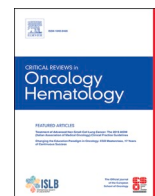




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The 2022 Assisi Think Tank Meeting: White paper on optimising radiation therapy for breast cancer

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ARTICLE INFO

Keywords:

Breast cancer
Radiation therapy
Combined modality treatment
Immunotherapy
Re-irradiation in relapsed patients

ABSTRACT

The present white paper, referring to the 4th Assisi Think Tank Meeting on breast cancer, reviews state-of-the-art data, on-going studies and research proposals. <70% agreement in an online questionnaire identified the following clinical challenges: 1: Nodal RT in patients who have a) 1–2 positive sentinel nodes without ALND (axillary lymph node dissection); b) cN1 disease transformed into ypN0 by primary systemic therapy and c) 1–3 positive nodes after mastectomy and ALND. 2. The optimal combination of RT and immunotherapy (IT), patient

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<https://doi.org/10.1016/j.critrevonc.2023.104035>

Received 23 February 2023; Received in revised form 11 May 2023; Accepted 23 May 2023

Available online 26 May 2023

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selection, IT-RT timing, and RT optimal dose, fractionation and target volume. Most experts agreed that RT- IT combination does not enhance toxicity. 3: Re-irradiation for local relapse converged on the use of partial breast irradiation after second breast conserving surgery. Hyperthermia aroused support but is not widely available. Further studies are required to finetune best practice, especially given the increasing use of re-irradiation.

1. Introduction

Since 2016 each "Assisi Think Tank Meeting" (ATTM) has involved European radiation and clinical oncologists who are dedicated to breast cancer (BC) treatment by identifying key radiation therapy (RT)-related issues and "grey" areas requiring further research (Aristei et al., 2016; Arenas et al., 2020; Aristei et al., 2022).

The present white paper refers to the 4th ATTM which was held in February 2022. Endorsed by the European Society for RadioTherapy & Oncology (ESTRO) and the Italian Association of Radiotherapy and Clinical Oncology (AIRO), it was conducted under the patronage of the European Society of Breast Cancer Specialists (EUSOMA).

2. Methods

The ATTM design was described elsewhere (Aristei et al., 2016). Controversial issues were identified through a review of the literature, with ATTM experts voting to analyse:

- 1) Tailoring indications, target volumes and RT doses;
- 2) RT and immunotherapy (IT);
- 3) Re-irradiation (re-RT).

An online questionnaire for the ATTM expert panel investigated clinical practice (see [Supplementary Material](#)). Under 70% agreement indicated uncertainty i.e., an area of contention. Working groups reviewed data, on-going studies and identified clinical challenges which were subjected to intense brainstorming during the ATTM.

3. Results

All voting results are reported in the [Supplementary Material](#).

3.1. Tailoring indications, target volumes and RT doses

3.1.1. Current evidence and areas of contention

Although RT techniques, volumes and planning objectives are crucial in controlling BC and treatment-related toxicity, their impact on clinical outcomes remains unclear. To improve target volume selection and definition, RT planning and delivery, ESTRO provides courses and recommends key objectives for successful outcomes (Offeresen et al., 2015; Offeresen et al., 2016; Kaidar-Person et al., 2019; Kaidar-Person et al., 2021a; Kaidar-Person et al., 2021b; Meattini et al., 2022a). Other atlases of target delineation criteria include, for example, the NRG/Alliance (NRG breast cancer atlas) and the Radiotherapy Comparative Effectiveness (RADCOMP) Atlas which guides contouring for patients in the proton vs photon therapy randomized trial (RADCOMP Breast Atlas).

Tailoring therapy leads to precision medicine which aims at identifying the best approach for each individual patient. It is crucial in BC, a heterogeneous disease with 70–80% cure rates in its early stages and poor outcomes when locally advanced or metastatic (<https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html>).

Controversial issues at the 2022 ATTM were:

3.1.1.1. Axillary treatment after upfront mastectomy and sentinel lymph node (SLN) macro-metastases. SLN biopsy (SLNB) is standard of care in patients with clinically negative axilla (cNO). Uncertainty persists as to whether axillary lymph node dissection (ALND) or axillary RT are suitable for clinically node-negative patients with macro-metastatic SLN/SLNs after mastectomy. Although omitting ALND is an option for

women who had received mastectomy, all clinical circumstances need to be carefully considered, and patient preferences taken into account.

No ATTM consensus was reached on the nuanced decision of routine ALND in a patient with 1 macro-metastatic SLN (56% against vs 44% for). If ALND was omitted, 92% supported post-mastectomy RT (PMRT), as suggested elsewhere (Burstein et al., 2021). Agreement $\geq 80\%$ was achieved for treating I-IV levels. Whether the chest wall needed to be irradiated was not specifically asked although 2 responders included it as target volume. The POSNOC trial results (Table 1) (Gloyal et al., 2021) are expected to provide the answer to the dilemma. At present, guidelines do not indicate mandatory chest wall RT (Brackstone et al., 2021) unless risk factors for relapse are present.

The International Breast Cancer Study Group (IBCSG) 23–01 multicentre phase III non inferiority trial randomized 934 patients (9% mastectomized) with 1–2 micrometastatic SLN/s to ALND or not. The main endpoint was disease-free survival with overall survival as the secondary. At a median follow-up of 5-years results showing no inter-group differences (Galimberti et al., 2013) were confirmed at the median 9.7year follow-up (Galimberti et al., 2018). Axillary failure in the no ALND group was 2% vs < 1% ALND. Stopping accrual before completing planned recruitment, the main limitation of the trial, meant the study was under-powered to demonstrate non-inferiority.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 phase III randomized trial (Giuliano et al., 2011) investigated ALND omission for cNO-pN1(1–2 involved SLN/s) patients after breast conserving therapy. Although almost half the SLNs were micro-metastatic, findings suggested ALND could be avoided in patients with 1 or 2 SLN metastases as long as whole breast irradiation (WBI) was performed. After ALND or SLNB, no significant differences emerged in local and nodal relapse at a 6.3-year median follow-up. Five years later, 1 nodal relapse occurred in the SLNB group and none in the ALND group. No significant differences emerged in overall survival (OS) or disease-free survival (DFS) (Giuliano et al., 2017). Results were attributed to the effects of incidental nodal irradiation during WBI after breast-conserving surgery (BCS) (Jagsi et al., 2014). Adopting the same design, the SINODAR-ONE phase III randomized clinical trial enrolled 889 patients from 2015 to 2020. At 34 months median follow-up, one axillary recurrence was observed in each group, with no difference in recurrence-free survival or OS (Tinterri et al., 2022). Biases in both studies were lack of power due to poor accrual and a lower than expected mortality rate.

The AMAROS trial randomized to ALND or axillary RT patients with T1 or T2, cNO disease with 1–2 macro-metastatic SLNs after BCS (1166 patients) or mastectomy (248 patients). The study was under-powered due to few events. The risk of lymphedema was significantly lower with axillary RT while axillary control and survival outcomes were not inferior (Donker et al., 2014; Bartels et al., 2022). At 10-years the incidence of second tumours was significantly, but unaccountably, higher in the axillary RT-arm. More than half of these second tumours occurred in sites that were distant from the irradiated area. Since mastectomy was not performed in the AZ0011 trial and in few patients in the other reported trials, no firm conclusions can be reached on mastectomized patients, for whom further studies are needed.

According to the results of the above phase III randomized trials, ALND could be avoided provided that post-surgical RT was delivered (Brackstone et al., 2021; Burstein et al., 2021; NCCN breast cancer guidelines). In patients who had not received ALND, RNI should be considered in cases of microscopic extracapsular extension in the SLN/SLNs, large primary tumour size and lympho-vascular invasion

Table 1
Clinical trials investigating lymph node treatment.

Trial	PI Country Accrual Time	Population and study summary	Number of patients required	Primary endpoint
POSNOC NCT02401685	Amit Goyal, University Hospitals of Derby and Burton NHS Foundation Trust, Derby UK Aug 2014- Jul 2026	Early BC with 1–2 positive nodes at SLNB Adjuvant systemic therapy only vs axillary treatment (ALND or axillary RT) and adjuvant systemic therapy	1900	5-year axillary RR
BOOG 2013–07 NCT02112682	The Netherland, Marjolein L Smidt, Maastricht University Medical Centre Hans JW de Wilt, Radboud University Medical Centre, The Netherland Jun 2014 – Mar 2018	Early BC undergoing mastectomy with 1–3 positive nodes at SLNB Completion of axillary treatment vs no completion	878	10-year regional RR
SENO MAC NCT02240472	Jana de Boniface, Karolinska Institutet, Solna, Sweden and International Jan2015-Dec 2026	Early BC with 1–2 positive nodes at SLNB Completion ALND vs no axillary surgery	2700	5-year BC specific survival
SUPREMO NCT00966888	Ian H. Kunkler, Edinburgh Cancer Centre at Western General Hospital, UK Jan2006-Jun2010	Early BC undergoing mastectomy and axillary treatment (pT1N1,pT2N0–1) CW RT vs no RT	3500	OS Acute and late morbidity
TAILOR-RT (MA.39) NCT03488693	Timothy Whelan, Juravinski Cancer Centre at Hamilton Health Sciences, Ontario Canada May 2018-Sept 2027	Early BC undergoing mastectomy and axillary treatment 1–2 node positive at SLNB; 1–3 node Positive at AD; cT3N0 Oncotype Dx recurrence score ≤ 25 RT to CW + RNI vs no RT	2140	10-year BC recurrence-free interval
SKAGEN 1 NCT02384733	Birgitte Offersen, Aarhus University Hospital, Denmark Mar 2015-Jul 2032	Early BC undergoing both BCS and mastectomy with indication to RNI Hypofractionated RT (40 Gy/15 fr) vs conventionally fractionated RT	2963	3-year arm lymphedema
HYPOG-01 NCT03127995	Sofia RIVERA, Gustave Roussy, Paris France Sept 2016-Sept 2030	Early BC undergoing both BCS and mastectomy with indication to RNI Hypofractionated RT (40 Gy/15 fr) vs conventionally fractionated RT	1265	5- and 10-year arm lymphedema
RHEAL NCT04228991	Timothy Whelan, Juravinski Cancer Centre at Hamilton Health Sciences, Ontario Canada Canada Feb2021-Dec2027	Early BC undergoing both BCS and mastectomy with indication to RNI Mild hypofractionation (40 Gy/15 fr) vs ultrahypofractionation (26 Gy/5fr)	588	3-year arm lymphedema
HeNRIetta NCT02515110	Massey Cancer Center Douglas W Arthur Virginia Commonwealth University, Massey Cancer Center, Richmond, Virginia USA Aug 2015-Oct 2024	Early BC undergoing both BCS and mastectomy with indication to RNI Single arm: hypofractionated RT (42.56 Gy/16 fr)	137	3-year arm lymphedema
FABREC NCT03422003	Rinaa Punglia and Julia Wong, Dana-Farber Cancer Institute, Boston USA Apr 2018- Apr 2030	BC patients undergoing mastectomy and immediate reconstruction Hypofractionated RT (42.56 Gy/16 fr) vs conventionally fractionated RT	400	PROMs using FACT-B at 6 months
DBCg Recon trial NCT03730922	Tove F Tvedskov, Denmark Jan 2020-Nov 2033	BC patients treated with mastectomy and PMRT(40 Gy/15fr) Delayed-immediate reconstruction vs Delayed reconstruction	590	Number of pts with Complication requiring surgical intervention 1 year after reconstruction
RT CHARM NCT03414970	Matthew Poppe, Huntsman Cancer Hospital, University of Utah USA, Canada Feb 2018-Aug 2035	BC patients (stage IIA-IIIa) undergoing mastectomy and reconstruction Hypofractionated RT (42.56 Gy/16 fr) vs conventionally fractionated RT	897	24-months reconstructive complication rate
Ohio State University NCT03786354	Ohio State University Comprehensive Cancer Center, USA USA December 2018 - December 2020	IMRT vs 3DCRT in node positive BC Pts receiving RNI	60	1-year patient-reported shoulder/arm morbidity
Mayo Clinic NCT04443413	Carlos E Vargas, Mayo Clinic USA Jun 2020-June 2024	25 fraction photon-based RT vs 5 fraction proton-based RT	98	24-month complication rate
NSABP-B51 NCT01872975	Norman Wolmark NSABP Foundation USA Aug 2013-Aug 2028	Early BC pts (cT1–3,N1) undergoing PST and BCS or mastectomy with ypN0 if early BC: WBI + RNI vs WBI if mastectomy: CW RT + RNI vs no RT	1636	Invasive BC relapse free interval

Abbreviations PI, Principal Investigator; BC, Breast Cancer; SLNB, Sentinel Lymph Node Biopsy; RR, Recurrence Rate; ALND, Axillary Lymph Node Dissection; RT, Radiation Therapy; CW, Chest Wall; AD, Axillary Dissection; RNI, Regional Nodal Irradiation; BCS, Breast Conserving Surgery; PROMs, Patient Reported Outcome Measures; PMRT, Post-Mastectomy Radiation Therapy; IMRT: Intensity-Modulated Radiation Therapy; 3DCRT Three-Dimensional Conformal Radiation Therapy; PST, Primary Systemic Treatment; WBI: Whole Breast Irradiation;

(LVI) (Morrow et al., 2018; Brackstone et al., 2021). ALND is required when axillary involvement could impact upon adjuvant systemic therapy or post-operative RT (Burstein et al., 2021).

3.1.1.2. PMRT for pT2N1 after ALND. The ATTM did not reach agreement on PMRT for patients with 1 macro-metastatic axillary node and 9 negative nodes after ALND (69% for vs 31% against). Agreement was reached for treating levels I, II and IV (15 responders) while, surprisingly, 67% of experts (14 responders) voted in favour of treating level III. One might hypothesize that the 15th expert was distracted in voting. Guidelines from the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO) and the Society of Surgical Oncology (SSO) stated that RNI should be considered for patients with 1–3 positive lymph nodes and adverse prognostic factors, such as extensive LVI, or a large, high-grade primary tumour with an unfavourable molecular profile (Recht et al., 2016). The randomized phase 3 European Organisation for Research and Treatment of Cancer (EORTC) 22922–10925 trial compared RT to the breast/chest wall ± medial supraclavicular (MS) and internal mammary (IM) nodes in patients with stage I–III breast cancer. Patients with external tumours had positive axillary nodes; patients with central or medial tumours were enrolled regardless of axillary involvement. Overall, 43% of cases were N + 1–3 (Poortmans et al., 2015). The 15-year results showed that BC mortality and any recurrence were significantly reduced after IM-MS irradiation. Late toxicity was limited, non BC-related mortality was not increased and OS was not significantly improved (Poortmans et al., 2020). RT techniques might have played a role in outcomes, with greater benefits being associated with more individualised techniques (Kaidar-Person et al., 2022). Similarly, the MA20 phase III trial reported no advantage in OS. After BCS, node-positive (85% N + 1–3) or node-negative, high-risk patients (primary tumour of 5 cm or more; or 2 cm or more with under 10 axillary nodes removed and at least one of the following: G3, oestrogen-receptor (ER) negativity, LVI) were randomised to WBI ± RNI (Whelan et al., 2015). RNI improved loco-regional and distant DFS and DFS. The Danish Breast Cancer Group Internal Mammary Node (IMN) Study enrolled node positive patients, 28% of whom (864) were N1. All received RT to the chest wall and nodal levels I–IV. Only patients with right-sided tumours received IMN irradiation. At a median follow-up of 14.8 years, significantly lower risks were reported of distant recurrence and death from BC after IMN irradiation. (Thorsen et al., 2022).

Deciding whether RNI, with or without IMN, is needed for contemporary pN1 patients usually derives from a multi-disciplinary team discussion, considering the patient's risk profile, comorbidities and preferences (Thorsen et al., 2022).

The ongoing TAILOR-RT-NCIC MA.39 trial (NCT03488693) was designed to assess whether RNI was needed after BCS or mastectomy in patients with pT1–2N1a (1–3 positive axillary nodes after ALND, 1–2 positive axillary nodes after BCS and SLN biopsy, 1 positive SLN after mastectomy) who were ER-positive, HER2-negative and at low biological risk (21-gene RS < 18). Randomized patients will receive RT to the breast after BCS or no RT after mastectomy vs RT to breast/chest wall and to the regional nodes (supraclavicular, non-dissected axillary, and internal mammary) (Parulekar et al., 2019). The results of this trial and others in Table 1 are expected to provide more precise recommendations for PMRT in N1 patients.

3.1.1.3. PMRT fractionation. ATTM agreement was not reached on moderate hypofractionation for chest wall irradiation ± RNI (67% for vs 33% against), perhaps because opinions were sought before presentation of the Skagen 1 trial results at the 2022 ESTRO meeting. 2879 node-positive breast cancer patients (48% mastectomized) were randomized to 50 Gy/25 fractions vs 40 Gy/15 fractions. The moderately hypofractionated schedule did not result in more arm lymphedema than standard fractionation. Furthermore, the 3-year loco-regional

recurrence risk was 1.8% in both groups and the risk of distant recurrence or death was not significantly different (Milo et al., 2022). ESTRO consensus recommendations and an AIRO position paper (Meattini et al., 2022a; Meattini et al., 2022b) stated moderate hypo-fractionation was suitable for chest wall irradiation, with or without reconstruction and/or RNI. Ultra-hypofractionation (26 Gy in five fractions in 1 week) can be offered for PMRT (without reconstruction or RNI) either as standard of care or within a randomized trial or prospective cohort.

In patients with a reconstructed breast the Alliance A221505 RT CHARM phase III non-inferiority randomized trial (NCT03414970) was designed to evaluate the safety and efficacy of PMRT as delivered in a hypofractionated schedule over 3 or 4 weeks. It will specifically assess radiation-related complications in reconstructed chest walls and whether the 3–4 week schedule is safe for the regional nodes, considering the nearby brachial plexus (Poppe et al., 2020).

3.1.1.4. RT technique for chest wall/RNI. Quality assurance is key to achieving the desired clinical outcome and widening the RT therapeutic window (Kaidar-Person et al., 2022), as demonstrated by low rates of long-term RT-related toxicity within the EORTC 22922/10925 study. No significant differences emerged between left- and right-sided IM-MS irradiation or in the incidence of second malignancies, contralateral BC or cardiovascular deaths (Poortmans et al., 2021). The 30-year follow up of the DBCG 82b&c trials showed PMRT improved BC-specific survival and OS (Overgaard et al., 2022) thanks to RT-quality assurance.

Only 21% of ATTM experts routinely use intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) or tomotherapy for irradiating the chest wall + regional nodes (12% for chest wall alone). As far as regards chest wall and regional node irradiation, for 48% choice was dictated by not reaching dosimetric objectives and for 13% by unfavourable anatomy. VMAT was the most popular technique, used by 54% of experts. Static IMRT was used by 21% and other techniques by 17%.

Strategies for assessing and managing respiratory motion have been developed over the past twenty years to deliver high precision RT and spare organs at risk (OARs), mainly the heart (Latty et al., 2015). The ATTM reached 87% agreement on applying these strategies.

Proton irradiation delivers the RT dose more conformally, thus potentially lowering the risks of cardiac and pulmonary toxicity and RT-related contralateral breast and lung cancer (Stick et al., 2021; Boersma et al., 2022). Proton facilities are not widespread because costs are high and evidence is lacking for their routine clinical use in BC (Stick et al., 2021). No expert voted in favour of proton irradiation as standard therapy.

3.1.1.5. PMRT after primary systemic therapy (PST) in ypT0N0 (cT2cN1 at diagnosis) regardless of axillary surgery. RNI after PST is widely debated, as randomised studies are lacking. There was no ATTM agreement (48% for, 40% against, 12% unsure) on administering RNI after ALND (all 10 nodes negative). Consensus was not reached on volumes; 63% agreed to irradiate axillary levels III and IV.

Whether PMRT is required in cN1 patients following ALND was discussed. A combined analysis of the B-18 and B-27 NSABP studies, which allowed only WBI after BCS, showed low incidences of loco-regional relapse (LRR) in patients who achieved a pathological complete remission (pCR) (Mamounas et al., 2012). In the B-40 and B-41 NSABP studies, which left post-operative RT to the physician's discretion (Vega et al., 2022), RNI was not associated with significantly improved OS, DFS, distant recurrence or LRR. Post-operative RT might be safely omitted not only in ypN0, but also in ypN1 with good prognostic features (de Wild et al., 2022).

ALND was not recommended when cN1 was histologically confirmed at diagnosis and patients had negative SLN after PST [11]. ATTM agreement on PMRT was not reached if 3 SLNs were negative (56% for vs 44% against) when targeted axillary dissection (TAD) was proposed.

The results of the NSABP-B51 trial (Mamounas et al., 2019) will assist with decision-making for therapy de-escalation. Data from the National Cancer Database were analysed in 14,690 patients who were treated with PST and mastectomy (69% received PMRT) (Haque et al., 2021). In patients who met the NSABP-B51 trial criteria, post-operative RT did not improve OS. Despite the retrospective design using a population-based registry which did not permit analysis of other outcome parameters, these data suggest PMRT might be avoided when pCR is achieved.

3.1.2. Ongoing clinical trials

The 2008–2014 DBCG IMN2 study results are expected in 2024. Around 5000 pN+ patients received IMN radiation on right, but not on left, sides, underwent mammography screening and received trastuzumab, taxanes, letrozole and CT-based RT as standard of care (<https://www.straaleterapi.dk/media/1930/demet-oezcan-uk.pdf>).

Other trials are reported in Table 1. Expected within the next few years the results from the POSNOC and SENOMAC trials (patients not treated with PST) and from the NSABP B51 and Alliance A11202 trials (patients treated with PST) will guide clinicians in the optimal treatment after PST or not. The answer to the dilemma as to whether ALND can be omitted is expected to be provided by the Alliance A011202 trial which was designed to explore ALD vs axillary radiation in cN1 patients with positive SLN after neoadjuvant chemotherapy (Alliance A011202 trial).

3.1.3. Proposed research strategy

An unmet need that the ATTM identified was a requirement for better quality and quality assurance in routine RT planning. The ATTM will invite as many centres as possible to use ESTRO guidelines for regional node planning and irradiation (Offeresen et al., 2015; Offeresen et al., 2016; Kaidar-Person et al., 2019; Donskov, F. 2007) according to breast planning objectives that, in previous trials were linked to low RT-related toxicity.

A web-based platform will be set up to record toxicity (mainly arm morbidity) at predefined time-points and compare it with toxicity in historical cohorts. It will achieve three aims that are in line with

ESTRO's vision: better quality RT planning, better patient care outside of clinical trials and guideline implementation in all centres across Europe.

3.2. Combining radiation and IT

3.2.1. Current evidence and areas of contention

Originally, IT consisted of highly toxic agents like Interleukin 2 (IL2) and interferon (IFN) which elicited good responses in immunogenic tumours like melanoma and renal cell carcinoma (Donskov, 2007; Dafni et al., 2019). Today, physiological immune checkpoint mechanisms may be exploited as they control immune responses by regulating T-cell pathways via the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) receptor, or via the programmed cell death-1 (PD-1) checkpoint. By blocking one or the other, T-cells are freed to attack tumour cells. Unlike CTLA-4 inhibition, the effect of PD-1/PD L1 inhibition takes place within the tumour itself, where tumour infiltrating lymphocytes (TILs) are present (Bense et al., 2017). With the advent of PD1/PDL-1 and CTLA-4 inhibitors, immune checkpoint inhibitors (ICIs) became established as treatment for several tumour types, particularly those with multiple mutations such as melanoma (Luke et al., 2017) and lung carcinoma (Gray et al., 2020).

Several studies focussed on the combination of RT with ICIs and the so-called abscopal effect, i.e., the disappearance of non-irradiated lesions following target lesion irradiation (Reynders et al. 2015). Fig. 1 illustrates the underlying biological mechanisms and Fig. 2 the signalling pathways influencing the abscopal effect. Fractionation achieved an abscopal effect in a preclinical mouse model comparing 1×20 Gy, 3×8 Gy and 5×6 Gy in combination with a CTLA-4 inhibitor [46]. Since the 3×8 Gy regimen was more efficacious than 5×6 Gy, an optimal therapeutic window may be identified.

A review of 23 case reports, 1 retrospective and 13 preclinical studies, 11 of which combined IT with RT (median total dose 32 Gy, fraction size 1.2–26 Gy). showed the abscopal effect is enhanced by targeted immune treatments (Reynders et al. 2015). The time to the

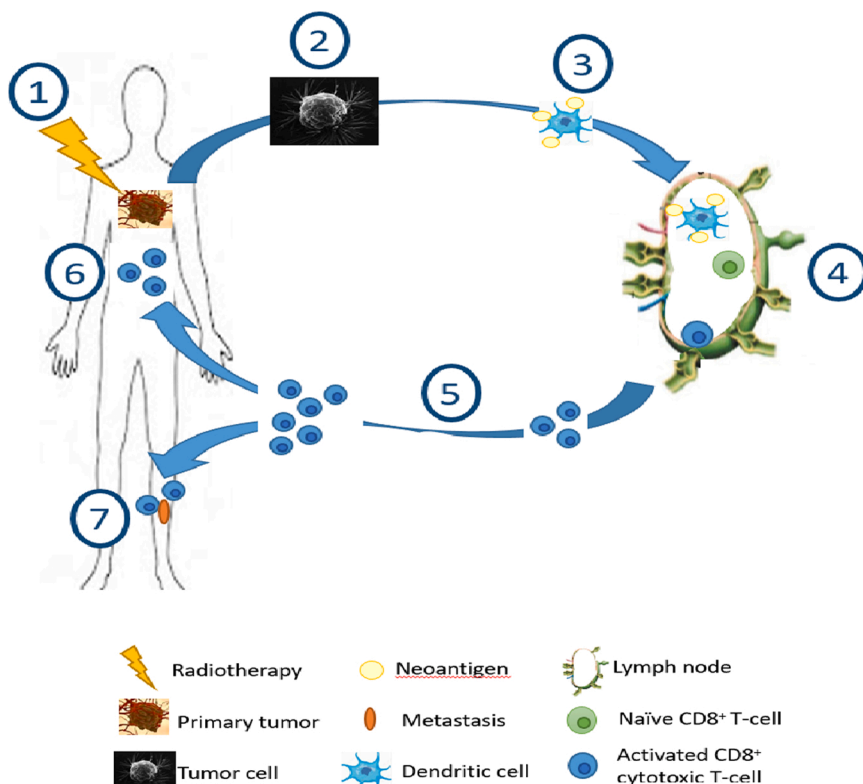


Fig. 1. 1. Radiotherapy to the primary tumour. 2. Tumour cells are killed, leading to release of neo-antigens. 3. The antigen presenting cells absorb the neoantigens, and migrate to the lymph node. 4. In the lymph nodes, the APCs activate the naïve CD8 positive T-cells. 5 Activated CD8 positive cytotoxic T-cells migrate from the lymph node/ 6/ The CD8 positive cytotoxic T-cells do not only eliminate the tumour cells in the primary tumour, but also 7. The tumour cells in the metastatic lesion. Modified from: Ansems and Verheij: *The abscopal effect of radiation therapy*. *Nederlands Tijdschrift voor Oncologie* 2022; 19; 58–64.

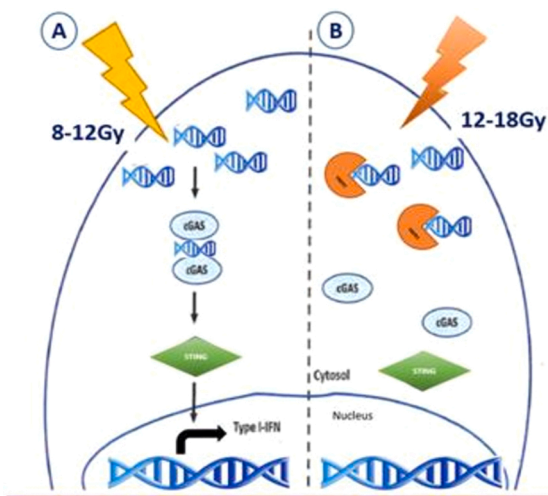


Fig. 2. Several signaling pathways influencing the abscopal effect. A: immunogenic radiotherapy doses (8–12 Gy) result in accumulation of dsDNA in the cytosol. cGAS binds to this dsDNA, and activates STING, resulting in Type I IFN production. B: Non-immunogenic radiotherapy doses can lead to production of the exonuclease TREX1, which removes dsDNA from the cytosol. Consequently, cGAS cannot bind to dsDNA, and cannot activate STING, such that it does not result in production of Type I IFN. Modified from: Ansems and Verheij: *The abscopal effect of radiation therapy*. *Nederlands Tijdschrift voor Oncologie* 2022; 19; 58–64.

abscopal effect ranged from less than 1 month to 24 months (median 5 months), and median response duration was 13 months (range 3–39 months). Concerns emerged about dosages, timing, patient selection and toxicity.

Since adjuvant breast RT was hypothesized to influence survival via the abscopal effect (Dewan et al., 2009; Jatoi et al., 2018), adding ICIs might enhance it even further, thus improving survival. Conversely, RT exerts immune suppression by reducing circulating lymphocytes which are required for the anti-tumoural immune response. Since lymphopenia was related to worse survival (Venkatesulu et al., 2018), RT-induced lymphopenia and its potential correlation with reduced survival should generate hypotheses for future studies. For example, when aiming for an increased abscopal effect in BC patients, RT-induced lymphopenia should be considered and target volumes should be limited (Chen et al., 2020). Stereotactic body RT (SBRT), when combined with IT, was associated with greater immune stimulation than traditional RT (45 Gy in 15 fractions) and resulted in less lymphopenia, as it irradiates smaller volumes of healthy lung (Chen et al., 2020).

ICIs may enhance the local effect of RT. A review of pre-clinical and clinical studies showed the radiation-enhancement factor for IT ranged from 1.7 to 9.1, which was much higher than e.g. for cisplatin (1.1), thus supporting use of combined RT and IT in the clinical setting (Vanneste et al., 2020). To our knowledge, clinical studies investigating IT enhancement of the RT local effect are not yet available for BC.

A recent systematic review and meta-analysis (Sha et al., 2020) selected 35 studies with 13,956 patients who had received ICI alone and 16 studies with 1442 patients who had been treated with ICI + RT. Grade 3–4 toxicities were similar in the 2 treatment groups while Grade 5 toxicity was slightly higher in the ICI+RT group. When stratified by RT timing and irradiated site localization, no significant differences emerged except for increased toxicity following anti-CTLA-4 therapy in melanoma patients. Clinical trials investigating diverse ICI agents combined with RT are expected to be safe.

Controversial issues in managing BC patients with RT and IT are:

3.2.1.1. Patient selection. ICIs are efficacious in triple negative (TN) tumours which are PD-L1 +, and/or harbour high TIL levels (Emens,

2018). Atezolizumab, a PD-L1 inhibitor, was administered to 902 patients with unresectable, locally advanced or metastatic TNBC. Patients with PD-L1 + disease had better OS (Emens et al., 2021). In the neo-adjuvant setting in early stage TNBC, atezolizumab with sequential nab-paclitaxel and anthracyclines significantly improved the pCR rate (Mittendorf et al., 2020).

Promising results were achieved with pembrolizumab in the phase 1b KEYNOTE-173 (Schmid et al., 2020a; Schmid et al., 2020b) and the phase 2 I-SPY2 (Nanda et al., 2020 a; Nanda et al., 2020b) trials. The phase 3 KEYNOTE-522 evaluated efficacy and safety in 1174 patients with stage II or III TNBC who received neoadjuvant chemotherapy and were randomized 2:1 to additional pembrolizumab or placebo. All received adjuvant chemotherapy and pembrolizumab or placebo. Preliminary results in the first 602 patients showed the pCR rate increased by almost 65% in the pembrolizumab arm, vs 51% in the placebo group (Schmid et al., 2020c). The benefit was confirmed in 1174 patients who displayed 85% vs 77% event-free survival at 36 months (Schmid et al., 2022). Pembrolizumab is entering standard clinical practice for TNBC patients as FDA recently approved it in the PST setting.

Patients should be treated with pembrolizumab in the neo(adjuvant) setting and with atezolizumab in the metastatic setting according to the Impassion 130 (Emens, 2021; Schmid et al., 2018; Schmid et al., 2020d) and Keynote-522 studies (Schmid et al., 2020c; Schmid et al., 2022) when PD-L1 expression was over 1% in stage II and III TNBC. The ATTM agreed PDL-1 expression should be determined in work-ups and almost 67% of responders supported assessing stromally located TILs (sTILs) and PD-L1 expression. The Society of Immunotherapy of Cancer reported clinical practice guidelines for BC immunotherapy (Ho et al., 2021).

It is unclear whether a tumour cell, lymphocyte or macrophage assay is best for determining PD-L1. The Impassion 130 study used the Ventana SP142 immunohistochemistry assay with a 1% cut-off, whilst the recommended cut-off was 5% or higher for tumours in other sites. The Impassion 130 cohort showed that assays, such as SP 263 and DAKO 22C3, may identify more PD-L1 positive patients (Rugo et al., 2021). The KEYNOTE-355 study showed longer median progression-free survival in metastatic BC patients receiving pembrolizumab (9.7 vs 5.6 months) as long as they had a combined positive score of at least 10 using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) (Cortes et al., 2020). When evaluating the results of different trials, it is important to note which assays were used. Future studies will need to find tests to identify patients that will benefit from IT.

3.2.1.2. RT- IT timing. Since the optimal RT-IT timing remains to be established, no ATTM consensus was reached.

A few small studies investigated IT-RT in BC (Page et al., 2022; Voorwerk et al., 2019; Ho et al., 2020a; Barroso-Sousa et al., 2020) (Table 2). Combining RT (5×6 Gy) concurrently with pembrolizumab seemed promising (Ho et al., 2020b). IT should be given concurrently or ≤ 7 days after SBRT (Swamy, 2022). Bearing in mind the potential for overall toxicity and persistent immunological interactions, day+ 2 after SBRT appeared optimal according to vascular permeability and pre-clinical outcome studies. Anti-CTLA-4 treatment before a short course of hypo-fractionated RT significantly delayed metastases and improved survival in a murine model of BC (Demaria et al., 2005).

These contradictory findings may be linked to different IT agents: e.g. anti CTLA-4 was most active when prescribed prior to RT, due to regulatory T-cell depletion (Young et al., 2016); an OX40 agonist antibody, which targets recently activated T-cells, was most active when prescribed one day after RT.

In summary, data on optimal timing are conflicting and translational research is required to unravel underlying biological mechanisms.

3.2.1.3. RT fractionation and ICI. When RT is combined with ICIs, fraction size and total dose need to be carefully evaluated as RT

Table 2
Clinical trials with RT and ICIs for metastatic breast cancer.

Trial	PI Country Accrual Time	Population and study summary	Number of patients required	Primary endpoint
Brain irradiation and tremelimumab in metastatic Breast cancer NCT02563925	Shanu Modi, New York, USA. Sept 2015 – Jul 2021	Pts received either WBRT or SRS, as per standard of care, with tremelimumab + /- anti-HER2 drugs	28	PFS
Phase Ib/II Study to Assess Efficacy, Safety & Immunological Biomarker of Anti PD-1 Antibody With Radiation Therapy in Patients With HER2-negative Metastatic Breast NCT03430479	Masahiro Takada Kyoto, Japan. Feb 2018 – March 2021	Efficacy and safety of nivolumab plus RT in HER2-negative m BC requiring palliative RT for bone metastases	32	Phase Ib: dose-limiting toxicity rate at 2 years Phase II: ORR of the unirradiated lesions
A phase 2 clinical trial assessing the efficacy and safety of pembrolizumab and radiotherapy in patients with metastatic triple-negative breast cancer NCT02730130	Alice Y. Ho, Boston, USA. Jun 2017 – May 2017	mTNBC pts received palliative RT [30 Gy with daily fraction of 6 Gy] and pembrolizumab starting within 3 days of the first RT fraction	17	ORR at week 13
A Phase II Study Of Pembrolizumab In Combination With Palliative Radiotherapy For Metastatic Hormone Receptor Positive Breast Cancer NCT03051672	Sara Tolaney, Boston, USA. Feb 2017 – Apr 2021	Palliative RT in combination with an immunotherapy as a possible treatment for metastatic HR positive, HER2-negative BC.	8	ORR: Tumor measurements are repeated every 6 weeks for the first 24 weeks and then every 9 weeks thereafter

Abbreviations: pts, patients; WBRT, Whole Brain Radiation Therapy; SRS, Stereotactic Radiosurgery; PFS, Progression Free Survival; RT Radiation Therapy; ORR, Objective Response Rate; m, metastatic; TNBC, Triple Negative Breast Cancer; HR, Hormone Receptor; BC, Breast Cancer.

immunomodulation varies with dose and fractionation. The ATTM achieved consensus that moderately hypo-fractionated schedules (2.67 Gy for 15 fractions), as now standard for WBI, do not need to be modified when combined with ICIs because no increase in toxicity was expected. When delivering radiation therapy to metastatic sites, agreement was achieved for SBRT schedules.

A review reported clinical and pre-clinical data on the immunomodulatory effects of single vs multiple large fractions of SBRT delivered to extracranial metastatic lesions. Preliminary data suggested synergism was best with 2–3 × 6–10 Gy before PDL1/PD1 inhibitors or early in their course (Swamy, 2022). A single > 12 Gy fraction caused immediate antigen release and was associated with endothelial damage, reduced blood flow, limited immune cell infiltration and TREX1 upregulation (Vanpouille-Box et al., 2017). A single 5–10 Gy dose limited endothelial disruption, but caused antigen release. Multiple fractions, each < 10 Gy, activated dendritic cells, upregulated IF-1 and promoted the abscopal effect, thus enhancing immune system activation (Buchwald et al., 2018). Although uncertainty persists, 2–3 times 5–10 Gy seems required for an SBRT-ICI immune modulatory effect.

3.2.1.4. IT and other agents. Although 95% of ATTM participants expected IT to play a major therapeutic role in the next 5 years, no consensus was reached on concomitant drugs as no study had made any comparisons.

As IT is more effective in tumours with high mutational burdens, interest focussed on interactions between ICIs and DNA repair pathways (Kasherman et al., 2021), particularly in patients with tumours lacking homologous recombination (such as malignancies associated with BRCA1 and BRCA2 mutations which are likely to be TN). PARP inhibitors enhanced tumour cell death by preventing DNA repair and replication [77], thus increasing the mutational load and sensitizing tumour cells to IT. Together with ICI and RT, PARP inhibitors may act as radiosensitizers (Jannetti et al., 2020) and delay single-strand break repair while causing double-strand breaks. Combining PARP inhibitors with RT ± ICI constitutes a challenging field of clinical research (Pusztai et al., 2021; Pilonis et al., 2020). A potential increase in severe toxicity must be considered and weighed up in the clinical cost/benefit evaluation.

3.2.2. Ongoing clinical trials

Combinations of RT with anti-PD-L1 agents and STING (stimulator of

interferon genes) agonists are associated with adverse events such as the cytokine storm and inflammatory- and immune-related toxicities. Adding immunomodulatory Toll-like receptors (TLR) ligands to an RT and ICI combination may enhance anti-tumour immune responses (Pilonis et al., 2020).

Table 3 summarizes ongoing trials in metastatic BC (Nguyen et al., 2021).

Table 4 shows preoperative and adjuvant RT and IT trials in primary non-metastatic BC (Ho et al., 2020b; Tarantino et al., 2021; Petroni et al., 2021). Primary end-points are usually RT immunomodulation and IT anti-tumour amplification. A secondary endpoint in some trials is RT upregulation of immune modifiers such as TILs.

3.2.3. Proposed research strategies

Given the lack of reliable data on dose, fractionation, timing and target volumes for optimal outcomes in the PST setting, the ATTM decided that a phase III study was premature, opting for a phase II trial in TNBC. Since a single dose was hypothesized to balance DNA damage with antigen release and endothelium preservation with immune cell recall (Swamy, 2022), 8 Gy will be administered to the macroscopic breast tumour plus 5 mm margins (PTV) before neoadjuvant PD-1/PD-L1 inhibition. Dose distribution to the PTV will be non-homogeneous. Several translational parameters such as TILs will be evaluated in the search for predictive biomarkers of pCR.

3.3. Re-irradiation

3.3.1. Current evidence and areas of contention

Salvage mastectomy is now no longer mandatory for patients with LR after BCS and WBI, unless clinically indicated e.g., a large tumour within a small breast (Burstein et al., 202; Harms et al., 2016). Improved survival, better imaging and survivorship care programs help detect small, usually mono-focal, relapses, making a second BCS an attractive option [84]. After repeated BCS without RT the incidence of LR ranged from 7% to 29% (median 20%), suggesting re-RT was needed. Until recently few data were available on the efficacy and safety of the second BCS with re-RT, raising concerns about radiation-related toxicity, poor cosmesis and suboptimal local control (Walstra et al., 2021; Bottero et al., 2021). Today increased use of re-RT may be due to favourable reports of brachytherapy-based series and widespread use of external beam RT for PBI in the post-operative setting in non-relapsing patients (Montagne

Table 3
Ongoing studies combining RT and Immune Checkpoint Inhibitors in metastatic breast cancer.

Trial	PI Country Accrual Time	Population and study summary	Number of patients required	Primary endpoints
Phase II Window of Opportunity Trial of Stereotactic Body Radiation Therapy and In Situ Oncolytic Virus Therapy in Metastatic Triple Negative Breast Cancer and Metastatic Non-Small Cell Lung Cancer Followed by Pembrolizumab NCT03004183	Jenny Chang, Texas, USA. Dec 20126 – Jul 2022	Pts with mTNBC and mNSCLC who underwent SBRT and in situ oncolytic virus therapy used as a window of opportunity treatment before pembrolizumab	57	ORR (Time Frame: 30 days after the last dose of pembrolizumab)
Pembrolizumab And Stereotactic Radiosurgery (Srs) Of Selected Brain Metastases In Breast Cancer Patients NCT03449238	Silvia Formenti, New York, USA Feb 2018 – Jun 2022	Pts with mBC with at least 2 brain metastases will receive pembrolizumab and SRS to one of the brain lesions	41	Tumor response for non-irradiated brain lesions at 8 weeks according to RECIST1.1 Correlation of abscopal responses with the RT dose (at 1 year) OS - assessed from the start of study drug until death in non-irradiation metastases in the rest of the body by routine imaging. (at 3 year) PFS at 24 months
A Randomised Phase II Trial Comparing the Efficacy of Single-fraction or Multi-fraction SABR (Stereotactic Ablative Body Radiotherapy) With Atezolizumab in Patients With Advanced Triple Negative Breast Cancer NCT03464942	Sherene Loi, Melbourne, Australia. March 2018 – May 2022	Pts with mTNBC will be randomised to receive either SBRT 20 Gy in one fraction or 24 Gy in 3 fractions, they will then go onto receive atezolizumab for up to 24 months	54	Recommended phase II dose (RP2D) of M7824 and RT in pts with metastatic HR+ /HER2- BC (6 weeks after first administration of M7824) Safety and tolerability in pts with m HR+ /HER2- BC (Start of study drug up to 30 days after study drug stopped) DLT (63 days from initiation of in situ vaccine- end of cycle 1 of pembrolizumab)
RACHEL1: A Phase I Radiation and Checkpoint Blockade Trial in Patients With Metastatic Hormone Receptor Positive, HER2 Negative Breast Cancer NCT03524170	Meghan Karuturi, Texas USA. May 2018 – March 2022	Anti-PD-L1/TGFbetaRII fusion protein M7824 (M7824) when given together with radiation therapy in treating patients with HR positive, HER2 negative mBC pts	24	Recommended phase II dose (RP2D) of M7824 and RT in pts with metastatic HR+ /HER2- BC (6 weeks after first administration of M7824) Safety and tolerability in pts with m HR+ /HER2- BC (Start of study drug up to 30 days after study drug stopped) DLT (63 days from initiation of in situ vaccine- end of cycle 1 of pembrolizumab)
In Situ Vaccination With Flt3L, Radiation, and Poly-ICLC Combined With Pembrolizumab in Patients With Non-Hodgkin's Lymphoma, Metastatic Breast Cancer, and Head and Neck Squamous Cell Carcinoma NCT03789097	Joshua Brody, New York, USA. Dec 2018 – Oct 2019	In Situ Vaccination With Flt3L, Radiation, and Poly-ICLC Combined With Pembrolizumab in Patients With Non-Hodgkin's Lymphoma, m BC, and Head and Neck Squamous Cell Carcinoma	56	DLT (63 days from initiation of in situ vaccine- end of cycle 1 of pembrolizumab)
Atezolizumab Combined With BDB001 AnD Immunogenic Radiotherapy in Patients With Advanced Solid Tumors (AGADIR) NCT03915678	Antoine Italiano, Bordeaux, France. Apr 2019 – Jul 2022	Six independent, multicenter, prospective, single-arm phase II trials, based on 2-stage Simon's optimal design, will be conducted in parallel to assess the efficacy of atezolizumab + BDB001 + SBRT (27–60 Gy in 3–5 fractions), separately, in distinct populations of solid tumors (Population 6: TNBC)	247	Assessment of the antitumor activity of atezolizumab combined with BDB001 and RT in pts with TNBC. (Within 6 months of treatment onset)
Phase II Study of Pembrolizumab and Ablative Radiotherapy With or Without Olaparib in Metastatic Triple-Negative or Hormone-Receptor Positive/Her2 Negative Breast Cancers NCT04683679	Atif Khan, New York, USA. Dec 2020 – Oct 2022	Pembrolizumab, with or without olaparib, in association to standard RT (8–9 Gy x 3 fractions or 30 Gy in 6 Gy per fraction) in mBC pts	34	ORR (8 weeks from baseline)
A Multi-institutional Phase II Study to Evaluate Efficacy and Safety of TAlazoparib, Radiotherapy and Atezolizumab in gBRCA 1/2 Negative Patients With PD-L1 + Metastatic Triple Negative Breast Cancer NCT04690855	Mylin Torres, Alabama, USA. Dec 2020 – Sept 2022	Talazoparib, high dose radiation (8 Gy will be given in 3 fractions), and atezolizumab in patients with mTNBC PD-L1 positive	23	ORR by RECIST (8 weeks)

Abbreviations: pts, patients; m, metastatic; TNB, Triple Negative Breast Cancer; NSCLC, Non-Small Cell Lung Cancer; SBRT, Stereotactic Body Radiation Therapy; ORR, Objective Response Rate; RT, Radiation Therapy; OS, Overall Survival; SRS, Stereotactic Radiosurgery; HR, Hormone Receptor; BC, Breast Cancer; Flt3L Fms-like tyrosine kinase 3 ligand; DLT, Dose Limiting Toxicity; PD-L1 programmed cell death.

et al., 2020). Partial breast irradiation (PBI) as re-RT was supported by a GEC-ESTRO multicentre study, reporting 78% of LR occurred in the same breast quadrant as the original tumour (Hannoun-Levi et al., 2013). The incidence of LR ranged from 2% to 24% after BCS with re-RT PBI (<10% in most studies) (Vila et al., 2014) which was similar to LR results after salvage mastectomy (3–10%) (Yi et al., 2011; Wapnir et al., 2017). When repeated BCS plus re-RT was compared with salvage mastectomy, no differences emerged in local control (Hannoun-Levi et al., 2021), and OS (Hannoun-Levi et al., 2021; Su et al., 2019; Chen et al., 2008). Repeated BCS without re-RT was associated with a significantly worse OS than salvage mastectomy (Su et al., 2019; Chen and Martinez, 2008; Wu et al. 2021).

As re-irradiated tissues were limited in volume, the toxicity profile was acceptable (Bottero et al. 2021), being comparable to RT for primary BC (Walstra et al., 2019).

The NRG Oncology/RTOG 1014 Phase II study included 58 in-breast relapsed patients who were treated with 45 Gy in 1.5 Gy twice-daily fractions to the tumour bed, using external-beam radiation. The primary endpoint was G3 side effects occurring within one year; breast fibrosis rates were < 2% (Arthur et al., 2017). At 5 years, the approach appeared safe, as G3 fibrosis rates remained at 7%. Supporting the efficacy of re-RT were a 5% incidence of recurring LR and 90% breast conservation (Arthur et al., 2020).

Attempting to distinguish between new primary good-prognosis

Table 4
Ongoing clinical trials on RT and Immune Checkpoint Inhibitors in non-metastatic breast cancer.

Trial	PI Country Accrual Time	Population and study summary	Number of patients required	Primary endpoints
PRE-OPERATIVE TRIALS				
Neo-adjuvant Chemotherapy Combined With Stereotactic Body Radiotherapy to the Primary Tumour +/- Durvalumab, +/- Oleclumab in Luminal B Breast Cancer: a Phase II Randomised Trial (Neo-CheckRaY) NCT03875573	Alex De Caluwe, Bruxelles, Belgium. Nov 2019 – Dec 2023	Pts with luminal B BC candidated for neo-adjuvant chemotherapy, randomized to received PST + pre-operative RT (boost dose) on the primary tumour in association to durvalumab vs. anti-CD73 antibody oleclumab	147	Evaluation of the immune related or RT related toxicity of special interest (7 months) Phase II: Demonstration of the tumour response in arms 2 or 3 vs arm 1 (24 months)
Effects of MK-3475 (Pembrolizumab) on the Breast Tumor Microenvironment in Triple Negative Breast Cancer With and Without Intra-operative RT: a Window of Opportunity Study NCT02977468	Eileen Connolly, New York, USA. Oct 2017 – Dec 2023	Pembrolizumab in TNBC With and Without IORT	15	Number of pts with significant mean percent change in TILs (3 months)
Preoperative Combination of Pembrolizumab and Radiation Therapy in Patients With Operable Breast Cancer NCT03366844	Stephen Shiao, Los Angeles, USA. Dec 2017 – Dec 2022	Pembrolizumab combined with standard RT to the tumor (tumor boost) before pts undergo standard treatment (breast-conserving surgery, RT to the entire breast/CW after surgery, and chemotherapy)	60	Number of pts who do not necessitate a delay in standard of care treatment after receiving the investigational combination of preoperative Pembrolizumab and RT (Time Frame: 8 weeks after trial initiation) Changes in TILs (Time Frame: 8 weeks after trial initiation)
Converting HR+ Breast Cancer Into an Individualized Vaccine (CBCV) NCT03804944	Silvia Formenti, New York, USA. Mar 2020 - Dec 2023	Newly diagnosed post-menopausal women with clinical stage II-III, HR+HER2- BC. Patients receiving 4 months of standard neoadjuvant ET with letrozole are randomly assigned to one of 4 arms of a trial testing focal hypo-fractionated RT alone or with immunotherapy combinations.	100	Tolerability will be demonstrated if no grade 3 or higher toxicities are observed in the first 8 pts, of each arm (3 years) Clinical response rate to RT + /-immunotherapy during standard ET for HR+ BC will be measured (3 years) Pathological response rate to RT + /-immunotherapy during standard endocrine therapy for HR+ BC will be measured (3 years)
A Randomized Phase II Study Evaluating Pathologic Response Rates Following Pre-operative Non-Anthracycline Chemotherapy, Durvalumab (MEDI4736) +/- RADIation Therapy (RT) in Triple Negative Breast Cancer (TNBC): The PANDORA Study. NCT03872505 WITHDRAWN (lack of funding)	Heather McArthur, Cedars-Sinai, Los Angeles, USA. Jul 2022 – Jul 2027	Pts with clinical stage II-III, TNBC candidated to PST with durvalumab and randomized to receive pre-operative RT boost, consisting of 8 Gy in 3 fractions for a total of 24 Gy.	140	Pathological complete response rate in the breast and axilla (20 weeks from randomization)
P-RAD/TBCRC-053: A Randomized Study of Preoperative Chemotherapy, Pembrolizumab and No, Low or High Dose RADIation in Node-Positive, HER2-Negative Breast Cancer NCT04443348	Alice Ho, Duke University, Durham North Carolina, USA Dec 2020 – Dec 2023	Combination of neoadjuvant RT, immunotherapy (pembrolizumab) and chemotherapy for lymph node-positive, TNBC or +/-HER2-negative BC.	120	TILs; CD3 + /CD8 + T-cell Breast Immunoscore) (Days 14 and 21) Rate of pathologic response in the lymph node (7 Months)
Preoperative Use of Radiation Boost to Enhance Effectiveness of Immune Checkpoint Blockade Therapy in Operable Breast Cancer (BreastVAX) NCT04454528	Julia C Tchou, Philadelphia, USA. Dec 2020 – Aug 2024	Pembrolizumab with a single fraction RT boost in pts with early/ operable BC (RT 7 Gy x 1 fraction).	27	Feasibility of preoperative pembrolizumab administration combined with RT boost in pts with operable BC Assess clinical response of treatment
ADJUVANT TRIALS				
A Randomized, Phase III Trial to Evaluate the Efficacy and Safety of Pembrolizumab (MK-3475) as Adjuvant Therapy for Triple Receptor-Negative Breast Cancer With >/= 1 CM Residual Invasive Cancer or Positive Lymph Nodes (ypN1mi, ypN1-3) After Neoadjuvant Chemotherapy NCT02954874	Lajos Pusztai, National Cancer Institute (NCI), USA. Nov 2016 – Dec 2026	TNBC with residual disease after NAC undergo to WBI (all schedules allowed) + /- pembrolizumab	1155	Invasive DFS (from date of randomization to date of first invasive recurrence, second invasive primary cancer (breast or not), or death due to any cause, assessed up to 10 years) Severity of fatigue (55 weeks after randomization) Physical function (55 weeks after randomization)
A Multicenter, Randomised, Open-label Phase II Study to Evaluate the Clinical Benefit of a Post-operative Treatment Associating Radiotherapy + Nivolumab + Ipilimumab Versus Radiotherapy + Capecitabine for Triple Negative Breast Cancer Patients With Residual Disease After Neoadjuvant Chemotherapy (BreastImmune03) NCT03818685	Olivier Tredan, Lyon, France. Jan 2019 – Jul 2022	Post-operative adjuvant therapy combining RT + Nivolumab + Ipilimumab versus radiotherapy + Capecitabine in TNBC pts with residual disease after NAC	95	DFS at 2 years

Abbreviations: pts, patients; BC, Breast Cancer; PST, Primary Systemic Treatment; RT, radiation therapy; TNBC, Triple negative breast cancer; IORT, intraoperative radiation therapy; TILs, Tumor Infiltrating Lymphocytes; CEW chest wall; ET, endocrine therapy; HR, Hormone Receptor; NAC, neoadjuvant chemotherapy; WBI, Whole Breast Irradiation; DFS, Disease Free Survival;

tumours and true LR which may have a worse prognosis (Smith et al., 2000), most 2021 St. Gallen panellists supported a second BCS for low-risk BC (i.e., small size, luminal A-like), especially if occurring over five years after initial treatment (Burstein et al., 2021). Patient eligibility for re-RT should be evaluated case-by-case, focusing on tumour features and toxicity risk (Montagne et al., 2019).

Few data are available on the management of relapsing patients after PBI (Shah et al., 2012; Leonard et al., 2020; Müller, et al., 2011). In a multicentre study on LR after intra-operative RT with electrons, no difference emerged between salvage mastectomy and BCS plus re-RT when adjusted by tumour stage. Repeated BCS and no re-RT was associated with worse outcomes than re-RT, despite a more favourable tumour profile and older age.

Controversial issues in the management of relapsing patients after BCS or mastectomy were:

3.3.1.1. WBI vs PBI after a second BCS. ATTM agreed (90%) PBI should be used for luminal A-like tumours and when RNI was not indicated (i.e., pNO relapse). Although limited data exist on WBI as re-RT option in the postoperative setting (Resch et al., 2002), 41% opted for WBI for TNBC relapse (vs 10% for luminal A).

WBI may provide better LC than PBI (Leonard et al., 2020). Surgical margin status and re-RT timing significantly impacted survival. When re-RT was not performed at first recurrence, LC significantly decreased and survival trended downwards (75% vs 43%) (Müller, et al., 2011). In the CALOR trial (Walstra et al., 2021), a second LR was a harbinger of poor prognosis, leading to 46% BC-specific mortality. Whatever the anatomical site of first LR, sub-analysis of second LR patterns identified the chest wall and nodal regions as common sites (Wapnir et al., 2017). Breast and nodal volumes should be irradiated in some cases, after assessing tissue status and dosimetric analyses.

3.3.1.2. Fractionation and techniques. The most common schedule was 2 Gy daily fractionation (Harms et al., 2016; Bagley and Smith, 2019; Buchholz et al., 2020), as hypofractionation was rare, except in the palliative setting (Merino et al., 2015). Dose escalation for re-RT above 60 Gy did not appear beneficial (Skinner et al., 2013). Although ATTM consensus was not reached on fractionation for WBI or PBI ± RNI, 67% of experts favoured 40 Gy in 15 fractions for WBI and 32 Gy in 8 fractions for PBI with high dose-rate brachytherapy. When RNI was indicated most experts proposed 40 Gy in 15 fractions.

Although all techniques are suitable for delivering PBI as re-RT, interstitial brachytherapy is currently supported by the most robust data (Montagne et al., 2020). ATTM panellists preferred IMRT, helical therapy or VMAT as they provided better conformality and OAR sparing than the standard 3DRT (Lamberth et al., 2014). No consensus was reached on the best technique. Proton therapy reduces doses to OARs more than photons, due to greater target conformity (Fattahi et al., 2020). Although its clinical benefit remains unclear and its availability is limited, it was used to re-treat extended loco-regional target volumes (Fattahi et al., 2020; Choi et al., 2021) and areas at high risk of complications. Since more outcome data are required, no consensus was reached.

3.3.1.3. Re-irradiating a progressing relapsed single supraclavicular node after systemic therapy. ATTM agreed (83%) to treat only the positive lymph node, with 57% in favour of SBRT-type fractionation to achieve disease ablation. The brachial plexus was the main concern for 83% as it is the major dose-limiting factor in nodal re-irradiation. Brachial plexus-radiation related neuropathy increased dramatically as doses exceeded 70 Gy (Emami et al., 1991). In a small cohort, the 1-year freedom from

complication rate was 91% with cumulative $D_{max} < 95$ Gy and over two years between radiation courses (Chen et al., 2017); the short-term toxicity evaluation must be interpreted with caution and risk/benefit ratio carefully assessed.

3.3.1.4. Irradiating a small, isolated visualized IMN relapse after systemic therapy. All ATTM experts agreed to irradiate the IMN region with curative intent; almost 50% opted for a boost to the positive node. Three fractionation schedules were proposed: moderate hypofractionation 39%; SBRT-type fractionation 35%; standard fractionation 26%. The heart was the main OAR concern for 74% of experts.

3.3.1.5. Hyperthermia + RT for superficial chest wall recurrences. ATTM consensus was reached (74%); 57% of hyperthermia supporters said it was not available in their centres as it requires specialist equipment and expertise.

Hyperthermia enhanced RT effectiveness through protein denaturation, damage repair inhibition and better re-oxygenation (Datta et al., 2016). A meta-analysis of recurrent and locally advanced inoperable BC showed that adding hyperthermia to RT improved complete response rates (Datta et al., 2016). Despite limited data on hyperthermia after LR resection in recurrent disease (Linthorst et al., 2013), RT schedules included 32 Gy in 8 fractions (twice a week with one-weekly hyperthermia session), 36 Gy in 12 fractions (four times a week with two-weekly hyperthermia sessions), and conventional or moderate hypofractionation (1.6–2.5 Gy, five times a week with 1–2 weekly hyperthermia sessions). LC was significantly related to thermal dose (Kaidar-Personet et al., 2018) and favourable clinical factors (especially small tumours) (Bakker et al., 2021). Acute severe toxicity was mainly associated with large RT fields and late toxicity with a high dose per fraction or high total dose (Kaidar-Person et al., 2018), Oldenberg et al., 2015; Linthorst et al., 2015).

3.3.2. Ongoing clinical trials (Table 5)

As gathering data from randomized large-scale sources is challenging, the E²-RADlatE multi-cohort platform prospectively collects real-world data in prospective RT data registries and will answer questions stemming from current and future cohorts. Over five years, 250–500 patients are expected for each anatomic site.

The E²-RADlatE (EORTC 1811) study, deriving from strong EORTC-ESTRO collaboration, was designed to satisfy the demand for evidence of the efficacy, safety, and dose constraints of high-dose re-RT. The ReCare cohort (EORTC 2011-RP) will gather data on patients treated with high-dose re-RT for LR, new primary or secondary cancer (see at <https://project.eortc.org/e2-radiate/cohorts>).

3.3.3. Proposed research strategies

Given the lack of prospective studies on re-RT, the ATTM experts proposed:

a randomised PBI trial after second BCS comparing 26 Gy in 5 fractions with 40 Gy in 15 fractions (control);

a randomised trial based on the same rationale as the IMPORT-Low PBI trial (Coles et al., 2017) PBI: 26 Gy in 5 fractions, PBI: 40 Gy in 15 fractions, adapted WBI: 24 Gy WBI with integrated 26 Gy PBI in 5 fractions (Fig. 3);

participation in the ReCare study by specifically focusing on re-RT in the BC cohort.

4. Conclusions

Blending a real-life meeting with online technology facilitated

Table 5
On-going trials investigating breast re-irradiation.

Trial	PI, city country accrual time	Population and study summary	Number of patients required	Primary end point
Personalized Second Chance Breast Conservation (PSCBC): A Prospective Phase II Clinical Study (Second Chance) NCT04371913	John Ng, Weill Medical College of Cornell University, New York, USA Dec 2022- Dec 2027 John Ng, M.D. Weill Medical College of Cornell University	Partial Breast re-irradiation 30 Gy in 5 fractions over 1–2 weeks	60	Rate of treatment related AE graded by CTCAE version 5.0
Prospective Assessment of quality of life in patients with locally recurrent breast cancer and hyperthermic radiotherapy NCT04878666	Vanessa Heinrich, University Hospital Tubingen, Germany Dec 2021- Dec 2026	Pts with locally recurrent BC after close R0, R1 or R2 resection or local inoperability treated with RT and hyperthermia	20	Evaluation of the health-related QoL during and after hyperthermic RT measured by EORTC QLQ BR 23
A prospective observational registry cohort on high-dose Re-irradiation within the E2-RADlatE platform (EORTC211-RP) NCT03818503	Collaborative effort between ESTRO and EORTC Jun 2019-Apr 2024	Re-irradiated cases data registry	500	https://project.eortc.org/e2-radiate/cohorts

Abbreviations: AE, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; pts, patients; BC, breast cancer; QoL, Quality of Life; RT, radiation therapy; ESTRO, European Society for Radiotherapy and Oncology; EORTC, European Organization for Research and Treatment of Cancer.

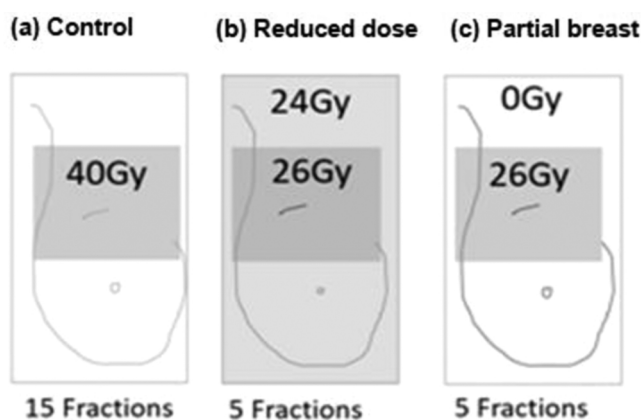


Fig. 3. Proposed randomised trial with 2 experimental groups. Control arm: (a) PBI 40 Gy in 15 fractions Experimental arms: (b) WBI 24 Gy in 5 fractions and 26 Gy to index quadrant and (c) PBI 26 Gy in 5 fractions.

worldwide participation in the 4th ATTM, thereby fulfilling its educational objectives as well as encouraging interest in clinical studies. The 2022 ATTM white paper reports in-depth analysis of the state of the art in RT for BC, open questions and proposals for decision-making when evidence is insufficient and/or opinions divided. Finally, international

collaboration is encouraged in setting up clinical trials to improve BC management and outcomes.

Disclosures

- Maria Cristina Leonardi reports speaker fee from Accuray Inc.
- Icro Meattini reports occasional speaker honoraria supported by Eli Lilly, Novartis, Pfizer, Accuray, and Seagen, outside the submitted work.
- Philip Poortmans is medical advisor of Sordina IORT Technologies, S.p.A., not related to the subject of this work.
- Ivica Ratoša received a Personal fee from Swixx Biopharma (Advisory Board) outside the submitted work.

All other authors have declared no conflicts of interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

C. Aristei and Philip Poortmans wrote and edited the paper. Topic 1: M. Arenas reviewed the main evidence, P. Franco reviewed the relevant clinical trials. O. Kaidar-Person wrote this section, B. Offeresen revised the drafts. Topic 2: R. Pfeffer reviewed the main evidence, V Kouloulias reviewed the relevant clinical trials, L. Boersma wrote the section, C. Bourcier revised the drafts. Topic 3: M.C. Leonardi reviewed the main evidence and wrote the section, Y. Bölükbaşı reviewed the relevant clinical trials, C. Coles and I. Meattini revised the drafts. Critical comments were received from: A. Montero Luis, V. Masiello, I. Palumbo, A. Morganti, E. Perrucci, V. Tombolini, M.Krengli, F. Marazzi, L. Trigo, S. Borghesi, A. Ciabattani, I. Ratoša, V. Valentini. All the authors read and approved the final draft.

Declaration of Competing Interest

On behalf of my co-authors (O. Kaidar-Person, L. Boersma, M. C. Leonardi, B. Offeresen, P. Franco, M. Arenas, C. Bourcier, R. Pfeffer, V Kouloulias, Y. Bölükbaşı, I. Meattini, C. Coles, A. Montero Luis, V. Masiello, I. Palumbo, A. Morganti, E. Perrucci, V. Tombolini, M. Krengli, F. Marazzi, L. Trigo, S. Borghesi, A. Ciabattani, I. Ratoša, V. Valentini, P. Poortmans) I declare there is no conflict of interest in this study and that no funding was received from any source.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.critrevonc.2023.104035](https://doi.org/10.1016/j.critrevonc.2023.104035).

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