD-L1 expression on tumor cells, thereby creating favorable conditions for combination with anti-PD-1 therapy [43]. Similarly, in tumor bearing mouse models, the combination of radionuclide therapy and immune checkpoint inhibitors can produce synergistic antitumor effects and establish durable antitumor immunity [44]. In ovarian cancer models, combined delivery of PARPi and USP1 inhibitors enhances DNA damage, activates the STING pathway, and remodels the tumor microenvironment by increasing CD8+ T cell infiltration, thereby improving tumor sensitivity to immune checkpoint blockade therapy [51]. This evidence indicates that PARPi + RNT not only downregulates immunosuppressive cells (e.g., MDSCs) but also exposes the tumor's immune vulnerabilities by inducing PD-L1 upregulation, paving the way for sequential combination with immune checkpoint inhibitors to achieve deep and durable immune clearance.

Synergistic Immune Activation Combined With Immune Checkpoint Inhibitors

Relieving T Cell Exhaustion and Amplifying Effector T Cell Function

The combination of PARP inhibitors and radiation can initiate antitumor immune responses and promote the infiltration of effector T cells into the tumor microenvironment [46]. However, these infiltrating T cells often enter a functionally limited "exhausted" state within the TME due to persistent antigen stimulation and immunosuppressive signals [52]. Exhausted T cells, particularly terminally exhausted CD8+ T cells, exhibit significantly reduced proliferation, cytokine secretion, and cytotoxic killing capacity [53,54]. Immune checkpoint inhibitors (ICI), such as drugs targeting the PD-1/PD-L1 pathway, can block these inhibitory signals, thereby "reinvigorating" exhausted T cells and restoring their function [55]. In the TME pre-remodeled by PARPi+RNT, this "reinvigoration" effect is greatly enhanced. The synergistic effect of PARPi and radiotherapy can induce DNA double-strand breaks, activate the cGAS-STING pathway, trigger immunogenic cell death, and release a large number of tumor neoantigens and inflammatory signals, such as type I interferons and chemokines like CXCL9 and CXCL10 [46]. This TME, rich in tumor antigens and inflammatory signals, provides a more favorable environment for ICI action. At this point, a greater number of newly activated T cells are available for "rescued", and the inflammatory environment is conducive to sustained T cell activation [56]. Preclinical studies con-

firm that in pancreatic cancer models, olaparib combined with radiotherapy enhances type I interferon-mediated immune signaling, increases the frequency and activity of CD8+ terminally differentiated effector T cells, thereby significantly improving tumor sensitivity to αPD-L1 therapy [56]. Furthermore, in immunologically cold tumor models, the combined use of RNT and ICI can activate the production of pro-inflammatory cytokines in the TME, promote the invasion and clonal expansion of effector CD8+ T cells, and reduce spontaneous metastasis [57]. Therefore, based on the PARPi + RNT-induced immunostimulatory TME, ICI can more effectively relieve T cell exhaustion and amplify effector T cell function, resulting in a powerful and durable antitumor immune effect.

Induction of Abscopal Effects and Immune Memory Formation

An important potential advantage of the "triple therapy" (PARPi + RNT + ICI) is its potential to induce "abscopal effects", whereby treatment of a locally irradiated tumor lesion can trigger immune-mediated regression of distant, non-irradiated metastatic lesions. The key mechanism lies in the local treatment triggering a systemic antitumor immune response (Fig. 2). The combination of PARPi and radiotherapy can induce significant DNA damage and activate the cGAS-STING pathway, which not only triggers immunogenic cell death in the primary tumor but also remodels the immune microenvironment of distant (abscopal) tumors [46]. This remodeling manifests as the release of type I interferons and specific chemokines (e.g., CXCL9, CXCL10, CXCL11, CCL5), thereby amplifying T cell priming against tumor neoantigens, leading to the influx of activated, neoantigen-specific CD8+ T cells into distant tumors [46]. These systemically activated T cells, particularly those with memory potential, can recognize and attack tumor cells expressing the same antigens in other parts of the body via the bloodstream [58]. Preclinical models have confirmed that compared to any single or dual therapy, the combination of PARPi, radiotherapy, and ICI can more effectively control the growth of primary and metastatic lesions and prolong survival [46,56]. For example, in hepatocellular carcinoma models, olaparib enhances the systemic antitumor effects induced by radiotherapy by activating the STING-chemokine signaling pathway, thereby improving responsiveness to immune checkpoint inhibitors [46]. In pancreatic cancer models, olaparib combined with radiotherapy not only enhances type I interferon production, sensitizing tumors to αPD-L1, but also induces durable immune memory, as evidenced by cured mice rejecting tumors upon rechallenge [56]. In preclinical models of small cell lung cancer and BRCA1-mutated tumors, radiotherapy combined with PARP inhibitors and immune checkpoint inhibitors could remodel the tumor microenvironment and improve systemic antitumor effects [59,60]. Although the delivery methods of radionuclide therapy and external beam radiotherapy differ, the radiobiological mechanisms they induce are comparable [61]. Although there are currently no definitive research results for "PARPi + RNT + ICI" triple therapy, these findings regarding external beam radiotherapy suggest that the PARPi + RNT combined with ICI strategy may not only be a local intensification therapy but also a potential systemic immunotherapy strategy. By inducing systemic immune responses and immune memory formation, it holds significant promise for controlling advanced metastatic tumors.

Preclinical Evidence and Current Status of Clinical Trials

Key Preclinical Model Studies

In various preclinical tumor models (including neuroendocrine tumors, small cell lung cancer, and pancreatic cancer), ^{177}Lu-targeted radiotherapy combined with PARPi has shown the potential to delay tumor growth and prolong survival more effectively than monotherapy [6,62,63]. In preclinical studies on small cell lung cancer (SCLC), Rauch H *et al.* [6] evaluated the combined efficacy of SSTR2-targeted radionuclide therapy ([^{177}Lu]Lu-DOTA-TOC) with PARPi (olaparib or rucaparib). Although SCLC cell lines (H69 and H446) exhibited low SSTR2 expression levels, *in vitro* experiments showed that combination therapy significantly enhanced efficacy, increasing treatment potency by 2.9 to 67 times compared with [^{177}Lu]Lu-DOTA-TOC alone, and leading to decreased clonogenic survival and more persistent DNA damage [6]. In tumor-bearing mouse models, combination therapy also significantly prolonged tumor doubling time and median survival of mice, with effects superior to any monotherapy [6]. This study indicated that even for tumors with low SSTR2 expression, adding PARPi could significantly enhance the efficacy of targeted radionuclide therapy [6]. This combination therapy not only directly kills tumor cells but also remodels the tumor microenvironment (TME). When further combined with immune checkpoint inhibitors (ICI) like anti-PD-1, stronger immune activation effects can be observed, specifically manifested as a significant increase in tumor-infiltrating CD8+ T cells, a reduction in regulatory T cells (Tregs), and the potential induction of "abscopal effects" against distant untreated tumors, providing strong evidence for overcoming tumor immunosuppression [64]. Luna-Gutiérrez M *et al.* [65] developed a PD-L1-targeted radiolabeled peptide [^{177}Lu]Lu-iPD-L1. *In vitro* and *in vivo* experiments demonstrated that this agent exhibited specific targeting ability toward PD-L1 and could deliver considerable radiation doses to tumors [65]. The results showed that [^{177}Lu]Lu-iPD-L1 treatment significantly increased the expression levels of activated macrophages, PD-L1, IL-10, and TGFβ in PD-L1-positive tumors, suggesting immunomodulatory effects [65]. In another study, a novel dimeric radiopharmaceutical [^{177}Lu]Lu-DOTA-2P(FAPI)2

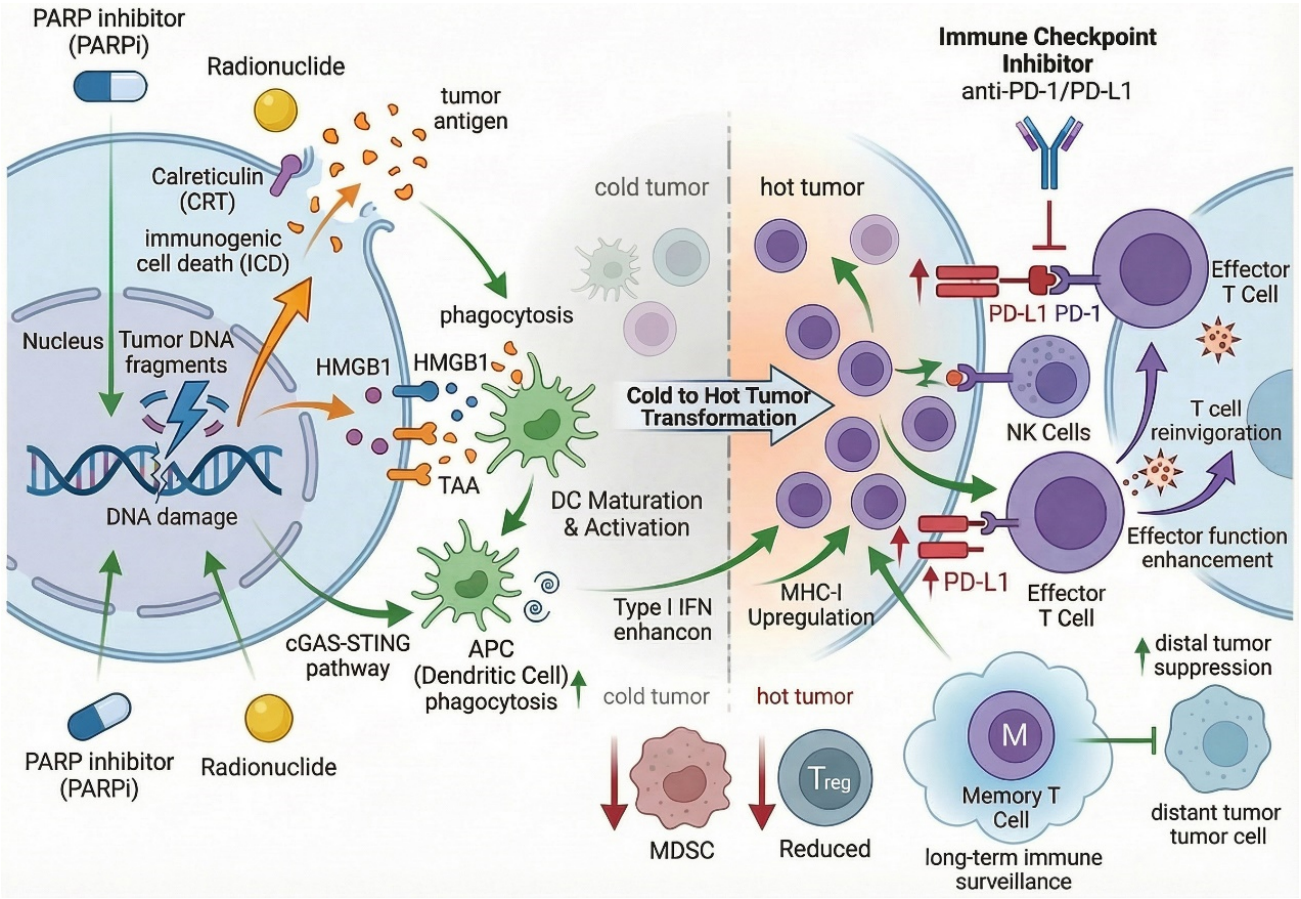

Fig. 2. The mechanism of action of RNT, PARPi, and ICIs in their triple antitumor activity. The combined action of PARPi and RNT causes DNA damage, triggers ICD, activates the type I interferon signaling pathway, reshapes the tumor microenvironment, and then synergizes with immune checkpoint inhibitors for immune activation. Drawn with jova.ai (https://jova.ai/). PARPi, poly (ADP-ribose) polymerase inhibitor; ICD, immunogenic cell death; CRT, calreticulin; HMGB1, high mobility group box 1; TAA, tumor-associated antigen; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; APC, antigen-presenting cells; DC, dendritic cell; NK cell, natural killer cell; IFN, interferon; MHC-I, major histocompatibility complex class I; MDSC, myeloid-derived suppressor cell; PD-1, programmed death 1; PD-L1, programmed death-ligand 1.

effectively induced DNA double-strand breaks and upregulated PD-L1 expression [66]. When [^{177}Lu]Lu-DOTA-2P(FAPI)2 was combined with anti-PD-L1 monoclonal antibodies, it showed excellent antitumor efficacy in animal models, even eliminating tumors and inducing 100% tumor rechallenge rejection, indicating the generation of immune memory [66]. Mechanistic studies revealed that this combination therapy could remodel the tumor microenvironment, increasing CD8+ T cell infiltration while reducing regulatory T cells [66]. In ovarian cancer (especially those harboring BRCA mutations or homologous recombination deficiency-positive) and triple-negative breast cancer models, similar synergistic patterns have been validated. PARPi, by sensitizing RNT targeting folate receptors and other targets, when combined with ICI, showed enhanced antitumor activity across different tumor types [67]. This suggests that the triple strategy (PARPi + RNT + ICI) may have universal, cross-tumor potential. However, in preclinical studies on prostate cancer, combining prostate-specific membrane antigen-targeted radionuclide therapy (PSMA-TRT) with three PARPi (veliparib, olaparib, talazoparib) showed that the combination did not synergistically affect clonogenic survival or cell viability *in vitro* [68]. DNA damage analysis indicated that only the combination with veliparib significantly increased DNA breaks, while no such effect was observed with other PARPi [68]. *In vivo* experiments also failed to show improved tumor control with combination therapy compared to PSMA-TRT monotherapy [68]. Therefore, the data from this study do not support the hypothesis that combining PSMA-TRT with PARPi would produce synergistic antitumor effects in prostate cancer models [68]. This highlights the necessity for in-depth preclinical validation of combination therapies in different cancer models.

Table 1. Ongoing clinical trials on the combined treatment of RNT, PARPi, and ICIs[a].

NCT Number	Conditions	PARPi	RNT	ICIs	Phases	Study Status
NCT05392686	Lung Cancer	PARP inhibitor	No	PD-1 inhibitor	II	Recruiting
NCT06502691	Metastatic Breast Carcinoma	PARP inhibitor	Fluorine F 18 Fluorthanatrace	Immune Checkpoint Inhibitor	I/II	Recruiting
NCT06446206	Platinum-sensitive Relapsed Ovarian Cancer	Fluzoparib	No	Adebrelimab	II	Not yet recruiting
NCT05524935	Uveal Melanoma, Ocular Melanoma	Olaparib	No	Pembrolizumab	II	Recruiting
NCT07269158	Biliary Tract Neoplasms	Venadaparib	No	Durvalumab or Pembrolizumab	I/II	Not yet recruiting
NCT05201612	Metastatic Colorectal Cancer	Olaparib	No	Pembrolizumab	II	Recruiting
NCT04592211	Gastric Cancer Stage IV	Olaparib	No	Pembrolizumab	I/II	Recruiting
NCT02484404	Colorectal Neoplasms, Breast Neoplasms	Olaparib	No	Durvalumab	I/II	Active, not recruiting
NCT04375267	Neuroendocrine Tumors, Thymoma	Olaparib	^{177}Lu-DOTATATE	No	I	Active, not recruiting
NCT05053854	Neuroendocrine Tumors	Talazoparib	^{177}Lu-DOTA-octrotate	No	I	Recruiting
NCT06607692	Solid Tumor Cancer	Olaparib	^{177}Lu-DOTATATE	No	II	Recruiting
NCT05870423	Neuroendocrine Tumors	Olaparib	^{177}Lu-DOTATATE	No	I	Recruiting
NCT04086485	Gastroenteropancreatic Tumors, Neuroendocrine Tumors	Olaparib	^{177}Lu-DOTATATE	No	I/II	Recruiting
NCT05150236	Prostatic Neoplasms, Genital Neoplasms	No	^{177}Lu-PSMA-617	Ipilimumab, Nivolumab	II	Active, not recruiting
NCT07059494	Hepatocellular Carcinoma	No	Y^90 Radioembolization	Atezolizumab	IV	Recruiting
NCT03215095	Thyroid Cancer	No	Radioiodine (RAI)	Durvalumab	I	Active, not recruiting
NCT02914405	Neuroblastoma	No	131-I Metaiodobenzylguanidine	Nivolumab	I	Active, not recruiting
NCT04261855	Metastatic Merkel Cell Carcinoma	No	^{177}Lu-DOTATATE	Avelumab	IB/II	Recruiting

ICI, immune checkpoint inhibitor; RNT, radionuclide therapy; PARPi, poly (ADP-ribose) polymerase inhibitor.

[a] Source https://www.clinicaltrials.gov, limited to studies with “Not yet recruiting”, “Recruiting”, “Enrolling by invitation” and “Active, not recruiting” status.

Ongoing Clinical Studies

Currently, clinical research on the combination of radionuclides with PARPi and ICI is primarily in Phase I, with the focus on exploring adverse reactions and patient tolerance. A Phase I clinical trial evaluated the feasibility and toxicity of combining the PARP inhibitor olaparib with the radionuclide therapy ^{177}Lu-DOTATATE in patients with somatostatin receptor-positive tumors [69]. The study enrolled 18 patients, most of whom had pancreatic or small intestinal neuroendocrine tumors or atypical lung carcinoids. Patients received standard-dose ^{177}Lu-DOTATATE (7400 MBq, up to 4 cycles) combined with dose-escalated olaparib (50–300 mg, twice daily) [69]. The results showed that the combination of ^{177}Lu-DOTATATE and olaparib was generally well-tolerated. The main dose-limiting toxicity was thrombocytopenia, observed in 3 patients in the 300 mg olaparib dose group. Other toxicities were mild, primarily manifested as low-grade myelosuppression, nausea, and fatigue [69]. Based on these findings, the researchers suggested a starting dose of olaparib at 200 mg twice daily for future studies, with consideration for escalation to 300 mg twice daily based on patient tolerance [69]. A Phase I clinical study on Lutathera (^{177}Lu-DOTATATE) combined with nivolumab for treating lung neuroendocrine tumors enrolled 9 patients. It was the first to demonstrate that the combination of Lutathera (PRRT) and nivolumab (immunotherapy) is safe and feasible for lung neuroendocrine tumors (including SCLC), and preliminary antitumor activity was observed. However, the sample size was small, and the study was an early exploratory trial, limiting definitive conclusions regarding efficacy [70]. In contrast, another Ib phase clinical trial evaluating the safety and efficacy of atezolizumab combined with radium-223 dichloride in patients with metastatic castration-resistant prostate cancer (mCRPC) reported higher toxicity in the combination therapy than that of either agent alone, without clear evidence of clinical benefit in terms of efficacy. This study tested a theoretically justified combination therapy (radiotherapy + immunotherapy) but failed to achieve the expected synergistic effect in mCRPC patients, instead increasing risks. Therefore, it did not support further clinical development [71]. Nevertheless, preliminary case experiences suggest that the combination of ^{177}Lu-PSMA with pembrolizumab, or sequential use after olaparib pretreatment, may be tolerable in individual patients, providing a preliminary safety and feasibility basis for future larger-scale clinical studies [72]. In summary, based on current data analysis, some combination therapies have not demonstrated the theoretically expected synergistic efficacy but are associated with increased toxicity, while other clinical evidence supports the benefit of combination therapy. However, most studies are in the Phase I exploratory stage. Future clinical research should further investigate the feasibility of combination therapy across different tumor types, molecular phenotypes, drug dosages, and treatment sequences. Ongoing clinical studies investigating radionuclide-based combination therapies are shown in Table 1.

Challenges and Future Perspectives

Toxicity Management and Therapeutic Window Optimization

The primary challenge in the clinical translation of combination therapy (PARP inhibitors, radionuclide therapy, and immune checkpoint inhibitors) is the potential for overlapping toxicities. Both PARP inhibitors and radionuclide therapy can cause myelosuppression, while immune checkpoint inhibitors may trigger a range of immune-related adverse events. PARPi-related hematological toxicities, including anemia, neutropenia, and thrombocytopenia, have been widely reported in real-world studies across various cancers such as ovarian and prostate cancer [73,74]. A retrospective study by Hatch RV *et al.* [73] on patients with ovarian and endometrial cancer showed that approximately half of the patients required dose adjustments due to toxicity. PARP inhibitors like niraparib also exhibit distinct toxicity profiles, such as hypertension and thrombocytopenia [75]. Radionuclide therapies, such as peptide receptor radionuclide therapy (PRRT) and PSMA-targeted therapy, also carry risks of myelosuppression and specific organ toxicities, such as radiation damage to the kidneys and salivary glands [76,77]. Immune checkpoint inhibitors can lead to various immune-related adverse events, including pneumonitis, colitis, hepatitis, and myocarditis [78,79]. Therefore, meticulous dose exploration and optimization of administration regimens are crucial. Future research should manage toxicity through strategies such as intermittent dosing and sequential administration, supplemented by active supportive care [80]. Another important direction for expanding the therapeutic window is the development of novel agents. For example, developing new radionuclide drugs with higher tumor targeting and lower normal tissue toxicity, such as alpha-particle emitters (e.g., 225Ac), which demonstrate potent antitumor efficacy and a relatively favorable toxicity profile [81]. In addition, radiolabeled antibodies that specifically target tumors, such as Y-90 ibritumomab tiuxetan and I-131 tositumomab targeting CD20, have been approved for use in non-Hodgkin lymphoma and have shown significant therapeutic effects [82]. In order to increase tumor-to-healthy organ activity concentration ratios and further improve the therapeutic effect, a pre-targeting strategy has been developed, which involves first injecting unlabeled antibodies, followed by administering radioactive ligands after they bind to the tumor [83]. Concurrently, developing next-generation, more selective PARP1-selective inhibitors aims to improve efficacy and widen the therapeutic window [84]. Furthermore, utilizing targeted nanoplatforms for the simultaneous delivery of radionuclides and PARPi, or designing bifunctional small-molecule drugs, can achieve more precise tumor targeting

and synergistic effects, thereby enhancing efficacy while reducing systemic toxicity [85].

Exploration of Biomarkers and Patient Stratification

Not all patients benefit equally from combination therapy, and discovering reliable predictive biomarkers for precise patient stratification is an urgent need. Potential biomarkers span multiple levels. The first is the tumor-intrinsic DNA damage repair gene defect status, such as BRCA1/2 mutations and homologous recombination deficiency scores. Substantial evidence indicates that tumors harboring BRCA mutations or HRD are highly sensitive to PARP inhibitors, and this sensitivity may extend to combination therapies [86,87]. The second is the baseline immune profile of the tumor microenvironment, such as CD8+ T-cell infiltration density, PD-L1 expression levels, and specific immune gene signatures. These features can reflect the tumor's immunogenicity and its potential responsiveness to immunotherapy [88]. Thirdly, treatment-induced dynamic biomarkers include peripheral blood levels of interferon-gamma (IFN-γ), dynamic changes in circulating tumor DNA (ctDNA), and shifts in immune cell subsets (e.g., T cells, myeloid-derived suppressor cells). For instance, in a window-of-opportunity trial in head and neck cancer, olaparib treatment upregulated tumor PD-L1 expression, suggesting that treatment-induced changes in the immune microenvironment can serve as biomarkers [89]. Dynamic monitoring of ctDNA has been shown to assess PARP inhibitor activity and may be used to identify therapeutic windows [86]. Integrating multi-omics data (e.g., genomic, transcriptomic, proteomic) to build predictive models is a future trend. This comprehensive analytical approach can more holistically capture tumor heterogeneity, immune status, and potential for treatment response, thereby guiding individualized treatment decisions to ensure that triple therapy is applied to patient populations most likely to benefit, while avoiding unnecessary toxicity in patients who are non-responsive or at high risk [88].

Novel Combinations and Technological Innovations

Beyond combination with PD-1/PD-L1 inhibitors, future explorations could involve combining PARP inhibitors and radionuclide therapy with other immunomodulators to further activate or modulate immune responses. For example, combinations with anti-CTLA-4 antibodies, agonistic antibodies (e.g., anti-OX40, anti-GITR), cytokine therapies, or cancer vaccines are possible [90]. These combinations aim to overcome resistance that may arise from single immune checkpoint inhibition and synergistically enhance antitumor immunity through multiple pathways. In terms of technological innovation, developing targeted nanoplatforms capable of simultaneously delivering radionuclides and PARP inhibitors, or designing bifunctional/multifunctional small-molecule drugs, is a crucial direction for achieving more precise tumor targeting and synergy. For instance, research has utilized tumor-targeting peptide-modified mesoporous polydopamine nanoparticles to co-deliver a WEE1 inhibitor and a PARP inhibitor, significantly reducing toxicity while enhancing therapeutic efficacy in ovarian cancer [85]. Similarly, functionalized carbon nanotubes can serve as carriers for selective tumor targeting of radionuclides or drugs, thereby reducing "on-target, off-tumor" toxicity [91]. Furthermore, leveraging artificial intelligence to optimize treatment planning and dose prediction will greatly enhance the precision of radionuclide therapy. In radionuclide therapy, accurate quantitative SPECT imaging and individualized dosimetry are critical for assessing organ (e.g., kidney, bone marrow) absorbed doses and predicting efficacy and toxicity [92,93]. Ryhiner M *et al.* [94] established a mathematical model specifically designed to investigate combination treatment regimens involving radiopharmaceutical therapy and PARP inhibitors. This model predicts outcomes based on DNA absorbed dose and the resulting radiobiological response, and was calibrated and validated through *in vitro* experiments. The study treated NCI-H69 cells with [177Lu]Lu-DOTA-TOC combined with different PARP inhibitors (e.g., olaparib, rucaparib, talazoparib). Model validation showed that predicted values deviated from experimental results within the error margin [94]. Simulation analyses indicated that during lutetium therapy, the radiosensitizing effect of rucaparib could reduce tumor cell numbers by 99.2%, and in tumors with homologous recombination deficiency, reductions could reach 99.99%. The model also predicted relative tumor shrinkage after combination therapy (e.g., with olaparib) based on patient body weight [94]. These results provide a computational modeling foundation for systematically exploring and optimizing such combination clinical protocols [94]. Collectively, these technological innovations and novel combination strategies complement each other, jointly advancing targeted radio-immunotherapy toward greater efficacy and safety.

Conclusion

In summary, radionuclide therapy is a rapidly evolving field aimed at treating patients with metastatic cancer. Its triple-therapy combination with PARP inhibitors and immune checkpoint inhibitors represents a significant exploration in the paradigm shift of cancer treatment from single-targeted approaches to systemic, sequential immune modulation. Its core logic lies in constructing a complete cascade from inducing DNA damage in tumor cells to triggering adaptive immune responses. The synergy between PARP inhibitors and RNT is not merely an additive cytotoxic effect; however, more importantly, by inducing replication stress and DNA double-strand breaks, it triggers immunogenic cell death and activation of the cGAS-STING pathway—a crucial "turning point" that transforms local damage events into signals for systemic immune activation.

This mechanism serves as the "cornerstone" for the subsequent action of immune checkpoint inhibitors, substantially reshaping the tumor microenvironment, converting "cold tumors" into "hot tumors", and creating prerequisites for immunotherapy. Although the outcomes of the various combination therapies discussed in this review vary across different cancer types, the positive results of the triple-therapy combining radiotherapy, PARP inhibitors, and immune checkpoint inhibitors in preclinical models suggest that, at least in certain specific tumor types, the combination of TRT, PARP inhibitors, and immune checkpoint inhibitors is a promising strategy, warranting further in-depth preclinical research.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, JFR, LQM and YX; investigation, YC, JFR, XZ and HJZ; supervision, YC; funding acquisition, LQM. JFR have been involved in drafting the manuscript and all authors have been involved in revising it critically for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by Health Commission of Sichuan Province Medical Science and Technology Program (No.25QNMP116).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Li M, Sagastume EA, Lee D, McAlister D, DeGraffenreid AJ, Olewine KR, *et al*. $^{203/212}$Pb Theranostic Radiopharmaceuticals for Image-guided Radionuclide Therapy for Cancer. Current Medicinal Chemistry. 2020; 27: 7003–7031. https://doi.org/10.2174/0929867327999200727190423.

[2] Mourtada F, Tomiyoshi K, Sims-Mourtada J, Mukai-Sasaki Y, Yagihashi T, Namiki Y, *et al*. Actinium-225 Targeted Agents: Where Are We Now? Brachytherapy. 2023; 22: 697–708. https://doi.org/10.1016/j.brachy.2023.06.228.

[3] Madsen MT, Bushnell DL, Juweid ME, Menda Y, O'Dorisio MS, O'Dorisio T, *et al*. Potential increased tumor-dose delivery with combined 131I-MIBG and 90Y-DOTATOC treatment in neuroendocrine tumors: a theoretic model. Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine. 2006; 47: 660–667.

[4] Mattana F, Muraglia L, Barone A, Colandrea M, Saker Diffalah Y, Provera S, *et al*. Prostate-Specific Membrane Antigen-Targeted Therapy in Prostate Cancer: History, Combination Therapies, Trials, and Future Perspective. Cancers. 2024; 16: 1643. https://doi.org/10.3390/cancers16091643.

[5] Malenge MM, Maaland AF, Repetto-Llamazares A, Middleton B, Nijland M, Visser L, *et al*. Anti-CD37 radioimmunotherapy with 177Lu-NNV003 synergizes with the PARP inhibitor olaparib in treatment of non-Hodgkin's lymphoma *in vitro*. PloS One. 2022; 17: e0267543. https://doi.org/10.1371/journal.pone.0267543.

[6] Rauch H, Kitzberger C, Janghu K, Hawarihewa P, Nguyen NT, Min Y, *et al*. Combining [^{177}Lu]Lu-DOTA-TOC PRRT with PARP inhibitors to enhance treatment efficacy in small cell lung cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2024; 51: 4099–4110. https://doi.org/10.1007/s00259-024-06844-1.

[7] Foxton C, Cornelissen B, O'Neill E, Waldron B, Pretzmann F, Grønlund RV, *et al*. A novel synergistic drug combination of a mitogen-activated extracellular signal-regulated kinase inhibitor with [^{177}Lu]Lu-rhPSMA-10.1 for prostate cancer treatment: Results of a preclinical evaluation. Nuclear Medicine and Biology. 2025; 146–147: 109042. https://doi.org/10.1016/j.nucmedbio.2025.109042.

[8] Savio E, Reyes L, Giglio J, Alfaya L, Falasco G, Urrutia L, *et al*. Preclinical evaluation of [^{225}Ac]Ac-PSMA-617 and in vivo effect comparison in combination with ^{177}Lu-PSMA-617 for prostate cancer. Nuclear Medicine and Biology. 2025; 146–147. https://doi.org/10.1016/j.nucmedbio.2025.109032.

[9] Pauwels EKJ, Bourguignon MH. PARP Inhibition and Beyond in BRCA-Associated Breast Cancer in Women: A State-Of-The-Art Summary of Preclinical Research on Risk Reduction and Clinical Benefits. Medical Principles and Practice: International Journal of the Kuwait University, Health Science Centre. 2022; 31: 303–312. https://doi.org/10.1159/000525281.

[10] Canman CE. Which Holds the Key to BRCAness: Inability to Repair the Break, Protect the Fork, or Prevent the Gap? Cancer Research. 2021; 81: 1214–1215. https://doi.org/10.1158/0008-5472.CAN-20-4340.

[11] Pernin V, Mégnin-Chanet F, Pennaneach V, Fourquet A, Kirova Y, Hall J. PARP inhibitors and radiotherapy: rational and prospects for a clinical use. Cancer Radiotherapie: Journal De La Societe Francaise De Radiotherapie Oncologique. 2014; 18: 790–798; quiz 799–802. https://doi.org/10.1016/j.canrad.2014.05.012. (In French)

[12] Wu Z, Cui P, Tao H, Zhang S, Ma J, Liu Z, *et al*. The Synergistic Effect of PARP Inhibitors and Immune Checkpoint Inhibitors. Clinical Medicine Insights. Oncology. 2021; 15: 1179554921996288. https://doi.org/10.1177/1179554921996288.

[13] Shen J, Zhao W, Ju Z, Wang L, Peng Y, Labrie M, *et al*. PARPi Triggers the STING-Dependent Immune Response and Enhances the Therapeutic Efficacy of Immune Checkpoint Blockade Independent of BRCAness. Cancer Research. 2019; 79: 311–319. https://doi.org/10.1158/0008-5472.CAN-18-1003.

[14] Wang J, Ma J, Xie F, Miao F, Lv L, Huang Y, *et al*. Immunogenic cell death-based cancer vaccines: promising prospect in cancer

therapy. Frontiers in Immunology. 2024; 15: 1389173. https://doi.org/10.3389/fimmu.2024.1389173.

[15] Janssens S, Rennen S, Agostinis P. Decoding immunogenic cell death from a dendritic cell perspective. Immunological Reviews. 2024; 321: 350–370. https://doi.org/10.1111/imr.13301.

[16] Yamazaki T, Vanpouille-Box C, Demaria S, Galluzzi L. Immunogenic Cell Death Driven by Radiation-Impact on the Tumor Microenvironment. Cancer Treatment and Research. 2020; 180: 281–296. https://doi.org/10.1007/978-3-030-38862-1_10.

[17] Sprooten J, Laureano RS, Vanmeerbeek I, Govaerts J, Naulaerts S, Borras DM, *et al*. Trial watch: chemotherapy-induced immunogenic cell death in oncology. Oncoimmunology. 2023; 12: 2219591. https://doi.org/10.1080/2162402X.2023.2219591.

[18] Fujimura T, Aiba S. Significance of Immunosuppressive Cells as a Target for Immunotherapies in Melanoma and Non-Melanoma Skin Cancers. Biomolecules. 2020; 10: 1087. https://doi.org/10.3390/biom10081087.

[19] Liu Y, Gong L, Feng J, Xiao C, Liu C, Chen B, *et al*. Co-delivery of axitinib and PD-L1 siRNA for the synergism of vascular normalization and immune checkpoint inhibition to boost anticancer immunity. Journal of Nanobiotechnology. 2025; 23: 194. https://doi.org/10.1186/s12951-025-03170-y.

[20] Chen K, Luo L, Li Y, Yang G. Reprogramming the immune microenvironment in lung cancer. Frontiers in Immunology. 2025; 16: 1684889. https://doi.org/10.3389/fimmu.2025.1684889.

[21] Ma Y, Zhang L, Liu W. Immunosuppressive tumor microenvironment and advance in immunotherapy in melanoma bone metastasis. Frontiers in Immunology. 2025; 16: 1608215. https://doi.org/10.3389/fimmu.2025.1608215.

[22] Li J, Cao P, Chen Y, Wang J, Sun X, Chen R, *et al*. Anlotinib combined with the PD-L1 blockade exerts the potent antitumor immunity in renal cancer treatment. Experimental Cell Research. 2022; 417: 113197. https://doi.org/10.1016/j.yexcr.2022.113197.

[23] Wei C, Ma Y, Wang F, Liao Y, Chen Y, Zhao B, *et al*. Igniting Hope for Tumor Immunotherapy: Promoting the "Hot and Cold" Tumor Transition. Clinical Medicine Insights. Oncology. 2022; 16: 11795549221120708. https://doi.org/10.1177/11795549221120708.

[24] Li X, Li Y, Tuerxun H, Zhao Y, Liu X, Zhao Y. Firing up "cold" tumors: Ferroptosis causes immune activation by improving T cell infiltration. Biomedicine & Pharmacotherapy. 2024; 179: 117298. https://doi.org/10.1016/j.biopha.2024.117298.

[25] Feng Y, Yang H, Liang G, Chen J, Li T, Wang Y, *et al*. Immune Checkpoint Inhibitors Combined with Oncolytic Virotherapy: Synergy, Heterogeneity, and Safety in Cancer Treatment. Oncology Research. 2025; 33: 3801–3836. https://doi.org/10.32604/or.2025.067824.

[26] Hang L, Xin H, Li H, Fang L, Wen H, Fang J, *et al*. Oxygen-vacancy MoO_{3-x} nanodots induce immunogenic cell death and STING activation for synergistic cancer immunotherapy. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2025; 388: 114319. https://doi.org/10.1016/j.jconrel.2025.114319.

[27] Jagodinsky JC, Jin WJ, Bates AM, Hernandez R, Grudzinski JJ, Marsh IR, *et al*. Temporal analysis of type 1 interferon activation in tumor cells following external beam radiotherapy or targeted radionuclide therapy. Theranostics. 2021; 11: 6120–6137. https://doi.org/10.7150/thno.54881.

[28] van Beek L, McClay É, Patel S, Schimpl M, Spagnolo L, Maia de Oliveira T. PARP Power: A Structural Perspective on PARP1, PARP2, and PARP3 in DNA Damage Repair and Nucleosome Remodelling. International Journal of Molecular Sciences. 2021; 22: 5112. https://doi.org/10.3390/ijms22105112.

[29] Onji H, Murai J. Reconsidering the mechanisms of action of PARP inhibitors based on clinical outcomes. Cancer Science. 2022; 113: 2943–2951. https://doi.org/10.1111/cas.15477.

[30] Lavrik OI. PARPs' impact on base excision DNA repair. DNA Repair. 2020; 93: 102911. https://doi.org/10.1016/j.dnarep.2020.102911.

[31] Gout J, Perkhofer L, Morawe M, Arnold F, Ihle M, Biber S, *et al*. Synergistic targeting and resistance to PARP inhibition in DNA damage repair-deficient pancreatic cancer. Gut. 2021; 70: 743–760. https://doi.org/10.1136/gutjnl-2019-319970.

[32] Rajabi F, Smith R, Liu-Bordes WY, Schertzer M, Huet S, Londoño-Vallejo A. DNA damage-induced EMT controlled by the PARP-dependent chromatin remodeler ALC1 promotes DNA repair efficiency through RAD51 in tumor cells. Molecular Biology of the Cell. 2024; 35: ar151. https://doi.org/10.1091/mbc.E24-08-0370.

[33] Ruigrok EAM, van Vliet N, Dalm SU, de Blois E, van Gent DC, Haeck J, *et al*. Extensive preclinical evaluation of lutetium-177-labeled PSMA-specific tracers for prostate cancer radionuclide therapy. European Journal of Nuclear Medicine and Molecular Imaging. 2021; 48: 1339–1350. https://doi.org/10.1007/s00259-020-05057-6.

[34] Bi Y, Verginadis II, Dey S, Lin L, Guo L, Zheng Y, *et al*. Radiosensitization by the PARP inhibitor olaparib in BRCA1-proficient and deficient high-grade serous ovarian carcinomas. Gynecologic Oncology. 2018; 150: 534–544. https://doi.org/10.1016/j.ygyno.2018.07.002.

[35] Kim H, Aliar K, Tharmapalan P, McCloskey CW, Kuttanamkuzhi A, Grünwald BT, *et al*. Differential DNA damage repair and PARP inhibitor vulnerability of the mammary epithelial lineages. Cell Reports. 2023; 42: 113256. https://doi.org/10.1016/j.celrep.2023.113256.

[36] Nonnekens J, van Kranenburg M, Beerens CEMT, Suker M, Doukas M, van Eijck CHJ, *et al*. Potentiation of Peptide Receptor Radionuclide Therapy by the PARP Inhibitor Olaparib. Theranostics. 2016; 6: 1821–1832. https://doi.org/10.7150/thno.15311.

[37] Palma Dos Reis AF, Faulkner LG, Lai IW, Dev H, Pacey S. Expanding PARP Inhibitor Use in Prostate Cancer Beyond DNA Repair Defects. Clinical Oncology (Royal College of Radiologists (Great Britain)). 2025; 44: 103804. https://doi.org/10.1016/j.clon.2025.103804.

[38] Minute L, Teijeira A, Sanchez-Paulete AR, Ochoa MC, Alvarez M, Otano I, *et al*. Cellular cytotoxicity is a form of immunogenic cell death. Journal for Immunotherapy of Cancer. 2020; 8: e000325. https://doi.org/10.1136/jitc-2019-000325.

[39] Luri-Rey C, Gomis G, Glez-Vaz J, Manzanal A, Martinez Riaño A, Rodriguez Ruiz ME, *et al*. Cytotoxicity as a form of immunogenic cell death leading to efficient tumor antigen cross-priming. Immunological Reviews. 2024; 321: 143–151. https://doi.org/10.1111/imr.13281.

[40] Moriya T, Kitagawa K, Hayakawa Y, Hemmi H, Kaisho T, Ueha S, *et al*. Immunogenic tumor cell death promotes dendritic cell migration and inhibits tumor growth via enhanced T cell immunity. iScience. 2021; 24: 102424. https://doi.org/10.1016/j.isci.2021.102424.

[41] Dogheim GM, El Feel NE, Abd El-Maksod EA, Amer SS, El-Gizawy SA, Abd Elhamid AS, *et al*. Nanomedicines as enhancers of tumor immunogenicity to augment cancer immunotherapy. Drug Discovery Today. 2024; 29: 103905. https://doi.org/10.1016/j.drudis.2024.103905.

[42] Fabian KP, Wolfson B, Hodge JW. From Immunogenic Cell Death to Immunogenic Modulation: Select Chemotherapy Regimens Induce a Spectrum of Immune-Enhancing Activities in the Tumor Microenvironment. Frontiers in Oncology. 2021; 11: 728018. https://doi.org/10.3389/fonc.2021.728018.

[43] Zhang N, Gao Y, Huang Z, Dai P, Luo Y, Wu Q, *et al*. PARP inhibitor plus radiotherapy reshapes an inflamed tumor microen-

vironment that sensitizes small cell lung cancer to the anti-PD-1 immunotherapy. Cancer Letters. 2022; 545: 215852. https://doi.org/10.1016/j.canlet.2022.215852.

[44] Qi Z, Pei P, Zhang Y, Chen H, Yang S, Liu T, *et al*. ^{131}I-αPD-L1 immobilized by bacterial cellulose for enhanced radioimmunotherapy of cancer. Journal of Controlled Release : official journal of the Controlled Release Society. 2022; 240–249. https://doi.org/10.1016/j.jconrel.2022.04.029.

[45] Wang K, Wang D, Tong J, Liao Z, Zhang Z, Miao Q, *et al*. Dual PARP/NAMPT Inhibitors for BRCA Wild-Type Triple-Negative Breast Cancer: Disrupting Homologous Recombination Repair and Activating Antitumor Immunity. Journal of Medicinal Chemistry. 2026; 69: 2746–2772. https://doi.org/10.1021/acs.jmedchem.5c02659.

[46] Chen G, Zheng D, Zhou Y, Du S, Zeng Z. Olaparib enhances radiation-induced systemic anti-tumor effects via activating STING-chemokine signaling in hepatocellular carcinoma. Cancer Letters. 2024; 582: 216507. https://doi.org/10.1016/j.canlet.2023.216507.

[47] Zeng B, Ling K, Yuan Q, Chen Z, Zhang G, Kang W, *et al*. An organolutetium nanosensitizer synergizes with PARP inhibition to unleash STING-mediated immunity for low-dose radioimmunotherapy. Theranostics. 2026; 16: 1720–1739. https://doi.org/10.7150/thno.124034.

[48] Zhong Y, Zhang H, Wang P, Zhao J, Ge Y, Sun Z, *et al*. Auger emitter in combination with Olaparib suppresses tumor growth via promoting antitumor immune responses in pancreatic cancer. Investigational New Drugs. 2024; 42: 442–453. https://doi.org/10.1007/s10637-024-01454-y.

[49] Wang T, Liu W, Shen Q, Tao R, Li C, Shen Q, *et al*. Combination of PARP inhibitor and CDK4/6 inhibitor modulates cGAS/STING-dependent therapy-induced senescence and provides "one-two punch" opportunity with anti-PD-L1 therapy in colorectal cancer. Cancer Science. 2023; 114: 4184–4201. https://doi.org/10.1111/cas.15961.

[50] Yi XF, Gao RL, Sun L, Wu ZX, Zhang SL, Huang LT, *et al*. Dual antitumor immunomodulatory effects of PARP inhibitor on the tumor microenvironment: A counterbalance between antitumor and pro-tumor. Biomedicine & Pharmacotherapy. 2023; 163: 114770. https://doi.org/10.1016/j.biopha.2023.114770.

[51] Zhang H, Sun Y, Zhang L, Shen M, Tong X, Zhao D, *et al*. Polymer-PARPi Conjugates Delivering USP1i for Maximizing Synthetic Lethality to Stimulate STING Pathway in High-Grade Serous Ovarian Cancer. Advanced Materials (Deerfield Beach, Fla.). 2026; 38: e12962. https://doi.org/10.1002/adma.202512962.

[52] Li J, Zhou J, Kai S, Wang C, Wang D, Jiang J. Functional and Clinical Characterization of Tumor-Infiltrating T Cell Subpopulations in Hepatocellular Carcinoma. Frontiers in Genetics. 2020; 11: 586415. https://doi.org/10.3389/fgene.2020.586415.

[53] Luo Y, Xia Y, Liu D, Li X, Li H, Liu J, *et al*. Neoadjuvant PARPi or chemotherapy in ovarian cancer informs targeting effector Treg cells for homologous-recombination-deficient tumors. Cell. 2024; 187: 4905–4925.e24. https://doi.org/10.1016/j.cell.2024.06.013.

[54] Farhood B, Najafi M, Mortezaee K. CD8$^+$ cytotoxic T lymphocytes in cancer immunotherapy: A review. Journal of Cellular Physiology. 2019; 234: 8509–8521. https://doi.org/10.1002/jcp.27782.

[55] Lin L, Zhang S, Yang W. Comment on "An Injectable Hydrogel to Modulate T Cells for Cancer Immunotherapy". Small (Weinheim an Der Bergstrasse, Germany). 2024; 20: e2302812. https://doi.org/10.1002/smll.202302812.

[56] Valvo VM, Zhang Q, Jiang L, Holcomb EA, Pearson AN, Edmunds AG, *et al*. Olaparib and Radiotherapy Induce Type I Interferon- and CD8+ T Cell-Dependent Sensitization to Immunotherapy in Pancreatic Cancer. Molecular Cancer Therapeutics. 2025; 24: 843–858. https://doi.org/10.1158/1535-7163.MCT-24-0210.

[57] Patel RB, Hernandez R, Carlson P, Grudzinski J, Bates AM, Jagodinsky JC, *et al*. Low-dose targeted radionuclide therapy renders immunologically cold tumors responsive to immune checkpoint blockade. Science Translational Medicine. 2021; 13: eabb3631. https://doi.org/10.1126/scitranslmed.abb3631.

[58] Traboulsi W, Gaur P, Kundu S, Ramlaoui Z, Priestley-Milianta C, Iyengar A, *et al*. PARP inhibition generates enhanced CD8$^+$ central memory T cells by transcriptional and metabolic reprogramming. Nature Immunology. 2026; 27: 189–199. https://doi.org/10.1038/s41590-025-02383-5.

[59] Ran X, Wu BX, Vidhyasagar V, Song L, Zhang X, Ladak RJ, *et al*. PARP inhibitor radiosensitization enhances anti-PD-L1 immunotherapy through stabilizing chemokine mRNA in small cell lung cancer. Nature Communications. 2025; 16: 2166. https://doi.org/10.1038/s41467-025-57257-z.

[60] Khoury R, Longobardi G, Barnatan TT, Venkert D, García Alvarado A, Yona A, *et al*. Radiation-guided nanoparticles enhance the efficacy of PARP inhibitors in primary and metastatic BRCA1-deficient tumors via immunotherapy. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2025; 383: 113812. https://doi.org/10.1016/j.jconrel.2025.113812.

[61] Delbart W, Karabet J, Marin G, Penninckx S, Derrien J, Ghanem GE, *et al*. Understanding the Radiobiological Mechanisms Induced by ^{177}Lu-DOTATATE in Comparison to External Beam Radiation Therapy. International Journal of Molecular Sciences. 2022; 23: 12369. https://doi.org/10.3390/ijms232012369.

[62] Purohit NK, Shah RG, Adant S, Hoepfner M, Shah GM, Beauregard JM. Potentiation of ^{177}Lu-octreotate peptide receptor radionuclide therapy of human neuroendocrine tumor cells by PARP inhibitor. Oncotarget. 2018; 9: 24693–24706. https://doi.org/10.18632/oncotarget.25266.

[63] Boyle AJ, Cao PJ, Cai Z, Chan C, Hedley DW, Reilly RM. Radioimmunotherapy of human pancreatic cancer xenografts in NOD-scid mice with [^{64}Cu]Cu-NOTA-panitumumab F(ab')$_2$ alone or combined with radiosensitizing gemcitabine and the PARP inhibitor, rucaparib. Nuclear Medicine and Biology. 2020; 84–85: 46–54. https://doi.org/10.1016/j.nucmedbio.2020.02.001.

[64] Pouget JP, Chan TA, Galluzzi L, Constanzo J. Radiopharmaceuticals as combinatorial partners for immune checkpoint inhibitors. Trends in Cancer. 2023; 9: 968–981. https://doi.org/10.1016/j.trecan.2023.07.014.

[65] Luna-Gutiérrez M, Azorín-Vega E, Oros-Pantoja R, Ocampo-García B, Cruz-Nova P, Jiménez-Mancilla N, *et al*. Lutetium-177 labeled iPD-L1 as a novel immunomodulator for cancer-targeted radiotherapy. EJNMMI Radiopharmacy and Chemistry. 2025; 10: 5. https://doi.org/10.1186/s41181-025-00328-9.

[66] Chen J, Zhou Y, Pang Y, Fu K, Luo Q, Sun L, *et al*. FAP-targeted radioligand therapy with ^{68}Ga/^{177}Lu-DOTA-2P(FAPI)$_2$ enhance immunogenicity and synergize with PD-L1 inhibitors for improved antitumor efficacy. Journal for Immunotherapy of Cancer. 2025; 13: e010212. https://doi.org/10.1136/jitc-2024-010212.

[67] Franzese O, Graziani G. Role of PARP Inhibitors in Cancer Immunotherapy: Potential Friends to Immune Activating Molecules and Foes to Immune Checkpoints. Cancers. 2022; 14: 5633. https://doi.org/10.3390/cancers14225633.

[68] Ruigrok EAM, Verkaik NS, de Blois E, de Ridder C, Stuurman D, Roobol SJ, *et al*. Preclinical Assessment of the Combination of PSMA-Targeting Radionuclide Therapy with PARP Inhibitors for Prostate Cancer Treatment. International Journal of Molecular Sciences. 2022; 23: 8037. https://doi.org/10.3390/ij

ms23148037.

[69] Hallqvist A, Brynjarsdóttir E, Krantz T, Sjögren M, Svensson J, Bernhardt P. ^{177}Lu-DOTATATE in Combination with PARP Inhibitor Olaparib Is Feasible in Patients with Somatostatin-Positive Tumors: Results from the LuPARP Phase I Trial. Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine. 2025; 66: 707–712. https://doi.org/10.2967/jnumed.124.268902.

[70] Kim C, Liu SV, Subramaniam DS, Torres T, Loda M, Esposito G, *et al*. Phase I study of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (lutathera) in combination with nivolumab in patients with neuroendocrine tumors of the lung. Journal for Immunotherapy of Cancer. 2020; 8: e000980. https://doi.org/10.1136/jitc-2020-000980.

[71] Fong L, Morris MJ, Sartor O, Higano CS, Pagliaro L, Alva A, *et al*. A Phase Ib Study of Atezolizumab with Radium-223 Dichloride in Men with Metastatic Castration-Resistant Prostate Cancer. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2021; 27: 4746–4756. https://doi.org/10.1158/1078-0432.CCR-21-0063.

[72] Prasad V, Zengerling F, Steinacker JP, Bolenz C, Beer M, Wiegel T, *et al*. First Experiences with ^{177}Lu-PSMA Therapy in Combination with Pembrolizumab or After Pretreatment with Olaparib in Single Patients. Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine. 2021; 62: 975–978. https://doi.org/10.2967/jnumed.120.249029.

[73] Hatch RV, Patel SU, Cambareri C, Uritsky T, Martin LP. Evaluation of the management of PARP inhibitor toxicities in ovarian and endometrial cancer within a multi-institution health-system. Journal of Oncology Pharmacy Practice: Official Publication of the International Society of Oncology Pharmacy Practitioners. 2022; 28: 1102–1110. https://doi.org/10.1177/10781552211024728.

[74] Cassuto O, Mathieu R, Helissey C, Schmitt A, Gobert A, Mourey L, *et al*. Prevention and management of PARP inhibitor-related haematological toxicities in prostate cancer: French expert opinion using the Delphi method. Therapeutic Advances in Medical Oncology. 2025; 17: 17588359251367308. https://doi.org/10.1177/17588359251367308.

[75] Gonzalez A, Kistenfeger Q, Cosgrove CM. Patient Selection for the Use of Niraparib in Advanced Ovarian Cancer: A Review. International Journal of Women's Health. 2024; 16: 2239–2246. https://doi.org/10.2147/IJWH.S466250.

[76] Mokoala K, Lawal I, Lengana T, Kgatle M, Giesel FL, Vorster M, *et al*. PSMA Theranostics: Science and Practice. Cancers. 2021; 13: 3904. https://doi.org/10.3390/cancers13153904.

[77] Parihar AS, Chopra S, Prasad V. Nephrotoxicity after radionuclide therapies. Translational Oncology. 2022; 15: 101295. https://doi.org/10.1016/j.tranon.2021.101295.

[78] Durrechou Q, Domblides C, Sionneau B, Lefort F, Quivy A, Ravaud A, *et al*. Management of Immune Checkpoint Inhibitor Toxicities. Cancer Management and Research. 2020; 12: 9139–9158. https://doi.org/10.2147/CMAR.S218756.

[79] Zarifa A, Kim JW, Lopez-Mattei J, Palaskas N, Iliescu C, Kim PY. Cardiac Toxicities Associated with Immune Checkpoints Inhibitors: Mechanisms, Manifestations and Management. Korean Circulation Journal. 2021; 51: 579–597. https://doi.org/10.4070/kcj.2021.0089.

[80] Selle F, Boffa JJ, Etienne G, Angelergues A, Augereau P, Berton D, *et al*. Practical management of PARP inhibitors: A French DELPHI consensus. Bulletin du Cancer. 2022; 109: 1245–1261. https://doi.org/10.1016/j.bulcan.2022.06.011. (In French)

[81] Chandekar KR, Bal C. Advances With ^{225}Ac-DOTATATE Targeted Alpha Therapy in Somatostatin Receptor Positive Neuroendocrine Tumors. Seminars in Nuclear Medicine. 2025. https://doi.org/10.1053/j.semnuclmed.2025.06.008. (online ahead of print)

[82] Kawashima H. Radioimmunotherapy: a specific treatment protocol for cancer by cytotoxic radioisotopes conjugated to antibodies. TheScientificWorldJournal. 2014; 2014: 492061. https://doi.org/10.1155/2014/492061.

[83] Keinänen O, Brennan JM, Membreno R, Fung K, Gangangari K, Dayts EJ, *et al*. Dual Radionuclide Theranostic Pretargeting. Molecular Pharmaceutics. 2019; 16: 4416–4421. https://doi.org/10.1021/acs.molpharmaceut.9b00746.

[84] Ngoi NYL, Leo E, O'Connor MJ, Yap TA. Development of Next-Generation Poly(ADP-Ribose) Polymerase 1-Selective Inhibitors. Cancer Journal (Sudbury, Mass.). 2021; 27: 521–528. https://doi.org/10.1097/PPO.0000000000000556.

[85] Wang W, Xiong Y, Hu X, Lu F, Qin T, Zhang L, *et al*. Codelivery of adavosertib and olaparib by tumor-targeting nanoparticles for augmented efficacy and reduced toxicity. Acta Biomaterialia. 2023; 157: 428–441. https://doi.org/10.1016/j.actbio.2022.12.021.

[86] Chopra N, Tovey H, Pearson A, Cutts R, Toms C, Proszek P, *et al*. Homologous recombination DNA repair deficiency and PARP inhibition activity in primary triple negative breast cancer. Nature Communications. 2020; 11: 2662. https://doi.org/10.1038/s41467-020-16142-7.

[87] Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Targeted Oncology. 2021; 16: 255–282. https://doi.org/10.1007/s11523-021-00796-4.

[88] Cha J, Kim CG, Sim NS, Kim G, Son W, Kim D, *et al*. 4-1BB^{+} Tregs and inhibitory progenitor exhausted T cells confer resistance to anti-PD-L1 and anti-CTLA-4 combination therapy. Cell Reports. Medicine. 2025; 6: 102408. https://doi.org/10.1016/j.xcrm.2025.102408.

[89] Moutafi M, Koliou GA, Papaxoinis G, Economopoulou P, Kotsantis I, Gkotzamanidou M, *et al*. Phase II Window Study of Olaparib Alone or with Cisplatin or Durvalumab in Operable Head and Neck Cancer. Cancer Research Communications. 2023; 3: 1514–1523. https://doi.org/10.1158/2767-9764.CRC-23-0051.

[90] Pandey A, Rai SK, Ma L, Higa L, Khadka V, Yang H, *et al*. Combination Immunotherapy as a Promising Strategy to Overcome Immunotherapy Resistance: From Emergence to Next-Generation Approaches. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2026; e18960. https://doi.org/10.1002/advs.202518960.

[91] Sabanis CD, R Kannan B, Ramesh Joga, Simran, Kumar S, Kumar N. Potential of novel self-assembled functionalized carbon nanotubes for selective tumor targeting. Pharmaceutical Patent Analyst. 2022; 11: 111–117. https://doi.org/10.4155/ppa-2022-0001.

[92] Frezza A, Desport C, Uribe C, Zhao W, Celler A, Després P, *et al*. Comprehensive SPECT/CT system characterization and calibration for ^{177}Lu quantitative SPECT (QSPECT) with dead-time correction. EJNMMI Physics. 2020; 7: 10. https://doi.org/10.1186/s40658-020-0275-6.

[93] Zhang H, Shi Y, Tang H, Gu H, Luo F, Ma D, *et al*. Feasibility study of ^{225}Ac-PSMA-CY313 dosimetry in mCRPC patients using SPECT. EJNMMI Physics. 2025; 13: 14. https://doi.org/10.1186/s40658-025-00831-7.

[94] Ryhiner M, Song Y, Hong J, Ferreira CVG, Rominger A, Kossatz S, *et al*. A mathematical model for the investigation of combined treatment of radiopharmaceutical therapy and PARP inhibitors. European Journal of Nuclear Medicine and Molecular Imaging. 2025; 52: 3252–3265. https://doi.org/10.1007/s00259-025-07144-y.