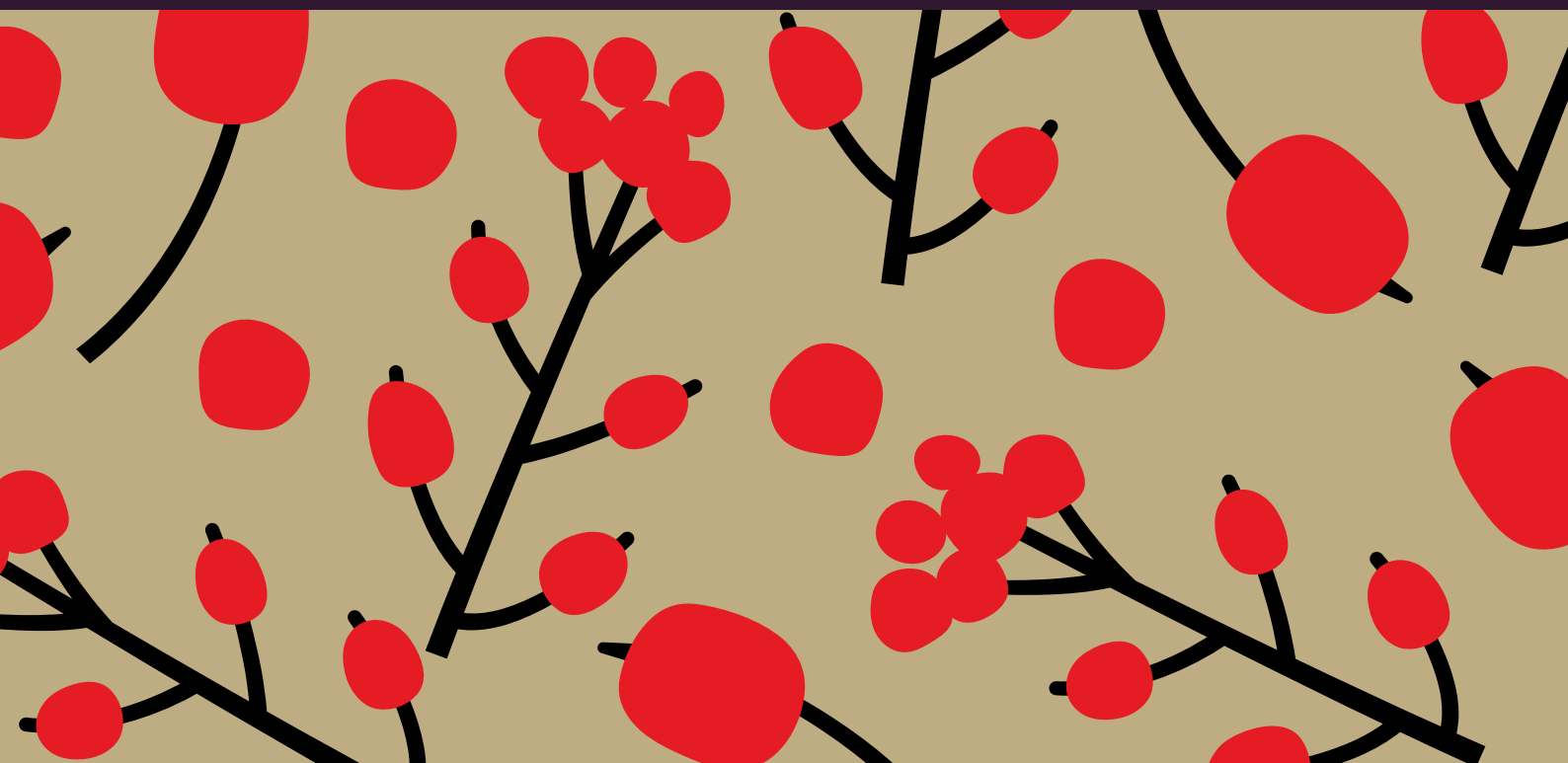
Adjuvant Endocrine therapy in HR positive Breast Cancer



Adjuvant therapies

→ Adjuvant endocrine therapy

① SERM - Tamoxifen 20mg OD

EBCTCG Analysis showed Tamoxifen for 5 years

- Reduced recurrence - by 41%
- Reduced death rate - by 34%

- Benefits independent of Age | menopausal status | adjuvant ChT.

5 yrs Vs 10 years - ATLAS trial

Adjuvant Tamoxifen : Longer Against Shorter
- 10 years showed better OS & DFS compared to 5 years. in Pre menopausal women.

Side effect - Thrombo embolism
- Endometrial cancer

(2) Aromatase inhibitors 2.5mg OD letrozole

Post menopausal ♀ - Peripheral conversion

Androgen $\xrightarrow{\text{Aromatase}}$ estrogens

Pre menopausal ♀ - Residual ovarian function produces Aromatase enzyme and overcomes effect of AI.

AI

Steroidal ← → Non steroidal

- Letrozole
- Anastrozole

Same efficacy

Side effect in both

Reduced Bone mineral density.

- exemestane.

AI can be given as

- Upfront therapy instead of Tamoxifen
- Sequential therapy: 2-3 years Tamoxifen f/b AI
- extended therapy after 5yrs of Tamoxifen.

Same DFS benefit in all modalities.

* Modality of AI → upfront vs sequential –

→ Breast International Group 1-98 } equal rates of local recurrence at 5 years.
→ Tamoxifen & Exemestane in EBC Study }

* Duration of adjuvant endocrine therapy:

* ATLAS trial – 5 vs 10 yrs Tamoxifen
* MA 17R trial – Additional 5 yrs of letrozole after 5 yrs AI + T
* NSABP B42 – 5 yrs AI + T f/b 5 yrs AI.
* ABSCG trial – 7 vs 10 yrs endocrine therapy in Low risk ER +ve EBC.

All trials showed that longer duration of endocrine therapy lowered the incidence of 2nd breast cancer in IDC and CLC Breast

↓ But

higher side effects

Tamoxifen – risk of endometrial cancer
AI – Bone fracture.
Both – Hot flashes, vaginal dryness.

Clinical point:

* Letrozole can be started simultaneously with adjuvant RT, but Tamoxifen should not be given with RT.
* Reason – Tamoxifen causes ↑ Radioresistance as cells arrest in G0-G1 phase
↑ Pulmonary fibrosis
↑ Skin reaction.

→ ovarian suppression therapy in BC:

SOFT trial, TEXT trial } Both trials showed that ovarian function suppression (OFS) reduced recurrence more than adjuvant endocrine therapy alone in HIGH RISK BC:

- premenopausal, age < 40 years
- ≥ 5 LN positive (or)
- 1–3 LN positive & high grade / Tumor ≥ 5 cm.

↓

OFS can be done by

Methods for OFS
- GNRH agonists
  - Goserelin 3.6 mg SC every 4w or 10.8 mg SC every 12w
  - Leuprolide 3.75–7.5 mg IM every 4w or 11.25–22.5 mg IM every 12w
- Radiation therapy
- Bilateral oophorectomy → permanent.

Initiation of OFS
- With start of chemotherapy (neoadjuvant or adjuvant)
- If no chemotherapy planned, then OFS should be started alone for at least 1-2 cycles or concurrently with tamoxifen until estradiol level in postmenopausal range at which time an aromatase inhibitor could considered.
  - Concurrently with RT or upon completion

Duration of OFS
- 5 years optimal according to SOFT and TEXT trial. No efficacy or safety date to support prolonged OFS. It is encouraged to complete a minimum 2 years of OFS (The 8-year DFS was 85.4% with OFS + tamoxifen versus 80.2% with tamoxifen alone.[c]
- Premenopausal patients wishing to continue adjuvant endocrine therapy after OFS stopped should use tamoxifen.

* Assessment of menopausal status before starting therapy:

Definition of menopause → Permanent cessation of menstruation for ≥ 12 months with Estradiol and FSH in post menopausal range.

(0-30 pg/mL) (25-134 IU/L)

. menopausal status cannot be assessed while on OFS:

* Tamoxifen causes amenorrhoea without ovarian suppression
* OFS with GnRH analogues does not cause permanent menopause.
* chemotherapy induced amenorrhoea is reversible, especially in those <40 yrs age.

→ Role of adjuvant CDK 4/6 inhibitors in Non metastatic Bc

PENELOPE-B trial — Palbociclib x 1 year
PALLAS trial — Palbociclib x 2 years
} NO BENEFIT.

MONARCH-E trial — Abemaciclib x 2 years → Decrease rate of Recurrence by 4-5% @ 3 years.
→ NO OS BENEFIT.

↓

FDA approved for high risk stage 2/3 ER +ve / HER 2 -ve Ki 67 > 20% Bc.

→ Role of adjuvant bisphosphonate therapy / Denosumab:

- For bone health
- For Reduction of risk of recurrence
  - LR
  - Distant recurrence
  - Bone recurrence
  - Breast cancer mortality.

* Bone mineral Density / DEXA scan interpretation:

T-score

- For post menopausal
- T score = 0 − BMD of patient.
  - = −1 → healthy bone
  - −1 to −2.5 → osteopenia
  - −2.5 → osteoporosis.

Z-score

Z-score is for premenopausal/ younger individuals.

Z score = −2.0 is osteoporosis.

→ Resistance to endocrine therapy (ET)

Definition	Primary Resistance	Secondary Resistance
For MBC	Progression within 6 months of starting ET	Progression after 6 months of starting ET.
For Non metastatic Bc	Relapse within 2 years of completing Adj ET.	Relapse after 2 years of Completing Adj ET.

↓

CDK 4|6 inhibitors

mTOR inhibitors

PIK3Ca kinase inhibitors

Chemotherapy.

↓

Acquired resistance in ER gene (ESR1)

↓

Constitutively activates receptor even in the absence of estrogen.

↓

Resistance usually only to Aromatase inhibitors

↓

Switch to SERDs

- Fulvestrant - injectable
- Elacestrant - oral

under trials.

* strategies for Prevention | delaying resistance :

- Combination therapies to target multiple growth factor pathways in cell cycle.