Aksilla Pozitif Meme Kanserinde Sistemik Adjuvan Tedaviler

Handan Onur

Ankara, 29 Mart 2014

Adjuvant Sistemik Tedavi

Primer cerrahi tedavi sonrasında belirlenebilir tümör lezyonu olmayan, ancak olası mikrometastazlar nedeni ile nüks riski bulunan hastalarda küratif amaçla uygulanan tedavidir.

Erken Evre Meme Kanserinde Adjuvant Sistemik Tedavi

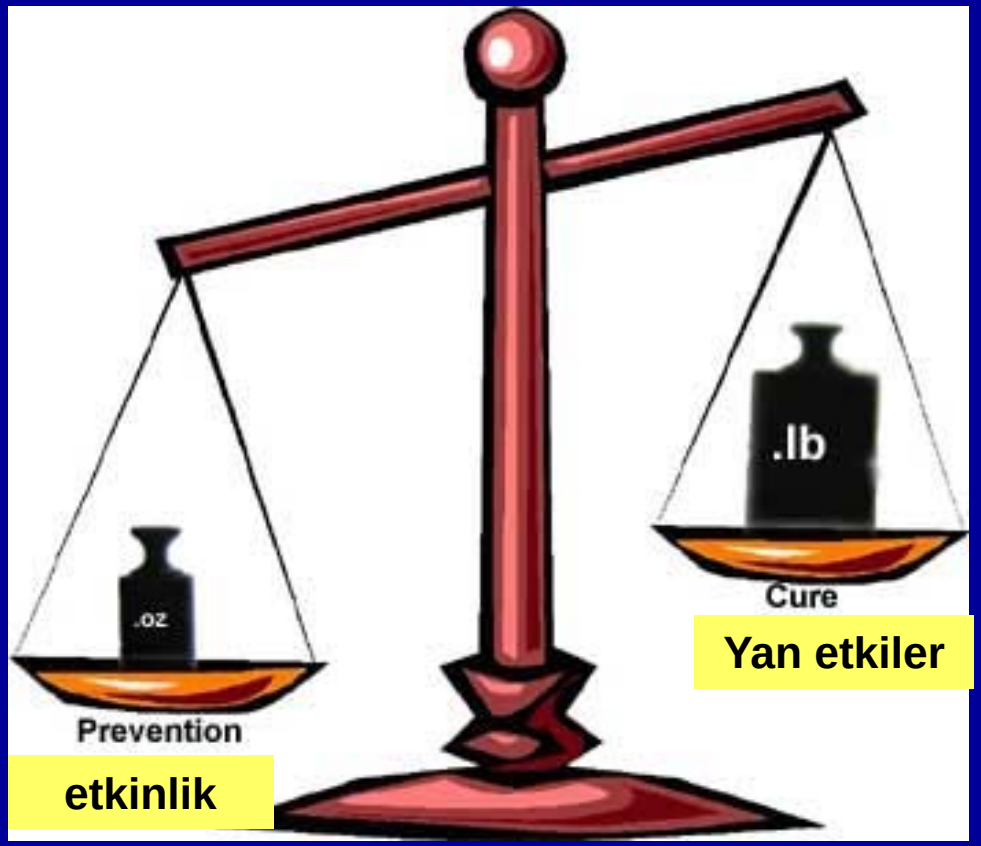
- **Kemoterapi**
- **Hormonoterapi**
- **Hedefe Yönelik Tedaviler**

(Trastuzumab)

Meme Kanserinde Adjuvant Tedavi Seçiminde:

- Tümörün özellikleri
- Hastalıksız sağkalım süresi
- Total Sağkalım süresi
- Yan etkiler
- Hastanın diğer hastalıkları
- Tedavinin maliyeti

önemlidir.



Operabl Meme Kanserinde Prognostik Faktörler

1. Yaş (premenopozal vs postmenopozal)
2. Aksiller LN tutulumu -/+, sayısı,
3. Tümör çapı,
4. Lenfatik ve vasküler invazyon,
5. Tümör greydi (Grade I-III),
6. Hormon reseptör durumu (ER, PR),
7. Onkogenler, (Her 2/neu yada c-erbB2),

Operabl Meme Kanserinde Prognostik Faktörler:

- **Aksilladaki lenf nodu metastazı durumu**, en önemli prognostik faktördür. Metastatik lenf nodu sayısı arttıkça, prognoz kötüleşir

  5 yıllık sağkalım oranı:

LN met yok	% 78-82
1-3 LN met (+)	% 47-50
≥ 4 LN met (+)	% 21-31

- **Evre**, çok önemli bir prognostik faktördür. 5 yıllık sağkalım oranı:

Evre IV'de	% 5-10
Evre IIIB de	% 20-35
evre IIIA'da	% 40-55

Operabl Meme Kanserinde Prognostik Faktörler:

- **Östrojen ve progesteron reseptörleri (ER,PR)**
  postmenopozal kadınlarda % 60-80 (+) premenopozal hastalarda % 30-60 (+)

  Hormon reseptörlerinin pozitif olması iyi prognostik kriterdir.

- **c- erb B2 ekspresyonu ve Katepsin- D düzeyleri kötü prognozu ifade etmektedir.**

- **DNA flow sitometride anöplodi, S- faz fraksiyonları aksilla negatiflerde, *kötü prognoz* habercisi kabul edilebilir.**

Meme kanserinin Moleküler Sınıflandırması

- **Luminal A:** ER (+), PR (+), c-Erb B2 (-)
- **Luminal B:** ER (±), PR (±), c-Erb B2 (±)
- **HER-2 (+):** ER (-), PR (-), c-Erb B2 (+)
- **Triple (üçlü) Negatif:**
  - **Normal-like:** ER (-), PR (-), c-Erb B2 (-), CK5/6 (-), EGFR (-)
  - **Basal-like:** ER (-), PR (-), c-Erb B2 (-), CK5/6 (+), EGFR (+)

St Gallen 2009
Sistemik Adjuvan Tedavi Seçimi

- Tümör özellikleri
- Hastaya ait faktörler
  - Menopozal durum
  - Yaş
  - Kalp hastalığı
  - Tromboemboli öyküsü
  - Eşlik eden hastalıklar
- Hasta tercihi

Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013

A Goldhirsch, E. P. Winer, A. S. Coates, R. D. Gelber, M. Piccart-Gebhart, B. Thürlimann, H.-J. Senn, **Panel members**

Ann Oncol 2013; 24 (9): 2206-2223.

Son Araştırmalara ait Bulgular

- Hedefe yönelik tedaviler
- EBCTCG meta-analiz mesajları: Ktden yararlanmayan grup?
- Mutasyonal analizler
- Bireysel tedavi
- İntrinsik subtipler (ER, PgR, Ki-67, HER-2)
- Yaşam tarzı ile ilgili durumlar
- Hormonal etkiler
- Herediter meme kanseri
- Obezite ve yağ
- Metastaz, mikroçevre, kemik ve bifosfonatlar
- Metronomik kemoterapi

Son Araştırmalara ait Bulgular

- **Risk Değerlendirmesi ve Tahmin**
- **İmmunite ve Aşılar:** ***tümörle ilişkili lenfositler NAKT de A/T KTlere yanıtın bağımsız prediktoru. N+ ER- HER-2 – MKde artmış lenfosit infiltrasyonu çok olumlu prognostik***
- **Primer tümör cerrahisi**
- **Aksilla cerrahisi**
- **Radyoterapi Hipofraksiyone RT etkili**
- **Adjuvan Kemoterapi**
- **Neoadjuvan Kemoterapi**
- **Anti-HER-2 Tedavi**
- **Endokrin Tedavi**
- **Genç Kadınlar**
- **İzlem**

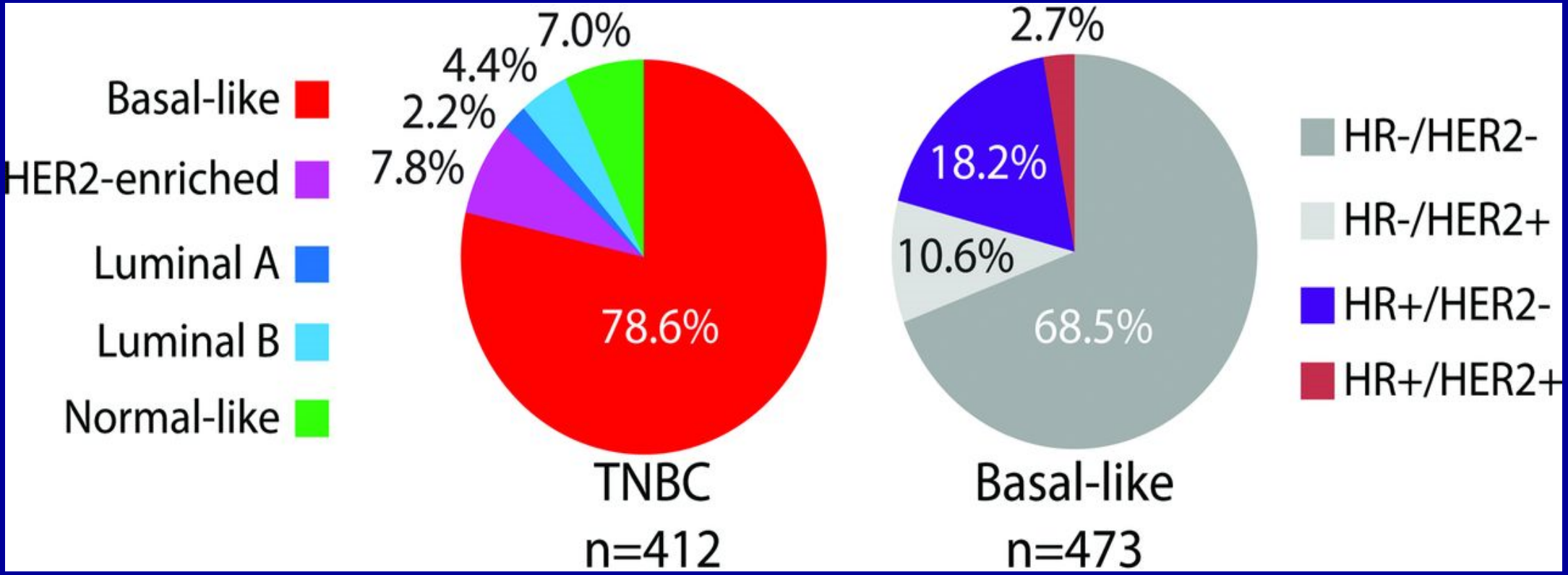
Surrogate definitions of intrinsic subtypes of breast cancer. St. Gallen 2013

Intrinsic subtype	Clinico-pathologic surrogate definition	Notes
Luminal A	**Luminal A-like** *all of:* ER and PgR positive HER2 negative Ki-67 'low'[a] Recurrence risk 'low' based on multi-gene-expression assay (if available)[b]	The cut-point between 'high' and 'low' values for Ki-67 varies between laboratories.[a] A level of <14% best correlated with the gene-expression definition of Luminal A based on the results in a single reference laboratory [23]. Similarly, the added value of PgR in distinguishing between 'Luminal A-like' and 'Luminal B-like' subtypes derives from the work of Prat et al. which used a PgR cut-point of ≥20% to best correspond to Luminal A subtype [24]. Quality assurance programmes are essential for laboratories reporting these results.
Luminal B	**Luminal B-like (HER2 negative)** ER positive HER2 negative and *at least one of:* Ki-67 'high' PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available)[b]	'Luminal B-like' disease comprises those luminal cases which lack the characteristics noted above for 'Luminal A-like' disease. Thus, either a high Ki-67[a] value or a low PgR value (see above) may be used to distinguish between 'Luminal A-like' and 'Luminal B-like (HER2 negative)'.
	Luminal B-like (HER2 positive) ER positive HER2 over-expressed or amplified Any Ki-67 Any PgR	
Erb-B2 overexpression	**HER2 positive (non-luminal)** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**Triple negative (ductal)** ER and PgR absent HER2 negative	There is an 80% overlap between 'triple-negative' and intrinsic 'basal-like' subtype. Some cases with low-positive ER staining may cluster with non-luminal subtypes on gene-expression analysis. 'Triple negative' also includes some special histological types such as adenoid cystic carcinoma.

A. Goldhirsch et al. Ann Oncol 2013; 24 (9): 2206-2223

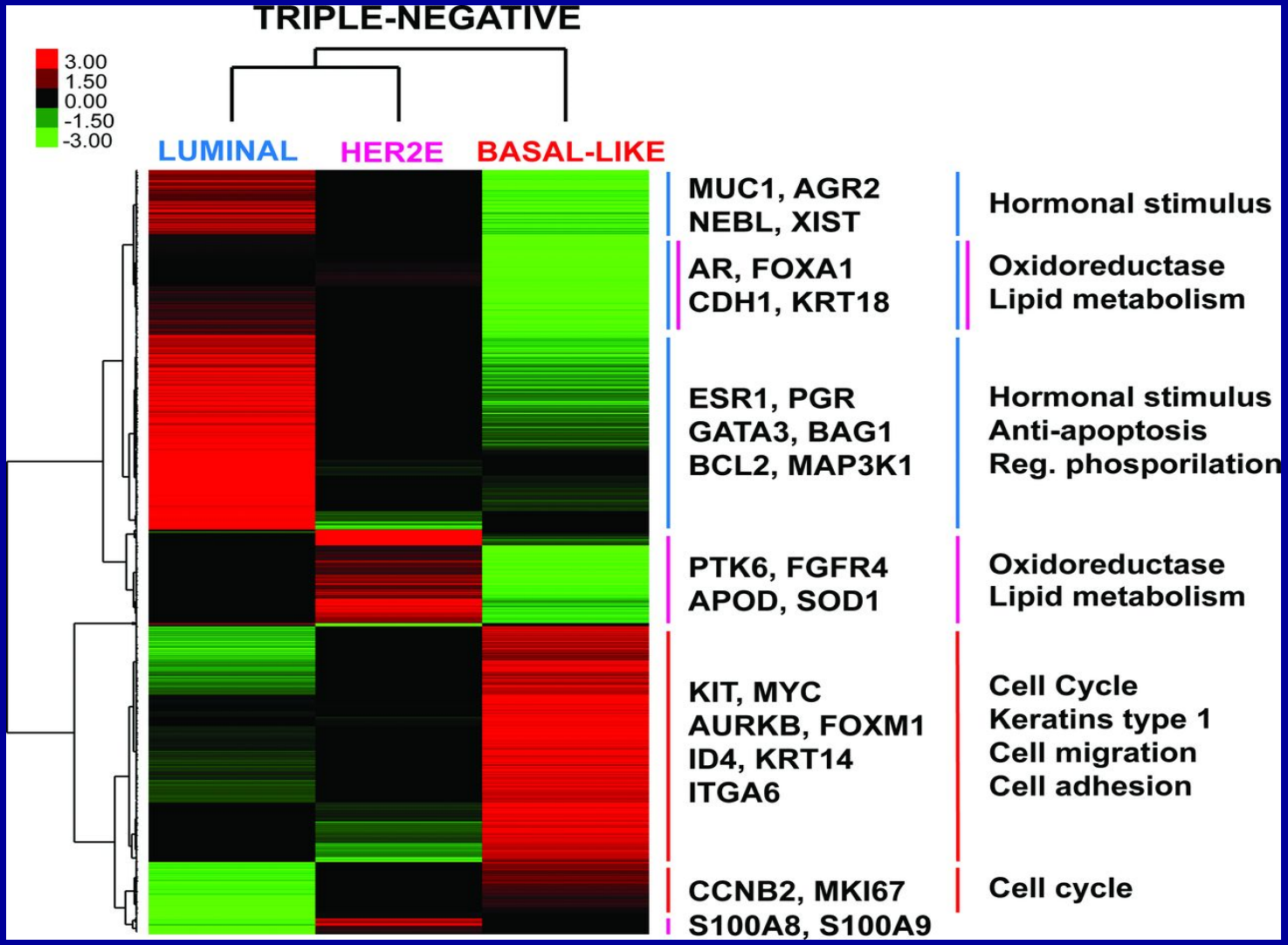
Distribution of the intrinsic molecular and pathology-based subtypes within triple-negative and basal-like tumors.

Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.



Prat A et al. The Oncologist 2013;18:123-133

Subtype-specific gene expression profiles within triple-negative disease.



Prat A et al. The Oncologist 2013;18:123-133

Hastalık tekrar skoru (RS) (21 gen paneli)

Proliferasyon
Ki67,
STK15,
Survivin,
CCNB1 (cyclin B1),
MYBL2

İnvazyon
MMP11 (stromolysin 3),
CTSL2 (cathepsin L2)

HER2
GRB7,
HER2

GSTM1

CD68

BAG1

Östrojen
ER
PGR
BCL2
SCUBE2

Referans
ACTB (*b*-actin)
GAPDH
RPLPO
GUS
TFRC

Paik et al. A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-negative Breast Cancer. n engl j med. 351;27. 2004.

RS Genes	Mutiplication Factor	RS Genes	Mutiplication Factor
HER2		Invasion	
Grb7	+0.47	Stromelysin 3	+0.1
HER2		Cathepsin L2	
Estrogen		CD68	+0.05
ER	−0.34	GSTM1	−0.08
PR		BAG-1	−0.07
Bcl-2		Reference Genes	
Scube2		β-actin	1
Proliferation		GAPDH	
Ki-67	+1.04	RPLPO	
STK15		GUS	
Survivin		TFRC	
Cyclin B1			
MYBL2			

Recurrence Score Risk Stratification	
Category	RS (0-100)
Low risk	< 18
Intermediate risk	≥ 18 and < 31
High risk	≥ 31

Sparano JA, TailorX: Trail assigning individualized options for treatment. Clinical Breast Cancer , 2006

Systemic treatment recommendations: St. Gallen 2013

'Subtip'	Tedavi
'Luminal A-like'	Endokrin tedavi, sıklıkla tek başına
'Luminal B-like (HER2 negative)'	Endokrin Tedavi tüm hastalar için, KT çoğu hasta için
'Luminal B-like (HER2 positive)'	KT + anti-HER2 + ET

Bazı hastalarda KT gerekebilir.
KT için relatif endikasyonlar:
✓Yüksek 21-gen RS (i.e. >25),
✓ 70-gen analizinde yüksek risk durumu;
✓ grade 3 hastalık;
✓≥4 Lenf Bezi tutulumu
(bazılarına göre 1 LB yeterli)
✓ <35 yaş olmak (tartışmalı)

A. Goldhirsch et al. Ann Oncol 2013; 24 (9): 2206-2223

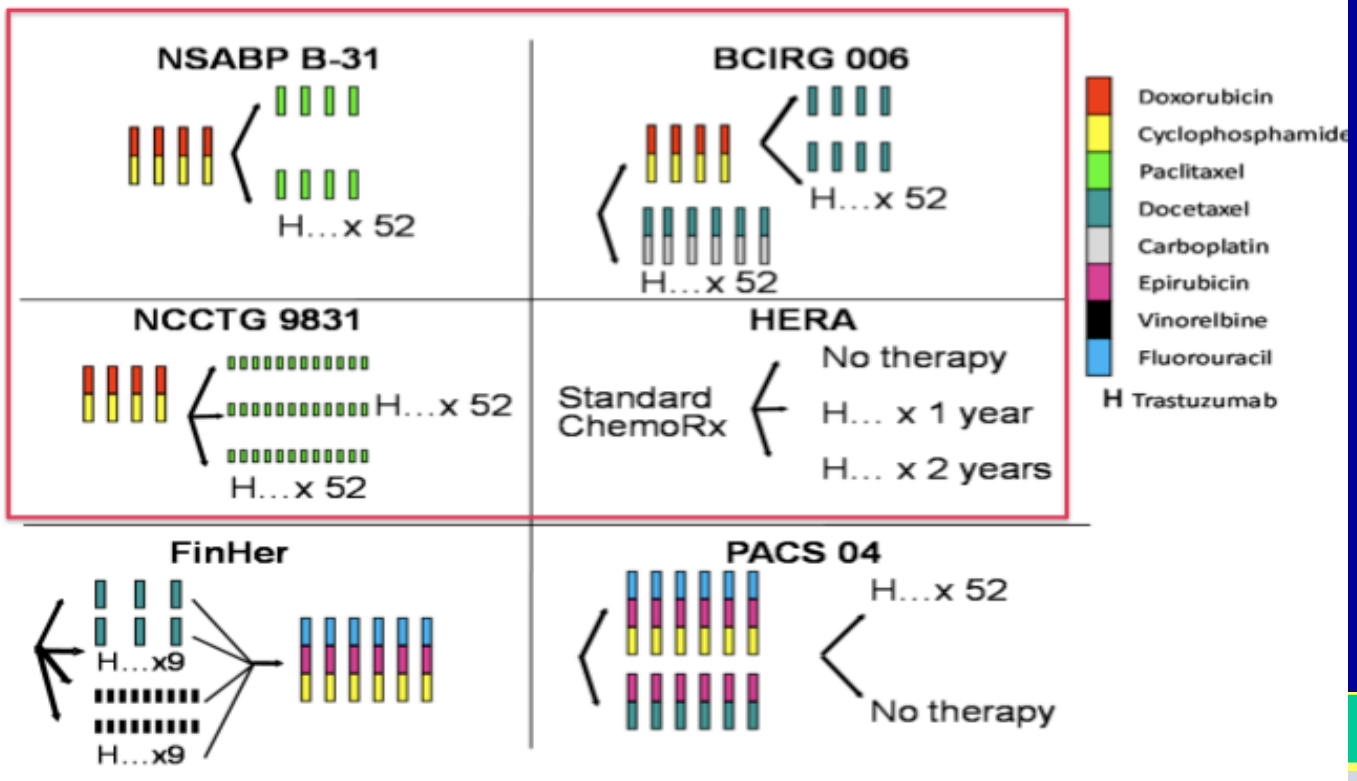
Systemic treatment recommendations: St. Gallen 2013

'Subtype'	Type of therapy	Notes on therapy
'HER2 positive (non-luminal)'	KT + anti-HER2	Threshold for use of anti-HER2 therapy was defined as pT1b or larger tumour or node-positivity.
'Triple negative (ductal)'	Kemoterapi	
'Special histological types'		
A. Endocrine responsive	Endokrin Tedavi	
B. Endocrine non-responsive	Kemoterapi	Adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

Special histological types: endocrine responsive (cribriform, tubular and mucinous); endocrine non-responsive (apocrine, medullary, adenoid cystic and metaplastic).

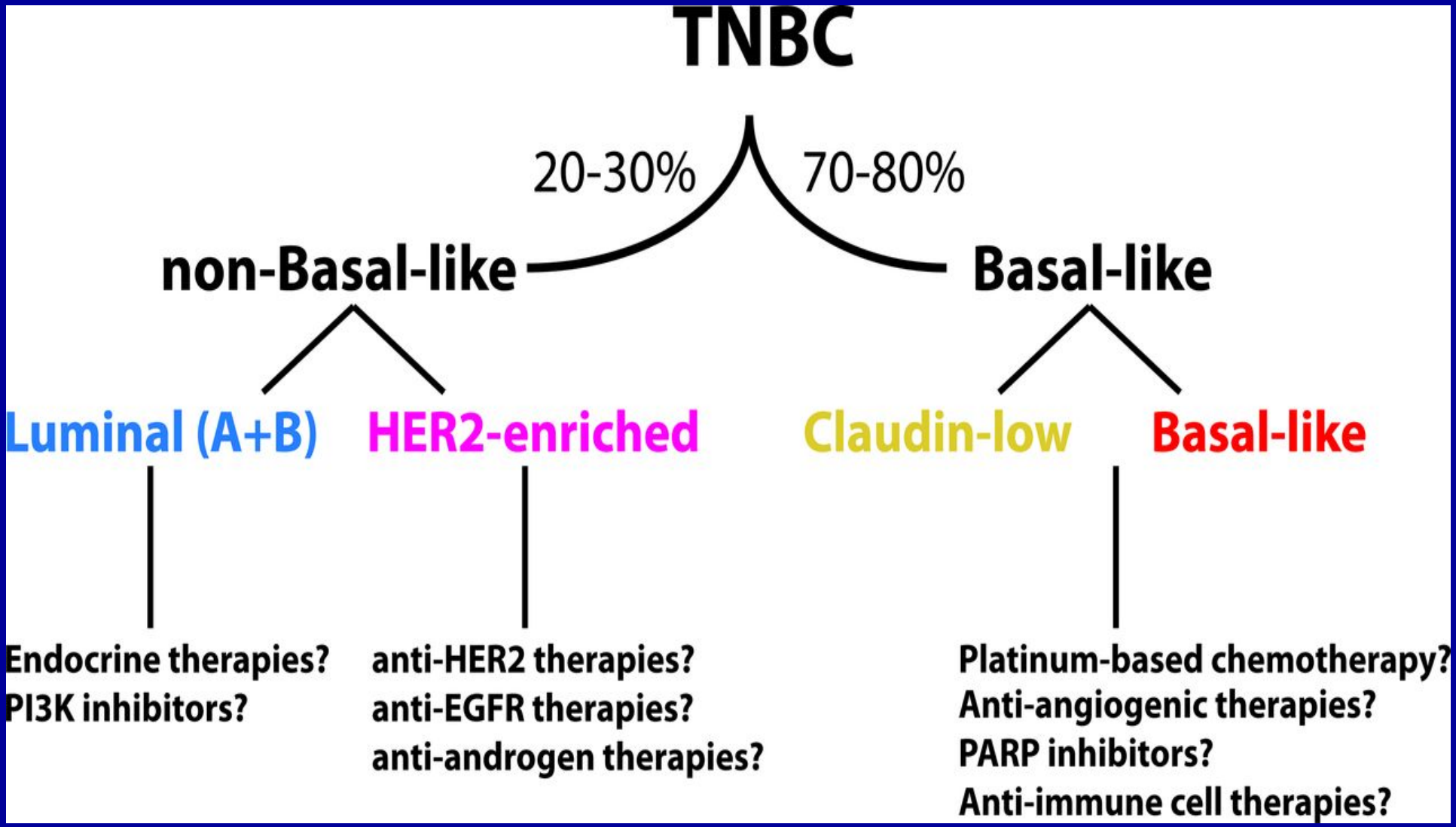
A. Goldhirsch et al. Ann Oncol 2013; 24 (9): 2206-2223

First-Generation Trastuzumab Trials



	Follow-up yr	HR DFS (T vs no T)
HERA (0 vs 1 y)	4 8	.76 .76
NSABP B31/ NCTTG 9831	4 8	.52 .60
BCIRG 006 ACTH TCH	5 5	.64 .75
FinHER	3 (RFS) 5 (DDFS)	.42

Proposed algorithm of stratification of triple-negative tumors.Abbreviations: EGFR, epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerase.



Prat A et al. The Oncologist 2013;18:123-133

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CLINICAL STAGE

Stage I
T1, N0, M0
or
Stage IIA
T0, N1, M0
T1, N1, M0
T2, N0, M0
or
Stage IIB
T2, N1, M0
T3, N0, M0
or
Stage IIIA
T3, N1, M0

WORKUP

- History and physical exam
- CBC, platelets
- Liver function tests and alkaline phosphatase
- Diagnostic bilateral mammogram; ultrasound as necessary
- Pathology review[a]
- Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status[b]
- Genetic counseling if patient is high risk for hereditary breast cancer[c]
- Breast MRI[d] (optional), with special consideration for mammographically occult tumors
- Fertility counseling if premenopausal[e]

For clinical stage I-IIB, consider additional studies only if directed by signs or symptoms:[f]

- Bone scan indicated if localized bone pain or elevated alkaline phosphatase
- Abdominal ± pelvic diagnostic CT or MRI indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis
- Chest diagnostic CT (if pulmonary symptoms present)

If clinical stage IIIA (T3, N1, M0) consider:

- Chest diagnostic CT
- Abdominal ± pelvic diagnostic CT or MRI
- Bone scan or sodium fluoride PET/CT[g] (category 2B)
- FDG PET/CT[h,i] (optional, category 2B)

See Locoregional Treatment (BINV-2)

[a] The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. ttp://www.cap.org.
[b] See Principles of HER2 Testing (BINV-A).
[c] See NCCN Guidelines for Genetics/Familial High-Risk Assessment: Breast and Ovarian.
[d] See Principles of Dedicated Breast MRI Testing (BINV-B).
[e] See Fertility and Birth Control (BINV-C).
[f] Routine systemic staging is not indicated for early breast cancer in the absence of symptoms.
[g] If FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.
[h] FDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.
[i] FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

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LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0

Lumpectomy with surgical axillary staging (category 1)[j,k,l]

- **≥4 positive[o] axillary nodes** → Radiation therapy to whole breast with or without boost[p] (by photons, brachytherapy, or electron beam) to tumor bed (category 1), infraclavicular region and supraclavicular area. Strongly consider radiation therapy to internal mammary nodes[q] (category 2B). Radiation therapy should follow chemotherapy when chemotherapy is indicated.
- **1-3 positive axillary nodes** → Radiation therapy to whole breast with or without boost[p] (by photons, brachytherapy, or electron beam) to tumor bed (category 1) following chemotherapy when chemotherapy is indicated. Strongly consider radiation therapy to infraclavicular region and supraclavicular area (category 2B). Strongly consider radiation therapy to internal mammary nodes[q] (category 2B). Radiation therapy should follow chemotherapy when chemotherapy is indicated.
- **Negative axillary nodes** → Radiation therapy to whole breast with or without boost[p] (by photons, brachytherapy, or electron beam) to tumor bed or consideration of partial breast irradiation (PBI) in selected patients.[p,r] Radiation therapy should follow chemotherapy when chemotherapy is indicated.[s]

→ See BINV-4

or

Total mastectomy with surgical axillary staging[j,k,m] (category 1) ± reconstruction[n] → See Locoregional Treatment (BINV-3)

or

If T2 or T3 and fulfills criteria for breast-conserving therapy except for size[l] → Consider Preoperative Systemic Therapy Guideline (BINV-10)

[j] See Surgical Axillary Staging (BINV-D).

[k] See Axillary Lymph Node Staging (BINV-E) and Margin Status in Infiltrating Carcinoma (BINV-F).

[l] See Special Considerations to Breast-Conserving Therapy (BINV-G).

[m] Except as outlined in the NCCN Guidelines for Genetics/Familial High-Risk Assessment: Breast and Ovarian and the NCCN Guidelines for Breast Cancer Risk Reduction, prophylactic mastectomy of a breast contralateral to a known unilateral breast cancer is discouraged. When considered, the small benefits from contralateral prophylactic mastectomy for women with unilateral breast cancer must be balanced with the risk of recurrent disease from the known ipsilateral breast cancer, psychological and social issues of bilateral mastectomy, and the risks of contralateral mastectomy. The use of a prophylactic mastectomy contralateral to a breast treated with breast-conserving therapy is very strongly discouraged.

[n] See Principles of Breast Reconstruction Following Surgery (BINV-H).

[o] Consider imaging for systemic staging, including diagnostic CT or MRI, bone scan, and optional FDG PET/CT (category 2B) (See BINV-1).

[p] See Principles of Radiation Therapy (BINV-I).

[q] Radiation therapy should be given to the internal mammary lymph nodes that are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph nodes.

[r] PBI may be administered prior to chemotherapy.

[s] Breast irradiation may be omitted in those 70 y of age or older with estrogen-receptor positive, clinically node-negative, T1 tumors who receive adjuvant endocrine therapy (category 1).

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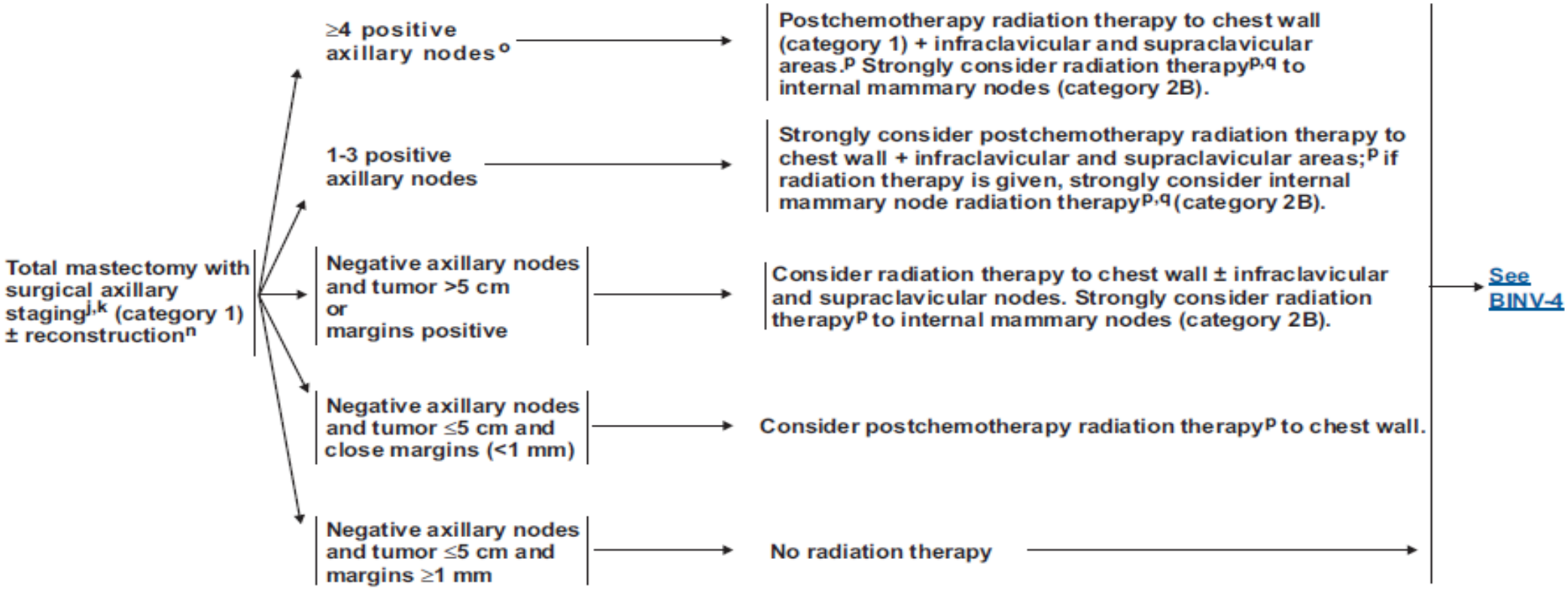

[j] See Surgical Axillary Staging (BINV-D).
[k] See Axillary Lymph Node Staging (BINV-E) and Margin Status in Infiltrating Carcinoma (BINV-F).
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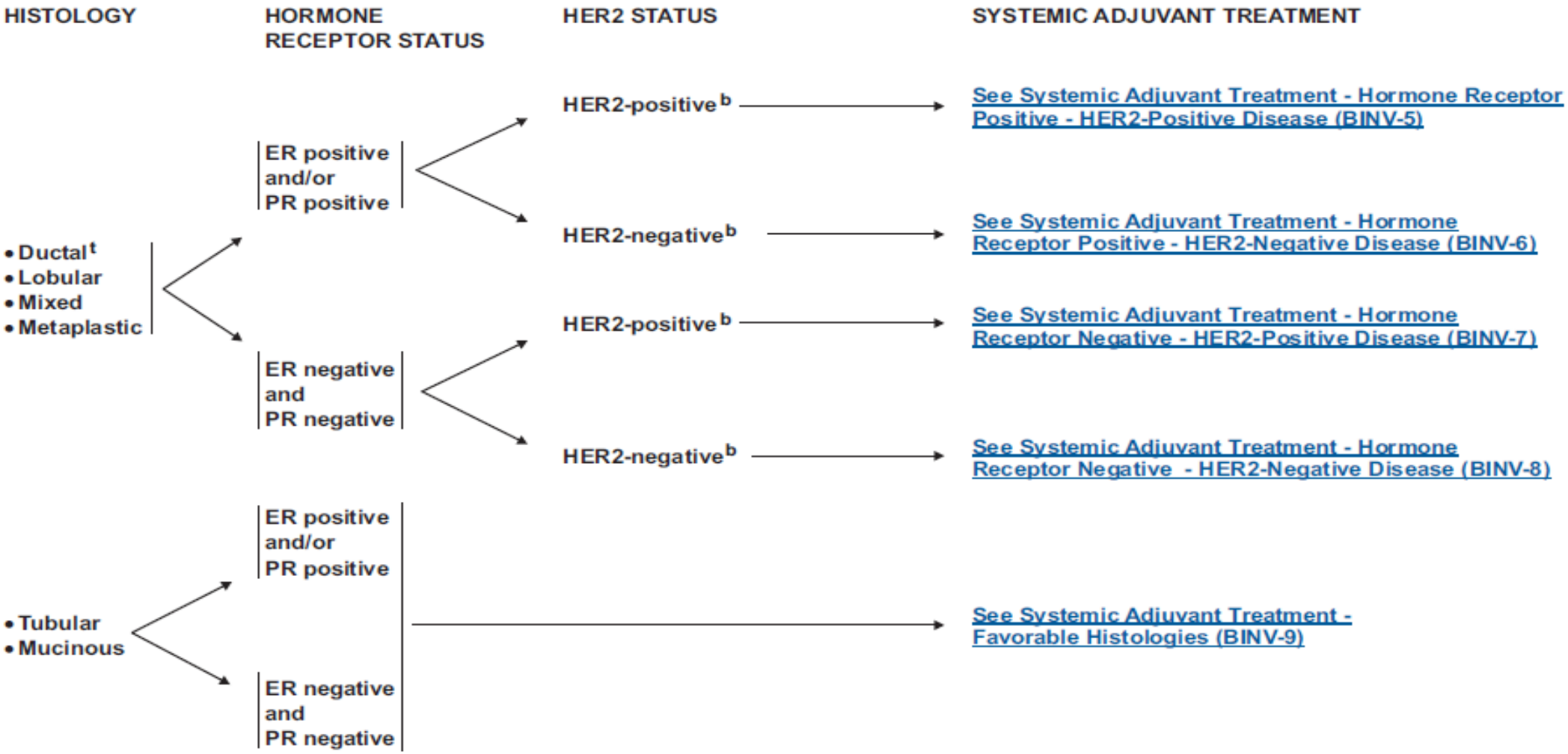

[b] See Principles of HER2 Testing (BINV-A).
[t] This includes medullary and micropapillary subtypes.

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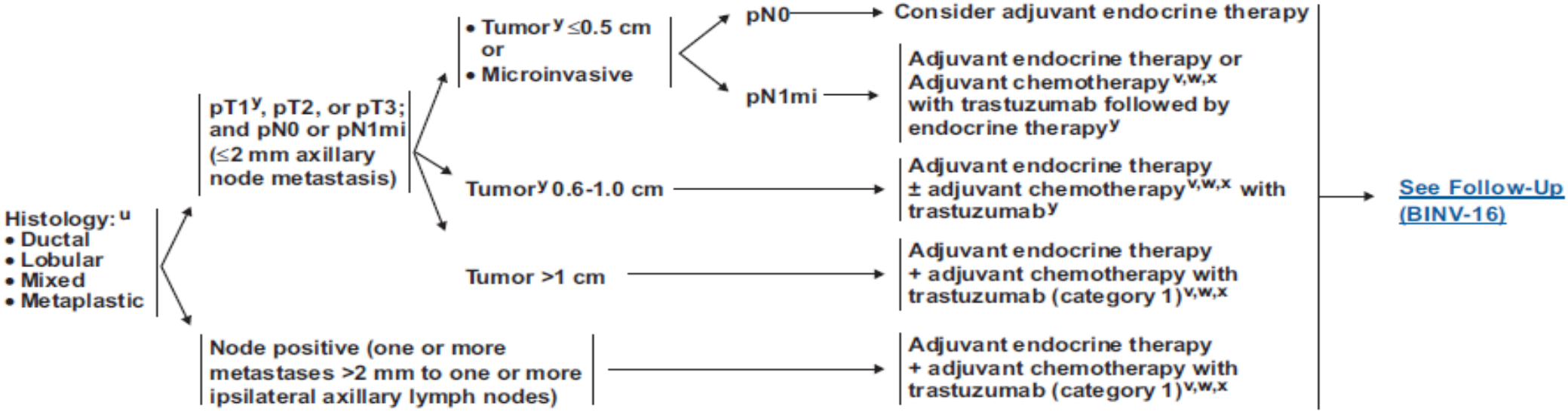
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE[b]



See Adjuvant Endocrine Therapy (BINV-J) and Neoadjuvant/Adjuvant Chemotherapy (BINV-K)

[b] See Principles of HER2 Testing (BINV-A).

[u] 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.

[v] 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. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

[w] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

[x] There are limited data to make chemotherapy recommendations for those >70 y old. Treatment should be individualized with consideration of comorbid conditions.

[y] The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or over-expressed. 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.

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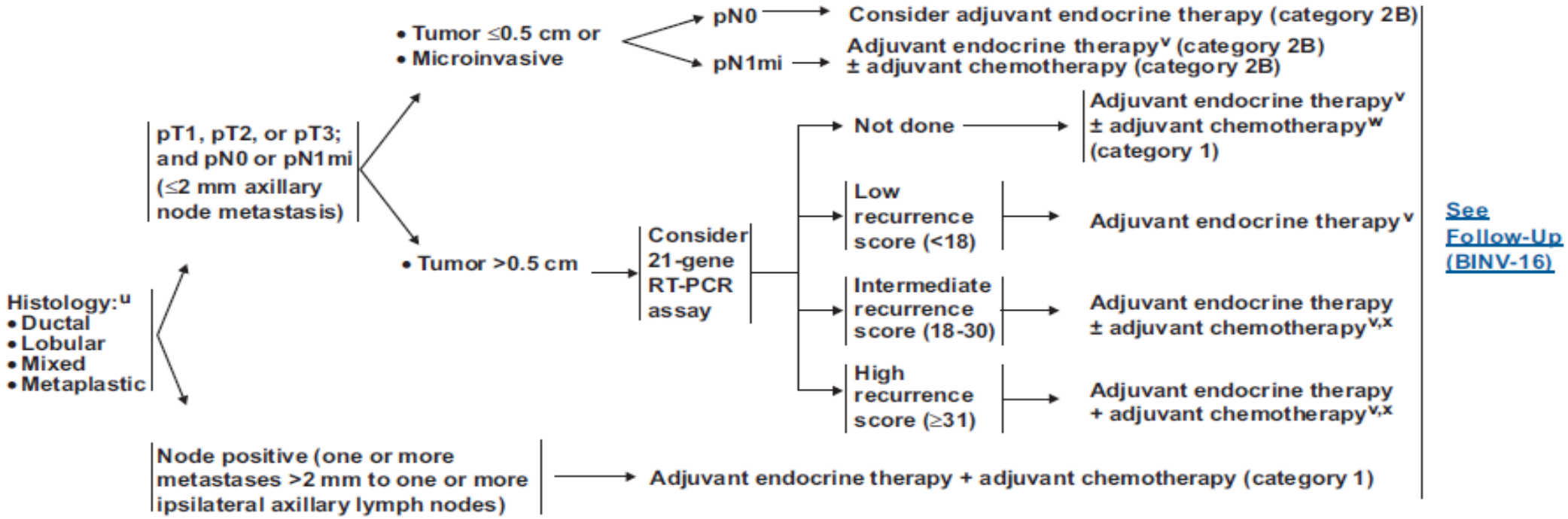

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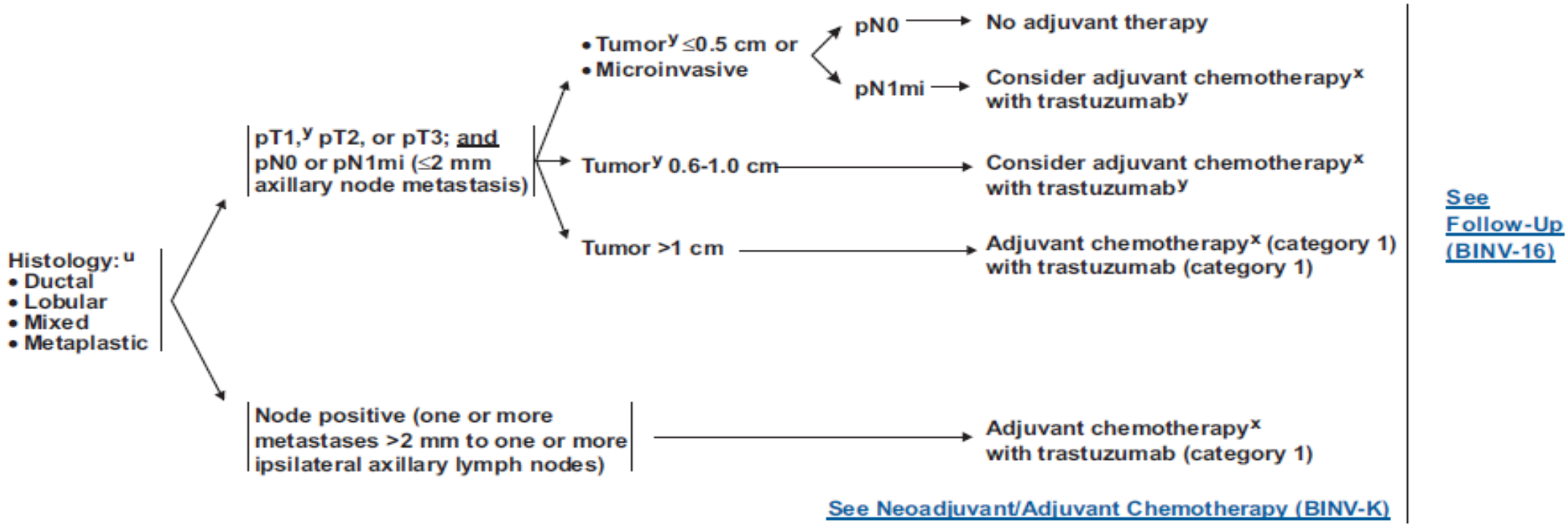

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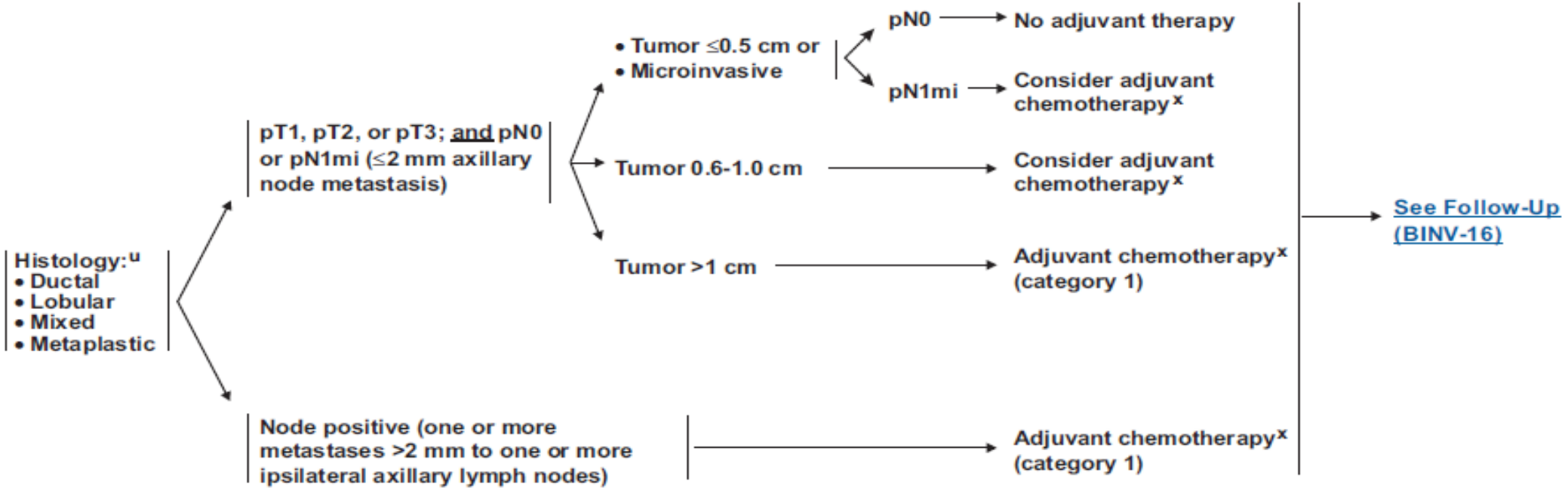

See Neoadjuvant/Adjuvant Chemotherapy (BINV-K)

[b] See Principles of HER2 Testing (BINV-A).

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Invasive Breast Cancer

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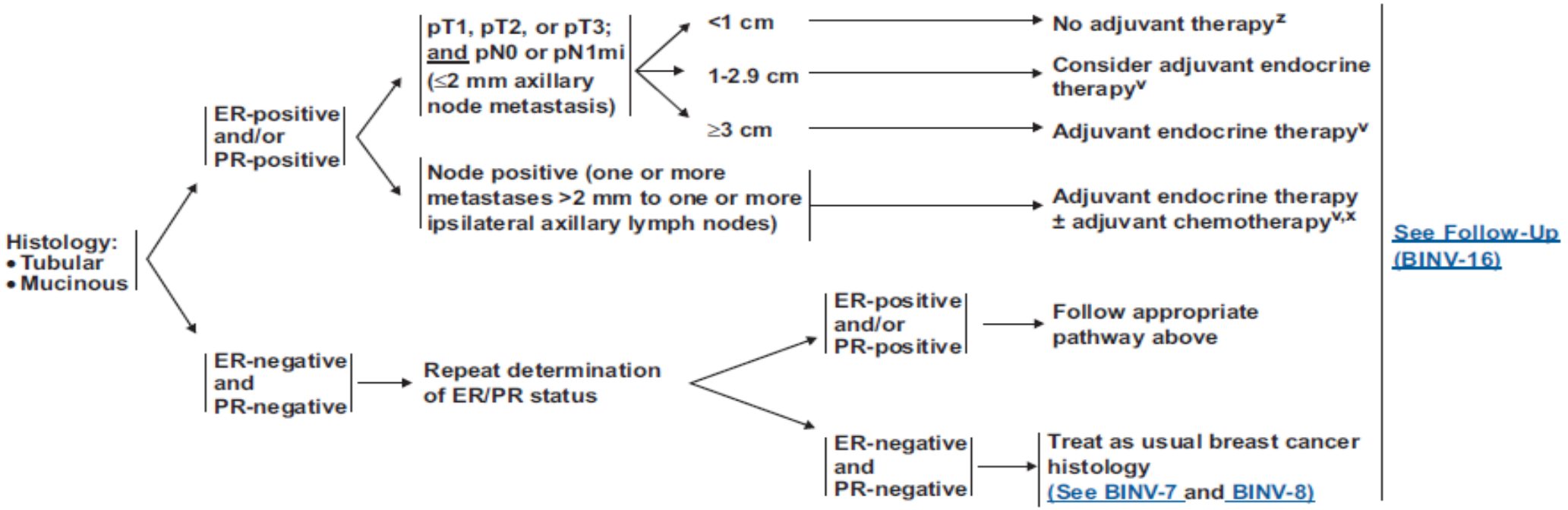
Breast Cancer Table of Contents
Discussion

SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES



See Adjuvant Endocrine Therapy (BINV-J) and Neoadjuvant/Adjuvant Chemotherapy (BINV-K)

[v]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. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

[x]There are limited data to make chemotherapy recommendations for those >70 y old. Treatment should be individualized with consideration of comorbid conditions.

[z]If ER-positive, consider endocrine therapy for risk reduction and to diminish the small risk of disease recurrence.

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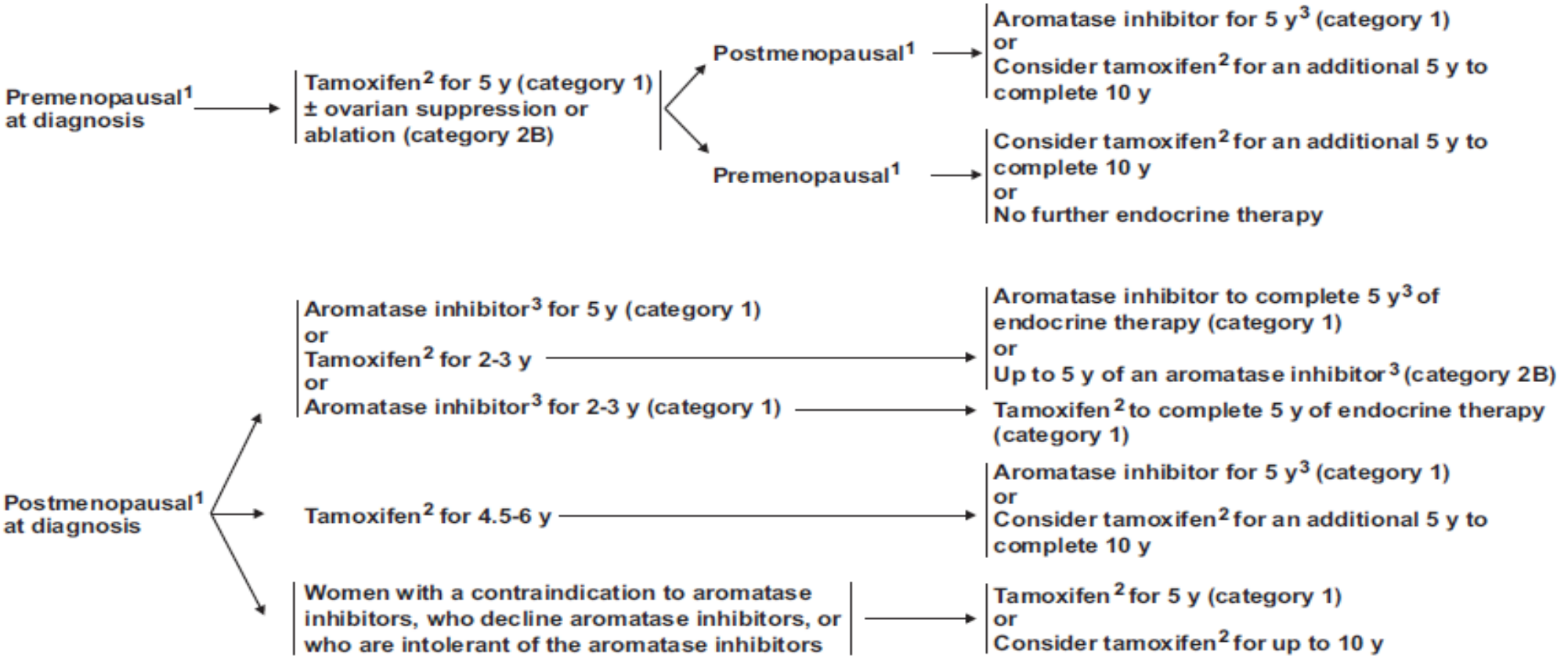
ADJUVANT ENDOCRINE THERAPY



[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] 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.

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NEOADJUVANT/ADJUVANT CHEMOTHERAPY[1,2,3,4]

Regimens for HER2-negative disease (all category 1[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)
- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)
- FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- 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]
- FEC followed by docetaxel + trastuzumab + pertuzumab[9]
- FEC followed by paclitaxel + trastuzumab + pertuzumab[9]
- 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 first. All other chemotherapy regimens should be given prior to radiotherapy.

[4] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.

[5] The regimens listed for HER2-negative disease are all category 1 when used in the adjuvant setting.

[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. Patients who have not received a neoadjuvant pertuzumab-containing regimen can receive adjuvant pertuzumab.

[9] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

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DOSING SCHEDULES FOR COMBINATIONS FOR HER2-NEGATIVE DISEASE: PREFERRED REGIMENS

OTHER REGIMENS LISTED ON NEXT PAGE

Dose-dense AC followed by paclitaxel chemotherapy[1]
- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 14 days for 4 cycles.
Followed by
- Paclitaxel 175 mg/m² by 3 h IV infusion day 1

Cycled every 14 days for 4 cycles.
(All cycles are with filgrastim support)

Dose-dense AC followed by weekly paclitaxel chemotherapy[1]
- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 14 days for 4 cycles.
Followed by
- Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 wks.

TC chemotherapy[2]
- Docetaxel 75 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles.
(All cycles are with filgrastim support)

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

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See References (BINV-K 7 of 7)

DOSING SCHEDULES FOR COMBINATIONS FOR HER2-NEGATIVE DISEASE: OTHER REGIMENS

AC chemotherapy[3]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.

TAC chemotherapy[4]
- Docetaxel 75 mg/m^2 IV day 1
- Doxorubicin 50 mg/m^2 IV day 1
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 days for 6 cycles.
(All cycles are with filgrastim support)

FAC chemotherapy[5,6]
- 5-fluorouracil 500 mg/m^2 IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m^2 IV day 1 (or by 72-h continuous infusion)
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 days for 6 cycles.

CAF chemotherapy[7]
- Cyclophosphamide 100 mg/mv PO days 1-14
- Doxorubicin 30 mg/m^2 IV days 1 & 8
- 5-fluorouracil 500 mg/m^2 IV days 1 & 8

Cycled every 28 days for 6 cycles.

CEF chemotherapy[8]
- Cyclophosphamide 75 mg/m^2 PO days 1-14
- Epirubicin 60 mg/m^2 IV days 1 & 8
- 5-fluorouracil 500 mg/m^2 IV days 1 & 8

With cotrimoxazole support.
Cycled every 28 days for 6 cycles.

CMF chemotherapy[9]
- Cyclophosphamide 100 mg/m^2 PO days 1-14
- Methotrexate 40 mg/m^2 IV days 1 & 8
- 5-fluorouracil 600 mg/m^2 IV days 1 & 8

Cycled every 28 days for 6 cycles.

AC followed by docetaxel chemotherapy[10]
- Doxorubicin 60 mg/m^2 IV on day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.
Followed by
- Docetaxel 100 mg/m^2 IV on day 1

Cycled every 21 days for 4 cycles.

AC followed by weekly paclitaxel[10]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.
Followed by
- Paclitaxel 80 mg/m^2 by 1 h IV infusion weekly for 12 wks.

EC chemotherapy[11]
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 830 mg/m^2 IV day 1

Cycled every 21 days for 8 cycles.

FEC followed by docetaxel chemotherapy[12]
- 5-fluorouracil 500 mg/m^2 IV day 1
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 days for 3 cycles.
Followed by
- Docetaxel 100 mg/m^2 IV day 1

Cycled every 21 days for 3 cycles.

FEC followed by weekly paclitaxel[13]
- 5-fluorouracil 600 mg/m^2 IV day 1
- Epirubicin 90 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.
Followed by:
- 3 weeks of no treatment

Followed by:
- Paclitaxel 100 mg/m^2 IV infusion weekly for 8 wks.

FAC followed by weekly paclitaxel
- 5-fluorouracil 500 mg/m^2 IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m^2 IV day 1 (or by 72 h continuous infusion)
- Cyclophosphamide 500 mg/m^2 IV day 1

Cycled every 21 days for 6 cycles.
Followed by
- Paclitaxel 80 mg/m^2 by 1 h IV infusion weekly for 12 wks.

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

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See References (BINV-K 7 of 7)

DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: PREFERRED REGIMENS

AC followed by T chemotherapy with trastuzumab[14]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.
Followed by
Paclitaxel 80 mg/m^2 by 1 h IV weekly for 12 wks
With
- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by
- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.

Cardiac monitoring at baseline, 3, 6, and 9 mo.

AC followed by T chemotherapy with trastuzumab + pertuzumab
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles.
Followed by
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Paclitaxel 80 mg/m^2 IV days 1, 8, and 15

Cycled every 21 days for 4 cycles
- Trastuzumab 6 mg/kg IV day 1

Cycled every 21 days to complete 1 y of trastuzumab therapy
Cardiac monitoring at baseline, 3, 6, and 9 mo.

Dose-dense AC followed by paclitaxel chemotherapy with trastuzumab[15]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 14 days for 4 cycles.
Followed by
- Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1

Cycled every 14 days for 4 cycles.
(All cycles are with filgrastim support).
With
- Trastuzumab 4 mg/kg IV with first dose of paclitaxel

Followed by
- Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.

Cardiac monitoring at baseline, 3, 6, and 9 mo.

TCH chemotherapy[16]
- Docetaxel 75 mg/m^2 IV day 1
- Carboplatin AUC 6 IV day 1

Cycled every 21 days for 6 cycles
With
- Trastuzumab 4 mg/kg IV wk 1

Followed by
- Trastuzumab 2 mg/kg IV for 17 wks

Followed by
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 mo.

TCH chemotherapy + pertuzumab[17]
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Docetaxel 75 mg/m^2 IV day 1
- Carboplatin AUC 6 IV day 1

Cycled every 21 days for 6 cycles
Followed by
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 mo.

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

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OTHER REGIMENS LISTED ON NEXT PAGE
See References (BINV-K 7 of 7)

DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: OTHER REGIMENS

AC followed by docetaxel chemotherapy with trastuzumab[16]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles
Followed by
- Docetaxel 100 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles
With
- Trastuzumab 4 mg/kg IV wk 1

Followed by
- Trastuzumab 2 mg/kg IV weekly for 11 wks

Followed by
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 mo.

AC followed by docetaxel chemotherapy with trastuzumab and pertuzumab
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 4 cycles
Followed by
- 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/m^2 IV day 1

Cycled every 21 days for 4 cycles
Followed by
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 mo.

FEC chemotherapy followed by pertuzumab + trastuzumab + docetaxel[17]
- Fluorouracil 500 mg/m^2 IV day 1
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 3 cycles
Followed by
- 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/m^2 IV day 1

Cycled every 21 days for 3 cycles
Followed by
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 mo.

FEC chemotherapy followed by pertuzumab + trastuzumab + paclitaxel
- Fluorouracil 500 mg/m^2 IV day 1
- Epirubicin 100 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1

Cycled every 21 days for 3 cycles
Followed by
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Paclitaxel 80 mg/m^2 IV days 1, 8, and 15

Cycled every 21 days for 3 cycles
Followed by
- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 mo.

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See References (BINV-K 7 of 7)

DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: OTHER REGIMENS (continued)

Pertuzumab + trastuzumab + docetaxel followed by FEC chemotherapy[18]
Neoadjuvant therapy:
- **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/m^2 IV day 1**

Cycled every 21 days for 4 cycles
Followed by adjuvant therapy
- **Fluorouracil 600 mg/m^2 IV day 1**
- **Epirubicin 90 mg/m^2 IV day 1**
- **Cyclophosphamide 600 mg/m^2 IV day 1**

Cycled every 21 days for 3 cycles
Followed by
- **Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy**

Cardiac monitoring at baseline, 3, 6, and 9 mo.

Pertuzumab + trastuzumab + paclitaxel followed by FEC chemotherapy
Neoadjuvant therapy:
- **Pertuzumab 840 mg IV day 1 followed by 420 mg IV**
- **Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV**
- **Paclitaxel 80 mg/m^2 IV days 1, 8, and 15**

Cycled every 21 days for 4 cycles
Followed by adjuvant therapy
- **Fluorouracil 600 mg/m^2 IV day 1**
- **Epirubicin 90 mg/m^2 IV day 1**
- **Cyclophosphamide 600 mg/m2 IV day 1**

Cycled every 21 days for 3 cycles
Followed by
- **Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy**

Cardiac monitoring at baseline, 3, 6, and 9 mo.

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

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See References (BINV-K 7 of 7)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

NCCN Guidelines Version 1.2014
Breast Cancer Updates

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Summary of changes in the 1.2014 version of the NCCN Guidelines for Breast Cancer from the 3.2013 version include:

LCIS-1

- Modified footnote b: Some variants of LCIS (pleomorphic LCIS) may have a similar biological behavior to that of DCIS. Clinicians may consider complete excision with negative margins for pleomorphic LCIS, but outcome data regarding the efficacy of surgical excision to negative margins ~~and/or radiotherapy~~ are lacking. *There are no data to support using radiotherapy in this setting.*

DCIS-1

- Added footnote e: The use MRI has not been shown to increase likelihood of negative margins or decrease conversion to mastectomy. Data to support improve long-term outcomes are lacking.

DCIS-2

- Risk reduction therapy for ipsilateral breast following breast-conserving surgery. Divided the first bullet into two separate statements:
  - Patients treated with breast-conserving therapy (lumpectomy) and radiation therapy (category 1) especially for those with ER-positive DCIS.
  - The benefit of tamoxifen for ER-negative DCIS is uncertain.

BINV-1, BINV-10, and BINV-14

- Workup: Changed "Consider fertility counseling if indicated" to "Fertility counseling if premenopausal."

BINV-10

- Changed the title of the page from "Preoperative Chemotherapy Guideline" to "Preoperative Systemic Therapy Guideline."

BINV-11

- Preoperative chemotherapy breast and axillary evaluation, desires breast preservation, "Core biopsy with placement of image-detectable marker(s), if not previously performed must be done to demarcate the tumor bed for post-chemotherapy surgical management."
- Clinically negative axillary lymph node(s), added "should have axillary ultrasound; suspicious nodes should be sampled by FNA or core biopsy and clipped with image-detectable marker; positive clipped lymph nodes must be removed if FNA or core biopsy was positive prior to neoadjuvant therapy."
- Clinically positive axillary lymph node(s), added "should be sampled by FNA or core biopsy and clipped with image-detectable marker; positive clipped lymph nodes must be removed if FNA or core biopsy was positive prior to neoadjuvant therapy."

BINV-12

- Added footnote dd: "A pertuzumab-containing regimen may be administered preoperatively to patients with T2 or N1, HER2-positive, early stage breast cancer. See Neoadjuvant/Adjuvant Chemotherapy (BINV-K)."

BINV-13

- Revised footnote gg: "Axillary staging following preoperative systemic therapy may include sentinel node biopsy or level I/II dissection. Level I/II dissection should be done for when patients were proven node-positive prior to neoadjuvant therapy (category 2B)." Included the following references:

Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14(7):609-18. Epub 2013/05/21.

Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. Jama. 2013;310(14):1455-61. Epub 2013/10/09.

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Summary of changes in the 1.2014 version of the NCCN Guidelines for Breast Cancer from the 3.2013 version include:

BINV-15

- Added footnote dd: "A pertuzumab-containing regimen may be administered preoperatively to patients with T2 or N1, HER2-positive, early stage breast cancer. (See BINV-K).
- Added footnote hh: "For patients with skin and/or chest wall involvement (T4 non-inflammatory) prior to neoadjuvant therapy, breast conservation may be performed in carefully selected patients based upon a multidisciplinary assessment of local recurrence risk. In addition to standard contraindications to breast conservation (see BINV-G), exclusion criteria for breast conservation include: inflammatory (T4d) disease before neoadjuvant therapy and incomplete resolution of skin involvement after neoadjuvant therapy."

BINV-19

- Footnote tt, deleted the following hazard ratio information: "(HR for recurrence 0.80; 95% CI, 0.68-0.94; stratified log-rank P = 0.007) and improvement in overall survival (HR 0.81; 95% CI, 0.65-1.00; stratified log-rank P = 0.049)."

BINV-20 and BINV-21

- Changed "No response to 3 sequential regimens" to "No benefit after 3 sequential lines of chemotherapy."

BINV-21

- Systemic treatment of recurrent or stage IV disease, replaced"trastuzumab + lapatinib" with "other HER2-targeted therapy."
- Modified footnote ww: "Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzamab and pertuzumab with an anthracycline should be avoided."

BINV-A

- Updated Principles of HER2 Testing for consistency with ASCO/CAP HER2 testing guideline.
- Removed: "Carlson RW, Moench SJ, Hammond, MEH, et al. HER2 testing in breast cancer: NCCN task force report and recommendations. JNCCN 4:S-1-S-24, 2006."
- Added: "Laboratory must participate in a quality assurance accreditation program for HER2 testing. Otherwise, tissue specimen should be sent to an accredited laboratory for testing. Health care systems and providers must cooperate to ensure the highest quality testing."
- Edited footnote 4 to read "Evidence from trastuzumab adjuvant trials show that HER2 testing by ISH or IHC have similar utility to predict clinical benefit from HER2-targeted therapy."
- Replaced the following footnotes:
  - Borderline IHC samples (eg, IHC 2+) are subjected to reflex testing by a validated complementary (eg, in situ hybridization [ISH]) method that has shown at least 95% concordance between IHC 0, 1+ results and ISH non-amplified results, and IHC 3+ results and ISH amplified results.
  - Borderline in situ hybridization (ISH) samples (eg, an average HER2 gene/chromosome 17 ratio of 1.8 - <2 or an average HER2 gene copy number of >4 - <6) should undergo: counting of additional cells, retesting by ISH, or reflex testing by a validated IHC method.

BINV-C

- Modified page title Fertility and Birth Control ~~After Adjuvant Breast Cancer Treatment.~~
- Added a link to the NCCN Guidelines for Adolescent and Young Adult Oncology.

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NCCN Guidelines Version 1.2014
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Summary of changes in the 1.2014 version of the NCCN Guidelines for Breast Cancer from the 3.2013 version include:

BINV-E

- Axillary lymph node staging, first sentence, changed "In the absence of definitive data demonstrating superior survival from the performance of axillary lymph node dissection, patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected, for the elderly, or those with serious comorbid conditions, the performance of axillary lymph node dissection may be considered optional." Changed "performance of axillary lymph node dissection may be considered optional."
- Axillary lymph node staging, second sentence, added "In the absense of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dirsi muscle laterally to the medial border of the pectoralis minor muscle (Level I/II).

BINV-F

- Margin status in infiltrating carcinoma, removed "If multiple margins remain positive, mastectomy may be required for optimal local control."

BINV-G

- Removed "Prior radiation therapy to the chest wall or breast; knowledge of doses and volumes prescribed is essential" from absolute contraindication to relative contraindication.

BINV-H

- Principles of breast reconstruction following surgery, this page has been extensively revised.

BINV-I

- Under APBI section, added second sentence "However, compared to standard whole breast radiation, several recent studies document an inferior cosmetic outcome with APBI. Follow-up (removed "however") is limited.
- Under neoadjuvant chemotherapy section, changed the first sentence to "Indications for radiation therapy and fields of treatment should be based on the worst stage pretreatment or post-treatment tumor characteristics in patients treated with neoadjuvant chemotherapy."

BINV-J

- For pre- and postmenopausal patients, removed "(category 1) for tamoxifen therapy."

BINV-K

- Changed subtitles to "Regimens for HER2-negative disease" and Regimens for HER2-positive disease."
- Neoadjuvant/adjuvant chemotherapy, regimens for HER2-negative disease; other regimens:
  - Changed AC to specify "Dose-dense AC (doxorubicin/cyclophosphamide)."
  - Added "AC followed by weekly paclitaxel."
  - Added the following footnote: "The regimens listed for HER2-negative disease are all category 1 when used in the adjuvant setting."
- Regimens for HER2-positive disease; preferred:
  - AC followed by T + concurrent trastuzumab, added "± pertuzumab."
  - TCH; added "± pertuzumab."
- Regimens for HER2-positive disease; other:
  - AC followed by docetaxel + trastuzumab, added "± pertuzumab."
  - Added "AC followed by paclitaxel + trastuzumab ± pertuzumab."
  - Added "FEC followed by docetaxel + trastuzumab + pertuzumab."
  - Added "FEC followed by paclitaxel + trastuzumab + pertuzumab."
  - Added "Pertuzumab + trastuzumab + docetaxel followed by FEC."
  - Added "Pertuzumab + trastuzumab + paclitaxel followed by FEC."
- Removed the regimens/dosing schedules for the following:
  - Docetaxel + trastuzumab followed by FEC chemotherapy
  - T followed by FEC chemotherapy with trastuzumab.
- Modified footnote 4, changed "tamoxifen" to "endocrine therapy." Chemotherapy and *endocrine therapy* used as adjuvant therapy should be given sequentially with *endocrine therapy* following chemotherapy.

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.

Continued on next page

NCCN Guidelines Version 1.2014
Breast Cancer Updates

Summary of changes in the 1.2014 version of the NCCN Guidelines for Breast Cancer from the 3.2013 version include:

BINV-K (Continued)

- Added the following footnotes:
  - 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).
  - 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.
  - Pertuzumab can be administered to patients with T2 or N1 early stage breast cancer. Patients who have not received neoadjuvant pertuzumab can receive adjuvant pertuzumab.
- Added the following references"
  - Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278-2284.
  - Gianni L, al e. Neoadjuvant pertuzumab (P) and trastuzumab (H): Antitumor and safety analysis of a randomized phase II study (NeoSphere) [abstract]. San Antonio Breast Cancer Symposium 2010;Abstract S3-2.

BINV-N

- Subsequent endocrine therapy for systemic disease, postmenopausal patients, added exemestane + everolimus.
- Modified footnote 1: "A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI, or any time on tamoxifen)."

BINV-O

- Other first-line agents for HER2-positive disease: Changed "trastuzumab with to trastuzumab alone or with."
- Trastuzumab + vinorelbine: Added dose vinorelbine 30-35 mg/m^2 IV days 1 and 8. Cycled every 21 days.
- Added the following reference: Gasparini G, Dal Fior S, Panizzoni GA, et al. Weekly epirubicin versus doxorubicin as second line therapy in advanced breast cancer. A randomized clinical trial. Am J Clin Oncol 1991;14:38-44.

IBC-1

- Workup: added "History and physical *by a multidisciplinary team.*"
- Workup: added "Fertility counseling if premenopausal."
- Added footnote d: "See Fertility and Birth Control (BINV-C).

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.

- Adjuvant kemoterapi ve hormonal tedavi verilecek hastalarda **önce KT ve ardından HT olarak ARDIŞIK kullanılmalıdır.**
- KT + HT additif etkiye sahiptir.
- KT ve HT nin birlikte kullanılması **toksisiteyi arttırabilir.**

ER Durumu kemoterapi yanıtını gösterir.

- **ER (-) olan hastalarda kemoterapinin sağkalıma ve hastalıksız sağkalıma yararı daha fazladır**
  - ***IBSCG çalışmaları (CMF + Tam)***
  - ***NSABP-B20 (Antrasiklinli)***
  - ***CALGB 8541 ve 9344 ve 9741 (Antrasiklin ve taksan)***

- 50-69 arası grupta yarıdan daha az risk azalması olur.

  Ör. %25 risk %14.7' ye düşer.

- Taksanlar > Antrasiklinler > CMF > KTsiz

Early Breast Cancer Trialists Collaborative Group (EBCTCG) çalışmaları

Triple (-) hastalarda öneri

Taksan + DNA hasarı yapan ilaçlar

- Platin bileşikleri
- Alkile edici ajanlar

Topo II-a ekspresyonu saptanan hastalarda öneri

– Risk değerlendirmesi de yaparak

antrasiklin ve/veya taksan içeren ilaçlar

Adjuvant Kemoterapi

LN Negatif:

- CMF
- FAC/CAF
- AC

LN Pozitif

- FAC/CAF veya FEC/CEF
- AC ± ardışık paclitaxel
- EC
- TAC
- A ⟶ CMF
- E ⟶ CMF
- CMF
- AC x 4 + ardışık paclitaxel x 4, 2 haftada bir + G-CSF desteği
- A ⟶ T ⟶ C, 2 haftada bir + G-CSF desteği

HER-2 (+) olgularda Trastuzumab (Herceptin), 1 yıl süre ile, haftada bir veya 3 haftada bir tedaviye eklenmeli, antrasiklinlerle eşzamanlı kullanılmamalıdır !!!

Adjuvant Hormonal Tedavi

Premenopozal:

- **Tamoksifen 5 yıl süre ile 20 mg/gün PO**
- **Ovarian ablasyon (cerrahi/RT ile ooferektomi) (İrreverzibl)**
- **LHRH-A ile Ovarian Supresyon 2 yıl subkutan (Reverzibl)**
- **Tamoksifen (5 yıl) + LHRH-A (2 yıl)**
- ***Adjuvant KT almış olan premenopozal kadınlarda tedaviye OA/OS eklenmesinin sağkalıma mutlak katkısı nispeten azdır.***

Adjuvant Hormonal Tedavi

Premenopozal

- **Tamoksifen 2-3 yıl ± OS/OA**
  - **Postmenopozal:**
    - **TMX 5 yıla tamamlanır ve ardından Letrozole 5 yıl süre ile verilir**
    - **Examestane veya Anastrozole ile 5 yıla tamamlanır.**
  - **Premenopozal:**
    - **TMX 5 yıla tamamlanır**
      - **Postmenopozal ise Letrozole 5 yıl süre ile verilir**
      - **Premenopozal ise HT sonlandırılır.**

Adjuvant Hormonal Tedavi

Postmenopozal

- Anastrozole veya Letrozole 5 yıl
- Tamoksifen 2-3 yıl ve ardından Exemestane veya Anastrozole ile 5 yıla tamamlanır
- Tamoksifen 4.5-6 yıldan sonra Letrozole 5 yıl
- Aİ' ne kontrendike durumu olan veya Aİ alırken tolere edemeyen hastalarda Tamoksifen 5 yıl

Teşekkür Ederim