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REVIEW

Toxicity Profiles and Management Strategies in Targeted Therapy–Radiotherapy Combinations

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SUMMARY

The integration of stereotactic body radiotherapy (SBRT) with targeted agents has emerged as a promising strategy in modern oncology, offering the potential for enhanced tumor control through synergistic biological mechanisms. SBRT achieves high local doses with sub-millimeter precision, while targeted therapies act on molecular pathways critical for tumor proliferation, angiogenesis, and immune evasion. When used concurrently, these modalities may reinforce each other's effects, but this synergy is not limited to tumor cells. Normal tissues within or adjacent to the radiation field may also experience heightened sensitivity, leading to an increased risk of adverse events. Reported toxicities include potentiation of vascular injury, exacerbation of mucosal inflammation, and augmentation of immune-related adverse effects, depending on the specific class of agent administered. Consequently, while the combination of SBRT and targeted therapies holds substantial therapeutic promise, its implementation requires judicious patient selection, careful sequencing, and vigilant toxicity monitoring to maximize efficacy while minimizing harm.

Keywords: Adverse events; immunotherapy; radiotherapy; SBRT; targeted therapies.

INTRODUCTION

Molecular medicine is undergoing rapid advancements, with numerous novel agents recently receiving approval from the U.S. Food and Drug Administration (FDA) for a wide range of oncologic indications. As a result, integrating these agents with established treatment modalities remains a complex challenge. Therefore, much of the available evidence regarding concurrent administration, particularly in combination with radiotherapy, has been derived from small retrospective series and the clinical experiences of high-volume cancer centers.

The combination of stereotactic body radiotherapy (SBRT) and targeted agents offers the potential for synergistic antitumor efficacy, but it also raises important concerns regarding toxicity profiles. SBRT delivers ablative radiation doses to limited tumor volumes with high precision, thereby minimizing exposure to surrounding normal tissues. When combined with targeted therapies—such as tyrosine kinase inhibitors, angiogenesis inhibitors, or immune checkpoint modulators—the local cytotoxic effects of SBRT may be amplified through enhanced radiosensitization and disruption of tumor microenvironmental repair pathways.[1,2] However, this synergy can extend beyond tumor control to normal tissue toxicity, resulting in an increased incidence or severity of adverse effects. For example, vascular toxicities, mucosal inflammation, or gastrointestinal ulceration may be potentiated when anti-angiogenic agents are used concurrently with SBRT,[3,4] while immune-related adverse events—particularly respiratory toxicities like pneumonitis or pneumonia—can be exacerbated in the setting of ICI

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use [5,6] Therefore, careful patient selection, vigilant toxicity monitoring, and evidence-based sequencing strategies are essential to balance the therapeutic advantages of this synergistic approach against the risk of treatment-limiting side effects.

In recent years, however, substantial efforts have been devoted to systematically evaluating these therapeutic combinations. This growing body of research has yielded more robust evidence supporting the safe and effective concurrent use of many molecular agents alongside radiotherapy. Consequently, the evolving integration of targeted therapies into multimodal cancer management is beginning to reshape clinical practice and improve patient outcomes.

Targeted Agents, Mechanisms of Action, and Efficacy/Adverse Effects

The integration of molecularly targeted agents with radiotherapy has gained increasing attention in recent years, with several classes of compounds demonstrating both radiosensitizing potential and unique toxicity considerations. Among epidermal growth factor receptor (EGFR) inhibitors, small-molecule tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, lapatinib, and sorafenib have been evaluated in combination with external beam radiotherapy. These agents act primarily through interference with repopulation and reoxygenation mechanisms, thereby enhancing tumor radiosensitivity. However, because EGFR is also expressed in epithelial tissues, dermatologic and mucosal toxicities are common; acneiform rash and gastrointestinal adverse events represent the most frequently reported complications. Case reports have described bowel perforation during palliative spinal irradiation, underscoring the potential for severe events in selected patients. Furthermore, the combination of cetuximab with chemoradiation has been associated with unacceptable toxicity in phase II trials, leading to early termination in some studies.[7,8]

Vascular endothelial growth factor (VEGF) inhibition has also been explored as a radiosensitizing approach, based on its ability to transiently normalize tumor vasculature and improve oxygenation. Bevacizumab, the most extensively studied anti-VEGF monoclonal antibody, has been combined with radiotherapy in glioblastoma and pancreatic cancer. While some studies suggested improved tumor control, significant adverse effects were observed, including optic neuritis leading to blindness in glioblastoma patients and gastrointestinal toxicities in up to one-third of pancreatic cancer patients. Cediranib, a VEGF receptor tyrosine kinase inhibitor with a reported half-life of approximately 20 hours, remains under clinical investigation, with preliminary data indicating an acceptable safety profile.[9,10]

Another promising class comprises poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib and veliparib, which modulate the repair of single-strand DNA breaks. Preclinical and early clinical evidence suggests that PARP inhibition enhances the cytotoxic effect of radiotherapy and temozolomide in glioblastoma. Early-phase studies have shown that the combination with chemotherapy is generally safe, although an increased incidence of hematological toxicity has been noted in trials involving melanoma patients.[11,12]

Taken together, these data highlight the dual potential of targeted agents to potentiate radiotherapy efficacy and increase the risk of treatment-related adverse events. More recently, immunotherapeutic agents have also become integral components of modern oncological practice, and—similar to targeted therapies—they demonstrate both promising synergistic effects with radiotherapy and the possibility of exacerbated adverse events.[13] The indications, mechanisms of action, and fundamental pharmacological properties of these targeted agents and immunotherapeutics are summarized in Tables 1 and Table 2.

Targeted Therapies and Immunotherapies Used in Non-Small Cell Lung Cancer

Summary of targeted agents in breast cancer and their compatibility with radiotherapy can be seen on Table 3.

Targeted Therapies with Radiotherapy in NSCLC

The concurrent administration of targeted therapies with thoracic radiotherapy has been extensively explored, but available evidence consistently emphasizes the need for caution. Among monoclonal antibodies, the EGFR inhibitor cetuximab has been investigated in pilot studies such as SCRATCH, NEAR, and RTOG 0617.[14] These trials demonstrated that cetuximab can be administered safely with conventionally fractionated thoracic radiotherapy. However, when combined with chemotherapy, its use is discouraged due to an increased risk of severe (grade ≥3) pneumonitis.[7,8]

In contrast, VEGF inhibition with bevacizumab has raised substantial safety concerns. Data from ECOG-3598 and SWOG S0533 reported life-threatening complications, including tracheoesophageal fistula and severe esophagitis, leading to the consensus that con-

Table 1 Targeted therapies used in oncology

Drug name	Cancer type	Overview of targeted therapy	Half-life	5 half-lives
1. Monoclonal antibodies				
Cetuximab (Erbitux)	Colorectal, lung, head and neck (EGFR inh)	EGFR inhibitor; blocks EGFR-mediated signaling pathways, inhibiting cell proliferation.	114 h	24 days
Bevacizumab (Avastin)	Colorectal, lung, kidney, brain (VEGF inh)	VEGF inhibitor; prevents angiogenesis by blocking VEGF-A.	20 days	100 days
Trastuzumab (Herceptin)	HER2 (+) breast and gastric ca	HER2 monoclonal antibody; blocks HER2 signaling and induces antibody-dependent cellular cytotoxicity.	456 h	95 days
Pertuzumab (Perjeta)	Breast ca with trastuzumab	HER2 dimerization inhibitor; prevents HER2-HER3 heterodimer formation, enhances trastuzumab efficacy.	480 h	100 days
Trastuzumab-Emtansine (Kadcyla, TDM-1)	HER2 (+) breast	HER2-targeted antibody-drug conjugate (trastuzumab linked to DM1 cytotoxic agent).	96 h	20 days
Trastuzumab-Deruxtecan (Enhertu)	HER2 (+) breast	HER2-targeted antibody-drug conjugate delivering topoisomerase I inhibitor payload.	168 h	35 days
2. Tyrosine Kinase Inhibitors (TKIs)				
Erlotinib (Tarceva)	Lung ca (EGFR mutant)	EGFR tyrosine kinase inhibitor; inhibits ATP binding to mutant EGFR.	36 h	5 days
Osimertinib (Tagrisso)	Lung ca (EGFR mutant)	Third-generation EGFR TKI; effective against T790M-resistant mutations.	44 h	8 days
Gefitinib (Iressa)	Lung ca (EGFR mutant)	First-generation EGFR TKI; competes with ATP at EGFR tyrosine kinase binding site.	40 h	7 days
Afatinib (Giotrif)	Lung ca (EGFR mutant)	Second-generation irreversible EGFR/HER2 TKI.	37 h	5 days
Lapatinib (Tykerb)	HER2 (+) breast ca	Dual TKI; inhibits HER2 and EGFR pathways.	24 h	5 days
Sorafenib (Nexavar) (VEGF inh)	Renal, hepatocellular, thyroid (multikinase inh)	Multikinase inhibitor; blocks VEGFR, PDGFR, RAF kinases, reducing angiogenesis and proliferation.	25–48 h	2–4 days
Sunitinib (Sutent) (VEGF inh)	Renal tumors, GIST (multikinase inh)	Multikinase inhibitor; inhibits VEGFR, PDGFR, KIT, FLT3.	18 h	1–2 days
Imatinib (Gleevec)	GIST and CML	TKI against BCR-ABL, KIT, and PDGFR; first targeted therapy for CML and GIST.	–	–
3. ALK inhibitors				
Alectinib (Alecensa)	Lung ca (ALK mutant)	Selective ALK inhibitor; effective against CNS metastases.	–	–
Crizotinib (Xalkori)	Lung ca (ALK mutant)	First-generation ALK/MET/ROS1 inhibitor.	–	–
Lorlatinib (Lorbrena)	Lung ca (ALK mutant)	Third-generation ALK inhibitor; active against resistant ALK mutations, penetrates CNS.	42 h	3.5 days
4. PARP inhibitors				
Olaparib (Lynparza)	Breast and ovarian ca (BRCA mutant)	PARP inhibitor; impairs single-strand DNA repair, leading to synthetic lethality in BRCA-mutant cells.	15 h	3 days
Veliparib (ABT-888)	Breast ca	PARP-1/2 inhibitor; enhances cytotoxicity of DNA-damaging agents.	–	–
5. CDK4/6 inhibitors				
Palbociclib (Ibrance)	Breast ca, HR (+) and HER2 (-)	Selective CDK4/6 inhibitor; blocks cell cycle progression at G1-S checkpoint.	28.8 h	6 days
Ribociclib (Kisqali)	Breast ca, HR (+) and HER2(-)	Selective CDK4/6 inhibitor; synergistic with endocrine therapy.	29.7–54.7 h	6–11 days
Abemaciclib (Verzenio)	Breast ca, HR (+) and HER2(-)	Potent CDK4/6 inhibitor with higher single-agent activity.	24.8 h	5 days
6. PI3K Inhibitors				
Alpelisib (Piqray)	Breast ca, PIK3CA mutant, HR (+)	Selective PI3Kα inhibitor; blocks PI3K/AKT/mTOR signaling, reducing tumor growth.	8–9 h	1.8 days
7. VEGF Inhibitors				
Pazopanib (Votrient)	Renal tumors, sarcomas (multikinase inh.)	Multikinase inhibitor; targets VEGFR, PDGFR, and c-KIT, blocking angiogenesis.	30 h	–
Axitinib (Inlyta)	Renal tumors	Selective VEGFR inhibitor; blocks tumor angiogenesis.	2.5–6 h	–
8. BRAF inhibitors				
Dabrafenib (Tafinlar)	Melanoma (BRAF mutant)	Selective BRAF V600E inhibitor; blocks MAPK signaling.	5 h	–

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Table 1 Cont.

Drug name	Cancer type	Overview of targeted therapy	Half-life	5 half-lives
Vemurafenib (Zelboraf)	Melanoma (BRAF mutant)	Selective BRAF V600E inhibitor; inhibits oncogenic BRAF signaling.	30–120 h	–
9. mTOR Inhibitors				
Everolimus (Afinitor)	Renal tumors, breast ca, pancreatic neuroendocrine tumors	mTOR inhibitor; blocks mTORC1 signaling, reducing protein synthesis and tumor growth.	30 h	–

Table 2 Pharmacokinetic properties and clinical indications of selected immune checkpoint inhibitors

Drug name	Target mechanism	Approved indications	Half-life	5 × Half-life
Pembrolizumab (Keytruda)	PD-1 inhibitor	Non–small cell lung cancer (NSCLC), breast cancer, melanoma, head & neck squamous cell carcinoma, gastric cancer, renal cell carcinoma	22 days	110 days
Nivolumab (Opdivo)	PD-1 inhibitor	NSCLC, head & neck cancer, melanoma, renal cell carcinoma	24 days	121 days
Atezolizumab (Tecentriq)	PD-L1 inhibitor	NSCLC, small cell lung cancer (SCLC)	27 days	135 days
Durvalumab (Imfinzi)	PD-L1 inhibitor	NSCLC, SCLC	18–21 days	90–105 days
Avelumab (Bavencio)	PD-L1 inhibitor	Urothelial carcinoma, Merkel cell carcinoma	6 days	30 days
Ipilimumab (Yervoy)	CTLA-4 inhibitor	Melanoma, renal cell carcinoma	16 days	80 days

- PD-1 inhibitors (e.g., pembrolizumab, nivolumab) block the programmed cell death-1 receptor on T cells, enhancing antitumor immune activity.
- PD-L1 inhibitors (e.g., atezolizumab, durvalumab, avelumab) block the ligand on tumor or immune cells, preventing immune evasion.
- CTLA-4 inhibitors (e.g., ipilimumab) act earlier in the immune response by enhancing T-cell activation.
- Pharmacokinetic values are approximate and may vary based on population, dosing, and combination regimens.

current administration of bevacizumab and thoracic radiotherapy is contraindicated. Treatment discontinuation at least three weeks prior to radiation is strongly recommended.[15]

Small-molecule EGFR tyrosine kinase inhibitors (TKIs)-such as erlotinib, gefitinib, afatinib, and osimertinib-have been evaluated in trials including RTOG 0972, NRG/RTOG 1306, and SWOG/CALGB. [16–18] While these agents are generally safe in combination with fractionated radiotherapy, toxicities such as pulmonary inflammation, esophagitis, and grade 3 pneumonitis have been reported when used concurrently with chemoradiotherapy. Clinical guidance therefore recommends a short drug washout, typically two days before stereotactic body radiotherapy (SBRT), to reduce toxicity risk. Importantly, osimertinib exhibits superior central nervous system (CNS) penetration, which may affect both its therapeutic potential and toxicity profile in cranial irradiation settings.[19]

Similarly, ALK inhibitors—including alectinib, crizotinib, and lorlatinib—pose challenges in concurrent use.[20] Reports from NRG-RTOG 1306 and institutional experiences have highlighted pulmonary toxicity, esophagitis, and an elevated risk of radionecrosis following whole-brain radiotherapy. [21] Nonetheless, emerging evidence suggests that their combination with SBRT may be safe in carefully selected patients. Next-generation inhibitors with improved CNS penetration, such as lorlatinib, may alter toxicity risks further, necessitating careful clinical monitoring.[22]

Immunotherapies with Radiotherapy in NSCLC

Immune checkpoint inhibitors (ICIs) have revolutionized the management of NSCLC and are increasingly being integrated with radiotherapy in both clinical trials and real-world practice. PD-1 inhibitors such as nivolumab and pembrolizumab have been evaluated in the ETOP NICOLAS and Keynote-001 trials, as well as in institutional abscopal studies from MD Anderson Cancer Center.[23,24] These studies suggest that ICIs can be safely administered concurrently with chemoradiotherapy or sequentially following stereotactic radiosurgery (SRS), provided a short interval (approximately seven days) is observed between treatments.

Table 3 Summary of targeted agents in breast cancer and their compatibility with radiotherapy

Group	Drug	Clinical toxicities	Recommendation for concurrent RT	5 × Half-life (days)
CDK4/6 inhibitors	Palbociclib	Increased toxicity	Use with caution	5.8
CDK4/6 inhibitors	Ribociclib	Increased toxicity	Use with caution	6.7
CDK4/6 inhibitors	Abemaciclib	Increased toxicity	Use with caution	5
PI3K inhibitor	Alpelisib	Very limited data	Not recommended	1.9
mTOR inhibitor	Everolimus	Recall syndromes / very limited data	Not recommended	6.2
Anti-HER agents	Trastuzumab	Generally safe	Suitable	175
Anti-HER agents	Pertuzumab	Generally safe	Suitable	90
Anti-HER agents	T-DM1 (trastuzumab-emtansine)	Pneumonitis, radionecrosis risk	With caution, esp. with cranial RT	20
Anti-HER agents	T-DXd (trastuzumab-deruxtecan)	Interstitial lung disease / pneumonitis	Not recommended	29
Anti-HER agents	Lapatinib	Generally safe	Limited data	5
PARP inhibitors	Olaparib	Increased toxicity	Possibly suitable? / Limited data	3.1
PARP inhibitors	Veliparib	Skin toxicity	Not recommended	18.7
Immunotherapy	Pembrolizumab	Generally safe (based on other cancer data)	Suitable	110

- CDK4/6 inhibitors: Usually withheld before RT due to potential additive toxicity.
- PI3K/mTOR inhibitors: Limited safety data; generally not recommended with concurrent RT.
- HER2-directed antibodies: Trastuzumab and pertuzumab are safe; antibody–drug conjugates (T-DM1, T-DXd) require caution due to pneumonitis/radionecrosis risks.
- PARP inhibitors: Olaparib may be considered cautiously; veliparib has higher toxicity.
- Immunotherapy: Pembrolizumab appears safe with RT, though most data are extrapolated from non-breast cancer trials.

PD-L1 inhibitors, particularly durvalumab and atezolizumab, have demonstrated robust survival benefits when combined with radiotherapy. The PACIFIC trial established durvalumab consolidation after chemoradiotherapy as a standard of care, with only a modest increase in pneumonitis risk. Nevertheless, immune-related toxicities such as hepatitis, pancreatitis, and cytopenias have also been observed in patients receiving PD-L1 blockade alongside radiation.[25]

By contrast, CTLA-4 inhibitors such as tremelimumab and ipilimumab have been associated with higher rates of treatment-related complications. Institutional reports indicate increased risks of cranial radionecrosis and pneumonitis, necessitating greater caution. Current recommendations advise withholding CTLA-4 inhibitors at least two days prior to radiotherapy to mitigate these risks.[13]

Overall, immunotherapies appear both feasible and beneficial in combination with radiotherapy for NSCLC, but toxicity profiles vary significantly by drug class. PD-1/PD-L1 inhibitors are supported by the strongest prospective evidence, whereas CTLA-4 blockade remains experimental due to its higher association with radionecrosis and systemic immune-related adverse events (Fig. 1).

Group / Drug	Recommendation
Monoclonal Antibodies	
Cetuximab (EGFR)	Safe with fractionated RT; Not with chemo (↑ pneumonitis).
Bevacizumab (VEGF)	Contraindicated with RT; stop ≥3 weeks before RT.
Small-Molecule Inhibitors	
EGFR-TKIs (Erlotinib, Gefitinib, Afatinib, Osimertinib)	Safe with fractionated RT; 2-day interval with SBRT. Risks: esophagitis, pneumonitis.
ALK inhibitors (Alectinib, Crizotinib, Lorlatinib)	Risk of pulmonary toxicity and radionecrosis; SBRT safer than WBRT.
Immunotherapies	
PD-1 (Nivolumab, Pembrolizumab)	Safe with CRT; post-SRS (≥7 days).
PD-L1 (Durvalumab, Atezolizumab)	Supported (PACIFIC); mild ↑ pneumonitis.
CTLA-4 (Tremelimumab, Ipilimumab)	↑ Risk of radionecrosis, pneumonitis; Withhold ≥2 days before RT.

Fig. 1. Summary of recommendations for concurrent use of targeted agents and immunotherapeutics in lung carcinoma.

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Drug	Clinical Setting	RT Compatibility
Trastuzumab (Herceptin)	Adjuvant	Safe with concurrent adjuvant RT
Pertuzumab (Perjeta)	Adjuvant / Metastatic	Safe with adjuvant RT; limited to bone RT in metastatic
T-DM1 (Kadcyla)	Adjuvant (residual) / Metastatic	Concurrent RT possible; risk of CNS radionecrosis
Trastuzumab-Deruxtecan (Enhertu)	Metastatic	Data limited; ILD/pneumonitis risk ↑
Lapatinib (Tykerb)	Metastatic	Not with RT; only with capecitabine
Tucatinib (Tukysa)	Metastatic	Not with RT; only with capecitabine
Neratinib (Nerlynx)	Metastatic / Extended Adjuvant	Concurrent RT permitted in extended adjuvant

Fig. 2. Summary of HER2-targeted agents and their compatibility with radiotherapy.

Targeted Therapies and Immunotherapies with Radiotherapy in Breast Cancer

CDK4/6 Inhibitors

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors—palbociclib, ribociclib, and abemaciclib—represent a major therapeutic advance in hormone receptor–positive (HR+), HER2-negative breast cancer. In pivotal phase III trials (PALOMA-2/3, MONALEESA-2/3/7, MONARCH-2/3), these oral agents demonstrated significant improvements in progression-free and overall survival in metastatic patients. However, concurrent use with radiotherapy has not been routinely permitted. In clinical practice, palbociclib and ribociclib are generally discontinued at least one week before RT, with radiotherapy restricted to palliative bone treatments in some studies. Abemaciclib differs from the others in that recent data from the monarchE trial (2023 interim analysis) support its use in high-risk node-positive early-stage disease, and emerging evidence suggests that concurrent RT may be feasible in this context.[26–28]

Toxicities associated with combined use include neutropenia, radiodermatitis, esophagitis, diarrhea (particularly with abemaciclib), hepatotoxicity, QT prolongation, and rare cases of radiation recall pneumonitis. Current consensus is that treatment interruption remains the standard during metastatic RT, with abemaciclib representing the only agent with preliminary data to support concurrent use in early-stage adjuvant settings.[26]

PI3K and mTOR Inhibitors

The PI3K inhibitor alpelisib (evaluated in the SOLAR trial) and the mTOR inhibitor everolimus (BOLERO trials) are approved in metastatic HR+/HER2− disease. Neither drug is recommended for concurrent use with radiotherapy, and guidelines typically advise discontinuation at least four weeks before initiating RT.[29,30] Evidence in breast cancer is limited; however, experience from other tumor sites suggests increased toxicity when combined with radiation. Alpelisib has been linked to enhanced gastrointestinal and mucosal toxicities in head and neck cancers, NSCLC, and gliomas, whereas everolimus has been associated with radiation recall phenomena, including gastritis, bladder stenosis, esophagitis, and colitis.

HER2-Directed Therapies

For HER2-positive disease, the combination of HER2-directed therapies with radiotherapy has been widely studied. Trastuzumab (HERA trial) and pertuzumab (APHINITY, CLEOPATRA) can be safely administered concurrently with adjuvant radiotherapy, although metastatic trials typically limited RT to palliative bone lesions.[31,32] Antibody–drug conjugates (ADCs) such as trastuzumab emtansine (T-DM1, EMILIA, KATHERINE) and trastuzumab deruxtecan (T-DXd, DESTINY) represent newer agents (Fig. 2). T-DM1 has been safely combined with RT after neoadjuvant therapy in patients with residual disease; however, retrospective series suggest cranial radionecrosis rates up to 50% when combined with stereotactic radiosurgery.[33,34] T-DXd use is generally limited to metastatic settings, with palliative RT permitted except in the lungs due to the risk of interstitial lung disease (ILD).

HER2-directed tyrosine kinase inhibitors (TKIs) such as lapatinib, tucatinib, and neratinib have shown variable compatibility. Most studies excluded concurrent RT except in selected palliative contexts. Lapatinib and neratinib have been used with capecitabine but not typically with RT, while tucatinib remains investigational in this regard. Evidence is strongest for adjuvant settings with trastuzumab/pertuzumab, with ADCs and TKIs requiring more caution.[35–37]

HER2-Targeted TKIs with Radiotherapy

Small-molecule TKIs offer the advantage of CNS penetration. Retrospective studies and early-phase trials (NCT01622868, NCT0026358, NCT01218529) suggest that lapatinib, tucatinib, and neratinib may be safely combined with RT in metastatic patients, including those undergoing brain SRS. Benefits include improved local control, systemic disease reduction, and potentially lower radionecrosis risk.[34,38,39] Nonetheless, robust prospective data are lacking, and concurrent use is not yet standard in early-stage settings.

PARP Inhibitors and Immunotherapy in TNBC

In triple-negative breast cancer (TNBC), PARP inhibitors and immunotherapy are increasingly relevant. Olaparib, investigated in OLYMPIA and OLYMPIAD, is recommended in the adjuvant and metastatic settings but should not be given concurrently with RT; a washout of 2–10 weeks is advised. Veliparib appears safe with cranial RT but has been linked to high rates of late toxicities in other radiation contexts.

Immunotherapy with pembrolizumab has shown promise in both the adjuvant (KEYNOTE-522) and metastatic (KEYNOTE-355) settings. Concurrent use with adjuvant RT may be feasible in selected patients; however, in metastatic disease, a minimum two-week interval is advised to minimize toxicity risks.[40,41]

Targeted Therapies in Other Indications

The integration of targeted agents with radiotherapy in malignancies beyond breast and lung cancer has been extensively explored, though concerns regarding safety remain prominent. BRAF inhibitors, widely used in melanoma, are associated with distinct radiosensitization toxicities. Cutaneous reactions—including radiation recall, follicular cystic proliferation, and cutis verticis gyrata—are particularly pronounced when combined with cranial irradiation. Although whole-brain radiotherapy (WBRT) appears generally safe, concurrent use with stereotactic radiosurgery (SRS) is discouraged due to an increased risk of radionecrosis, necessitating drug discontinuation at least one week before and after treatment.[42,43] Reports of recall pneumonitis, mucosal injury, and hepatotoxicity further emphasize the need for withholding BRAF inhibitors in thoracic, mucosal, and liver irradiation settings. Similarly, VEGF and VEGFR inhibitors such as bevacizumab, sorafenib, and sunitinib pose significant risks of gastrointestinal perforation and bleeding, prompting strong recommendations against concurrent administration with RT. Treatment interruption of 5–10 days for VEGFR TKIs and 3–4 weeks for bevacizumab remains standard.[10,15] Finally, the use of cetuximab in head and neck cancer underscores the importance of timing, as concurrent chemoradiotherapy markedly increases toxicity; temporary discontinuation during the week of RT is generally advised.[7] Overall, these findings highlight that while targeted therapies can synergize with radiotherapy, rigorous patient selection and careful sequencing are essential to mitigate severe adverse effects (Table 4).

Adverse Event Management

The clinical integration of targeted therapies into oncology practice has been accompanied by a spectrum of class-specific toxicities, many of which differ from those typically observed with conventional chemotherapy. These adverse effects often reflect the molecular targets of the drugs and may also be potentiated when combined with radiotherapy. Dermatologic toxicities such as rash, pruritus, and nail changes are especially common with EGFR and MEK inhibitors, while gastrointestinal side effects, including diarrhea and mucositis, occur frequently with TKIs and mTOR inhibitors. More severe complications, such as hepatobiliary dysfunction, pulmonary pneumonitis, and cardiotoxicity, necessitate vigilant monitoring and, in some cases, treatment discontinuation. Furthermore, systemic metabolic disturbances—including diabetes, thyroid dysfunction, and hyperlipidemia—require multidisciplinary management involving endocrinology and cardiology specialists. Early recognition and proactive intervention are essential to maintaining treatment adherence, minimizing dose reductions, and optimizing both efficacy and patient quality of life (Table 5).

DISCUSSION

The concurrent use of targeted agents and immunotherapies with radiotherapy (RT) represents a rapidly evolving area in oncology, offering the potential for synergistic antitumor activity but also raising concerns regarding toxicity. Evidence derived from retrospective series, early-phase trials, and large cancer centers underscores that the interaction between systemic targeted therapies and local irradiation is highly agent-specific and influenced by treatment timing, dosing, and organ-at-risk sensitivity.

A systematic review by Kroeze et al.[44] generated consensus recommendations on combining SBRT with targeted or immunomodulatory agents. It emphasized the need for risk mitigation strategies, identifying optimal timing for drug interruption, and potential modifications in radiation dose and fractionation to ensure safety in oligometastatic patients.

Separately, ESMO and ESTRO conducted Delphi-based consensus on 207 drug–RT scenarios, achieving ≥90% agreement on most statements regarding safety profiles of various targeted agents and immunotherapies in combination with RT.[45]

CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) are associated with hematologic and gastrointestinal toxicities, which may be amplified by RT. Current data recommend cautious use, with most

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Table 4 Targeted agents used in other cancers and their compatibility with radiotherapy

Drug	Toxicities	Concurrent Use	Recommendations
BRAF inhibitors (Melanoma) - Skin	Skin toxicity: Radiation recall, Follicular cystic proliferation, Cutis verticis grata	With cranial RT, skin toxicity increases	Independent of BRAF dose, RT skin dose should be minimized. Steroids are ineffective → BRAF inhibitors must be withheld. Stop drug 3 days before and after fractionated RT.
BRAF inhibitors (Melanoma) - Cranial WBRT	–	Safe	–
BRAF inhibitors (Melanoma) - Cranial SRS	–	Not recommended	Stop drug 1 week before and after SRS. Pay special attention to exit dose. Prefer RT fraction dose <4 Gy.
BRAF inhibitors (Melanoma) - Lung RT	Toxic (recall pneumonitis)	–	–
BRAF inhibitors (Melanoma) - Mucosal RT	Toxic	–	–
BRAF inhibitors (Melanoma) - Liver RT	Toxic	–	–
VEGF/VEGFR inhibitors	GI toxicity, bleeding	Concurrent use with RT is strictly NOT recommended	Bevacizumab: stop 3–4 weeks before and after RT. Sunitinib, Sorafenib: stop 5–10 days before and after RT.
Cetuximab	Very toxic with chemo-RT	Head & neck RT: caution at SBRT doses	Withhold drug during RT week.

- BRAF inhibitors: Cranial RT requires special caution, especially with SRS due to risk of radionecrosis and skin toxicity.
- VEGF inhibitors: Strongly contraindicated with RT due to risk of GI perforation and bleeding.
- Cetuximab: Major risk with concurrent chemoradiotherapy; timing adjustment needed.

guidelines suggesting temporary interruption before and during RT, particularly when large fields or thoracic irradiation are involved.[45]

PI3K and mTOR inhibitors (alpelisib, everolimus) exhibit radiosensitizing properties that may exacerbate mucosal, gastrointestinal, and recall toxicities. Both ESTRO–ESMO and the OligoCare consortium emphasize avoiding concurrent administration, recommending a washout period of at least 1–2 weeks before RT initiation.[45]

For HER2-targeted therapies, monoclonal antibodies such as trastuzumab and pertuzumab are generally considered safe with RT, supported by the HERA and APHINITY trials. However, antibody–drug conjugates (T-DM1, T-DXd) pose significant risks of pneumonitis and radionecrosis, particularly with cranial or thoracic RT. As highlighted in the OligoCare recommendations, these agents should be avoided during RT, with particular attention to lung dose constraints.[45]

Tyrosine kinase inhibitors (lapatinib, tucatinib, neratinib) are small molecules with central nervous system penetration, which may improve intracranial control when combined with stereotactic radiosurgery (SRS). Lapatinib has been shown to be well tolerated with concurrent brain SRS, whereas safety data for newer TKIs remain limited, and guidelines suggest sequential rather than concurrent use until prospective evidence is available.[45]

PARP inhibitors (olaparib, veliparib) demonstrate potential radiosensitization, particularly in triple-negative breast cancer. However, the OligoCare consortium emphasizes caution due to overlapping gastrointestinal and hematologic toxicities. Adjuvant settings generally require treatment breaks of 2–10 weeks prior to RT.[45]

Immune checkpoint inhibitors (ICIs), including anti–PD-1/PD-L1 agents (nivolumab, pembrolizumab, atezolizumab, durvalumab) and CTLA-4 inhibitors (ipilimumab, tremelimumab), have shown encouraging synergy with RT by enhancing systemic immune activation and the abscopal effect. The PACIFIC trial established durvalumab after chemoradiotherapy as a

Table 5 Management of adverse effects associated with targeted therapies

Adverse effect	Drugs	Description	Management
Skin toxicity	EGFR inh, VEGFR inh, mTOR inh, PI3K inh	Appears in weeks 2–4, directly related to treatment response	Sun protection, avoid alcohol-based cleansers, topical hydrocortisone, oral tetracyclines
Hand–foot syndrome	BRAF inh, MEK inh	Directly related to treatment response	Steroid cream, lidocaine patch, urea/salicylic acid creams, silver sulfadiazine
Pruritus	EGFR inh, mTOR inh, ALK inh	–	Steroid cream, oral antihistamines, oral GABA inhibitors
Paronychia (nail changes)	EGFR inh, MEK inh, mTOR inh	–	Avoid trauma, topical iodine/ antibiotics, oral antibiotics (14 days)
Diarrhea	Sunitinib, Sorafenib, Gefitinib, Erlotinib, Bevacizumab, Imatinib	Ischemic mucosal injury, immune activation	Dietary advice (banana, rice, etc.), loperamide, discontinue therapy if severe/with bleeding
Mucositis	Everolimus, Sunitinib, Sorafenib	Common in first 5 days (Everolimus)	Oral care, bicarbonate gargle, steroid pastes, topical NSAIDs,analgesics, erythromycin, fluconazole
Hepatobiliary toxicity	Trastuzumab, Lapatinib, Sorafenib, Sunitinib, Gefitinib, Vemurafenib	AST/ALT elevation (independent of bilirubin)	Discontinue therapy if AST/ALT >5× upper limit
Pulmonary toxicity (Interstitial, Pneumonitis)	mTOR inh, ALK inh, Trastuzumab-DM1, Trastuzumab-DXd	Often post-RT	High-dose steroids, O_2 support, antibiotics
Diabetic adverse effects	Alpelisib, ALK inh, mTOR inh	Monitor HbA1c	Oral antidiabetic therapy, discontinue if insulin required
Hypoglycemia	Sorafenib, Sunitinib, Imatinib	Imatinib effect persists long after therapy	–
Hypothyroidism	Sunitinib, Axitinib, Cabozantinib	Consider RT field effect	Hormone replacement if TSH >4.5
Hyperlipidemia	mTOR inh, ALK inh	Monitor lipid profile	Discontinue therapy if triglycerides >500
Cardiac Toxicity	Multiple agents (very common)	Prolonged QT, hypertension, LV dysfunction	Cardiology follow-up essential
Nephrotoxicity	Cetuximab, Erlotinib, Sorafenib, Sunitinib, Gefitinib	Hypophosphatemia, hypomagnesemia, ↑creatinine	Discontinue if creatinine >3× baseline
Ocular Toxicity	EGFR inh, MEK inh	Conjunctivitis, corneal abnormalities, visual disturbances	–

- Dermatologic toxicities (skin rash, pruritus, paronychia) are common with EGFR and MEK inhibitors; early management improves compliance.
- GI toxicities (diarrhea, mucositis) are frequent with TKIs and mTOR inhibitors; dose modifications may be required.
- Hepatic and pulmonary toxicities demand close monitoring; antibody–drug conjugates and mTOR inhibitors require special caution with RT.
- Systemic effects (diabetes, hypothyroidism, hyperlipidemia, cardiotoxicity) require regular labs and specialist co-management.

standard of care in NSCLC, supporting sequential integration. Concurrent use, however, is associated with increased risk of pneumonitis and hepatic toxicity, requiring close monitoring.

The EORTC–ESTRO OligoCare consortium recognizes ICIs as the most promising systemic partners for RT in the oligometastatic setting, recommending individualized scheduling and toxicity surveillance. Concurrent administration is considered feasible in selected cases, particularly with SBRT to non-thoracic sites.[44], but careful dose planning and exclusion of high-risk patients (e.g., pre-existing autoimmune disease, prior severe pneumonitis) are essential.[45]

Clinical Recommendations

- Temporary interruption of most targeted agents during RT is recommended, especially for PI3K/mTOR inhibitors and ADCs.

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- HER2 monoclonal antibodies can generally be continued, whereas ADCs and VEGF inhibitors should be withheld.
- TKIs may be considered in combination with intracranial SRS in highly selected cases, though prospective data remain limited.
- Immunotherapy appears safe in many settings, but concurrent use should be guided by tumor site, RT technique, and prior toxicities.
- Washout intervals vary from 3–10 days for TKIs to 3–4 weeks for VEGF inhibitors, as suggested by EORTC–ESTRO and ESTRO–ESMO guidance.

CONCLUSION

The integration of targeted therapies and immunotherapies with RT offers opportunities for enhanced tumor control but requires careful multidisciplinary coordination. Recommendations from ESTRO–ESMO and the EORTC–ESTRO OligoCare consortium converge on a cautious, individualized approach, emphasizing temporary discontinuation of high-risk agents, vigilant toxicity monitoring, and prioritization of patient safety. Ongoing prospective studies will further clarify optimal sequencing strategies to balance efficacy with tolerability.

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