Adjuvant Extended Hormonal treatment in HR-positive Breast Cancer, Who is candidate?

An ASCO 2013 CPG Focused Update – Based Presentation

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ASCO 2013 CPG Focused Update

- This update is a direct response to the emerging data from randomized clinical trials (RCTs) that addressed duration of endocrine therapy (ET).
- This guideline update reviews only evidence on durations of tamoxifen (TAM) of greater than 5 years. Evidence regarding duration of adjuvant ET up to only 5 years, ET sequencing, and evidence on AIs is reviewed in the 2010 CPG update.
- The information present in this update is not intended to substitute for the independent professional judgement of the treating physician.

Methods

- The ASCO update committee conducted a systematic review of RCTs from Jan 2009 to June 2013 and analyzed 3 historical trials.

- Only ***Five RCTs*** met the eligibility criteria of this updated review, each of them compared ***5*** years of TAM versus longer durations: either **indefinitely** or for a total of ***10*** years. Out of these 5 RCTs, there was 3 relatively small and old, and 2 recently reported ones.

- The **primary endpoint** for all of these trials was therapeutic efficacy; defined as overall survival (OS), DFS, recurrence-free survival (RFS), time to recurrence (TTR), event rate ratio (ERR). Adverse events were a **secondary endpoint** of interest.

Methods

These five RCTs are:

Trial	Year
ECOG, Tormey	1996
NSABP B-14, Fisher	2001
Scottish Cancer Trials, Breast Group, Stewart	2001
ATLAS, Davies	2012
aTTom, Gray	2013

NB:

ATLAS: Adjuvant Tamoxifen Longer Against Shorter.

aTTom: Adjuvant Tamoxifen; To Offer More.

Results

- OS and Mortality: **Mixed results**
  - ATLAS, aTTom, and the ECOG trials: suggested a survival benefit for EHT e.g. in the ATLAS trial: Cancer specific mortality (CSM) was 2.8% lower for the EHT population ($p = 0.01$).
  - However, mortality was higher in the remaining 2 historical studies.

- DFS and RFS: **Mixed results**
  - ATLAS, aTTom, and ECOG trials: reported lowered risk of BC recurrence with EHT.
  - NSABP and Scottish trials: EHT was associated with greater risk of recurrence.

Results …… continued

- Contralateral Breast Cancer Risk:
  - ATLAS, aTTom, and ECOG: all showed a lower risk for contralateral breast cancer in the EHT group of patients, e.g. the ATLAS trial reported a 12% lower risk with extended TAM treatment ($p = 0.05$).
  - Again, the other two smaller trials showed no statistically significant differences between patients populations.
- Adverse Events:
  - Endometrial Cancer: was significantly more common among women who received extended HT with TAM compared to those who did not, e.g., the % cumulative risk calculated in the ATLAS and aTTom trials:

Trial	5 ys with TAM	10 ys with TAM
ATLAS	1.6%	3.1%
aTTom	1.3%	2.9%

Results …… continued

- Pulmonary embolism: higher risk with extended TAM treatment.
- Ischemic heart disease: lower risk with ext. TAM arm in the ATLAS trial while the NSABP trial reported increased the very same risk.

- Analysis by Menopausal Status
  - TAM is active regardless of the menopausal status.
  - Women who were pre-or perimenopausal derived substantial benefit from extended therapy with TAM, this was particularly shown in the ATLAS trial.

Conclusion and Guidelines

- The 2010 ASCO CPGs have recommended treatment of premenopausal women with 5 years of TAM, and of postmenopausal women with a minimum of 5 years of adjuvant therapy using either an AI or a sequence of TAM followed by AI.

- On the basis of the emerging data outlined in this Focused Update, the ASCO committee made separate recommendations for women who are pre and postmenopausal.

Conclusion and Guidelines

- If women are **pre- or perimenopausal** and have received 5 years of adjuvant TAM, they should be offered 10 years total duration of TAM.

- If women are **postmenopausal** and have received 5 years of adjuvant TAM, they should be offered the choice of continuing tamoxifen or switching to an aromatase inhibitor for 10 years total adjuvant ET.

- For **postmenopausal** women who start treatment with AI, there is no data showing that longer durations clinically effective, nor are there efficacy data for switching to TAM after 5 years of AI.

Conclusion and Guidelines

- Extensive clinical data, specifically collected from extended adjuvant hormonal treatment, indicate that smaller and/or node-negative cancers are at lower risk of recurrence at 5 years of adjuvant ET than are larger and/or node-positive tumors. For that, extended ET magnitude of benefit for patients with stage I disease is certainly lower than for those with higher stage tumors.

- Although patients with favorable prognosis tumors have more risk than benefit with extended adjuvant treatment, the clinicopathological factors defining such patients are not established.

Limitations of the Research

1. Different amounts of median follow-ups for the different eligible studies.
2. Studies were performed in different eras resulting in insufficient information to assess the quality of the three older trials.
3. Some of the populations in these studies did not have HR-positive breast cancer and/or their HR status was unknown.

ADJUVANT ENDOCRINE THERAPY

Premenopausal[1] at diagnosis → **Tamoxifen[2,3] for 5 y (category 1) ± ovarian suppression or ablation (category 2B)**

- **Postmenopausal[1]** → **Aromatase inhibitor for 5 y[4] (category 1) or Consider tamoxifen[2] for an additional 5 y to complete 10 y**
- **Premenopausal[1]** → **Consider tamoxifen[2] for an additional 5 y to complete 10 y or No further endocrine therapy**

Postmenopausal[1] at diagnosis

- **Aromatase inhibitor[4] for 5 y (category 1) or Tamoxifen[2] for 2–3 y or Aromatase inhibitor[4] for 2–3 y (category 1)** → **Aromatase inhibitor to complete 5 y[4] of endocrine therapy (category 1) or Up to 5 y of an aromatase inhibitor[4] (category 2B)**
- **Tamoxifen[2] for 4.5–6 y** → **Aromatase inhibitor for 5 y[4] (category 1) or Consider tamoxifen[2] for an additional 5 y to complete 10 y**
- **Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors** → **Tamoxifen[2] for 5 y (category 1) or Consider tamoxifen[2] for up to 10 y**

[1] See Definition of Menopause (BINV-L).

[2] Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

[3] Aromatase inhibitor for 5 y + ovarian suppression may be considered as an alternative option based on SOFT and TEXT clinical trial outcomes. Pagani O, Regan M, Walley B, et al. Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2014; 371:107-118.

[4] The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and neoadjuvant settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Expert Opinion

- **Adam M. Brufsky, MD, PhD**

  (Professor of Medicine and Co-Director of Comprehensive Breast Cancer Center at University of Pittsburgh, PA, USA.)

Based on this Focused Update, his recommendations for the duration of adjuvant HT (TAM) for ER+ BC are:

Criterion	5 y only if	10 y are appropriate
Tumor size	Small (1-2 cm) and	Larger (5-7 cm) or
LN status	Negative	Positive (8-10)

Genomic assays are available to help determining the recurrence risk in ER+ LN-ve BC patients (Early breast Cancer): Breast Cancer Index (BCI) is an example which can categorize these patients into low, intermediate, and high risk. The 5 years recurrence rate for the low-risk category is 4% as compared to 13% for the intermediate-risk group

ATLAS Trial

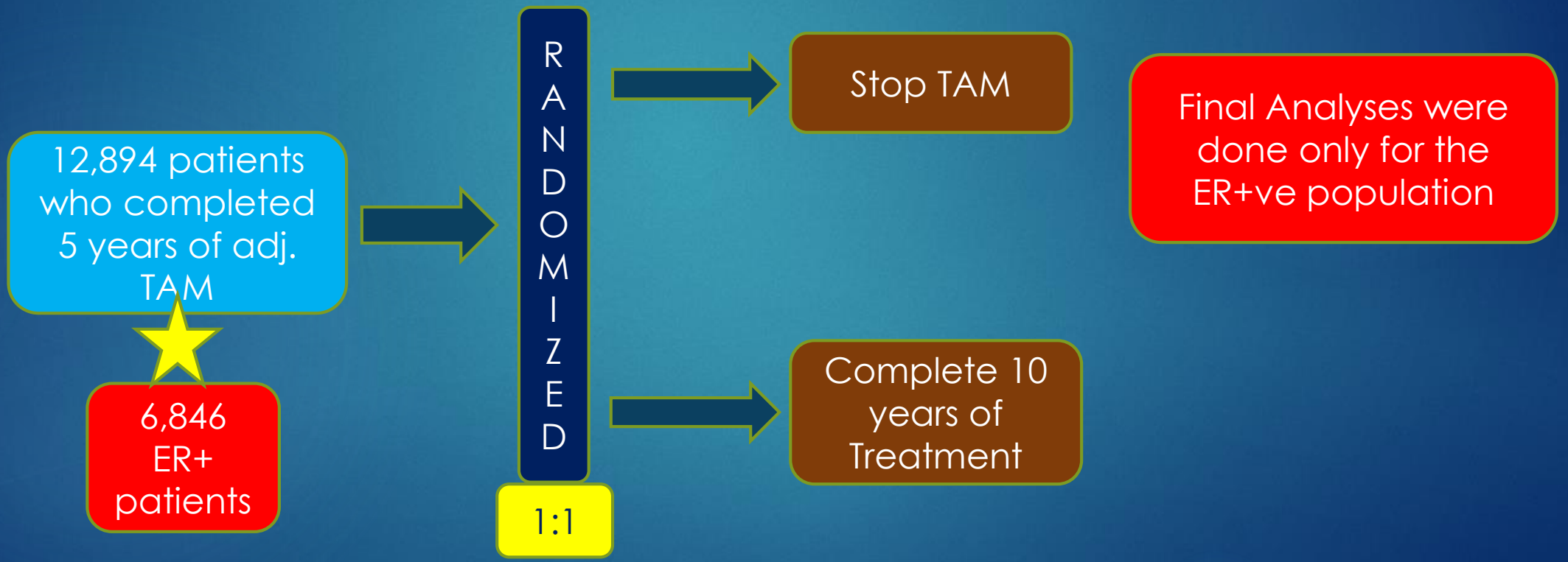
- This is a worldwide (US,UK, Australia, NZ, ..) randomized trial included 12,894 patients (with different ER Statuses), of whom, the total number of patients remained for final analysis were only 6846 (had ER-positive disease), approximately 90% of them were postmenopausal.

- Patients who received 5 years of Adjuvant TAM were randomly allocated (1:1) to stop TAM or to continue for another 5 years.

- The primary study goal is to compare breast cancer risk of recurrence and mortality between the 2 groups of patients

ATLAS Trial .....

Study Design



ATLAS Trial … Patients characteristics

Status at diagnosis (n = 6846)	10 ys of TAM (n = 3428)	5 ys of TAM (n = 3418)
Age		
< 45	640 (19%)	630 (18%)
45 – 54	1090 (32%)	1099 (32%)
55 – 69	1373 (40%)	1357 (40%)
> 70	325 (9%)	332 (10%)
Menopausal Status		
Premenopausal	326 (10%)	304 (9%)
Postmenopausal	3035 (**89%**)	3044 (**89%**)
Unknown	67 (2%)	70 (2%)
Nodal status		
LN-negative	1832 (**53%**)	1845 (**54%**)
N1-3	938 (27%)	893 (26%)
N4 or more	536 (16%)	534 (16%)
Unknown	122 (4%)	146 (4%)
Tumor diameter		
1-20 mm	1660 (**48%**)	1620 (**47%**)
21-50 mm	1309 (**38%**)	1328 (**39%**)
> 50 mm	251 (7%)	252 (6%)
Unknown	208 (6%)	218 (6%)

ATLAS Trial ..... **Results**

Parameter	10 years of TAM	5 years of TAM	p-value
BC rec.	18%	21%	0.002
BC disease-sp deaths	9.6%	11.6%	0.01
Cumulative Rec Risk years 5 -14	21.4%	25.1%	
BC mortality during years 5 - 14	12.2%	15% (Absolute mortality reduction of 2.8%)	
Cumulative risk of endometrial cancer (years 5 – 14)	3.1%	1.6%	

Parameter	10 vs. 5 years of TAM
Pulmonary embolism risk ratio	1.87%
IHD risk ratio	0.76
Endometrial cancer risk ratio	1.74%

ATLAS Trial ..... **Conclusion**

The Adjuvant Tamoxifen: Longer Against Shorter **(ATLAS)** trial, with a mean of 7 · 6 years of further follow-up after entry at year 5, shows that recurrence and breast cancer mortality during the second decade after diagnosis are reduced more effectively by 10 years of adjuvant tamoxifen than by 5 years. Although known side-effects were increased (at least in postmenopausal women) by longer treatment, the absolute reduction in breast cancer mortality was an order of magnitude greater than the absolute increase in mortality due to these side-effects. Taken together with the results from trials of 5 years of tamoxifen versus none, the results from ATLAS show that 10 years of effective endocrine therapy can approximately halve breast cancer mortality during years 10–14 after diagnosis.

Thank You

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