Tailoring adjuvant therapy for hormone receptor-positive breast cancer

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Chapter 2

Extended adjuvant endocrine therapy in hormone-receptor positive early breast cancer: current and future evidence

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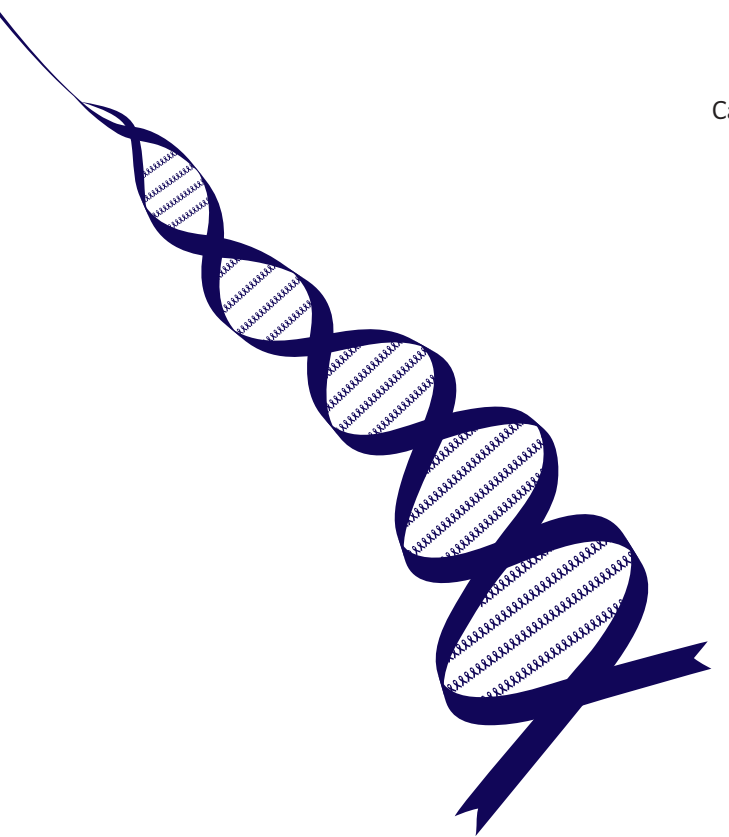


Abstract

The optimal duration and regimen of adjuvant hormonal therapy for premenopausal and postmenopausal patients with hormone receptor positive early breast cancer has not yet been established. This review will give an overview of published and ongoing studies concerning extended endocrine treatment. Most of the currently published studies are based on the adjuvant treatment regime of 5 years tamoxifen, which has been proven to be inferior compared to aromatase inhibitor (AI)-containing regimes. Therefore, until today, there is no clear evidence for the extension of endocrine therapy after upfront AI-based adjuvant treatment regimes. Multiple clinical trials, which will be discussed in this review, are ongoing to elucidate on this matter. We emphasize the need for tailoring of extended adjuvant endocrine treatment. The quest for predictive biomarkers, which are currently being investigated in the context of decision-making whether or not to start adjuvant chemotherapy, should be expanded to include the feasibility of extended endocrine treatment based on these markers. By tailoring the extension of endocrine treatment, overtreatment, side effects and unnecessary costs will be prevented.

Introduction

Nowadays, endocrine treatment is one of the mainstays of breast cancer treatment, but the optimal duration is yet to be determined. It is estimated that 75% of all breast cancer patients are hormone receptor-positive (HR+) breast cancer, and therefore might benefit from endocrine treatment.[1] Endocrine therapy significantly reduced the risk of death among patients with HR-positive tumors compared to those with ER and PgR-negative tumors. Five years of adjuvant tamoxifen reduced the breast cancer mortality by about a third throughout the first 15 years.[2] However, estimations for the long term risk of recurrence show that HR- positive breast cancer patients remain at a significant risk of recurrence until at least 15 years post diagnosis, whereas the risk for recurrence for ER/PgR negative patients is highest shortly after diagnosis but decreases below that of ER/PgR positive patients later on.[2,3] There is scientific evidence that it is beneficial to use extended tamoxifen after 5 years of adjuvant tamoxifen[4,5] and to start using an aromatase inhibitor after having received tamoxifen for 5 years, even if tamoxifen was stopped a considerable time ago.[6]

Adjuvant endocrine therapy

Ever since the first oophorectomy performed by dr. Beatson in 1896[7], endocrine therapy has been established as a treatment option for HR+ breast cancer. Currently, tamoxifen and aromatase inhibitors (AIs) are the two most important categories for endocrine treatment in postmenopausal patients. A third category of endocrine therapy, ovarian function suppression (OFS by GnRH agonists, ablation or radiotherapy) is used in premenopausal patients to diminish the ovarian function in combination with tamoxifen or AIs.[8]

After its introduction in 1970, the selective estrogen receptor antagonist tamoxifen soon became standard therapy in the treatment of advanced hormone receptor-positive breast cancer9. Initially, treatment was based on 1-2 year strategies as this was the optimal duration in advanced disease.[9,10] However, it became clear that 5 year adjuvant treatment improved the clinical outcome, and for decades this has been the standard treatment for hormone receptor-positive breast cancer.[11-13] Five years of adjuvant treatment with tamoxifen versus no treatment showed a relative risk reduction in 15 year recurrence risk of 40%, with an absolute gain of 13.2%.[2] Furthermore, a decrease of 15 year breast cancer mortality has been observed with a relative risk of 0.7, and an absolute benefit of 9.2%.

While tamoxifen was introduced, the first AIs were developed and proven to be efficient in metastatic breast cancer patients.[14] However, due to its inhibitory function on cytochrome P450, its effects on adrenal function and subsequent side effects, the first and second generation AIs did not become mainstream treatment for adjuvant treatment, and were only used in separate cases of metastatic disease.[14,15] AIs only became popular after the development of third generation compounds (anastrozole, letrozole and exemestane) which are less toxic. The first report of these third generation AIs in the setting of a large clinical trial was in the Anastrozole, Tamoxifen Alone or in Combination (ATAC) trial, in which anastrozole, tamoxifen and a combination of both were studied16. At initial 5 years and 10 years follow-up, this study showed the superiority of AIs over tamoxifen as a first line adjuvant treatment for early breast cancer in postmenopausal patients, and comparable results for the combination treatment.[16-18] After these findings, multiple trials examined the effect of switching to an AI compared to continuing with tamoxifen. A meta-analysis by Dowsett *et al* in 2010 showed a superiority of this switch scheme above continuing with tamoxifen.[19] This switch scheme consists of 2-3 years of tamoxifen, followed by 2-3 years of an AI. Two other major trials, BIG 1-98 and TEAM-trial, initially focused on the same research question whether AIs would be superior to tamoxifen. However, due to the results that AIs appeared superior to tamoxifen, they changed their design into a comparison of five years AI with the before-mentioned switch scheme. Both studies showed a borderline non-significant progressive decrease of disease free survival (DFS) or recurrence free survival (RFS) in the initial 2-3 years of tamoxifen. However, after the switch to an AI, the difference between both groups stabilized leading to a non-significant difference between both groups.[20,21] Therefore there is no evidence for superiority of either 5 years AIs or a switch scheme at long term follow-up.

For premenopausal patients monotherapy with tamoxifen was the standard therapy for a long time with a possible benefit from ovarian suppression for patients of 40 year and younger.[22,23] Recently, the results of the TEXT and SOFT trial revealed that for premenopausal patients addition of ovarian function suppression should be considered for patients younger than 35 years (5 year breast cancer free interval of 67.7% for tamoxifen vs 78.9% for tamoxifen plus OFS and 83.4% for exemestane plus OFS) or who received chemotherapy (5 year breast cancer free interval 78% for tamoxifen vs 82.5% for tamoxifen plus OFS vs 85.7% for exemestane plus OFS.[24]

Side effects of aromatase inhibitors are different from those of tamoxifen. Generally, tamoxifen is well tolerated, with most reported events to be hot flushes, osteoporosis, arthralgia and gynaecologic symptoms like vaginal bleeding and discharge.[17] More severe toxicities which have been described with the use of tamoxifen are venous thromboembolisms and a hazard ratio of approximately 2 for endometrial carcinomas and mood change or depression.[25-29] For aromatase inhibitors, hypertension, dyslipidaemia, arthralgia and osteoporosis are more frequently described. Gynaecological symptoms and hot flushes are less common.[16,17,30-32] Arthralgia is usually reported by patients as the most relevant side effect.[30,33] Generally, just as tamoxifen, aromatase inhibitors are relatively well tolerated. In designated trials comparing the switch scheme with aromatase inhibitors only, no important differences in side effects or quality of life were shown.[34] The TEAM trial showed that in general, there are more gynaecological and vascular side effects with the tamoxifen-containing switch scheme, while in the aromatase inhibitor group hypertension, dyslipidaemia and musculoskeletal complaints were more pronounced.[20] Similar results were observed in the BIG 1-98 study.[21] Therefore, regarding side effects and toxicity, therapy choices should be tailored on the individual patient taking co-morbidity and patients preference in consideration.

These findings have led to the conclusion that AIs should be included in the adjuvant treatment of early HR+ breast cancer in postmenopausal patients, and also in combination with ovarian suppression for premenopausal patients. However, there is no evidence for superiority of either 5 years aromatase inhibitors or a switch scheme of tamoxifen followed by an AI. This review will comment on the current evidence for therapy extension, ongoing studies and possible predictive markers suitable for decision-making concerning extended endocrine treatment.

Extended therapy

The current period of 5 or 10 years of adjuvant endocrine treatment for early breast cancer is based on early results of adjuvant tamoxifen.[2,5,35] However, it was shown that approximately 50% of recurrences happened after the initial 5 years of adjuvant treatment.[2,36] These findings initiated a debate on the optimal duration of therapy, and a number of studies was set up to elucidate on this matter.

The NCIC CTG MA.17 trial in 5187 patients showed that 10 years of treatment (5 years of tamoxifen followed by 5 years of letrozole) was superior to five years of tamoxifen.[6]

Table 1 – evidence for extended therapy

study	Nr of patients	initial therapy	extended treatment	control arm	FU time	HR DFS	p-value	HR OS	p-value	reference
MA.17	5187	5y TAM	5y letrozole	placebo	30	0.57	<0.0001	0.76	0.25	6
ABCSG	860	5y TAM	3y anastrozole	no treatment	62.3	0.62	0.031	0.89	0.57	39
NSABP B33	1598	5y TAM	5y exemestane	placebo	30	0.68	0.07	NA	NA	41
ATENA	448	5y TAM	5y exemestane	placebo	NA	NA	NA	NA	NA	40
ATLAS	6846	5y TAM	5y TAM	no treatment	NA	0,75*	0.002	0,87*	0.01	4
aTTom	6953	5y TAM	5y TAM	no treatment	NA	0,75*	NA**	0,86*	NA**	5

All major clinical trials on extended adjuvant endocrine treatment that have been published are shown in this table. For some studies, no data were available in the original publication (NA = not available).

* at >10y follow up

** no p-values provided, but significant based on confidence interval

After a median follow-up of 30 months, a hazard ratio of disease free survival of 0.58 was found, with a non-significant HR of 0.76 for overall survival. Upon these interim results the study was unblinded, and cross-over was allowed. However, with a 66% cross-over from the placebo to treatment arm, there was a significant loss of power for further follow-up. At 60 months of follow up, this has led to a HR for disease free survival of 0.68 (0.55-0.83), but no difference in overall survival (HR=0.98). With a statistical test called the inverse probability of censoring weighted analysis (IPCW-analysis), they estimated that the HR for overall survival would have been 0.61 (0.52-0.71) without cross-over.[6,37,38] Although this was the first proof of principle for extended endocrine therapy, the interpretation of these findings is difficult. Starting five years of letrozole after 5 years of tamoxifen is basically the same strategy as the switch scheme described above, only with longer treatment intervals. It could be stated that this study confirms the benefits of a (late) switch scheme, rather than a general benefit for extended therapy. In 2006, Ingle *et al* showed that the hazard ratios for disease free survival when using letrozole decreased over time, which was attributed to an increasing risk of recurrence in the placebo-controlled group.[39] These findings indicate a possible benefit for extending the treatment even further beyond the studied term of 5 years. Whether this also implies for patients who received up-front AI treatment is only supported by circumstantial evidence, and has not been studied yet.

Three other, smaller studies have confirmed the results of the MA.17 study (Table 1). The Austrian Breast and Colorectal Cancer Study Group (ABCSG)-6a study, had a similar setup in which 856 patients after 5 years of tamoxifen were randomized between 3 years of anastrozole or regular follow-up.[40] A reduction of 38% in the risk of breast cancer recurrence was observed (HR 0.62, 95% CI 0.4-0.96), which is in concordance with the MA.17 results. This study failed to show any benefit on overall survival, most likely due to the relative short follow-up of 5 years. Two other studies, both evaluating exemestane as extended therapy after 5 years of tamoxifen, were closed prematurely due to the results of the MA.17 trial.[41,42] One of them however published their underpowered results, already showing a borderline significant decrease in DFS at 30 months of follow-up42. A meta-analysis conducted with the four trials mentioned above, has led to an overall decrease in breast cancer recurrence of 43% (absolute decrease of 2.9%) and a (not statistically significant) decrease in mortality of 11% (absolute decrease of 0.5%) at 2.5 years of follow-up.[43] The consistent results in these four trials using letrozole, anastrozole and exemestane as AIs, lead to

another conclusion that the advantage of AIs is not limited to one specific type, but is a class effect. There appears to be no difference between the separate agents, making future comparisons and meta-analyses less complicated.

Extended therapy after 5 years of tamoxifen has comprehensively been studied. Early small studies did not show a benefit for extended tamoxifen, with an increase in toxicity. In 2013, the 15-year follow-up results from Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial were published4. This study, which randomized nearly 7000 ER-positive patients between 5 or 10 years tamoxifen, showed a benefit for continuing tamoxifen with an absolute benefit of 3.7% (21.4% vs 25.1%) on recurrence risk, and an absolute mortality reduction of 2.8% (12.2% vs 15%). Remarkably, these benefits were mainly observed in the period after 10 years when treatment was ceased. This was attributed to a carryover effect, which is well known for tamoxifen.[2] Similar results were observed in the British Adjuvant Tamoxifen - To Offer More (ATTOM) trial.[5]

Clinical implications

The interpretation of these extended therapy studies is difficult. As shown in Table 1, all available studies are based on 5 years of tamoxifen, before therapy was extended. Extended tamoxifen has shown a small but consistent overall survival benefit. The results of the ATAC, BIG 1-98 and TEAM trial clearly show that AI-containing adjuvant regimes, either as a monotherapy or as a switch-scheme, are preferred above tamoxifen monotherapy. As a result, there is no clear evidence for therapy extension of modern 'regular' AI-containing adjuvant treatment, and no direct evidence for extended therapy with an AI longer than 5 years. Furthermore, there are no studies available with a direct comparison between the extension with tamoxifen or letrozole.

The most recent ASCO guidelines, published in July 2014, support –based on recent literature data-multiple treatment strategies for the type and length of adjuvant endocrine therapy.[44] They offer four options: tamoxifen for 10 years, tamoxifen for 5 years followed by an AI for 5 years, AI for 5 years or a switch scheme starting with tamoxifen for 2-3 years followed by an AI for up to 5 years. Little evidence is available to compare these four options. Only a comparison between the switch scheme and 5 years of AI is available, which has led to no significant differences as discussed earlier. In a review published in 2013, Strasser-Weippl *et al* performed an unofficial analysis comparing extended therapy using AIs with tamoxifen after 5 years of tamoxifen. Comparing hazard ratios of two separate studies, they state that switching to an AI

after 5 years of tamoxifen appears beneficial over continuing with tamoxifen, and that it would lead to a larger recurrence rate reduction and a better overall survival.[45] Although comparing hazard ratios of different studies is controversial, this would be in accordance with the findings in 'regular' adjuvant treatment that AI-containing regimes have better outcomes compared to tamoxifen monotherapy.

For premenopausal women the evidence based choices are: tamoxifen 5-10 years, tamoxifen 5 years followed by AI 5 years, ovarian suppression with tamoxifen or AI which should be considered for higher risk patients (<35 years, premenopausal after prior chemotherapy and multiple positive axillary nodes). The optimal duration of ovarian suppression based therapy is uncertain; the SOFT and TEXT trial both studied 5 years.

Ongoing studies

Now that the first studies have reported a benefit of extended adjuvant endocrine therapy in early breast cancer, many challenges lie ahead. Basically, it comprises three main topics: (1) To validate the findings of earlier studies in modern AI-containing adjuvant therapy, (2) to determine the optimal duration of extended therapy and (3) to identify and further explore predictive factors for patients that would benefit most of extended therapy46. Figure 1 summarizes the ongoing and unpublished trials.[37,47,48]

The main study focussing on validation of extended therapy after modern, AI-containing, regimes is the NSABP B42 trial, in which nearly 4000 patients were randomized between 5 years of letrozole or placebo, after 5 years of regular adjuvant therapy either consisting of aromatase inhibitors or tamoxifen followed by aromatase inhibitors.[49] Also the Letrozole Adjuvant Therapy Duration (LEAD) and the Different Durations of Anastrozole after Tamoxifen (DATA) trials have the same perspective, by randomizing patients after 2-3 years of adjuvant tamoxifen between standard treatment (additional 2-3 years AI) and extended treatment (5-6 years of AI), respectively.[50,51] This creates a situation in which standard therapy is compared with 2.5 years extended therapy. Both the Secondary Adjuvant Long-term Study with Arimidex (SALSA; ABCSG-16) and Investigation on the Duration of Extended Adjuvant Letrozole treatment (IDEAL) randomize between 2-2.5 and 5 years of therapy extension, after any prior adjuvant endocrine treatment of 5 years.[52,53] The Study of Letrozole Extension (SOLE) trial compares 5 years of continuous AI therapy extension with intermittent letrozole extension. This intermittent scheme consists of

an annual cycle of 9 months therapy and a 3 months break, while the final (5th) year is 12 months of therapy.[54] Combined, these studies will presumably answer whether therapy extension after 5 years of AI-containing adjuvant treatment is relevant, and what would be the optimal duration of extension (2.5 vs 5 years). Finally, there is also an extension of the MA.17 trial, called the MA17R.[37] This study will extend the adjuvant therapy even further with another 5 years of letrozole versus placebo, which counts up towards 15 years of adjuvant therapy.

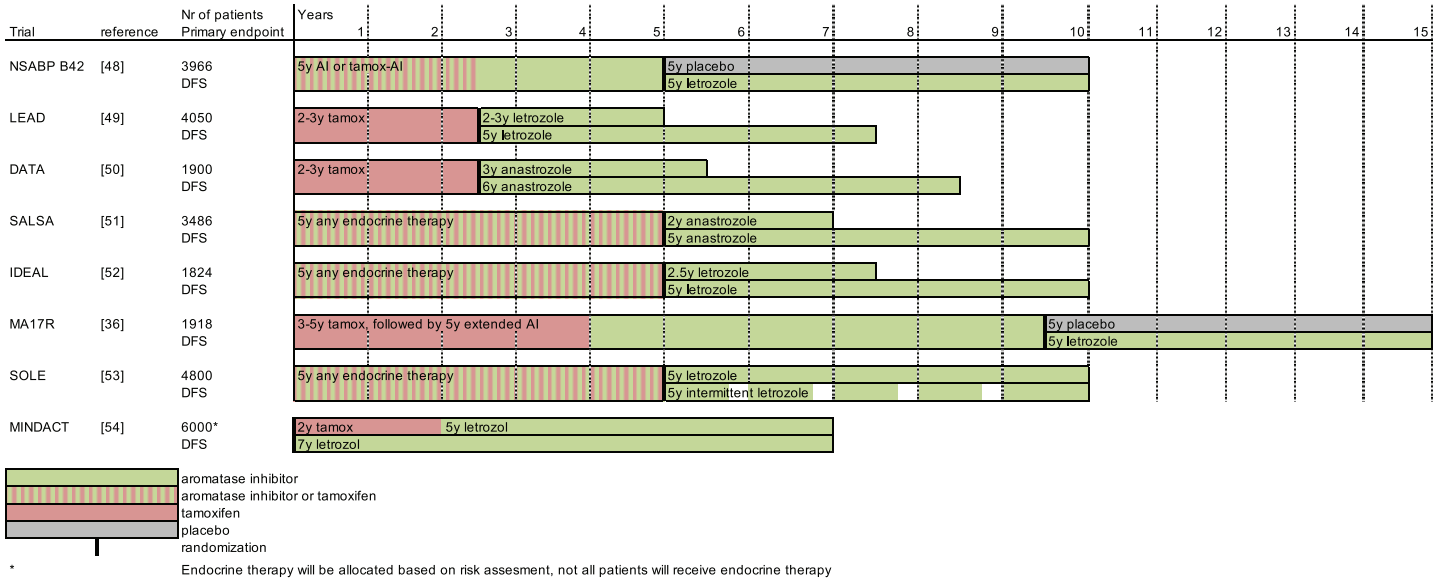
The MINDACT-trial, a large trial with the main purpose on decision making based on either epidemiological data or genetic data, also has a substudy in which 7 years of AI is compared to 2 years of tamoxifen followed by 5 years of AI.[55] Although this study is not focused on the optimal duration of therapy (both arms have the same treatment length), it will add more value to extended AI beyond 5 years.

Predictive markers

Because luminal breast cancer is a heterogeneous disease it is important to be able to select those patients that will benefit most from extended adjuvant therapy. For adjuvant endocrine treatment, many efforts have been made to identify biomarkers or molecular profiles capable of predicting response to endocrine treatment and the risk of recurrence after treatment.[56,57] Although research is still ongoing, established methods comprise both immunohistochemical and genetic approaches. However, most of these platforms are only validated for use in regular endocrine therapy, or for adjuvant chemotherapy. None of them is validated for extended endocrine treatment.

Classical risk factors like age and nodal status were analysed in the MA.17 trial, both showing no statistical differences between the subgroups.[6,37] Regular immunohistochemical (IHC) markers in breast cancer comprise the Estrogen Receptor (ER), Progesterone Receptor (PgR) and the Human Epidermal growth factor Receptor 2 (HER2). For the ER receptor it was shown in the TEAM trial, that a semi-quantitative expression analysis using IHC is predictive for adjuvant endocrine therapy response.[58] HER2, initially discovered as a predictive marker for poor prognosis and later on developed as a target for monoclonal antibodies against the Her2 receptor, such as trastuzumab (Herceptin®), was also associated with resistance against endocrine treatment.[59-61] Ki-67 also showed to be predictive for the response on endocrine treatment, and the difference in Ki-67 measurement after 2 weeks of neo-adjuvant endocrine therapy appeared to be predictive for the long term effect of endocrine treatment.[62,63]

figure 1 – Overview of ongoing trials



This figure shows the currently ongoing trials investigating extended endocrine treatment. In studies where time ranges instead of time points are used, the expected average treatment duration is plotted. Abbreviations: nr = number, AI = aromatase inhibitor, tam = tamoxifen, y = year, DFS = Disease Free Survival

Based on the immunohistochemical markers mentioned above, a number of multi-marker assays has been developed to predict recurrence risk. IHC4, which consists of a single score based on the expression of ER, PgR, HER2 and ki-67, has been developed as a platform to predict recurrence risk in early breast cancer.[64,65] This assay has been validated retrospectively in the setting of adjuvant endocrine treatment in the ATAC study. IHC4 is of value in clinical decision making, especially in combination with clinicopathologic parameters like tumour grade, size, nodal status and age.[66,67]

A similar platform, called the preoperative endocrine prognostic index (PEPI), was developed specifically for neo-adjuvant treatment. It comprises a combination of post-treatment ER expression, Ki67, histological grade, tumour size, nodal status, and treatment response. This platform was able to stratify patients in three risk groups, with relapse risks of 10%, 23%, and 48%68. The authors suggest that this assay would assist in the decision of starting adjuvant chemotherapy, but it could also be worthwhile to validate this platform for use in decisions concerning endocrine treatment extension.

Both the Mammaprint and Oncotype DX have been established as commercially available genetic testing platforms, depending on the expression of respectively 70 and 21 genes known to be correlated with recurrent disease. Both tests are capable of stratifying the risk of recurrence in low, medium (only for the Oncotype DX) and high. This stratification indirectly represents the likelihood of benefit from chemotherapy. Both tests are currently being validated in a prospective study, with regard to decision-making for adjuvant chemotherapy.[55,69] Another genetic platform called the Endopredict, which was developed as specific for endocrine therapy using eight genes involved in ER-signalling, was used to calculate risk of recurrence after 5 years of endocrine treatment.[70] Furthermore, the Breast Cancer Index (BCI) and Prosigma Risk of Recurrence (ROR), are multigene assays capable of predicting recurrence, although only the ROR-score provided significant prognostic information for late recurrences (5-10 years).[71,72]

To the authors' knowledge, none of these markers and platforms has been validated in a cohort of patients on extended endocrine treatment. It would not be unlikely that all these markers and platforms described, might also be valuable to assist in deciding whether or not to extend endocrine treatment. For this, validation in the setting of extended endocrine treatment is necessary. Although this is an expensive

and elaborative procedure, it is a crucial step towards tailoring of adjuvant endocrine treatment.

Furthermore, research into new predictive and prognostic markers like (epi)genetics, proteomics, circulating tumour DNA, circulating tumour cells (CTCs) and other promising techniques could be valuable in the setting of extension of endocrine treatment.

Conclusion

After almost 5 decades of endocrine therapy, there is still debate on the optimal combination and length of adjuvant therapy. Although studies currently available give strong suggestions that extension of endocrine therapy has benefits, there is actually no strong evidence to support this in the current clinical setting using AIs in the initial adjuvant treatment. Nonetheless, extended endocrine therapy is a promising strategy to further reduce the risk of recurrence. In future studies, emphasis should be laid on selection of subpopulations who benefit most from therapy extension. Patient tailored decision-making will eventually prevent overtreatment, side effects and costs, and add great value to the treatment of breast cancer.

Conflict of interest

All authors have declared that they have no conflicts of interest in regards to this manuscript.

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