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(REVIEW ARTICLE)

Navigating the New Frontier: Combining Radiotherapy and New Systemic Therapies in Breast Cancer

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Abstract

The revolution in targeted systemic therapies and immunotherapy has profoundly changed the management of breast cancer, raising major questions regarding their safe combination with radiotherapy.

We conducted a narrative literature review aiming to provide a critical and hierarchical analysis of current recommendations, including the 2024 international ESTRO consensus, by contextualizing them within the broader scientific landscape. The results, presented by therapeutic class, are illustrated with summary tables and a proposed decision-making algorithm.

The discussion addresses clinical and translational challenges, including potential biological interactions, the importance of pharmacokinetics, and the crucial need for predictive biomarkers. We conclude that the integration of radiotherapy and systemic treatment must evolve from an empirical and cautious approach towards a personalized strategy, guided by mechanistic understanding and robust prospective data, within the framework of strengthened multidisciplinary collaboration.

Keywords: Breast Cancer; Radiotherapy; Targeted Therapies; Immunotherapy; Interactions; Toxicity; ESTRO Consensus; Personalized Medicine

1. Introduction

The last decade has been marked by a paradigm shift in breast cancer treatment, with the advent of a multitude of targeted systemic agents. From CDK4/6 inhibitors to revolutionary antibody-drug conjugates (ADCs) like trastuzumab deruxtecan, and immunotherapy in triple-negative breast cancer, these therapies have significantly improved prognoses, even at metastatic stages [1-3]. Concurrently, radiotherapy, a cornerstone of locoregional treatment, has seen its own advances with the widespread adoption of high-precision techniques such as stereotactic radiotherapy and hypofractionation, enabling dose escalation while sparing healthy tissues. These technical advancements equally demand rigorous documentation of radiotherapy parameters, including precise target volume delineation and standardized reporting of planning and outcomes, to enable reliable evaluation of interactions with new systemic therapies [4].

This combination could indeed potentiate the antitumor effect via synergistic mechanisms, such as disruption of DNA repair, modulation of the tumor microenvironment, or triggering of an abscopal immune response [5, 6]. However, these same interactions could also exacerbate tissue toxicity, leading to serious or unexpected adverse effects, particularly pulmonary, cutaneous, cardiac, or neurological.

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Faced with this rapidly changing landscape and the initial scarcity of specific data, the multidisciplinary oncology community had an urgent need for guidance. It was in this context that the international consensus of the European Society for Radiotherapy and Oncology (ESTRO), published in 2024, was developed, aiming to establish practical recommendations for the safe integration of radiotherapy with new systemic therapies [7]. This narrative review aims to synthesize and discuss the recommendations of the 2024 international ESTRO consensus on the combination of radiotherapy with modern systemic therapies in breast cancer, contextualizing them in relation to the literature data.

2. Methods

This narrative review is based on a critical analysis of the scientific literature concerning the combination of radiotherapy and new systemic therapies in breast cancer. Our analysis was structured around two main pillars:

1) the 2024 international ESTRO consensus [7], which served as the foundational reference and primary framework for this synthesis, and 2) the published scientific studies upon which this consensus is based, as well as relevant literature published thereafter.

To systematically identify relevant data, a bibliographic search was conducted in the PubMed and Scopus databases up to December 2025. The search strategy combined keywords and MeSH terms related to "breast cancer", "radiotherapy", and the relevant drug classes (e.g., "CDK4/6 inhibitors", "PI3K/mTOR inhibitors", "anti-HER2 therapies", "antibody-drug conjugates", "PARP inhibitors", "immunotherapy"). Searches were limited to studies published in English or French.

Titles and abstracts of retrieved records were screened for relevance. Full-text articles of selected studies were then reviewed. We included pivotal clinical trials, key observational studies, meta-analyses, and other relevant reviews that informed the safety, efficacy, or mechanistic insights into combining radiotherapy with modern systemic agents in breast cancer. Our objective is to present a clear and up-to-date synthesis, integrating authoritative guideline recommendations with the latest concrete evidence from the literature.

Table 1 Documentary sources and the objective of their analysis in this review.

Source Category	Examples/Justification	Objective of analysis in this review
Consensus Document	Meattini et al. 2024 [7]	Understand and synthesize hierarchical recommendations.
Foundational Reviews and Meta-analyses	Becherini et al. 2023 [8], Salvestrini et al. 2023 [9]	Contextualize recommendations by examining the evidence supporting them.
Pivotal Clinical Trials	e.g.,MonarchE [10], NATALEE [11], KATHERINE [12]	Evaluate the primary database at the origin of the consensus.
Recent Complementary Literature	Recently published studies [13-15]	Integrate emerging data published after the consensus for an updated perspective.

3. Results: Critical Synthesis of Recommendations by Therapeutic Class

Recommendations vary considerably from one class to another, reflecting the diversity of mechanisms of action, toxicity profiles, and the quantity of available data.

3.1. CDK4/6 Inhibitors: An Encouraging Safety Profile but a Lack of Adjuvant Data

CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) have become the standard first- or second-line treatment for patients with hormone receptor-positive, HER2-negative metastatic breast cancer, demonstrating superior efficacy to hormone therapy alone [16]. Their integration into the therapeutic strategy, including in the adjuvant setting for high-risk disease [10, 11], poses a major practical question: their compatibility with concurrent radiotherapy. A critical analysis of the available literature reveals a substantial gap between common clinical practice and evidence from controlled trials.

A Data Gap from Pivotal Trials: It is crucial to note that the foundational phase III trials systematically excluded the concomitant administration of radiotherapy [10]. Protocols stipulated either prior completion of irradiation or

interruption of systemic treatment if radiotherapy was needed. This methodological exclusion leaves the clinical community without evidence-based guidance of high-level evidence, forcing empirical decisions. This critical point perfectly illustrates the gap between the rapid diffusion of a systemic therapy and the generation of combinatorial safety data.

Limited but Reassuring Retrospective Data: To fill this gap, a systematic review and meta-analysis [8] aggregated results from 11 retrospective studies, including 382 patients treated in a metastatic setting. Its conclusions, although drawn from low-level evidence data, are nonetheless informative. They indicate an overall acceptable tolerability profile for the combination, similar to that of the pivotal trials. The predominant toxicity remains hematological (14% grade ≥3 events), reflecting the known effect of CDK4/6 inhibitors, without significant increase in severe non-hematological radiation toxicities (3%). The alarming signal of increased interstitial pneumonitis is not confirmed [8]. To confirm this trend, a recent retrospective study specifically focusing on the combination of ribociclib and palliative radiotherapy also reported a favorable safety profile, without a significant increase in grade ≥3 toxicities compared to radiotherapy alone, confirming these observations [13].

Recommendations Reflecting Uncertainty: The resulting consensus recommendations clearly reveal persistent gray areas. The ESTRO consensus [7] notes acceptable tolerability during concomitant administration with extracranial palliative radiotherapy (Recommendation 1c, level B). Maximum caution is advised for scenarios where the consequences of synergistic toxicity would be severe: locoregional adjuvant radiotherapy and brain irradiation (whole brain or stereotactic) should only be combined with CDK4/6 inhibitors within the framework of clinical trials or prospective registry cohorts (Recommendation 1a and 1b, level A) [7]. Conversely, for palliative or ablative extracranial radiotherapy, the "real-world" data and the meta-analysis reinforce the consensus recommendation for possible use in the extracranial palliative context [7].

Ultimately, the combination of CDK4/6 inhibitors and radiotherapy constitutes a field not widely explored by regulatory trials, leaving a gap between real-world use and scientific evidence. The available observational data, although not robust, offer a first reassuring framework, particularly in the metastatic palliative context. However, this practice still largely relies on extrapolations. The validation of its safety and the optimization of its modalities, especially in the adjuvant setting, urgently require prospective data. Ongoing trials are therefore not only awaited but essential to support a now widespread but still insufficiently documented practice.

3.2. Anti-HER2 (non-ADC): A Well-Established Combination with Some Nuances

The practice of administering anti-HER2 treatments and radiotherapy simultaneously has become common. Accumulated evidence, drawn from pivotal clinical trials and observational studies, is largely favorable and has allowed for the formalization of guidelines.

- ***Trastuzumab and Pertuzumab:*** The combination of trastuzumab with adjuvant breast irradiation shows an acceptable safety profile in various studies, without notable aggravation of short- or long-term cardiac adverse events, and with mild and transient skin and esophageal reactions [17]. Long-term follow-up of the HERA study (median 11 years) indicates that breast radiotherapy, whether left or right-sided, has no significant impact on left ventricular function or cardiovascular events under trastuzumab [18]. In the APHINITY trial, the addition of pertuzumab to the adjuvant regimen including trastuzumab and radiotherapy did not generate a specific signal of cardiotoxicity [19]. For the management of brain metastases, the simultaneous administration of these antibodies with whole brain irradiation or stereotactic radiotherapy is also well tolerated [6].
- ***Tyrosine Kinase Inhibitors: Lapatinib:*** During the ALLTO and NeoALLTO trials, lapatinib was given concurrently with locoregional radiotherapy. An increased incidence of skin effects (rash) was noted with lapatinib, but this side effect is inherent to it and not attributable to the associated radiotherapy [20,21]. A systematic analysis reports that adding lapatinib to stereotactic radiotherapy for brain metastases may improve local control and survival while decreasing the risk of post-radiation necrosis compared to stereotactic radiotherapy alone [22].
- ***New Tyrosine Kinase Inhibitors (e.g., Tucatinib):*** Knowledge regarding their concomitant use remains fragmentary. The protocol of the HER2 CLIMB study mandated a temporary suspension of tucatinib: interruption one week before irradiation, resumption at least 7 days after stereotactic radiotherapy or 21 days after whole brain irradiation. A prospective evaluation of the potential synergistic effects of this combination remains necessary. [23].

3.3. Synthesis of Recommendations

- Trastuzumab/Pertuzumab + Locoregional Breast Radiotherapy: A validated option [I, A] (Unanimous consensus: 100%).
- Trastuzumab/Pertuzumab + Brain Radiotherapy: A possible option [IV, B] (Strong consensus: 97.5%).
- Lapatinib + Locoregional Breast Radiotherapy: Safe combination [II, B] (Consensus: 85%).
- Lapatinib + Brain Radiotherapy: Possible combination [II, B] (Consensus: 87.5%).
- New TKIs (Neratinib, Tucatinib) + Radiotherapy: To be evaluated in dedicated studies [V, C] (Strong consensus: 97.5%).

It is deduced that the concomitant administration of trastuzumab and pertuzumab with radiotherapy (whether breast or brain) is recognized as safe and does not require dose modifications. The combination with lapatinib is also considered acceptable, despite its characteristic skin toxicity. For the newest tyrosine kinase inhibitors like tucatinib, additional data are needed to optimize treatment sequences and identify potential synergistic effects.

3.4. Antibody-Drug Conjugates (ADC): The T-DM1 Safety Paradox

Regarding trastuzumab emtansine (T-DM1): The phase 3 KAITLIN study [24] allowed the use of T-DM1 with pertuzumab in combination with postoperative breast radiotherapy. No excess specific pulmonary toxicity was observed, and patient-reported outcomes were similar to those in the trastuzumab plus pertuzumab group without radiotherapy. In the KATHERINE trial [12], the incidence of acute skin toxicity and radiation pneumonitis was overall low for both T-DM1 and trastuzumab. However, a numerical trend suggested a potential increase in radiation pneumonitis with T-DM1 (1.5% vs. 0.7% with trastuzumab). The ATEMPT trial [25] observed a non-significant increase in grade 2 or higher skin toxicity with the T-DM1/radiotherapy combination compared to trastuzumab/radiotherapy, with a similar rate of pneumonitis. Other smaller studies have shown consistent results, indicating that the use of T-DM1 is relatively safe during adjuvant breast radiotherapy [24,26]. In contrast, the combination of T-DM1 with stereotactic radiotherapy significantly increases the risk of late symptomatic radiation-induced necrosis compared to radiotherapy alone [27]. Data are currently insufficient to assess the safety of its combination with whole brain radiotherapy or extracranial palliative radiotherapy.

These findings are synthesized in the ESTRO recommendations [7], which indicate that T-DM1 could be considered during adjuvant locoregional radiotherapy for breast cancer [II, B] (Strong consensus: 92.5%), but should not be proposed in combination with whole brain radiotherapy or ablative intracranial radiosurgery [IV, D] (Strong consensus: 90%).

3.5. Regarding new antibody-drug conjugates

- ***For trastuzumab deruxtecan (T-DXd),*** the DESTINY-BREAST03 trial allowed concomitant palliative radiotherapy (excluding the lung region), without any adverse event specifically linked to this combination (notably an increased risk of interstitial lung disease) being reported [28]. These data are complemented by a recent retrospective study of 33 patients treated with T-DXd and concomitant radiotherapy, reporting an acceptable tolerability profile [14].
- ***For sacituzumab govitecan***, the ASCENT trial did not include a specific analysis on concomitant radiotherapy, leaving a lack of safety data regarding this combination [29].

In line with these still limited data, the ESTRO recommendations specify that new ADCs (such as trastuzumab deruxtecan) should be investigated within the framework of clinical trials or prospective registry cohorts [V, C] (Unanimous consensus: 100%).

3.6. PARP Inhibitors and Immunotherapy:

PARP Inhibitors: Data on the concomitant combination of PARP inhibitors and radiotherapy in breast cancer remain preliminary.
Non-metastatic setting: The phase 1 TBCRC 024 trial evaluated veliparib with adjuvant radiotherapy in patients with inflammatory or locally recurrent breast cancer. It reported a high rate of severe late toxicity, notably fibrosis within the radiation field in 40% of patients at 3 years [30].

The phase 1 RADIOPARP trial studied olaparib concurrent with radiotherapy for triple-negative breast cancers with residual disease. At 2 years of follow-up, no grade ≥3 treatment-related toxicity (cardiac, pulmonary, gastrointestinal)

was reported, indicating an initially favorable safety profile. An isolated case of grade 4 thrombocytopenia occurred at 1 year under subsequent chemotherapy [31].

The phase 3 OlympiA trial, which demonstrated the benefit of adjuvant olaparib, specifically required radiotherapy to be completed between 2 and 12 weeks before inclusion, thus avoiding concomitant administration [32]. Metastatic setting (notably cerebral): A phase 1 study evaluated veliparib concurrent with whole brain radiotherapy for brain metastases (including breast cancers). The addition of veliparib did not reveal unexpected acute toxicity compared to radiotherapy alone [33].

Synthesis and Consensus Recommendations:

Despite apparent acute tolerability, long-term data are scarce and no significant clinical benefit has been clearly demonstrated for this combination. Consequently, current recommendations [7], based on strong consensus, are cautious:

The combination should be investigated within the framework of clinical trials or prospective cohorts for primary, adjuvant, and metastatic breast cancers [II, A] (Strong consensus: 97.5%).

It should not be proposed routinely for advanced breast cancer outside of clinical trials [II, D] (Consensus: 80%). Although some combinations seem feasible in the short term (notably olaparib), the potential risk of severe late toxicities (as observed with veliparib) and the lack of proven benefit impose a rigorous and experimental approach. Further research is needed to define the place of this strategy.

Immunotherapy: Immunotherapy is a cornerstone of treatment for triple-negative breast cancer, validated by major trials like KEYNOTE-522 [34], IMPASSION-130 [35], and KEYNOTE-355 [36]. Despite an initial lack of data, the safety of its combination with radiotherapy is increasingly supported.

KEYNOTE-522 (neoadjuvant/adjuvant): After amendment, the concomitant administration of pembrolizumab and postoperative radiotherapy was authorized. The combination proved well-tolerated and showed a benefit in event-free survival [34]. A recent analysis notes a slight increase in rates of pneumonitis and grade ≥3 skin toxicity compared to placebo [37].

Palliative/advanced setting: Several small studies and data from other solid cancers support the safety of the combination, even with ultrahypofractionated stereotactic radiotherapy schedules [38,39].

Consensus Recommendations: The combination can be considered during locoregional breast radiotherapy [II, B].

It can be proposed for advanced breast cancer, including with stereotactic radiotherapy schedules [II, B].

Although additional data are useful to optimize parameters (timing, dose), current evidence supports the safety and feasibility of the concomitant immunotherapy-radiotherapy combination in breast cancer, leading to favorable recommendations.

3.7. PI3K/AKT/mTOR Inhibitors: A Combination Advised Against Given Current Knowledge

For these two therapeutic classes, safety data for concomitant combination with radiotherapy are extremely limited, if not absent. The pivotal trials (SOLAR-1 [40], BYLieve [41], BOLERO-2 [42]) systematically excluded patients with recent radiotherapy.

In the complete absence of studies specifically evaluating the tolerability of these combinations, and considering the strict exclusion criteria of the trials that demonstrated their efficacy as monotherapy or with hormone therapy, the recommended practice is sequential administration. Radiotherapy and these signaling pathway inhibitors should not be administered concomitantly outside of research protocols specifically designed for this purpose [7]. Future studies are needed to assess any potential interaction, beneficial or toxic.

Table 2 Synthesis of ESTRO 2024 consensus by Therapeutic Class

Therapeutic Class	Scenario / Type of Radiotherapy	ESTRO Recommendation	Level of Evidence & Consensus	Primary Justification (according to consensus)
1. CDK4/6 Inhibitors	Adjuvant locoregional RT	Should be investigated within clinical trials or prospective cohorts.	[V, A] Unanimous consensus (100%)	Absence of specific data in this context. Need for prospective evidence.
	Brain RT (whole or stereotactic)	Should be investigated within clinical trials or prospective cohorts.	[IV, A] Strong consensus (92.5%)	Absence of specific data in this context. Need for prospective evidence.
	Palliative or ablative extracranial RT	Could be proposed.	[IV, B] Strong consensus (90%)	Safety profile considered acceptable in this context, based on existing data.
2. PIK3 Inhibitors	Concomitant RT (all situations)	Should NOT be proposed.	[V, D] Strong consensus (90%)	Absence of safety data. Advised against given current knowledge.
3. mTOR Inhibitors	Concomitant RT (all situations)	Should NOT be proposed.	[V, C] Strong consensus (95%)	Absence of safety data. Advised against given current knowledge.
4. Anti-HER2 (non-ADC)	Trastuzumab/Pertuzumab + Locoregional breast RT	Could be proposed.	[I, A] Unanimous consensus (100%)	Option validated by robust data and strong consensus on its safety.
	Trastuzumab/Pertuzumab + Brain RT	Could be proposed.	[IV, B] Strong consensus (97.5%)	Favorable tolerability data in brain metastases.
	Lapatinib + Locoregional breast RT	Safe combination.	[II, B] Consensus (85%)	Acceptable safety profile established, with known and manageable skin toxicity.
	Lapatinib + Brain RT	Could be proposed.	[II, B] Consensus (87.5%)	Data suggesting a possible association with potential benefit.
	New TKIs (e.g., Tucatinib) + RT	Should be investigated within clinical trials.	[V, C] Strong consensus (97.5%)	Fragmentary data. Urgent need for prospective evaluations.
5. Antibody-Drug Conjugates (ADC)	T-DM1 + Adjuvant breast RT	Could be considered.	[II, B] Strong consensus (92.5%)	Acceptable safety reported in the extracranial context.
	T-DM1 + Brain RT (whole or stereotactic)	Should NOT be proposed.	[IV, D] Strong consensus (90%)	Increased risk of symptomatic radiation-induced necrosis. Contraindicated.
	New ADCs (e.g., Trastuzumab Deruxtecan) + RT	Should be investigated within clinical trials.	[V, C] Unanimous	Preliminary/limited data. Need to generate safety evidence.

			consensus (100%)	
6. PARP Inhibitors	Concomitant RT (primary, adjuvant, metastatic)	Should be investigated within clinical trials.	[II, A] Strong consensus (97.5%)	Limited and conflicting data. No clear benefit demonstrated. Need for research.
	Concomitant RT for advanced cancer	Should NOT be proposed routinely outside trials.	[II, D] Consensus (80%)	Precautionary principle in the face of lack of evidence for long-term safety and benefit.
7. Immunotherapy	Locoregional breast RT	Could be considered.	[II, B] Strong consensus (95%)	Safety established in pivotal trials (e.g., KEYNOTE-522).
	RT for advanced cancer (including stereotactic)	Could be offered.	[II, B] Strong consensus (92.5%)	Favorable safety data, including with ultrahypofractionated schedules.

4. Discussion

The ESTRO 2024 consensus [7] fills a critical void by offering the first structured roadmap for the combination of radiotherapy and new systemic therapies in breast cancer. Its analysis reveals a contrasting therapeutic landscape, where the level of recommendation directly reflects the maturity of clinical data.

On one side, some combinations already seem robust and without major danger, such as the combination of radiotherapy with trastuzumab/pertuzumab or, to a lesser extent, with immunotherapy for triple-negative cancers. At the other extreme, combinations with PI3K/AKT/mTOR inhibitors or ADCs like T-DM1 in an intracranial context are clearly advised against, either due to a total lack of data or because of a signal of severe toxicity.

Between these two poles, a substantial "gray zone" emerges, illustrated by CDK4/6 inhibitors and new ADCs. For these classes, concomitant practice, notably palliative, is already widespread, supported by reassuring observational data, even though pivotal trials systematically excluded them. This paradox highlights the inevitable gap between the rapid innovation of systemic treatments and the slower generation of evidence on their locoregional interactions. The cautious consensus recommendations – "to be investigated" or "can be considered" – for these therapies reflect this uncertainty and argue for a nuanced approach, based on an individual benefit/risk assessment and a preference for sequential administration when possible.

Beyond the hierarchical classification by class, this consensus highlights several persistent cross-cutting challenges: the chronic lack of dedicated prospective data, the necessity for long-term monitoring of late toxicities (notably pulmonary, cardiac, and radiation necrosis), and the crucial importance of multidisciplinary communication to adapt therapeutic sequences.

5. Conclusion

The ESTRO 2024 consensus reveals a critical gap between rapid pharmacological innovation and the limited scientific evidence concerning its combination with radiotherapy in breast cancer. While some combinations are validated or advised against, many common practices still rely on fragile data, creating risky "gray zones." This document calls for a rigorous and humble approach, transforming the therapeutic decision from a sometimes empirical act into an informed strategic choice. It emphasizes the urgency of conducting prospective studies to master synergies and fully exploit, and in complete safety, the potential of these multimodal associations. Optimal integration will require targeted collaborative research and strengthened multidisciplinary decision-making, guiding the transition from a cautious practice to truly personalized medicine.

Compliance with ethical standards

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The authors declare no competing interests

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Author contributions

- All authors contributed to the conception, literature search, analysis, and manuscript drafting.
- All authors approved the final manuscript.

Data availability

All data are contained within the article and its references.

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