# ASSOCIATION OF BREAST SURGERY GUIDELINES

# ENDOCRINE TREATMENT FOR BREAST CANCER

# Association of Breast Surgery Guidelines
## Endocrine Treatment for Breast Cancer

NICE guidance on adjuvant treatment of breast cancer was updated in July 2018, including recommendations for adjuvant endocrine therapy which can be found here

This updated NICE guidance includes evidence reviews on the optimal duration of adjuvant endocrine therapy and on the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women which can be found here
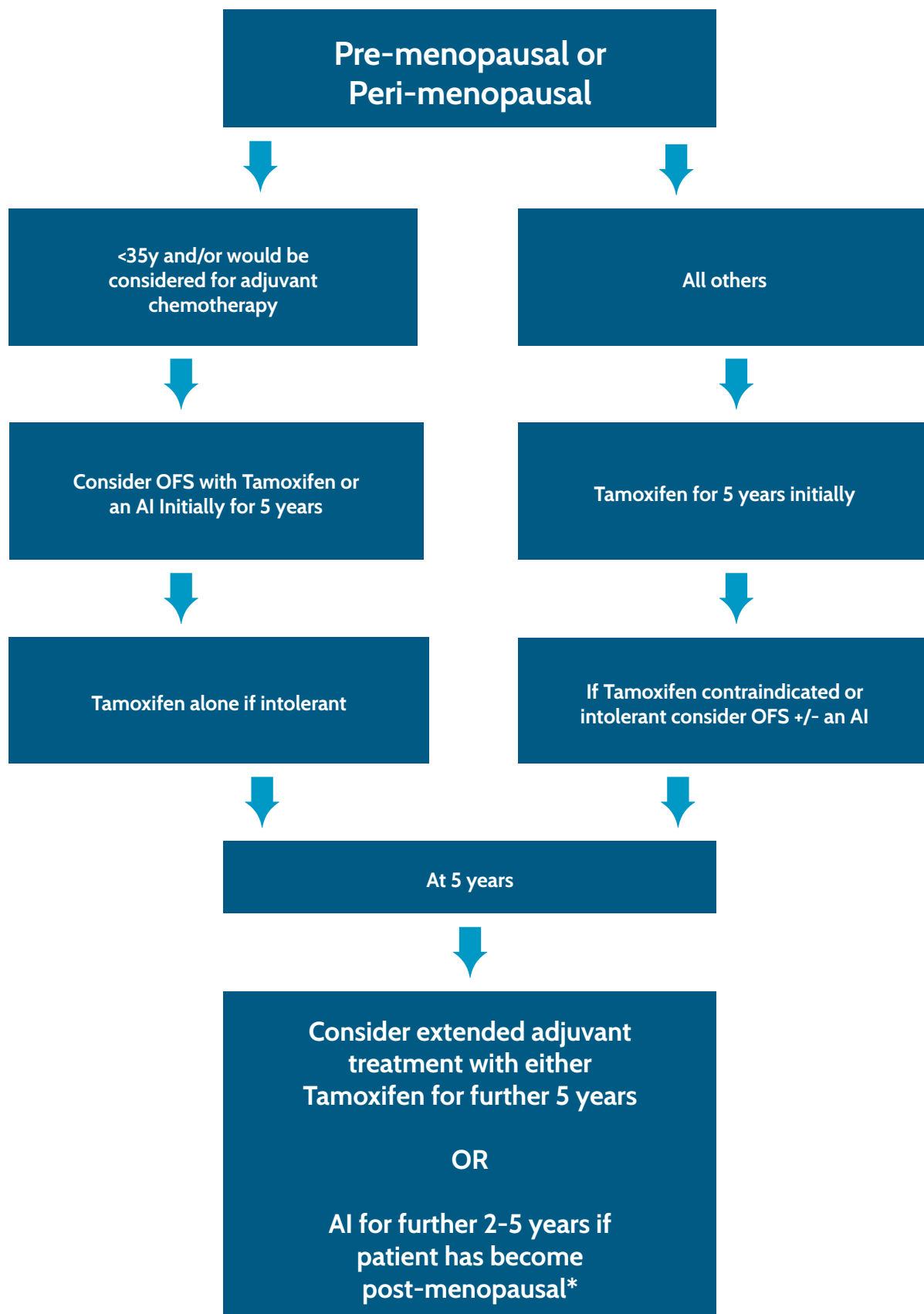
The aim of this document is not to supplant this guidance but to provide suggestions and advice for its implementation and to give evidence-based opinions on areas which are not included in the NICE guidance.

Figure 1 is a flow sheet summarising the main issues covered in this document.

**EXECUTIVE SUMMARY**

- In the adjuvant setting for premenopausal women use tamoxifen and consider OFS plus tamoxifen or an AI, in women <35y and/or who have higher risk breast cancers (would be considered for adjuvant chemotherapy).

- For men with breast cancer use tamoxifen in the adjuvant setting

- In postmenopausal women offer an AI unless tumour low risk or the patient is intolerant of AI.

- Use extended adjuvant endocrine therapy in premenopausal patients on tamoxifen for 10 years or consider swap to AI if patients become postmenopausal during this time.

- Those postmenopausal patients already on an AI may benefit from extending their treatment for 2-5 years but tolerability including bone health must be taken into consideration.

- It is reasonable to offer NET to post-menopausal women with strongly ER positive, HER 2 negative cancers as these patients often do not respond well to NACT. Due to the paucity of data in premenopausal women, the use of NET should be reserved for clinical trials.

- It is reasonable to discuss endocrine therapy in women with ER positive DCIS, following breast conserving surgery, especially if they are not having RT.

**Figure 1: Flowchart and summary**

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┌─────────────────────────────────────┐
│      Pre-menopausal or               │
│      Peri-menopausal                 │
└─────────────────────────────────────┘
         │                    │
         ▼                    ▼
┌──────────────────┐  ┌──────────────────┐
│ <35y and/or      │  │                  │
│ would be         │  │  All others      │
│ considered for   │  │                  │
│ adjuvant         │  │                  │
│ chemotherapy     │  │                  │
└──────────────────┘  └──────────────────┘
         │                    │
         ▼                    ▼
┌──────────────────┐  ┌──────────────────┐
│ Consider OFS     │  │                  │
│ with Tamoxifen   │  │ Tamoxifen for 5  │
│ or an AI         │  │ years initially  │
│ Initially for    │  │                  │
│ 5 years          │  │                  │
└──────────────────┘  └──────────────────┘
         │                    │
         ▼                    ▼
┌──────────────────┐  ┌──────────────────┐
│                  │  │ If Tamoxifen     │
│ Tamoxifen alone  │  │ contraindicated  │
│ if intolerant    │  │ or intolerant    │
│                  │  │ consider OFS     │
│                  │  │ +/- an AI        │
└──────────────────┘  └──────────────────┘
         │                    │
         ▼                    ▼
     ┌──────────────────────────┐
     │      At 5 years          │
     └──────────────────────────┘
              │
              ▼
     ┌──────────────────────────┐
     │ Consider extended        │
     │ adjuvant treatment       │
     │ with either Tamoxifen    │
     │ for further 5 years      │
     │                          │
     │          OR              │
     │                          │
     │ AI for further 2-5       │
     │ years if patient has     │
     │ become post-menopausal*  │
     └──────────────────────────┘
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*NB Must be appropriately assessed (see section 2.1.2)

## 1. Initial Adjuvant Endocrine Treatment

The 2018 NICE guidance on initial endocrine treatment is as follows:

- Offer tamoxifen as the initial adjuvant endocrine therapy for men and premenopausal women with ER positive invasive breast cancer.

- Offer an aromatase inhibitor as the initial adjuvant endocrine therapy for postmenopausal women with ER positive invasive breast cancer who are at medium or high risk of disease recurrence. Offer tamoxifen to women who are at low risk of disease recurrence, or if aromatase inhibitors are not tolerated or are contraindicated.

The guidance defines "medium or high risk" as "may include people who have lymph node positive breast cancer, with tumours that are T2 or greater and higher grade" and "low risk" as may include people with lymph node negative breast cancer, with smaller or lower grade tumours.

### 1.1 Background and Implementation

The most recent Early Breast Cancer Trialists' overview (Davies et al) confirms that 5 years of tamoxifen reduces the risk of breast cancer mortality by about a third throughout the first 15 years, compared to no adjuvant endocrine treatment, (RR 0·71 during years 0-4, 0·66 [0·05] during years 5-9, and 0·68 during years 10-14). This benefit is independent of patient and tumour characteristics.

The additional benefit of using aromatase inhibitors compared to 5 years of tamoxifen for post-menopausal women on risk of breast cancer mortality is demonstrated by the EBCTCG 2015 meta-analysis (Dowsett at al) which included individual patient data from almost 32,000 women. The data was divided into 3 cohorts:

  i. AI vs tamoxifen for 5y. This showed a lower 10-year breast cancer mortality for the AI treated group, (RR 0.85, 95% CI 0.75-0.96).

  ii. Tamoxifen for a short period followed by an AI for a total of 5 years vs tamoxifen alone for 5 years. Again there was a lower breast cancer mortality for the patients who switched to an AI, (RR 0.84, 95% CI 0.72-0.96)

  iii. AI alone for 5 years vs tamoxifen for a short period followed by an AI for a total of 5 years. Here there was a trend towards reduced breast cancer mortality, but this did not reach statistical significance (RR 0.89, 95% CI 0.78-1.03).

These data underlie the NICE recommendation to initiate AI treatment for post-menopausal patients with moderate to high risk breast cancer.

An alternative strategy of a short period of AI followed by tamoxifen vs tamoxifen only has also been studied in the BIG 1-98 study of over 8000 women (Regan et al) which had 4 arms: either drug as monotherapy for 5 years or a short period (2-3 years) of an AI followed by tamoxifen or vice versa. Breast cancer outcomes were better for letrozole compared with tamoxifen monotherapy, consistent with the EBCTCG meta-analysis findings. However, there was no significant difference in either DFS or OS between the sequential therapies and letrozole monotherapy. This is consistent with the observation that the highest risk of recurrence is within the first few years and that an AI is therefore preferable initially. However, once patients have remained disease free for the first few years switching to tamoxifen is similarly effective to continuing on Letrozole. These are reassuring data for women who are struggling to tolerate an AI that switching to tamoxifen after the first few years is reasonable. Moreover, whilst Letrozole was associated with a lower risk of contralateral breast cancer in the first 10 years of treatment this reversed after 10 years (0 to 5, 5 to 10, and >10-year HRs, 0.62, 0.47, and 1.35, respectively), suggesting that there is a greater carry-over effect of tamoxifen in reducing the risk of contralateral breast cancer (Ruhstaller et al).

In implementing these recommendations it is important that the patient's menopausal status is properly ascertained: **if in doubt it is safer to assume that a patient is pre-menopausal.** Diagnosing menopause is

fraught with difficulty in women who have had adjuvant chemotherapy since ovarian function can recover many months after completing chemotherapy and amenorrhoea is not a reliable indicator of menopausal status. It is also known that women who recover ovarian function having been started on an aromatase inhibitor after chemotherapy have worse disease free-survival than those who do not recover ovarian function (Guerrero et al). **Hence women who were pre-menopausal pre chemotherapy and have chemotherapy-induced amenorrhoea should be treated as pre-menopausal and should not be given aromatase inhibitors without ovarian function suppression** (discussed below).

There is no agreed published consensus for the diagnosis of menopause in younger women treated for breast cancer. In the absence of such, the British Menopause Society (for the Association of Breast Surgery) has agreed a consensus statement.

As recommended by NICE, tamoxifen is the endocrine treatment of choice for men with breast cancer.

## 1.2 Ovarian Function Suppression (OFS)
The 2018 NICE guidance on ovarian function suppression is as follows:

- Consider ovarian function suppression in addition to endocrine therapy for premenopausal women with ER positive invasive breast cancer.

- Discuss the benefits and risks of ovarian function suppression in addition to endocrine therapy with premenopausal women with ER positive invasive breast cancer. Explain to women that ovarian function suppression may be most beneficial for those women who are at sufficient risk of disease recurrence to have been offered chemotherapy.

### 1.2.1 Background and Implementation
Data for a benefit of OFS in addition to endocrine treatment with either tamoxifen or an AI come from two large scale trials, Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT). Overall, in the SOFT trial (Francis et al) for the whole population there was a modest benefit of OFS added to tamoxifen vs tamoxifen alone on overall survival at 8 years (93.3 versus 91.5 percent; HR 0.67, 95% CI 0.48-0.92), but no apparent additional benefit of OFS plus exemestane compared to tamoxifen (92.1 percent; HR 0.85, 95% CI 0.62-1.15).

Subsequently, sub-group analysis has identified groups where there is a greater benefit of adding OFS to endocrine treatment (Pagani et al). In particular, for very young women there was a much greater benefit: in the 233 women under 35 years in the combined analysis of the SOFT and TEXT trials the breast cancer free survival rates were 67.7% for tamoxifen only vs 78.7% for OFS + tamoxifen (95% confidence interval 69.8% - 85.8%)  vs 83.4% (74.9% - 89.3%) for OFS + exemestane. Almost all of these women (94%) had also received adjuvant chemotherapy.

A greater benefit for adding in OFS to endocrine treatment has also been demonstrated in women who received adjuvant chemotherapy. In the SOFT trial the 8y DFS was 71.4% in the tamoxifen only arm vs 76.7% for tamoxifen + OFS; HR 0.76 (0.6 – 0.97) vs 80.4% for exemestane + OFS; HR 0.68 (0.53 – 0.88). There was also a significant improvement in overall survival at 8 years for the tamoxifen + OFS arm 89.4% vs tamoxifen only 85.1%, HR 0.59 (0.42 to 0.84). Again there was no benefit on overall survival of the exemestane +OFS arm vs tamoxifen only 87.2%; HR 0.79 (0.57 – 1.09). Similarly, in the TEXT trial the 8y DFS was higher for exemestane + OFS, 84.6% vs tamoxifen +OFS, 77.7%; HR 0.69 (0.53 – 0.95), but no significant difference in overall survival, 91.7% vs 89.8%; HR 0.74 (0.52 – 1.04). However, the authors note that given the long natural history of ER positive breast cancer that conclusions regarding overall survival remain premature.

It should also be noted that because of improvements in understanding of prognosis and prediction of the benefit of chemotherapy there would be differences in the population of women offered adjuvant chemotherapy now compared to since these trials were begun. This would include both women who would now be offered chemotherapy who would not in the past and vice versa: hence these data should be applied with caution.

The additional toxicity of OFS in combination with either tamoxifen or exemestane is significant as shown in both the SOFT and TEXT trials. In particular, there was a high rate of musculoskeletal symptoms in

patients receiving OFS + exemestane (11% experiencing grade 3 or 4 toxicity vs 5.2% for patients on OFS + tamoxifen). Similarly there was a high rate of osteoporosis in women on OFS + exemestane (11% grade 3 or 4 toxicity) vs 0.3% for patients on tamoxifen. Hot flushes were very common in both groups; 93.3% and 91.7% respectively for patients on OFS + tamoxifen and OFS + exemestane respectively. Overall 21.9% of women randomised to an arm including OFS had discontinued the OFS at 4 years.

Hence, whilst OFS should be considered, as recommended by the NICE guidance, for those women with lower risk breast cancers it may be felt that the potential modest benefits of OFS do not justify these additional risks. Many clinicians would favour reserving OFS for those in the subgroups where the additional benefit was greater, as outlined above. The choice of tamoxifen vs exemestane with OFS is somewhat contentious: some clinicians feel that the improvement in DFS, as outlined above, justifies the additional toxicity of exemestane compared to tamoxifen, whilst others argue that tamoxifen is a better choice given the current absence of overall survival benefit for exemestane + OFS. There are few data using the non-steroidal aromatase inhibitors (anastrazole/letrozole) in conjunction with OFS in this setting. However, given that data in post-menopausal women show similar outcomes for all the aromatase inhibitors, any of these would be appropriate options.

In both the SOFT and TEXT trials the method of ovarian function suppression used was ongoing treatment with a leutinising hormone-releasing (LHRH) analogue. Appropriate drugs in this class include goserelin, leuporelin and triptorelin. In the trials the LHRHa was given monthly and therefore this is the preferred option, although there is a preparation of leuporelin which is licensed for use every three months. An alternative to LHRHa use is oophorectomy which gives rapid and reliable reduction in circulating oestradiol but does carry the risks of surgery and anaesthesia and is irreversible. Therefore, it is generally recommended that this should be considered as an alternative for women who are established on LHRHa and are tolerating this well, and who have no interest in future childbearing. In the past radiotherapy has been used to ablate ovarian function but given its small bowel toxicity this is now rarely used and is not recommended.

In implementing these recommendations some clinicians favour initiating treatment with OFS + an AI, switching to tamoxifen if this is not tolerated, whilst others prefer to start with OFS + tamoxifen, then considering switching to an AI if this is well tolerated. In both SOFT and TEXT trials the LHRHa was started concurrently with either tamoxifen or exemestane. However, some clinicians prefer a more cautious approach of waiting 2-3 months after initiation of LHRHa before starting an AI because of the risk of a delay in achieving ovarian suppression, which is more likely in younger women.

In addition, it should be noted that a proportion of women do not achieve consistently low levels of oestradiol when treated with LHRHa + AI: in a prospective substudy of the SOFT trial, SOFT-EST, oestradiol levels were checked regularly in a central laboratory (Bellet et al). At each timepoint at least 17% were found to have oestradiol levels which were above the usual range for post-menopausal women. The clinical significance of this is unclear. However, it is known that women who were treated with an aromatase inhibitor (without OFS) but regained ovarian function have lower DFS at 2 years than those who did not regain ovarian function. Therefore a cautious approach would be to regularly monitor ovarian function for women on LHRHa + AI and switch from an AI to tamoxifen if the oestradiol levels increase beyond the usual levels in post-menopausal women (this will vary by laboratory).

For women who have completed an initial 5 years of endocrine treatment with OFS and either tamoxifen or an AI extended adjuvant treatment should be considered, as discussed below. However, as agreed in the consensus statement by the British Menopause Society, if the patient has been treated with a combination of a LHRHa and AI (irrespective of prior chemotherapy use), a washout period of 12 weeks should be allowed in order to reverse the former's suppressive effect on the hypothalamic-pituitary axis before performing serial FSH assays to reliably determine the patient's menopausal status.

There is also evidence to suggest that OFS with LHRHa given during chemotherapy (for both ER+ and ER- cancers) protects women from premature ovarian insufficiency, reducing the risk of early menopause and improving prospects for fertility (Halle et al).

## 1.3 Combinations of Endocrine and Targeted Treatment
There is a great deal of interest in combining adjuvant endocrine treatment with the CDK4/6 inhibitors, which have already demonstrated substantial benefits in the metastatic setting.

Recently, initial results of the MonarchE trial have been presented. Patients with high risk ER positive, HER2 negative breast cancer (>4 nodes or 1- 3 nodes with other risk factors) on standard adjuvant endocrine therapy (for at least 5 years) were randomised to 2 years' treatment with the CDK4/6 inhibitor Abemaciclib or placebo (Johnston et al). The trial met its primary end point, showing a significant improvement in invasive DFS of 25% (HR 0.75, p=0.01, 95% CI 0.60-0.93). The 2 year invasive DFS rates were 92.2% vs 88.7% and the 2 year distant relapse-free survival showed a 28% reduction in risk (HR 0.72, p=0.01, 95% CI 0.56-0.92). Safety data were consistent with the known safety profile of abemaciclib: the main toxicities were diarrhoea (82.2% vs 7.1% any grade, 7.6% vs 0.1% grade 3) and leukopenia (36.8% vs 6.1% any grade, 10.8% vs 0.4% grade 3). There was also an increased thrombotic risk with abemaciclib (2.3% vs 0.5%). However, hot flushes and arthralgia were worse in the standard treatment arm. The number of deaths recorded, were balanced in both arms. On the basis of these results it is hoped that regulatory approval will be granted to introduce this treatment into standard practice.

The formal results of a similar trial, PALLAS, of another CDK4/6 inhibitor palbociclib in conjunction with endocrine therapy are awaited but a press release from the manufacturer of this drug, Pfizer, on 29/5/20 states that the "trial is unlikely to show a statistically significant improvement in the primary endpoint of invasive disease free survival". A third adjuvant trial, NATALEE, of the CDK4/6 inhibitor, ribociclib, is ongoing.

## 2. Extended Adjuvant Endocrine Treatment

### 2.1 After initial treatment with tamoxifen
The 2018 NICE guidance after initial treatment with tamoxifen is as follows:

- Offer extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER positive invasive breast cancer who are at medium or high risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years.

- Consider extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER positive invasive breast cancer who are at low risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years.

- Consider extending the duration of tamoxifen therapy for longer than 5 years for both premenopausal and postmenopausal women with ER positive invasive breast cancer.

- Discuss the benefits and risks of extended endocrine therapy with women. Topics to discuss include those in the following table:

| | Extended tamoxifen therapy (after an initial 5 years of tamoxifen therapy) | Extended endocrine therapy with an aromatase inhibitor (after 5 years of tamoxifen therapy) |
|---|---|---|
| **Definition** | Continuing to take tamoxifen after 5 years of tamoxifen therapy. | Switching to an aromatase inhibitor after 5 years of tamoxifen therapy. |
| **Who can take this therapy** | Premenopausal or postmenopausal women with ER positive invasive breast cancer. | Postmenopausal women with ER positive invasive breast cancer. |
| **Effect on breast cancer recurrence**<br><br>*NOTE: The benefit for an individual person will depend on the risk of their cancer returning. For people with a low risk of recurrence, the benefits may not outweigh the risks or side effects.*<br><br>*Medium or high risk may include people who have lymph node positive breast cancer, with tumours that are T2 or greater and higher grade. Low risk may include people with lymph node negative breast cancer, with smaller or lower grade tumours.* | Lower rates of breast cancer recurrence compared with 5 years of tamoxifen therapy. | Lower rates of breast cancer recurrence compared with 5 years of tamoxifen therapy.<br><br>In postmenopausal women, switching to an aromatase inhibitor may be more effective at reducing recurrence than continuing with tamoxifen. |
| **Side effects**<br><br>NOTE: These are common side effects experienced during additional years taking endocrine therapy. Most effects are reversible when tablets are stopped. | Side effects of endocrine therapy will continue for additional years (for example, menopausal symptoms such as hot flushes).<br><br>With extended use of tamoxifen: increased risk of thrombosis and endometrial cancer, and possibly bone density loss in premenopausal women. | Side effects of endocrine therapy will continue for additional years (for example, menopausal symptoms such as hot flushes).<br><br>With extended use of aromatase inhibitors: bone density loss, and joint and muscle pain. |
| **Fertility and family planning** | Effects on fertility and family planning will continue for additional years as women should not become pregnant while taking tamoxifen or for at least 2 months after stopping, because it may have adverse effects on the baby. | Not applicable as postmenopausal women only. |

### 2.1.1 Background and Implementation

The rationale for considering continuing endocrine treatment beyond the previously standard initial 5 years of treatment derives from data showing that there is an ongoing risk of recurrence for at least 15 years for women who have completed 5 years of tamoxifen. A recent meta-analysis (Pan et al) has shown that the initial nodal status of the tumour and its size correlate well with the likelihood of recurrence: women with T1N0 cancers at diagnosis had a cumulative risk of recurrence between 5 and 20 years after diagnosis of 13%, whereas those with T2N4-9 the risk of recurrence was 41%. There was a smaller association of higher grade with increased risk of recurrence but neither PR status nor HER 2 status correlated with risk of recurrence (of note, none of the women in these studies received adjuvant Trastuzumab).

Some clinicians find it helpful to use the CTS 5 calculator  to discuss the likelihood of distant recurrence with patients after 5 years of endocrine therapy. This is a tool which was developed using data from 2 large trials to predict the likelihood of late distant recurrence, dividing the likelihood of distant recurrence between 5 to 10 years into low (<5%), intermediate (5-10%) and high (>10%; Dowsett et al).  The tool has also recently been validated in patients from the TEAM and IDEAL trials (Noordhoek et al): there were significantly more distant recurrences in the CTS5 high and intermediate groups than the low risk group, although the rates of distant recurrence were lower in the high risk group than predicted by the CTS5 tool. The predict tool has also been updated to include an option to estimate the benefit of an additional 5 years of hormone therapy after an initial 5 years of hormone treatment – i.e. survival from years 5 to 15 after diagnosis.

The evidence underlying the recommendation for continuing pre-menopausal women who have completed 5 years of tamoxifen to a total of 10 years is from the ATLAS and aTTOM studies (Davies et al, Gray et al). These studies randomised almost 13,000 women to 10 years vs 5 years of tamoxifen. Overall there was an absolute benefit of 2.8% on overall survival for the 10 year arm. There was a small but significant increase in endometrial cancer 3.1% in the 10 year arm vs 1.6% (HR 1.74), with associated mortality of 0.4% in the 10 year arm vs 0.2%. There was also an increased risk of pulmonary embolus in the 10 year arm 0.64% vs 0.32% cases (HR 1.87) but a reduction in the risk of ischaemic heart disease for the 10 year arm of 2% vs 2.5% cases (HR 0.75) and no significant difference in the risk of stroke, 2% vs 1.9%.

The evidence underlying the recommendation for considering extended adjuvant treatment with an AI after initial treatment with tamoxifen comes from the MA 17 trial (Goss et al). This trial randomised almost 5,000 postmenopausal women who had completed 5 years of tamoxifen to either letrozole or placebo. Letrozole was associated with an improvement in DFS compared with placebo (hazard ratio [HR] 0.52, 95% CI 0.45-0.61) and an improvement in OS for node positive patients (HR 0.61, 95% CI 0.52-0.71).

There is no randomised data comparing continuing on tamoxifen versus switching to an AI after 5 years of tamoxifen. However, cross trial comparisons suggest that switching to an AI may be better. This would also be consistent with the data showing the additional benefit of including an AI in the adjuvant treatment for post-menopausal women.

### 2.1.2 Switching from Tamoxifen to AI in Women Who Were Initially Pre-menopausal

As noted above it is not possible to reliably assess menopausal status in women who are on tamoxifen; women can be amenorrhoeic but still have biochemical recovery of ovarian function. Hence care must be taken when switching from tamoxifen to an AI for women under 60. The British Menopause Society consensus guidance on the definition of menopause in this setting is:

1. If adjuvant systemic therapy in premenopausal women consists of tamoxifen alone, the diagnosis of menopause can be made if there has been amenorrhoea for at least twelve months combined with elevated FSH levels (i.e. FSH >30 IU/l) on two blood samples taken four to six weeks apart. As serum FSH assays can be unreliable in the presence of tamoxifen, the latter should be stopped six to eight weeks in advance of performing this investigation.

2. Following chemotherapy exposure, the diagnosis of premature menopause may be based on a combination of the presence of menopausal symptoms, absence of menstruation and elevated FSH levels on two blood samples taken 4-6 weeks apart. In chemotherapy-treated women, amenorrhoea for two years is a reasonable time frame for suspecting the possibility of an early onset of menopause. If tamoxifen is being used, it should be stopped for 6 to 8 weeks prior to checking serial FSH serum assays.

### 2.1.3 After 5 years of AI

There is currently no NICE guidance on extended adjuvant endocrine treatment and this area remains controversial. There have been a number of trials which have examined this issue as follows: MA17R (Goss et al), NSABP B42 (Mamounas et al), DATA (Tjan-Heijnen et al) IDEAL (Blok et al), ABCSG 16 (Gnant et al), AERAS (Ohtani et al) and GIM4 (Del Masto et al). The data from these trials is difficult to interpret since the trial designs vary, the results are inconsistent and in some the data are immature. A recent review of the data (Benson et al) provides a detailed analysis.

Overall the trials demonstrate a clear benefit in reducing the risk of a second cancer, as an example in the NSABP42 trial the incidence of contralateral breast cancer was 1.5% in the extended adjuvant arm versus 3% in the placebo arm. In the MA17R trial there was also an improvement in disease free survival for the extended adjuvant group 95% (95% confidence interval intervals 93% to 96%) compared to placebo 91% (95% confidence intervals 89% to 93%) and there were similar findings in the NSABP-B42 and GIM4 trials. However, these findings have not been replicated in the other trials, which is likely to be at least partly due to the use of different definitions. To date none of the trials shows an improvement in overall survival. Moreover, all of the trials show significantly greater toxicity associated with extended adjuvant AI, in particular with higher rates of osteoporosis, bone fractures and bone pain.

Decisions about extended adjuvant treatment therefore need to be made after careful discussion with individual patients. Since the likelihood of recurrence out to 20 years is known to correlate with the size and nodal status of the primary it may be assumed that any benefits of extended adjuvant AI in reducing the risk of recurrence are likely to be greater in those who have larger, node positive cancers, rather than those with smaller, node negative cancers. Hence, a reasonable approach would be to offer extended adjuvant treatment to those women with larger T2 cancers and beyond and/or who are node positive, or who fall into the high risk group using the CTS5 tool (discussed above). This decision making must take into account how well the patient has tolerated the treatment to date, bone health, age (in relation to life expectancy) and whether there is a contralateral breast (in relation to potential benefits of reduction of contralateral breast cancer) as well as a frank discussion of the additional toxicity of extended adjuvant treatment, in particular the long-term impact on bone density. A recent DEXA scan is helpful in informing this discussion.

### 2.1.4 Duration of extended adjuvant AI
Most of the trials which have examined this question have considered an additional 5 years of extended adjuvant AI. Preliminary presentation of the ABCSG 16 trial suggest that 2 years had equivalent results for disease-free survival but with fewer bone fractures (Gnant et al). However, it should be noted that these data are relatively immature. It is therefore suggested that where extended adjuvant endocrine treatment has been started that this should be reviewed after an initial further two years. This would allow a further discussion of the risks and benefits of continuing treatment, taking into account any updates in the available data as well as the patient's experience with toxicity, including consideration of an updated DEXA scan.

## 3. Endocrine Therapy as Initial Treatment of Early Breast Cancer

Endocrine therapy may be chosen as initial treatment of early ER positive breast cancer in varying circumstances as follows:

i) Neoadjuvant endocrine therapy (NET) – where the intention is to reduce the size of the tumour prior to surgery, often to enable BCS when this is desired but is not initially feasible, and where there is no definite indication for chemotherapy.

ii) Primary Endocrine Therapy – where there is no intention to operate. This is usually because the patient is unfit for surgery, and there is no expectation that s/he will become so, or because s/he declines surgery.

iii) Preoperative "bridging" endocrine therapy – where surgery would be preferred as the initial treatment but is currently not feasible, because either:
   a. the patient has co-morbidities which preclude immediate surgery but there is a realistic expectation that s/he will become fit for surgery or
   b. there are practical challenges that preclude immediate surgery e.g. lack of theatre time due to competing pressures on health systems e.g. Covid pandemic

iv) Preoperative "window" endocrine therapy – where endocrine treatment is given for a short period prior to surgery with the aim to detect biological effects of the treatment and/or to predict or determine the long-term outcome. At present this remains experimental but there are encouraging results for this approach, for example the POETIC trial (Robertson et al).

### 3.1 Neoadjuvant Endocrine Therapy (NET)
NICE guidance [2018] on the use of neo-adjuvant endocrine therapy is as follows:

• Consider neoadjuvant endocrine therapy for postmenopausal women with ER positive invasive breast cancer as an option to reduce tumour size if there is no definite indication for chemotherapy.

• Advise premenopausal women that neoadjuvant chemotherapy may be more likely to produce a clinical response than neoadjuvant endocrine therapy, but that some tumours do respond to neoadjuvant endocrine therapy.

• Discuss with women the benefits and risks of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy. Topics to discuss include those in the following table.

**Benefits and risks of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy**

| | Neoadjuvant endocrine therapy | Neoadjuvant chemotherapy |
|---|---|---|
| **Definition** | Tamoxifen or an aromatase inhibitor started before surgery.<br><br>Only an option for women with ER positive breast cancer. | Chemotherapy given before surgery.<br><br>Only an option for people who would be recommended adjuvant (after surgery) chemotherapy. |
| **Administration** | Tablet taken once a day at home. | Intravenous administration in hospital, as an outpatient. |
| **Effectiveness** | For postmenopausal women: may be as effective as neoadjuvant chemotherapy in terms of breast conservation rates and shrinking the tumour.<br><br>For premenopausal women: less effective than neoadjuvant chemotherapy at shrinking the tumour (but some tumours may respond so may be effective in some women). | For postmenopausal women: effective at improving breast conservation rates and shrinking the tumour.<br><br>For premenopausal women: more effective than endocrine therapy at shrinking the tumour. |
| **Potential disadvantages** | If neoadjuvant endocrine therapy is not effective, then women may proceed to surgery earlier or may still need to have chemotherapy, either before or after surgery. | |
| **Side effects** | All endocrine therapies: menopausal symptoms such as hot flushes.<br><br>For tamoxifen: increased risk of thrombosis and endometrial cancer.<br><br>For aromatase inhibitors: joint and muscle pain, urogenital symptoms, bone density loss (may also occur with tamoxifen in premenopausal women).<br><br>Side effects may persist long term.<br><br>May allow women to avoid the additional side effects of chemotherapy (although women may still need adjuvant chemotherapy after surgery). | Side effects may include nausea and vomiting, risk of infections that may be life threatening, fatigue, neuropathy, cardiac toxicity, diarrhoea, constipation, sore mouth, skin and nail changes, risk of blood clots, risk of second malignancies, fluid retention, allergic reactions and hair loss.<br><br>Side effects are usually reversible. |
| **Fertility and family planning** | Women should not become pregnant while taking tamoxifen, or within 2 months of stopping, because it may have adverse effects on the baby. | Often causes temporary infertility.<br><br>May cause permanent infertility. |
| **Length of course** | May take longer than chemotherapy to shrink the tumour enough for breast conserving surgery. | The duration of neoadjuvant chemotherapy is shorter than neoadjuvant endocrine therapy. |

Overall there are far fewer data on the use of neo-adjuvant endocrine therapy compared to neo-adjuvant chemotherapy and there is an urgent need for further research in this area.

The use of NET in post-menopausal patients with ER positive HER 2 negative cancers is particularly appealing because it is known that the response rates to chemotherapy in this group are much lower as shown in a meta-analysis of trials of neoadjuvant chemotherapy (Cortazar et al): in this group of patients only 16% achieved a pathological complete response.

In post-menopausal women there are data from a meta-analysis (Spring et al) to suggest that response rates to NET are similar to those for neoadjuvant chemotherapy and with the advantage of much less toxicity. However, there are no survival data available for NET. It should also be noted that very few trials have directly compared NET with neoadjuvant chemotherapy although response rates in those which have (Semiglazov et al and Alba et al) are similar for NET and neo-adjuvant chemotherapy in post-menopausal women. It is also known in post-menopausal women that tumours which are strongly ER positive respond better to NET: this was shown in a study of 324 patients in which there was a good correlation between Allred score and clinical response rate for both letrozole and tamoxifen (Ellis et al).

There is also much research interest in identifying new biological markers to predict responsiveness to NET. For example, the 21 gene Oncotype DX Recurrence score has been evaluated in several studies, including a

trial in which 87 post-menopausal women received NET which demonstrated a higher response for those with low scores compared to those with intermediate or high risk scores, 64% versus 31% (Akashi-Tanaka et al). However, it should be noted that these are comparatively early data and the Oncotype DX Recurrence score should not currently be used to guide choice of neo-adjuvant therapy outside of a clinical trial.

Hence, it is reasonable to offer NET to post-menopausal women with strongly positive ER positive, HER 2 negative cancers where breast-conserving surgery is desired but is not feasible, and for whom there is no definite indication for chemotherapy. Counselling for these women should include discussion that mastectomy may still need to be considered if the response to NET is poor. Note that for patients with ER positive HER 2 positive cancers NET is not recommended for fit patients, given the much higher rates of response for chemotherapy and HER 2 directed therapy. It should also be noted that whilst evidence from the PRIME II trial (Kunkler et al) demonstrates that adjuvant radiotherapy can be omitted for patients >65 years with node negative cancers which are <3cm, this trial excluded patients who had received NET.

For pre-menopausal women there are even fewer data on the use of neo-adjuvant endocrine therapy, only two phase 2 trials (Torrisi et al, Alba et al) have examined this issue, both finding better response rates for neoadjuvant chemotherapy. Hence, until more information about which pre-menopausal women will respond well to NET, it is generally recommended that this should be avoided for fit patients, outside of a clinical trial, although it is acknowledged, as stated in the NICE guidance, that some tumours in pre-menopausal women would respond well. In circumstances where the cancer is inoperable and a patient is not fit for, or declines, neo-adjuvant chemotherapy, combination ovarian function suppression with an aromatase inhibitor is preferable to tamoxifen.

As in the adjuvant setting there are a number of on-going studies (in both pre- and postmenopausal women) examining combinations of NET with newer targeted drugs and in combination with chemotherapy. However, whilst some are promising, these are still at a comparatively early stage and are not ready for routine use.

### *3.1.1  Duration of Neoadjuvant Endocrine Therapy*
The optimal duration of NET is uncertain and will vary for individual patients. Response to NET may not be evident for at least 3 months and maximal response may be 6 months or more, as demonstrated in a study in which extending letrozole beyond 3 months increased the proportion of patients suitable for BCS from 60 to 72% (Dixon et al). It is suggested that if the tumour is stable or responding at 6 months but BCS is not feasible it is reasonable with extreme caution, to continue this treatment, if the patient remains keen to avoid mastectomy. This must be kept under close review to avoid the risk of disease progression, rendering the cancer inoperable, and having a detrimental effect on OS.

## 3.2  Primary Endocrine Therapy
For patients where there is no intention to operate, either because they will never be fit for this or who decline surgery, primary treatment with an AI (with ovarian function suppression in pre-menopausal women) is appropriate and is often durable: in the study by Dixon et al median time to treatment failure had not been reached at 3 years. Where there is progression it would be reasonable to consider switching endocrine treatment to either tamoxifen or fulvestrant.

## 4. Management of Toxicity associated with Endocrine Therapy

As discussed above endocrine treatment for breast cancer is associated with a number of toxicities. The 2018 NICE Guidance on the prevention and management of bone loss associated with endocrine therapy is as follows:

- Offer a baseline dual energy X ray absorptiometry (DEXA) scan to assess bone mineral density (BMD) in women with invasive breast cancer who are not receiving bisphosphonates as adjuvant therapy and who:
    – are starting adjuvant aromatase inhibitor treatment or
    – have treatment induced menopause or
    – are starting ovarian ablation/suppression therapy.

- Do not offer a DEXA scan to women with invasive breast cancer who are receiving tamoxifen alone, regardless of their pretreatment menopausal status.

- Offer bisphosphonates to women identified by algorithms 1 and 2 in: Guidance for the management of breast cancer treatment induced bone loss: a consensus position statement from a UK expert group.

There is separate ABS guidance on other toxicities of endocrine treatment in: The management of oestrogen deficiency symptoms and arthralgia in women treated for breast cancer.

## 5. Endocrine Therapy for Ductal Carcinoma in Situ

NICE guidance is as follows:

- Offer endocrine therapy after breast conserving surgery for women with ER positive DCIS if radiotherapy is recommended but not received.

- Consider endocrine therapy after breast conserving surgery for women with ER positive DCIS if radiotherapy is not recommended.

- Discuss the benefits and risks of endocrine therapy after breast conserving surgery for women with ER positive DCIS. Topics to discuss include those in table 3.

**Table 3: Effects of endocrine therapy after breast-conserving surgery for women with ER-positive DCIS**

| | Endocrine therapy after breast-conserving surgery for women with ER-positive DCIS |
|---|---|
| **Definition** | Tamoxifen or an aromatase inhibitor for 5 years. Taken as a once-daily tablet. |
| **Effect on survival and disease recurrence**<br><br>NOTE: The benefit for an individual person will depend on the risk of their cancer returning. For people with low risk of recurrence, the benefits may not outweigh the risks or side effects.<br><br>Risk can be estimated using a range of standardised tools and clinical expertise. | No effect on how many women are alive 5 and 10 years after diagnosis.<br><br>Lower rate of recurrence of DCIS and lower rate of invasive breast cancer, compared with women who did not receive endocrine therapy or radiotherapy after surgery. |
| **Side effects** | All endocrine therapies: menopausal symptoms such as hot flushes.<br><br>For tamoxifen: increased risk of thrombosis, endometrial cancer and possibly bone density loss in premenopausal women.<br><br>For aromatase inhibitors: joint and muscle pain, urogenital symptoms and bone density loss. |
| **Fertility and family planning** | Effects on fertility and family planning as women should not become pregnant while taking tamoxifen, or within 2 months of stopping, because it may have adverse effects on the baby. |

There is no survival benefit with the use of endocrine therapy in DCIS, however there is a lower rate of recurrence of DCIS and invasive cancer, compared to those patients who did not receive either radiotherapy or endocrine therapy after surgery. One must weigh the benefit versus the side effects during the decision making process. The majority of patients who received RT had no additional benefit from ET. The NICE guidelines mention the use of either tamoxifen or an AI in DCIS. There is no clear efficacy difference between the two drugs in DCIS (Forbes et al)

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Date: December 2020

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