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Original article

Efficacy of extended aromatase inhibitors for hormone-receptor–positive breast cancer: A literature-based meta-analysis of randomized trials

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ABSTRACT

Background: Endocrine treatment with Tamoxifen and aromatase inhibitors (AIs) is a staple in the management of hormone receptor positive breast cancer (HR + BC). It has become clear that HR + BC carries a consistent risk of relapse up to 15 years post-diagnosis. While increasing evidence supports the use of extended adjuvant Tamoxifen over 5 years, controversial data are available on the optimal duration of extended AIs adjuvant treatment.
We performed a meta-analysis to assess the real impact of extended adjuvant therapy with AIs on disease-free survival (DFS).
Methods: A literature-based meta-analysis of randomized controlled trials (RCTs) was undertaken. Relevant publications from PubMed, the Cochrane Library, and abstracts from American Society of Clinical Oncology (ASCO) and San Antonio Breast Cancer (SABCS) symposia were searched. Primary and secondary endpoints were Disease Free Survival (DFS) and overall survival (OS) respectively. A subgroup analysis was also performed to elucidate the impact of nodal involvement.
Results: The pooled analysis revealed a significant increase in DFS in the extended AIs group (hazard ratio (HR): 0.78, 95% CI: 0.68–0.90; P = 0.0006). The subgroup analysis according to nodal status showed a greater DFS benefit with extended AIs in patients with positive nodes (HR = 0.67 versus 0.80). Our analysis also demonstrated no improvement in OS with extended AIs (HR = 0.99, 95%CI: 0.87–1.12; P = 0.84).
Conclusion: This work confirmed the efficacy of extended adjuvant treatment with AIs for HR + early breast cancer, with a 22% increase in DFS, but no impact on OS. Greater efficacy was observed in women with positive nodal status.

1. Introduction

Even though hormone receptor positive (estrogen receptor (ER) and/or progesterone receptors (PgR) (HR) early breast cancer (eBC) is a highly curable disease, this molecular subtype is characterised by a persistent risk of late recurrence, even after decades from the initial diagnosis. Fifty-percent of relapses and most of the specific cancer-related mortality occur beyond the fifth year after surgery [1]. Choosing the right therapeutic option in order to prevent late recurrences becomes therefore very important. The main reason for the long survival and late relapse rates in HR + eBC is likely due to

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adjuvant endocrine treatment, prescribed to the majority of patients during the first years after surgery [2,3]. This evidence motivates the hypothesis that an extension of endocrine therapies beyond 5 years would further reduce the risk of recurrence and mortality.

Adjuvant Tamoxifen for up to 10 years after diagnosis has been shown to decrease the risk of relapse in BC patients, as well as BC mortality, in a time-dependent fashion, with the major impact seen after the 9th and 10th year of follow up, suggesting a carryover benefit [4,5]. Based on these results, obtained on 18,599 patients overall, ASCO and ESMO released updated guidelines recommending extended adjuvant treatment with tamoxifen up to 10 years for premenopausal patients with HR + eBC [6–8].

On the other hand, the optimal duration of AIs in the adjuvant setting is still being debated. Discordant data emerged from clinical trials conducted in the last few years, without a definitive conclusion. In particular, MA.17, MA.17R and 6a trials have shown a benefit in terms of DFS [9–11], with MA.17 also showing an improvement in OS in node positive patients and in those who had previously taken Tamoxifen for 5 years [10]. However, the latest randomized trials have not fully confirmed these results [12–14]. In fact, amongst these trials, only MA.17 [10] showed a statistically significant benefit in terms of DFS and/or OS, in particular in higher risk patients, including the ones presenting with larger and/or node-positive tumours.

It is therefore clear how the optimal choice and duration of adjuvant endocrine treatment in eBC remains unknown. As data continue to emerge in both pre- and postmenopausal women, discussion is still open. The question of what to offer to patients who are on AIs or switched from tamoxifen onto AIs is pressing, also considering the "limiting" issue of treatment-related toxicity. Moreover, the comparative benefits of these two therapeutic options and the selection of patients most likely to benefit from long-term adjuvant endocrine therapy are important topics for further research.

Tamoxifen has been the standard endocrine therapy for decades. As showed by the updated results of the TEXT and SOFT trials [15], tamoxifen in combination with ovarian function suppression (OFS) is recommended for low-risk pre-menopausal women. The use of exemestane plus OFS, which resulted in even higher rates of disease free survival in SOFT and TEXT, is currently reserved for patients with high risk of recurrence. In post-menopausal women, AIs (letrozole, anastrozole, or exemestane) are superior to tamoxifen in preventing recurrences, but only letrozole has been shown to improve survival [16,17]. The clinical advantage of AIs is mainly confined to high-risk cancers; on the other hand, tamoxifen, compared to AIs, seems to provide very similar outcomes for low-risk patients and represents a possible alternative in the presence of specific contraindications to AIs or in case of patient's refusal.

Traditionally, endocrine therapy is administered for 5 years; however, women with eBC and specific tumour biological subtypes (i.e. Luminal A-B) remain at risk of relapse for 10 or more years.

Considering the lack of clear and definitive conclusions on this important issue, we performed a meta-analysis to assess the real impact of extended adjuvant therapy with AIs on DFS.

2. Materials and methods

2.1. Data retrieval strategies

We conducted a meta-analysis of randomized controlled trials (RCTs) in accordance with the preferences for reported items in systematic reviews and meta-analyses guidelines [18]. Relevant publications from PubMed and the Central Registry of Controlled Trials of the Cochrane Library were identified. The initial search was focused on terms describing breast cancer, adjuvant treatment, hormonal therapy and extended treatment; the following medical subject heading (MeSH) terms therefore were used: "breast cancer" AND "letrozole OR anastrozole OR tamoxifen" AND "prospective" OR "clinical" OR "human" OR "adjuvant"). After the first search, article types were chosen as follows: "clinical trial" and "humans" were used as searching criteria in PubMed and no restrictions were used for the Cochrane library search. In addition, we manually searched through abstracts submitted to the ASCO and SABCS meetings from 2012 onwards for applicable trials. To minimize the risk of selection or information bias, the search criteria were limited to articles reporting the results of phase II or phase III RTCs. The computer search was supplemented with a manual search of the primary studies referenced in all of the retrieved review articles. When the results of a study were reported in subsequent analyses, only the most recent and complete version was included in this meta-analysis.

2.2. Inclusion criteria

The studies were identified according to the following inclusion criteria: 1) participants with BC treated with adjuvant endocrine therapy; 2) an extended treatment in the experimental arm (defined as adjuvant treatment prolonged after 5 years), 3) a primary outcome of DFS expressed as hazard ratio (HR) and secondary outcome of OS expressed as HR. The following exclusion criteria were used: 1) insufficient data availability to estimate the outcomes; 2) size of each arm <10 participants and 3) non-randomized studies. Two authors (GR and DG) screened the studies according to the above inclusion and exclusion criteria. The decisions regarding contentious studies were made in consultation with a third author (SP).

2.3. Data extraction

Two authors independently extracted the relevant data including the name of the first author, publication year, patient demographics (i.e. age, number of enrolled patients, drug administered and type of tumour), median follow-up, median treatment duration, study design (i.e. blinding and control types and randomization methods), survival outcomes expressed as HRs for DFS and OS. For each trial, the extended endocrine treatment arm was considered to be the experimental arm and placebo or observation the control.

2.4. Quality assessment and statistical analysis

Study quality was assessed using the Jadad 5-item scale, taking into account randomization, double blinding and withdrawals. The final score ranges from 0 to 5 [19]. The statistical analyses were performed with Revman 5.3. The summary estimates were generated using a fixed-effect model (Mantel–Haenszel method) or a random-effect model (DerSimonian–Laird method) [20,21], depending on the absence or presence of heterogeneity. Statistical heterogeneity was assessed with the Q-test and the I^2 statistic. I^2 values of 25%, 50% and 75% were used to indicate low, moderate and high heterogeneity, respectively. [22] When $P > 0.1$ and $I^2 < 50\%$, the fixed-effects model was used; otherwise, the random-effects model was used. HRs with 95% confidence intervals (CI) were calculated for each study. Stratification according to nodal involvement was added to evaluate predictive value of this variable. For all the statistical analyses, a p-value of <0.05 was regarded as statistically significant, and all tests were two-sided.

3. Results

The search yielded 991 potentially relevant articles. A total of 586 studies were excluded as duplicates. After viewing the titles and abstracts of the 405 remaining studies, the full text of 12 studies was retrieved and 8 studies [9–14,23,24] were included in the analysis (Fig. 1). Extended endocrine therapy with letrozole was investigated in 4 studies, whilst anastrozole was evaluated in 3 and exemestane in 1 study. The majority of the included studies evaluated the effects of further extension of adjuvant AIs up to 5 additional years. All studies' characteristics, as well as the definition of DFS for each study have been summarized in Tables 1 and 2. A total of 19345 cases were included; amongst these, 9629 cases were in the experimental arm and 9716 cases in the control group.

The median Jadad score was 5 (Table 1). Due to the small number of trials that were included (<10), no publication bias or sensitivity analysis was performed.

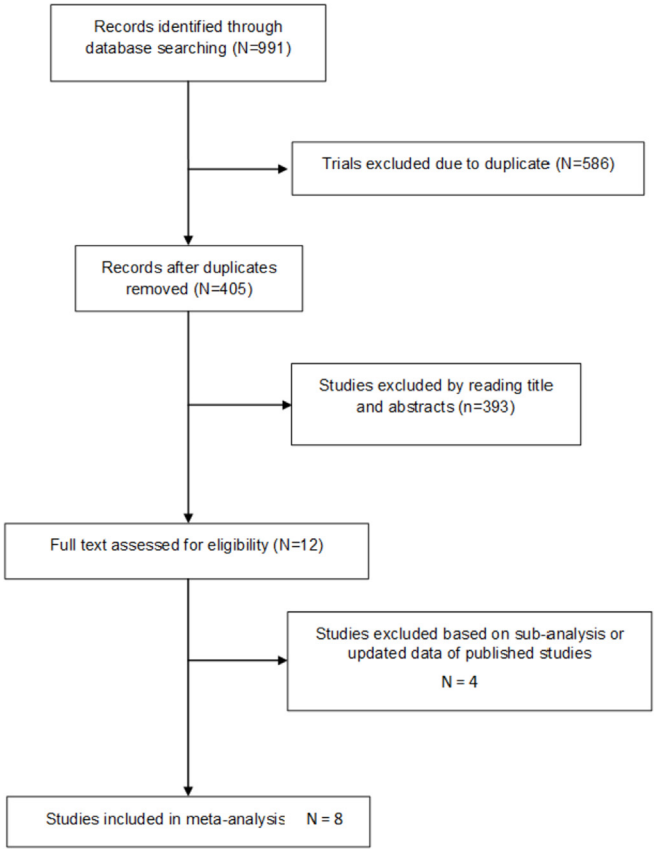

Fig. 1. Trail selection flow chart.

Table 2
Definition of disease-free survival.

Study	Definition of disease free survival
ABCSG Trial 6a	Recurrence-free survival: interval between the start of anastrozole treatment or of the observation period (for the no further treatment group) and the first evidence of locoregional recurrence, contralateral breast cancer, or distant metastasis.
DATA	The DFS beyond 3 years after randomization to AI therapy because initially all patients received the same AI therapy for 3 years. ADFS events included (non-) invasive breast cancer recurrences (local, regional, distant), second primary (non-) invasive (breast) cancers, and death of any cause.
MA -17	Time from randomization to the earliest recurrence of breast cancer (breast, chest wall, regional nodes, or distant metastasis) or a contralateral new primary breast cancer.
MA -17R	Time from randomization to recurrence of breast cancer (in the breast or chest wall or at nodal or metastatic sites) or the development of a new primary breast cancer. The occurrence of a second type of cancer or death without breast cancer recurrence were not included as events in the analysis of disease-free survival; data for patients who died without breast cancer recurrence were censored at the date of death.
NSABP B-33	Local recurrence in the chest wall after mastectomy or in the ipsilateral breast after lumpectomy, regional and distant recurrence, second primary cancer (other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or lobular carcinoma in situ of the breast), and death resulting from any cause before recurrence or second primary.
NSABP B-42	Local recurrence, regional recurrence, distant recurrence, second primary cancer (other than squamous and basal cell carcinoma of the skin, melanoma in situ, or carcinoma in situ of the colon and cervix), and death from any cause before recurrence or second primary cancer.
IDEAL	Time from random assignment to recurrence (either local, regional, or distant), new primary breast tumours (ductal carcinoma in situ or invasive) or death due to any cause, whichever came first.
ABCSG-16 (SALSA)	Time from random assignment to recurrence (either local, regional, or distant), new primary breast tumours (ductal carcinoma in situ or invasive) or death due to any cause, whichever came first.

Data on definition of DFS is reported in Table 2. All trials except NSABP-33 analysed DFS.

Our analysis showed that, after a median follow-up of 64.1 months, extended endocrine therapy with AIs improved DFS when compared to control (HR = 0.78, 95%CI: 0.68–0.90; P = 0.0006, $I^2 = 64\%$ Fig. 2). The analysis was performed using a random-effects model ($I^2 = 64\%$). Moreover, when we stratified patients according to nodal-status, the subgroup analysis (Fig. 3) showed a greater DFS benefit in patients with positive lymph nodes in the experimental arm, in comparison to control (HR = 0.67 in positive nodal status versus 0.80 in negative nodal status), this last analysis involving 5 studies [9,10,13,14,24].

Table 1
Trials Included in the analysis.

Study	Experimental Regimen (number)	Control Regimen (number)	Previous Adjuvant therapy	Primary End-point	Median Follow-up (months)	Jadad's score
ABCSG Trial 6a	386 (anastrazole 3 Y)	466 (no treatment)	Tamoxifen ± aminoglutethimide	DFS	62.3	4
DATA	1912 (total) (anastrazole 3Y)	1912 (total) (anastrazole 2Y)	Tamoxifen	ADFS	49.2	4
MA - 17	2583 (letrozole 5Y)	2587 (placebo 5Y)	Tamoxifen	DFS	30	5
MA-17R	959 (letrozole 5Y)	959 (placebo 5Y)	AI ± previous Tamoxifen	DFS	75	5
NSABP B-33	783 (exmestane 5Y)	779 (placebo 5Y)	Tamoxifen	DFS	30	5
NSABP B-42	1959 (letrozole 5Y)	1964 (placebo 5Y)	AI ± previous Tamoxifen	DFS	82.8	4
IDEAL	670 (letrozole 5Y)	669 (letrozole 2.5 Y)	5 Y of adjuvant therapy	DFS	78	5
ABCSG 16 (SALSA)	377 (anastrozole 2Y)	380 (anastrozole 5Y)	5 Y tamoxifen or AIs	DFS	106.2	4

Y: years (DFS: disease-free survival).
AI: aromatase inhibitor.

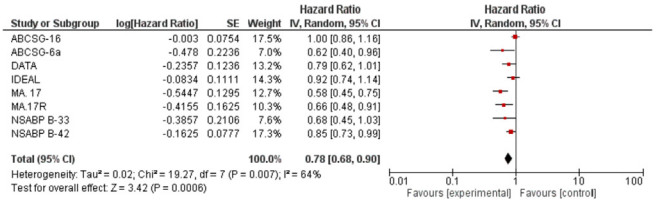

Fig. 2. Forest plots of hazard ratios (HRs) for disease free survival comparing extended hormonal therapies to control arm.

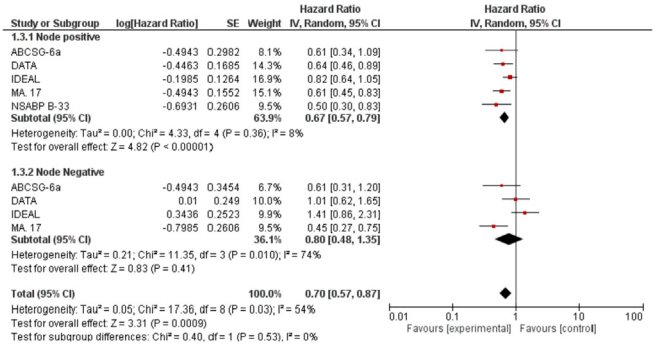

Fig. 3. Subgroup analysis according nodal status of hazard ratios (HRs) for disease free survival comparing extended hormonal therapies to control arm.

The pooled analysis revealed no improvement in OS with extended AIs endocrine therapy (HR = 0.99, 95%CI: 0.87–1.12; P = 0.84 Fig. 4) (data available from 6 trials) [9–14]. The fixed-effects model was used for the analysis of the OS data due to the presence of low heterogeneity ($I^2 = 22\%$) between the trials.

4. Discussion

Adjuvant endocrine therapy significantly reduces the risk of recurrence and death in women with HR + eBC. In pre-menopausal women, the use of exemestane with ovarian suppression results in higher rates of disease-free survival in comparison to the combination of tamoxifen and ovarian function suppression, in particular in women of less than 40 years of age, with higher-risk clinicopathological features factors (low hormone receptor expression, high grade, high proliferation index, genomic signature assays high scores), receiving chemotherapy [15]. In post-menopausal women AIs are significantly more effective than tamoxifen in preventing recurrence [25]. Extended adjuvant endocrine therapy with an AI (post-menopausal) or tamoxifen, beyond initial 5 years of tamoxifen, further reduces the risk of relapse [4,5,9,10].

In the postmenopausal group, adequate use of available agents and the selection of candidates to long-term endocrine therapy are clinically relevant questions requiring further evidence. Furthermore, the optimal duration of therapy with an AI started upfront, rather than after tamoxifen, represents an important issue given

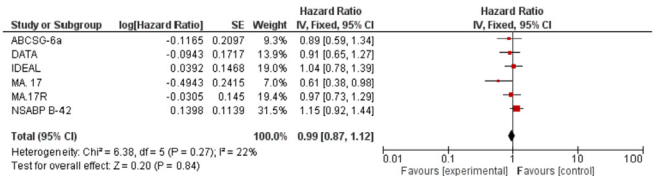

Fig. 4. Forest plots of hazard ratios (HRs) for overall survival comparing extended hormonal therapies to control arm.

the toxicity profile of these agents.

Whilst important studies such as MA 17, MA.17 R, NSABP B-33 and 6a trials have shown significant advantage deriving from extended endocrine treatment with letrozole beyond 5 years of tamoxifen, in particular in the group of patients with higher risk of relapse [10], such improvement has not been confirmed in more recent studies. In particular NSABP B42, DATA and IDEAL trials all failed to show an improvement in DFS and OS [12–14]. In addition, ABCSG 16 (SALSA) results were released at SABCS 2017 [23]. The study compared 2 years versus 5 years of extended adjuvant endocrine therapy with anastrozole, after initial 5 years treatment with tamoxifen or AIs, and found that 2 years of therapy are sufficient as extended adjuvant treatment. No differences in outcomes were seen between the two arms, but added toxicity was observed in the 5 years arm. Lastly, results of SOLE (Study Of Letrozole Extension) were released at ASCO 2017 and published last year [26,27]. This trial looked at two different schedules of extended adjuvant letrozole (continuous and intermittent) for a total of 5 years in post-menopausal patients who had already completed 4–6 years of adjuvant endocrine therapy for their node-positive eBC. Whilst DFS was not affected by the two different letrozole regimens, patients randomized to intermittent therapy reported a better quality of life and fewer side effects [27]. These results are consistent with a previous meta-analysis by He et al. [28], which provided evidence that restarting adjuvant hormone therapy after discontinuation is associated with positive breast cancer outcomes.

SOLE was not included in our meta-analysis as the trial was not designed to test superiority of extended adjuvant endocrine therapy to control, but rather the superiority of one administration regime over the other.

Our meta-analysis showed a significant benefit from a longer duration of AIs, with a general 22% increase in DFS. This improvement appears greater in the node-positive patients' subgroup. This data is in accordance with the results of MA.17, which demonstrated a clear benefit of extended endocrine therapy in higher risk tumours (mainly defined by nodal status, tumour size and previous chemotherapy) [10]. Furthermore, a post-hoc subgroup analysis of the DATA trial also showed a higher benefit of extended AIs in patients with node-positive disease (n = 849; HR 0·64 [95% CI 0·46–0·89], p = 0·0075) [14].

A previous meta-analysis by Petrelli et al. evaluated overall survival, breast cancer-specific survival (BCSS) and relapse-free survival (RFS) with adjuvant endocrine therapy (with tamoxifen or an AI) extended beyond the standard 5 years of tamoxifen. The authors were able to show a significant OS benefit in hormone receptor positive patients treated beyond 5 years, together with better locoregional control and decreased risk of relapse [29].

In contrast, we failed to identify any statistically significant benefit in terms of OS.

However, a statistically significant reduction of the risk of BC recurrence was seen in all trials included in this report, together with an improvement in breast cancer–free interval. Also, a 28% reduction in the cumulative risk of distant recurrence was seen [12]. These results seem to suggest that the absence of statistical significance does not necessarily imply absence of clinical benefit. In particular, the reduction of the distant recurrence risk could possibly translate in an OS benefit with longer follow-up. It could be hypothesized that further stratification of patients on the basis of their primary cancer stage might also yield different results.

In addition, endpoints used for outcome evaluations are heterogeneous and could impact the results. First of all, the definition of DFS varied across the trials (Table 2) and death from any causes was not included in the DFS analysis of the ABCSG 6a, MA 17 and MA 17R trials. For instance, an OS advantage could possibly be lacking in NASABP-B-33, as well as in B-42 and DATA trials, due to

the fact that new primary non-breast cancers and deaths from any cause were included in the DFS definition, whilst this was not the case in MA 17, MA 17R and 6a trials. A specific statistical analysis conducted on the MA 17R trial showed that DFS reached hazard ratios similar to the ones found in NSABP B-42 when both non-breast cancers and death from any cause were included in survival analysis, with consequent loss of statistical significance. Interestingly, if breast cancer free survival becomes a specific endpoint in NSABP B-42, the survival analysis shows statistical difference between the two arms (HR 0.71, $p = 0.003$). This fact reiterates the concept that the endpoints' choice can impact on the results of a trial [30].

Another crucial issue to take into consideration is the comparison of treatment duration and follow-up periods. In the DATA and IDEAL trials duration of extended therapy (2–3 years) or follow-up were possibly too short if we take into account the previous findings. In fact, we know that endocrine therapy has a carryover effect with an absolute survival benefit which increases over time and becomes extremely significant in the second decade after diagnosis, when compared to the first 5 years of follow up [5,25]. It becomes therefore clear that an adequate follow-up period is paramount in the attempt to evaluate the benefit of extended endocrine adjuvant treatment. In this context, treatment schedule and follow-up time were different between studies (e.g. the DATA study compared 2–3 years of tamoxifen plus 3 or 6 years of anastrozole) and the carryover effect could have been lost as either treatment was not long enough or the follow-up period too short.

Moreover, an OS advantage was only identified in the MA.17 study (HR for OS = 0.61, $p < 0.001$) in the node-positive population (i.e. after stratification). As OS is the result of breast cancer-related and not-related events, it can be argued that it is really difficult to obtain a statistically significant OS difference in the presence of a low number of events. Events not correlated with disease recurrence could overtake the ones related to BC morbidity and mortality, thus masking the actual experimental treatment benefit.

Nevertheless, all trials considered in our meta-analysis showed a statistically significant decrease of contralateral breast cancers and distant recurrences, even if this doesn't translate to survival benefit.

A final consideration concerns the utility of BC gene profiling. Platforms like Oncotype DX and Mammaprint have shown their ability to inform treatment choice in the adjuvant setting, identifying patients more likely to benefit from chemotherapy [31,32]. These gene signatures are less effective in evaluating the likelihood of late recurrences [33]. Second generation gene signature platforms (e.g. PAM 50, Breast Cancer Index and Endopredict) could be more effective in predicting the risk of late recurrence as they employ a higher number of ER signalling related genes [34]. These molecular signatures could help dissecting low- and high-risk patients, for whom different and tailored durations of endocrine therapy could be decided (Fig. 5). This hypothesis should be confirmed by prospective trials.

Our work has some important limitations: first of all the heterogeneity of the outcome measures definitions across the trials, which could impact the final results, and second, the retrospective nature of this literature-based analysis. However, even in the presence of high heterogeneity between trials design characteristics, endocrine therapy duration and type, as well as differences in the outcome measures definition, our data suggest a general benefit of extended adjuvant therapy with AIs, in particular in the node-positive disease population.

Identification of new meaningful biomarkers for patient stratification, as well as the integration of molecular assays able to predict the risk of recurrence into clinical practice, will hopefully help identify the subgroup of patients which will gain the most benefit from longer endocrine therapy duration.

Nevertheless, at this stage, selection of patients for extended AIs therapy should take into account the initial endocrine regime, together with the biology of the tumour and the biological risk, treatment-associated toxicities, risk of recurrence and patients'

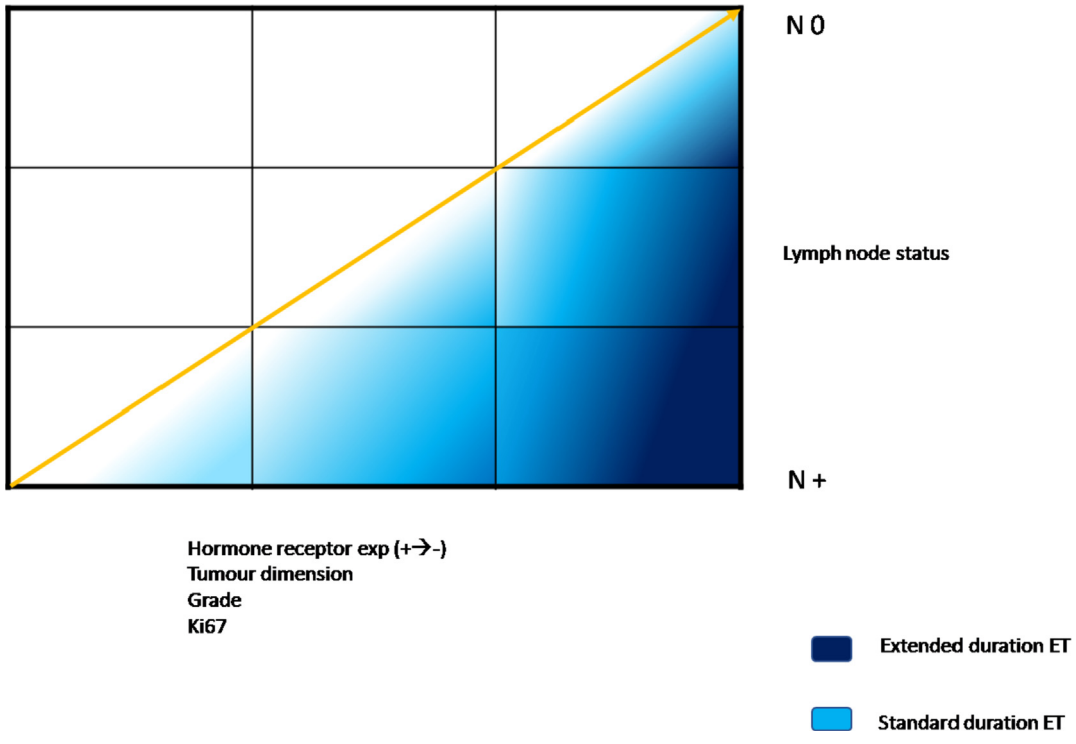

Fig. 5. Endocrine Therapy Indications according to risk factor and nodal status.

preferences.

Conflicts of interest

The authors of this work Silvia Paola Corona, Giandomenico Roviello, Carla Strina, Manuela Milani, Serena Madaro, Daniele Zanoni, Giovanni Allevi, Sergio Aguggini, Maria Rosa Cappelletti, Michele Francaviglia, Carlo Azzini, Alessandra Cocconi, Marianna Sirico, Marina Bortul, Fabrizio Zanconati, Fabiola Giudici, Pietro Rosellini, Francesco Meani, Olivia Pagani and Daniele Generali all declare no conflict of Interest.

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