Penn Medicine

Early Stage Breast Cancer: Who needs adjuvant therapy?

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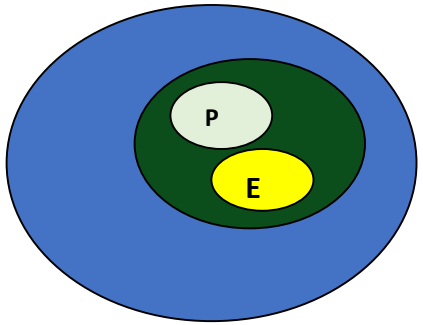
the cure is within
ABRAMSON CANCER CENTER

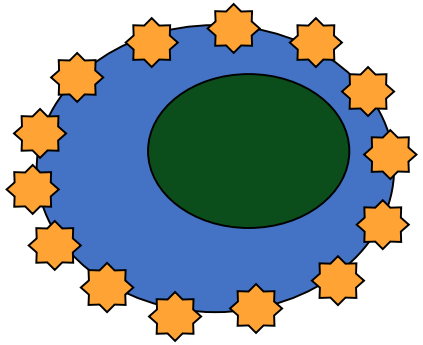
Overview

- Review of Breast Cancer Subtypes
- What is adjuvant therapy and why do we give it?
- Chemotherapy
  - Who benefits?
  - What are the options?
- Hormone therapy
  - What are the options, and how do they work?
    - Tamoxifen
    - Aromatase inhibitors
    - Ovarian suppression?
  - What is the optimal duration?
- Adjuvant Clinical trials

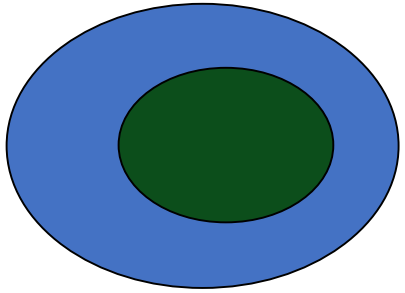
Subtypes and Targets



Hormone-receptor positive (ER+ and/or PR+)
- Anti-estrogens/“Hormone therapy”
-Chemotherapy



Her2-positive
- Anti-Her2 targeted therapy
- Chemotherapy



Receptor Negative (“Triple-negative”):
- Chemotherapy
- Looking for new “targets”

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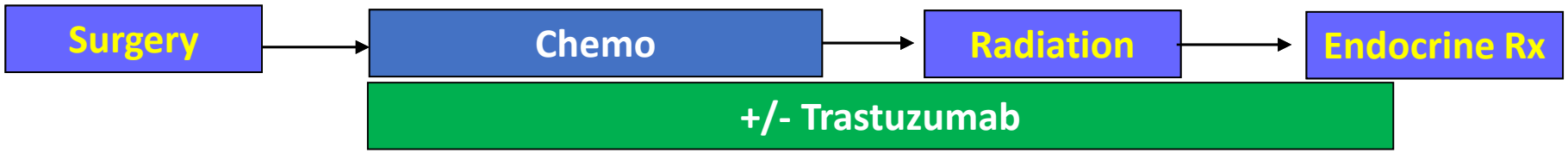
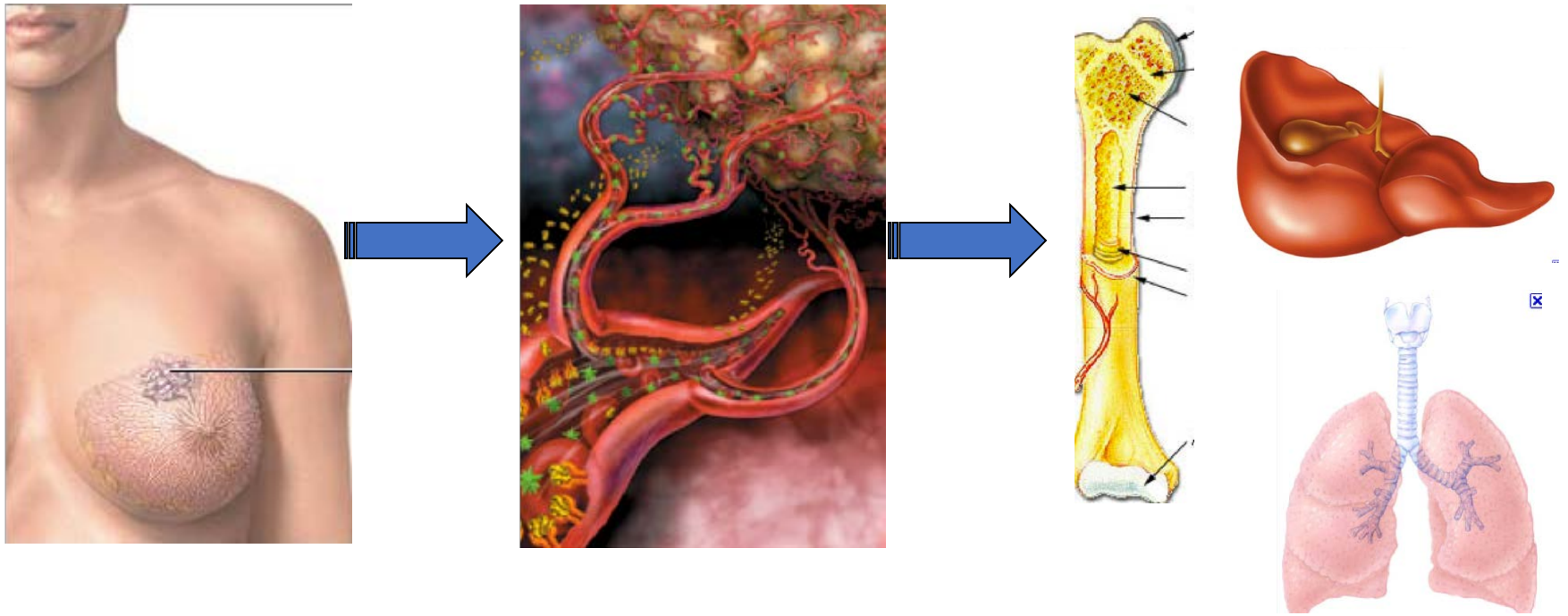
What is adjuvant therapy?

- "Adjuvant" = postoperative therapy
  - +/- Chemotherapy
  - +/- Hormonal therapy
  - +/- Trastuzumab (Herceptin)
  - Radiation

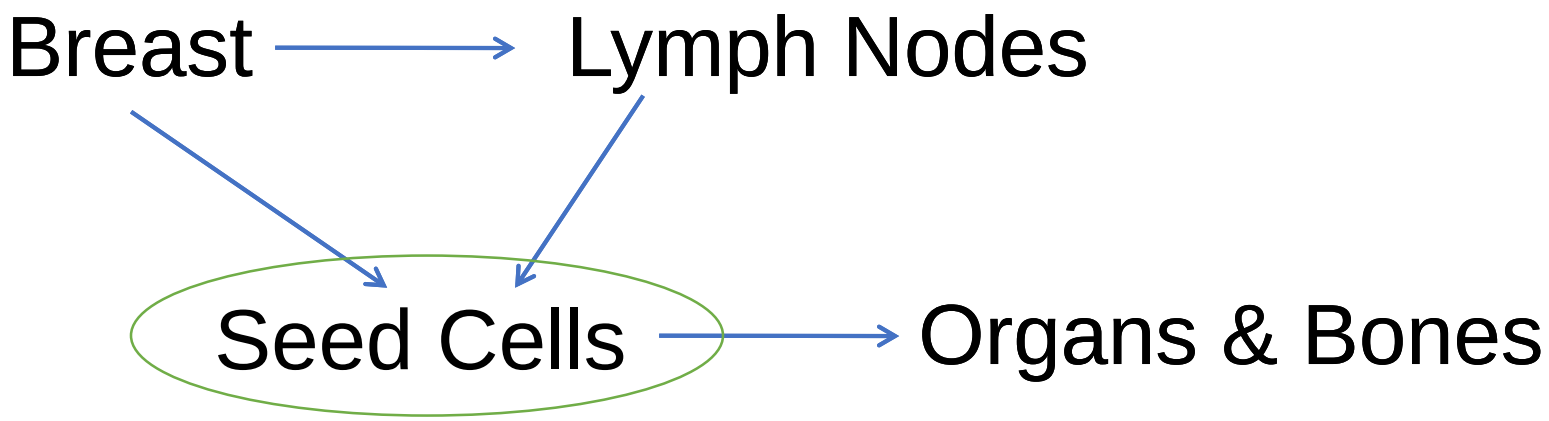


How does cancer become “metastatic”



Circulating tumor cell “seeds” can travel to new sites and form tumors

Goal of Adjuvant Therapy



- Kill seed cells
- Prevent development of Stage IV disease
- Risk of seed cells vs side effect/benefit of therapy

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Who needs chemo?

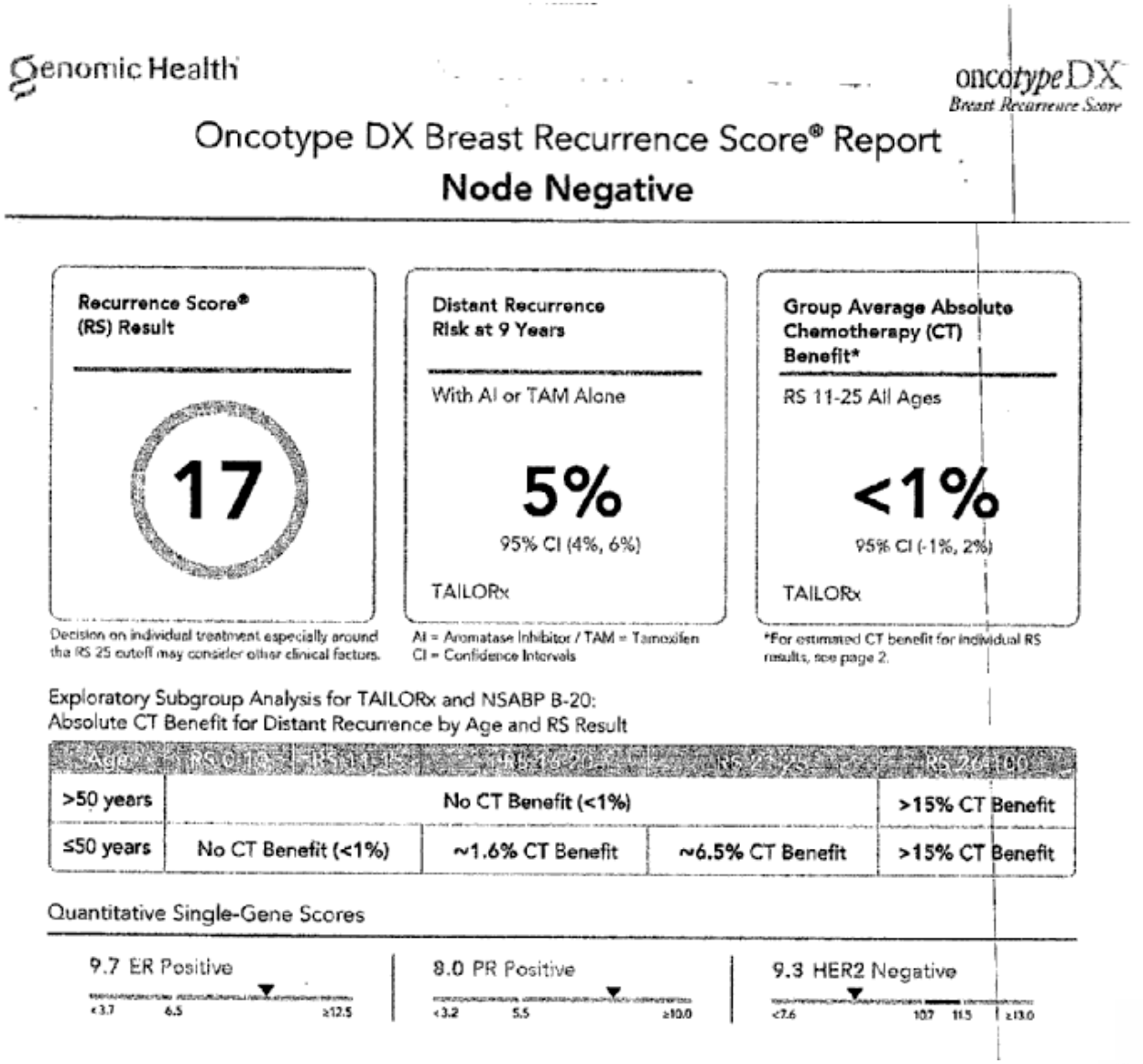
- **Triple negative BC:** YES!
- **HER2 positive BC:** YES!

- **Hormone Positive Breast Cancer:** MUCH less clear!
- **Factors considered:**
  - Age and menopausal status
  - Other medical problems
  - Tumor size
  - Lymph node involvement
  - Oncotype DX recurrence score

What is the Oncotype DX™?

- Genetic test of breast tumor (usually removed at lumpectomy/mastectomy)
  - Assesses genes involved in invasion, cell growth, ER and HER2
- Validated for use in LYMPH NODE NEGATIVE, ER/PR+ breast cancer
- Reported as a "Recurrence Score" from 0 – 100
- Provides PROGNOSTIC and PREDICTIVE information
  - PROGNOSTIC: What is the risk of distant recurrence?
  - PREDICTIVE: What is the benefit of chemotherapy?
- Can help us determine which patients with ER/PR+ breast cancer benefit from chemotherapy

Sample Oncotype DX™ Report: Page 1



Genomic Health

oncotype DX
Breast Recurrence Score

Oncotype DX Breast Recurrence Score® Report

Node Negative

Recurrence Score® (RS) Result

17

Distant Recurrence Risk at 9 Years

With AI or TAM Alone

5%

95% CI (4%, 6%)

TAILORx

Group Average Absolute Chemotherapy (CT) Benefit*

RS 11-25 All Ages

<1%

95% CI (-1%, 2%)

TAILORx

Decision on individual treatment especially around the RS 25 cutoff may consider other clinical factors.

AI = Aromatase Inhibitor / TAM = Tamoxifen
CI = Confidence Intervals

*For estimated CT benefit for individual RS results, see page 2.

Exploratory Subgroup Analysis for TAILORx and NSABP B-20:
Absolute CT Benefit for Distant Recurrence by Age and RS Result

Age	RS 0-10	RS 11-15	RS 16-20	RS 21-25	RS 26-100
>50 years	No CT Benefit (<1%)				>15% CT Benefit
≤50 years	No CT Benefit (<1%)	~1.6% CT Benefit		~6.5% CT Benefit	>15% CT Benefit

Quantitative Single-Gene Scores

9.7 ER Positive

<3.7 6.5 ≥12.5

8.0 PR Positive

<3.2 5.5 ≥10.0

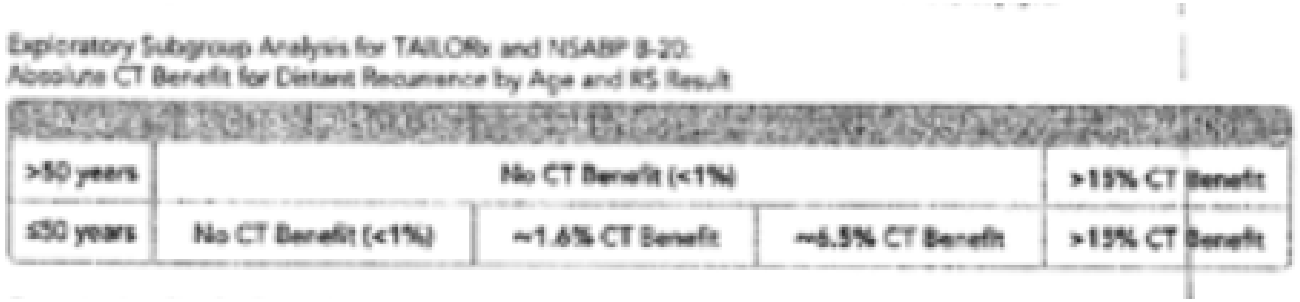
9.3 HER2 Negative

<7.6 10.7 11.5 ≥13.0

Chemotherapy Decision-making in ER+, LN- Breast Cancer

TAILORx Study:

- RS ≥26 → chemotherapy + endocrine therapy
- RS <15→ endocrine therapy only
- RS 15 – 25 →Age may matter



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Age >50

- RS <26 → Endocrine therapy only

Age ≤ 50

- RS 21-25 → *Strongly consider chemotherapy* (benefit appears worth it in most cases)
- RS 16 – 20→ *Consider chemotherapy* (benefit even smaller)

Disclaimer: Every individual is different and factors such as tumor size, magnitude of ER/PR+, other health issues also play a role

Chemotherapy Decision-Making in ER+, LN+ Breast Cancer

- >3 lymph nodes→ chemotherapy beneficial for ALL

- 1-3 lymph nodes: more controversy
  - Pre-menopausal: Most likely benefit from chemotherapy (still standard)
  - Post-menopausal: *May* benefit from chemotherapy

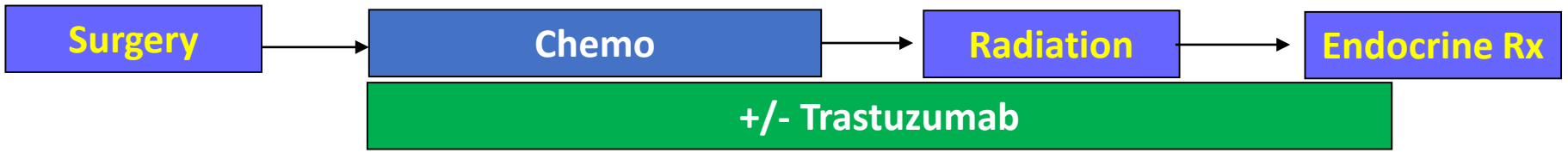
Disclaimer: Every individual is different and factors such as tumor size, magnitude of ER/PR+, other health issues also play a role

Chemotherapy Options

- 1-3 chemotherapy drugs given every 1-3 weeks over the course of 3-6 months
  - Selection of regimen depends on tumor stage, receptor status, side effect profile
- Commonly used for adjuvant chemotherapy:
  - Adriamycin
  - Cyclophosphamide
  - Taxane (paclitaxel, docetaxel)
  - Carboplatin
- Anti-HER2 directed therapy incorporated ALWAYS if HER2+
  - Trastuzumab (Herceptin)
  - Pertuzumab (Perjeta)

What happens after chemotherapy?

- If you are a candidate for radiation→ Radiation
- HER2-directed therapy will continue for a year (may overlap with radiation and endocrine therapy)
- Endocrine therapy follows chemotherapy + radiation



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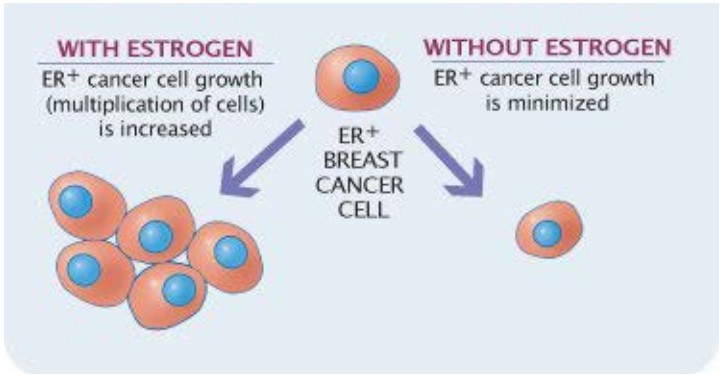
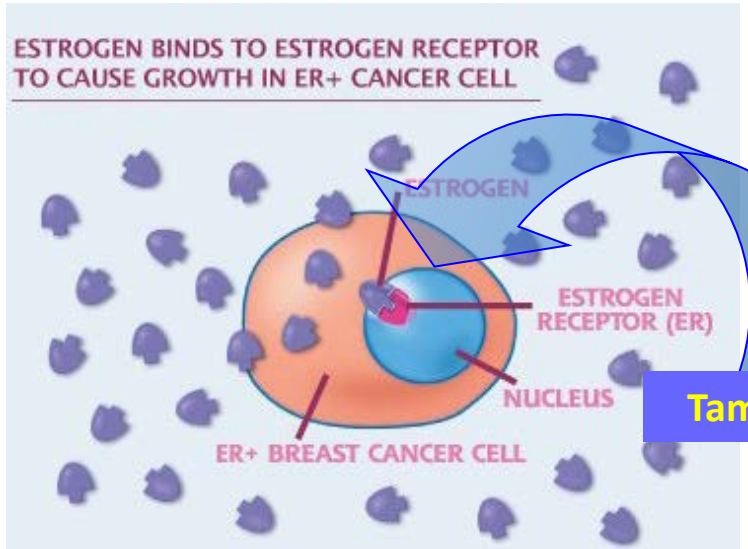
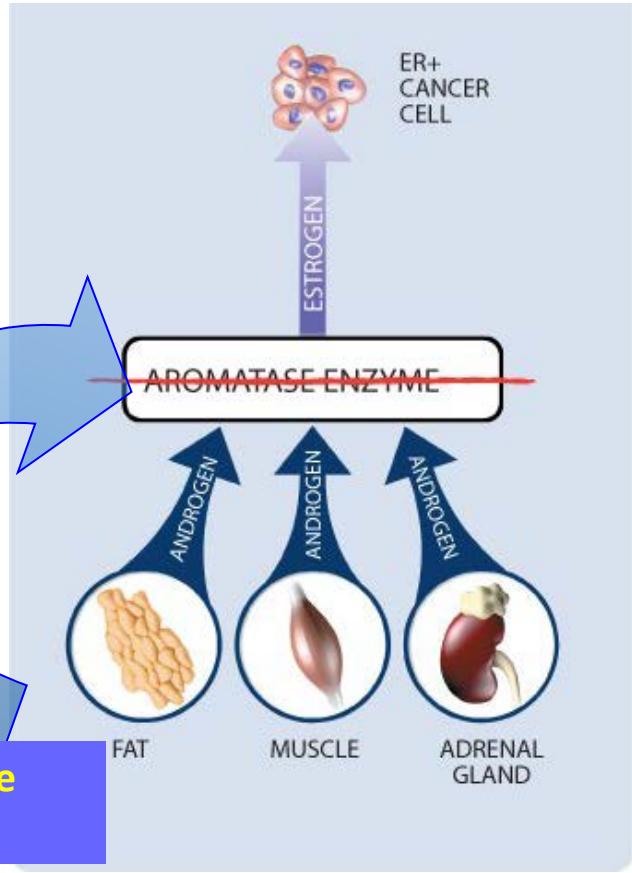
How Hormone Therapies Work





Tamoxifen/SERM

Appropriate for pre- and post-menopausal women



Aromatase Inhibitor

Appropriate for post-menopausal women or pre-menopausal women with suppressed ovaries

Who Benefits from Endocrine Therapy?

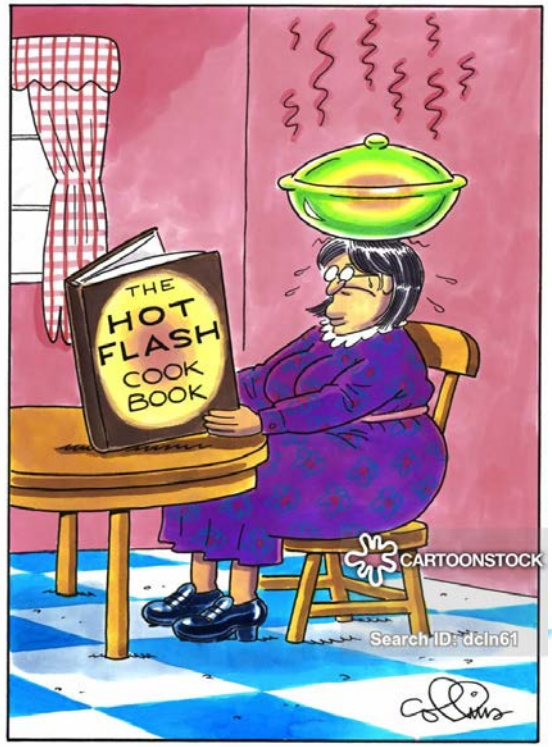
- Anyone with ER and/or PR positive breast cancer
  - Reduces risk of breast cancer recurrence
  - Reduces risk of a second ER+ breast cancer

Tamoxifen: Candidates and Considerations

- Appropriate for women REGARDLESS of menopausal status
  - Slightly less effective than aromatase inhibitors so not preferred in post-menopausal women unless
    - Osteoporosis
    - Intolerance to AI's
- Hot flashes, leg cramps, changes in periods
- Increased risk of blood clots
  - Similar to that seen with oral contraception/birth control
- Increased risk of endometrial cancer
  - Overall low risk (<2% risk over 5 years)
  - Must be evaluated if atypical bleeding

Aromatase Inhibitors (AI): Candidates and Considerations

- Must not have functioning ovaries
  - Post-menopausal
  - History of oophorectomy
  - Medical ovarian suppression [monthly or every 3 month injections – leuprolide or goserelin]
- Increased risk of osteopenia/osteoporosis
  - Monitor bone density (DEXA)
- Joint and muscle aches, stiffness
- Hot flashes



Who benefits from Ovarian Suppression + AI?

- SOFT/TEXT
  - Pre-menopausal women who received chemotherapy derived a greater benefit from adding ovarian suppression to endocrine therapy (tamoxifen or AI)
  - Younger women (<35 years old) benefit the most

➢ Youngest, highest risk women

- BUT…long-term data is still limited
  - Weigh the benefits of improved breast cancer risk with quality of life and risks of “early menopause” (osteoporosis, cardiovascular disease)

What is the optimal duration of endocrine therapy?

- At a minimum – 5 years

- The decision to continue beyond 5 years depends on many things:
  - Prior therapy (what have you been taking the last 5 years)
  - Age and other health problems
  - Baseline recurrence risk
  - Side effects/tolerability of therapy

Extended Therapy Options

- 10 years tamoxifen
- 2-5 years of tamoxifen followed by 5 -10 years aromatase inhibitor
- 10 years of AI

  - Absolute benefits of extended therapy increase the greater the risk of recurrence (more lymph nodes involved)

Endocrine Therapy Duration: Bottom Line

Lowest risk

- Lymph node negative
- Small tumors
- Low Oncotype

5 years probably sufficient

Highest risk

- Multiple positive LNs

Aim for 10 years

Intermediate risk

- 1-3+ lymph nodes
- Intermediate or high Oncotype

Need to weigh benefits with risk (quality of life, bone health)

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Adjuvant Therapy Clinical Trials

- Can any additional medications or interventions not currently approved help further reduce the risk of recurrence, or reduce the toxicity of treatment?

Examples:

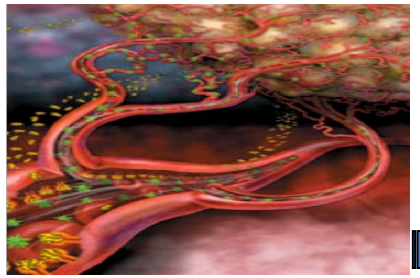
- Adding targeted therapies to endocrine therapy (eg CDK4/6 inhibitors: palbociclib, ribociclib, abemaciclib)
  - PALLAS: Endocrine therapy + Palbociclib – completed, awaiting results
- Targeting “minimal residual disease” (MRD)

Conceptual Model of Recurrence During Surveillance

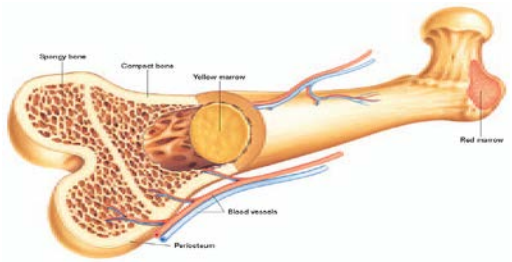
Primary Cancer
Breast

CTCs
cfDNA

Minimal Residual Disease
Blood & Bone Marrow

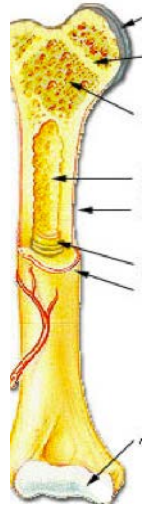


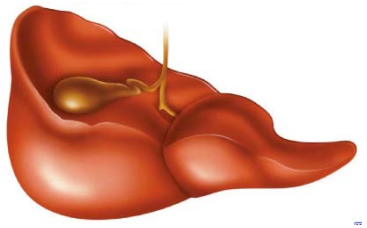
DTCs

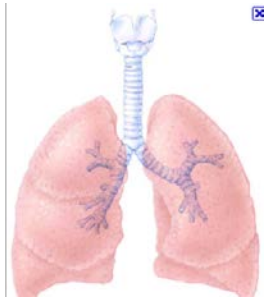


CTCs
cfDNA

Recurrence
Metastatic Sites







"Seed cells" leave primary tumor

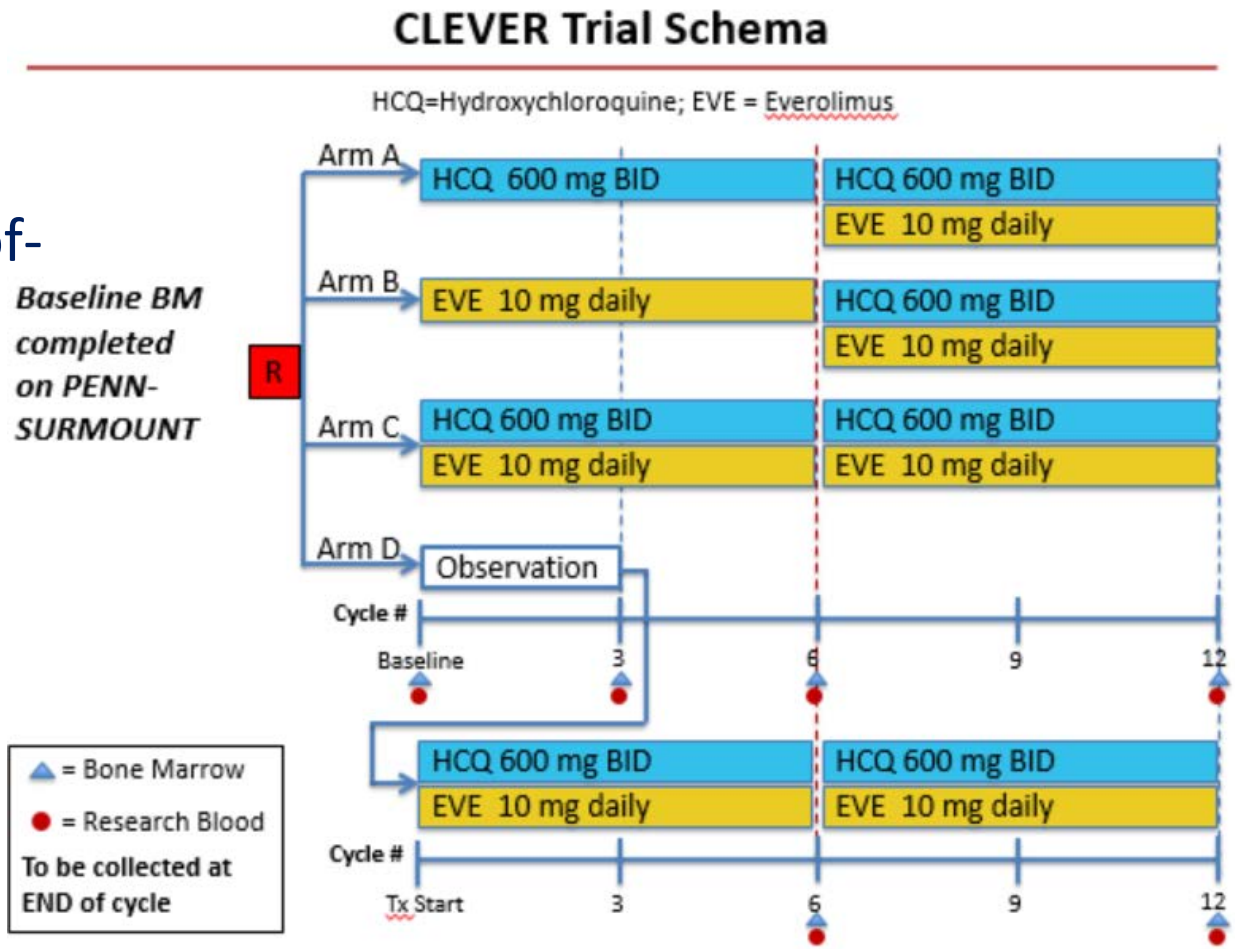
Find sanctuary site, enter dormant state, stop dividing

Awaken, reactivate, start dividing

Travel to distant metastatic sites, begin multiplying

CLEVER Pilot Trial Design

- Patients screened via BM aspirate/ IHC for DTCs
  - Disclosure via phone
  - Education on test characteristics
- DTC+ enter CLEVER trial
  - Randomized, controlled, open label proof-of-concept
  - Oral, continuous daily dosing:
    - Hydroxychloroquine (HCQ)
    - Everolimus (EVE)
  - Primary endpoint: feasibility
  - Secondary: DTC-clearance
  - 3-year recurrence-free survival
- Speak with a clinical trial navigator Monday-Friday, 9:00am to 5:00pm Toll Free: **1-855-216-0098**



Summary

- Chemotherapy, radiation and endocrine therapy are incorporated in the adjuvant setting to prevent breast cancer recurrence
- Both breast cancer-specific and patient-specific factors are considered when determining an individual treatment plan
  - Chemotherapy or no? Which regimen? Type and duration of endocrine therapy
- With the improvements in adjuvant therapy, more breast cancer patients are becoming long-term survivors
- Studies are ongoing to increase the number of patients cured of breast cancer

Thank You!

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