Endocrine therapy with accelerated Partial breast irradiation or exclusive ultra-accelerated Partial breast irradiation for women aged ≥ 60 years with Early-stage breast cancer (EPOPE): The rationale for a GEC-ESTRO randomized phase III-controlled trial

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Purpose: Breast cancer in the elderly has become a public health concern; there is a need to re-design its treatment with a view to de-escalation. Our paper sets out the rationale for a phase 3 randomized trial to evaluate less burdensome adjuvant procedures that remain effective and efficient.

Materials and methods: For low-risk breast cancer in the elderly, adjuvant treatment has been adjusted in order to make it more suitable and efficient. Hypofractionated radiation therapy based on accelerated or non-accelerated regimens as well as accelerated and ultra-accelerated partial breast irradiation (APBI) protocols were reviewed. Withdrawal of radiation (RT) or endocrine therapies (ET) from the adjuvant procedure were also investigated. Based on molecular and APBI classifications, inclusion criteria were discussed.

Results: Phase 3 randomized trials which compared standard vs. accelerated/non-accelerated hypofractionated regimens confirmed that the latter were non-inferior in terms of local control. Similarly, except for intraoperative-based techniques, APBI achieved non-inferior local control rates compared to whole breast irradiation for low-risk breast cancer. In phase 2 prospective trials using ultra APBI, encouraging results were observed regarding oncological outcome and toxicity profile. In phase 3 trials, adjuvant ET without RT significantly increased the rate of local relapse with no impact on overall survival while RT alone proved effective. Elderly patients aged 60 or more with low-risk, luminal A breast cancer were chosen as the target population in a phase 3 randomized trial comparing APBI + 5-year ET vs. uAPBI (16 Gy 1f) alone.

Conclusion: To investigate de-escalation adjuvant treatment for elderly breast cancer patients, we have defined a road map for testing more convenient strategies. This EPOPE phase 3 randomized trial is supported by the GEC-ESTRO breast cancer working group.

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1. Introduction

Over the two last decades, it has been clearly demonstrated that adjuvant radiation therapy is mandatory in the case of breast cancer conservative treatment in order to achieve optimal local control and avoid radical mutilating surgery [1]. In the long term, adjuvant breast irradiation not only significantly improves local control but also overall survival [2].

In its initial schedule, breast cancer irradiation was delivered for 6 to 7 consecutive weeks, based on standard fractionation using 2 Gy per fraction, for a total dose of 50 Gy delivered to the whole breast, followed by a 10 to 16 Gy boost on the tumor bed [3]. However, for reasons relating to radiobiology, quality of life, radiation therapy department organization and total cost (irradiation, transportation, cessation of professional activity, etc.), the principle of decreasing overall irradiation treatment time gained in respectability and popularity, with the validation of innovative hypofractionated regimes. These new protocols were based on 5 to 16 fractions with accelerated [4–8] or non-accelerated schedules [9–11]. Accelerated and non-accelerated hypofractionated regimens were evaluated in numerous phase III randomized trials, which reported equivalent results in terms of oncological outcomes and late toxicity profile (Table 1).

In light of the above, and given that ipsilateral breast tumor recurrence occurs in or close to the primary tumor bed in 70 to 80% of cases, the concept of accelerated partial breast irradiation (APBI) was proposed for selected patients. Despite initial doubts [12], the Groupe Européen de Curiethérapie of the European Society for Radiotherapy and Oncology (GEC-ESTRO), the American Society of Radiation Oncology (ASTRO), and the American Brachytherapy Society (ABS) published different patient classifications regarding the risk of local relapse in order to specify the inclusion criteria for accelerated and partial breast irradiation (APBI) [13–15]. Numerous Phase III randomized trials compared whole breast irradiation (WBI) versus APBI for low-risk breast cancer by using non-inferiority or equivalent statistical methodological approaches. Different irradiation techniques were used: brachytherapy [16–18,25], intra-operative radiation therapy with electrons [20] or low-energy photons [21] or external beam brachytherapy based on 3D conformal [22–25] or intensity modulated radiation therapy [26,27] (Table 2).

2. Ultra accelerated partial breast irradiation (uAPBI)

In the wake of breast irradiation hypofractionation, which has moved from conventional to soft, and from soft to extreme hypofractionated breast cancer irradiation regimens, we wish to discuss ultra-Accelerated Partial Breast Irradiation (uAPBI) regimens based on 1 to 3 treatment days. Two important questions arise. First, if the final goal is to reduce the total number of fractions as much as possible, why consider 3- or 2-treatment day protocols if a single day is technically available and clinically feasible [28]? Second, what about intra-operative breast irradiation, an attractive solution combining lpectomy and adjuvant tumor bed irradiation in the same procedure [20;21]? Despite the debatable results of different randomized trials, which failed to prove non-inferiority in a comparison between WBI and APBI, intraoperative radiation therapy still exposes at least 15% of patients to whole breast re-irradiation owing to the lack of definitive pathologic results [29].

Two additional, important remarks are warranted. The first is radiobiological. Decreasing the total number of fractions decreases the total delivered dose but increases the dose per fraction. For 3, 2 and mainly 1 treatment days, the dose/fraction is higher than 7 to 8 Gy, which is considered the limit beyond which the linear-quadratic model ceases to apply in the calculation of equivalent dose at 2 Gy; furthermore, to make an accurate calculation, other factors, such as vascular damage, should probably be considered [30]. The second remark, which is partly linked to the first, concerns the irradiation technique used to perform uAPBI. According to uAPBI experiences reported in literature, the uAPBI techniques used high-dose rate brachytherapy approaches (in-breast irradiation device) with either multicatheter interstitial brachytherapy [31–38] or balloon-based brachytherapy [39–42] (Table 3). For example, with a single fraction of 16 Gy delivered by multicatheter brachytherapy in breast cancer [α/4], the EQD2 is about 53 Gy, but close to 85 Gy if the hyperdose volumes inside the clinical target volume are considered [43]. However, this result could be different if the single fraction of 16 Gy is delivered using a balloon-based brachytherapy (EQD2 and irradiated volume).

The different series of uAPBI reported in literature show encouraging and promising results in terms of oncological outcome with no local relapse observed in the cohorts with a median follow-up of

### Table 1

**Non-accelerated and accelerated hypofractionated phase III randomized trials for breast cancer.**

| Hypofractionated protocols | Non-accelerated | Accelerated |
|----------------------------|-----------------|-------------|
| Study                      | UK-START-A      | UK-FAST-9   |
|                           | UK-START-B      | Ontario [5] |
|                           | UK-IMPORT       | FAST-Forward|
|                           | HYPO trial      |             |
| Year of publication        | 2008            | 2011        |
|                           | 2010            | 2017        |
|                           | 2017            | 2020        |
|                           | 2020            |             |
| # patients                 | 2236            | 2215        |
|                           | 2195            | 2018        |
|                           | 2017            | 2040        |
|                           | 2017            | 2014        |
| Period of inclusion        | 1998–2002       | 2000–2007   |
|                           | 1999–2002       | 1993–1996   |
|                           | 1999–2001       | 2007–2010   |
|                           | 2011–2014       | 2009–2014   |
| MFU (y)                    | 5.1             | 3.1         |
|                           | 6.0             | 6.0         |
|                           | 6.0             | 7.3         |
| Treatment arms             | Gy              | fr          |
|                           | Gy             | fr          |
|                           | Gy             | fr          |
|                           | Gy             | fr          |
| Ref.                       | 50             | 50          |
|                           | 50             | 50          |
|                           | 50             | 50          |
| Exp. 1                     | 41.6           | 41.6        |
|                           | 41.6           | 42.5        |
|                           | 40             | 40          |
|                           | 40             | 40          |
| Exp. 2                     | 39             | 39          |
|                           | 39             | 39          |
|                           | 39             | 39          |
| Mean age (y)               | 57.2           | 63          |
|                           | 54.5           | 54.5        |
|                           | 63             | 63          |
| Mastectomy (%)             | 15             | 0           |
|                           | 0              | 0           |
|                           | 0              | 0           |
| N+ (%)                     | 28.8           | 0           |
|                           | 0              | 0           |
|                           | 0              | 0           |
| Regional RT                | 14.2           | 0           |
|                           | 0              | 0           |
|                           | 0              | 0           |
| 10-y LR (%)                | 6.7            | 12.1        |
|                           | 5.2            | 4.5         |
|                           | 2.3            | 1.5         |
| Changes in breast appear  | 42.9           | 20.9        |
| low (%)                    | 35.4           | 35.4        |
|                           | 42.2           | 42.2        |
| Ex./Good breast cosmesis   | 79.2           | 77.9        |
| low (%)                    | 85 vs. 85      |             |
| Mean FU (y)                | 5.1            | 3.1         |
|                           | 9.3            | 6.0         |
|                           | 7.3            |             |
| Median FU: median follow-up | reference arm | reference arm |
| Ex./Good breast cosmesis   | 79.2           | 77.9        |
| low (%)                    | 85 vs. 85      |             |

Median FU: median follow-up; Ref.: reference arm; Exp. 1: experimental arm 1; Exp. 2: experimental arm 2; N+: percentage of positive axillary lymph node dissection; Regional RT: regional radiation therapy; 10-y LR: Local recurrence rate at 10 years; Ex./Good breast cosmesis: excellent and good cosmesis results; #fr: number of fractions; #w: number of weeks; #d: number of days; μmet: axillary micro-metastasis.
at least 60 months [36;37;42]. Regarding the toxicity profile, while the peri-irradiation period must be managed carefully, the rate of late G3 toxicity appears very low in well documented series (total number of patient and/or median follow-up) [36;37;41;42] (Table 3).

3. Rationale for promoting uAPBI

It is estimated that in 2040, the total number of cancers in the world, irrespective of type, patient gender or age, will be 29 532 994 i.e. an increase of about 40% compared with 2018 (18 078 957) [44]. The increase in breast cancer will be about 30%, with the same forecasts for elderly women (>70 years) [44]. Furthermore, these data must be considered in the context of global aging: between 2015 and 2050, the >60-year population will double (0.9 billion vs. 2.1 billion) [45,46]. These demographic and epidemiologic factors reinforce the need to re-consider breast cancer treatment strategy in the elderly.

The road map for managing breast cancer in the elderly could therefore be based on the four following goals: efficient treatment that preserves quality of life based on a cost-effective approach predicated on patient waiting-list and radiation therapy department organization (linac number, human resources, increase in the incidence of other cancers, etc.) [47].

Assuming that after breast surgery, adjuvant treatment is commonly based on radiation and endocrine therapies, breast cancer therapeutic de-escalation in the elderly complies with this road map. One of the first ways to engage this therapeutic de-escalation process is based on the hypothesis that adjuvant breast irradiation could be removed from the breast treatment process.

Numerous phase III randomized trials involving postmenopausal/elderly women presenting with early breast cancers compared endocrine therapy (ET) with or without adjuvant external beam radiation therapy (RT) [48–52] (Table 4). Except for the Italian trial [52], all the randomized trials confirmed that the suppression of adjuvant RT was associated with a statistically significant higher rate of in-breast local relapse with no significant impact on overall survival [47]. Matuschek et al. reported the results of a meta-analysis of these phase III randomized trials and concluded that adding RT to ET did improve local relapse in breast cancer patients but did not show significant impact on overall survival [53]. Furthermore, Jayasekera et al. reported the results of another meta-analysis of randomized trials which evaluated RT after lumpectomy in women with low-risk breast cancer by including gene expression profiling as patient selection criteria [54]. While 48% of the patients were older than 60 years, the authors concluded that omission of RT may lead to an increase in local recurrence event rates, but does not appear to increase the rate of distant recurrence or death [54].

Currently, new phase III randomized trials are exploring the identification of low-risk patients for whom RT after breast conserving surgery may be safely omitted. The EXPERT trial (NCT02889874—Examining PErsonalised Radiation Therapy for Low-risk Early Breast cancer) is an Australian and New Zealand breast cancer study that is compares standard radiation therapy plus endocrine therapy versus endocrine therapy only (omission of radiation therapy) in a population of women (≥50 years) with low-risk breast cancer assessed by multigene assays including the PAM50-based Prosigna Assay that identifies intrinsic subtypes and generates a Risk of Recurrence score (ROR) to quantify individual risk

Table 2
Phase III randomized trials which compared whole breast versus partial breast irradiation according to the irradiation technique used.

| Studies          | # pts | MFU (years) | Method. | Diff. | Technique                  | APBI (Gy) | 5-year LRR (%) | APBI p value | 5-year OS (%) | APBI p value |
|------------------|-------|-------------|---------|-------|----------------------------|-----------|----------------|--------------|---------------|--------------|
| Budapest [19]    | 258   | 10.2        | Ni      | 6     | Int. Brachy.               | 7 – 5.2   | 5.9            | 5.1          | 0.77          | 80           | 82          | NS           | 0.06         |
| GEC-ESTRO [16]   | 1184  | 6.6         | Ni      | 3     | Int. Brachy.               | 50/32     | 1.4            | 0.9          | 0.42          | 97.3         | 95.5        | 0.11         |
| NSABP B-39/RTG 0413 [25] | 4216 | 10.2        | Eq.     |       | HRS90/5CI < 1.50           | 3D-CRT    | 38.5/34        | 4.6          | 3.9           | 1.22         | 1.58        | 90.6         | 91.3         |
| RAPID [24]       | 2135  | 8.6         | Ni      |       | HRS90/5CI < 2.02           | 3D-CRT    | 38.5           | 3            | 2.8           | 1.27         | 1.91        | –            | –            |
| UK-IMPORT Low [6] | 2018 | 6           | Ni      | 2.5   | IMRT                      | 40        | 0.5            | 1.1          | 0.76          | –            | –           | NS           | –            |
| Barcelona [22]   | 102   | 5           | Ni      | 10    | 3D-CRT                    | 37.5      | 0              | 0            | 0             | –            | –           | –            | –            |
| Florence [27]    | 520   | 5           | Ni      | 5     | IMRT                      | 30        | 1.5            | 1.5          | 0.86          | 99.4         | 96.6        | 0.057        |
| ELIOT [20]       | 1305  | 5.8         | Eq.     | 7.5   | Intra-OP e-                | 21        | 4.4            | 0.4          | <0.0001       | 96.8         | 96.9        | 0.59         |
| TARGET-A [21]    | 3451  | 2.4         | Ni      | 2.5   | Intra-OP 50 kV            | 20        | 3.3            | 1.3          | 0.042         | 96.1         | 94.7        | 0.099        |

#pts: number of patients; MFU: median follow-up; Method. (ITT): statistical methodology intention to treat; Diff.: threshold percentage for non-inferiority; APBI: accelerated partial breast irradiation; LRR: local relapse rate; OS: overall survival; Ni: non-inferiority; Eq. equivalence; HRS90/5CI: hazard ratio 90% confidence interval; Int. brachy.: interstitial brachytherapy; 3D-CRT: 3D conformal radiation therapy; Intra-OP e-: intra-operative radiation therapy using electrons; Intra-OP 50 kV: intra-operative radiation therapy using low-energy photons (50 kV); NS: non-significant.

Table 3
Very Accelerated Partial Breast Irradiation (vAPBI) Phase II trials according to the brachytherapy technique used.

| Authors          | # pts | MFU (months) | Irradiation Tech. | Total dose (Gy) | D/f (Gy) | AG3 tox (%) | LG3 tox (%) | LF (%) | RF (%) | DM (%) | Ex/good Cosm. |
|------------------|-------|--------------|-------------------|-----------------|----------|-------------|-------------|--------|--------|--------|---------------|
| Sacchini et al. [31] | 18/34 | 31           | HDRİORT           | 20/18           | 20/18    | 7.7         | –           | 0      | –      | –      | –             |
| Khan et al. [40]  | 30    | 11           | Balloon          | 28              | 7 (BID)  | 0           | 0           | –      | –      | –      | –             |
| Wilkinson et al. [42] | 45    | 74           | Balloon          | 28              | 7 (BID)  | 13.3        | 2           | 0      | 0      | 0      | 91            |
| Showalter et al. [32] | 28   | 6            | HDRİORT          | 12.5            | 12.5     | 0           | –           | –      | –      | –      | –             |
| Latorre et al. [35] | 20    | 24           | HDRİOM           | 18              | 18       | 0           | 0           | 0      | 0      | 0      | 5 80          |
| Khan et al. [41]  | 200   | 12           | HDRİOM/Balloon   | 22.5            | 7.5      | 1.5         | –           | 1      | –      | –      | 97            |
| Jethwa et al. [39] | 73    | 14           | Balloon          | 21              | 7        | 3           | –           | –      | –      | –      | –             |
| SIFEBI [37]       | 26    | 63           | HDRİOM          | 16              | 16       | 7.6         | 0           | 0      | 0      | 0      | 88            |
| Kinj et al. [31]  | 48    | 64           | HDRİOM          | 16              | 16       | 6.3         | 0           | 0      | 0      | 0      | 100           |
| GEC-ESTRO [38]    | 81    | 20           | HDRİOM          | 25/22.35        | 6.25/7.45| –           | 0           | –      | –      | –      | 97.5          |

#pts = number of patients; MFU = median follow-up; HDRİOM = high-dose rate brachytherapy performed intra-operatively; HDRİORT = high-dose rate multicatheter interstitial brachytherapy; Dose f = dose per fraction; AG3 tox = acute Grade 3 toxicity; LG3 tox = late Grade 3 toxicity; LF = local failure; RF = regional failure; DM = distant metastasis; Ex/gd cosmetic results = percentages of excellent and good cosmetic results; APBI = accelerated partial breast irradiation.

aCosmetic result was better with 18 Gy compared to 20 Gy.
ual risks of distant relapse [55]. The DBCG RT Natural phase III trial (NCT03646955—Danish Breast Cancer Cooperative Group) is comparing, in patients (≥60 years) with low-risk breast cancer, partial breast irradiation (external beam irradiation 40 Gy/15/3 weeks) versus no irradiation; endocrine therapy is accepted in both arms [56]. The EUROPA phase III trial (NCT04134598—ExclUsive endocrine Therapy Or Partial Breast Irradiation for Women Aged >70 Years Early Stage Breast Cancer) is comparing partial breast irradiation alone (overall treatment time from 1 to 3 weeks) versus endocrine therapy alone in low-risk breast cancer in an elderly population (≥70 years) [57].

Some phase II prospective trials aim to evaluate the impact on local control of the omission of adjuvant irradiation in highly selected low-risk breast cancer populations. TOP-1 trial (BOOG study number 2016-01—Tailored treatment in Older Patients study) is a prospective cohort study which evaluates the risk of local relapse after endocrine therapy alone (without adjuvant breast irradiation) for elderly patients (≥70 years) with low-risk breast cancer [58]. PRIMETIME is a prospective, biomarker-directed case cohort study comprising two different patient populations, (≥60 years) with “very low” and “low, intermediate, high” risk of local relapse according to Ki67 test, without and with adjuvant irradiation respectively [59]. IDEA Study (NCT02400190—Indi vidualized Decisions for Endocrine Therapy Alone) aims to collect prospective data supporting the idea that in a population at low risk of local relapse (≥50 years with low-risk breast cancer and Oncotype-DX RS ≤18), omission of adjuvant radiation is acceptable [60].

Currently, without stronger evidence, adjuvant breast irradiation remains mandatory the lowest risk of local relapse in the elderly. However, with a view to reducing the burden of breast irradiation, APBI appears an attractive alternative to radiation therapy omission [61,62].

### 4. Breast cancer adjuvant therapeutic de-escalation program and patient selection criteria

As removing adjuvant breast RT could lead to a non-acceptable rate of local relapse in patients who still have a life expectancy of 10 to 15 years, it has been proposed to re-consider breast cancer therapeutic de-escalation in the elderly by avoiding endocrine therapy [63,64]. The rationale behind this new therapeutic de-escalation is based on two main factors. First, in terms of aromatase inhibitors, arthralgia and myalgia are considered the most frequent and disabling side effects [64]. As recently reported by Ferreira et al. compared to chemotherapy, ET induced persistent QoL deterioration (at 2 years) mainly in post-menopausal women [66]. Consequently, ET remains an issue for adjuvant breast cancer treatment with a compliance rate of approximately 70% [67]. Second, for elderly women with biologically favorable breast cancer treated with lumpectomy, recent investigations suggested that adjuvant RT alone (without ET) could be an acceptable option in terms of overall survival rates [63,64]. Based on the National Cancer Database (2010–2014), Buszek et al. identified 2995 elderly women with biologically favorable breast cancer (≥70 years, T1N0, hormone receptor-positive, HER-2-negative) who underwent lumpectomy with adjuvant RT or ET (propensity score/ match-paired analysis). After a median follow-up of 45 months, the authors reported equivalent 5-year overall survival rates [63]. Based on a constructed patient-level Markov model, Ward et al. compared 5 years of ET (anastrozole) alone to RT without ET (oncological outcome data obtained from NSABP-B21, CLG B 9343 and PRIME II trials) [64]. The authors reported that while ET was superior in preventing contralateral cancers, RT was superior in preventing ipsilateral breast tumor recurrence [64]. In a prospective randomized clinical trial (2 × 2 factorial design) Blamey et al. analyzed the rate of local relapse in 1171 pts with low-risk breast cancer after RT + ET (Tamoxifen), RT alone, ET alone or no therapy [68]. After a median follow-up of 121 months, with a median age of 57 years [33–69], the rates of local relapse were 10.2% vs. 3.9% for RT- vs. RT+ respectively and 11.7% vs. 4.2% for ET- vs. ET+ respectively while receipt of both therapies conferred a significantly lower risk of local relapse than RT alone (p = 0.01) or than ET alone (p = 0.006) [68]. More recently, Kurian et al. retrospectively analyzed the recurrence-free survival (RFS) rate in a cohort of 1166 elderly women with low-risk breast cancer who underwent BCS alone, adjuvant RT alone, adjuvant ET alone or adjuvant RT + ET [69]. The authors observed that <60% of women completed 5-years of ET. With a median follow-up of 76.5 months, compared to surgery alone, RT resulted in significant improvement in RFS (p < 0.001), similar to ET (p = 0.007) and RT + ET (p < 0.001) [69].

After describing the different therapeutic de-escalation options, it remains crucial to accurately define the patient population that could truly benefit from this personalized treatment opportunity. The data analyzed in this paper point to elderly low-risk breast cancer patients as the best candidates for such a de-escalation program. Pandit et al. reported the prevalence of breast cancer molecular subtypes in a population of 2062 patients [70]. The authors observed that, in the sub-group of elderly women (≥70 years), luminal A sub-type represented >70% of the population and the highest rate regarding the whole cohort [70]. Breast cancer molecular classification considers the following items: histological grade, expression of estrogen and progesterone receptors as well as Her2 over-expression and Ki67 [71] (Table 5). Furthermore, APBI classifications are also used in order to propose a RT de-escalation program to selected patients [13–15]. The GEC-ESTRO APBI classification considers the following items: patient age, multicentricity, multifocality, histological data (type, associated LCIS, DCIS), histo-prognostic factors (extensive intraductal component, lympho-vascular invasion; estrogen receptor; progesterone receptor, sentinel lymph node biopsy, surgical margins) and neoadjuvant chemotherapy [131] (Table 6).

| Table 4 | Phase III randomized trials comparing endocrine therapy with or without adjuvant external beam radiation therapy for postmenopausal/elderly women with low-risk breast cancers. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Studies | Inclusion period | No. pts | Age (years) | MFU (months) | T. size (mm) | ET | Radiation/RT | 5-y IBTE (%) | 5-y OS (%) |
| Fyles et al. [48] | 1992–2000 | 769 | > 50 | 67 | 50 | TAM | 40/16 | 12.5/5 | 0.6 | 7.7 | 92.8 | 93.2 |
| CALGB [49] | 1994–1999 | 636 | 70 | 60 | 40 | TAM | 45/25 | 0 | 0.6 | 4.1 | 87.0 | 86.0 |
| ABCSG [50] | 1996–2004 | 869 | Postmeno | 53.8 | 30 | TAM | 50/25 | 10 | 0.4 | 5.1 | 97.9 | 94.5 |
| PRIME II [51] | 2003–2009 | 1326 | 65 | 60 | 30 | TAM | 40–50/15–25 | 10–15 | 1.3 | 4.1 | 93.9 | 93.9 |
| Tinti et al. [52] | 2001–2005 | 749 | > 55 | 108 | 25 | TAM | 50/25 | 10 | 4.4 | 3.4 | 81.4 | 83.7 |

No. pts: number of patients; MFU: median follow-up; T. size: tumor size; ET: endocrine therapy; WBI: whole breast irradiation; IBTE: ipsilateral breast tumor event rate; OS: overall survival; RT: radiation therapy; no-RT: no radiation therapy; TAM: tamoxifen; AI: aromatase inhibitors.
breast cancer patients who will be the best candidates for therapeutic de-escalation adjuvant breast cancer treatment. Consequently, this sub-group can be defined as follows: elderly patient (≥70 years), luminal-A (regarding molecular classification) within the low-risk group GEC-ESTRO APBI classification.

5. Rationale for a randomized phase III-controlled trial

Considering the oncological and toxicity profile results obtained after uAPBI based on a single fraction of HDR MIB [72] and the potential advantages of removing ET from adjuvant treatment in the elderly [66–70], low-risk breast cancer patients according to the MAPBI classification could represent the cohort that benefits most from a breast cancer adjuvant therapeutic de-escalation program. This program could combine uAPBI without ET to comply with the mandatory road map for managing breast cancer in the elderly (efficient, cost-effective treatment, in regard to quality of life and radiation therapy department organization). A Phase III randomized trial comparing standard treatment combining APBI with 5 years of ET versus uAPBI without ET is required to accurately analyze the impact of breast cancer adjuvant therapeutic de-escalation in low-risk breast cancers in the elderly.

The Breast Cancer Working Group (BCWG) of the GEC-ESTRO has proposed such a trial, entitled “Endocrine therapy with accelerated Partial breast irradiation or exclusive ultra-accelerated Partial breast irradiation for women aged ≥60 years with Early stage breast cancer (EPOPE) (Fig. 1). In this prospective trial, the primary endpoint is to determine the oncological outcome (DFS) after APBI with ET as compared to exclusive uAPBI following conservative breast surgery in low-risk early breast cancer patients aged ≥60. Secondary endpoints consider quality of life (QLQ-C30; QLQ-BR23), patient-reported outcome (HRQoL measured by ELD14; Functional Assessment of Chronic Illness Therapy—Fatigue (FACT-F), geriatric COrereG DataSet (G-CODE) assessment as well as oncological outcome (local/regional/contralateral/metastatic recurrence; specific and overall survival) and cosmetic result [73].

In this prospective, randomized trial, we propose to enroll all patients aged over 60 years with non-metastatic, histologically proven, early-stage breast cancer (pT1-2 < 30 mm) and pathological N0 stage (isolated tumor cells [i + ] allowed). Primary tumor must be resected by breast conserving surgery with microscopically negative margins for invasive carcinoma and any associated ductal carcinoma in situ (no cancer cells adjacent to any inked edge/surface of specimen) or re-excision showing no residual disease. Regarding molecular classification, only Luminal A-like/B-like patients will be accepted. Molecular status will be defined by immunohistochemistry (IHC) with Ki67 ≤ 20% and > 20% for Luminal-A and Luminal-B (Her2-2) respectively. Age, tumor size and molecular Luminal A/B status were three major inclusion criteria discussed in depth by the BCWG, which acknowledged that the majority of patients will be 70 years or more, with pT1, Luminal-A breast cancer.

Multifocal or multicentric invasive breast cancer, T4 disease, Grade 3 histology, lymphovascular invasion, neo-adjuvant systemic therapy or prior breast or thoracic RT for any condition were considered as non-inclusion criteria.

In the experimental arm, uAPBI will deliver a single fraction (1 day) of 16 Gy using multicatheter-based high-dose rate brachytherapy (HDB) [37]. In the control arm, APBI will use the same brachytherapy technique for delivering 32 Gy in 8 fractions (8 × 4 Gy, twice-daily, during 5 days) or 30.3 Gy in 7 fractions (7 × 4.3 Gy, twice-daily, during 4 days) [16] combined with ET for a total theoretical programmed length of 5 years (tamoxifen, steroidal, and non-steroidal aromatase inhibitors). In both arms, HDR brachytherapy has to be performed no later than 10 weeks after surgery.

Regarding the study design, patients will be randomized on the basis of local pathology results of the resection specimen from their breast cancer surgery (BCS) with sentinel node biopsy, showing pT1, c/pN0 (i+ ), Luminal A-like or Luminal B-like tumors. Patients in both arms will be followed every 6 months for the first 5 years and thereafter annually until 10 years after enrolment. In the event the patient develops disease recurrence, she will be trea-

Table 5
Breast cancer molecular classification [71].

| Molecular subtypes     | Grade | ER  | PR  | Her2 | Ki67 |
|------------------------|-------|-----|-----|------|------|
| Luminal-A              | I/II  | +   | +   | -    | < 20%|
| Luminal-B              | II/III| +   | +   | -    | ≥ 20%|
| Her2-                  | II/III| +   | +   | +    |   γ  |
| Luminal-B              | γ     | -   | -   | +    |   γ  |
| Her2+ Basal (TN)       | γ     | -   | -   | -    |   γ  |
| Luminal-B Her2- II/III+ | +   | +   | +   | +    |   γ  |

Luminal-B Her2- = Luminal-B molecular subtype without over-expression of Her2; Luminal-B Her2+ = Luminal-B molecular subtype with over-expression of Her2; Her2+ = over-expression of Her2; TN = Triple negative; ER = estrogen receptor; PR = progesterone receptor; HER2+/IHC staining), (positive if Her2+ = over-expression of Her2; TN = Triple negative; ER = estrogen receptor; HER2+/IHC staining).

Table 6
GEC-ESTRO APBI classification [13].

| Characteristics | Low-risk group | Intermediate-risk group | High-risk group |
|----------------|----------------|-------------------------|-----------------|
| Patient age    | > 50 years     | ≥ 40–50 years           | ≤ 40 years      |
| Histology      | IDC, mucinous, tubular, medullary, colloid cc | IDC, ILC, mucinous, tubular, medullary, and colloid cc | – |
| ILC            | Not allowed    | Allowed                 | –               |
| Associated LCIS| Allowed        | Allowed                 | –               |
| DCIS           | Not allowed    | Allowed                 | –               |
| HG             | Any            | Any                     | –               |
| T. size        | pT1-2 (<30 mm) | pT1-2 (<30 mm)          | pT2 > 30 mm, pT3-4 |
| S. margins     | Negative (<2 mm) | Negative but close (<2 mm) | Positive |
| Multicentricity| Uncentric      | Uncentric               | Multicentric    |
| Multifocality  | Unifocal       | Multifocal (limited within 2 cm of the index lesion) | Multifocal (limited > 2 cm of the index lesion) |
| EIC            | Not allowed    | Not allowed             | Present         |
| LVI            | Not allowed    | Not allowed             | Present         |
| ER, PR status  | Any            | Any                     | –               |
| Nodal status   | pN0 (SLND, ALND) | pN1mic, pN1a (ALND) | pN2 ≥ pN2a (≥4N + ) |
| Neoadjuvant CT | Not allowed    | Not allowed             | If used         |

APBI = accelerated partial-breast irradiation; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; DCIS = ductal carcinoma in situ; HG = histologic grade; T. size = Tumor size; EIC = extensive intraductal component; LVI = lympho-vascular invasion; ER = estrogen receptor; PR = progesterone receptor; Neoadjuvant CT = Neoadjuvant chemotherapy; SLND = sentinel lymph node dissection; ALND: axillary lymph node dissection.
Endocrine therapy with accelerated Partial breast irradiation or exclusive ultra-accelerated Partial breast irradiation for women aged ≥ 60 years with Early stage breast cancer (EPOPE): A randomized phase III-controlled trial of the BCWG of the GEC-ESTRO

6. Conclusion

In light of recent data on the aging of the population around the world and consequently the cancer incidence forecasts in this patient sub-group, breast cancer in the elderly has become a public health concern. Its specific histologic and molecular features call for re-thinking the rules governing breast cancer treatment in the elderly; the aim of this de-escalation approach is to offer more convenient procedures that remain both efficient and effective. The road map we have defined in this manuscript sets out the rationale for testing new adjuvant treatment in the EPOPE phase 3 randomized trial supported by the breast cancer working group of the GEC-ESTRO.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N. Engl. J. Med. 2002;347(16):1227–32.

[2] EBCTCG (Early Breast Cancer Trialists’ Collaborative Group), McGale, P., Taylor, C., Correa, C., Cutter, D., Duane, F., et al., 2014 Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 383:9935, 2127–2235.
Five-year follow-up of a randomised, phase 3 trial. Lancet Oncol. 2015;16(11):1083–91.

Polgár C, Major T, Takácsi-Nagy Z, Fodor M. Breast-conserving surgery followed by hypofractionated versus whole-breast radiotherapy: Twenty-years results of a phase 3 clinical study. Int. J. Radiat. Oncol. Biol. Phys. 2021;104(4):998–1006. https://doi.org/10.1016/j.ijrobp.2020.11.006.

Ronaldsson H, Orecchia R, Canepa R, Jonneweide P, Viale G, Rotmenzén S, Sangalli C. Intermittent radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. Lancet Oncol. 2013;14(13):1269–77.

Veldman T, Bulsara M, Blum M, Tobias JA, TARGIT-A trialists. Single-dose intraoperative radiotherapy during lumpectomy for breast cancer: An innovative patient-centred treatment. Br. J. Cancer 2021;1–6. https://doi.org/10.1038/s41416-021-01233-5.

Verey F, Moncayo P, Foro P, Membre I, Reig A, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiotherapy to deliver accelerated partial breast irradiation. Int. J. Radiol. Biol. Phys. 2013;87(5):4038–45.

Whelan TJ, Whelan TP, Duff S, Kim DH, Berrang T, Truong PT, et al. Intermediate cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiotherapy. J. Clin. Oncol. 2013;31(32):4038–45.

Whelan TJ, Whelan TP, Duff S, Kim DH, Germain I, Nichol AM, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): A randomised controlled trial. Lancet Oncol. 2016;17(9):1244–53.

Vicini FA, Cecchi RS, White JR, Arthur DW, Julian TB, Raboinvitch RA, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early stage breast cancer: A randomised, controlled, phase 3, non-inferiority trial. Lancet Oncol. 2018;19(11):1037–45.

Vicini FA, Cecchi RS, White JR, Arthur DW, Julian TB, Raboinvitch RA, et al. Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early stage breast cancer: A randomised, controlled, phase 3, non-inferiority trial. Lancet Oncol. 2018;19(11):1037–45.

Lin M, Zeng WM, Lee JS, Shi YM, Yang Y, et al. Accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation in early breast cancer after breast-conserving surgery (GEC-ESTRO): 5-year results of a randomised, phase 3 trial. Lancet Oncol. 2018;19(6):834–44.
applicators is feasible and safe: First results from the triumph-T trial. Int. J. Radiat. Oncol. Biol. Phys. 2019;104(1):67–74.

[42] Wilkinson JB, Chen PY, Wallace MF, Shah CS, Benitez PR, Martinez AA, et al. Six-year results from a phase I/II trial for hypofractionated accelerated partial breast irradiation using a 2-day dose schedule. Am. J. Clin. Oncol. 2018;41(10):986–91.

[43] Hannoun-Levi JM, Chaud-Fouche ME, Dejean C, Courdi A. Dose gradient impact on equivalent dose at 2 Gy for high dose rate intersitial brachytherapy. J. Contemp. Brachytherapy 2012;4(1):14–20.

[44] World health organization. International agency for research on cancer. Globocan. http://gco.iarc.fr/tomorrow/graphic-lineType=0&population=900&mode=population&sex=2&cancer=39&age_group=65-2B&apc_male=0&apc_female=0. Access on line 20/20/20.

[45] United Nations – UN projects world population to reach 8.5 billion by 2030, driven by growth in developing countries. 2015. https://news.un.org/en/story/2015/07/505352-un-projects-world-population-reach-85-billion-2030-driven-growth-developing-UNWRI%3fM_U. Access on line 20/20/20.

[46] United Nations. Department of Economic and social affairs. World population aging 2019. https://www.un.org/en/development/desa/population/publications/pdf/aging/WorldPopulationAging2019-Highlights.pdf. Access on line 20/20/20.

[47] Hannoun-Levi JM, Hannoun A, Downs-Canner S, Zabor EC, Wind T, Cobovic A, Downs-Canner E, et al. Lumpectomy plus tamoxifen vs. or without breast irradiation in women 50 years of age or older with early breast cancer. J. Natl. Med. 2004;351(10):963–70.

[48] Hughes KS, Schnaper LA, Berry D, Cirrincione C, McCormick B, Shank B, et al. Breast and Cancer: A Randomized Evaluation of Adjuvant Therapy Oncology Group (Eastern Cooperative Oncology Group). Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N. Engl. J. Med. 2004;351(10):971–7.

[49] Potter K, Grannit M, Kwasny W, Tausch C, Handl-Zeller L, Pakisch B, et al. Austrian Breast and Colorectal Cancer Study Group. Lumpectomy plus tamoxifen or anastrozole with or without breast irradiation in women with favorable early breast cancer. Int. J. Radiat. Oncol. Biol. Phys. 2007;68(2):334–40.

[50] Künkler H, Williams LJ, Jack WJ, Cameron DA, Dixon JM. PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): A randomised controlled trial. Lancet Oncol. 2015;16(3):266–73.

[51] Tintzeri C, Gatzemeier W, Costa A, Gentilini MA, Zanini V, Regolo L, et al. Austrian Breast and Colorectal Cancer Study Group. Lumpectomy plus tamoxifen or anastrozole with or without breast irradiation in women aged 65 years or older with low-risk breast cancer. A randomised trial. Int. J. Radiat. Oncol. Biol. Phys. 2007;68(2):334–40.

[52] Matuschek C, Bölke E, Haussmann J, Mohrmann S, Nestle-Krämer C, Gerber PA, et al. The benefit of adjuvant radiotherapy after breast conserving surgery in older patients with low risk breast cancer: a meta-analysis of randomized trials. Radiat. Oncol. 2017;12(1):60.

[53] Jayasekera J, Schecter CR, Sparano JA, Jagi R, White J, Chapman JW, et al. CISNET-BOLD Collaborative Group. Effects of radiotherapy in early-stage, low-recurrence-risk, hormone-sensitive breast cancer. J. Natl. Cancer Inst. 2019;112(12):1370–9.

[54] Examiing PERsonalised Radiation Therapy for Low-risk Early Breast Cancer (EXPERT). ClinicalTrials.gov Identifier: NCT02889874. https://clinicaltrials.gov/ct2/show/NCT02889874?term=EXPERT&cond=Breast+Cancer&draw=2&rank=1.

[55] DBCG RT Natural Trial: Partial Breast Versus No Irradiation for Women ≥60 Years Operated With Breast Conservation for an Early Breast Cancer: a Clinically Controlled Randomized Phase III Trial. ClinicalTrials.gov Identifier: NCT03646955. https://clinicaltrials.gov/ct2/show/NCT03646955.

[56] Meitini I, Poormtanz PMP, Marrazzo L, Desideri I, Brain E, Hamaker M, et al. Exclusive endocrine therapy or partial breast irradiation for women aged ≥70 years with luminal A-like early stage breast cancer (NCT04134598—EUROPA): Proof of concept of a randomized controlled trial comparing health related quality of life by patient reported outcome measures. J. Geriatr. Oncol. 2021 Mar;12(2):182–9. https://doi.org/10.1016/j.jgc.2020.07.013.

[57] de Boer, A.Z., Bastaanmet, E., de Glaas, N.A., Marang-van de Meeu P.J., Dekkers, O.M., et al., 2019 Effectiveness of radiotherapy after breast-conserving surgery in older patients with T1-2N0 breast cancer. Breast Cancer Res. Treat. 17(1), 637–645. 10.1007/s10549-019-05412-8 (Epub 2019 Aug 26 PMID:31451977 PMCID:PMC6817758.

[58] Kirwan CC, Coles CE, Bliss J. It's PRIMETIME Postoperative avoidance of radiotherapy: biomarker selection of women at very low risk of local recurrence. Clin. Oncol. 2016;28:594–6.

[59] IDEA Study (Individualized Decisions for Endocrine Therapy Alone). ClinicalTrials.gov Identifier: NCT02400190. https://clinicaltrials.gov/ct2/show/NCT02400190?term=Hormone+Single+Endocrine+therapy+Cancer&draw=2&rank=3.

[60] Poormtanz PMP, Arenas M, Livi L. Over-irradiation. Breast 2017 Feb;31:295–302. https://doi.org/10.1016/j.breast.2016.07.012.

[61] Summohlo S, Levy J, Chamoeve E, Lam Cham Kee D, Chang ME, Gautier M, et al. Accelerated partial breast irradiation for elderly women with early breast cancer: A compromise between whole breast irradiation and omission of radiotherapy. Brachytherapy 2017;16(3):929–34.

[62] Buszek SM, Lin HY, Bedrosian I, Tamirisa N, Babiera GV, Shen Y, et al. Lumpectomy plus hormone or radiation therapy alone for women aged 70 years or older with hormone receptor-positive early stage breast cancer in the modern era: An analysis of the National Cancer Database. Int. J. Radiat. Oncol. Biol. Phys. 2019;105(5):795–802.

[63] Ward MC, Vicini F, Chadha M, Pierce L, Recht A, Hayman J, et al. Radiation therapy without hormone therapy for women age 70 or above with low-risk early breast cancer: A microsimulation. Int. J. Radiat. Oncol. Biol. Phys. 2019;105(2):296–306.

[64] Roberts KE, Rickett K, Fong S, Vagenas D, Woodward NE. Exercise therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer. Cochrane Database Syst. Rev. 2020;1(1):CD012988.

[65] Ferrera AR, Di Meglio A, Pissuti B, Gbenou AS, El-Mouhebb M, Dauchy S, et al. Differential impact of endocrine therapy and chemotherapy on quality of life in breast cancer survivors: A prospective patient-reported outcomes analysis. Ann. Oncol. 2019;30(11):1784–55.

[66] Chirgwin JH, Goldbie-Hurder A, Coates AS, Price KN, Ejlertsen B, Debled M, et al. Treatment adherence and its impact on disease-free survival in the breast international group 1–98 trial of tamoxifen and letrozole, alone and in sequence. J. Clin. Oncol. 2016;34(21):2452–9.

[67] Blamey RW, Bates T, Chetty U, Duffy SW, Ellis IO, George D, et al. Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. Eur. J. Cancer 2013;49(10):2294–302.

[68] Kurian J, Zebak S, Alba V, Mah K, Au C, Vos L, et al. Adjuvant breast radiotherapy, endocrine therapy, or both after breast conserving surgery in older women with low-risk breast cancer: Results from a population-based study. Radiother. Oncol. 2021;154:93–100.

[69] Pandit P, Patil R, Palve V, Gandhe S, Patil R, Nagarik R. Prevalence of molecular subtypes of breast cancer: A single institutional experience of 2062 patients. Eur. J. Breast Health 2019;16(1):39–43.

[70] Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature 2000;406:747–52.

[71] J.M. Hannoun-Lévi, L. Montagne, S. Sumodhee, R. Schiappa, R. Boulahssass, M. Babiera, G. Shen, et al. Prostate Cancer and Leukemia Group B; Radiation Therapy Oncology Group; Eastern Cooperative Oncology Group. Lumpectomy plus tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer: A comparative analysis of oncological outcome and late toxicity. The PROSTATE Study. Int. J. Radiat. Oncol. Biol. Phys. 2019;105(2):596–606.

[72] Harris JR, Levene MB, Svensson G, Hellman S. Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. Int. J. Radiat. Oncol. Biol. Phys. 1979;5:257–61.