Critical Reviews in Oncology / Hematology 187 (2023) 104035

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

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

C. Aristei [a,*,2], O. Kaidar-Person [b,1], L. Boersma [c,1], M.C. Leonardi [d,1], B. Offersen [e], P. Franco [f], M. Arenas [g], C. Bourgier [h], R. Pfeffer [i], V. Kouloulias [j], Y. Bölükbaşı [k], I. Meattini [l], C. Coles [m], A. Montero Luis [n], V. Masiello [o], I. Palumbo [a], A.G. Morganti [p,q], E. Perrucci [r], V. Tombolini [s], M. Krengli [t], F. Marazzi [o], L. Trigo [u], S. Borghesi [v], A. Ciabattoni [w], I. Ratoša [x], V. Valentini [y], P. Poortmans [z,aa]

[a] Radiation Oncology Section, Department of Medicine and Surgery, University of Perugia and Perugia General Hospital, Perugia, Italy
[b] Breast Radiation Unit, Radiation Oncology, Sheba Medical Center, Ramat Gan, Israel
[c] Radiation Oncology (Maastro), GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, the Netherlands
[d] Division of Radiation Oncology, IEO European Institute of Oncology, IRCCS, Milan, Italy
[e] Department of Experimental Clinical Oncology, Department of Oncology, Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark
[f] Depatment of Translational Medicine, University of Eastern Piedmont and Department of Radiation Oncology, 'Maggiore della Carita`' University Hospital, Novara, Italy
[g] Universitat Rovira I Virgili, Radiation Oncology Department, Hospital Universitari Sant Hoan de Reus, IISPV, Spain
[h] Radiation Oncology, ICM-Val d' Aurelle, Univ Montpellier, Montpellier, France
[i] Oncology Institute, Assuta Medical Center, Tel Aviv and Ben Gurion University Medical School, Israel
[j] 2nd Department of Radiology, Radiotherapy Unit, Medical School, National and Kapodistrian University of Athens, Greece
[k] Koc University, Faculty of Medicine, Department of Radiation Oncology, Istanbul, Turkey
[l] Department of Experimental and Clinical Biomedical Sciences "M. Serio", University of Florence & Radiation Oncology Unit – Oncology Department, Azienda Ospedaliero Universitaria Careggi, Florence, Italy
[m] Department of Oncology, University of Cambridge, UK
[n] Department of Radiation Oncology, University Hospital HM Sanchinarro, HM Hospitales, Madrid, Spain
[o] Unità Operativa di Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Gemelli IRCSS Roma, Italy
[p] DIMES, Alma Mater Studiorum Bologna University, Bologna, Italy
[q] Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Alma Mater Studiorum Bologna University, Bologna, Italy
[r] Radiation Oncology Section, Perugia General Hospital, Perugia, Italy
[s] Radiation Oncology, Department of Radiological, Oncological and Pathological Science, University "La Sapienza", Roma, Italy
[t] DISCOG, Università di Padova e Istituto Oncologico Veneto - IRCCS, Italy
[u] Service of Brachytherapy, Department of Image and Radioncology, Instituto Português Oncologia Porto Francisco Gentil E.P.E., Portugal
[v] Radiation Oncology Unit of Arezzo-Valdarno, Azienda USL Toscana Sud Est, Italy
[w] Department of Radiation Oncology, San Filippo Neri Hospital, ASL Rome 1, Rome, Italy
[x] Division of Radiation Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia; Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[y] Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Università Cattolica del Sacro Cuore e Fondazione Policlinico Gemelli IRCSS Roma, Italy
[z] University of Antwerp, Faculty of Medicine and Health Sciences, Antwerp, Belgium
[aa] Department of Radiation Oncology, Iridium Kankernetwerk, Antwerp, Belgium, Faculty of Medicine and Health Sciences, Antwerp, Belgium

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

* Correspondence to: Radiation Oncology Section, Department of Medicine and Surgery, University of Perugia and Perugia General Hospital, 06156 Perugia, Italy.
*E-mail address:* cynthia.aristei@unipg.it (C. Aristei).
[1] The authors contributed to the same extent.
[2] ORCID 0000-0002-9749-649X

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

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 (Offersen et al., 2015; Offersen 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 (cN0). 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 micrometatastic 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 intergroup 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 cN0-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, cN0 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 trail 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<br>Country<br>Accrual Time | Population and study summary | Number of patients required | Primary endpoint |
|---|---|---|---|---|
| **POSNOC**<br>**NCT02401685** | Amit Goyal,<br>University Hospitals of Derby and Burton NHS Foundation Trust, Derby UK<br>Aug 2014- Jul 2026 | Early BC with 1–2 positive nodes at SLNB<br>Adjuvant systemic therapy only vs axillary<br>treatment (ALND or axillary RT)<br>and adjuvant systemic therapy | 1900 | 5-year axillary RR |
| **BOOG 2013–07**<br>**NCT02112682** | The Netherland, Marjolein L Smidt,<br>Maastricht University Medical Centre<br>Hans JW de Wilt, Radboud University Medical Centre, The Netherland<br>Jun 2014 – Mar 2018 | Early BC undergoing mastectomy with 1–3 positive nodes at SLNB<br>Completion of axillary treatment vs no completion | 878 | 10-year regional RR |
| **SENOMAC**<br>**NCT02240472** | Jana de Boniface, Karolinska Institutet, Solna, Sweden and<br>International<br>Jan2015-Dec 2026 | Early BC with 1–2 positive nodes at SLNB<br>Completion ALND vs no axillary surgery | 2700 | 5-year BC specific survival |
| **SUPREMO**<br>**NCT00966888** | Ian H. Kunkler,<br>Edinburgh Cancer Centre at Western General Hospital, UK<br>Jan2006-Jun2010 | Early BC undergoing mastectomy and axillary treatment (pT1N1,pT2N0–1)<br>CW RT vs no RT | 3500 | OS<br>Acute and late morbidity |
| **TAILOR-RT (MA.39)**<br>**NCT03488693** | Timothy Whelan, Juravinski Cancer Centre at Hamilton Health Sciences, Ontario Canada<br>May 2018-Sept 2027 | Early BC undergoing mastectomy and axillary treatment<br>1–2 node positive at SLNB; 1–3 node Positive at AD; cT3N0<br>Oncotype Dx recurrence score $\leq$ 25<br>RT to CW + RNI vs no RT | 2140 | 10-year BC recurrence-free interval |
| **SKAGEN 1**<br>**NCT02384733** | Birgitte Offersen,<br>Aarhus University Hospital, Denmark<br>Mar 2015-Jul 2032 | Early BC undergoing both BCS and mastectomy<br>with indication to RNI<br>Hypofractionated RT (40 Gy/15 fr) vs conventionally fractionated RT | 2963 | 3-year arm lymphedema |
| **HYPOG-01**<br>**NCT03127995** | Sofia RIVERA,<br>Gustave Roussy, Paris<br>France<br>Sept 2016-Sept 2030 | Early BC undergoing both BCS and mastectomy with<br>indication to RNI<br>Hypofractionated RT (40 Gy/15 fr) vs conventionally fractionated RT | 1265 | 5- and 10-year arm lymphedema |
| **RHEAL**<br>**NCT04228991** | Timothy Whelan, Juravinski Cancer Centre at Hamilton Health Sciences, Ontario Canada<br>Canada<br>Feb2021-Dec2027 | Early BC undergoing both BCS and mastectomy<br>with indication to RNI<br>Mild hypofractionation (40 Gy/15 fr) vs ultrahypofractionation (26 Gy/5fr) | 588 | 3-year arm lymphedema |
| **HeNRIetta**<br>**NCT02515110** | Massey Cancer Center<br>Douglas W Arthur Virginia Commonwealth University, Massey Cancer Center, Richmond, Virginia<br>USA<br>Aug 2015-Oct 2024 | Early BC undergoing both BCS and mastectomy with indication to RNI<br>Single arm: hypofractionated RT (42.56 Gy/16 fr) | 137 | 3-year arm lymphedema |
| **FABREC**<br>**NCT03422003** | Rinaa Punglia and Julia Wong, Dana-Farber Cancer Institute, Boston USA<br>Apr 2018- Apr 2030 | BC patients undergoing mastectomy and immediate reconstruction<br>Hypofractionated RT (42.56 Gy/16 fr) vs conventionally fractionated RT | 400 | PROMs using FACT-B at 6 months |
| **DBCG Recon trial**<br>**NCT03730922** | Tove F Tvedskov,<br>Denmark<br>Jan 2020-Nov 2033 | BC patients treated with mastectomy and PMRT(40 Gy/15fr)<br>Delayed-immediate reconstruction vs Delayed reconstruction | 590 | Number of pts with Complication requiring surgical intervention 1 year after reconstruction |
| **RT CHARM**<br>**NCT03414970** | Matthew Poppe,<br>Huntsman Cancer Hospital, University of Utah USA, Canada<br>Feb 2018-Aug 2035 | BC patients (stage IIA-IIIA) undergoing mastectomy and reconstruction<br>Hypofractionated RT (42.56 Gy/16 fr) vs conventionally fractionated RT | 897 | 24-months reconstructive complication rate |
| **Ohio State University**<br>**NCT03786354** | Ohio State University Comprehensive Cancer Center, USA<br>USA<br>December 2018 - December 2020 | IMRT vs 3DCRT in node positive BC Pts receiving RNI | 60 | 1-year patient-reported shoulder/arm morbidity |
| **Mayo Clinic**<br>**NCT04443413** | Carlos E Vargas, Mayo Clinic USA<br>Jun 2020-June 2024 | 25 fraction photon-based RT vs 5 fraction proton-based RT | 98 | 24-month complication rate |
| **NSABP-B51**<br>**NCT01872975** | Norman Wolmark<br>NSABP Foundation USA<br>Aug 2013-Aug 2028 | Early BC pts (cT1–3,N1) undergoing PST and BCS or mastectomy with ypN0<br>if early BC: WBI + RNI vs WBI<br>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 the3–4 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 (Offersen et al., 2015; Offersen 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 CLTA-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

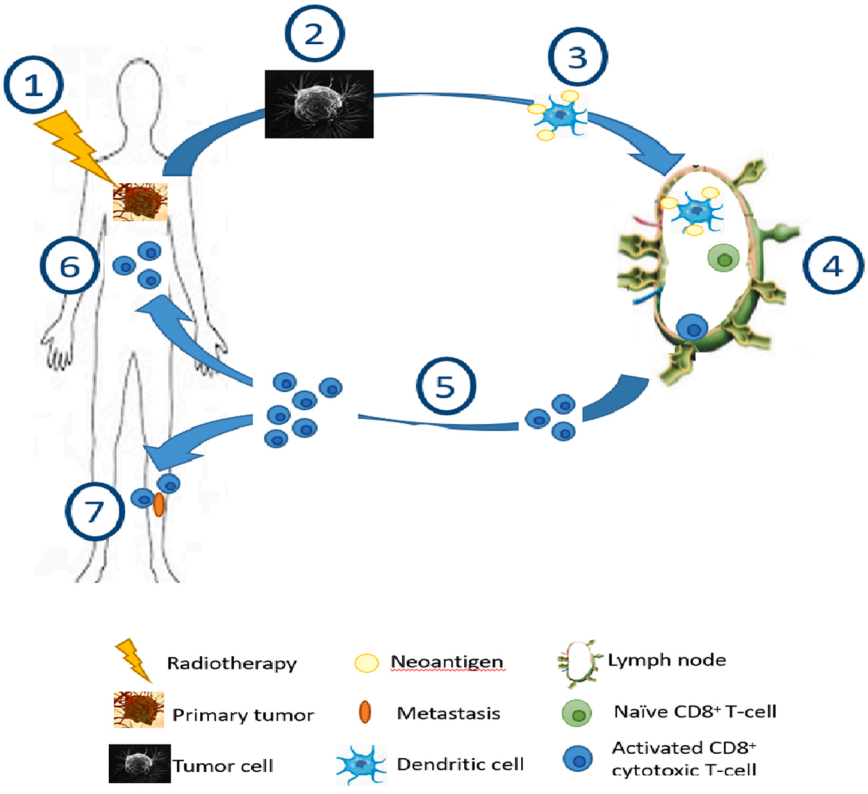


**Fig. 1.** 1. Radiotherapy to the primary tumour. 2. Tumour cells are killed, leading to release of neo-antigens. 3. The antigen presenting cells absorb the neoantigens, and migrate to the lymph node. 4. In the lymph nodes, the APCs activate the naïve CD8 positive T-cells. 5 Activated CD8 positive cytotoxic 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 Oncology 2022; 19; 58–64.*

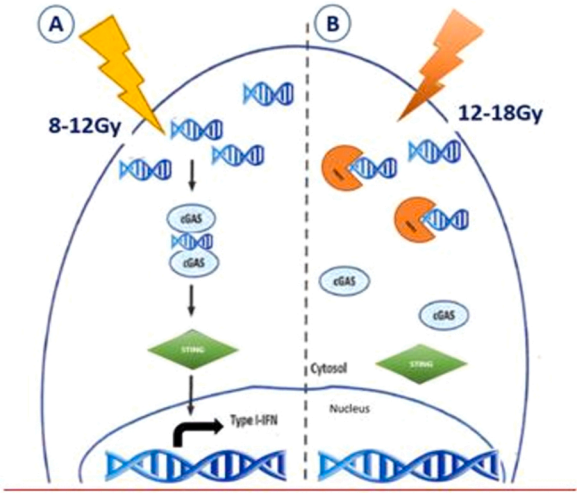


**Fig. 2.** Several signaling pathways influencing the abscopal effect. A: immunogenic radiotherapy doses (8–12 Gy) result in accumulation of dsDNA in the cytosol. cGAS binds to this dsDNA, and activates STING, resulting in Type 1 IFN production. B: Non-immunogenic radiotherapy doses can lead to production of the exonuclease TREX1, which removes dsDNA from the cytosol. Consequently, cGAS cannot bind to dsDNA, and cannot active STING, such that it does not result in production of Type 1 IFN. *Modified from: Ansems and Verheij: The abscopal effect of radiation therapy. Nederlands Tijdschrift voor Oncology 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 neoadjuvant 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 et al., 2020d) and Keynote-522 studies (Schmid et 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-L-1. 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 $\leq$ 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 preclinical 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<br>Country<br>Accrual Time | Population and study summary | Number of patients required | Primary endpoint |
|---|---|---|---|---|
| **Brain irradiation and tremelimumab in metastatic Breast cancer**<br>**NCT02563925** | Shanu Modi, New York, USA.<br>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**<br>**NCT03430479** | Masahiro Takada Kyoto, Japan.<br>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<br>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**<br>**NCT02730130** | Alice Y. Ho, Boston, USA.<br>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**<br>**NCT03051672** | Sara Tolaney, Boston, USA.<br>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;Pilones 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 (Pilones 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<br>Country<br>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<br>NCT03004183 | Jenny Chang, Texas, USA.<br>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<br>NCT03449238 | Silvia Formenti, New York, USA<br>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<br>Correlation of abscopal responses with the RT dose (at 1 year)<br>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) |
| 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<br>NCT03464942 | Sherene Loi, Melbourne, Australia.<br>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 | PFS at 24 months |
| RACHEL1: A Phase I Radiation and Checkpoint Blockade Trial in Patients With Metastatic Hormone Receptor Positive, HER2 Negative Breast Cancer<br>NCT03524170 | Meghan Karuturi, Texas USA.<br>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)<br>Safety and tolerability in pts with m HR+ /HER2- BC (Start of study drug up to 30 days after study drug stopped) |
| 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<br>NCT03789097 | Joshua Brody, New York, USA.<br>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)<br>NCT03915678 | Antoine Italiano, Bordeaux, France.<br>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 atezolimab + 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<br>NCT04683679 | Atif Khan, New York, USA.<br>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<br>NCT04690855 | Mylin Torres, Alabama, USA.<br>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<br>Country<br>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 ll Randomised Trial (Neo-CheckRaY)<br>NCT03875573 | Alex De Caluwe, Bruxelles, Belgium.<br>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)<br>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<br>NCT02977468 | Eileen Connolly, New York, USA.<br>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<br>NCT03366844 | Stephen Shiao, Los Angeles,<br>USA.<br>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)<br>Changes in TILs (Time Frame: 8 weeks after trial initiation) |
| Converting HR+ Breast Cancer Into an Individualized Vaccine (CBCV)<br>NCT03804944 | Silvia Formenti, New York, USA.<br>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)<br>Clinical response rate to RT + /-immunotherapy during standard ET for HR+ BC will be measured (3 years)<br>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.<br>NCT03872505<br>WITHDRAWN (lack of funding) | Heather McArthur, Cedars-Sinai, Los Angeles, USA.<br>Jul 2022 – Jul 2027 | Pts with clinical stage II-III, TNBC candidated to PST with durvalumab and randomized to receveive 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<br>NCT04443348 | Alice Ho, Duke University, Durham North Carolina, USA<br>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)<br>(Days 14 and 21)<br>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<br>(BreastVAX)<br>NCT04454528 | Julia C Tchou, Philadelphia, USA.<br>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<br>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<br>NCT02954874 | Lajos Pusztai, National Cancer Institute (NCI), USA.<br>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)<br>Severity of fatigue (55 weeks after randomization)<br>Physical function<br>(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)<br>NCT03818685 | Olivier Tredan, Lyon, France.<br>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; Leonardi 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., pN0 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 (Leonardi 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 metanalysis 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 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), Oldenborg 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 $E^2$-RADIatE 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 $E^2$-RADIatE (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-RADIatE 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.

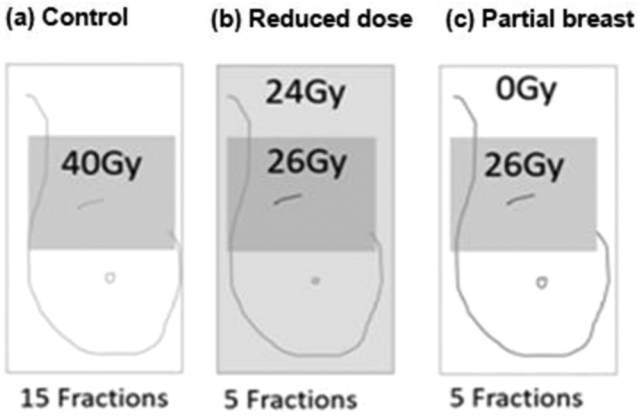


**Fig. 3.** Proposed randomised trial with 2 experimental groups. Control arm: (a) PBI 40 Gy in 15 fractions Experimental arms: (b) WBI 24 Gy in 5 fractions and 26 Gy to index quadrant and (c) PBI 26 Gy in 5 fractions.

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 Ratosa 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. Offersen revised the drafts. Topic 2: R. Pfeffer reviewed the main evidence, V Kouloulias reviewed the relevant clinical trials, L. Boersma wrote the section, C. Bourgier 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. Ciabattoni, 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. Offersen, P. Franco, M. Arenas, C. Bourgier, 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. Ciabattoni, 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.

## References

Alliance A011202 trial, https://clinicaltrials.gov/ct2/show/NCT01901094. (Accessed 5 May 2023).

Arenas, M., Selek, U., Kaidar-Person, O., et al., 2020. The 2018 assisi think tank meeting on breast cancer: International expert panel white paper. Crit. Rev. Oncol. Hematol. 151, 102967 https://doi.org/10.1016/j.critrevonc.2020.102967.

Aristei, C., Kaidar-Person, O., Arenas, M., et al., 2016. The 2016 Assisi Think Tank Meeting on breast cancer: white paper. Breast Cancer Res. Treat. 160 (2), 211–221 https://doi.org/:10.1007/s10549-016-3998-2.

Aristei, C., Bölükbaşı, Y., Kaidar-Person, O., et al., 2022. Ways to improve breast cancer patients' management and clinical outcome: The 2020 Assisi Think Tank Meeting. Crit. Rev. Oncol. Hematol. 177, 103774 https://doi.org/10.1016/j.critrevonc.2022.103774.

Arthur, D.W., Winter, K.A., Kuerer, H.M., et al., 2017. NRG Oncology-Radiation Therapy Oncology Group Study 1014: 1-year toxicity report from a phase 2 study of repeat breast-preserving surgery and 3-dimensional conformal partial-breast reirradiation for in-breast recurrence. Int. J. Radiat. Oncol. Biol. Phys. 98 (5), 1028–1035. https://doi.org/10.1016/j.ijrobp.2017.03.016.

Arthur, D.W., Winter, K.A., Kuerer, H.M., et al., 2020. Effectiveness of breast-conserving surgery and 3-dimensional conformal partial breast reirradiation for recurrence of breast cancer in the ipsilateral breast: The NRG Oncology/RTOG 1014 Phase 2 Clinical Trial. JAMA Oncol. 6 (1), 75–82. https://doi.org/10.1001/jamaoncol.2019.4320.

Association between tumor immune response and risk of recurrence in breast cancer patients treated with radiotherapy. Available at: https://www.straaleterapi.dk/media/1930/demet-oezcan-uk.pdf (Accessed: 10 January2023).

Bagley, A.F., Smith, B.D., 2019. Radiated, reconstructed, recurred. Int. J. Radiat. Oncol. Biol. Phys. 105 (3), 471–472. https://doi.org/10.1016/j.ijrobp.2019.05.070.

Bakker, A., Tello Valverde, C.P., van Tienhoven, G., et al., 2021. Post-operative re-irradiation with hyperthermia in locoregional breast cancer recurrence: temperature matters. Radiother. Oncol. 167, 149–157. https://doi.org/10.1016/j.radonc.2021.12.036.

Barroso-Sousa, R., Krop, I.E., Trippa, L., et al., 2020. A Phase II Study of pembrolizumab in cancer. Clin. Breast Cancer 20 (3), 238–245. https://doi.org/10.1016/j.clbc.2020.01.012.

Bartels, S.A.L., Donker, M., Poncet, C., et al., 2022. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer: 10-year results of the randomized controlled EORTC 10981-22023 AMAROS trial. JCO2201565 J. Clin. Oncol.. https://doi.org/10.1200/JCO.22.01565.

Bense, R.D., Sotiriou, C., Piccart-Gebhart, M.J., et al., 2017. Relevance of tumor-infiltrating immune cell composition and functionality for disease outcome in breast cancer. J. Natl. Cancer Inst. 109 (1), djw192. https://doi.org/10.1093/jnci/djw192.

Boersma, E.J., Sattler, M.G.A., Maduro, J.H., et al., 2022. Model-based selection for proton therapy in breast cancer: development of the national indication protocol for proton therapy and first clinical experiences. Clin. Oncol. 34 (4), 247–257. https://doi.org/10.1016/j.clon.2021.12.007.

Bottero, M., Borzillo, V., Pergolizzi, S., et al., 2021. The Italian Association of Radiotherapy and Oncology Recommendation for breast tumor recurrence: grades of recommendation, assessment, development and evaluation criteria. J. Breast Cancer 24, 241–252 https://doi.org10.4048/jbc.2021.24.e27.

Brackstone, M., Baldassarre, F.G., Perera, F.E., et al., 2021. Management of the axilla in early-stage breast cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J. Clin. Oncol. 39 (27), 3056–3082. https://doi.org/10.1200/JCO.21.00934.

Buchholz, T.A., Ali, S., Hunt, K.K., 2020. Multidisciplinary management of locoregional recurrent breast cancer. J. Clin. Oncol. 38 (20), 2321–2328. https://doi.org/10.1200/JCO.19.02806.

Buchwald, Z.S., Wynne, J., Nasti, T.H., et al., 2018. Radiation, immune checkpoint blockade and the abscopal effect: A critical review on timing, dose and fractionation. Front. Oncol. 8, 612. https://doi.org/10.3389/fonc.2018.00612.

Burstein, H.J., Curigliano, G., Thürlimann, B., et al., 2021. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer. Ann. Oncol. 32 (10), 1216–1235. https://doi.org/10.1016/j.annonc.2021.06.023.

Chen, A.M., Yoshizaki, T., Velez, M.A., et al., 2017. Tolerance of the brachial plexus to high-dose reirradiation. Int. J. Radiat. Oncol. Biol. Phys. 98, 83–90. https://doi.org/10.1016/j.ijrobp.2017.01.244.

Chen, D., Patel, R.R., Verma, V., et al., 2020. Interaction between lymphopenia, radiotherapy technique, dosimetry, in lung cancer patients receiving combined immunotherapy and radiotherapy. Radiother. Oncol. 150, 114–120. https://doi.org/10.1016/j.radonc.2020.05.051.

Chen, S.L., Martinez, S.R., 2008. The survival impact of the choice of surgical procedure after ipsilateral breast cancer recurrence. Am. J. Surg. 196 (4), 495–499. https://doi.org/10.1016/j.amjsurg.2008.06.018.

Choi, J.I., Khan, A.J., Powell, S.N., et al., 2021. Proton reirradiation for recurrent or new primary breast cancer in the setting of prior breast irradiation. Radiother. Oncol. 165, 142–151. https://doi.org/10.1016/j.radonc.2021.10.010.

Coles, C.E., Griffin, C.L., Kirby, A.M., et al., 2017. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non- inferiority trial. Lancet 390 (10099), 1048–1060. https://doi.org/10.1016/S0140-6736(17)31145-5.

Cortes, J., Cescon, D.W., Rugo, H.S., et al., 2020. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 396 (10265), 1817–1828. https://doi.org/10.1016/S0140-6736(20)32531-9.

Dafni, U., Michielin, O., Lluesma, S.M., et al., 2019. Efficacy of adoptive therapy with tumor-infiltrating lymphocytes and recombinant interleukin-2 in advanced cutaneous melanoma: a systematic review and meta-analysis. Ann. Oncol. 30 (12), 1902–1913. https://doi.org/10.1093/annonc/mdz398.

Datta, N.R., Puric, E., Klingbiel, D., et al., 2016. Hyperthermia and radiation therapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. Int. J. Radiat. Oncol. Biol. Phys. 94 (5), 1073–1087. https://doi.org/10.1016/j.ijrobp.2015.12.361.

Demaria, S., Kawashima, N., Yang, A.M., et al., 2005. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. Clin. Cancer Res. 11 (2 Pt 1), 728–734.

Dewan, M.Z., Galloway, A.E., Kawashima, N., et al., 2009. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin. Cancer Res. 15 (17), 5379–5388. https://doi.org/10.1158/1078-0432.CCR-09-0265.

Donker, M., van Tienhoven, G., Straver, M.E., et al., 2014. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 15 (12), 1303–1310. https://doi.org/10.1016/S1470-2045(14)70460-7.

Donskov, F., 2007. Interleukin-2 based immunotherapy in patients with metastatic renal cell carcinoma. Dan. Med. Bull. 54 (4), 249–265.

Emami, B., Lyman, J., Brown, A., et al., 1991. Tolerance of normal tissue to therapeutic irradiation. Int. J. Radiat. Oncol. Biol. Phys. 21 (1), 109–122. https://doi.org/10.1016/0360-3016(91)90171-y.

Emens, L.A., 2018. Breast cancer immunotherapy: facts and hopes. Clin. Cancer Res. 24 (3), 511–520. https://doi.org/10.1158/1078-0432.CCR-16-3001.

Emens, L.A., Adams, S., Barrios, C.H., et al., 2021. First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. Ann. Oncol. 32 (8), 983–993. https://doi.org/10.1016/j.annonc.2021.05.355.

Fattahi, S., Ahmed, S.K., Park, S.S., et al., 2020. Reirradiation for locoregional recurrent breast cancer. Adv. Radiat. Oncol. 6 (1), 100640 https://doi.org/10.1016/j.adro.2020.100640.

Galimberti, V., Cole, B.F., Viale, G., et al., 2018. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol. 19, 1385–1393. https://doi.org/10.1016/S1470-2045(18)30380-2.

Giuliano, A.E., Hunt, K.K., Ballman, K.V., et al., 2011. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305 (6), 569–575. https://doi.org/10.1001/jama.2011.90.

Giuliano, A.E., Ballman, K.V., McCall, L., et al., 2017. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Zoo11 (Alliance) randomized clinical trial. JAMA 318 (10), 918–926. https://doi.org/10.1001/jama.2017.11470.

Goyal, A., Mann, G.B., Fallowfield, L., et al., 2021. POSNOC Trialists. POSNOC-POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy: a randomised controlled trial of axillary treatment in women with early-stage breast cancer who have metastases in one or two sentinel nodes. BMJ Open 11 (12), e054365. https://doi.org/10.1136/bmjopen-2021-054365.

Gray, J.E., Villegas, A., Davey, D., et al., 2020. Three-year overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC - Update from PACIFIC. J. Thorac. Oncol. 15 (2), 288–293. https://doi.org/10.1016/j.jtho.2019.10.002.

Hannoun-Levi, J.M., Resch, A., Gal, J., et al., 2013. GEC-ESTRO Breast Cancer Working Group. Accelerated partial breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast tumour recurrence: multicentric study of the GEC-ESTRO Breast Cancer Working Group. Radiother. Oncol. 108 (2), 226–231. https://doi.org/10.1016/j.radonc.2013.03.026.

Hannoun-Levi, J.M., Gal, J., Van Limbergen, E., et al., 2021. Salvage mastectomy versus second conservative treatment for second ipsilateral breast tumor event: a propensity score-matched cohort analysis of the GEC-ESTRO Breast Cancer Working Group Database. Int. J. Radiat. Oncol. Biol. Phys. 110 (2), 452–461. https://doi.org/10.1016/j.ijrobp.2020.12.029.

Haque, W., Singh, A., Verma, V., et al., 2021. Postmastectomy radiation therapy following pathologic complete nodal response to neoadjuvant chemotherapy: A prelude to NSABP B-51? Radiother. Oncol. 162, 52–59. https://doi.org/10.1016/j.radonc.2021.06.032.

Harms, W., Budach, W., Dunst, J., et al., 2016. Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). DEGRO practical guidelines for radiotherapy of breast cancer VI: therapy of locoregional breast cancer recurrences. Strahlenther. Onkol. 192 (4), 199–208. https://doi.org/10.1007/s00066-015-0939-7.

Ho, A.Y., Barker, C.A., Arnold, B.B., et al., 2020a. A phase 2 clinical trial assessing the efficacy and safety of pembrolizumab and radiotherapy in patients with metastatic triple-negative breast cancer. Cancer 126 (4), 850–860. https://doi.org/10.1002/cncr.32599.

Ho, A.Y., Wright, J.L., Blitzbau, R.C., et al., 2020b. Optimizing radiation therapy to boost systemic immune responses in breast cancer: a critical review for breast radiation oncologists. Int. J. Radiat. Oncol. Biol. Phys. 108 (1), 227–241. https://doi.org/10.1016/j.ijrobp.2020.05.011.

Ho, A.Y., Kalinsky, K., McArthur, H.L., et al., 2021. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of breast cancer. J. Immunother. Cancer 9 (8), e002597. https://doi.org/10.1136/jitc-2021-002597.

https://www.nrgoncology.org/ciro-breast. (Accessed 5 May 2023).

https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html (Accessed: 10 January 2023).

Jagsi, R., Chadha, M., Moni, J., et al., 2014. Radiation field design in the ACOSOG Zoo11 (Alliance) trial. J. Clin. Oncol. 32 (32), 3600–3606. https://doi.org/10.1200/JCO.2014.56.5838.

Jannetti, S.A., Zeglis, B.M., Zalutsky, M.R., et al., 2020. Poly (ADP-Ribose) Polymerase (PARP) inhibitors and radiation therapy. Front. Pharmacol. 11, 170. https://doi.org/10.3389/fphar.2020.00170.

Jatoi, I., Benson, J.R., Kunkler, I., 2018. Hypothesis: can the abscopal effect explain the impact of adjuvant radiotherapy on breast cancer mortality? NPJ Breast Cancer 4, 8. https://doi.org/10.1038/s41523-018-0061-y.

Kaidar-Person, O., Oldenborg, S., Poortmans, P., 2018. Re-irradiation and hyperthermia in breast cancer. Clin. Oncol. (R. Coll. Radiol. ) 30 (2), 73–84. https://doi.org/10.1016/j.clon.2017.11.004.

Kaidar-Person, O., Offersen, B.V., Hol, S., et al., 2019. ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation

therapy after implant-based immediate reconstruction for early stage breast cancer. Radiother. Oncol. 137, 159–166. https://doi.org/10.1016/j.radonc.2019.04.010.
Kaidar-Person, O., Dahn, H.M., Nichol, A.M., et al., 2021a. A Delphi study and international consensus recommendations: the use of bolus in the setting of postmastectomy radiation therapy for early breast cancer. Radiother. Oncol. 164, 115–121. https://doi.org/10.1016/j.radonc.2021.09.012.
Kaidar-Person, O., Offersen, B.,V., Boersma, L., et al., 2021b. Tricks and tips for target volume definition and delineation in breast cancer: Lessons learned from ESTRO breast courses. Radiother. Oncol. 162, 185–194. https://doi.org/10.1016/j.radonc.2021.07.015.
Kaidar-Person, O., Fortpied, C., Hol, S., et al., 2022. The association of internal mammary and medial supraclavicular lymph node radiation technique with clinical outcomes: results from the EORTC 22922/10925 randomised trial. Radiother. Oncol. 172, 99–110. https://doi.org/10.1016/j.radonc.2022.05.006.
Kasherman, L., Karakasis, K., Oza, A.M., 2021. With our powers combined: exploring parp inhibitors and immunotherapy. Cancer J. 27 (6), 511–520. https://doi.org/10.1097/PPO.0000000000000557.
Lamberth, F., Guilbert, P., Gaillot-Petit, N., et al., 2014. Indications potentielles de la tomothérapie hélicoïdale dans les cancers du sein [Potential indications for helical tomotherapy in breast cancers]. Cancer Radio. 18, 7–14. https://doi.org/10.1016/j.canrad.2013.07.148.
Latty, D., Stuart, K.E., Wang, W., et al., 2015. Review of deep inspiration breath-hold techniques for the treatment of breast cancer. J. Med. Radiat. Sci. 62 (1), 74–81. https://doi.org/10.1002/jmrs.96.
Leonardi, M.C., Tomio, L., Radice, D., et al., 2020. Study Groups "Brachytherapy, Interventional Radiotherapy and Intraoperative Radiotherapy" and "Reirradiation" of the Italian Radiotherapy and Clinical Oncology Society (AIRO). Local failure after accelerated partial breast irradiation with intraoperative radiotherapy with electrons: an insight into management and outcome from an Italian multicentric study. Ann. Surg. Oncol. 27 (3), 752–762. https://doi.org/10.1245/s10434-019-08075-3.
Linthorst, M., van Geel, A.N., Baaijens, M., et al., 2013. Re-irradiation and hyperthermia after surgery for recurrent breast cancer. Radiother. Oncol. 109 (2), 188–193. https://doi.org/10.1016/j.radonc.2013.05.010.
Linthorst, M., Baaijens, M., Wiggenraad, R., et al., 2015. Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. Radiother. Oncol. 117 (2), 217–222. https://doi.org/10.1016/j.radonc.2015.04.019.
Luke, J.J., Flaherty, K.T., Ribas, A., et al., 2017. Targeted agents and immunotherapies: optimizing outcomes in melanoma. Nat. Rev. Clin. Oncol. 14 (8), 463–482. https://doi.org/10.1038/nrclinonc.2017.43.
Mamounas, E.P., Anderson, S.J., Dignam, J.J., et al., 2012. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J. Clin. Oncol. 30 (32), 3960–3966. https://doi.org/10.1200/JCO.2011.40.8369.
Mamounas, E.P., Bandos, H., White, J.R., et al., 2019. NRG Oncology/NSABP B-51/RTOG 1304: Phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) reduces invasive breast cancer recurrence free interval (IBCRFI) in patients (pts) with positive axillary (PAx) nodes who are ypN0 after neoadjuvant chemotherapy (NC). J. Clin. Oncol. 37 (Suppl), 15. https://doi.org/10.1200/JCO.2019.37.15_suppl.TPS600.
Meattini, I., Becherini, C., Boersma, L., et al., 2022a. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol. 23 (1), e21–e31. https://doi.org/10.1016/S1470-2045(21)00539-8.
Meattini, I., Palumbo, I., Becherini, C., et al., 2022b. The Italian Association for Radiotherapy and Clinical Oncology (AIRO) position statements for postoperative breast cancer radiation therapy volume, dose, and fractionation. Radiol. Med. 127 (12), 1407–1411. https://doi.org/10.1007/s11547-022-01563-9.
Merino, T., Tran, W.T., Czarnota, G.J., 2015. Re-irradiation for locally recurrent refractory breast cancer. Oncotarget 6 (33), 35051–35062. https://doi.org/10.18632/oncotarget.6036.
Milo, M.L., Lörincz, T., Nielsen, M.H., et al., 2022. Acute toxicity after loco regional breast radiation therapy in the randomized DBCG SKAGEN trial 1. Radiother. Oncol. Suppl 1), 0829.
Mittendorf, E.A., Zhang, H., Barrios, C.H., et al., 2020. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet 396 (10257), 1090–1100. https://doi.org/10.1016/S0140-6736(20)31953-X.
Montagne, L., Gal, J., Chand, M.E., et al., 2019. GEC-ESTRO APBI classification as a decision-making tool for the management of 2nd ipsilateral breast tumor event. Breast Cancer Res. Treat. 176 (1), 149–157. https://doi.org/10.1007/s10549-019-05221-z.
Montagne, L., Hannoun, A., Hannoun-Levi, J.M., 2020. Second conservative treatment for second ipsilateral breast tumor event: a systematic review of the different re-irradiation techniques. Breast 49, 274–280. https://doi.org/10.1016/j.breast.2020.01.003.
Morrow, M., 2018. Management of node-positive axilla in breast cancer in 2017. Sel. Right Option JAMA Oncol. 4 (2), 250–251. https://doi.org/10.1001/jamaoncol.2017.3625.
Müller, A.C., Eckert, F., Heinrich, V., et al., 2011. Re-surgery and chest wall re-irradiation for recurrent breast cancer: a second curative approach. BMC Cancer 11, 197. https://doi.org/10.1186/1471-2407-11-197.
Nanda, R., Liu, M.C., Yau, C., et al., 2020a. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. JAMA Oncol. 6 (5), 676–684. https://doi.org/10.1001/jamaoncol.2019.6650.
Nanda, R., Liu, M.C., Yau, C., et al., 2020b. Effect of pembrolizumab plus neo-adjuvant chemotherapy on pathological complete response in women with early-stage breast cancer. JAMA Oncol. 6 (5), 676–684. https://doi.org/10.1001/jamaoncol.2019.6650.
NCCN breast cancer guidelines version 4.23 https://www.nccn.org/professionals/physician _gls/pdf/breast.pdf. (Accessed 5 May 2023).
Nguyen, A., Shiao, S., McArthur, H., 2021. Advances in combining radiation and immunotherapy in breast cancer. Clin. Breast Cancer 21 (2), 143–152. https://doi.org/10.1016/j.clbc.2021.03.007.
Offersen, B.V., Boersma, L.J., Kirkove, C., et al., 2015. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother. Oncol. 114 (1), 3–10. https://doi.org/10.1016/j.radonc.2014.11.030.
Offersen, B.V., Boersma, L.J., Kirkove, C., et al., 2016. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1. Radiother. Oncol. 118 (1), 205–208. https://doi.org/10.1016/j.radonc.2015.12.027.
Oldenborg, S., Griesdoorn, V., van Os, R., et al., 2015. Reirradiation and hyperthermia for irresectable locoregional recurrent breast cancer in previously irradiated area: size matters. Radiother. Oncol. 117 (2), 223–228. https://doi.org/10.1016/j.radonc.2015.10.017.
Overgaard, M., Nielsen, H.M., Tramm, T., et al., 2022. Postmastectomy radiotherapy in high-risk breast cancer patients given adjuvant systemic therapy. A 30-year long-term report from the Danish breast cancer cooperative group DBCG 82bc trial. Radiother. Oncol. 170, 4–13. https://doi.org/10.1016/j.radonc.2022.03.008.
Page, D.B., Beal, K., Linch, S.N., et al., 2022. Brain radiotherapy, tremelimumab-mediated CTLA-4-directed blockade +/- trastuzumab in patients with breast cancer brain metastases. NPJ Breast Cancer 8 (1), 50. https://doi.org/10.1038/s41523-022-00404-2.
Parulekar, W.R., Berrang, T., Kong, I., et al., 2019. Cctg MA.39 tailor RT: a randomized trial of regional radiotherapy in biomarker low-risk node-positive breast cancer (NCT03488693).Journal of Clinical Oncology 37:15_suppl. TPS602-TPS602.
Petroni, G., Cantley, L.C., Santanbrogio, L., et al., 2021. Radiotherapy as a tool to elicit clinically actionable signaling pathways in cancer. Nat. Rev. Clin. Oncol. 19 (4), 114–131. https://doi.org/10.1038/s41571-021-00579-w.
Pilones, K.A., Charpentier, M., Garcia-Martinez, E., et al., 2020. Radiotherapy cooperates with IL15 to induce antitumor immune responses. Cancer Immunol. Res. 8 (8), 1054–1063. https://doi.org/10.1158/2326-6066.CIR-19-0338.
Poortmans, P.M., Collette, S., Kirkove, C., et al., 2015. Internal mammary and medial supraclavicular irradiation in breast cancer. New Engl. J. Med 373 (4), 317–327. https://doi.org/10.1056/NEJMoa1415369.
Poortmans, P.M., Weltens, C., Fortpied, C., et al., 2020. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. Lancet Oncol. 21 (12), 1602–1610. https://doi.org/10.1016/S1470-2045(20)30472-1.
Poortmans, P.M., Struikmans, H., De Brouwer, P., et al., 2021. Side effects 15 years after lymph node irradiation in breast cancer: randomized EORTC trial 22922/10925. J. Natl. Cancer Inst. 113 (10), 1360–1368. https://doi.org/10.1093/jnci/djab113.
Poppe, M.M., Yehia, Z.A., Baker, C., et al., 2020. 5-year update of a multi-institution, prospective phase 2 hypofractionated postmastectomy radiation therapy trial. Int. J. Radiat. Oncol. Biol. Phys. 107 (4), 694–700. https://doi.org/10.1016/j.ijrobp.2020.03.020.
Pusztai, L., Yau, C., Wolf, D.M., et al., 2021. Durvalumab with olaparib and paclitaxel for high-risk HER2- negative stage II/III breast cancer: results from the adaptively randomized I-SPY trial. Cancer Cell 39 (7), 989–998. https://doi.org/10.1016/j.ccell.2021.05.009.
RADCOMP Breast Atlas v.3 - bigreduced.pdf (nrgoncology.org) (Accessed 5 May 2023).
Recht, A., Comen, E.A., Fine, R.E., et al., 2016. Postmastectomy radiotherapy: an American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology focused guideline update. Pract. Radiat. Oncol. 6 (6), e219–e234. https://doi.org/10.1016/j.prro.2016.08.009.
Resch, A., Fellner, C., Mock, U., et al., 2002. Locally recurrent breast cancer: pulse dose rate brachytherapy for repeat irradiation following lumpectomy - a second chance to preserve the breast. Radiology 225 (3), 713–718. https://doi.org/10.1148/radiol.2253011913.
Reynders, K., Illidge, T., Siva, S., et al., 2015. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. Cancer Treat. Rev. 41 (6), 503–510. https://doi.org/10.1016/j.ctrv.2015.03.011.
Rugo, H.S., Loi, S., Adams, S., et al., 2021. PD-L1 immunohistochemistry assay comparison in atezolizumab plus nab-paclitaxel treated advance triple negative breast cancer. J. Natl. Cancer Inst. 113 (12), 1733–1743. https://doi.org/10.1093/jnci/djab108.
Schmid, P., Adams, S., Rugo, H.S., et al., 2018. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. New Engl. J. Med. 379 (22), 2108–2121. https://doi.org/10.1056/NEJMoa1809615.
Schmid, P., Salgado, R., Park, Y.H., et al., 2020a. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann. Oncol. 31 (5), 569–581 https://doi.org/d10.1016/j.annonc.2020.01.072.
Schmid, P., Cortes, J., Pusztai, L., et al., 2020b. Pembrolizumab for early triple negative breast cancer. New Engl. J. Med. 382 (9), 810–821. https://doi.org/10.1056/NEJMoa1910549. c.

Schmid, P., Rugo, H.S., Adams, S., et al., 2020c. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 21 (1), 44–59. https://doi.org/10.1016/S1470-2045(19)30689-8.

Schmid, P., Salgado, R., Park, Y.H., et al., 2020d. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann. Oncol. 31 (5), 569–581. https://doi.org/10.1016/j.annonc.2020.01.072.

Schmid, P., Cortes, J., Dent, R., et al., 2022. Event-free survival with pembrolizumab in early triple-negative breast cancer. New Engl. J. Med. 386 (6), 556–567. https://doi.org/10.1056/NEJMoa2112651.

Sha, C.M., Lehrer, E.J., Hwang, C., et al., 2020. Toxicity in combination immune checkpoint inhibitor and radiation therapy: a systematic review and meta-analysis. Radiother. Oncol. 151, 141–148. https://doi.org/10.1016/j.radonc.2020.07.035.

Shah, C., Vicini, F., Keisch, M., et al., 2012. Outcome after ipsilateral breast tumor recurrence in patients who receive accelerated partial breast irradiation. Cancer 118 (17), 4126–4131. https://doi.org/10.1002/cncr.27400.

Skinner, H.D., Strom, E.A., Motwani, S.B., et al., 2013. Radiation dose escalation for loco-regional recurrence of breast cancer after mastectomy. Radiat. Oncol. 8, 13. https://doi.org/10.1186/1748-717X-8-13.

Smith, T.E., Lee, D., Turner, B.C., et al., 2000. True recurrence vs new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. Int. J. Radiat. Oncol. Biol. Phys. 48 (5), 1281–1289. https://doi.org/10.1016/s0360-3016(00)01378-x.

Stick, L.B., Lorenzen, E.L., Yates, E.S., et al., 2021. Selection criteria for early breast cancer patients in the DBCG proton trial - the randomised phase III trial strategy. Clin. Transl. Radiat. Oncol. 27, 126–131. https://doi.org/10.1016/j.ctro.2021.01.012.

Su, Y., Guo, R., Xue, J., et al., 2019. Increased mortality with repeat lumpectomy alone after ipsilateral breast tumor recurrence. Oncologist 24 (9), e818–e827. https://doi.org/10.1634/theoncologist.2018-0606.

Swamy, K., 2022. Stereotactic body radiotherapy immunological planning - a review with a proposed theoretical model. Front. Oncol. 12, 729250 https://doi.org/10.3389/fonc.2022.729250.

Tarantino, P., Gandini, S., Trapani, D., et al., 2021. Immunotherapy addition to neoadjuvant chemotherapy for early triple negative breast cancer: a systemic review and meta-analysis of randomized clinical trials. Crit. Rev. Oncol. Hematol. 159, 103223 https://doi.org/10.1016/j.critrevonc.2021.103223.

Thorsen, L.B.J., Overgaard, J., Matthiessen, L.W., et al., 2022. Internal mammary node irradiation in patients with node-positive breast cancer: fifteen-year results from the Danish Breast Cancer Group Internal Mammary Node Study. J. Clin. Oncol. 40 (36), 4198–4206. https://doi.org/10.1200/JCO.22.00044.

Tinterri, C., Gentile, D., Gatzemeier, W., et al., 2022. Preservation of axillary lymph nodes compared with complete dissection in T1-2 breast cancer patients presenting one or two metastatic sentinel lymph nodes: the SINODA-ONE multicenter randomized clinical trial. Ann. Surg. Oncol. 29 (9), 5732–5744. https://doi.org/10.1245/s10434-022-11866-w.

Vanneste, B.G.L., Van Limbergen, E.J., Dubois, L., et al., 2020. Immunotherapy as sensitizer for local radiotherapy. Oncoimmunology 9 (1), 1832760. https://doi.org/10.1080/2162402X.2020.1832760.

Vanpouille-Box, C., Alard, A., Aryankalayil, M.J., et al., 2017. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Nat. Commun. 8, 15618. https://doi.org/10.1038/ncomms15618.

Vega, R.B.M., Wang, S., Brooks, E.D., et al., 2022. Evaluating regional node irradiation allocation and association with oncologic outcomes in NSABP B-18, B-27, B-40 and B-41. Int. J. Radiat. Oncol. Biol. Phys. 113 (3), 542–551. https://doi.org/10.1016/j.ijrobp.2022.03.007.

Venkatesulu, B.P., Malick, S., Lin, S.H., et al., 2018. A systematic review of the influence of radiation-induced lymphopenia on survival outcomes in solid tumors. Crit. Rev. Oncol. Hematol. 123, 42–51. https://doi.org/10.1016/j.critrevonc.2018.01.003.

Vila, J., Garcia-Etienne, C.A., Vavassori, A., et al., 2014. Conservative surgery for ipsilateral breast tumor recurrence. J. Surg. Oncol. 110 (1), 62–67. https://doi.org/10.1002/jso.23629.

Voorwerk, L., Slagter, M., Horlings, H.M., et al., 2019. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nat. Med. 25 (6), 920–928. https://doi.org/10.1038/s41591-019-0432-4.

Walstra, C.J.E.F., Schipper, R.J., Poodt, I.G.M., et al., 2019. Repeat breast-conserving therapy for ipsilateral breast cancer recurrence: A systematic review. Eur. J. Surg. Oncol. 45 (8), 1317–1327. https://doi.org/10.1016/j.ejso.2019.02.008.

Walstra, C.J.E.F., Schipper, R.J., van Riet, Y.E., et al., 2021. Repeat breast-conserving treatment of ipsilateral breast cancer recurrence: a nationwide survey amongst breast surgeons and radiation oncologists in the Netherlands. Breast Cancer Res. Treat. 187 (2), 499–514. https://doi.org/10.1007/s10549-021-06154-2.

Wapnir, I.L., Gelber, S., Anderson, S.J., et al., 2017. CALOR trial investigators. Poor prognosis after second locoregional recurrences in the CALOR Trial. Ann. Surg. Oncol. 24 (2), 398–406. https://doi.org/10.1245/s10434-016-5571-y.

Whelan, T.J., Olivotto, I.A., Parulekar, W.R., et al., 2015. Regional nodal irradiation in early-stage breast cancer. New Engl. J. Med. 373 (4), 307–316. https://doi.org/10.1056/NEJMoa1415340.

de Wild, S.R., de Munck, R., Simons, J.M., et al., 2022. De-escalation of radiotherapy after primary chemotherapy in cT1–2N1 breast cancer (RAPCHEM; BOOG 2010–03): 5-year follow-up results of a Dutch, prospective, registry study. Lancet Oncol. 23 (9), 1201–1210. https://doi.org/10.1016/S1470-2045(22)00482-X.

Wu, Y., Shi, X., Li, J., et al., 2021. Prognosis of surgical treatment after ipsilateral breast tumor recurrence. J. Surg. Res 258, 23–37. https://doi.org/10.1016/j.jss.2020.07.045.

Yi, M., Kronowitz, S.J., Meric-Bernstam, F., et al., 2011. Local, regional, and systemic recurrence rates in patients undergoing skin-sparing mastectomy compared with conventional mastectomy. Cancer 117 (5), 916–924. https://doi.org/10.1002/cncr.25505.

Young, K.H., Baird, J.R., Savage, T., et al., 2016. Optimizing timing of immunotherapy improves control of tumors by hypofractionated radiation therapy. PLoS One 11 (6), e0157164. https://doi.org/10.1371/journal.pone.0157164.

**Cynthia Aristei,** MD is Full Professor of Radiation Oncology in the Department of Medicine and Surgery at the University of Perugia, Italy and Head of the Radiation Oncology Unit at Perugia General Hospital. Breast and gynecologic cancer, such as hematological malignancies, are her main field of interest in radiation oncology. She is involved in clinical and translational research project and has been presenting her research findings at Italian and International Conferences for almost 30 years. Furthermore, she has engaged in organizing national and international meetings. She is an ASTRO, ESTRO, EUSOMA and ASCO member.

**Orit Kaidar-Person,** MD is radiation oncologist & the Head of Breast Cancer Radiotherapy Unit at Sheba Medical Center, Ramat Gan, and senior lecturer at Tel Aviv University, Israel. She is member of the ESTRO breast cancer faculty, of the educational faculty of FALCON-ESTRO (Fellowship in Anatomic delineation and CONtouring) and of the ESTRO-ACROP breast cancer focus group. She also is currently a foreign PhD student at GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands, focusing on improving radiation therapy outcomes of breast cancer patients after mastectomy, especially related to breast reconstruction.

**Liesbeth Boersma**, MD is radiation oncologist at Dept. Radiation Oncology making and innovation implementation. She is member of the Dutch (Maastro), GROW-School for Oncology and Reproduction, Maastricht University Medical Centre, Maastricht, The Netherlands, and professor at the University of Maastricht, The Netherlands. Her fields of interest include radiotherapy for breast cancer, shared decision Committee for Breast Cancer Guidelines, (co-) PI of several studies, and member of the Dutch Breast Cancer Research Group (BOOG) Locoregional Treatment. She is chair of the Dutch Platform for Proton Therapy. In addition, she is faculty member of the ESTRO course multidisciplinary treatment of breast cancer, and of the ESTRO-(ACROP) guideline committee, breast cancer subgroup.

**Maria Cristina Leonardi** is a Deputy Director of the Division of Radiation Therapy at the European Institute of Oncology, Milan, Italy, where she has worked since 1997. She is member of the Board of Specialization School in Radiotherapy at University of Milan and of ISIORT Europe. She has experience in intraoperative radiotherapy and IMRT treatments. Pivotal publications focus on breast cancer. The main field of interest addresses partial breast irradiation and hypofractionation.

**Birgitte V. Offersen** is a clinical oncologist, PhD, at Department of Experimental Clinical Oncology & Dept Oncology & Danish Center for Particle Therapy at Aarhus University Hospital, Denmark. She is clinical professor at Aarhus University, chair of the Danish Breast Cancer Group (DBCG) Board and chair of the DBCG RT Committee. She is PI on 5 national and international clinically controlled randomised trials developing new radiation therapies for early breast cancer patients. In addition, she is faculty member of the ESTRO course on multidisciplinary treatment of breast cancer and of the ESTRO guideline committee breast cancer subgroup. Main interests are radiation therapy, breast cancer, tumour microenvironment, clinical trials, shared decision making and patient involvement.

**Pierfrancesco Franco**, MD, PhD is a radiation and clinical oncologist. He is currently appointed as Associate Professor of Radiation Oncology, at the Department of Translational Medicine, University of Eastern Piedmont, in Novara, Italy. He is specifically working on breast and head and neck cancers and gastrointestinal malignancies. He is involved in clinical research and cancer education collaborating with the ESTRO, ESO and EORTC. He has a special interest in psycho oncology and professional well-being.

**Meritxell Arenas Prat,** MD, PhD is specialist in Radiation Oncology. In 2000 she started working at the Hospital Universitari Sant Joan de Reus (HUSJR) (Tarragona, Catalonia, Spain) as first specialist responsible of Breast Cancer Radiotherapy. In 2008 she realized the doctoral thesis in basic research (Radiobiology) in University of Barcelona ("Anti-inflammatory effects of low-dose radiotherapy in an experimental model of systemic inflammation in mice"). In 2010 was selected as Head of Radiation Oncology Department at the HUSJR, were she is still serving. She is Coordinator of Radiation Oncology Research Group at Institut d'Investigacions Sanitàries Pere Virgili (IISPV), Associate Professor at Universitat Rovira i Virgili (URV) and President of Catalan Oncology Society. The main research line of Dr. Arenas is the identification of molecular biomarkers based on energy metabolism, oxidative stress and immune system in patients with breast cancer.

**Celine Bourgier** is radiation oncologist at the department of radiation oncology of the Institut du Cancer de Montpellier, France, and Professor at the University of Montpellier, France. She is strongly involved in breast cancer field as PI of several clinical trials. She is also actively involved in late radio-induced toxicities prevention and management as PI of

several clinical trials and as coordinator in Radiobiology & targeted radiotherapy team of radiobiology research, INSERM U1194, Montpellier, France.

**Raphael Pfeffer**, MD is Head of Oncology Institute, Assuta Medical Center, Tel Aviv. Research projects included the effects of combined modality therapy of radiation with chemotherapy and hyperthermia and the combination of novel biological agents with radiotherapy. Clinical projects included stereotactic irradiation for both CNS and non-CNS tumors and MR guided focused ultrasound in cancer treatment. Participated in EORTC Radiotherapy Group clinical studies and other locally initiated and international clinical studies. Member of the following scientific organizations: ASTRO, ESTRO, ASCO. Organizing committee, 3rd biennial meeting of ISRS (International Society for RadioSurgery), 2001 and member of the scientific committee of ISRS in 2003, 2005 and 2009. Chairman of the 2010 annual meeting of the Israel Society for Clinical Oncology and Radiation Therapy. Professional positions: 2014–2021, board member & treasurer ISCORT (Israel Society for Clinical Oncology and Radiation Therapy). Chairman of the Israel Radiotherapy Group 2001–2006, 2004–2014 Chairman of the Radiotherapy Examination Committee of the Israel Board of Clinical Oncology and Radiotherapy. 1998–2012 Member of the Helsinki Ethics Committee at the Chaim Sheba Medical Center. 2017- Member of committee for revision of European Syllabus in Radiotherapy & Oncology.

**Vassilis Kouloulias** is radiation oncologist and the head of radiotherapy unit of the 2nd Dept. of Radiology at ATTIKON University Hospital, Athens, Greece. He is a Professor of Radiation Oncology in Medical School of the National and Kapodistrian University of Athens, Greece. He has also a degree of Physics along with a PhD in Biomedical Engineering. His field of interest are breast, prostate and head-neck cancer. He is PI of several studies in Greece. He is the President of the Greek Society of Radiation Oncology as well as the Greek Society of Hyperthermic Oncology. He is a meber of SAG of ESTRO, while he is also the local organizer of many ESTRO courses held in Greece, for several years. He is also the president of the scientific committee of stereotactic radiotherapy of the Greek Ministry of Health.

**Yasemin Bolukbasi,** MD is Chair & Professor of Department of Radiation Oncology at Koc University School of Medicine since 2020, as well as being an adjunct Professor of U.T. M. D. Anderson Cancer Center, Department of Radiation Oncology, and Professor of American Hospital-MD Anderson Radiation Treatment Center in Istanbul. Dr. Bolukbasi is a reviewer for a number of international journals and has authored numerous articles in peer-reviewed journals and book chapters. She is a member of ESTRO, ASTRO and "Turkish Society for Radiation Oncology".

**Icro Meattini** is radiation and clinical oncologist consultant at the Florence University Hospital, and associate professor at the Department of Clinical and Experimental Biomedical Sciences "M. Serio" of the University of Florence, Italy. He is actively involved in ESTRO, EORTC, ESMO, ESO, and ESSO networks. Currently he is member of the steering committee of the EORTC breast cancer group and of the EORTC radiation oncology scientific council and founder of the Clinical Oncology Breast Cancer Group (COBCG) cooperative network. He is member of the ESTRO-ACROP breast cancer focus group and of the ESTRO breast cancer faculty.

**Charlotte Coles** is Professor of Breast Cancer Clinical Oncology and Deputy Head of Department of Oncology, University of Cambridge. Her research aims are to provide cancer patients with the best chance of cure with least side effects by personalising radiation techniques. She was awarded a National Institute of Health Research (NIHR) Research Professorship in 2019 for her risk-adapted breast RT research programme. Charlotte successfully led the Cancer Research UK (CRUK) Radiation Research Centre of Excellence award at Cambridge to develop a translational research pipeline from basic radiation research through to clinical trials, with a focus on DNA damage response and genetic approaches to define drug-RT combinations. She is Chief Investigator for 5 multicentre clinical trials: IMPORT LOW & HIGH, PRIMETIME, NEO-RT and PARABLE. Charlotte chaired the NCRI Early Disease Breast Cancer sub-group and is a member of the NIHR Health Technology Assessment Committee and the CRUK Clinical Research Committee. International roles include scientific tracks/faculty for SABCS, ESMO, EBCC and ESTRO. Charlotte was Editor-in-Chief of Clinical Oncology journal from 2015 to 21. She stepped down in 2021 to lead the Lancet Commission for Breast Cancer.

**Ángel Montero Luis,** MD, PhD, is Professor at the Radiation Oncology Department of the Clara Campal Integral Oncology Center (CIOCC), University Hospital HM Sanchinarro, Madrid, Spain. His educational activities include professor at the University of Francisco de Vitoria, University of Murcia, as well as in Center for Biosanitary Professions HM Hospitals. He is principal investigator and collaborating researcher in several national and international studies and (co-)author of more than 50 scientific publications and 40 chapters in (inter)national books. Finally, he is coordinator of the Spanish Group of Radiation Oncology in Breast Cancer (GEORM) co-inventor of the IRMAPRON® device, immobilizer for radiotherapy of the breast in the prone position, and co-director of the iOncoR mobile application.

**Valeria Masiello** is radiation oncologist and she works at Radiochemotherapy Day Hospital Art4Art Unit at Fondazione Policlinico Agostino Gemelli IRCCS. She is member of AIRO, ESTRO and ESMO. Her fields of interest is in breast cancer and artificial intelligence for big data extraction.

**Isabella Palumbo** MD, is a Research Assistant Professor of Radiation Oncology at the Department of Medicine and Surgery - University of Perugia. She is a radiation oncologist and medical oncologist. She is involved in clinical and translational research project in breast cancer treatment. She is an AIRO and ESTRO member and the Coordinator of the AIRO Breast Cancer Study Group (2022–2023).

**Alessio G. Morganti** is professor of radiotherapy and chair of the radiotherapy department of the Bologna university, chair of the postgraduate program in radiotherapy, professor in medical school, PhD program of oncology, and RTT school (Bologna University). He is also professor in the postgraduate program in radiotherapy, of the Catholic University (Rome), coordinator of 32 research projects, lecturer in international teaching courses (ESTRO, IAEA), member of the editorial board of several journals and reviewer of scientific projects for several international scientific societies and the Italian Ministry of University. He is involved in several successful European and institutional grants.

**Elisabetta Perrucci** MD, is a Radiation Oncologist, Gynaecological cancer and Brachytherapy expert, Deputy Director and Quality Manager at Radiation Oncology Section of Perugia General Hospital, Italy. Interests in breast cancer radiotherapy, gynecological cancer radiotherapy, brachytherapy, stereotactic radiotherapy research.

**Vincenzo Tombolini,** MD is Full Professor of Radiation Oncology at University Sapienza of Rome Department of Radiological, Oncological et Anatomo-Pathological Sciences. He is Head of Department of Radiotherapy at Policlinico Umberto I Rome and Head of Integrated Assistential Department of Hematology, Oncology and Dermatology at Policlinico Umberto I Rome. Areas of interest are Radiobiology, Prostate Cancer, Head and Neck Cancer and Flash-Therapy. AIRO Member AIRB Member.

**Marco Krengli** is a Full Professor of Radiation oncology of the University of Padua, Italy. The main research fields include head and neck and breast cancer, particle therapy and intraoperative radiotherapy. He is President-elect of the Italian Association for Radiotherapy and Clinical Oncology.

**Fabio Marazzi** is radiation oncologist and medical oncologist and the head of Radiochemotherapy Day Hospital Art4Art Unit at Fondazione Policlinico Agostino Gemelli IRCCS. He is member of ESTRO and ESMO. He is interested in all solid tumors field, in particular breast cancer, for which manage both systemic therapy and radiotherapy.

**Lurdes Trigo** is a Senior Graduate Assistant in Radioncology and the head of Brachytherapy Service of the Dept. Sciences of Image and Radioncology at Instituto Portuguès Oncologia Porto, Portugal and is the President of the Portuguese Society of Radiation Oncology, since 2009. She received her MD in Oporto University, 1982 and the title of Master in Oncology (MSc) also in Oporto University, 1997. As a brachytherapy expert her research work is about this field (breast and prostate cancer and head and neck focus) and is the PI of several clinical trials. She is member of editorial board: "Reports of Practical Oncology and Radiotherapy" (RPOR), 2022; Co-editor & Revisor Reports of Practical Oncology and Radiotherapy" (RPOR), 2010 – 2021 and Revisor of Journals: "The Breast" and "Radiotherapy & Oncology" (Green Journal)", 2021–2022. She has been UEMS Radiation Oncology and Radiotherapy and National Societies representative at ESTRO, while he is also the local organizer of many ESTRO courses held in Porto, Portugal, for years

"**Simona Borghesi,** MD is radiation and medical oncologist and Head of the Radiation Oncology Unit of Arezzo-Valdarno, Italy. Her main fields of interest are breast and genito-urinary cancers.

**Antonella Ciabattoni** MD is radiation oncologist at the Radiotherapy Unit in San Filippo Neri Hospital, ASL Roma 1, Rome, Italy. She graduated at the Catholic University of Rome in 1989 and specialized in Radiation Oncology in 1993 in the same University and in Diagnostic Radiology in 2007 in Campus Biomedico University of Rome. Since 1999 she has been working at San Filippo Neri Hospital with many interests, acquiring a high degree of specialization for breast, gastrointestinal and head and neck cancers. She is referent for Quality, Training and Research in her institution. In the last 20 years she has been actively working in the field of intraoperative radiotherapy, being member of the board of the International Intraoperative Radiotherapy Society (ISIORT). She is member of the AIRO and ESTRO societies and has been working in AIRO Breast Cancer Group, as coordinator in the years 2017–2019. She is adjunct professor in the degree courses for Physiotherapists and Technicians for Medical Radiology and Radiotherapy at Sapienza University of Rome.

**Ivica Ratosa,** MD, PhD, is a radiation oncologist at the Institute of Oncology Ljubljana. She has been a member of the ESTRO Guidelines Committee Sub-Group on Breast since 2021 and is active in the treatment of patients with breast cancer. In addition to breast cancer, her main research interests and areas of focus are stereotactic body radiotherapy, radiation treatment for benign disorders, particularly non-invasive cardiac radioablation, financial toxicity for cancer patients, and the use of telemedicine in oncology.

**Vincenzo Valentini** is Full Professor of Radiation Oncology at the School of Medicine of the Università Cattolica S. Cuore in Rome and Director of Department of Radiology, Radiation Oncology and Hematology at Fondazione Policlinico Universitario A.Gemelli -IRCCS of Rome. He is author of publications in peer-reviewed journal as well as book chapters and international guidelines. He was President of ESTRO in 2011–2014.

**Philip Poortmans** is radiation oncologist at the department of radiation oncology of the Iridium Netwerk, Wilrijk-Antwerp, and associate professor at the University of Antwerp, Belgium. His special interests include breast cancer and FLASH radiation therapy. He is

former president of the ESTRO. He is actively involved in research activities of the EORTC and is faculty member for breast cancer-related educational activities of ESTRO, ESSO, ESMO and ESO, including as course director for ESTRO's breast cancer courses and chairperson of the ESTRO-ACROP breast cancer focus group.