Extended Adjuvant Endocrine Therapy
why bother?
After all, 5 years Tamoxifen works..

• For women with ER+ primary breast cancer, previous studies have shown that treatment with tamoxifen for 5 years has a carry-over effect:

  – Significantly **decreases breast cancer recurrence** throughout the first **10-15** years
  – Substantially **reduces breast cancer mortality** throughout the first **10-15** years after diagnosis
But...
relapses still happen….

Breast Cancer Recurrences

Breast Cancer Deaths

![Graph showing Breast Cancer Recurrences and Deaths with Tamoxifen and Control groups.](image)

EBCTG Lancet, 1998
And….

• Before the latest studies, little was known about how 10 years of Tamoxifen compares to the current standard treatment of 5 years.
LOOKING BACK...
2 versus 5 years of tamoxifen
• Women aged 50 to 70 years, randomised to stop tamoxifen at 2 years (n=958) or continue for a further 3 years (n=943)

• After 52 months follow-up, in ER+ patients, 5 years resulted in a statistically significant prolonged DFS, although no difference in OS could be detected

• No differences in rates of endometrial cancers, cardiac or cerebrovascular events, or fractures were detected

• There was a doubling in the risk of thromboembolic events with 5 years use

• Conclusion: 5 years of tamoxifen decreases recurrence compared to 2 years in patients with ER-positive breast cancer  
  [Sacco, M. et al, 2003 ASCO paper ]

• But...

• Data was collected from 1989 to 1996 when ER testing was not as routine or reliable

• ER+ was not a criteria for entry into the study (nor was grade or menopausal status)
• Women aged 50 to 81 (recruited between 1987 and 1997 from 71 hospitals in Europe and Asia), randomised after 2 years tamoxifen to stop (n=1724) or continue for another 3 years (n=1725)
• After a median follow-up of 10 years:
  – 5 years Tam = a 17% lower risk of recurrence, 30% lower risk of contralateral breast cancer
• Benefits seen in pre and post menopausal women
• And 9% lower risk of death from breast cancer (i.e. differences OS and breast cancer deaths were also improved)
• And 35% lower risk of cardiovascular events in women aged 50-59 (unplanned analysis)

Hackshaw et al, Journal of Clinical Oncology, 2011, 29 (13), 1657-63
National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14

- initiated 1981
- second randomization on patients who were disease free after 5yrs Tam (n= 1166) to stop or continue for a further 5 years
- early un-blinding because of concerns over endometrial cancer (2-3 fold increase) and trend indicated high statistical likelihood that prolonged Tam wouldn’t be beneficial, and may lead to more recurrences
- even updated follow-up continued to show stopping at 5 years is more beneficial than 8 years for DFS (significant) and OS (trend) and halved endometrial cancer rates
- 2 other small trials also showed no benefits with extended tam [although subset analysis did hint at benefits for ER+ patients!]
- FDA amendment
- hence routine practice of 5 years duration
NSABP B-14: After 5 yrs Tamoxifen, 5 more years v Placebo
1152 ER+ve N- patients randomised

- Tamoxifen demonstrated higher rates of endometrial cancer, ischemic heart disease, and cerebrovascular disease.

Duration of Tamoxifen: Scottish Adjuvant Trial 15 Years

- Started 1978 Median FU 15 years
- 1323 pts after mastectomy
- Tam 20mg x 5yrs
- Tam pts disease-free at 5 yrs randomised to continue (173) or stop (169)
- Strong trend AGAINST >5 years for DFS and OS

*Stewart et al JNCI 93:456  2001*
aTTOM (Adjuvant Tamoxifen to Offer More)

- UK trial 1991 - 2005
- 6953 pts who had taken ≥4 years tamoxifen
- Known ER+ve 39% (node neg 53%)
- Randomised 5 more years or stop
aTTOM (Adjuvant Tamoxifen to Offer More)

- Absolute reduction in breast cancer recurrence of 4% (580 with 10 years versus 672 with 5 years) (significant)
- Absolute reduction in breast cancer mortality of 2% (849 with 10 years versus 910 with 5 years) (not quite significant)

ASCO 2013
The trial team concluded that the benefits of taking tamoxifen for longer than 5 years *outweigh the risks.*
ATLAS (Adjuvant Tamoxifen: Longer Against Shorter)

- International (36 countries), 1996 - 2005
- 12,894 women early breast cancer completed 5 years tamoxifen
- Randomised to 5 more years (10 in all) or stop

Davies et al Lancet on-line Dec 5th 2012
ATLAS Trial Design

Eligibility (n = 12,894)*
- Early breast cancer (BC)
- Completed 5 y of TAM

R

Continue TAM therapy to 10 years (n = 6,454)
Stop TAM therapy at 5 years (n = 6,440)

* Of the study’s entire population, ER-positive BC: 6,846 (53%); ER-negative BC: 1,248 (10%); unknown ER status: 4,800 (37%)
ATLAS: 10 vs. 5 Years of Tamoxifen

N=6,846

**Recurrence**

- Continue tamoxifen to 10 years
- Stop tamoxifen at 5 years

5–9 years: RR 0.90 (0.79–1.02)
≥10 years: RR 0.75 (0.62–0.90)
All years: log-rank p=0.002

**Breast Cancer Mortality**

5–9 years: RR 0.97 (0.79–1.18)
≥10 years: RR 0.71 (0.58–0.88)
All years: log-rank p=0.01

Davies et al. Lancet 2012
### Recurrence Rate for Patients with ER-Positive BC

<table>
<thead>
<tr>
<th>No. of years since diagnosis</th>
<th>Continue TAM to 10 y (n = 3,428)</th>
<th>Stop TAM at 5 y (n = 3,418)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y (study entry)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10 y (treatment end)</td>
<td>13.1%</td>
<td>14.5%</td>
</tr>
<tr>
<td>15 y (10 y since study entry)</td>
<td>21.4%</td>
<td>25.1%</td>
</tr>
</tbody>
</table>

- BC recurrences (continuing TAM to 10 y vs stopping at 5 y): 617 vs 711

Benefits independent of age (<55 v >55) or nodes
Absolute risk reduction of nearly 4% (3.7%) at 15 years
No benefit seen until year 10
**Breast cancer mortality for women with ER+ breast cancer**

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>5 y (study entry)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>10 y (treatment end)</td>
<td>5.8%</td>
<td>6.0%</td>
</tr>
<tr>
<td>15 y (10 y since study entry)</td>
<td>12.2%</td>
<td>15.0%</td>
</tr>
</tbody>
</table>

*BC mortality (continuing TAM to 10 y vs stopping at 5 y): 331 vs 397*

**Benefits independent of age (<55 v >55) or nodes**

Absolute risk reduction of 2.8%

Also reduced overall mortality (639 vs 722 deaths)
### Select Adverse Events (Any ER Status)

<table>
<thead>
<tr>
<th>Event</th>
<th>Continue TAM to 10 y (no.)</th>
<th>Stop TAM at 5 y (no.)</th>
<th>Event RR (2p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second cancer incidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral BC</td>
<td>419</td>
<td>467</td>
<td>0.88 (0.05)</td>
</tr>
<tr>
<td>Endometrial cancer*</td>
<td>116</td>
<td>63</td>
<td>1.74 (0.0002)</td>
</tr>
<tr>
<td>Nonneoplastic disease†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>130</td>
<td>119</td>
<td>1.06 (0.63)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>41</td>
<td>21</td>
<td>1.87 (0.01)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>127</td>
<td>63</td>
<td>0.76 (0.02)</td>
</tr>
</tbody>
</table>

Higher rate of hospitalisation due to PE
Risk of developing endometrial cancer was 3.1% in the extended group versus 1.6%.
The mortality risk of these new endometrial cancers was 0.4% in the extended group versus 0.2% (absolute increase of 0.2%).
An extra 2 per 1,000 women on extended tam will die of endometrial cancer.
• ‘herald a change in practice’

• ‘game changer’

• ‘the results are spectacular’

• ‘standard of care should now be 10 years adjuvant tamoxifen’

• ‘begins a new era of extended adjuvant endocrine therapy’

• ‘proof beyond reasonable doubt’
Taking a common breast cancer drug for ten years could save 300 extra lives, study suggests

Women should take tamoxifen for breast cancer for ten years rather than five, a study has suggested, after showing that it continues to cut mortality for years after stopping it.
5 December 2012 Last updated at 13:32

Tamoxifen use 'should double' to stop breast cancer returning

A decade's treatment with tamoxifen could stop the return of breast cancer for many more women than the current recommendation for five years, say researchers.

University of Oxford scientists say the doubling cuts both the risk of the cancer returning and deaths from the disease.

Writing in The Lancet, they say this outweighs the risk of side effects.

Cancer Research UK said the study added important clarity.

Tamoxifen tablets have long been part of the daily routine for women in the years after remission from 'ER-positive' breast cancer.

ER-positive tumour growth is accelerated by the female sex hormone oestrogen, and tamoxifen blocks the hormone.

An international group of scientists, led by Dr Christina Davies from the University of Oxford, looked at the effect of sustained tamoxifen on the likelihood that cancer would return.

They looked at 6,847 women with the ER-positive version of the disease.
Breast cancer deaths halved if patients given 'wonder drug' Tamoxifen for 10 years, not five

- Tamoxifen is an anti-oestrogen drug that was developed over 30 years ago
- Most of the extra protection occurred after the end of the 10 year treatment period

By DAILY MAIL REPORTER
PUBLISHED: 18:01, 5 December 2012 | UPDATED: 08:44, 6 December 2012

Breast cancer deaths can be halved after 10 years of treatment with the drug tamoxifen, research has shown.

The widely used drug prevents oestrogen fuelling breast cancer in hormone-sensitive patients.

Usual current practice is to administer daily tamoxifen for five years. This is known to reduce death rates by around a third during the first 15 years after diagnosis.

The new trial, called Atlas, looked
WHAT ELSE IS THERE?
Extended Adjuvant Therapy with AIs

MA 17 (5000 pts)
- Tamoxifen 5 years
- Letrozole 5 years
- Placebo

NSABP-B33 (1598 pts)
- Tamoxifen 5 years
- Exemestane 5 years
- Placebo

ABCSG-6a (856 pts)
- Tamoxifen + AG 3 years
- Anastrozole 5 years
- Placebo

Goss et al. JNCI 2005
Mamounas et al. JCO 2008 26; 1965-1971
Jakesz et al. JNCI 2007;99(24):1845-1853
MA.17: Trial Design

Randomization
(all patients disease-free)

Tamoxifen

Placebo

Femara 2.5 mg

Approx. 5 years adjuvant

0-3 months

5 years extended adjuvant
Extended AI therapy beyond 5 years

- Significant overall survival benefits in lymph node positive patients in MA-17 study
- All trials show significantly reduced risk of recurrence (local, contralateral and distant)

So there are benefits to be gained from prolonging therapy after 5 years. Tamoxifen with an AI, but the optimum duration remains undetermined and there are no trials comparing different durations and different AIs.
Extended Letrozole after a gap of no treatment

• Post unblinding after 30 months:
• Femara given as delayed therapy in women randomised to placebo (n=1655) (61% chose to switch)
• some had a delay of several years (4-6 years Tamoxifen plus 1-5 years placebo)

• After 54 months follow-up:
• significant reductions in risk of breast cancer recurrence (69% reduction), risk of distant disease (72%) and risk of death (47%) compared to those post unblinding who elected no further treatment post 5 years of Tamoxifen for LN+ patients (only DFS for LN-)
• demonstrates benefits of Letrozole even after a prolonged delay

• [More arthralgia, no difference in fracture risk]
MA17: significance of menopausal status at primary diagnosis

- Premenopausal (n=889)
  - under 50 years and periods at diagnosis but became post menopausal with treatment (bilateral oopherectomy or chemotherapy)

- Post menopausal (n=4277)
  - no periods for at least a year prior to diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal (n=425)</th>
<th>Postmenopausal (n=1,957)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>8.2%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

- women premenopausal at diagnosis experienced significantly greater benefit with letrozole in terms of DFS than those postmenopausal at diagnosis
- data indicate that women premenopausal at the time of diagnosis but become postmenopausal anytime before, or during, adjuvant tamoxifen should be considered for extended adjuvant therapy with letrozole
- more arthralgia with Letrozole (24 v 16%)
- less vaginal bleeding with Letrozole (10 v 16%)

Goss PE et al. SABCS 2009;Abstract 12
Remember letrozole remains the only AI approved in this setting in both the USA and Europe
**AIs**

- Better for hot flushes and night sweats
- Better for vaginal discharge and bleeding (less than half as much)
- Better for DVT risk
- Worse for fracture rate
- Worse for joint pain

**Tamoxifen**

- Worse for hot flushes and night sweats
- Worse for vaginal discharge and bleeding
- Worse for DVT risk
- (Endometrial cancer risk)
- Better for bone protection
Skipping breast cancer drugs costs lives, warns charity

Hundreds of women may be dying from breast cancer in the UK each year as they have stopped taking their medication, a charity is warning.

A five-year course of tamoxifen is lifesaving, but the drug has considerable side effects, including nausea, headaches and exhaustion.

Breast Cancer Campaign estimated that 500 died as the side effects meant they could not finish their prescription.

It wants the NHS to do more to help women stick to their medication.

Tamoxifen is prescribed to women with oestrogen-positive breast cancer, often after surgery or other treatment, as it can reduce the risk of the cancer coming back.

It is a widely used drug and there have even been calls to double the length of treatment to 10 years. The NHS in England, Wales and Scotland has also announced that women with a high family risk of breast cancer should be offered the drug.

Cost to NHS
So what might clinicians do?

• In moderate/high risk pre or post menopausal women already taking 5 years tamoxifen – consider continuing tam (or an AI if not contraindicated) for a further 5 years (10 years in total)

• In premenopausal women who become post menopausal during treatment and who have had 5 years tamoxifen – consider a further 5 years of letrozole (checking serum hormone levels and baseline bone density)
So what might clinicians do?

- In moderate/high risk older women on an AI up front for 5 years - at present no direct evidence for extended AI (because trials were stopped or not matured), but strong indirect evidence
  - continue an AI or switch to tamoxifen for a total of 10 years
  - consider side effects and co-morbidities
So what might clinicians do?

• What about women who have already stopped treatment?

• ? predict risk of long term relapse

• [conflict with other treatment trends]
EXCELLENT

MY WORK HERE IS DONE.