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REVIEW

New Targets, New Agents, and Radiotherapy in Breast Cancer

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SUMMARY

Breast cancer is a biologically complex and heterogeneous disease composed of several molecular subtypes, each characterized by unique genomic alterations and specific therapeutic responses. Despite significant advancements achieved through systemic therapies and radiotherapy (RT), treatment resistance and disease recurrence continue to represent major obstacles, particularly in patients with advanced-stage or high-risk tumors. The introduction of novel targeted and immune-modulating therapies including CDK4/6 inhibitors, PI3K/mTOR pathway inhibitors, PARP inhibitors, HER2-targeted monoclonal antibodies, antibody–drug conjugates (ADCs), and immune checkpoint inhibitors (ICIs) has revolutionized the management of breast cancer by enabling a more personalized approach based on tumor biology. Both experimental and clinical evidence indicate that combining these systemic treatments with radiotherapy can produce synergistic antitumor effects through several biological mechanisms. These mechanisms include the enhancement of radiation-induced DNA damage, inhibition of DNA repair processes, and modulation of the tumor immune microenvironment. Such therapeutic interactions may improve local tumor control, enhance radiosensitivity, and allow for treatment de-escalation in carefully selected patients, provided that close attention is paid to safety, particularly regarding hematologic, gastrointestinal, and pulmonary toxicities. The purpose of this review is to provide a comprehensive understanding of the biological mechanisms, preclinical and clinical evidence, and safety considerations that form the foundation for integrating radiotherapy with emerging systemic therapies in breast cancer. A deeper insight into these interactions could optimize therapeutic outcomes while minimizing adverse effects. Furthermore, strategic optimization of dose, timing, and treatment sequencing holds the potential to develop individualized, balanced, and multimodal treatment strategies for breast cancer in the future.

Keywords: CDK4/6 inhibitors; antibody–drug conjugates; breast cancer; HER2-targeted therapy; immunotherapy; PARP inhibitors; radiotherapy; targeted therapy.

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy among women and continues to be the leading cause of cancer-related death worldwide, accounting for over 2.3 million new cases and nearly 685,000 deaths annually.[1] Despite significant progress in early detection methods, advances in surgical techniques, and improvements in systemic therapies and radiotherapy (RT), the prognosis for patients with advanced or recurrent disease remains poor. The main reasons for these unsatisfactory outcomes are the biological heterogeneity of tumors and the development of therapeutic resistance.[2]

Historically, breast cancer treatment has relied on surgery, often combined with adjuvant or neoadjuvant systemic therapy and RT, tailored according to disease stage and individual risk factors. However,

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these conventional strategies have reached a therapeutic plateau, offering limited improvement in long-term survival. In the last decade, developments in molecular and genomic profiling have profoundly changed the biological understanding of breast cancer, enabling the identification of distinct molecular subtypes such as Luminal A, Luminal B, HER2-positive, and triple-negative breast cancer (TNBC) (Table 1). Each of these subtypes is associated with specific oncogenic pathways, prognostic implications, and therapeutic susceptibilities.[3] This molecular insight has ushered in the era of precision oncology, where treatment decisions are increasingly guided by tumor biology rather than traditional anatomical staging.

The introduction of targeted therapies and immune-based treatments has dramatically reshaped the therapeutic landscape of breast cancer across all stages. Innovative agents such as CDK4/6 inhibitors, PI3K/mTOR pathway inhibitors, PARP inhibitors, HER2-directed monoclonal antibodies, antibody–drug conjugates (ADCs), and immune checkpoint inhibitors (ICIs) have significantly improved progression-free and overall survival in appropriately selected patient populations.[4] Furthermore, preclinical and clinical studies suggest that these systemic therapies can act synergistically with radiotherapy through mechanisms such as enhanced DNA damage, inhibition of DNA repair pathways, modulation of the tumor microenvironment, and activation of antitumor immune responses.[5]

Despite these promising results, the integration of RT with targeted and immune-based therapies presents unique clinical and safety challenges. Concurrent use of these modalities may lead to overlapping toxicities, particularly hematologic, gastrointestinal, and pulmonary, necessitating careful patient selection, optimized treatment sequencing, and coordinated multidisciplinary management.[6] The ideal schedule, dose fractionation, and radiotherapy field design when combined with systemic agents are still under active investigation. Reflecting these challenges, the European Society for Radiotherapy and Oncology (ESTRO) consensus report suggested that concurrent RT with certain targeted therapies could be feasible under specific conditions, but emphasized the importance of individualized treatment planning and sufficient washout periods to reduce the risk of adverse events.[7]

Overall, these advancements underscore the importance of understanding the biological mechanisms, clinical evidence, and safety considerations underlying the integration of radiotherapy with modern systemic therapies in breast cancer. This review aims to provide a comprehensive overview of the mechanistic rationale, clinical outcomes, and future perspectives of combining radiotherapy with targeted and immune-based therapies, highlighting their potential role in advancing personalized breast cancer management.

CDK4/6 Inhibitors and Radiotherapy

Among the molecular subtypes of breast cancer, hormone receptor positive (HR+) and HER2 negative tumors are the most common and biologically diverse group. The development of cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors such as palbociclib, ribociclib and abemaciclib has significantly changed the treatment approach for luminal breast cancer by targeting a key checkpoint in the cell cycle. These agents inhibit the CDK4/6 Cyclin D complex, preventing phosphorylation of the retinoblastoma (Rb) protein

Table 1 Molecular subtypes and corresponding targeted therapeutic strategies in breast cancer

Luminal (HR+/HER2–)	HER2-positive	Triple-negative (TNBC)
CDK4/6 Inhibitors: Palbociclib, Ribociclib, Abemaciclib	Monoclonal Antibodies: Trastuzumab, Pertuzumab, Margetuximab	PARP Inhibitors: Olaparib, Talazoparib, Veliparib
PI3K Pathway Inhibitor: Alpelisib	Antibody–Drug Conjugates (ADCs): Trastuzumab emtansine (T-DM1), Trastuzumab deruxtecan (T-DXd)	Immunotherapy: Pembrolizumab, Atezolizumab
mTOR Inhibitor: Everolimus	Tyrosine Kinase Inhibitors (TKIs): Lapatinib, Tucatinib, Neratinib	ADC: Sacituzumab govitecan, Datopotamab deruxtecan
Selective Estrogen Receptor Degraders (SERDs): Fulvestrant (IM), Elacestrant (oral), Camizestrant, Amcenestrant	–	–

ADC: Antibody–drug conjugate; CDK4/6: Cyclin-dependent kinase 4 and 6; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; mTOR: Mechanistic target of rapamycin; PARP: Poly (ADP-Ribose) polymerase; PI3K: Phosphatidylinositol-3-kinase; SERD: Selective estrogen receptor degrader; TKI: Tyrosine kinase inhibitor; TNBC: Triple-negative breast cancer

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Table 2 Summary of trials evaluating the combination of radiotherapy with CDK4/6 inhibitors

Trial/study	Phase	Year	Patient number	Intervention	Primary outcome	Outcomes
PALOMA-2 / PALOMA-3 (NCT01740427 / NCT01942135)	III	2015–2019	666/521	Palbociclib + ET (Letrozole or Fulvestrant)→RT sequentially (no concurrent use; paused ≥7 days before RT)	PFS (months)	PALOMA-2: Median PFS 24.8 vs 14.5 mo; HR 0.58; 95% CI 0.46–0.72; p<0.001. PALOMA-3: HR 0.46; 95% CI 0.36–0.59; p<0.001. RT performed post-CDK4/6 without excess toxicity. No G3–4 GI events after RT.
MONALEESA-2, -3, -7 (NCT01958021 / NCT02422615 / NCT02278120)	III	2016–2020	>2000 (combined)	Ribociclib + ET (Letrozole or Fulvestrant)→RT for bone metastases only (no concurrent use)	PFS/OS	MONALEESA-7: OS HR 0.71; 95% CI 0.54–0.95; p=0.009. PFS HR 0.55; 95% CI 0.44–0.69; p<0.001. Typical RT 20–30 Gy to spine/pelvis; well tolerated; no delay or additive toxicity observed.
MONARCH-2 / MONARCH-3 (NCT02107703 / NCT02246621)	III	2017–2020	669/493	Abemaciclib + Fulvestrant / Letrozole →RT administered sequentially (treatment withheld during RT)	PFS/OS	MONARCH-2: Median PFS 16.4 vs 9.3 mo; HR 0.55; 95% CI 0.45–0.68; p<0.001. OS HR 0.76; 95% CI 0.61–0.95; p=0.01. No dedicated RT subgroup; limited concurrent data. Potential overlapping GI and hematologic toxicities noted.
MonarchE (NCT03155997)	III (Adjuvant)	2020–2023	≈2,500	Abemaciclib+Endocrine Therapy → Sequential RT (no concurrent use)	Invasive disease-free survival (IDFS)	HR 0.713; 95% CI 0.583–0.871; p=0.0009. >95% received RT (50.4 Gy/28 fx or 42.4 Gy/15–16 fx). Sequential approach safe; no added late RT toxicity; Concurrent safety unproven.

RT: Radiotherapy; fx: Fractions; ET: Endocrine Therapy; HR: Hazard Ratio; CI: Confidence Interval; PFS: Progression-Free Survival; OS: Overall Survival; IDFS: Invasive Disease-Free Survival; GI: Gastrointestinal; HR+: Hormone Receptor Positive; HER2–: Human Epidermal Growth Factor Receptor 2 Negative

and blocking the transition from the G1 to the S phase. This mechanism results in cell cycle arrest, reduced proliferation, and restoration of endocrine sensitivity in tumors that have developed resistance to hormonal therapy.[8]

Beyond their antiproliferative properties, preclinical research indicates that CDK4/6 inhibitors can increase tumor radiosensitivity through several biological mechanisms. Experimental evidence shows that blocking CDK4/6 interferes with homologous recombination repair, prolongs radiation induced DNA double strand breaks, and promotes apoptosis and senescence.[9] Laboratory studies also demonstrate that combining radiotherapy with CDK4/6 inhibition leads to the accumulation of γH2AX, prolonged G1 arrest, and decreased clonogenic survival, suggesting a mechanistic synergy. Additionally, these inhibitors may limit tumor repopulation and alter the tumor microenvironment, improving local control when administered together with radiotherapy.

Clinical studies have confirmed the effectiveness of CDK4/6 inhibitors in several phase III trials. The PALOMA, MONALEESA and MONARCH trials consistently demonstrated significant improvements in progression free survival (PFS) and, in some cases, overall survival (OS) when these drugs were used with endocrine therapy compared with endocrine therapy alone (Table 2). For example, in the PALOMA 2 study, the combination of palbociclib and letrozole achieved a median PFS of 27.6 months versus 14.5 months with placebo.[10] Similar improvements were seen in the MONALEESA 2 and MONARCH 3 trials, while the monarchE study established adjuvant abemaciclib as a standard treatment for patients with node positive, high risk early stage

Table 3 Reported toxicities associated with concurrent CDK4/6 inhibition and radiotherapy

Type of toxicity	Drugs involved	Average incidence	Notes / clinical remarks
Neutropenia	Palbociclib, Ribociclib	60–70% (Grade 3–4)	Most frequent hematologic toxicity; may lead to transient treatment interruption during RT.
Lymphopenia	All CDK4/6 inhibitors	30–40%	May be exacerbated by concurrent RT, particularly in large-field irradiation.
Diarrhea	Abemaciclib	Up to 80%	Dose-dependent; more pronounced with pelvic or abdominal RT.
Mucositis / enteritis	Abemaciclib + RT	Limited data	Observed mainly in patients receiving bowel irradiation; rare but can lead to treatment delay.
Pneumonitis	Palbociclib + thoracic RT	Rare (<1%)	Occasional reports of interstitial pneumonitis; close monitoring required.
Fatigue	All drugs	20–40%	Common overlapping toxicity; usually mild to moderate.
Hepatotoxicity	Ribociclib	10–15%	Elevation of transaminases; concurrent RT contribution unclear.
QT Prolongation	Ribociclib	3–5%	Not RT-related; consider ECG monitoring during combined therapy.

RT: Radiotherapy; CDK4/6: Cyclin-Dependent Kinase 4 and 6; ECG: Electrocardiogram

HR positive and HER2 negative breast cancer, showing a 30 percent reduction in invasive disease free survival events after four years.[11]

Given their mechanisms, CDK4/6 inhibitors have been considered potential radiosensitizers. However, their concurrent use with radiotherapy requires careful evaluation due to safety concerns. Although most phase II and III trials excluded simultaneous radiotherapy, emerging retrospective and real world data suggest that this combination may be feasible with close monitoring. A systematic review found no significant increase in severe toxicities of grade 3 or higher, although mild hematologic suppression and gastrointestinal irritation were sometimes reported.[12] The European Society for Radiotherapy and Oncology (ESTRO) emphasized that concurrent CDK4/6 inhibition could raise the risk of pneumonitis during thoracic irradiation and gastrointestinal toxicity during pelvic irradiation, while short palliative courses such as those used for bone metastases are generally safe and well tolerated.[7]

Institutional studies that investigated concurrent radiotherapy and CDK4/6 inhibitors, mostly involving patients with bone or brain metastases, have shown good tolerability without unexpected acute or late side effects.[13,14] However, some isolated reports described severe radiation dermatitis, mucositis, and cytopenia when high dose or large field radiotherapy overlapped with palbociclib treatment. These findings underline the importance of careful radiotherapy field planning and adequate pharmacologic washout periods.[15]

From a safety perspective, CDK4/6 inhibitors have a predictable toxicity profile including hematologic suppression, especially neutropenia with palbociclib and ribociclib, gastrointestinal effects such as diarrhea with abemaciclib, fatigue, and temporary liver enzyme elevation. When used together with radiotherapy, these overlapping toxicities can increase the risk of prolonged cytopenia, particularly during pelvic or spinal irradiation involving bone marrow rich areas (Table 3). Thoracic radiotherapy may also worsen pulmonary inflammation, as both radiotherapy and abemaciclib can induce pneumonitis through cytokine mediated pathways. In chest wall or neck irradiation, more severe radiation dermatitis has occasionally been observed, possibly due to reduced epithelial repair during G1 phase arrest.

In summary, current evidence supports a careful and individualized approach when combining CDK4/6 inhibitors with radiotherapy. Palliative radiotherapy for bone or brain metastases can generally be performed safely during ongoing therapy, whereas concurrent treatment in curative settings should be assessed on a case by case basis. Future prospective trials are needed to determine optimal treatment sequencing, radiation dose limitations, and appropriate

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Table 4 Summary of phase II–III trials on PI3K/AKT pathway inhibitors and radiotherapy

-Study / trial	Drug / combination	Phase	Year	Patient population	RT use / policy	RT timing / eligibility	Primary outcome	Toxicity / safety / outcomes
SOLAR-1 (NCT02437318)	Alpelisib + Fulvestrant vs Placebo + Fulvestrant	III	2015–2019	HR+/HER2– advanced breast cancer (post-endocrine therapy)	Extensive RT not allowed; limited palliative RT permitted	RT within 2–4 weeks before enrollment excluded	PFS (months)	Median PFS 11.0 vs 5.7 mo; HR 0.65; 95% CI 0.50–0.85; p<0.001. No RT-related safety data reported; Grade ≥3 hyperglycemia 36%.
BYLieve (NCT03056755)	Alpelisib + Fulvestrant (post-CDK4/6i)	II III	2017–2021	HR+/HER2– metastatic breast cancer after CDK4/6i progression	RT considered exclusion criterion	≥4 weeks gap required after RT	PFS (months)	Median PFS 7.3 mo; 95% CI 5.6–8.3. No RT-related data available; safety consistent with prior studies (hyperglycemia, rash).
CAPItello-291 (NCT04305496)	Capivasertib + Fulvestrant vs Placebo + Fulvestrant		2020–2023	HR+/HER2– advanced breast cancer (after AI ± CDK4/6i)	Limited RT allowed; extensive RT within last 4 weeks excluded	RT within 4 weeks = exclusion	PFS (months)	Median PFS 7.2 vs 3.6 mo; HR 0.60; 95% CI 0.51–0.71; p<0.001. No RT-specific data; 13% grade ≥3 rash, 12% diarrhea.

RT: Radiotherapy; HR: Hazard Ratio; CI: Confidence Interval; PFS: Progression-Free Survival; HR+: Hormone Receptor Positive; HER2–: Human Epidermal Growth Factor Receptor 2 Negative; AI: Aromatase Inhibitor; CDK4/6i: Cyclin-Dependent Kinase 4/6 inhibitor

washout intervals. Moreover, translational biomarkers such as DNA damage response profiles, circulating tumor DNA (ctDNA), and senescence related signatures may help refine patient selection and advance precision guided radiotherapy in luminal breast cancer.

Luminal Subtype: PI3K/mTOR Inhibitors and Radiotherapy

The phosphatidylinositol 3 kinase (PI3K) / AKT / mammalian target of rapamycin (mTOR) signaling cascade is one of the most frequently altered molecular pathways in breast cancer and plays a crucial role in regulating cell growth, metabolism, proliferation, and survival. Approximately 40 percent of hormone receptor positive (HR+) and HER2 negative breast cancers harbor activating PIK3CA mutations that lead to constant downstream signaling activity, thereby promoting endocrine therapy resistance.[16] When PI3K is activated, it phosphorylates AKT, which subsequently stimulates the mTOR complex, resulting in increased protein synthesis and uncontrolled cell proliferation.

PI3K inhibitors such as alpelisib selectively block the p110α catalytic subunit of PI3K, effectively suppressing abnormal signaling in tumors that carry PIK3CA mutations. This inhibition decreases AKT phosphorylation, limits cell growth, and causes G1 phase cell cycle arrest. Importantly, blocking PI3K also disrupts DNA repair processes, particularly homologous recombination, making cancer cells more sensitive to radiation induced DNA double strand breaks.[17] Radiotherapy produces oxidative stress and DNA damage, and when combined with PI3K inhibition, these cytotoxic effects are intensified, resulting in greater apoptosis and reduced capacity for cellular repair after radiation exposure.

mTOR inhibitors such as everolimus and temsirolimus act further downstream in the same signaling pathway by targeting the mTORC1 complex. This inhibition reduces protein synthesis, angiogenesis, and metabolic adaptation within tumor cells. Preclinical studies have shown that inhibition of mTOR enhances radiosensitivity by suppressing pro survival signaling and impairing DNA repair regulated by hypoxia inducible factor 1 alpha (HIF 1α).[18] Additionally, mTOR blockade has been demonstrated to slow tumor cell repopulation between radiation fractions, further supporting its use with radiotherapy as a radiosensitizing strategy.

Clinically, targeting the PI3K/mTOR pathway has become essential for managing endocrine resistant HR positive and HER2 negative breast cancer. The phase III SOLAR 1 trial (Table 4) established alpelisib plus fulvestrant as a standard therapy for postmenopausal women with PIK3CA mutant advanced breast cancer, showing a median progression free survival (PFS) of 11.0 months compared to 5.7 months for fulvestrant alone.[19] Similarly, the BOLERO 2 study demonstrated that everolimus in combination with exemestane significantly improved PFS in endocrine resistant metastatic HR positive and HER2 negative breast cancer (10.6 vs. 4.1 months).[20] Although these findings confirm the systemic effectiveness of PI3K/mTOR inhibition, there is still limited data on their concurrent use with radiotherapy since most clinical trials have excluded this combination.

Experimental data consistently indicate that blocking the PI3K/mTOR pathway enhances radiosensitivity by delaying DNA repair and promoting tumor regression in various breast cancer models.[17,18] Early phase clinical results have reported acceptable safety profiles. In a phase I study of alpelisib combined with palliative radiotherapy in patients with metastatic HR positive and HER2 negative breast cancer, only mild hyperglycemia and grade 1 to 2 mucositis were observed.[21] Another observational study suggested that everolimus can be administered close to radiotherapy safely, provided metabolic and mucosal toxicities are closely monitored.[22] Nevertheless, both PI3K and mTOR inhibitors can amplify radiation related side effects such as mucositis, dermatitis, and gastrointestinal inflammation due to their influence on epithelial repair and vascular integrity.

The toxicity profiles of these inhibitors are well characterized. PI3K inhibitors commonly cause hyperglycemia, rash, diarrhea, and fatigue, while rare cases of pneumonitis and hepatotoxicity have also been reported. Hyperglycemia induced by alpelisib, resulting from impaired insulin signaling, may worsen oxidative stress in irradiated tissues, particularly when large radiation fields are used. mTOR inhibitors such as everolimus and temsirolimus are associated with stomatitis, mucositis, anemia, fatigue, and noninfectious pneumonitis. Severe esophagitis and radiation recall dermatitis have been documented in some cases where everolimus overlapped with thoracic or head and neck radiotherapy.[23,24]

To minimize toxicity, most current guidelines recommend using PI3K/mTOR inhibitors sequentially rather than concurrently with radiotherapy. Foundational preclinical studies have demonstrated that activation of the PI3K/AKT/mTOR pathway promotes radioresistance, whereas its inhibition enhances radiosensitivity by impairing DNA damage repair, oxidative stress responses, and cancer stem-cell survival mechanisms.[25-27] These biological insights provide a strong rationale for therapeutic combination; however, translational and early clinical studies—including phase I trials combining mTOR inhibitors with thoracic radiotherapy—have reported dose-limiting pulmonary toxicities such as pneumonitis, pulmonary hemorrhage, and treatment-related deaths when these agents overlap with radiation, particularly in organs with limited regenerative capacity such as lung, and potentially mucosa or skin.[28,29] Consequently, careful scheduling with appropriate washout intervals, individualized radiation planning, and vigilant toxicity monitoring are essential. Emerging mechanistic and translational research continues to refine optimal sequencing strategies and identify molecular determinants of radiosensitization, guiding safer integration of PI3K/AKT/mTOR inhibitors with radiotherapy in the future.[30]

Trastuzumab Deruxtecan (T-DXd) and Radiotherapy

Trastuzumab deruxtecan (T-DXd) is a next-generation HER2-targeted antibody–drug conjugate (ADC) that has transformed the management of both HER2-positive and HER2-low breast cancers. Structurally, it is composed of a humanized anti-HER2 monoclonal antibody (trastuzumab) linked via a cleavable peptide linker to a potent topoisomerase I inhibitor payload, deruxtecan. Following attachment to HER2-expressing tumor cells, the complex undergoes receptor-mediated internalization and lysosomal cleavage, leading to intracellular release of the cytotoxic deruxtecan payload.[31] The released agent induces DNA double-strand breaks, resulting in cell-cycle arrest, apoptosis, and immunogenic cell death. Unlike its predecessor T-DM1, deruxtecan is membrane permeable and can diffuse into nearby tumor cells with low HER2 expression, producing a "bystander effect" that broadens therapeutic efficacy in heterogeneous tumors.[32]T-DXd has demonstrated remarkable clinical efficacy across HER2-positive and HER2-low breast cancer populations. Regulatory agencies such as the FDA and EMA have approved it for patients with HER2-positive metastatic or locally advanced breast cancer who have previously received at least one anti-HER2 therapy, and for those with HER2-low disease (IHC 1+ or 2+/

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Table 5 Clinical use and regulatory approval of Anti-HER2 monoclonal antibodies in breast cancer

Drug	Regulatory approval	Clinical indication	Line of therapy / key clinical notes
Trastuzumab	FDA & EMA approved	HER2-positive early-stage and metastatic breast cancer	Standard of care for first-line therapy; used in both adjuvant and metastatic settings in combination with chemotherapy. Significant OS and DFS benefit established in pivotal phase III trials.
Pertuzumab	FDA & EMA approved	HER2-positive neoadjuvant and metastatic breast cancer	Administered with trastuzumab and a taxane as first-line therapy. Shown to improve PFS and OS in CLEOPATRA and NeoSphere trials.
Margetuximab	FDA approved (not EMA)	HER2-positive metastatic breast cancer with prior trastuzumab exposure	Approved for patients previously treated with ≥2 anti-HER2 regimens. Demonstrated improved PFS vs trastuzumab in SOPHIA trial.
Trastuzumab deruxtecan (T-DXd)	FDA & EMA approved	HER2-positive and HER2-low metastatic breast cancer	ADC combining trastuzumab with a topoisomerase I inhibitor payload; showed marked efficacy (DESTINY-Breast03, DESTINY-Breast04) and durable response.
Tucatinib	FDA & EMA approved	Advanced HER2-positive breast cancer including brain metastases	Highly selective HER2 TKI; improved CNS control and OS in HER2CLIMB trial when added to trastuzumab + capecitabine.

HER2: Human Epidermal Growth Factor Receptor 2; FDA: U.S. Food and Drug Administration; EMA: European Medicines Agency; ADC: Antibody–Drug Conjugate; OS: Overall Survival; DFS: Disease-Free Survival; PFS: Progression-Free Survival; TKI: Tyrosine Kinase Inhibitor; CNS: Central Nervous System

FISH–) after prior chemotherapy (Table 5). In the DESTINY-Breast03 trial, T-DXd showed superior outcomes compared with T-DM1, with a hazard ratio of 0.28 for progression or death and an objective response rate of approximately 80% versus 34% with T-DM1.[33,34] Later, the DESTINY-Breast04 study extended this benefit to patients with HER2-low tumors, establishing T-DXd as the first targeted therapy to significantly improve survival in this subgroup (Table 6).[35]

The most frequently observed adverse effects of T-DXd include nausea, fatigue, alopecia, and myelosuppression, reflecting the pharmacologic activity of topoisomerase I inhibition. However, interstitial lung disease (ILD) has emerged as the most serious toxicity, occurring in approximately 10–15% of treated patients and occasionally resulting in fatal outcomes.[36] Because ILD and radiation pneumonitis share overlapping symptoms and radiographic features, the concurrent use of T-DXd with radiotherapy (RT) may potentiate pulmonary toxicity.[36,37]

At present, simultaneous administration of T-DXd and RT is not recommended outside of clinical trials. Sequential scheduling is preferred, ideally completing radiotherapy before initiating T-DXd, or allowing a washout period of roughly 3–4 weeks between modalities. The ongoing DESTINY-Breast05 trial (NCT04622319) aims to further elucidate the safety, sequencing, and potential interactions of T-DXd with RT in patients with early-stage HER2-positive breast cancer.[38]

HER2-Targeted Tyrosine Kinase Inhibitors (TKIs) and Radiotherapy

Activation of the HER2 receptor triggers intrinsic tyrosine kinase activity, leading to downstream signaling through the RAS RAF MEK ERK and PI3K AKT mTOR pathways, which promote cellular proliferation, angiogenesis, and survival. Tyrosine kinase inhibitors (TKIs) inhibit these enzymatic cascades, thereby blocking oncogenic signaling and promoting apoptosis. Preclinical evidence suggests that TKIs can enhance radiosensitivity by suppressing DNA repair and checkpoint activation, thereby amplifying radiation-induced cytotoxicity.[39]

Lapatinib, one of the first dual HER2/EGFR inhibitors, has been evaluated extensively in combination with radiotherapy. The ALTTO trial demonstrated that lapatinib could be safely administered concurrently with postoperative locoregional RT without increasing the incidence of dermatitis, cardiac toxicity, or pneumonitis.[40] Moreover, a recent meta-analysis found that combining lapatinib with radiotherapy, particu-

Table 6 Summary of clinical trials evaluating T-DM1 and radiotherapy

Study / trial	Design and participants	Regimen with RT	RT timing / setting	Main findings	Adverse events (RT-related)
KAITLIN (NCT01966471)	Phase III, adjuvant; HER2⁺ early breast cancer (n≈1,846)	T-DM1 + Pertuzumab + RT vs Trastuzumab + Pertuzumab + RT	Adjuvant; RT to chest wall/breast ± regional lymph nodes	No additional toxicity reported with concurrent RT. Efficacy of systemic therapy maintained.	No significant pulmonary toxicity or increased dermatitis.
KATHERINE (NCT01772472)	Phase III, adjuvant; HER2⁺ residual disease post-neoadjuvant therapy (n≈1,486)	T-DM1 (± RT) vs Trastuzumab	Adjuvant; RT allowed concurrently or sequentially	T-DM1 safely combined with RT; improved invasive disease-free survival (HR 0.50; 95% CI 0.39–0.64; p<0.001).	Low incidence of RT-related dermatitis (≈1–2%) and pneumonitis (<1%).
ATEMPT (NCT01853748)	Phase II, adjuvant; Stage I HER2⁺ breast cancer (n=383)	T-DM1 + RT vs Trastuzumab + RT	Adjuvant; whole breast or chest wall RT	Comparable rates of ≥ Grade 2 skin toxicity between treatment arms.	Pneumonitis: 1.5% (T-DM1) vs 0.7% (Trastuzumab). Generally well tolerated.
HERACLES-RT (Institutional cohort)	Retrospective series; HER2⁺ metastatic breast cancer with brain metastases	T-DM1 + stereotactic radiosurgery (SRS)	Metastatic; CNS-directed RT	Local control preserved; improved intracranial response. No significant neurologic toxicity.	Occasional radionecrosis (~2–3%). Mild fatigue and headache most common.
Bologna Series (2022)	Institutional, 52 patients with chest wall/bone irradiation	T-DM1 with concurrent or sequential RT	Adjuvant/metastatic; thoracic or skeletal sites	Combination feasible; no compromise in systemic efficacy.	Mild dermatitis (≤Grade 2) in 10%; no ≥Grade 3 pneumonitis observed.
Small-scale series / retrospective reports	Various institutional observational studies (HER2⁺ breast cancer)	T-DM1 + RT (varied sequencing)	Adjuvant or metastatic; chest wall, brain, or bone lesions	Combination generally well tolerated; local control maintained.	Serious RT-related events rare (<2%). Fatigue and mild dermatitis most common.

RT: Radiotherapy; T-DM1: Trastuzumab Emtansine; HR: Hazard Ratio; CI: Confidence Interval; IDFS: Invasive Disease-Free Survival; HER2⁺: Human Epidermal Growth Factor Receptor 2 Positive; BC: Breast Cancer

larly stereotactic radiosurgery (SRS) for brain metastases, improved local control and overall survival compared with RT alone while lowering the risk of radionecrosis.[41]

Neratinib is an irreversible pan-HER inhibitor targeting HER1, HER2, and HER4, and it is approved for use in both metastatic disease and extended adjuvant therapy. The ExteNET trial demonstrated a significant improvement in invasive disease-free survival when neratinib was administered following trastuzumab-based adjuvant therapy, supporting its role as an extended adjuvant agent. In the metastatic setting, the NALA trial reported that the combination of neratinib and capecitabine achieved superior progression-free survival compared to lapatinib plus capecitabine.[42]

Tucatinib is a highly selective HER2-targeted TKI with minimal inhibition of EGFR, resulting in fewer gastrointestinal and dermatologic adverse effects compared to earlier agents. The phase III HER2CLIMB study showed that tucatinib significantly improved overall survival and central nervous system (CNS) progression-free survival, particularly in patients with active brain metastases.[43] Based on expert recommendations derived from this trial, tucatinib therapy should ideally begin about seven days after stereotactic radiosurgery or approximately 21 days following whole-brain radiotherapy (WBRT) to reduce overlapping toxicities.

Collectively, HER2-targeted TKIs represent essential therapeutic options for patients with

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HER2-positive breast cancer, especially those with CNS metastases where effective blood-brain barrier penetration is critical. Lapatinib appears to be safe when administered concurrently with locoregional RT and may even decrease radionecrosis risk when used with SRS. Neratinib, due to its gastrointestinal and hepatic side effects, should generally be used sequentially after RT completion. Tucatinib, with its favorable CNS efficacy and tolerability profile, is a promising candidate for integration with CNS-directed RT when appropriate timing intervals are observed. Until additional prospective data become available, concurrent radiotherapy with HER2-targeted TKIs should be reserved for carefully selected patients, taking into account tumor burden, irradiation site, and comorbid conditions.

Triple-Negative Breast Cancer (TNBC): PARP Inhibitors and Radiotherapy

Triple negative breast cancer (TNBC) is an aggressive subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. This form of breast cancer frequently exhibits deficiencies in DNA damage repair mechanisms, particularly homologous recombination deficiency (HRD), which often arises from mutations in genes such as BRCA1, BRCA2, and PALB2. Under normal conditions, single strand DNA breaks are repaired through the base excision repair (BER) pathway mediated by poly ADP ribose polymerase (PARP) enzymes, while double strand breaks are corrected via BRCA1 and BRCA2 dependent homologous recombination repair (HRR). In tumors with BRCA mutations, the loss of HRR function forces cells to rely on PARP mediated BER for survival. PARP inhibitors (PARPi), including olaparib and talazoparib, block BER and cause the accumulation of single strand breaks, leading to replication fork collapse and subsequent double strand breaks. Because HR deficient cells cannot repair these lesions, this process, referred to as synthetic lethality, leads to selective death of tumor cells while sparing healthy tissues.[44]

Preclinical studies have shown that inhibition of PARP enhances the effects of radiotherapy through multiple mechanisms. These include destabilization of replication forks, induction of replication stress, suppression of ATM and ATR checkpoint activation, and the buildup of reactive oxygen species (ROS) that increase oxidative stress. Additionally, inhibition of PARP results in cytosolic DNA fragment accumulation, which activates the cGAS STING interferon signaling pathway and stimulates an antitumor immune response.[45,46] Together, these mechanisms produce synergistic radiosensitization, particularly in BRCA mutated and HRD positive TNBC, providing a strong biological rationale for combination treatment with radiotherapy.

Clinically, PARP inhibitors have become an important component in the management of HER2 negative, BRCA mutated breast cancer. The phase III OlympiA trial demonstrated that adjuvant olaparib significantly improved invasive disease free survival with a hazard ratio of 0.58 ($p<0.001$) and increased overall survival in patients with high risk, early stage, germline BRCA1 or BRCA2 mutations.[47] In metastatic disease, both olaparib and talazoparib outperformed standard chemotherapy in the OlympiAD and EMBRACA trials, respectively, showing favorable safety profiles that support potential use with radiotherapy.[48,49] Furthermore, new evidence suggests that HRD positive but BRCA wild type TNBC, including tumors with mutations in RAD51C, RAD51D, or PALB2, may also respond to PARP inhibition, even when combined with radiotherapy.[46]

Early clinical trials have demonstrated the feasibility and safety of combining PARP inhibitors with radiotherapy. The RADIOPARP phase I study evaluated concurrent olaparib with locoregional radiotherapy in TNBC patients with residual disease following neoadjuvant chemotherapy and reported no grade 3 or higher acute toxicities, as well as acceptable late effects after two years of follow up.[50] The TBCRC 024 trial combined veliparib with postoperative radiotherapy in patients with inflammatory or recurrent breast cancer, observing manageable acute toxicities but reporting late fibrosis in up to 40 percent of cases, suggesting sustained radiosensitization.[51] Another phase I study combining veliparib with whole brain radiotherapy for brain metastases reported good tolerability without unexpected neurologic effects, supporting its potential use in palliative settings.[52]

Beyond direct enhancement of radiation effects, PARP inhibitors also promote immune activation through the cGAS STING interferon pathway, which has inspired new studies exploring triple combinations of PARPi, radiotherapy, and immune checkpoint inhibitors. Ongoing trials, such as REPAIR-TNBC (NCT04490886) and PARADIGM-Breast (NCT05169437), are currently assessing the clinical utility of combining PARP inhibition, radiotherapy, and immune checkpoint blockade in triple-negative breast cancer.[53]

Because of the risk of overlapping toxicities, such as hematologic suppression, mucosal irritation, and pulmonary inflammation, concurrent administration of PARP inhibitors and radiotherapy remains experimental. Sequential treatment, where PARP inhibitors are introduced only after several drug half lives have passed following radiotherapy, is currently considered the safest approach. Caution is especially necessary for thoracic irradiation due to the risk of pneumonitis, and for re irradiation cases where cumulative bone marrow or skin toxicity may occur. Early studies involving brain directed radiotherapy have shown acceptable tolerability, but careful monitoring for radionecrosis is still required.

In summary, inhibition of PARP enhances the effectiveness of radiotherapy through mechanisms involving synthetic lethality, replication stress, DNA repair inhibition, and immune activation. Although preclinical and early clinical data are highly promising, concurrent administration remains investigational and should be limited to clinical trials. At present, sequential administration with careful toxicity monitoring represents the most appropriate strategy for integrating PARP inhibitors with radiotherapy in TNBC management.

Triple-Negative Breast Cancer (TNBC): Immunotherapy and Radiotherapy

Triple negative breast cancer (TNBC) is an aggressive and immunologically distinct subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. Among all breast cancer types, TNBC exhibits the highest tumor mutational burden (TMB), greatest PD-L1 expression, and the most abundant tumor-infiltrating lymphocytes (TILs), providing a strong biological basis for the use of immunotherapy. TNBC cells often evade immune surveillance through overexpression of PD-L1, which binds to the programmed death-1 (PD-1) receptor on cytotoxic T cells, leading to T-cell exhaustion and immune escape. Immune checkpoint inhibitors (ICIs) such as pembrolizumab (anti-PD-1) and atezolizumab (anti-PD-L1) block this inhibitory interaction, reactivating cytotoxic T-cell function and restoring immune-mediated tumor destruction.[54]

Radiotherapy (RT) complements immunotherapy by stimulating antitumor immunity through several mechanisms. RT induces immunogenic cell death, leading to the release of tumor antigens that activate dendritic cells and enhance antigen presentation. It also increases the expression of major histocompatibility complex (MHC) class I molecules on tumor cells, improving recognition by cytotoxic T cells. Moreover, RT remodels the tumor microenvironment by increasing effector T-cell infiltration while reducing suppressive myeloid cell populations. Radiation-induced DNA damage also activates the cGAS-STING pathway, promoting type I interferon production and systemic immune activation. These processes can elicit the abscopal effect, where regression of distant, non-irradiated metastases occurs as a result of systemic immune activation.[55]

Clinical data have confirmed that ICIs improve outcomes in both early-stage and advanced TNBC. In the phase III KEYNOTE-522 trial, neoadjuvant pembrolizumab combined with chemotherapy, followed by adjuvant pembrolizumab, significantly increased the pathological complete response (pCR) rate and event-free survival (EFS) compared to chemotherapy alone. Although concurrent radiotherapy was initially not permitted, later protocol amendments allowed adjuvant RT during pembrolizumab maintenance, with low incidences of pneumonitis (0.9%) and dermatitis (4.7%), indicating that concurrent or sequential use is feasible.[56] Current phase II–III studies (NCT04683679, NCT05062317) are further investigating the optimal sequencing and fractionation of RT in combination with ICIs.

In metastatic TNBC, the phase III KEYNOTE-355 trial demonstrated that pembrolizumab combined with chemotherapy significantly improved progression-free survival in PD-L1 positive patients (9.7 vs. 5.6 months; HR=0.65; $p<0.001$) without unexpected RT-related toxicity.[57] Similarly, the IMpassion-130 trial found that atezolizumab plus nab-paclitaxel provided a clinically meaningful overall survival benefit in PD-L1 positive patients (25.0 vs. 18.0 months), supporting the immune responsiveness of TNBC.[58] Although the FDA later withdrew the atezolizumab indication, the therapy remains approved by the EMA for PD-L1 positive disease.

Other ICIs such as nivolumab and durvalumab have also demonstrated potential in early-phase clinical studies. The TONIC trial showed that short-course RT (24 Gy in three fractions) administered before nivolumab treatment enhanced immune-related gene expression and increased objective response rates, suggesting that RT can function as an immune primer in TNBC.[59]

The biological interaction between RT and immunotherapy depends significantly on radiation dose and fractionation. Moderate fraction sizes (2–8 Gy per fraction) tend to enhance immune activation, while single high-dose fractions (>12–15 Gy) may lead to

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Table 7 Summary of concurrent use of systemic therapies with radiotherapy: Toxicity profiles and pharmacokinetic considerations

Drug group	Representative agents	Clinical toxic effects	Recommendation for concurrent use	Approximate five half-lives (days)
CDK4/6 inhibitors	Palbociclib, Ribociclib, Abemaciclib	Increased risk of myelosuppression and mucosal toxicity during concurrent RT.	Use with caution; concurrent use generally not recommended except in clinical trials.	5–7
PI3K inhibitor	Alpelisib	Limited data; potential enhancement of skin and GI toxicity when combined with RT.	Concurrent use not recommended due to limited safety evidence.	1.9
mTOR inhibitor	Everolimus	Reports of radiation recall dermatitis and pneumonitis; enhanced radiosensitivity possible.	Avoid concurrent administration; sequential therapy preferred.	6.2
Anti-HER2 therapies	Trastuzumab, Pertuzumab	Generally safe in combination with RT; no significant increase in pulmonary or cardiac toxicity.	Recommended for concurrent use with caution and cardiac monitoring.	90–175
Antibody–drug, conjugates (ADCs)	T-DM1, T-DXd	Risk of pneumonitis and radionecrosis, especially in thoracic or cranial irradiation fields.	Use with caution; consider sequential administration in high-risk settings.	20–29
Tyrosine kinase inhibitors (TKIs)	Lapatinib, Tucatinib, Neratinib	Generally well-tolerated with RT; mild diarrhea and skin reactions may occur.	Concurrent use acceptable with close monitoring.	5
PARP inhibitors	Olaparib, Veliparib	Potential for enhanced skin and hematologic toxicity; evidence limited.	Concurrent use not recommended outside clinical trials.	3–19

ADC: Antibody–Drug Conjugate; CDK4/6: Cyclin-Dependent Kinase 4 and 6; GI: Gastrointestinal; HER2: Human Epidermal Growth Factor Receptor 2; mTOR: Mechanistic Target of Rapamycin; PARP: Poly (ADP-Ribose) Polymerase; PI3K: Phosphatidylinositol-3-Kinase; RT: Radiotherapy; TKI: Tyrosine Kinase Inhibitor

lymphocyte depletion and reduce immune efficacy. Preclinical evidence supports the use of hypofractionated RT regimens (for example, 8 Gy × 3), which appear to stimulate systemic immunity more effectively than single ablative doses, promoting immune modulation rather than purely cytotoxic effects.[60]

A comprehensive meta-analysis including 51 clinical studies and approximately 15,400 patients treated with concurrent RT and ICIs across various cancers found no significant increase in severe (grade ≥3) toxicities, confirming the general safety of this therapeutic combination.[61] The most frequent immune-related adverse events (irAEs) include dermatitis, pneumonitis, and colitis, although their incidence in breast cancer remains relatively low, with severe events (grade ≥3) occurring in fewer than 5% of cases.[61,62]

Radiotherapy has also been shown to increase PD-L1 expression in both tumor and immune cells, potentially enhancing sensitivity to ICIs.[55,61] However, combining immunotherapy with thoracic RT requires caution due to possible additive pulmonary or cardiac toxicities. Current research is focused on optimizing RT dose, timing, and target volume design to maximize immune activation while minimizing toxicity to surrounding organs.

Overall, integrating immunotherapy with radiotherapy represents a rapidly evolving treatment strategy in TNBC. Current evidence supports either sequential administration or carefully timed concurrent therapy, particularly in patients with PD-L1 positive or oligometastatic disease. Future directions include identifying predictive biomarkers such as PD-L1 combined positive score (CPS), tumor mutational burden (TMB), and STING pathway activation, as well as developing triplet combinations that include RT, PARP inhibitors, and ICIs for BRCA-mutated or HRD-positive TNBC. As data from ongoing trials mature, immuno-radiotherapy is expected to become a cornerstone of precision medicine for TNBC, offering durable disease control through coordinated modulation of DNA repair and immune activation.

A detailed summary of systemic therapy combinations, toxicity profiles, and pharmacokinetic characteristics, including HER2-targeted TKIs, is presented in Table 7.

CONCLUSION AND FUTURE PERSPECTIVES

The integration of next-generation systemic therapies with radiotherapy has transformed the modern landscape of breast cancer management. With rapid advancements in molecular oncology and precision medicine, the conventional uniform treatment model has evolved into a subtype-specific, biology-driven therapeutic approach. Radiotherapy is now increasingly incorporated alongside targeted and immune-based systemic treatments to enhance local tumor control, improve overall survival, and achieve longer-lasting therapeutic responses. Nevertheless, the successful application of these combined strategies requires a comprehensive understanding of biological cross-talk, overlapping toxicity profiles, and the pharmacokinetic as well as pharmacodynamic behavior of each agent (Table 7).

In hormone receptor positive breast cancer, agents such as CDK4/6, PI3K, and mTOR inhibitors have considerably improved clinical outcomes. However, their combination with radiotherapy requires careful coordination to avoid cumulative toxicity. While these regimens are generally well tolerated, concurrent administration can heighten hematologic, gastrointestinal, or pulmonary side effects, making individualized planning and temporary drug discontinuation during radiotherapy advisable in many cases.

For HER2 positive disease, concurrent radiotherapy with monoclonal antibodies such as trastuzumab or pertuzumab has proven safe, with minimal risk of cardiac or radiation-induced toxicity. In contrast, HER2 targeted antibody drug conjugates (ADCs) like trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) present a higher risk of interstitial lung disease, pneumonitis, and radionecrosis, particularly when irradiating thoracic or central nervous system regions. Sequential rather than concurrent use is therefore preferred. Among tyrosine kinase inhibitors (TKIs), lapatinib has shown good safety when combined with locoregional radiotherapy, while data regarding newer agents such as neratinib and tucatinib remain limited and require validation in future prospective studies.

In triple negative breast cancer (TNBC), PARP inhibitors demonstrate strong radiosensitizing properties through inhibition of DNA repair pathways. However, their concurrent use with radiotherapy is still experimental, as it may exacerbate toxicity in healthy tissues. Ongoing clinical research is expected to clarify optimal dosing, timing, and safety profiles. On the other hand, immune checkpoint inhibitors (ICIs) such as pembrolizumab and atezolizumab have significantly changed the treatment paradigm for PD-L1 positive TNBC by improving both progression-free and overall survival. Radiotherapy acts as a synergistic partner in this setting, enhancing antigen presentation, triggering cGAS-STING-dependent interferon responses, and promoting systemic immune activation. Preliminary findings suggest that concurrent or sequential immuno-radiotherapy is feasible and effective, though longer follow-up is needed to evaluate potential delayed toxicities related to immune activation.

Pharmacokinetic and pharmacodynamic considerations are essential for safely combining systemic agents with radiotherapy. Drugs with long half-lives or delayed tissue clearance, such as T-DXd or everolimus, may heighten late-onset toxicity, whereas short-acting agents like CDK4/6 inhibitors can often be safely resumed soon after radiotherapy with appropriate monitoring. As a general clinical guideline, maintaining a washout period of approximately three to five drug half-lives between systemic and radiation therapy—particularly for thoracic, hepatic, or CNS-directed irradiation—is recommended to minimize cumulative tissue damage.

The effective implementation of integrated radio-systemic therapy relies on close multidisciplinary collaboration, early toxicity detection, and evidence-based clinical trial data. As the field of precision oncology continues to evolve, the fusion of targeted systemic agents with radiotherapy is poised to become a core element of personalized breast cancer treatment strategies.

In the coming decade, research in radio-systemic oncology will focus on optimizing treatment combinations to maximize therapeutic benefit while minimizing adverse effects. Identifying predictive biomarkers such as homologous recombination deficiency (HRD) scores, PD-L1 combined positive score (CPS), tumor-infiltrating lymphocyte (TIL) density, and STING pathway activation will refine patient selection and guide therapeutic sequencing. Advances in adaptive radiotherapy, incorporating pharmacokinetic modeling and biologically guided dose modulation, will allow treatment intensity to be adjusted in real time based on systemic drug levels and tumor response patterns.

Future directions are likely to emphasize triplet or multimodal strategies that combine radiotherapy with

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both targeted therapies and immunotherapy, such as PARP inhibitors with PD-1 blockade plus RT, to enhance antitumor activity in biomarker-defined patient subgroups. Emerging technologies including real-time molecular imaging, circulating tumor DNA (ctDNA) monitoring, and radiomic analysis will further facilitate early assessment of treatment efficacy and toxicity, enabling dynamic optimization of therapy.

The convergence of molecular profiling, targeted systemic therapy, and precision radiotherapy represents a new era of personalized radio-immuno-oncology. Treatment approaches are evolving to adapt not only to tumor subtype but also to each patient's biological response over time. The overarching goal is to achieve sustained tumor control with minimal toxicity, transforming radiotherapy from a primarily local modality into a central pillar of integrated, biologically guided cancer therapy.

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