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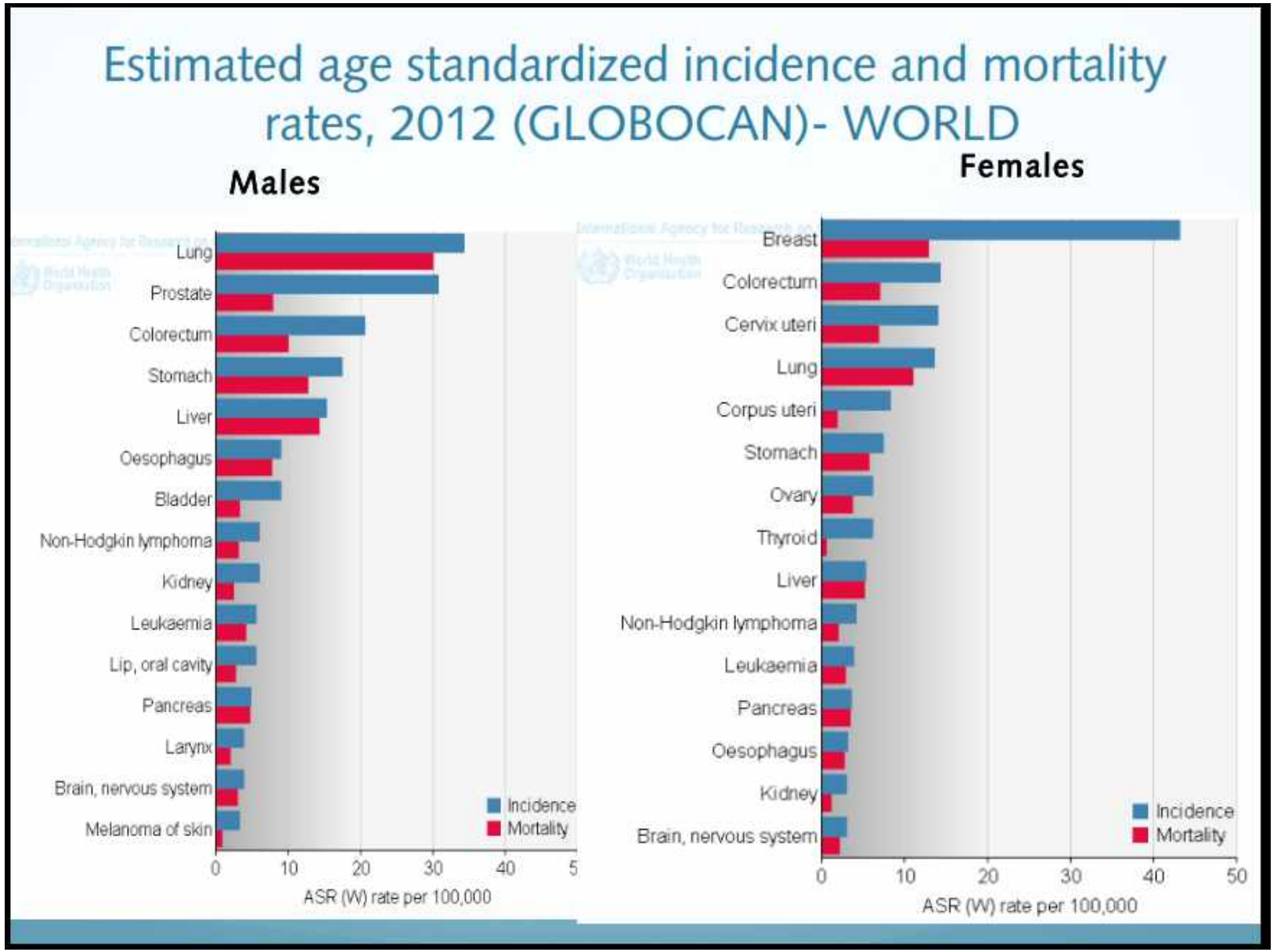
INSIDENCE AND MORTALITY BREAST CANCER 2012



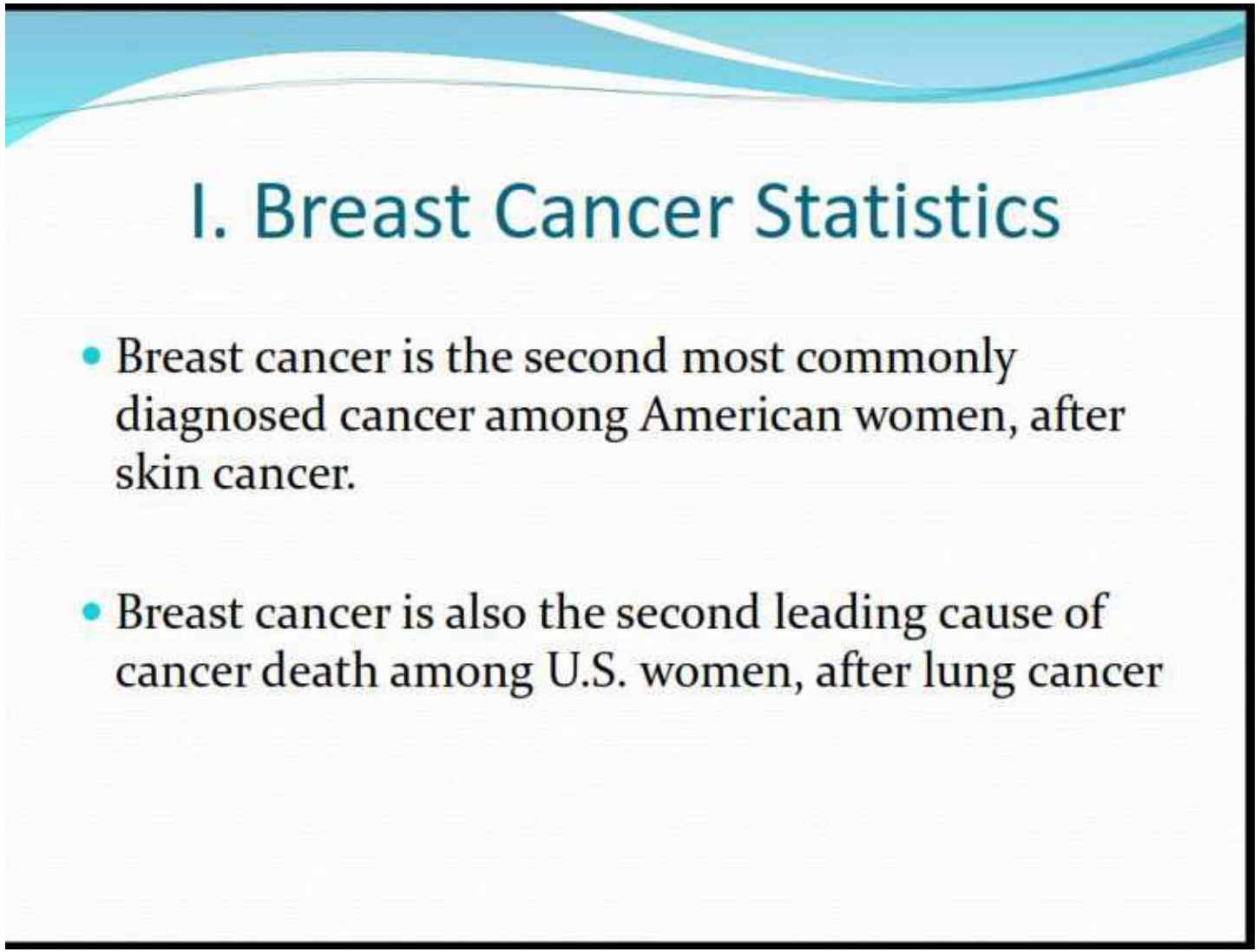
INTRODUCE: Incidence and mortality; 2012

GLOBOCAN DATABASE

2012-WORLD:

Breast cancer remain the second most common cause of cancer, estimated 1,67 million new cancer case diagnosed in 2012.

Females: Breast, colo-rectal and cervix cancer.



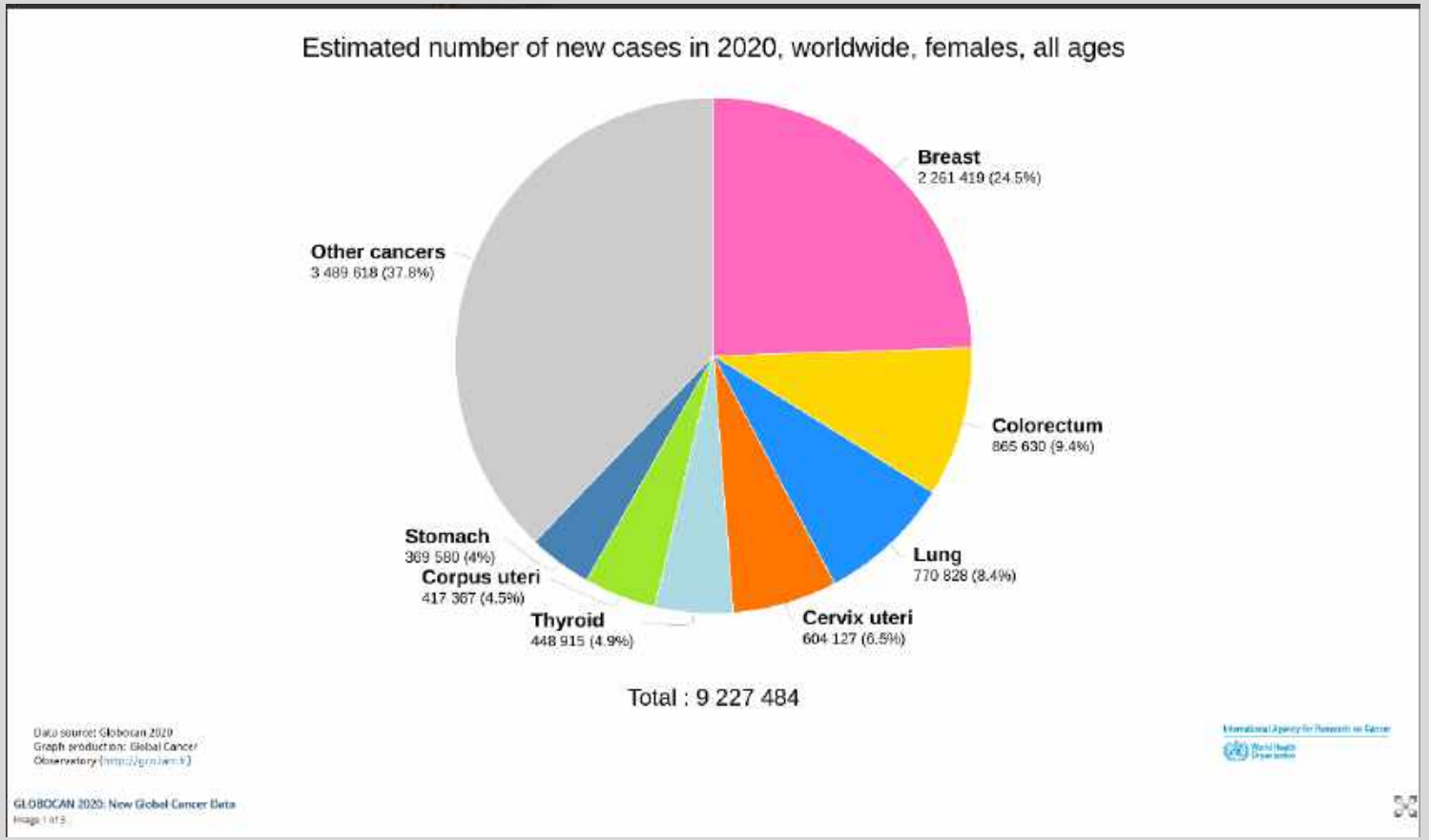
Breast cancer statistic in American

Breast cancer accounting 25% of all cancer.

In USA (2013): new breast cancer was estimated at 232.340 and the number of death at 39.620.

Incidence rate ranging from 27 per 100.000 in middle Africa and Eastern Asia.

GLOBOCAN DATABASE 2020; Estimated new case breast cancer in 2020



INSIDEN DI INDONESIA: RISKESDAS 2019

- Insiden kanker di Indonesia: 136,2/100.000 penduduk.
- Peringkat 8 di Asia Tenggara
- Peringkat 23 di Asia
- Pada Wanita: kanker payudara terbanyak: insiden 42,1/100.000 penduduk.
- Angka kematian: 17 per 100.000 penduduk.

Etiology/Risk factors of Breast Cancer

- Family History of Breast Cancer.
- Puberty in very early age.
- Menopause occurred at later age.
- History of infertility.
- Those who had their first child after 40 years have an increased risk of developing Breast Cancer.
- Estrogen therapy during post-menopausal period (5.2yrs).
- Obese women
- Women who drink more than moderate amounts of alcohol.

ETIOLOGY OF BREAST CANCER

Hereditary (10% of patients have first degree relatives).

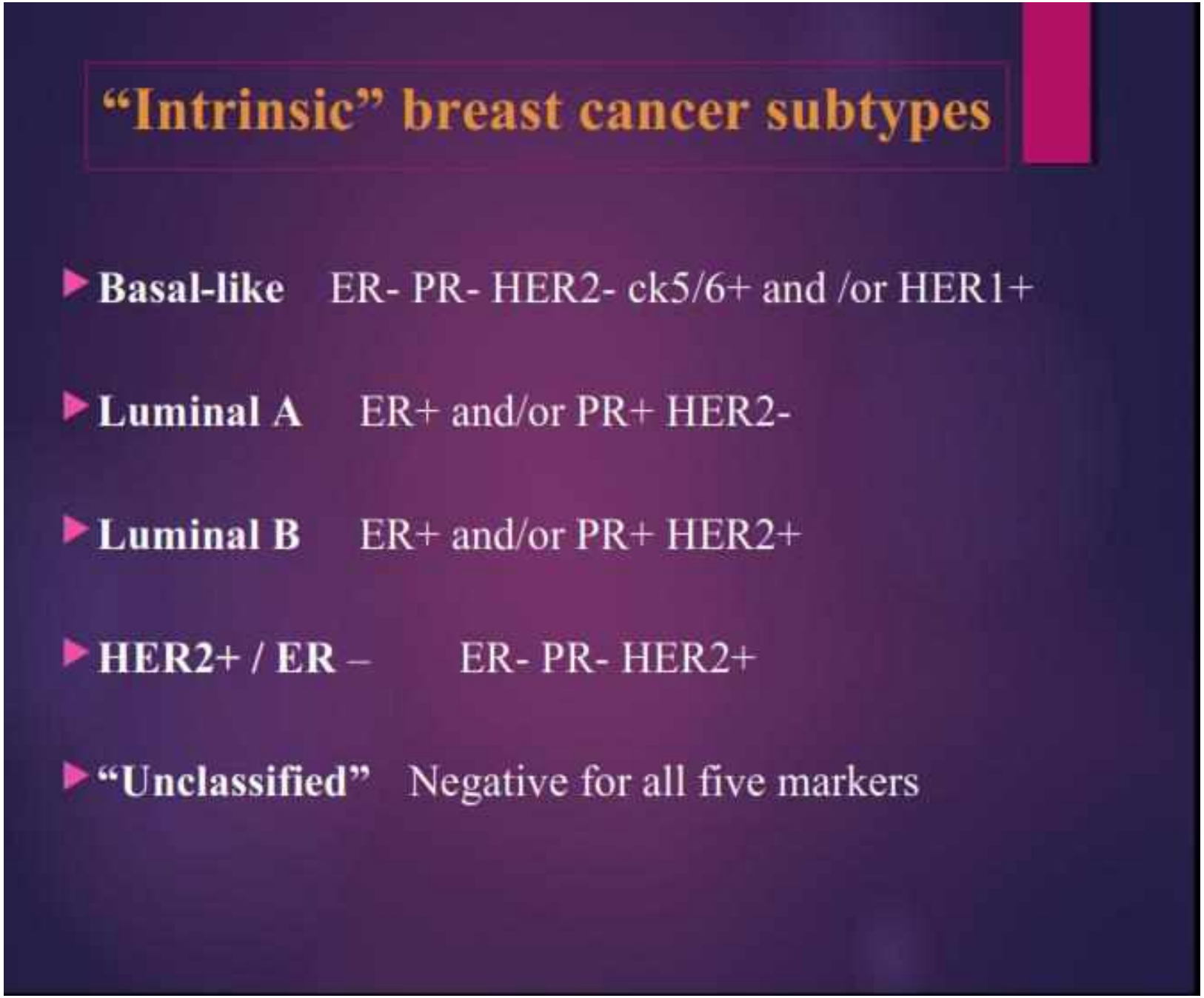
Genetic mutations: BRCA1 and BRCA2.

Radiation: history mantle radiotherapy during childhood (R/ Limfoma Hodgkin)

Hormonal factors: HRT (hormonal replacement treatment contain estrogen and progesterone)

PATHOLOGY:

- Carcinomas in situ: ductal carcinoma in situ (DCIS), Lobuler carcinoma in situ (LCIS)
- Invasive carcinomas:
  - Invasive ductal carcinoma (80%)
  - Invasive lobular carcinoma (10%)
  - Other invasive carcinoma: Medullary, papillary, tubular, cribriform, metaplastic, squamus, adenoid cystic, mucinous, secretory, and undifferentiated.



Subtype of Breast cancer

SYMPTOM OF BREAST CANCER

SYMPTOMS OF BREAST CANCER

- Earliest symptom is often a lump or thickening in the breast or under the arm.
- In the early stages the lump may move freely beneath the skin when it is pushed with the fingers.
- During advanced stages the lump may adhere to the chest wall or to the skin over it & cannot be moved.
- A change in the size, shape or contour of the breast or in the appearance of the skin of the breast or nipple can be a symptom of breast cancer.
- Sometimes the skin may appear puckered or dimpled.

SYMPTOMS OF BREAST CANCER

- The lump may be painful, but pain is an uncommon & unreliable sign.
- A discharge from the nipple may occur.
- Sometimes the breast becomes red & swollen.
- Sometimes the breast feels normal, but the lymph nodes in the underarm feel like hard small lumps & may be slightly tender.

7th Edition of TNM staging system

- TX Primary tumor cannot be assessed.
- T0 No evidence of primary tumor.
- Tis Carcinoma in situ.
- Tis (DCIS) DCIS.
- Tis (LCIS) LCIS.
- Tis (Paget) Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
- T1 Tumor ≤20 mm in greatest dimension.
- T1mi Tumor ≤1 mm in greatest dimension.
- T1a Tumor >1 mm but ≤5 mm in greatest dimension.
- T1b Tumor >5 mm but ≤10 mm in greatest dimension.
- T1c Tumor >10 mm but ≤20 mm in greatest dimension.
- T2 Tumor >20 mm but ≤50 mm in greatest dimension.
- T3 Tumor >50 mm in greatest dimension.
- T4 Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).
- T4a Extension to the chest wall, not including only pectoralis muscle adherence/invasion.
- T4b Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma.
- T4c Both T4a and T4b.
- T4d Inflammatory carcinoma.

TNM STAGING FOR BREAST CANCER AJCC 7th

AJCC: American joint committee on cancer: TNM staging

N stage 7th Edition

- NX Regional lymph nodes cannot be assessed (e.g., previously removed).
- N0 No regional lymph node metastases.
- N1 Metastases to movable ipsilateral level I, II axillary lymph node(s).
- N2 Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted. OR Metastases in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases.
  - **N2a** Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures.
  - **N2b** Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases.
- N3 Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement. OR Metastases in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases. OR Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.
  - **N3a** Metastases in ipsilateral infraclavicular lymph node(s).
  - **N3b** Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s).
  - **N3c** Metastases in ipsilateral supraclavicular lymph node(s).

TNM STAGING FOR BREAST CANCER AJCC 7th

N: Nodal

M stage 7th Edition

- **M0 :** No clinical or radiographic evidence of distant metastases.
- **cM0(i+) :** No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other non-regional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases.
- **M1 :** Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm.

TNM STAGING FOR BREAST CANCER AJCC 7th

M: metastasis

TNM Stage Groups

Stage:	Combinations:
0	Tis, N0, M0,
1A	T1, N0, M0
1B	T0 or T1, N1mic, M0
2A	T0, N1, M0 or T1, N1, M0 or T2, N0, M0
2B	T2, N1, M0 or T3, N0, M0
3A	T0-3, N2, M0 or T3, N1, M0
3B	T4, N0-2, M0
3C	Any T, N3, M0
4	And T, any N, M1

Staging

- Early breast cancer
  - Stage 0 - carcinoma in situ or disease not invaded basement membrane
  - Stage I - small primary tumour without lymph node involvement
  - Stage II- Metastasis to ipsilateral axillary lymph nodes
- Locally advanced breast cancer
  - Stage III - large tumour with extensive nodal involvement where node is fixed to chest wall, inflammatory breast cancer that is rapidly progressive
- Advanced or metastatic breast cancer
  - Stage IV - Metastases to organs distant from the primary tumour

STAGING OF BREAST CANCER (TNM)

TNM STAGING

T Primary Tumour	**T0** No evidence of primary tumour	**T1** Tumor 2cm or less in greatest diameter	**T2** Tumor size 2-5 cm	**T3** Tumor size >5 cm	**T4** Tumor of any size with direct extension to cest wall or skin
N Lymph Node	**N0** No palpable axillary nodes	**N1** Mobile palpable axillary nodes	**N2** Fixed axillary nodes	**N3** Fixed supraclavicular nodes	
M Metastasis	**M0** No evidence of distant metastasis	**M1** Distant metastasis			

STAGING OF BREAST CANCER

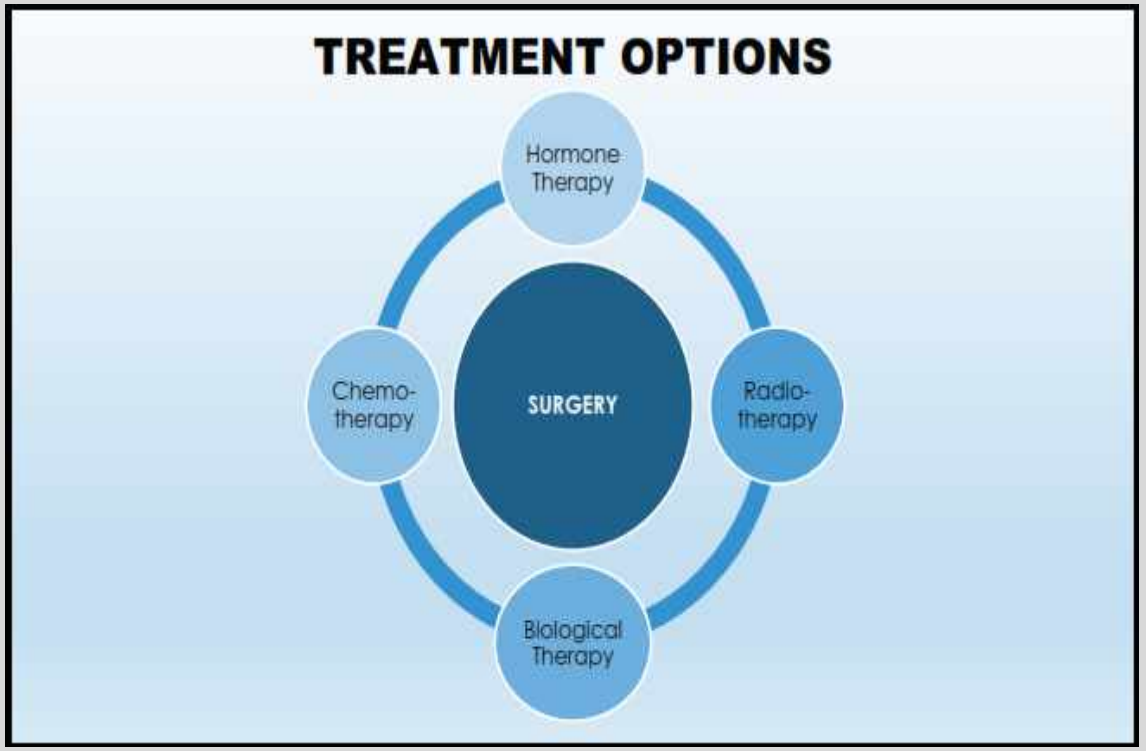
MANCHESTER STAGING

STAGE 1	TUMOUR SIZE <2 CM NO NODAL INVOLVEMENT NO DISTANT METASTSSIS
STAGE 2	TUMOUR SIZE 2-5 CM IPSILATERAL MOBILE NODAL METASTASIS NO DISTANT METASTASIS
STAGE 3A	TUMOR SIZE >5 CM IPSILATERAL FIXED NODAL METASTASIS NO DISTANT METASTASIS
STAGE 3B	TUMOR OF ANY SIZE INVADING SKIN OR CHEST WALL SUPRACLAVICULAR NODAL METASTASIS NO DISTANT METASTASIS
STAGE 4	TUMOUR OF ANY SIZE NODAL METASTASIS DISTANT METASTASIS

TREATMENT IN BREAST CANCER:

Treatment

- Early breast cancer
  - Local-regional therapy
  - Systemic adjuvant therapy
  - Adjuvant chemotherapy
  - Adjuvant endocrine therapy
- Locally advanced breast cancer
  - Primary/neoadjuvant/chemotherapy
- Metastatic breast cancer
  - Endocrine therapy
  - Chemotherapy



BREAST CANCER IN INDONESIA:

- Coming to hospital: with advance stage or metastasis.
- History with alternatif treatment: infection ???
- screening program???

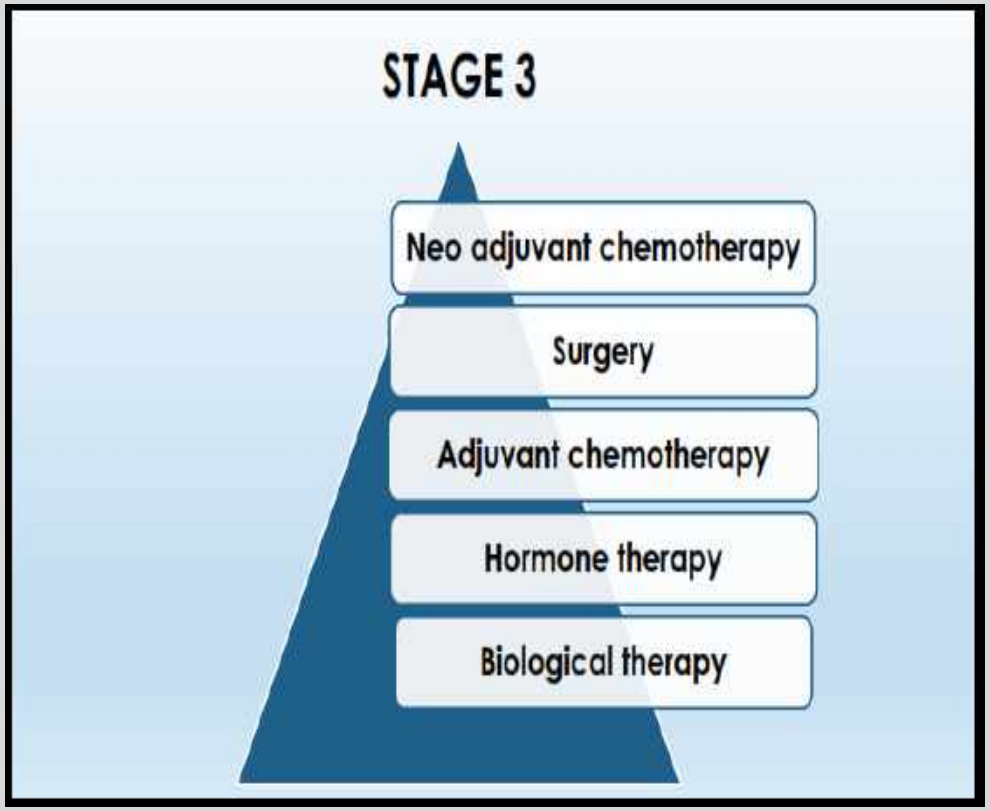
Goals of therapy

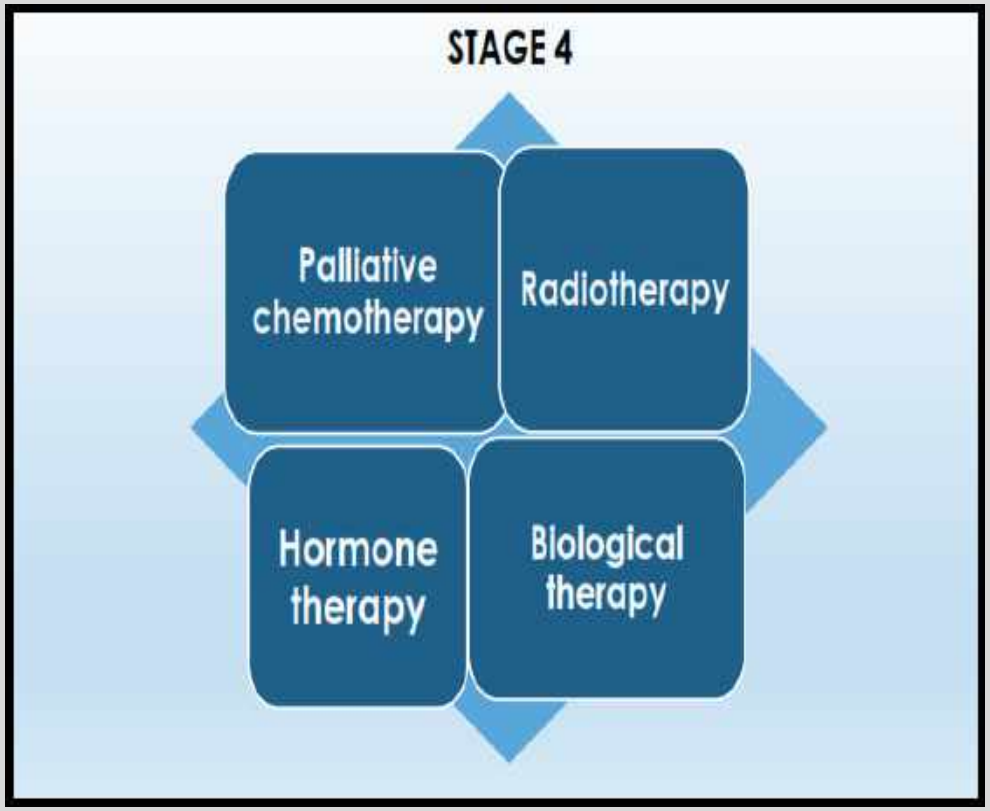
- For early & locally advanced breast cancer
  - Cure
- Metastatic breast cancer
  - Improve symptoms
  - Improve quality of life
  - Prolong survival

Early stage goals of therapy is cure

THERAPY OF BREAST CANCER

THERAPY OF BREAST CANCER:





Systemic therapy for breast cancer

- Systemic therapy:
  - Hormonal therapy
  - Chemotherapy (Neo-adjuvant or Adjuvant)
  - Targeted therapy
  - Immune therapy
  - Biological therapy

Systemic therapy for breast cancer

- Neoadjuvant systemic therapy: considered in patients with locally advance breast cancer, because tumor regression increase the opportunities for breast conserving treatment (BCT).

- Adjuvant systemic therapy: addresses the possibility of occult micro-metastasis, which can, with time grow into overt metastasis disease.

Systemic therapy for breast cancer

- Neoadjuvant and Adjuvant systemic therapy:
  - HORMONAL THERAPY OR CHEMOTHERAPY
  - Targeting therapy (anti-HER2)

INDICATION THERAPY:

- NEO-ADJUVANT OR ADJUVANT SYSTEMIC THERAPY: HORMONAL?? CHEMOTHERAPY?? TARGETED THERAPY?? OR THE OTHERS??
- GUIDELINES: NCCN…
- Based on: staging tumour, hormonal status and HER/EGFR (Epidermal growth factors receptor) status.
- Hormonal status: ER/PR
- HER : HER1,2,3 or 4

NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY

Breast Cancer, Version 3.2020

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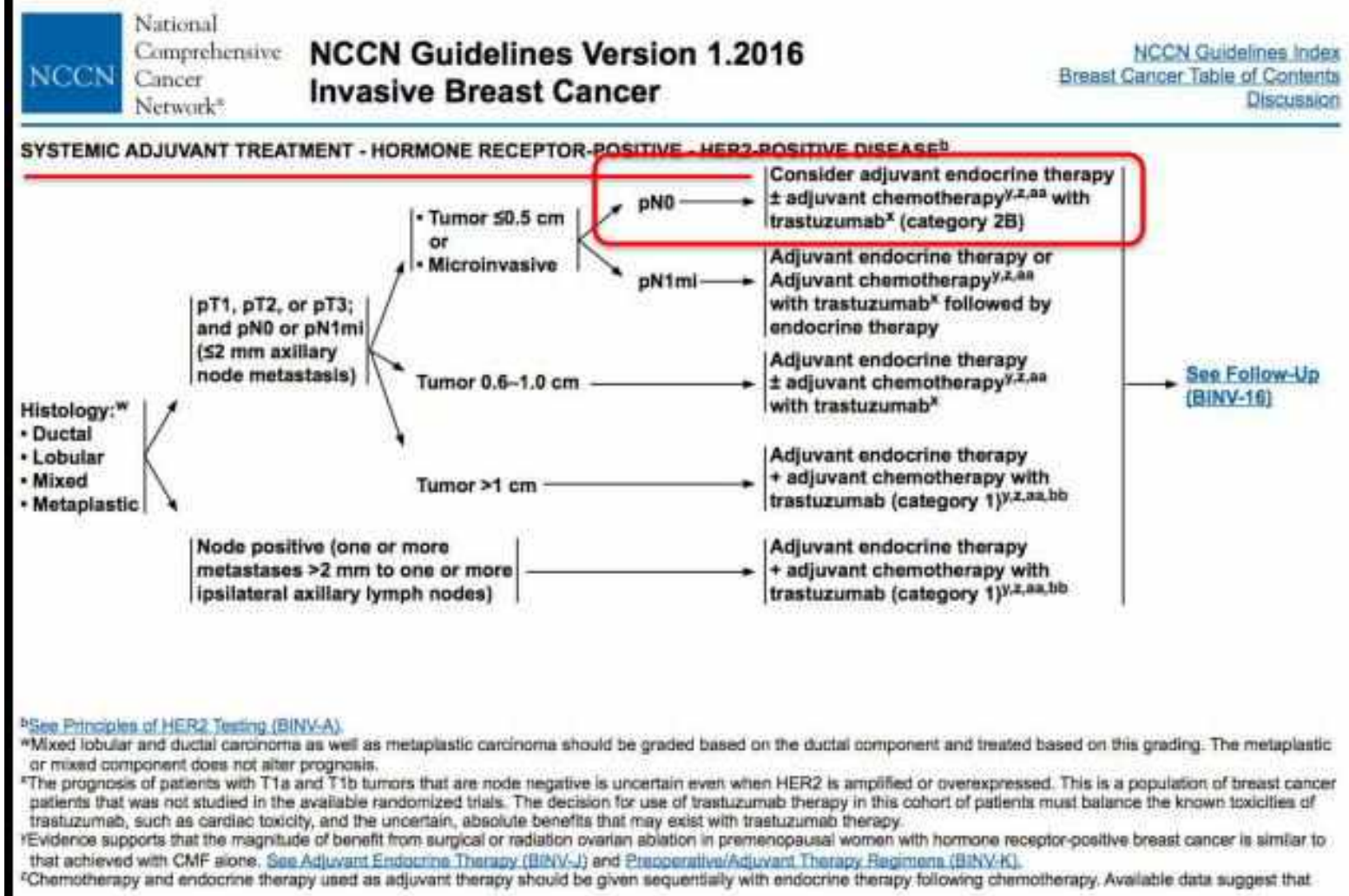
Systemic adjuvant treatment: hormone receptor and HER2 positive



[b]See Principles of HER2 Testing (BINV-A).
[w]Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.
[x]The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.
[y]Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).
[z]Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that

NCCN Guidelines (2016) Invasive Breast Cancer:

Systemic adjuvant Hormonal therapy:

Hormone receptor positive

(HR +)

HORMONAL AGENTS

- **Postmenopausal patients:** (AIs)
  - Anastrozole or Letrozole as first line
  - Exemestane as second line
  - Tamoxifen and Megace remain options for third line OR for patients who do not tolerate aromatase inhibitors.
- **Premenopausal patients:** (SERMs)
  - Tamoxifen as first line
  - Megace OR aromatase inhibitor with ovarian ablation as second line.

Hormonal agents, continued:

- **Megace** (megestrol acetate)
  - Is a progestin
  - Before aromatase inhibitors, was considered second-line therapy, after tamoxifen.
  - May still have activity in some patients who have failed tamoxifen and/or aromatase inhibitors.
  - Side effects: increased appetite, weight gain, increased risk of DVT/pulmonary embolism.

HORMONAL AGENTS

Hormonal agents:

- Tamoxifen: (SERMs)
  - Mixed estrogen receptor agonist-antagonist.
  - Can be used in premenopausal and postmenopausal women.
  - Response rates are 50-60%.
  - Duration of response may be years.
  - Toxicities: hot flashes, increased risks of DVT/ pulmonary embolism, endometrial cancer
  - May be associated with **tumour** reluctance in up to 13% of patients.

Hormonal agents, continued:

Aromatase inhibitors: (AIs)

- **Anastrozole** (Arimidex), non-steroidal
- **Letrozole** (Femara), non-steroidal
- **Exemestane** (Aromasin), steroidal

Method of action: block conversion of adrenal androgens to estrogen in adipose tissue and in the breast.

Use is ***restricted to postmenopausal*** women.

Side effects: hot flashes, myalgias/arthralgias, increased risk of osteoporosis, altered lipid profiles.

SYSTEMIC CHEMOTHERAPY

- NEO-ADJUVANT CHEMOTHERAPY
- ADJUVANT CHEMOTHERAPY

HUMAN DISEASES AND CONDITIONS COLLECTION

A. Malcolm Campbell, *Editor*

Neoadjuvant chemotherapy (NCCN 2016)[3] is given before any surgery to reduce the tumor size and to destroy any cancer cells that may be in the blood circulation or may have spread to distant parts of the body (also known as micrometastasis). The drugs are given once every three weeks for three cycles or sometimes weekly for two to three months. After this, depending on the tumor shrinkage, surgery is done. Usually as a thumb rule, total mastectomy is done, but in some Western countries, breast conservation is also done.

Neoadjuvant chemotherapy

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HUMAN DISEASES AND CONDITIONS COLLECTION

A. Malcolm Campbell, *Editor*

Chemotherapy given after primary surgery is called adjuvant chemotherapy. It is usually given two to three weeks after surgery once the surgical wound heals and the pathology reports pathological reports are available. Again, the regimen would depend on various factors like age, pathological stage of tumor, receptor status (ER, PR, or HER), other medical conditions like diabetes mellitus and cardiac disease, and the financial condition of the patient. An adjuvant chemotherapy is given for six to eight cycles at three-weekly intervals. Adjuvant chemotherapy regimens may also include targeted drugs like trastuzumab. Many times, adjuvant chemotherapy is also followed by radiation therapy.

Adjuvant chemotherapy

ADJUVANT CHEMOTHERAPY OF BREAST CANCER

- Combination regimens derived from those that produce highest response in advanced disease
- Doxorubicin containing regimens popular as they are superior to CMF regimens and require only 4 cycles
- Taxanes –newer class with activity against metastatic BC; in combination increase disease free survival in node positive BC
- Chemo initiated within 3 weeks of surgical removal, optimal duration of treatment – 12-24 weeks
- Short term toxicities of chemo countered by serotonin-antagonists and CSF

NCCN; FIRST LINE CHEMOTHERAPY BREAST CANCER HER2 NEGATIVE

CAF/FAC

- Cyclophosphamide 600 or 500mg/m2 IV day 1
- Doxorubicin 60 (or 50)mg/m2 IV day 1 (over 72 hr)
- Fluorouracil 600mg/m2 IV day 1 (or 500mg/m2 days 1,4)
- Repeat cycle every 21-28 days.

CMF

- Cyclophosphamide 100mg/m2 PO days 1-14 (or 600mg/m2 IV, day 1)
- Methotrexate 40mg/m2 IV days 1,8 (or day 1 only)
- Flurouracil 600mg/m2 IV days 1,8.
- Repeat cycle every 28 days.

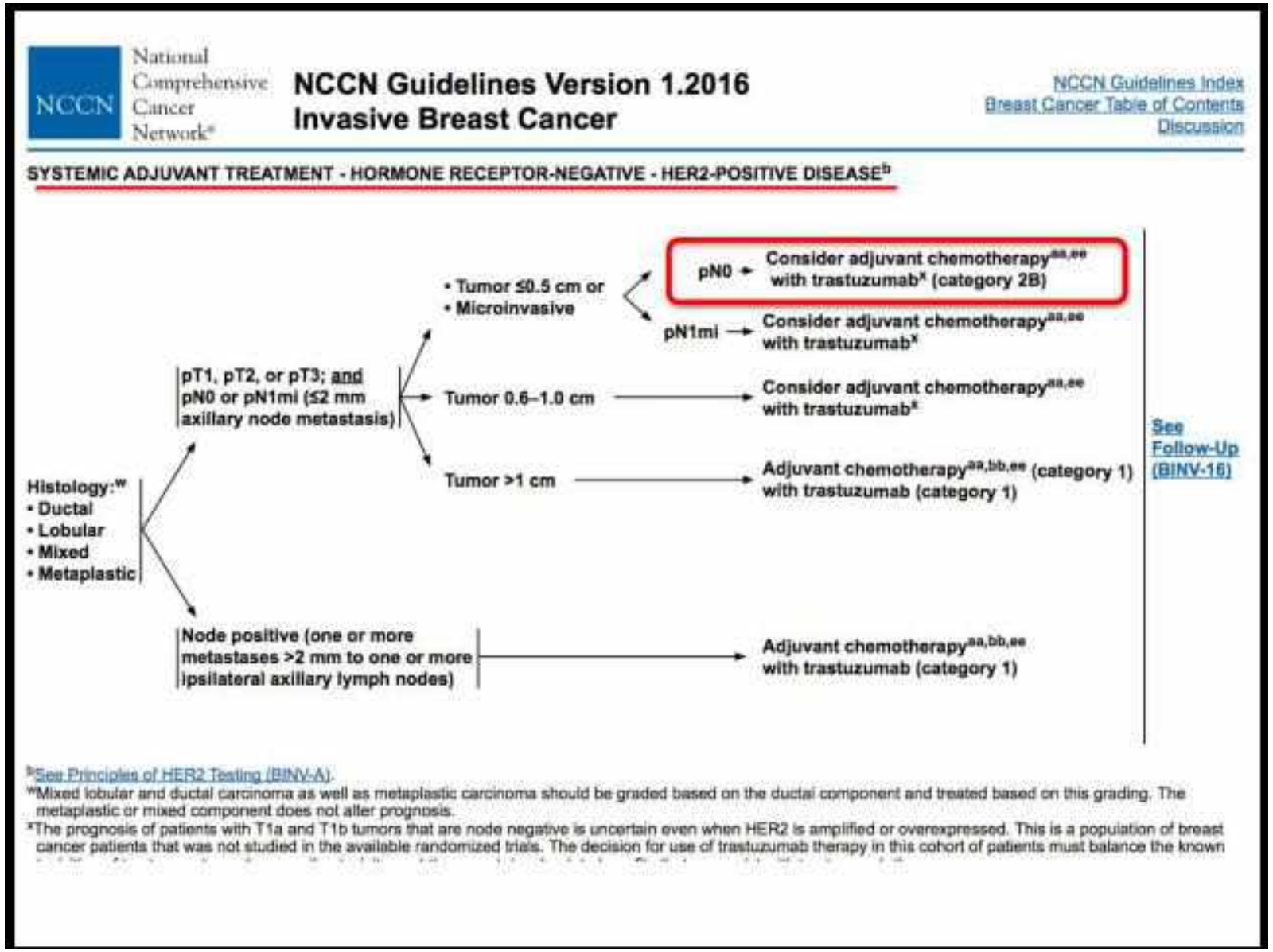
NCCN; FIRST LINE CHEMOTHERAPY BREAST CANCER HER2 NEGATIVE

AC regimen

- Doxorubicin 60mg/m2 IV day 1
- Cyclophosphamide 400-600mg/m2 IV day 1
- Repeat cycle every 21 days.

CEC /FEC

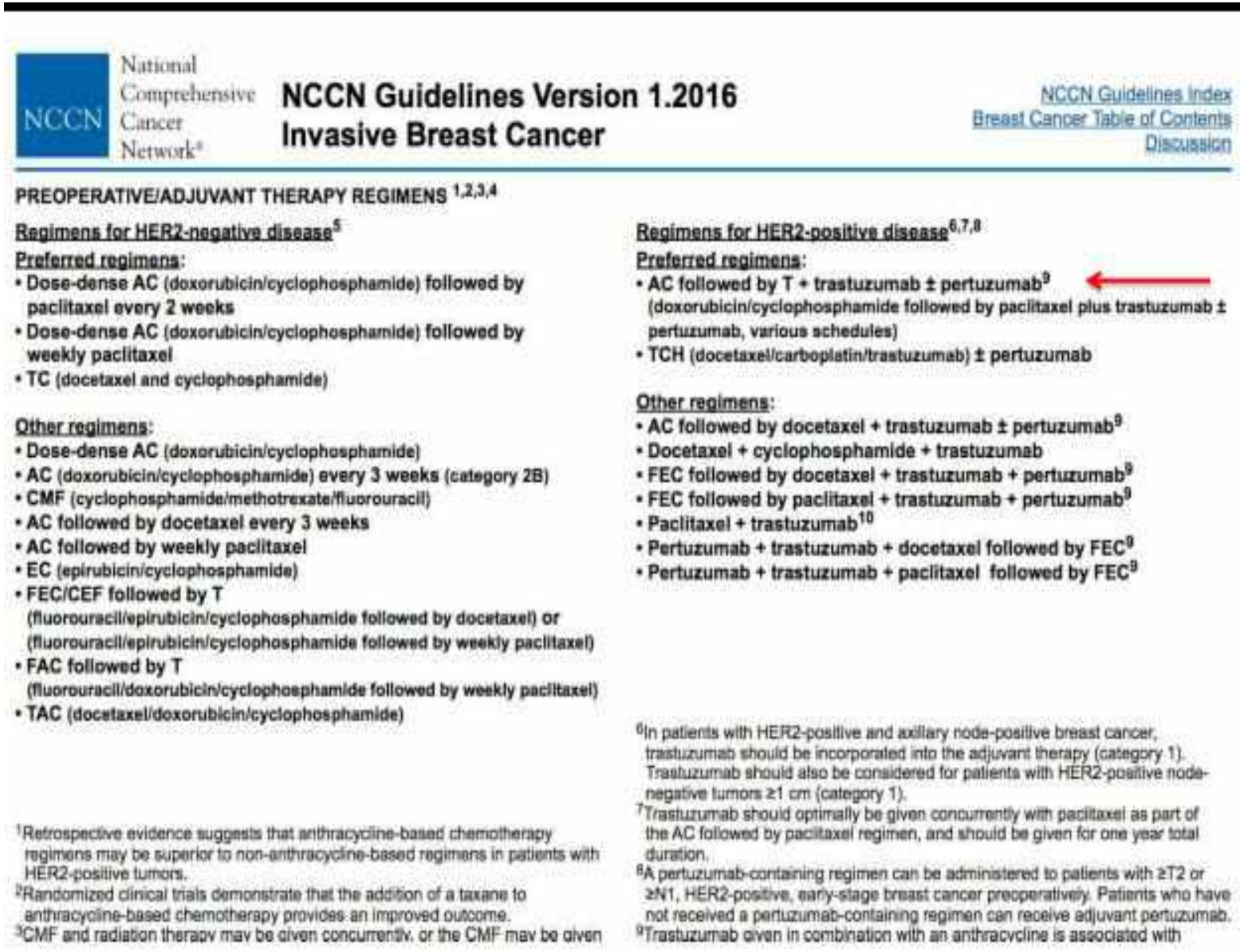
- Cyclophosphamide 75mg/m2 PO, days 1-14 (600mg/m2IV, day 1)
- Epirubicin 60 (or 100)mg/m2 IV, days 1, 8
- Fluorouracil 600 (or 500) mg/m2 IV, days 1,8
- Repeat cycle every 21 days



NCCN Guidelines (2016)
Invasive Breast Cancer:

Systemic adjuvant Chemotherapy:

Hormone receptor negative and HER2 positive disease



National Comprehensive Cancer Network

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS [1,2,3,4]

Regimens for HER2-negative disease[5]

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- AC followed by weekly paclitaxel
- EC (epirubicin/cyclophosphamide)
- FEC/CEF followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) or (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)
- FAC followed by T (fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:

- AC followed by T + trastuzumab ± pertuzumab[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

- AC followed by docetaxel + trastuzumab ± pertuzumab[9]
- Docetaxel + cyclophosphamide + trastuzumab
- FEC followed by docetaxel + trastuzumab + pertuzumab[9]
- FEC followed by paclitaxel + trastuzumab + pertuzumab[9]
- Paclitaxel + trastuzumab[10]
- Pertuzumab + trastuzumab + docetaxel followed by FEC[9]
- Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]

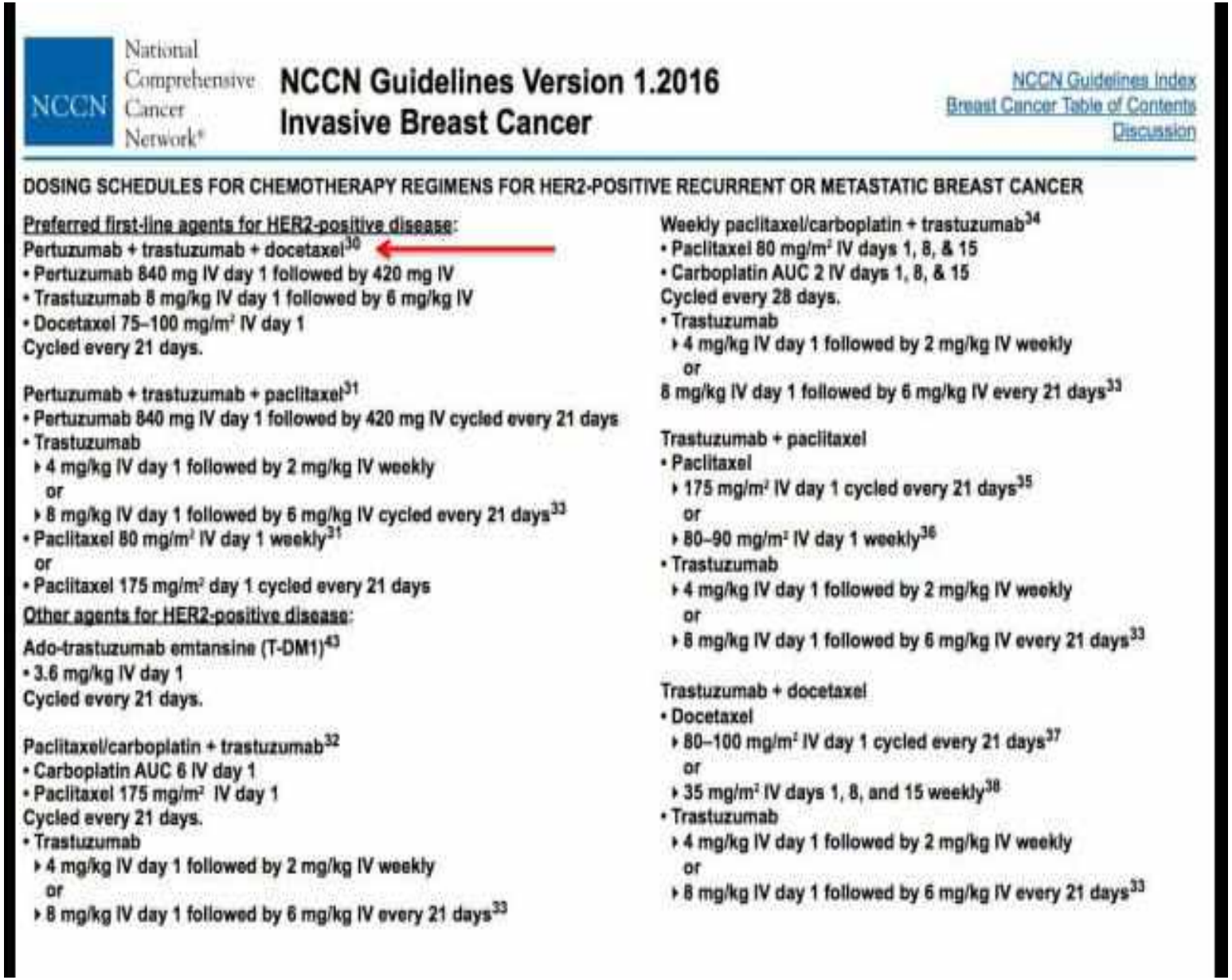
[1]Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.
[2]Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.
[3]CMF and radiation therapy may be given concurrently, or the CMF may be given

[6]In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥1 cm (category 1).
[7]Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for one year total duration.
[8]A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer preoperatively. Patients who have not received a pertuzumab-containing regimen can receive adjuvant pertuzumab.
[9]Trastuzumab given in combination with an anthracycline is associated with

NCCN Guidelines (2016) Invasive Breast Cancer:

HR negative and HER2 POSITIVE:

AC/TC + Trastuzumab or Pertuzumab



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Invasive Breast Cancer

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DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER2-POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Preferred first-line agents for HER2-positive disease:

Pertuzumab + trastuzumab + docetaxel[30]
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m² IV day 1

Cycled every 21 days.

Pertuzumab + trastuzumab + paclitaxel[31]
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days[33]
- Paclitaxel 80 mg/m² IV day 1 weekly[31]
  or
- Paclitaxel 175 mg/m² day 1 cycled every 21 days

Other agents for HER2-positive disease:

Ado-trastuzumab emtansine (T-DM1)[43]
- 3.6 mg/kg IV day 1

Cycled every 21 days.

Paclitaxel/carboplatin + trastuzumab[32]
- Carboplatin AUC 6 IV day 1
- Paclitaxel 175 mg/m² IV day 1

Cycled every 21 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Weekly paclitaxel/carboplatin + trastuzumab[34]
- Paclitaxel 80 mg/m² IV days 1, 8, & 15
- Carboplatin AUC 2 IV days 1, 8, & 15

Cycled every 28 days.
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or

8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

Trastuzumab + paclitaxel
- Paclitaxel
  - 175 mg/m² IV day 1 cycled every 21 days[35]
    or
  - 80–90 mg/m² IV day 1 weekly[36]
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

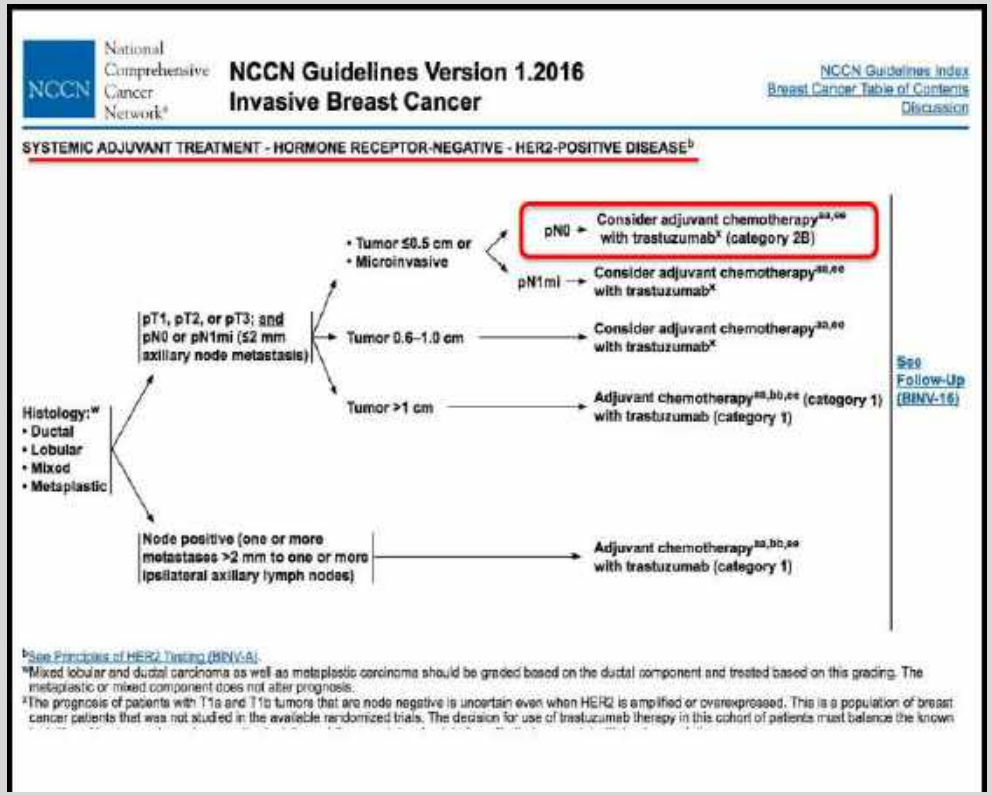
Trastuzumab + docetaxel
- Docetaxel
  - 80–100 mg/m² IV day 1 cycled every 21 days[37]
    or
  - 35 mg/m² IV days 1, 8, and 15 weekly[38]
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[33]

NCCN Guidelines (2016) Invasive Breast Cancer:

Systemic therapy for HER2 positive recurrent or metastatic Breast Cancer

Ado-trastuzumab emtansine (T-DM1): highly potent anti microtubule agent

NCCN; FIRST LINE CHEMOTHERAPY BREAST CANCER HER2 positive



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SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE[b]

Histology:[w]
- Ductal
- Lobular
- Mixed
- Metaplastic

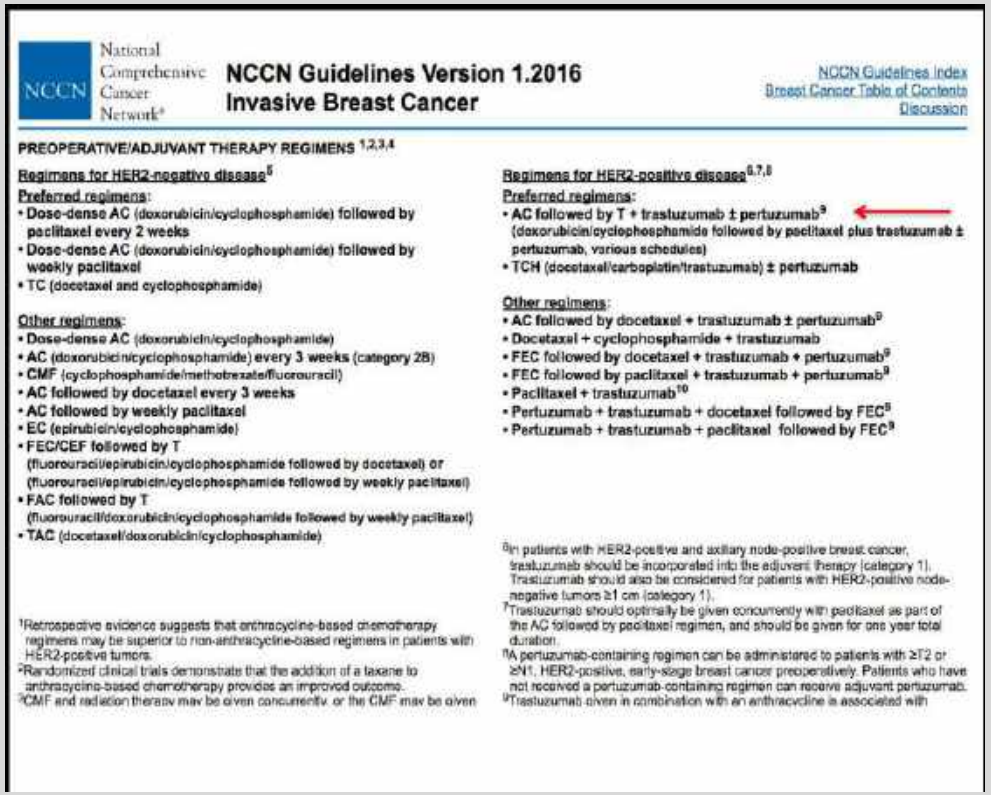
pT1, pT2, or pT3; and pN0 or pN1mi (≤2 mm axillary node metastasis)

- Tumor ≤0.5 cm or Microinvasive
  - pN0 → Consider adjuvant chemotherapy[aa,ee] with trastuzumab[x] (category 2B)
  - pN1mi → Consider adjuvant chemotherapy[aa,ee] with trastuzumab[x]
- Tumor 0.6–1.0 cm → Consider adjuvant chemotherapy[aa,ee] with trastuzumab[x]
- Tumor >1 cm → Adjuvant chemotherapy[aa,bb,ee] (category 1) with trastuzumab (category 1)

Node positive (one or more metastases >2 mm to one or more ipsilateral axillary lymph nodes) → Adjuvant chemotherapy[aa,bb,ee] with trastuzumab (category 1)

See Follow-Up (BINV-16)

[b] See Principles of HER2 Testing (BINV-A).
[w] Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.
[z] The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known



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PREOPERATIVE/ADJUVANT THERAPY REGIMENS [1,2,3,4]

Regimens for HER2-negative disease[5]

Preferred regimens:
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:
- Dose-dense AC (doxorubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- AC followed by weekly paclitaxel
- EC (epirubicin/cyclophosphamide)
- FEC/CEF followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) or (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)
- FAC followed by T (fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:
- AC followed by T + trastuzumab ± pertuzumab[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:
- AC followed by docetaxel + trastuzumab ± pertuzumab[9]
- Docetaxel + cyclophosphamide + trastuzumab
- FEC followed by docetaxel + trastuzumab + pertuzumab[9]
- FEC followed by paclitaxel + trastuzumab + pertuzumab[9]
- Paclitaxel + trastuzumab[10]
- Pertuzumab + trastuzumab + docetaxel followed by FEC[9]
- Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]

[1] Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.
[2] Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.
[3] CMF and radiation therapy may be given concurrently, or the CMF may be given

[6] In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥1 cm (category 1).
[7] Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for one year total duration.
[8] A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer preoperatively. Patients who have not received a pertuzumab-containing regimen can receive adjuvant pertuzumab.
[9] Trastuzumab given in combination with an anthracycline is associated with

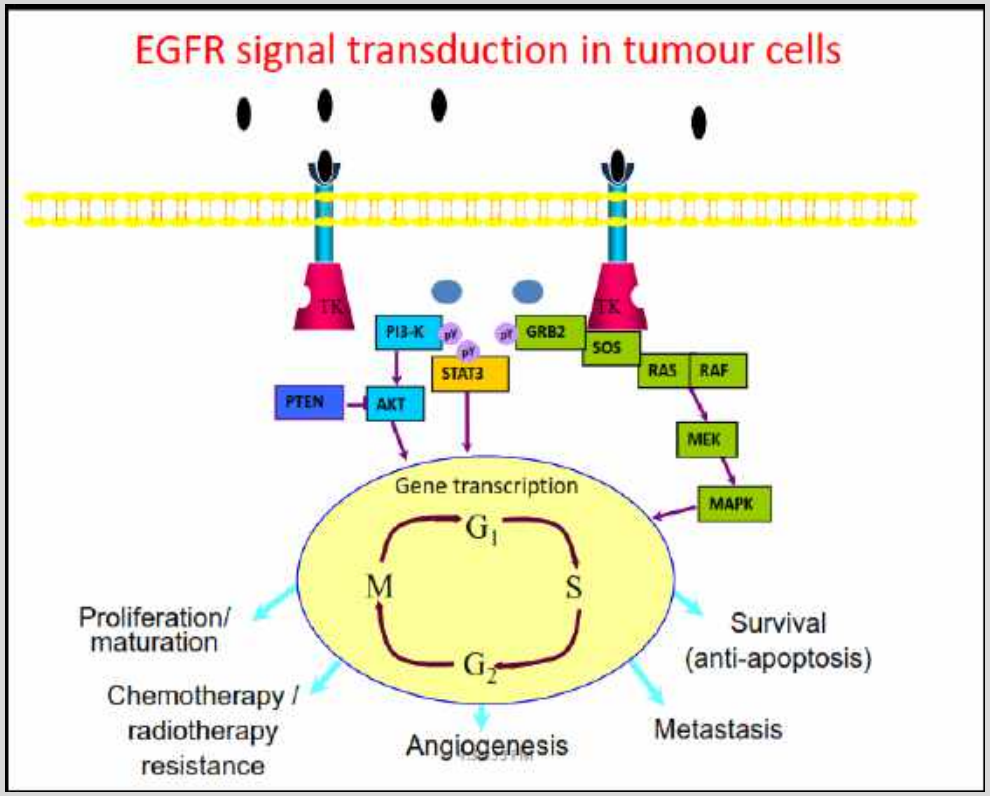
ANTI HER2 AGENTS:

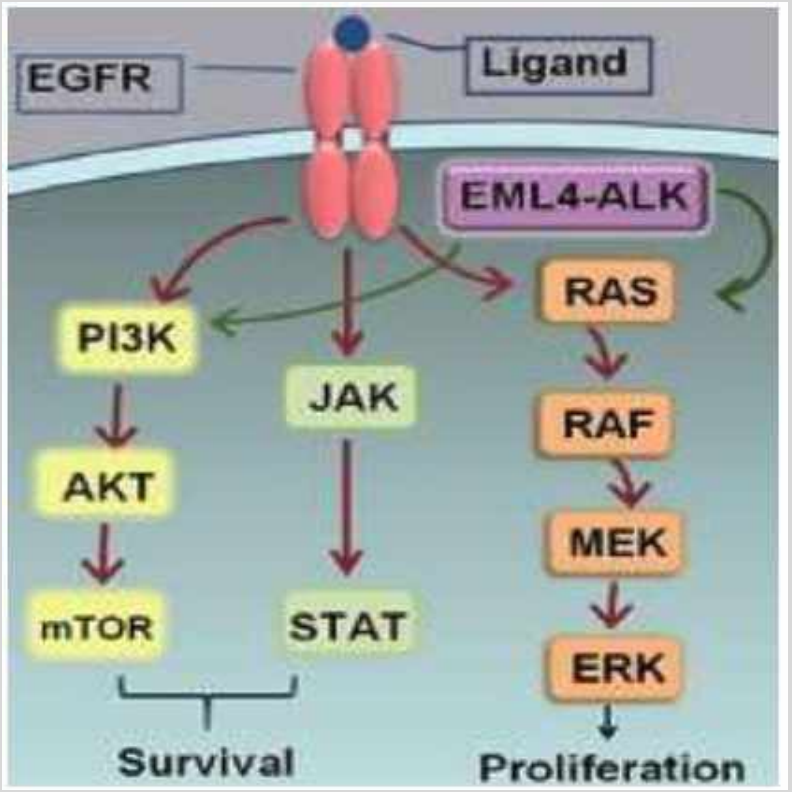
- Currently approved Anti HER2 agents are

1. Trastuzumab
2. Pertuzumab
3. T-DM1 or ado-Trastuzumab Emtansine

- Trastuzumab is the first humanized monoclonal antibody which binds with the HER2 (extracellular domain receptors IV) and reduces tumor cell proliferation and survival.
- MOA: inhibits tyrosine kinase signalling of receptor
  - Activates ADCC
  - G1 arrest by modulating CDKs
  - Induction of apoptosis

TRASTUZUMAB: Anti-Her2 extracellular domain

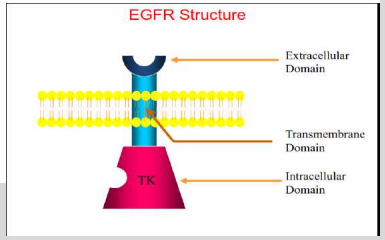




PERTUZUMAB:

- The HER2/HER3 heterodimer is considered the most potent HER dimer pair for ligand-induced tyrosine phosphorylation, and downstream signaling.

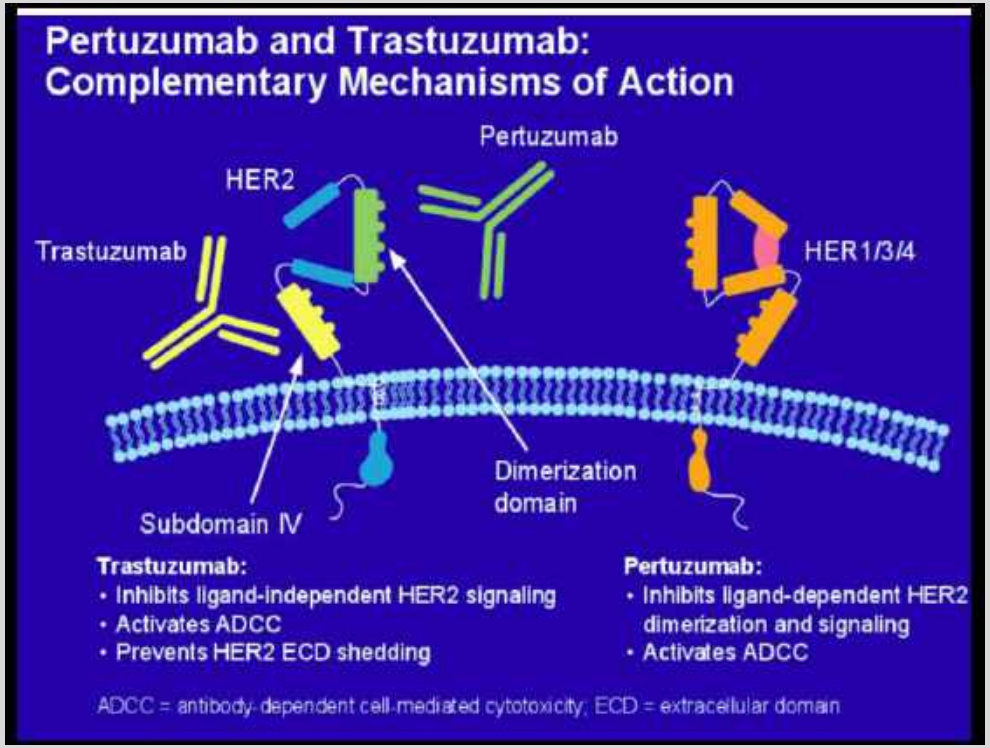
- Thus, there is a need for a potential agent, such as Pertuzumab, which can also prevent heterodimerization, resulting in more potent growth inhibition.

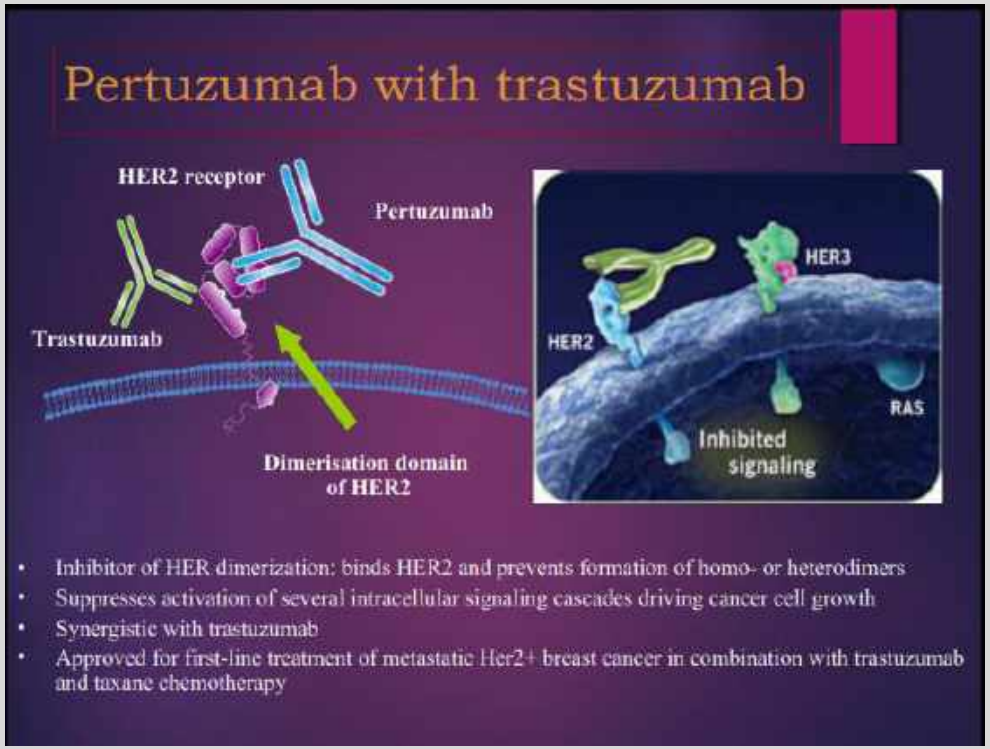


- Pertuzumab targets the extracellular dimerization domain (subdomain II) (while trastuzumab binds to domain IV.)

- of the HER2 receptor and blocks ligand-dependent heterodimerization of HER2 with other HER members (HER1, HER3, and HER4) and homodimerization with other HER2 receptors

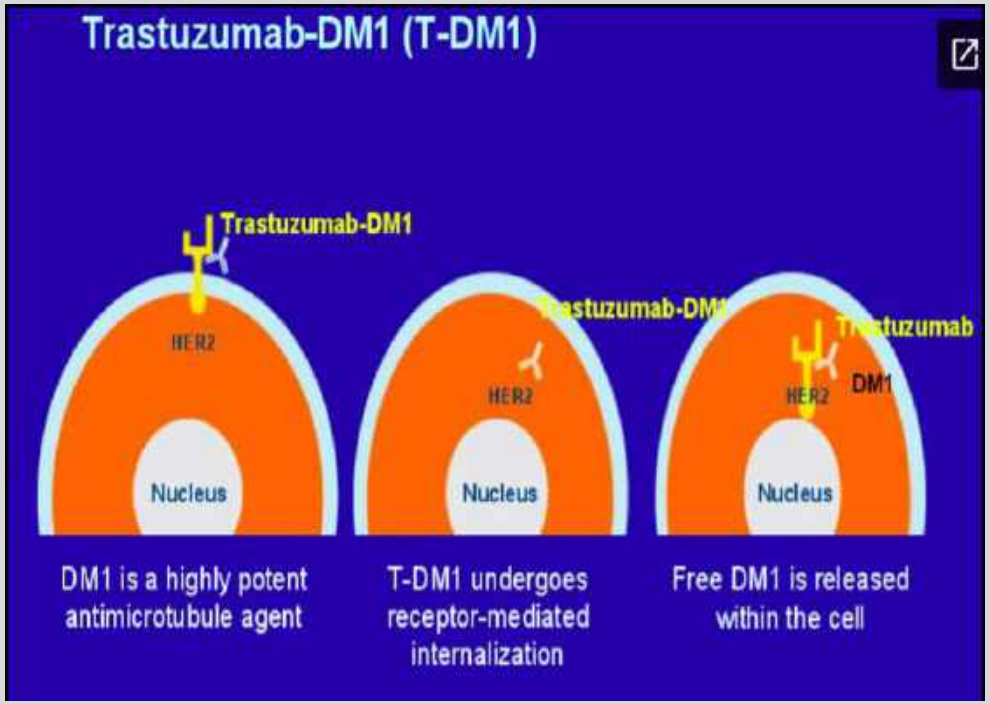
Mechanisms of action from trastuzumab and pertuzumab

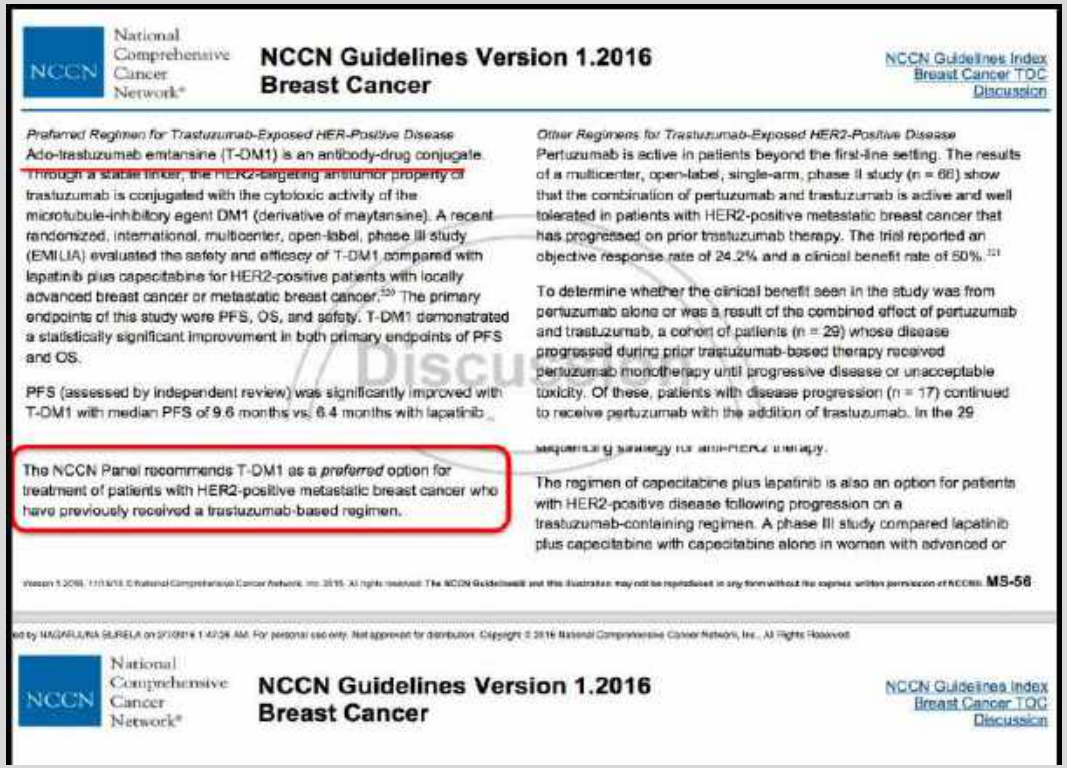




T-DM1: Ado trastuzumab Emtansine

Antibody-drug conjugate for metastasis breast cancer Her2 positive, who previously received a trastuzumab.





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Preferred Regimen for Trastuzumab-Exposed HER-Positive Disease

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate. Through a stable linker, the HER2-targeting antitumor property of trastuzumab is conjugated with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine). A recent randomized, international, multicenter, open-label, phase III study (EMILIA) evaluated the safety and efficacy of T-DM1 compared with lapatinib plus capecitabine for HER2-positive patients with locally advanced breast cancer or metastatic breast cancer.[320] The primary endpoints of this study were PFS, OS, and safety. T-DM1 demonstrated a statistically significant improvement in both primary endpoints of PFS and OS.

PFS (assessed by independent review) was significantly improved with T-DM1 with median PFS of 9.6 months vs. 6.4 months with lapatinib.

The NCCN Panel recommends T-DM1 as a *preferred* option for treatment of patients with HER2-positive metastatic breast cancer who have previously received a trastuzumab-based regimen.

Other Regimens for Trastuzumab-Exposed HER2-Positive Disease

Pertuzumab is active in patients beyond the first-line setting. The results of a multicenter, open-label, single-arm, phase II study (n = 66) show that the combination of pertuzumab and trastuzumab is active and well tolerated in patients with HER2-positive metastatic breast cancer that has progressed on prior trastuzumab therapy. The trial reported an objective response rate of 24.2% and a clinical benefit rate of 50%.[321]

To determine whether the clinical benefit seen in the study was from pertuzumab alone or was a result of the combined effect of pertuzumab and trastuzumab, a cohort of patients (n = 29) whose disease progressed during prior trastuzumab-based therapy received pertuzumab monotherapy until progressive disease or unacceptable toxicity. Of these, patients with disease progression (n = 17) continued to receive pertuzumab with the addition of trastuzumab. In the 29

The regimen of capecitabine plus lapatinib is also an option for patients with HER2-positive disease following progression on a trastuzumab-containing regimen. A phase III study compared lapatinib plus capecitabine with capecitabine alone in women with advanced or

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Patients with cardiac risk factors

- Potential risk factors associated with the development of trastuzumab-related cardiotoxicity include :

  - previous or concurrent anthracycline use,
  - age greater than 50,
  - pre-existing cardiac dysfunction,
  - high body mass index,
  - Treatment with antihypertensive agents.

- For patients with cardiac risk factors who are candidates for adjuvant HER2-directed treatment, careful monitoring of cardiac function during and after treatment is necessary.

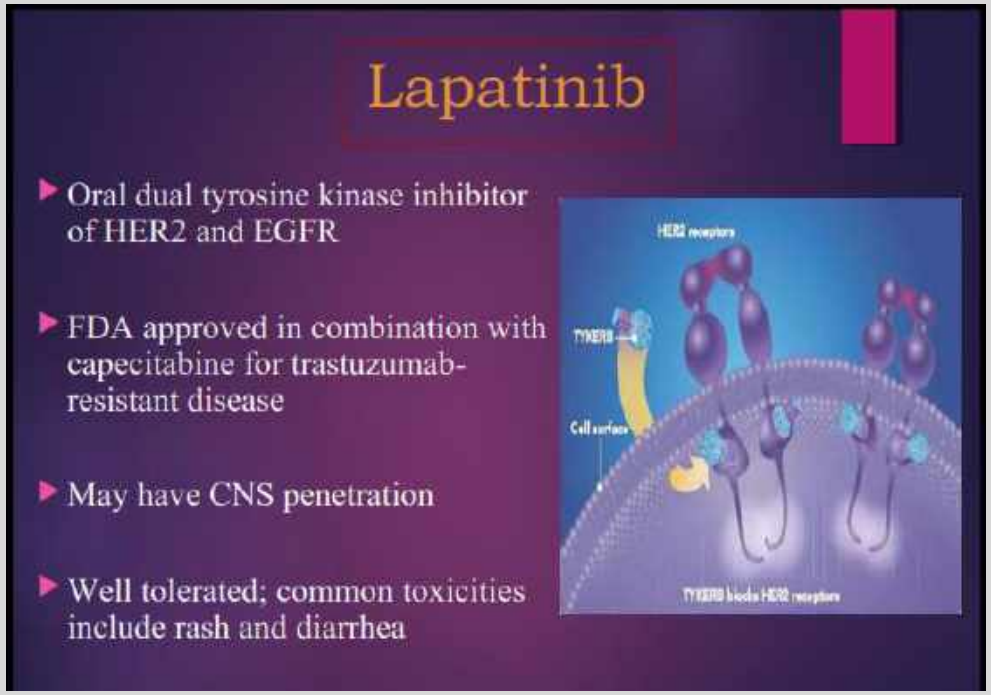
- **Presence of cardiac risk factors alone should not exclude HER2-positive patients from HER2-targeted therapy**

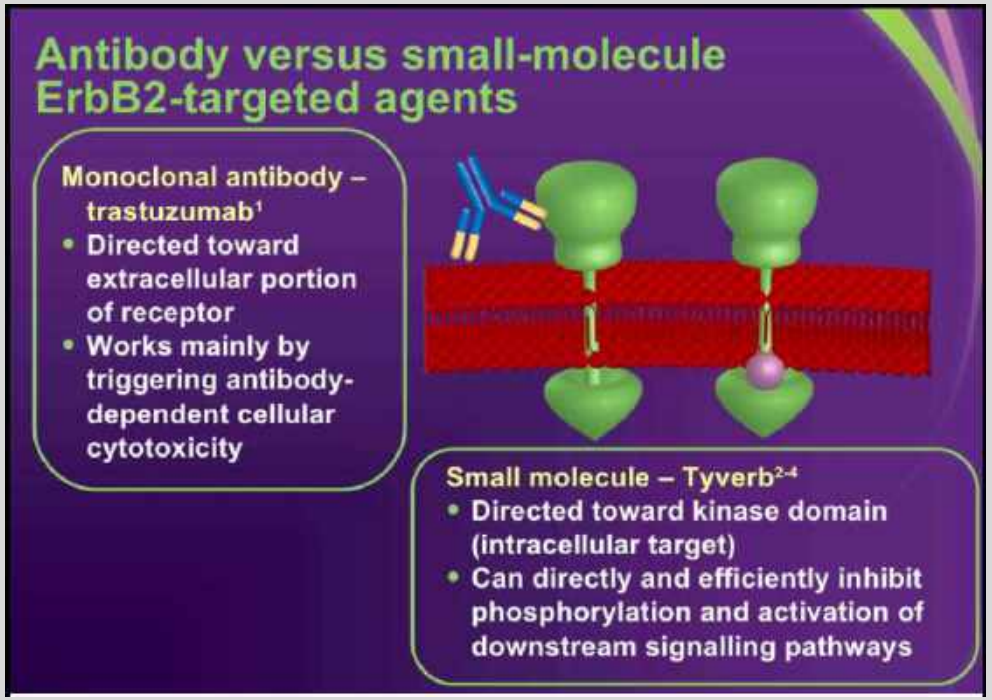
AVOIDABLE FOR TREATMENT WITH TRASTUZUMAB

Cardiotoxicity more concurrent with anthracycline agents

Other systemic therapy: lapatinib

Oral dual tyrosine kinase inhibitor; HER2 AND EGFR



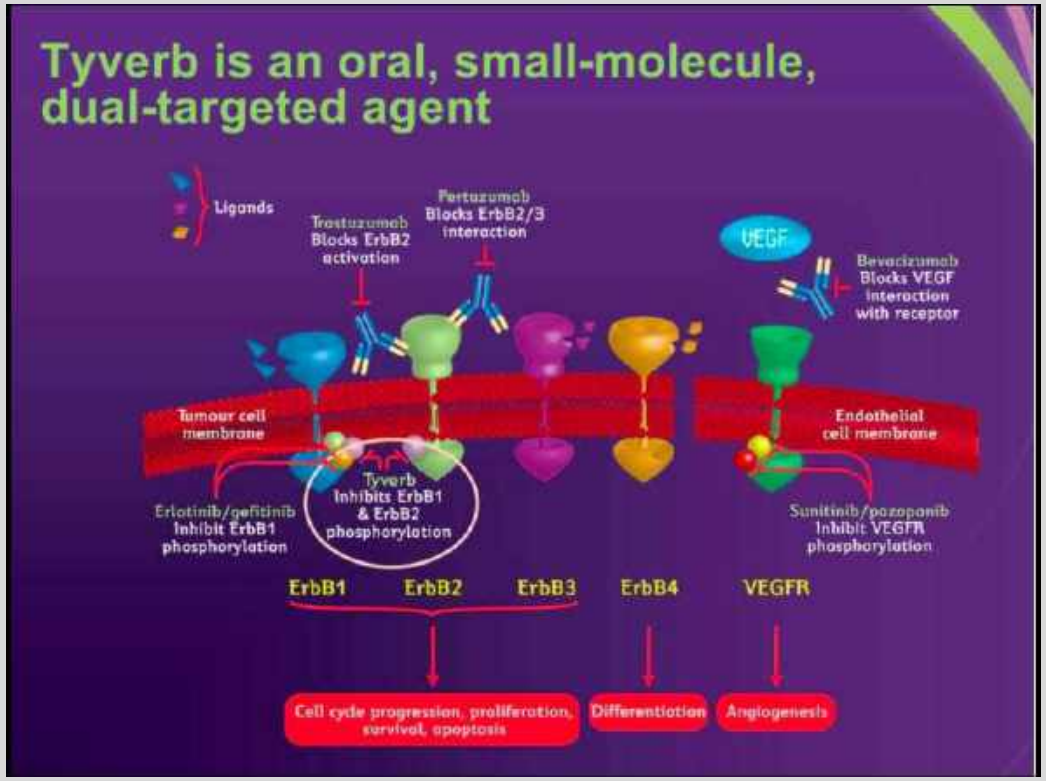


LAPATINIB (TYKERB): oral chemotherapy, small-molecule, dual target agent.

Lapatinib

- Inhibits the tyrosine kinase activity associated with two oncogenes,
  - EGFR (epidermal growth factor receptor) and
  - HER2/neu (Human EGFR type 2)

- ER+/EGFR+/HER2+ breast cancer patients and in patients who have HER2-positive advanced breast cancer that has progressed after previous treatment with other chemotherapeutic agents, such as anthracycline, taxane-derived drugs, or trastuzumab



PALBOCICLIB: CDK 4/6 inhibitors

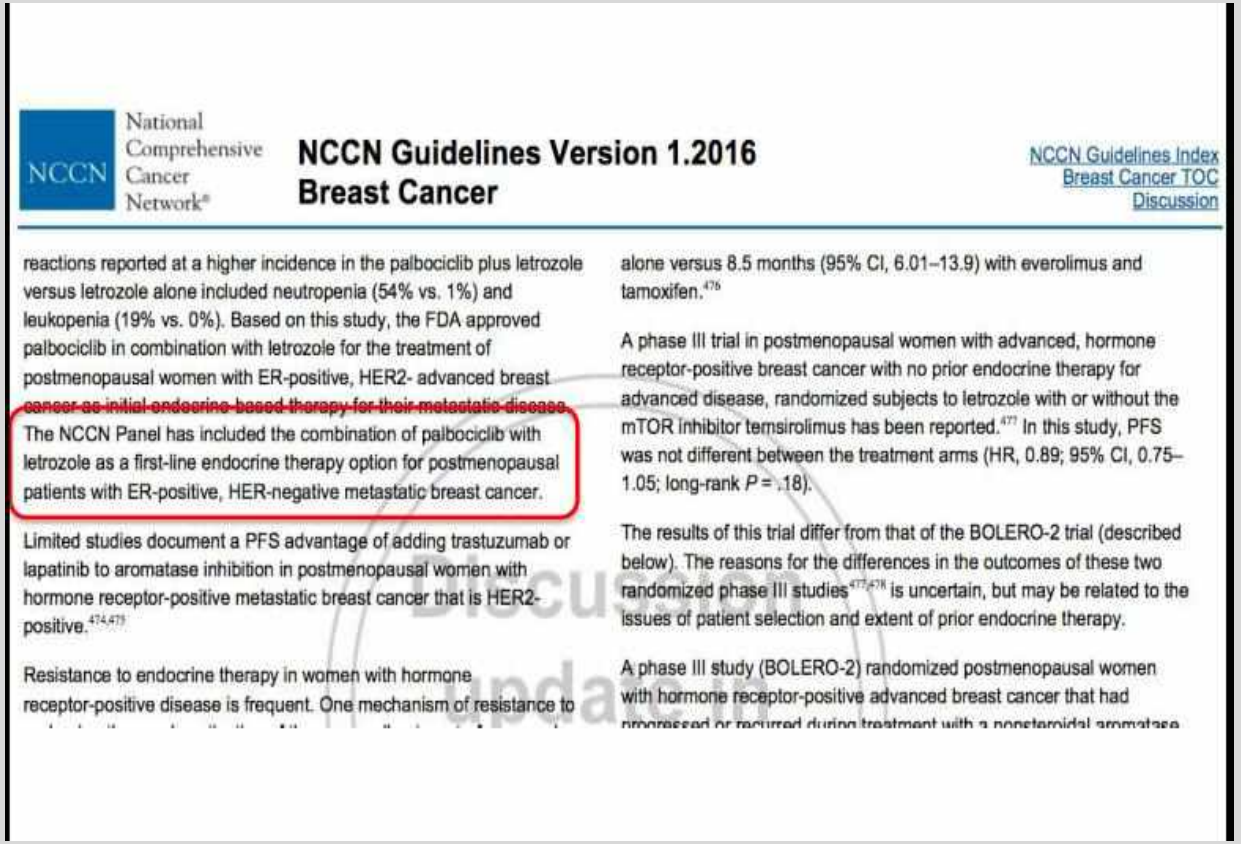
- Several cell-cycle checkpoint proteins control progression through cell division from G1/S through M-phase including cyclin-dependent kinase (CDK). Among these proteins, those targeted against the cyclin-dependent kinases, (*i.e.*, CDK inhibitors) are the most advanced therapeutics for breast cancer.

- CDK 4/6 and cyclin D regulate the G1/S transition through regulation of the retinoblastoma (RB) oncoprotein. When RB is phosphorylated, transcription factors are released allowing the cell to transition from G1 to S phase.

- Inhibitors of CDK 4/6, therefore, keep RB in the unphosphorylated state and transcription factors remain bound to it, ultimately resulting in G1 arrest.

PALBOCICLIB:

- Palbociclib is the first-in-class, oral, reversible, highly selective inhibitor of CDK4/6 that has been approved for front-line treatment of metastatic ER+/HER2- breast cancer in combination with an AI



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reactions reported at a higher incidence in the palbociclib plus letrozole versus letrozole alone included neutropenia (54% vs. 1%) and leukopenia (19% vs. 0%). Based on this study, the FDA approved palbociclib in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2- advanced breast cancer as initial endocrine-based therapy for their metastatic disease. The NCCN Panel has included the combination of palbociclib with letrozole as a first-line endocrine therapy option for postmenopausal patients with ER-positive, HER-negative metastatic breast cancer.

Limited studies document a PFS advantage of adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal women with hormone receptor-positive metastatic breast cancer that is HER2-positive.[474,475]

Resistance to endocrine therapy in women with hormone receptor-positive disease is frequent. One mechanism of resistance to

alone versus 8.5 months (95% CI, 6.01–13.9) with everolimus and tamoxifen.[476]

A phase III trial in postmenopausal women with advanced, hormone receptor-positive breast cancer with no prior endocrine therapy for advanced disease, randomized subjects to letrozole with or without the mTOR inhibitor temsirolimus has been reported.[477] In this study, PFS was not different between the treatment arms (HR, 0.89; 95% CI, 0.75–1.05; long-rank $P = .18$).

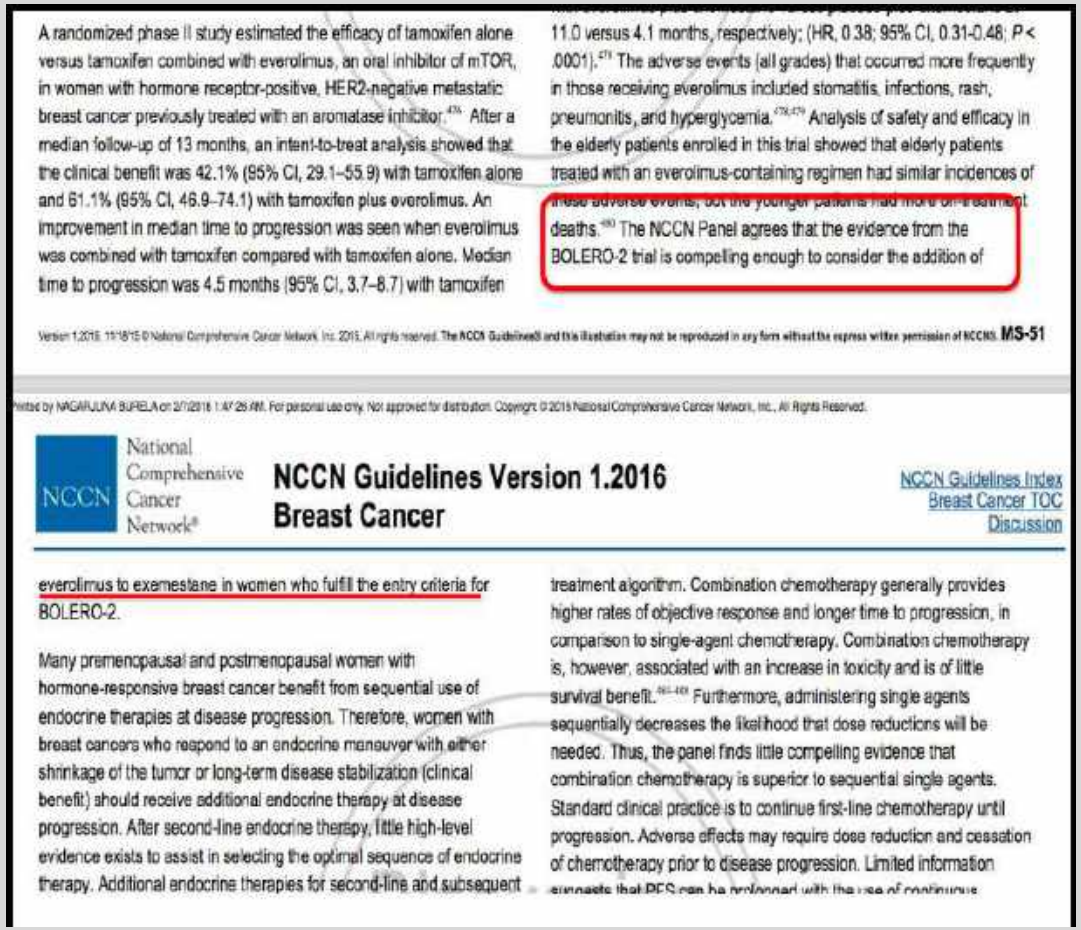
The results of this trial differ from that of the BOLERO-2 trial (described below). The reasons for the differences in the outcomes of these two randomized phase III studies[477,478] is uncertain, but may be related to the issues of patient selection and extent of prior endocrine therapy.

A phase III study (BOLERO-2) randomized postmenopausal women with hormone receptor-positive advanced breast cancer that had progressed or recurred during treatment with a nonsteroidal aromatase

EVEROLIMUS:

HR+: HORMONAL TREATMENT RESISTANCE, PI3K MUTATION

- In hormone receptor positive breast cancer cells, endocrine resistance develops as a result of aberrant signaling through the phosphatidylinositol 3-kinase (PI3K)-Akt-mTOR pathway.



A randomized phase II study estimated the efficacy of tamoxifen alone versus tamoxifen combined with everolimus, an oral inhibitor of mTOR, in women with hormone receptor-positive, HER2-negative metastatic breast cancer previously treated with an aromatase inhibitor.[476] After a median follow-up of 13 months, an intent-to-treat analysis showed that the clinical benefit was 42.1% (95% CI, 29.1–55.9) with tamoxifen alone and 61.1% (95% CI, 46.9–74.1) with tamoxifen plus everolimus. An improvement in median time to progression was seen when everolimus was combined with tamoxifen compared with tamoxifen alone. Median time to progression was 4.5 months (95% CI, 3.7–8.7) with tamoxifen

11.0 versus 4.1 months, respectively; (HR, 0.38; 95% CI, 0.31-0.48; P < .0001).[479] The adverse events (all grades) that occurred more frequently in those receiving everolimus included stomatitis, infections, rash, pneumonitis, and hyperglycemia.[478,479] Analysis of safety and efficacy in the elderly patients enrolled in this trial showed that elderly patients treated with an everolimus-containing regimen had similar incidences of

deaths.[480] The NCCN Panel agrees that the evidence from the BOLERO-2 trial is compelling enough to consider the addition of

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everolimus to exemestane in women who fulfill the entry criteria for BOLERO-2.

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at disease progression. Therefore, women with breast cancers who respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at disease progression. After second-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy. Additional endocrine therapies for second-line and subsequent

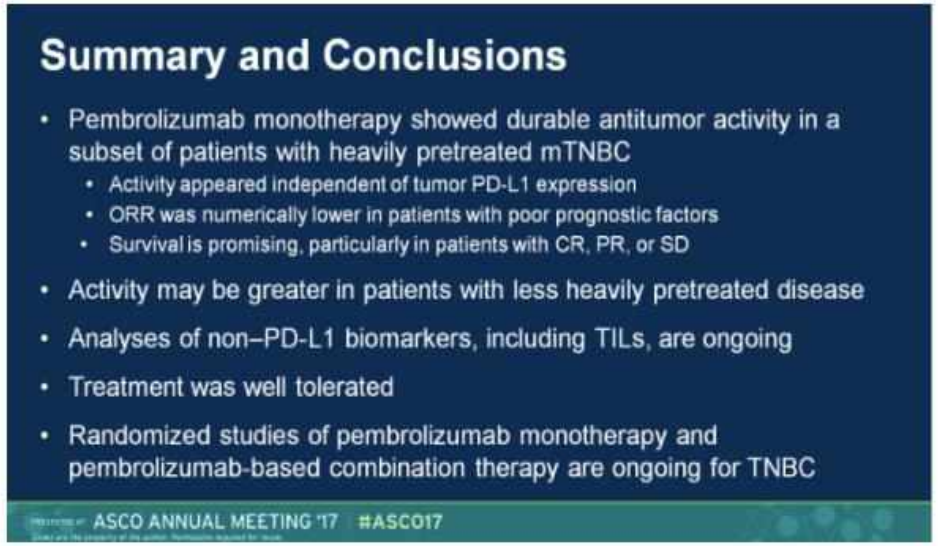
treatment algorithm. Combination chemotherapy generally provides higher rates of objective response and longer time to progression, in comparison to single-agent chemotherapy. Combination chemotherapy is, however, associated with an increase in toxicity and is of little survival benefit.[481-483] Furthermore, administering single agents sequentially decreases the likelihood that dose reductions will be needed. Thus, the panel finds little compelling evidence that combination chemotherapy is superior to sequential single agents. Standard clinical practice is to continue first-line chemotherapy until progression. Adverse effects may require dose reduction and cessation of chemotherapy prior to disease progression. Limited information

PEMBROLIZUMAB: IMMUNOTHERAPY (PD-L1)

Triple negative breast cancer

- How about immunotherapy?
- Pembrolizumab (Keytruda) is active in some cancers such as melanoma or lung cancer

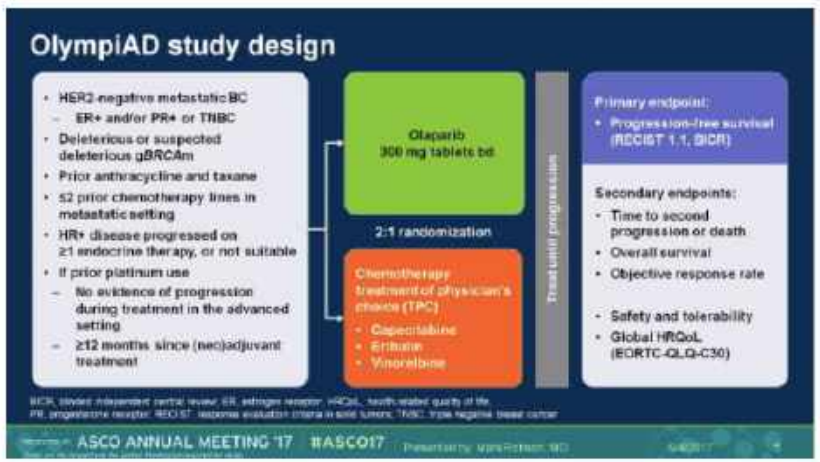
Immunotherapy has promise in metastatic breast cancer



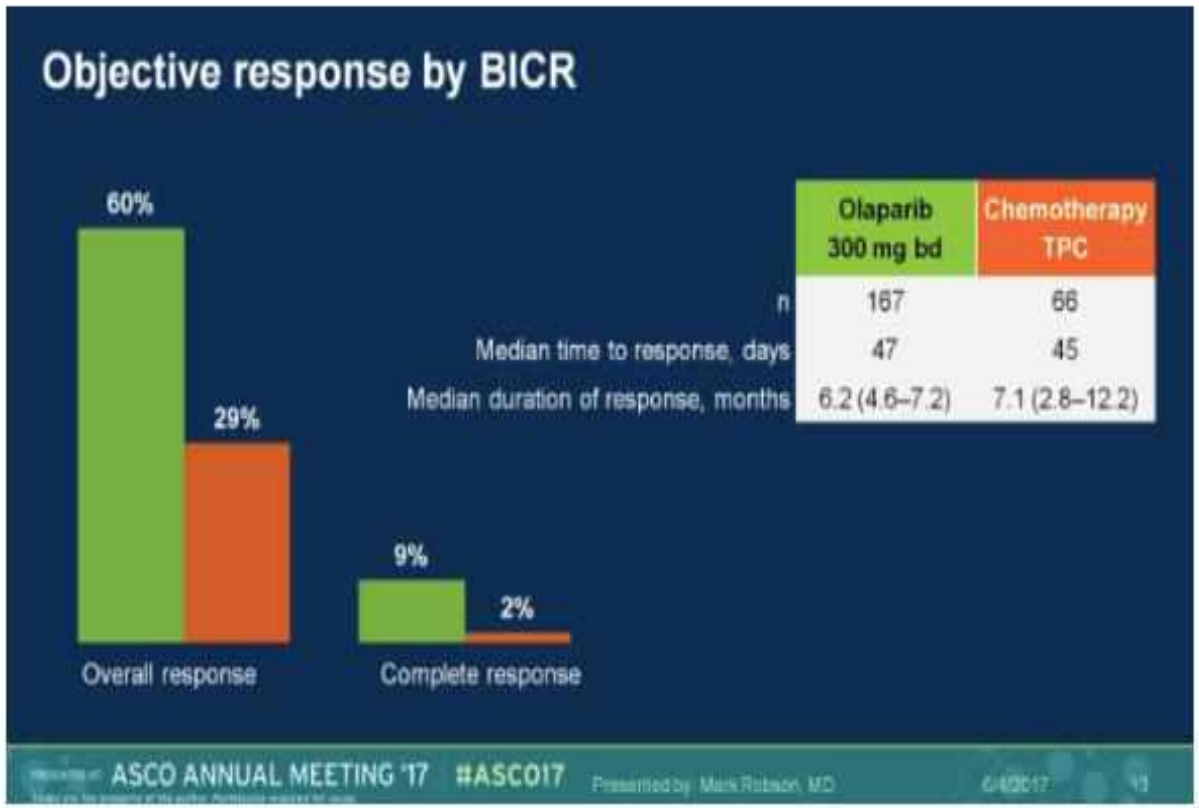
BRCA mutation carriers with metastatic breast cancer

: OLAPARIB, a PARP inhibitor

BRCA mutation carriers with metastatic breast cancer



- We have an active new drug: Olaparib, a PARP inhibitor



ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib	Category 1	Preferred
			Talazoparib	Category 1	Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[d]	Category 1	Preferred second-line therapy
HR-negative/ HER2-negative[c]	PD-L1 expression • Threshold for positivity: ≥1% on tumor-infiltrating immune cells	IHC	Atezolizumab + albumin-bound paclitaxel	Category 2A	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[e]	Category 2A	Useful in certain circumstances[e]
			Entrectinib[e]	Category 2A	Useful in certain circumstances[e]
Any	MSI-H/dMMR	IHC, PCR (tissue block)	Pembrolizumab[f]	Category 2A	Useful in certain circumstances[f]

[a] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline *BRCA1* or *BRCA2* mutation.

[b] For HR-positive/HER2-negative breast cancer, assess for *PIK3CA* mutations with tumor or liquid biopsy if HR-positive/HER2-negative and if considering therapy with to identify candidates for alpelisib plus fulvestrant. *PIK3CA* mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.

[c] For TNBC, assess PD-L1 expression biomarker status on tumor-infiltrating immune cells to identify candidates for atezolizumab plus albumin-bound paclitaxel.

[d] The safety of alpelisib in patients with Type 1 or uncontrolled Type 2 diabetes has not been established.

[e] Larotrectinib and entrectinib are indicated for the treatment of solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment.

[f] Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

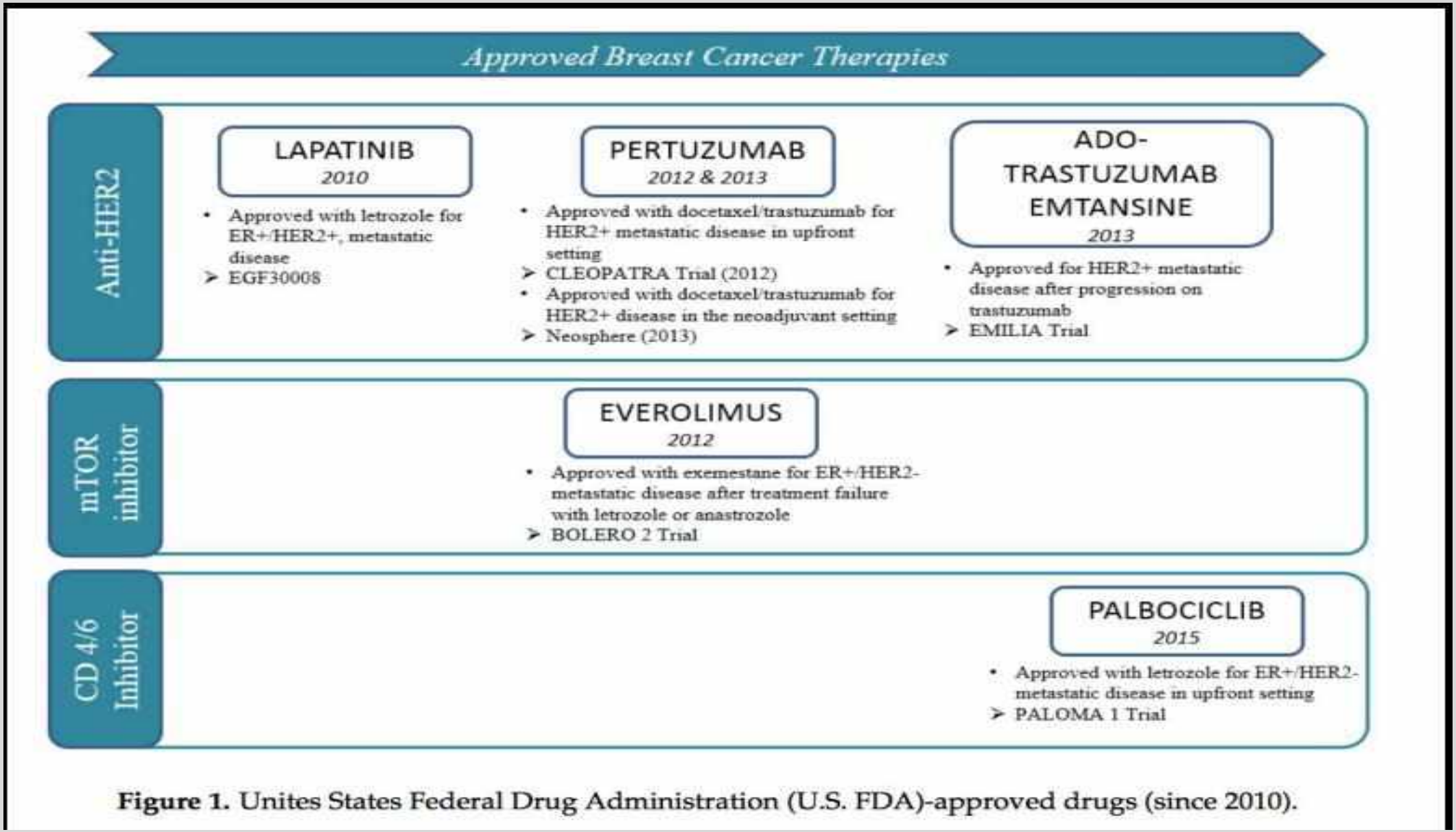
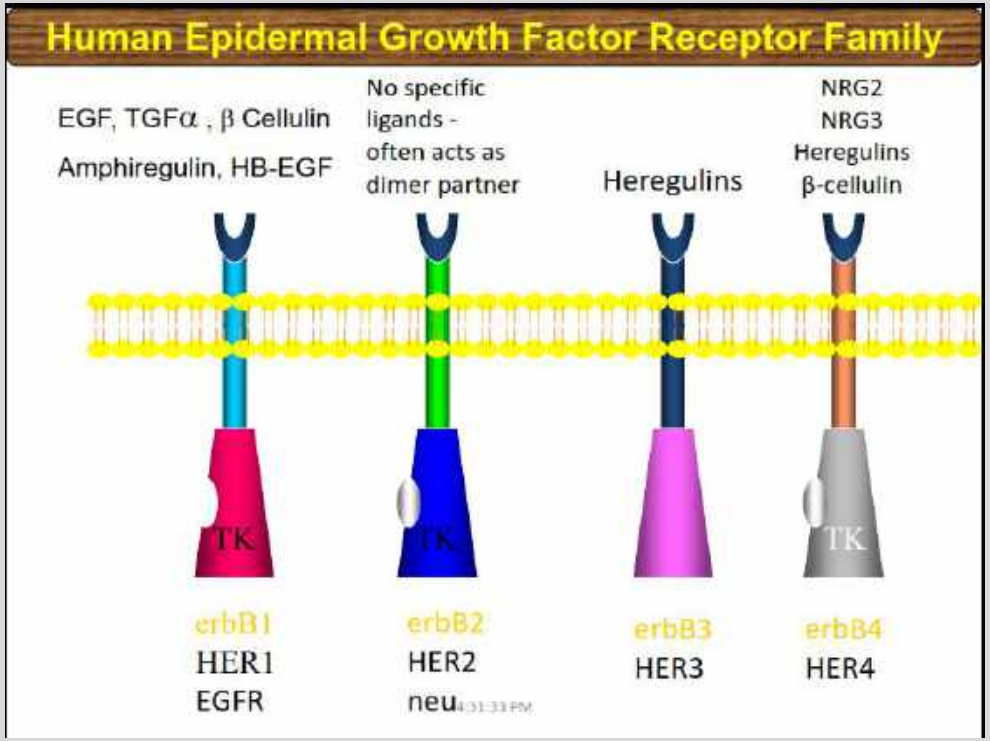


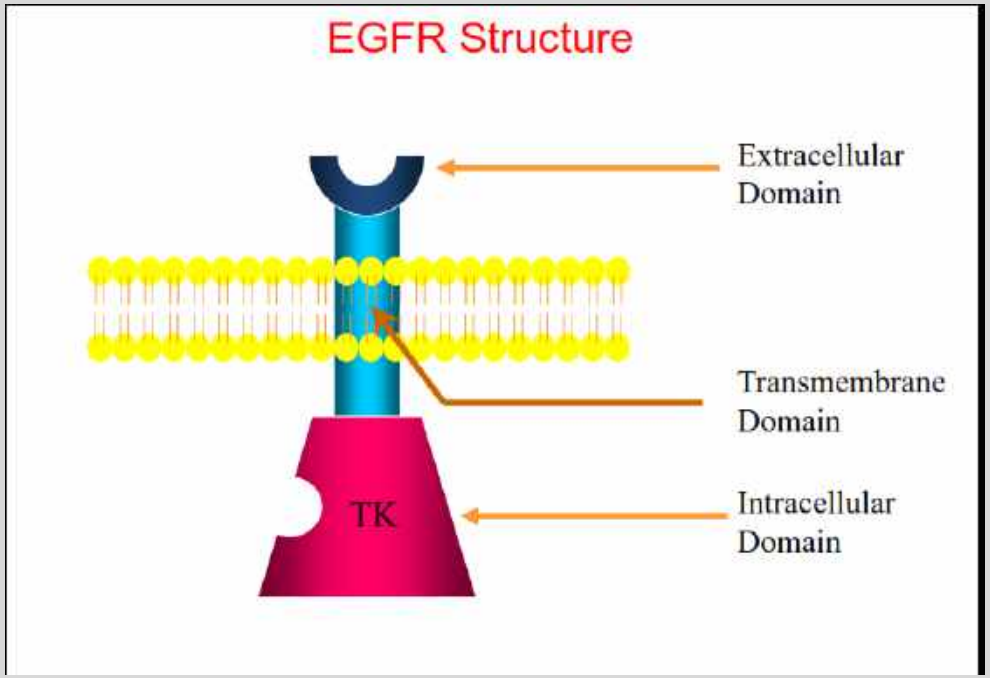
Figure 1. Unites States Federal Drug Administration (U.S. FDA)-approved drugs (since 2010).

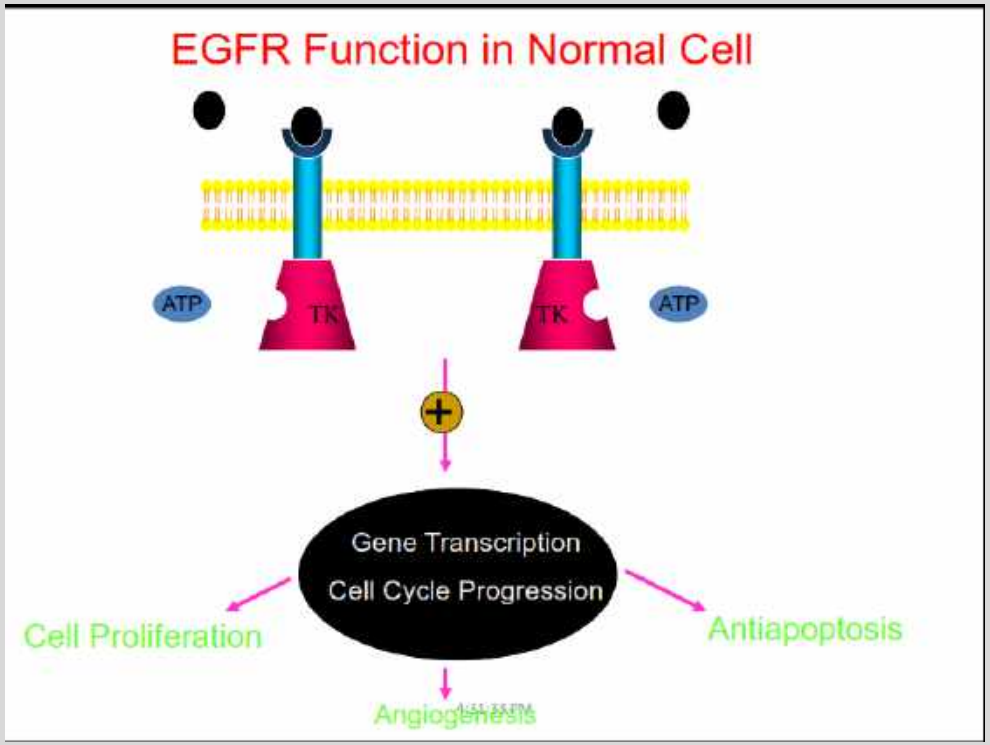
BREAST CANCER

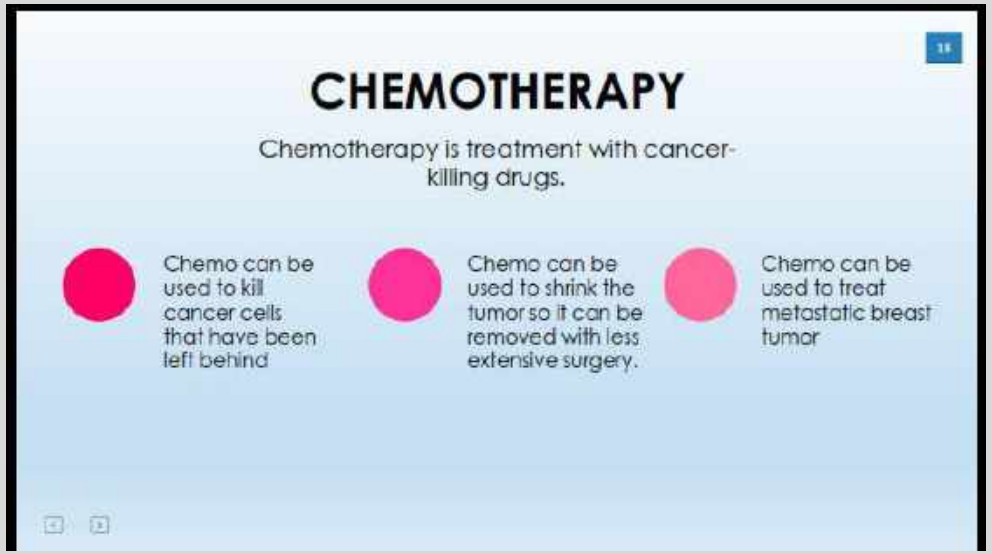
SUKSME

Thank you !!!


Human Epidermal Growth Factor Receptor Family
EGF, TGFα , β Cellulin
Amphiregulin, HB-EGF
No specific ligands - often acts as dimer partner
Heregulins
NRG2
NRG3
Heregulins
β-cellulin
TK
TK
TK
TK
erbB1
HER1
EGFR
erbB2
HER2
neu
erbB3
HER3
erbB4
HER4


EGFR Structure
Extracellular Domain
Transmembrane Domain
Intracellular Domain
TK


EGFR Function in Normal Cell
ATP
TK
TK
ATP
Gene Transcription
Cell Cycle Progression
Cell Proliferation
Antiapoptosis
Angiogenesis


CHEMOTHERAPY
Chemotherapy is treatment with cancer-killing drugs.
Chemo can be used to kill cancer cells that have been left behind
Chemo can be used to shrink the tumor so it can be removed with less extensive surgery.
Chemo can be used to treat metastatic breast tumor

WHEN IS CHEMOTHERAPY USED?

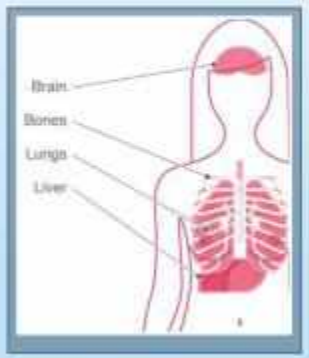
After Surgery

Adjuvant Chemotherapy

Before Surgery

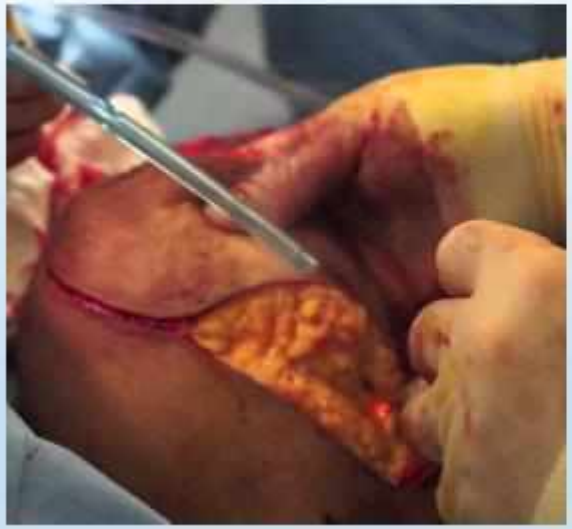
Neoadjuvant Chemotherapy

For advanced stage



Palliative Chemotherapy

ADJUVANT CHEMOTHERAPY



Used to try to kill any cancer cells that might have been left behind or have spread but can't be seen.

NEOADJUVANT CHEMOTHERAPY

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used to try to shrink the tumor so that it can be removed with less extensive surgery