STEM-S

Last Minute Revision

LMR NOTES

Breast

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Stem-S

Breast

- **Molecular Classification**

Subtype	ER/PR	HER2	Ki-67	Key Treatment
Luminal A	+	–	Low (<14%)	Endocrine therapy
Luminal B	+	– / +	High	Endocrine ± Chemo
HER2-enriched	–	+	High	Anti-HER2 + Chemo
Triple Negative (TNBC)	–	–	High	Chemotherapy ± IO

- **Exam Pearl**
  - Luminal A → **least aggressive, best prognosis**
  - TNBC → **most aggressive, early relapse**

2. Indications for Neoadjuvant Chemotherapy (NACT)

- **NACT preferred when:**
  - Tumor > 2 cm
  - Node-positive disease
  - HER2-positive
  - Triple-negative breast cancer
  - Locally advanced breast cancer

- **Benefits tested in NEET SS**
  - Downstaging → breast conservation
  - In-vivo chemosensitivity
  - **Pathological complete response (pCR) = prognostic marker**

3. Pathological Complete Response (pCR)

- **Definition**
  - No residual invasive cancer in breast and nodes (ypT0/is ypN0)
- **Highest pCR rates seen in**
  - HER2-positive (with dual HER2 blockade)
  - Triple-negative
- **Lowest pCR**
  - ER-positive Luminal A tumors

4. Chemotherapy Regimens (CORE)

Adjuvant / Neoadjuvant

- **Standard backbone**
  - Anthracycline + Taxane
- **Examples:**
  - AC → T
  - FEC → T
  - Dose-dense AC → T (better DFS)
- **TNBC**
- Platinum (Carboplatin) ↑ pCR

5. HER2-Positive Breast Cancer

- **Drugs**
  - Trastuzumab – backbone
  - Pertuzumab – dual blockade
  - T-DM1 – residual disease post-NACT
  - Lapatinib – rarely used now

- **Cardiotoxicity**
  - Trastuzumab → **reversible** **cardiomyopathy**
  - Avoid with low LVEF
  - Monitor ECHO every 3 months
- **Exam Pearl**
  - HER2 therapy duration = **1** **year**

6. Hormone Receptor Positive Breast Cancer

- **Premenopausal**
  - Tamoxifen ± ovarian suppression
  - Chemo → induces ovarian failure
- **Postmenopausal**
  - Aromatase inhibitors preferred
    - Letrozole
    - Anastrozole
    - Exemestane
- **Side effects tested**
  - AI → osteoporosis, arthralgia
  - Tamoxifen → DVT, endometrial cancer

7. CDK4/6 Inhibitors

Drug	Setting
Palbociclib	Metastatic HR+
Ribociclib	Metastatic HR+
Abemaciclib	High-risk adjuvant

- **Mechanism**
  - Cell cycle arrest at G1-S
- **Key toxicity**
  - Neutropenia (Palbo/Ribo)
  - Diarrhea (Abema)

8. Triple Negative Breast Cancer (TNBC)

- **Characteristics**
  - Early relapse
  - Visceral & brain mets common
  - No endocrine or HER2 targets
- **Treatment**
  - Anthracycline + Taxane
  - Platinum improves pCR
  - Immunotherapy (PD-1 inhibitors) in PD-L1 positive

9. Metastatic Breast Cancer – General Principles

- **Not curable**
- Aim: prolong survival + quality of life
- HR+ → Endocrine preferred
- Visceral crisis → Chemotherapy
- Bone mets → Bisphosphonates / Denosumab

10. Bone-Targeted Therapy

Drug	Mechanism
Zoledronic acid	Osteoclast inhibition
Denosumab	RANK-L inhibitor

- **Exam trap**
  - Denosumab preferred in renal failure

11. BRCA-Mutated Breast Cancer

- Sensitive to Platinum
- PARP inhibitors:
  - Olaparib
  - Talazoparib
- **Mechanism**
  - Synthetic lethality

- **HIGH-YIELD BREAST ONCOLOGY TRIALS**

Trial	Population	What Was Studied / Intervention	Key Result	Exam Pearl / Trap
ATLAS & aTTom	HR-positive breast cancer	Tamoxifen **5 years vs 10 years**	**10 years ↓ recurrence & ↓ breast cancer mortality**; benefit more pronounced **after year 10**	Extended tamoxifen ↑ **endometrial cancer risk**, but **survival benefit outweighs risk**
SOFT & TEXT	Premenopausal HR-positive	Tamoxifen alone vs Tamoxifen + ovarian suppression vs **AI + ovarian suppression**	**AI + ovarian suppression = best DFS**; highest benefit in **high-risk young women (<35 yrs, post-chemo)**	**AI never alone** in premenopausal women
MONALEESA-7	Premenopausal HR+ metastatic	**Ribociclib + endocrine therapy**	**Overall survival benefit proven**; first CDK4/6 trial to show OS in this group	Ribociclib → **QT prolongation**
MONARCH-E	High-risk, node-positive HR+ early	**Adjuvant Abemaciclib + endocrine therapy**	Improved **invasive DFS**	High risk = **≥4 nodes** OR **1–3 nodes + high grade / large tumor / high Ki-67**
HERA	HER2-positive breast cancer	Trastuzumab **1 year vs 2 years**	**1 year = standard**; no added benefit with 2 years	Trastuzumab → **reversible cardiomyopathy**
CLEOPATRA	Metastatic HER2-positive	**Trastuzumab + Pertuzumab + Docetaxel**	**Significant OS improvement**; established **dual HER2 blockade**	Pertuzumab blocks **HER2 dimerization**
KATHERINE	Residual disease after NACT (HER2+)	Trastuzumab vs **T-DM1**	**T-DM1 superior → ↓ recurrence**	**Standard of care** for residual invasive disease
APHINITY	Early HER2-positive	Trastuzumab + Pertuzumab (adjuvant)	Benefit mainly in **node-positive** patients	Minimal benefit in node-negative
CREATE-X	Residual disease after NACT (HER2-negative)	**Adjuvant Capecitabine**	Improved **DFS & OS; maximum benefit in TNBC**	Post-NACT residual **TNBC → Capecitabine**
IMpassion130	Metastatic TNBC	**Atezolizumab + Nab-paclitaxel**	Benefit **only in PD-L1 positive tumors**	Immunotherapy **not for all TNBC**
OlympiA	Germline BRCA-mutated, high-risk early	**Adjuvant Olaparib**	Improved **DFS & OS**	PARP inhibitors = **synthetic lethality**
CALGB 9344	Early breast cancer	AC vs **AC → Paclitaxel**	Adding paclitaxel **improves survival**	Established **anthracycline → taxane** sequence
EBCTCG Meta-analysis	Early breast cancer	Multiple systemic therapies	Anthracycline + taxane ↓ **recurrence & mortality**; endocrine benefit persists **>10 years**	Foundational evidence base

- **BREAST ONCOLOGY DRUGS —**

1. HORMONAL (ENDOCRINE) THERAPY

Drug	Class / Mechanism	Indication	Hallmark Toxicity	Exam Pearls
Tamoxifen	SERM (ER antagonist in breast, agonist in uterus & bone)	Premenopausal & postmenopausal HR+	**Endometrial cancer, DVT, hot flashes**	Drug of choice in **premenopausal** women
Letrozole	Aromatase inhibitor	Postmenopausal HR+	Osteoporosis, arthralgia	Most potent AI
Anastrozole	Aromatase inhibitor	Postmenopausal HR+	Bone loss, myalgia	AI superior to tamoxifen postmenopause
Exemestane	Steroidal AI	Postmenopausal HR+	Osteoporosis	Irreversible AI
Fulvestrant	SERD (ER degradation)	Metastatic HR+	Injection site pain	No agonist effect on uterus

- **Exam Trap**
  - **AI NEVER alone in premenopausal women**

2. CDK4/6 INHIBITORS (VERY HIGH YIELD)

Drug	Setting	Key Toxicity	Exam Point
Palbociclib	Metastatic HR+	**Neutropenia**	G1-S cell cycle arrest
Ribociclib	Metastatic HR+	**QT prolongation**, neutropenia	OS benefit (MONALEESA)
Abemaciclib	Metastatic + **Adjuvant**	**Diarrhea**, fatigue	Only CDK4/6 used in adjuvant (MONARCH-E)

3 HER2-TARGETED THERAPY

Drug	Mechanism	Indication	Hallmark Toxicity	Exam Pearl
Trastuzumab	HER2 receptor blockade	HER2+ early & metastatic	**Reversible cardiomyopathy**	Avoid if low LVEF
Pertuzumab	Blocks HER2 dimerization	HER2+ metastatic / high-risk adjuvant	Diarrhea	Dual HER2 blockade
T-DM1	Trastuzumab + emtansine (ADC)	Residual disease post-NACT	Thrombocytopenia	KATHERINE trial
Lapatinib	TKI (HER2/EGFR)	Refractory HER2+	Diarrhea, rash	Less used now

4. CHEMOTHERAPY (BACKBONE DRUGS)

Drug	Class	Key Toxicity	Exam Pearl
Doxorubicin	Anthracycline	**Cardiomyopathy**, alopecia	Lifetime dose limit
Cyclophosphamide	Alkylating agent	Hemorrhagic cystitis	Give mesna (high dose)
Paclitaxel	Taxane	**Peripheral neuropathy**	Given after AC
Docetaxel	Taxane	Edema, neutropenia	CLEOPATRA regimen
Capecitabine	Oral 5-FU prodrug	**Hand-foot syndrome**	CREATE-X trial
Carboplatin	Platinum	Myelosuppression	↑ pCR in TNBC

5. TRIPLE NEGATIVE BREAST CANCER (TNBC) DRUGS

Drug	Indication	Key Point
Anthracycline + Taxane	Backbone	First line
Carboplatin	Neoadjuvant TNBC	↑ pCR
Capecitabine	Residual TNBC	OS benefit
Atezolizumab	PD-L1+ metastatic TNBC	Only PD-L1 positive
Pembrolizumab	Early & metastatic TNBC	Immunotherapy role expanding

6. PARP INHIBITORS (HOT TOPIC)

Drug	Indication	Mechanism	Toxicity
Olaparib	BRCA-mutated breast cancer	Synthetic lethality	Anemia, fatigue
Talazoparib	BRCA-mutated	PARP inhibition	Myelosuppression

- **Exam Pearl**
  - Works only in **germline BRCA mutation**

7. BONE-TARGETED AGENTS

Drug	Mechanism	Use	Exam Pearl
Zoledronic acid	Osteoclast inhibition	Bone metastasis	Avoid in renal failure
Denosumab	RANK-L inhibitor	Bone mets	Safe in renal failure

• IMPORTANT

- Breast cancer drug selection is driven by **ER, HER2, and BRCA status**.
- **HR+ → endocrine ± CDK4/6**, **HER2+ → anti-HER2 therapy**, **TNBC → chemotherapy ± immunotherapy**.
- **Residual disease after NACT mandates escalation (T-DM1 or capecitabine).**

• ENDOCRINE THERAPY

Drug	Hallmark Toxicities (Exam-Favorite)
Tamoxifen	**Endometrial cancer**, DVT/PE, hot flashes
Letrozole	Osteoporosis, arthralgia
Anastrozole	Bone loss, myalgia
Exemestane	Osteoporosis
Fulvestrant	Injection-site pain

• CDK4/6 INHIBITORS

Drug	Key Toxicity	Unique Exam Point
Palbociclib	**Neutropenia**	Most marrow suppression
Ribociclib	**QT prolongation**, neutropenia	ECG monitoring
Abemaciclib	**Diarrhea**, fatigue	Least neutropenia

• HER2-TARGETED THERAPY

Drug	Hallmark Toxicity	Exam Trap
Trastuzumab	**Reversible cardiomyopathy**	NOT dose-dependent
Pertuzumab	Diarrhea	Less cardiotoxic
T-DM1	**Thrombocytopenia**, transaminitis	Antibody-drug conjugate
Lapatinib	Diarrhea, skin rash	TKI toxicity pattern

• CHEMOTHERAPY AGENTS

Drug	Signature Toxicity
Doxorubicin	**Cardiomyopathy**, alopecia
Cyclophosphamide	**Hemorrhagic cystitis**
Paclitaxel	**Peripheral neuropathy**, hypersensitivity
Docetaxel	Edema, neutropenia
Capecitabine	**Hand-foot syndrome**, diarrhea
Carboplatin	Myelosuppression

• TNBC-RELATED / IMMUNOTHERAPY

Drug	Key Toxicity
Atezolizumab	Immune-related adverse events
Pembrolizumab	Autoimmune toxicities (thyroiditis, colitis)

- **PARP INHIBITORS**

Drug	Hallmark Toxicity
Olaparib	**Anemia**, fatigue
Talazoparib	Myelosuppression

- **BONE-TARGETED AGENTS**

Drug	Key Toxicity	Exam Trap
Zoledronic acid	Renal toxicity, osteonecrosis jaw	Avoid in renal failure
Denosumab	Hypocalcemia, ONJ	Safe in renal failure

IMPORTANT

- **Tamoxifen → endometrial cancer**
- **Trastuzumab → reversible cardiomyopathy**
- **Ribociclib → QT prolongation**
- **Abemaciclib → diarrhea**
- **Capecitabine → hand-foot syndrome**

- **Aromatase Inhibitors**
  - **AI is NEVER used alone in premenopausal women**
  - Ovarian estrogen production continues → AI becomes ineffective
  - **Must add ovarian suppression**
- **Trap question**: Young woman + AI alone → **WRONG**
- **Tamoxifen Myths**
  - Tamoxifen **does cause endometrial cancer**
  - But **overall survival benefit > risk**
  - Hence **10 years > 5 years** (ATLAS/aTTom)
- **Exam trick:** "Stop tamoxifen early due to endometrial risk" →

Breast

- **Trastuzumab Cardiotoxicity**
  - **NOT dose-dependent**
  - **Reversible**
  - Unlike anthracyclines (dose-dependent, irreversible)
- If question asks “cumulative dose toxicity” → **Anthracycline, NOT trastuzumab**

- **Duration Confusion**
  - **Trastuzumab = 1 year**
  - 2 years gives **NO added benefit** (HERA)
- “Extend trastuzumab to 2 years” →

- **Residual Disease After NACT (HER2+)**
  - **Do NOT continue trastuzumab**
  - Must switch to **T-DM1** (KATHERINE)
- Biggest NEET SS trap

3. CDK4/6 Inhibitor Traps

- **All CDK4/6 Are NOT Same**
  - **Only Abemaciclib** → adjuvant setting
  - Palbociclib & Ribociclib → metastatic only
- "Adjuvant palbociclib" →
- **Toxicity Confusion**
  - Ribociclib → **QT prolongation**
  - Palbociclib → **neutropenia**
  - Abemaciclib → **diarrhea**, least neutropenia

4. Neoadjuvant Chemotherapy (NACT) Traps

- **pCR Misinterpretation**
  - pCR = **prognostic marker**, NOT indication to stop therapy
  - **pCR does NOT mean no adjuvant therapy**
- "pCR achieved → no further treatment" →
- **NACT in Luminal A**
  - Luminal A tumors have **poor pCR**
  - Chemo benefit is limited
- Chemo works best in **HER2+ & TNBC**

5. Triple Negative Breast Cancer (TNBC) Traps

- **Immunotherapy for All TNBC**
  - **ONLY PD-L1 positive** TNBC benefits
  - PD-L1 negative → chemo only
- "Give atezolizumab to all TNBC" →
- **Residual TNBC After NACT**
  - Do NOT observe
  - Must give **Capecitabine** (CREATE-X)
- Observation = wrong answer

6. BRCA-Mutated Breast Cancer Traps

- **PARP Inhibitors**
  - Work ONLY in **germline BRCA mutation**
  - Not for sporadic TNBC
- "Give olaparib in TNBC without BRCA" →
- **Platinum ≠ PARP**
  - Platinum sensitivity ≠ automatic PARP indication
  - BRCA status still required

7. Metastatic Breast Cancer Traps

- **Visceral Crisis**
  - HR+ disease usually → endocrine first
  - **Visceral crisis → chemotherapy**, not endocrine
- Liver mets ≠ visceral crisis

- Organ dysfunction = visceral crisis
- **Metastatic Disease Goal**
  - **NOT curative**
  - Aim = survival + quality of life
- Aggressive curative intent →

8. Bone Metastasis Traps

- **Zoledronic Acid vs Denosumab**
  - Zoledronic acid → **avoid in renal failure**
  - Denosumab → **safe in renal failure**
- Renal failure + zoledronic acid →

9. HER2 Status Confusion

- HER2 positivity must be **confirmed by IHC / FISH**
- Borderline IHC (2+) → needs FISH
- Starting trastuzumab on IHC 2+ alone →

10. Trial-Based Traps

Trial	Common Trap
CLEOPATRA	Used in **metastatic**, not adjuvant
KATHERINE	Applies only to **residual disease**
CREATE-X	HER2-negative only
SOFT/TEXT	AI always with ovarian suppression
MONARCH-E	Only **high-risk node-positive**

Breast

5-LINE NEET SS MEMORY TRAPS

- **AI never alone premenopause**
- **Residual disease = escalate therapy**
- **Only abemaciclib is adjuvant**
- **Trastuzumab cardiotoxicity ≠ anthracycline**
- **Immunotherapy only if PD-L1 positive**

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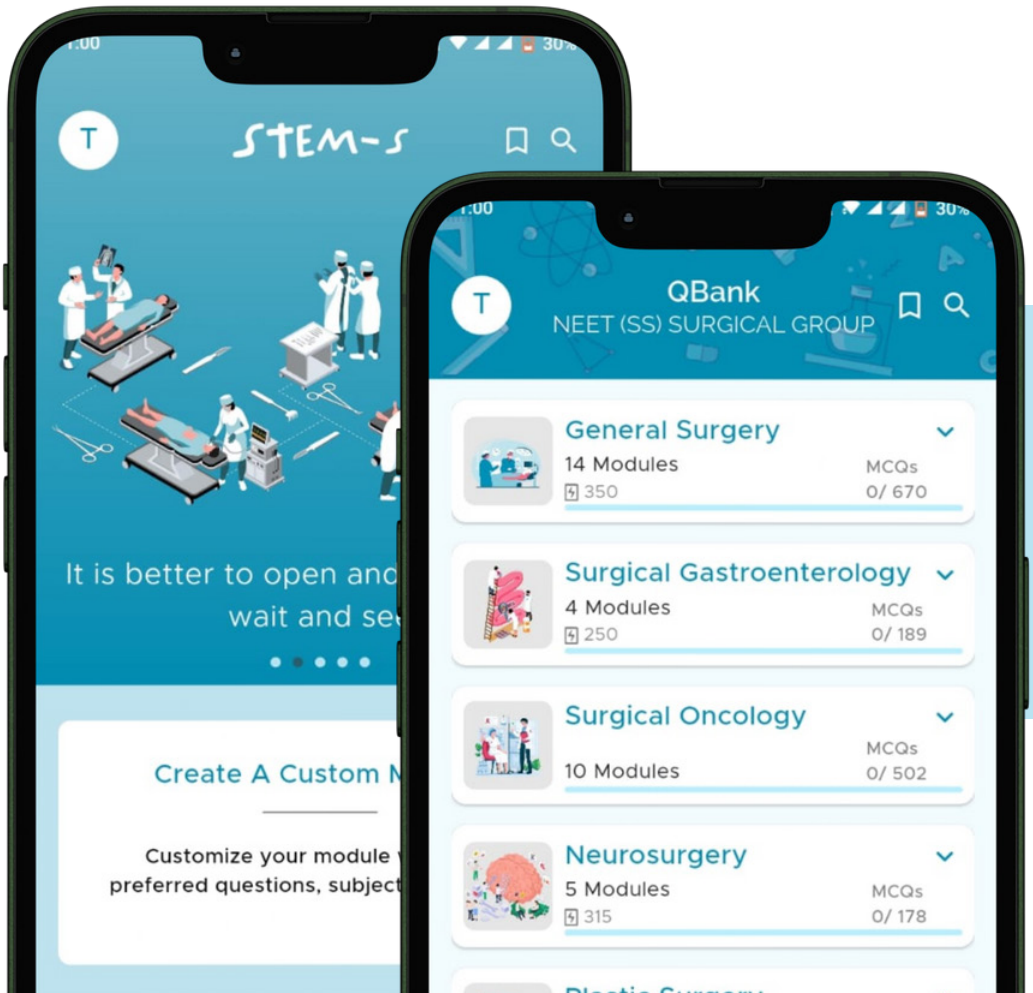

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