International multidisciplinary consensus on the integration of radiotherapy with new systemic treatments for breast cancer: European Society for Radiotherapy and Oncology (ESTRO)-endorsed recommendations

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Novel systemic therapies for breast cancer are being rapidly implemented into clinical practice. These drugs often have different mechanisms of action and side-effect profiles compared with traditional chemotherapy. Underpinning practice-changing clinical trials focused on the systemic therapies under investigation, thus there are sparse data available on radiotherapy. Integration of these new systemic therapies with radiotherapy is therefore challenging. Given this rapid, transformative change in breast cancer multimodal management, the multidisciplinary community must unite to ensure optimal, safe, and equitable treatment for all patients. The aim of this collaborative group of radiation, clinical, and medical oncologists, basic and translational scientists, and patient advocates was to: scope, synthesise, and summarise the literature on integrating novel drugs with radiotherapy for breast cancer; produce consensus statements on drug–radiotherapy integration, where specific evidence is lacking; and make best-practice recommendations for recording of radiotherapy data and quality assurance for subsequent studies testing novel drugs.

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Introduction

In the last 15 years, there have been substantial advances in the treatment of patients with breast cancer, with the introduction of novel anticancer drugs and other anticancer drugs in late stages of clinical development.[1–4] Targeted therapies in particular, such as antibody–drug conjugates and immunotherapy agents, have shown positive results within clinical trials and are now becoming a standard of care in breast cancer management globally.[3,4] The use of innovative preclinical models has been instrumental in identifying tumour targets and expediting the development of effective anticancer drugs. These preclinical models have led to a reduced time lag between preclinical discoveries and their clinical application, allowing for immediate relevance and applicability in breast cancer care. The availability of new systemic therapies has sparked an important discussion on how to effectively and safely integrate targeted drugs with local treatments, especially radiotherapy, in both curative and advanced breast cancer settings.[5,6]

Targeted drugs have a profound impact on various aspects of tumour biology, the tumour microenvironment, and cellular energetics, which can influence treatment outcomes following radiotherapy.[7] Although the potential for a synergistic effect exists, understanding the mechanistic effects, biodistribution, and pharmacokinetics of these new drugs is essential for optimising their combination with radiotherapy and establishing the most effective and safe approaches. One of the main challenges in extracting meaningful insights from current clinical data is the heterogeneity in radiotherapy target, dose, and fractionation prescriptions, particularly in the context of advanced disease. Furthermore, pivotal registration trials to evaluate new drugs often have little or no comprehensive quality assurance in radiotherapy and properly reported dosimetry data. In many cases, concurrent radiotherapy with targeted drugs is an exclusion criterion during trial therapy.[5]

The objective of this consensus is to present a comprehensive assessment of preclinical and clinical evidence regarding the integration of targeted drugs with radiotherapy for the optimal treatment of patients with breast cancer. The consensus recommendations, endorsed by the European Society for Radiotherapy and Oncology (ESTRO), aim to facilitate the widespread adoption of high-quality breast radiotherapy in clinical settings.

Methods

Consensus development process

The consensus statements were developed by a multidisciplinary writing committee (appendix pp 3–4), consisting of a core group and an expert panel of healthcare professionals from various fields (such as radiation and clinical oncologists, medical oncologists, radiobiologists, and translational researchers), a patient advocate, and representatives from the ESTRO guidelines committee. The writing committee conducted meetings via webinars and communicated through emails to carefully assess the available evidence and contribute to consensus development. The core group oversaw the preparatory and finalisation work, including key-topics identification, methodology, definition of critical or systematic literature needs, work-group identification, acquisition of level of evidence, identification of key statements, and the establishment of a (modified) Delphi consensus procedure.[8] The expert panel were selected and approved by the project coordinators and the ESTRO

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guidelines committee to ensure appropriate gender, profession, and country balance. The expert panel participated in the consensus-defining panel meeting, voting, and finalising and approving of the statements.

Modified Delphi process

The consensus statements were collected in a dedicated survey and presented using the online survey tool, Google Form. The survey ensured participant anonymity, allowing for confidential responses. A 5-point Likert scale was used, ranging from very low (1) to very high (5), to gauge participant agreement with each statement.[8] To achieve consensus, a threshold offset of at least 75% agreement was required. Consensus was categorised as: 100%, unanimous support; 90–99%, strong support; and 75–89%, support. Statements that achieved consensus (at least 75% support) in the first voting round (Delphi round 1) were excluded from further consideration. After considering suggestions provided by the panel, participants then voted again on the items that did not reach at least 75% agreement (Delphi round 2). Any statement that still did not reach a consensus after the second voting round was excluded. The consensus was established by combining all the statements that received support throughout first and second rounds of the survey process. During this phase of first and second voting rounds, only minor modifications to grammar and wording were accepted. The consensus-based guidance workflow is summarised in the figure.

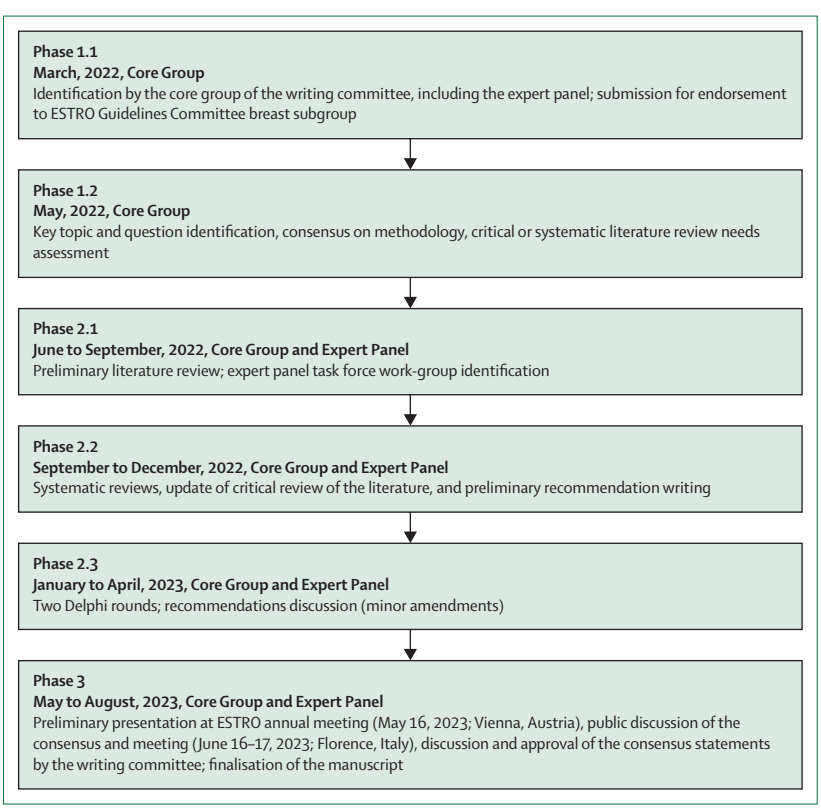

Figure: **Consensus-based guidance workflow based on the modified Delphi process**
The writing committee included Core Group and Expert Panel members. ESTRO=European Society for Radiotherapy and Oncology

Search strategy and selection criteria

A previously published critical review provided a comprehensive evaluation of the existing preclinical and clinical evidence on the combination of radiotherapy and targeted drugs for breast cancer.[8] This review served as the foundation for the development of this consensus recommendation project. The literature search for this systematic review was conducted in three phases. In the first phase, a comprehensive search was performed in PubMed and EMBASE databases for each drug category, including CDK4 and CDK6 inhibitors, PI3K ormTOR inhibitors, anti-HER2 drugs (non-antibody–drug conjugates), antibody–drug conjugate drugs, PARP inhibitors, and immunotherapies. The search followed the PRISMA guidelines, and all relevant systematic reviews within each subgroup were analysed.[9] The quality of the included systematic reviews was assessed using the AMSTAR2 tool to evaluate the risk of bias.[10] Additionally, the preclinical working group screened a series of integrative studies on the combinatory administration of radiotherapy with targeted drugs (appendix pp 5–9). In the second phase, the search results were presented to the expert panel to determine whether there was a need for additional systematic reviews on any missing topics. Finally, in the third phase, two identified new systematic reviews were conducted and published specifically focusing on CDK4/6 inhibitors[11] and the antibody–drug conjugate trastuzumab emtansine (T-DM1)[12] in combination with radiotherapy. The search strategy was implemented in accordance with PRISMA to search PubMed, MEDLINE, Embase, and Cochrane literature databases, and restricted to English language publications. For the T-DM1 systematic review, between January, 2010, and September, 2022, a specific research string based on the following keywords was developed: “breast” or “mammary” or “breast cancer” or “breast neoplas*”, “radiotherapy”, “irradiation”, “radiation”, “radio-therapy”, “concurrent*”, “concomitant*”, “combin*”, “associat*”, “simultaneous*”, “trastuzumab DM1”, “T-DM1”, “trastuzumab emtansine”, “trastuzumab-DM1”, “huN901-DM1”, “huN901 DM1”, and “huN901DM1”. For the CDK4/6 inhibitors systematic review, between Jan 1, 2000, and Nov 1, 2022, a specific research string based on the following keywords was developed: “breast” or “mammary” or “breast cancer” or “breast neoplas*”, “radiotherapy”, “irradiation”, “radiation”, “radio-therapy”, “concurrent*”, “concomitant*”, “combin*”, “associat*”, “simultaneous*”, “cyclin-dependent kinase 4/6 inhibitor”, “palbociclib”, “ribociclib”, and “abemaciclib”. Keywords used were “breast cancer”, “radiotherapy”, “concurrent”, “cyclin-dependent kinase 4/6 inhibitor”, “palbociclib”, “ribociclib”, and “abemaciclib”.

Key topics and voting rounds

The core group and expert panel were requested to assess the level of evidence for key topics in the consensus recommendations. These topics included: key question 1—what are the minimum requirements for reporting radiotherapy parameters in a clinical trial to evaluate the safety of combining a targeted systemic treatment with radiotherapy for breast cancer; and key question 2—based on the current evidence, what is the safety profile of a specific new systemic treatment when used in combination with ablative or palliative radiotherapy for intracranial or extracranial sites of disease in metastatic and curative settings. The level of evidence and grade of recommendations are provided in the appendix (p 10).[13]

Results

Key question 1 is represented within a case report form (appendix pp 11–15) which focused on establishing the minimum requirements for reporting radiotherapy parameters in both early and metastatic breast cancer trials. The consensus recommendations on key quware presented in panel 1.

Key question 2 addressed the consensus recommendations on the integration of main targeted drugs with radiotherapy for breast cancer treatment (panel 2). These recommendations encompass both early and metastatic breast cancer settings, including intracranial and extracranial disease.

After the initial voting round, consensus was reached among all 40 panellists for both of the two statements pertaining to key question 1, and 14 of the 17 statements pertaining to key question 2. Following panel discussions, two additional statements were introduced for key question 1, and adjustments were made to nine of the key question 2 statements, based on suggestions from the panellists, in the lead-up to the second voting round. In the second voting round, all 40 panellists responded and consensus was achieved for all consensus recommendations. The Delphi voting agreement results, stratified by voting rounds 1 and 2, are summarised in the appendix (pp 16–18).

Panel 1: Final consensus statements on key question 1—minimum requirements of reporting radiotherapy parameters in clinical trials assessing new systemic treatments for breast cancer

1a) Long-term safety data are needed for combining new biological drugs with radiotherapy for patients with early breast cancer [V, A]
- Strong consensus (95%)

1b) When combining new systemic treatments and radiotherapy, reporting of radiotherapy parameters and toxicity is mandatory when reporting safety data in both early and advanced disease settings [V, A]
- Unanimous consensus (100%)

1c) There are few or no high-quality clinical data concerning the combination of radiotherapy and new systemic treatments for breast cancer: prospective research studies are strongly recommended to strengthen the available evidence [V, A]
- Unanimous consensus (100%)

1d) The potential risks, benefits, and uncertainties regarding the combination of radiotherapy and new systemic treatments for breast cancer should be fully discussed with the patient [V, A]
- Unanimous consensus (100%)

Levels of evidence (I–V) and grades of recommendation (A–E) have been applied using the system shown in the appendix (p 10).

Discussion: minimum requirements of reporting radiotherapy parameters in clinical trials assessing new systemic treatments for breast cancer

Radiotherapy plays a crucial role in the treatment of patients with breast cancer. In cases of non-metastatic breast cancer, radiotherapy is typically included as part of the breast conservation approach, known as breast-conserving therapy.[14] The use of radiotherapy after mastectomy is on the rise, primarily due to its proven benefits in terms of local control and breast cancer mortality, both in cases of patients who are node-positive and patients who are node-negative.[15] Additionally, there is a growing trend towards de-escalating axillary surgery by replacing it with axillary radiotherapy in some cases.[16] In instances where patients have a local recurrence following breast-conserving surgery or mastectomy, re-irradiation can be considered as a treatment option.[17]

In the early-stage setting, it is essential to establish whether radiotherapy should be administered concurrently or sequentially with each drug or strategy, exploring the potential advantages and disadvantages of each approach. Future trials should consider evaluating the timing of radiotherapy and study drugs as a preplanned exploratory endpoint, a step that will accelerate and enhance our knowledge about the process of integrating therapies.

In the case of metastatic disease, the landscape of radiotherapy has undergone substantial changes. Patients with metastatic breast cancer now have prolonged survival rates, primarily due to advancements in systemic therapies. Also, the introduction of robust and adaptive (image-guided) radiotherapy treatment planning, along with the availability of innovative radiotherapy techniques, has revolutionised the approach to treating patients with metastatic disease. Traditional palliative radiotherapy for symptom control is no longer the only option. Instead, patients with few metastases, also known as oligometastatic patients, are often treated with high-dose per fraction radiotherapy using stereotactic ablative body radiotherapy (SABR) to effectively control the metastatic lesion. These patients

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See Online for appendix

Panel 2: **Final consensus statements on key question 2—current evidence regarding the safety profile of a specific new systemic treatment when used in combination with ablative or palliative radiotherapy for intracranial or extracranial sites of disease in the metastatic and locoregional settings**

1) CDK4 or CDK6 inhibitors

1a) CDK4 or CDK6 inhibitors and concomitant radiotherapy during adjuvant locoregional radiotherapy for breast cancer should be investigated in the context of clinical trials or prospective registration cohorts [V, A]*

- Unanimous consensus (100%)

1b) CDK4 or CDK6 inhibitors and concomitant radiotherapy during whole-brain radiotherapy or intracranial stereotactic radiotherapy should be investigated in the context of clinical trials or prospective registration cohorts [IV, A]

- Strong consensus (92·5%)

1c) CDK4 or CDK6 inhibitors and concomitant radiotherapy could be offered during palliative and ablative extracranial radiotherapy [IV, B]

- Strong consensus (90%)

2) PIK3 inhibitors

2a) PIK3 inhibitors and concomitant radiotherapy should not be offered [V, D]†

- Strong consensus (90%)

3) mTOR inhibitors

3a) mTOR inhibitors and concomitant radiotherapy should not be offered [V, C]†

- Strong consensus (95%)

4) Anti-HER-2 drugs (non-antibody–drug conjugates)

4a) Trastuzumab or pertuzumab and concomitant radiotherapy could be offered during locoregional radiotherapy for breast cancer [I, A]

- Unanimous consensus (100%)

4b) Trastuzumab or pertuzumab and concomitant radiotherapy could be offered during whole brain and ablative intracranial stereotactic radiotherapy [IV, B]

- Strong consensus (97·5%)

4c) Lapatinib and concomitant radiotherapy during locoregional radiotherapy for breast cancer is safe [II, B]‡

- Consensus (85%)

4d) Lapatinib and concomitant radiotherapy could be offered during whole brain and ablative intracranial stereotactic radiotherapy [II, B]

- Consensus (87·5%)

4e) Newer tyrosine kinase inhibitors (ie, neratinib, tucatinib) and concomitant radiotherapy should be investigated in the context of clinical trials or prospective registration cohorts [V, C]†

- Strong consensus (97·5%)

5) Antibody–drug conjugates

5a) Trastuzumab emtansine (T-DM1) and concomitant radiotherapy might be considered during adjuvant locoregional radiotherapy for breast cancer [II, B]

- Strong consensus (92·5%)

5b) T-DM1 and concomitant radiotherapy should not be offered for whole-brain and ablative intracranial stereotactic radiotherapy [IV, D]

- Strong consensus (90%)

5c) Newer antibody–drug-conjugates (ie, trastuzumab deruxtecan) and concomitant radiotherapy should be investigated in the context of clinical trials or prospective registration cohorts [V, C]†

- Unanimous consensus (100%)

6) PARP inhibitors

6a) PARP inhibitors and concomitant radiotherapy for primary, adjuvant, and metastatic breast cancer settings should be investigated in the context of clinical trials or prospective registration cohorts [II, A]

- Strong consensus (97·5%)

6b) PARP inhibitors and concomitant radiotherapy should not be offered for advanced breast cancer outside clinical trials [II, D]§

- Consensus (80%)

7) Immunotherapy

7a) Immunotherapy and concomitant radiotherapy could be considered during locoregional radiotherapy for breast cancer [II, B]

- Strong consensus (95%)

7b) Immunotherapy and concomitant radiotherapy including ultra hypofractionated regimens used for stereotactic radiotherapy could be offered for advanced breast cancer [II, B]¶

- Strong consensus (92·5%)

Levels of evidence (I–V) and grades of recommendation (A–E) have been applied using the system shown in the appendix (p 10). *No safety report for concomitant CDK4 or CDK6 inhibitors with postoperative locoregional radiotherapy for breast cancer; data derived from metastatic setting. †Currently, there is no clear evidence on the safety of combined treatment with these inhibitors in both metastatic and non-metastatic settings. ‡Lapatinib is not approved in the early breast cancer setting. §Safety data for PARP inhibitors and concomitant radiotherapy are scarce; few data are available in the metastatic setting. ¶Data derived from other solid organ tumours.

are often treated with curative intent, since they have the potential for improved survival, even in cases of brain metastases.[18,19]

Given the evolving landscape of systemic therapy for breast cancer, it is essential to prioritise proper documentation of radiotherapy, including accurate target volumes delineation and reporting on radiotherapy planning and outcomes, using a well defined, internationally recognised format.[20] With the introduction of new systemic therapies, the possibility of different types of toxicity when combined with radiotherapy might lead to the discontinuation of systemic therapy during

radiotherapy, potentially lowering the systemic control or the adaptive and synergistic effects on local control (appendix pp 19–20). Most pivotal trials that are testing new systemic therapies have adopted a conservative approach, avoiding concomitant treatment with radiotherapy. However, we recommend that, in cases with a strong biological and therapeutic rationale, studies involving combinations with radiotherapy should be considered as part of the design for early-phase studies in patients.

The half-life model is based on theoretical pharmacokinetic parameters. Particularly in situations involving drug toxicity, it can be challenging to implement this model in practice and use it as a tool for clinical decision making.[21] Approximately 94–97% of a drug is eliminated after four to five half-lives. Consequently, beyond this time frame, the plasma concentration of a given drug would fall below a clinically relevant concentration and be considered eliminated.[22] The plasma elimination half-lives of the main new systemic therapies for breast cancer treatment and the minimum wash out drug interval adopted in main pivotal trials are summarised in the appendix (p 21). We strongly recommend that trials evaluating new targeted drugs include radiotherapy quality assurance data in their reporting to enable further analysis of potential toxicity resulting from the interaction between the radiotherapy and systemic treatment modalities. Careful collection of granular data on radiotherapy doses, fractions, durations, and sites, patient characteristics, and immediate and delayed side-effects of the treatment combination is of utmost importance.

Discussion: safety profiles of drugs in combination with radiotherapy

CDK4/6 inhibitors with radiotherapy

CDK4/6 inhibitors have become the standard of care for first-line or second-line treatment in patients with hormone receptor positive or HER2 (also known as ERBB2)-negative metastatic breast cancer, showing improved efficacy compared with endocrine therapy alone.[23] Furthermore, both abemaciclib and ribociclib have shown a significant improvement in invasive disease-free survival among patients with early-stage high-risk disease.[24,25]

Unfortunately, we found no information regarding concurrent radiotherapy in the adjuvant setting; in all the published phase 3 trials, adjuvant radiotherapy should have been completed before patients entered the study, and if a patient required radiotherapy during the active treatment phase they were discontinued from the treatment and entered the follow-up phase.[24–27] A short-term follow-up analysis of patient-reported outcomes from the MonarchE trial found a similar rate of radiation pneumonitis in patients previously treated with radiotherapy in the two treatment arms.[28] Concurrent administration of radiotherapy with adjuvant CDK4/6 inhibitors might be an option in the future, but requires further investigation. In advanced disease, the combination of palliative radiotherapy and CDK4/6 inhibitors has only been specifically addressed in the PALOMA trials (NCT01942135 and NCT01740427, using palbociclib), in which it was recommended to temporarily suspend palbociclib for 7 days before the radiotherapy course.[29,30]

In the MONALEESA trials (NCT01958021, NCT02422615, and NCT02278120, using ribociclib), palliative radiotherapy was permitted solely for relieving bone pain, and in the MONARCH trials (NCT02107703 and NCT02246621, using abemaciclib), all patients with metastases requiring radiotherapy had to permanently discontinue therapy and undergo tumour assessment before receiving radiotherapy. Consequently, there is a shortage of information available on concomitant treatment from pivotal randomised trials.

To better understand the safety profile of combining CDK4/6 inhibitors with palliative and ablative radiotherapy for both metastatic and early breast cancer, we conducted and published a systematic review and meta-analysis of the existing literature published in English.[11] The review included 11 retrospective studies, all of which focused on the metastatic setting (appendix p 22). Most of the included studies had small sample sizes; however, the meta-analysis revealed that the side-effect profiles of drugs administered concurrently with radiotherapy is similar to those seen in the larger randomised controlled trials of CDK4/6 inhibitors in advanced breast cancer treated using sequential adjuvant radiotherapy.[29,30] The pooled proportion (weighed on a total of 382 patients) of grade 3 or worse (serious adverse event severity, NCI CTCAE version 5) haematological toxicities was 14% (95% CI 0·03–0·30), whereas the pooled proportion of grade 3 or worse non-haematological toxicities was 3% (95% CI 0·01–0·05). There is no evidence of an increased risk of interstitial lung disease. These findings suggest that the simultaneous administration of CDK4/6 inhibitors and radiotherapy is generally well tolerated, with predominantly haematological grade 3 or worse adverse events. In the European Organisation for Research and Treatment of Cancer (EORTC)-ESTRO OligoCare consortium recommendations, it was unanimously agreed that SABR should be performed for all treated organs without CDK4/6 inhibitor dose reduction, and without increasing the number of SABR fractions compared with SABR without concomitant systemic therapy.[6] Results from several ongoing trials evaluating the combination of CDK4/6 inhibitors and radiotherapy for breast cancer are expected to provide additional evidence regarding their safety (appendix p 23).

PI3K inhibitors and radiotherapy

In the clinical setting, there are few data available on the efficacy and safety of combining PI3K–AKT or mTOR signalling pathway-targeting drugs with radiotherapy, particularly in advanced breast cancer (appendix p 24). In the phase 3, randomised SOLAR-1 trial, which compared alpelisib plus fulvestrant with placebo plus fulvestrant in

patients with advanced breast cancer previously treated with endocrine therapy, the exclusion criteria included receiving radiotherapy within 4 weeks or limited-field radiotherapy for palliation within 2 weeks before randomisation.[31] Also, in the BYLieve phase 2 study, evaluating alpelisib plus fulvestrant in advanced breast cancer after a CDK4/6 inhibitor, radiotherapy within 4 weeks before randomisation was an exclusion criterion.[32]

Capivasertib, a new oral selective AKT1–3 inhibitor, combined with fulvestrant resulted in significantly longer progression-free survival than treatment with fulvestrant alone among patients with hormone receptor-positive advanced breast cancer whose disease had progressed during or after previous aromatase inhibitor therapy with or without a CDK4/6 inhibitor.[33] Radiotherapy with a wide field of radiation within 4 weeks before study treatment initiation was a main exclusion criterion for trial participation.[33] Currently, there is insufficient clear evidence regarding the safety of combining radiotherapy with PI3K–AKT inhibitors. Further studies are required to determine the optimum dosing of these drugs in combination with radiotherapy for maximum tumour response while minimising toxicity.

mTOR inhibitors and radiotherapy

Although mTOR inhibitors have demonstrated anticancer activity in various types of cancer, there is little information regarding their efficacy and safety when combined with radiotherapy, particularly in advanced breast cancer (appendix p 25). The BOLERO-2 trial, for instance, excluded patients who had received radiotherapy within 4 weeks before randomisation, except in cases where localised radiotherapy was administered for analgesic purposes or for osteolytic lesions at risk of fracture, provided it was completed within 2 weeks before randomisation.[34] Currently, there is insufficient evidence to support the safe combination of radiotherapy and mTOR inhibitors. Therefore, it is advisable to administer radiotherapy and mTOR inhibitors sequentially.

Anti-HER2 drugs (non-antibody–drug conjugates) and radiotherapy

Anti-HER2 therapies have profoundly transformed the treatment landscape for patients with HER2-positive breast cancer, leading to improved survival outcomes in both the adjuvant and metastatic settings.[5,35,36] The concomitant use of trastuzumab and postoperative breast cancer radiotherapy, both of which have the potential for cardiac toxic effects, has been studied in several retrospective cohorts in the adjuvant setting. Overall, the combination of trastuzumab and postoperative radiotherapy has shown good tolerability, with no apparent increase in acute or late cardiac toxic effects. Additionally, acute side-effects affecting the skin and oesophagus were minimal and reversible.[37–39] Prospective studies where trastuzumab might be given with radiotherapy have yielded similar results.[40–43] In the ATEMPT trial, concomitant administration of trastuzumab with postoperative whole-breast irradiation showed a low risk of pneumonitis (approximately 1% in both study groups) and generally low skin toxicity (no grade 3 or worse toxic effects in the trastuzumab group).[42] Analysis of cardiac function in the HERA trial, where trastuzumab was administered concomitantly with left-sided radiotherapy (n=1270), right-sided radiotherapy (n=1271), or no radiotherapy (n=780), revealed that radiotherapy did not significantly affect left ventricular ejection fraction or cardiovascular events at a median follow-up of 11 years.[43] In the APHINITY trial, which showed the benefit of adding pertuzumab to trastuzumab in the adjuvant setting, radiotherapy was administered concomitantly; although adverse events were not specifically analysed in relation to radiotherapy, no specific warnings or indications of increased cardiac toxic effects were reported.[44] Retrospective studies involving small cohorts have also indicated that the combination of pertuzumab and trastuzumab is safe.[45,46] For patients undergoing whole-brain radiotherapy or stereotactic radiotherapy for brain metastases, the concurrent use of trastuzumab, pertuzumab, or both has been well tolerated, with no increased risk of adverse events.[47,48] The recently published EORTC-ESTRO OligoCare recommendations on the use of targeted drugs in combination with SABR present a consensus that trastuzumab and pertuzumab can be administered concomitantly with radiotherapy, without the need for dose reduction.[6]

In the ALLTO and NeoALLTO trials, postoperative locoregional radiotherapy was administered concurrently with lapatinib tosilate, trastuzumab, or both. Although skin toxic effects were more prevalent in the lapatinib-containing treatment arms, this might not necessarily be attributable to concomitant radiotherapy, as rash is a common side-effect of lapatinib treatment, even in the absence of irradiation.[49,50] A systematic review based on retrospective studies showed that the combination of lapatinib with stereotactic radiotherapy improved local control and survival with a reduced risk of radiation-induced necrosis compared with stereotactic radiotherapy alone.[51] Scarce evidence is currently available regarding the concurrent use of other tyrosine kinase inhibitors, such as tucatinib, with radiotherapy. In the HER2 CLIMB trial,[52] in case of isolated intracranial progression without extracranial disease progression, patients were eligible to continue treatment with study drugs after completion of local treatment of brain metastases to allow for clinical benefit—however, tucatinib was to be withheld for 1 week before radiotherapy, and re-initiated 7 days or more after completion of stereotactic radiotherapy, and 21 days or more after whole brain radiotherapy. Further prospective evaluation of potential synergistic effects is warranted.

Antibody–drug conjugates and radiotherapy

The phase 3 KAITLIN study allowed the use of trastuzumab emtansine (T-DM1) with pertuzumab in combination with postoperative breast radiotherapy, although specific radiotherapy-related toxic effects were not reported.[53] No excess pulmonary toxic effects were observed, and patient-reported outcomes were similar to the trastuzumab plus pertuzumab group without radiotherapy. In the KATHERINE trial, the incidences of acute skin toxic effects and radiation pneumonitis were low for both T-DM1 and trastuzumab, although numerical values suggested a potential increase in radiation pneumonitis with T-DM1 (1·5% [11 of 740 cases] compared with 0·7% [five of 720 cases]).[54] In the ATEMPT trial (a small, non-randomised study treating 383 of 497 enrolled patients with T-DM1), a non-significant increase in grade 2 or worse skin toxic effects was observed with concurrent T-DM1 plus radiotherapy, compared with trastuzumab plus radiotherapy, and the rate of pneumonitis was similar.[42] Other smaller trials have shown consistent results, indicating that the use of T-DM1 is relatively safe during adjuvant breast radiotherapy.[55,56]

T-DM1 has been shown to cross the blood–brain barrier and to have clinical efficacy against brain metastases. However, combining T-DM1 with stereotactic radiotherapy substantially increases the risk of later symptomatic radiation-induced necrosis compared with radiotherapy alone.[57–59] The mechanism underlying these intracranial toxic effects is currently speculative, but T-DM1 targeting of reactive astrocytes might play a role.[59] There are insufficient data to evaluate the safety of whole-brain radiotherapy or extracranial palliative radiotherapy or stereotactic radiotherapy when combined with T-DM1.

In the DESTINY-BREAST03 trial, palliative radiotherapy (excluding lung area) was allowed concurrently with trastuzumab deruxtecan, but no adverse events related to concomitant radiotherapy (including increased risk of interstitial lung disease) were reported.[60] The ASCENT trial did not include information on radiotherapy (although restricted sequential palliative radiotherapy was allowed); thus, there is currently a shortage of safety data on the use of sacituzumab govitecan in relation to radiotherapy.[61]

PARP inhibitors and radiotherapy

In the context of non-metastatic settings, the TBCRC 024 multicentre, phase 1 trial aimed to determine the maximum tolerated dose of veliparib in combination with postoperative chest wall and regional nodal radiotherapy in women with inflammatory or locally-recurrent breast cancer after surgery. The incidence of grade 3 toxic effects increased over time, with severe late toxic effect rates observed, particularly in terms of fibrosis in the radiotherapy field (40% [five of 15 cases] at 3 years).[62] The RADIOPARP phase 1 trial focused on determining the maximum tolerated dose of olaparib concurrently with radiotherapy in patients with triple-negative breast cancer who had residual tumour or inoperable disease after neoadjuvant chemotherapy.[63] At 2-year follow-up, no grade 3 or worse treatment-related toxic effects or cardiac, pulmonary, or gastrointestinal adverse events were reported, indicating a favourable safety profile. Late presenting grade 3–4 events were rare, with one patient having grade 4 thrombocytopenia at 1 year follow-up while receiving further cytotoxic therapy for metastatic disease. These findings suggest that the concurrent use of veliparib or olaparib with radiotherapy is generally well tolerated, but that long-term monitoring is necessary to assess and manage potential late toxic effects. Data from the last few years have shown the effectiveness of olaparib in the high-risk early breast cancer setting as an adjuvant treatment following standard chemotherapy. The OlympiA phase 3 trial investigated the use of olaparib in the adjuvant setting after completion of local treatment and neoadjuvant or adjuvant chemotherapy; it was required that patients had completed the course of radiotherapy between 2 weeks and 12 weeks before enrolling in the trial.[64]

In patients with breast cancer with germline pathogenic variants in the *BRCA1* or *BRCA2* genes, PARP inhibitors as single agents are the standard of care in the metastatic setting.[65,66] A phase 1 study evaluated the concurrent use of veliparib with whole brain radiotherapy in patients with brain metastases, including patients with breast cancer.[67] Overall, the addition of veliparib to whole brain radiotherapy did not reveal unexpected toxic effects compared with radiotherapy alone.

Although no serious additional acute toxicity has been reported thus far from combining PARP inhibitors with radiotherapy, available data on this combination in breast cancer are scarce. Furthermore, there is a shortage of long-term safety data for this combination in breast cancer and there is little evidence demonstrating a clinically significant benefit. Similarly, there are insufficient safety and efficacy data for combining PARP inhibitors with radiotherapy in other solid organ malignancies. Considering these factors, it remains preferable to not use radiotherapy concurrently with PARP inhibitors until further research provides more comprehensive safety and efficacy data for this combination therapy. The main ongoing trials investigating PARP inhibitors and radiotherapy combinatory strategy are summarised in the appendix (p 26).

Immunotherapy and radiotherapy

Immunotherapy has emerged as a key treatment option in triple negative breast cancer, both in the neoadjuvant setting and as first-line therapy for PD-L1 positive tumours. The use of immunotherapy in triple negative breast cancer is supported by major clinical trials, such as KEYNOTE-522,[68] IMPASSION-130,[69] and KEYNOTE-355.[70] In the neoadjuvant KEYNOTE-522 trial, pembrolizumab was initially not allowed during

postoperative radiotherapy. However, an amendment based on safety data was made, allowing concurrent administration of pembrolizumab and radiotherapy.[68] An event-free survival benefit was observed in patients who received pembrolizumab with either concurrent or sequential adjuvant radiotherapy. The combination of pembrolizumab and radiotherapy appears to be well tolerated and does not seem to be associated with additional risks.[71] In the recently published event-free survival analysis, slightly higher rates of pneumonitis (grade 3 or worse 0·9% [seven of 783 cases] *vs* 0·5% [two of 389 cases]) and skin toxicity (grade 3 or worse 4·7% [37 of 783 cases] *vs* 0·3% [one of 389 cases]) were reported compared with the placebo group, who also received radiotherapy.[72]

The IMPASSION-130 trial allowed palliative radiotherapy before randomisation, but specific efficacy and toxicity data for this subgroup of patients are not reported.[69] In the KEYNOTE 355 trial, patients treated with radiotherapy were eligible for enrolment if at least 2 weeks had passed since the last dose of radiotherapy.[70] Pooled data from 68 prospective trials involving immune checkpoint inhibitors in 16 835 patients indicated that administering these drugs within 90 days following radiotherapy did not appear to increase the risk of serious adverse events.[73] Several small studies have investigated the effect of checkpoint inhibition with radiotherapy in the palliative setting. Overall, these studies indicate that the combination of immune checkpoint inhibitors and radiotherapy is safe and well tolerated.[74,75]

Clinical data on the combination of immunotherapy and radiotherapy in breast cancer remain scarce. Ongoing trials aiming to determine the optimal dose and timing of radiotherapy in combination with immunotherapy in breast cancer are shown in the appendix (pp 27–29). Although safety data for the combination of immunotherapy and radiotherapy in breast cancer are insufficient, evidence from other solid organ malignancies suggests that radiotherapy can be considered safe when given concurrently with immunotherapy. Nonetheless, certain aspects, such as patient selection, total dose, and dose per fraction, remain open for debate to achieve the best therapeutic outcomes.

Conclusions

These consensus statements emphasise the importance of considering radiotherapy parameters and comprehensive quality assurance in clinical trials assessing novel systemic therapies for breast cancer. Collection and timely reporting of long-term safety data is crucial when combining new biological drugs with radiotherapy, especially for patients with early breast cancer, for both sequential and concurrent therapy.

For specific targeted drugs, recommendations vary. Although CDK4/6 and PARP inhibitors with concomitant radiotherapy have shown promising safety data, further investigation within clinical trials or prospective cohort studies is warranted. PI3K–AKT and mTOR inhibitors showed safety signals warranting caution, discouraging their combination with radiotherapy. Immunotherapy agents and non-antibody–drug conjugate anti-HER2 drugs, such as trastuzumab, pertuzumab, and lapatinib, can be administered alongside radiotherapy safely, whether in adjuvant or metastatic settings. The antibody–drug conjugate T-DM1 appears to be safe for adjuvant radiotherapy, but prudence dictates avoiding its concurrent use with intracranial radiotherapy. The use of emerging tyrosine kinase inhibitors and antibody–drug conjugates concurrently with radiotherapy requires further investigation.

There is a crucial need for thoughtful and harmonious integration of radiotherapy into clinical trials for emerging breast cancer treatments. The main challenges include identifying the potential interactions between new systemic therapies and radiotherapy in both early and metastatic settings, and exploring the evolving possibilities presented by advanced radiotherapy techniques. Recognising the importance of considering the interplay between both systemic and locoregional therapies for optimising patient care is essential to obtain a comprehensive understanding of expected clinical outcomes. The creation of a research environment that accommodates these challenges and provides comprehensive guidance for the appropriate use of radiotherapy across various clinical scenarios is needed to ensure a synergistic approach that optimises both patient outcomes and the use of resources. Engaging in a comprehensive discussion with patients about the potential risks, benefits, and uncertainties associated with this therapeutic combination is an essential aspect of care.

Consensus Panellist Group

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All authors contributed to conceptualisation, data curation and analysis, investigation, methodology, supervision, validation, writing of the original draft, and review and editing of the manuscript. Authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication.

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