Monthly Oncology Tumor Boards: A Multidisciplinary Approach to Individualized Patient Care – Hormone Sensitive Breast Cancer

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Faculty Biography

Michael Berry, MD is Department Chairman and Surgeon at The West Clinic Comprehensive Breast Center and Clinical Assistant Professor at The University of Tennessee Health Science Center in Memphis, Tennessee.

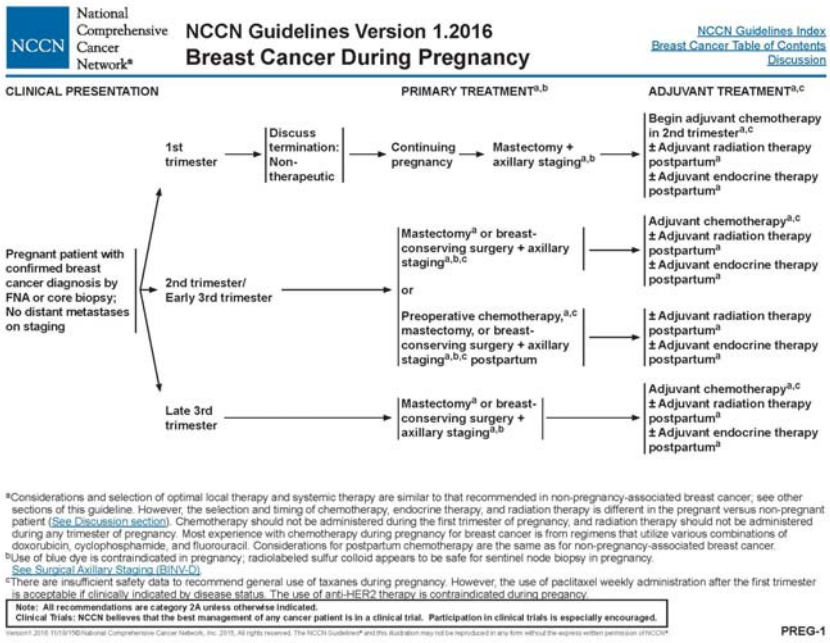
Lee Schwartzberg, MD is Professor of Medicine and Division Chief of Hematology/Oncology at The University of Tennessee Health Science Center and is the Executive Director of the West Cancer Center and Medical Director at The West Clinic in Memphis, Tennessee.

Case # 1

- 34 yo premenopausal white female noticed a lump in her left breast while camping. Lump is hard, nonmobile and nonpainful.
- Saw NP and had US with shadowing at 1 oclock. Seen by general surgeon and biopsy done
- Biopsy: grade 2 infiltrating ductal cancer, ER+90%, PR+ 90%, HER2 2+ by IHC, FISH pending
- PMHx: Hypothyroidism, Hypertension, Gestational diabetes; Cholecystectomy
- Gyn Hx; G4P2, 18 weeks pregnant on OCP
- Social Hx: Nurse, Married, 12 pack-year smoking hx, none in 5 years

Case # 1

- Physical exam: 4.5 x 3.5 mobile mass at 2 o'clock. No lymphadenopathy
- ECHO EF 60-65%
- Genetic testing: Multigene panel negative
- Patient wishes breast conservation
- FISH + for HER2 amplification



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Breast Cancer During Pregnancy

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CLINICAL PRESENTATION		PRIMARY TREATMENT[a,b]		ADJUVANT TREATMENT[a,c]
Pregnant patient with confirmed breast cancer diagnosis by FNA or core biopsy; No distant metastases on staging	1st trimester → Discuss termination: Non-therapeutic	→ Continuing pregnancy	→ Mastectomy + axillary staging[a,b]	→ Begin adjuvant chemotherapy in 2nd trimester[a,c] ± Adjuvant radiation therapy postpartum[a] ± Adjuvant endocrine therapy postpartum[a]
	2nd trimester/ Early 3rd trimester	→ Mastectomy[a] or breast-conserving surgery + axillary staging[a,b,c]		→ Adjuvant chemotherapy[a,c] ± Adjuvant radiation therapy postpartum[a] ± Adjuvant endocrine therapy postpartum[a]
		or		
		→ Preoperative chemotherapy,[a,c] mastectomy, or breast-conserving surgery + axillary staging[a,b,c] postpartum		→ ± Adjuvant radiation therapy postpartum[a] ± Adjuvant endocrine therapy postpartum[a]
	Late 3rd trimester	→ Mastectomy[a] or breast-conserving surgery + axillary staging[a,b]		→ Adjuvant chemotherapy[a,c] ± Adjuvant radiation therapy postpartum[a] ± Adjuvant endocrine therapy postpartum[a]

[a]Considerations and selection of optimal local therapy and systemic therapy are similar to that recommended in non-pregnancy-associated breast cancer; see other sections of this guideline. However, the selection and timing of chemotherapy, endocrine therapy, and radiation therapy is different in the pregnant versus non-pregnant patient (See Discussion section). Chemotherapy should not be administered during the first trimester of pregnancy, and radiation therapy should not be administered during any trimester of pregnancy. Most experience with chemotherapy during pregnancy for breast cancer is from regimens that utilize various combinations of doxorubicin, cyclophosphamide, and fluorouracil. Considerations for postpartum chemotherapy are the same as for non-pregnancy-associated breast cancer.
[b]Use of blue dye is contraindicated in pregnancy; radiolabeled sulfur colloid appears to be safe for sentinel node biopsy in pregnancy.
See Surgical Axillary Staging (BINV-D)
[c]There are insufficient safety data to recommend general use of taxanes during pregnancy. However, the use of paclitaxel weekly administration after the first trimester is acceptable if clinically indicated by disease status. The use of anti-HER2 therapy is contraindicated during pregancy.

Note: All recommendations are category 2A unless otherwise indicated.
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PREG-1

Surgery in Pregnant Women

- Modern anesthetic agents very safe in the setting of pregnancy
- General concerns regarding anesthesia on pregnant patient
  - 1st trimester - organogenesis
  - 2nd trimester - safest time to operate
  - 3rd trimester- premature labor

SLN Biopsy in Pregnant Women

- 25 cN0 patients had SNBx when pregnant
  - 8 (1st trim.), 9 (2nd trim.) and 8 (3rd trim.)
  - 16 TC-99 alone, 7 meth. blue alone and 2 ? method
  - Isosulfan blue does not have FDA clearance for pregnancy
  - 24/25 live born infants without complications, 1/25 with cleft palate (maternal risk factors)
  - SLN biopsy accurate and safe in pregnant pop.

Gropper AB,Ann Surg Oncol. Aug;21(8):2506-11

Breast Cancer in Pregnancy

- A fairly rare event, but increasing as age of pregnancy gets later (up to 36/100,000)
- Historically was considered to convey a poor prognosis in era before modern adjuvant rx
- Generally higher grade and advanced stage at diagnosis
- No randomized trials

Breast Cancer in Pregnancy: Recent studies

- Litton J, et al 2013
- Single institution (MDACC) case control study
- Prospective registry
- N=75 affected
- Published with 16 yr f/u 2013

- Amant F, et. al 2013
- Multinational European registry
- Prospective and retroactive
- 2003-2011

Clinical Pathologic Variables: European registry

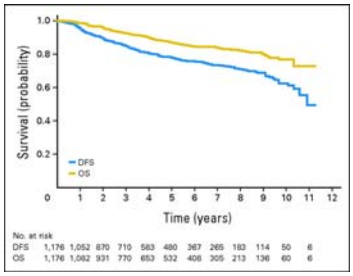
Variable	Pregnant Patients (n = 311)		Nonpregnant Patients (n = 865)		Missing Values			
					Pregnant Patients		Nonpregnant Patients	
	No.	%	No.	%	No.	%	No.	%
AJCC stage					1	0.3	2	0.2
1	48	15.4	263	30.4				
2	177	56.9	399	46.1				
3	86	27.7	203	23.5				
Grade					15	4.8	2	0.2
1	7	2.3	69	8.0				
2	67	21.5	307	35.5				
3	237	76.2	489	5.65				
Histology					4	1.3	1	0.1
IDA		97.4		91.0				
ILA		2.6		9.0				
ER and/or PR positive		46.6		74.5	0	0.0	7	0.8
HER2 positive		31.8		17.0	12	3.9	34	3.9
Triple negative		37.9		19.1	4	1.3	12	1.4

- NOTE. Descriptive statistics are reported after imputation of missing values.
- Abbreviations: AJCC, American Joint Committee on Cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDA, invasive ductal carcinoma; ILA, invasive lobular carcinoma; PR, progesterone receptor.

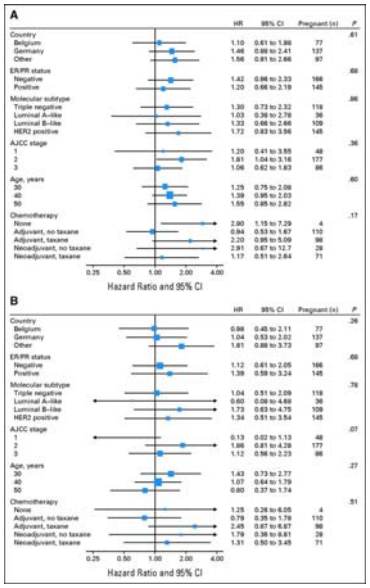
Pregnant patients:
Higher grade,
Higher stage,
Less ER+, more TN

Registry results

DFS: HR Pregnancy 1.34 (0.93-1.91, p=.14)
OS: HR Pregnancy 1.19 (0.73-1.93, p=.51)

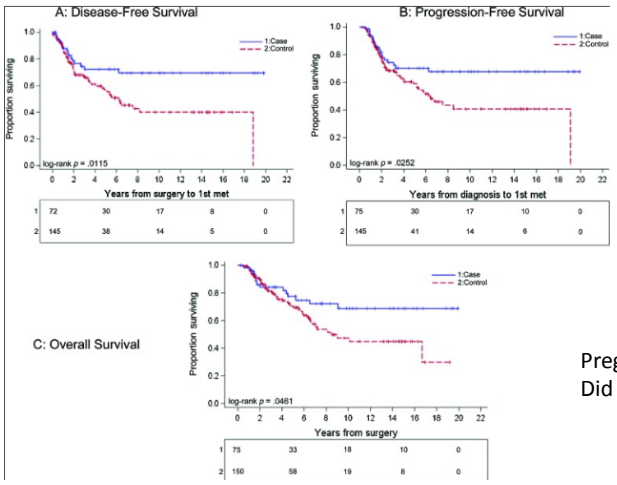


Amant F, et. al JCO 2013



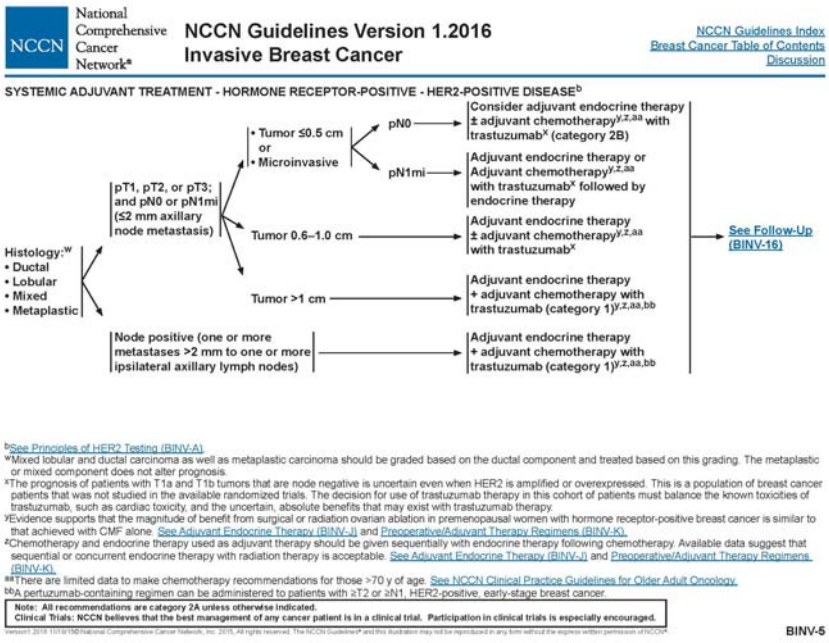
A: DFS, B: OS

Single Institution Cohort Study



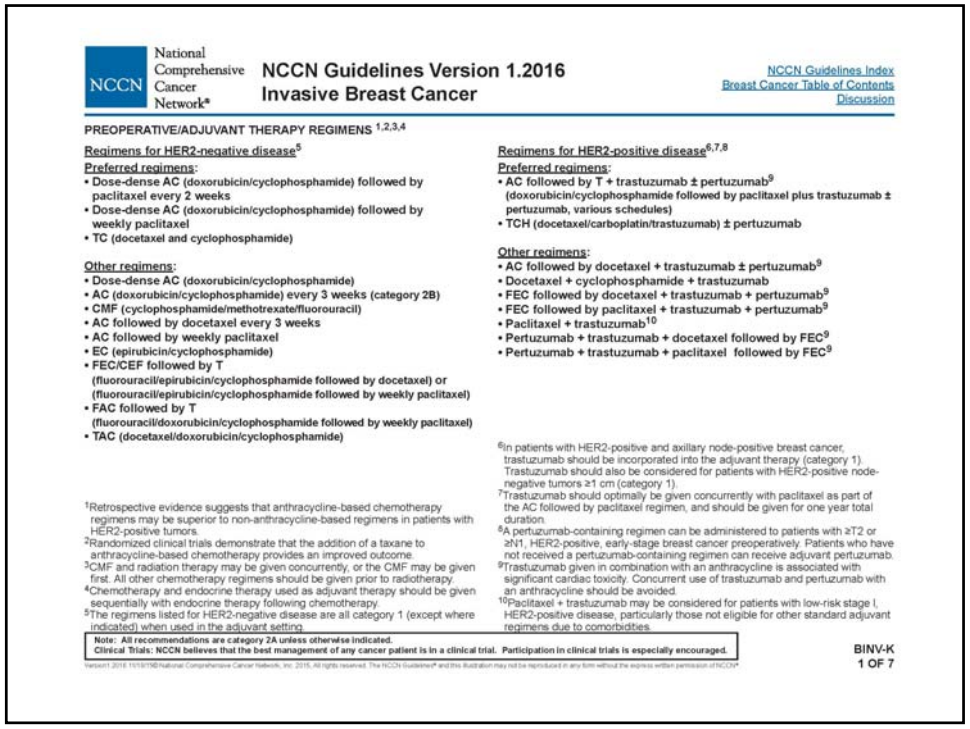
Pregnancy pts
Did better!

Litton J, Oncologist 2013



Chemotherapy during pregnancy

- Anthracyclines, cyclophosphamide (5 FU) safe during 2nd and 3rd trimester
- Taxanes not sufficiently studied
- Trastuzumab contraindicated
  - Oligohydramnios
  - Fetal effects



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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 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 (except where indicated) 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 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 significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[10]Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

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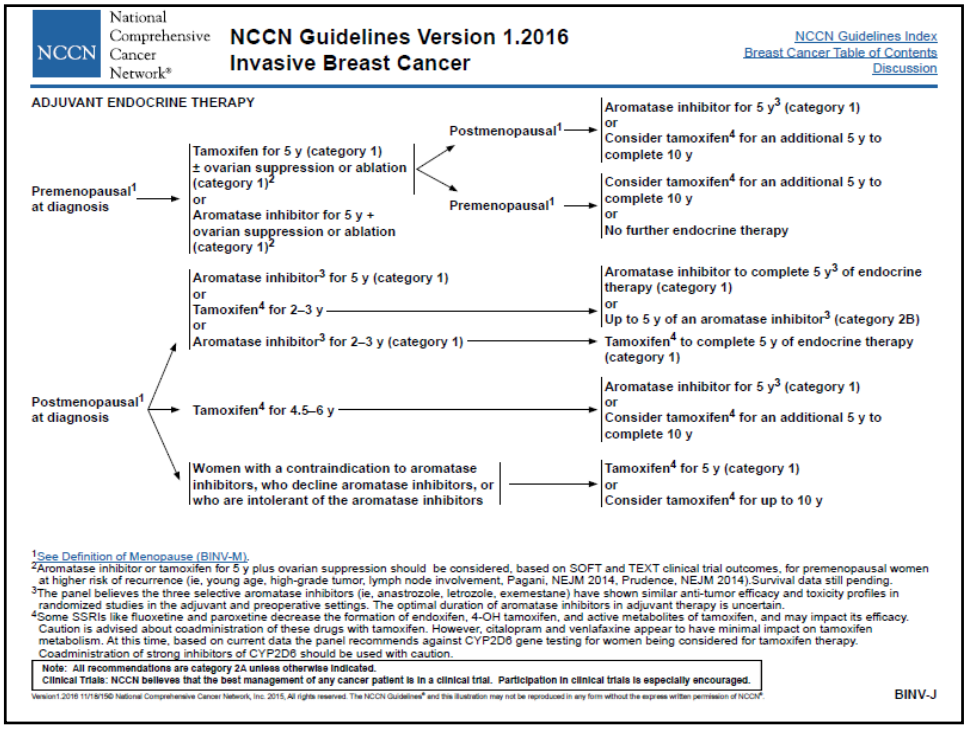
BINV-K
1 OF 7

Case #1

- Completing AC chemotherapy, every 3 weeks x 4
- Clinically responding to therapy with good partial response to AC
- Plan for adjuvant paclitaxel/trastuzumab followed by a year of trastuzumab after surgery

What is the optimal adjuvant endocrine therapy in this patient?



Endocrine Therapy: Tamoxifen or OFS/AI?

SOFT Trial: Efficacy Outcomes for OFS + Exemestane vs Tamoxifen Alone

5-Yr Outcome, %	OFS + Exemestane	Tamoxifen Alone	Risk Reduction	*P* Value
DFS	89.0	84.7	32	< .05
DDFS	93.0	90.7	29	< .05
FBC	90.9	86.4	36	< .05
OS	95.3	95.1	3	NS

Francis PA, et al. N Engl J Med. 2015;372:436-446.

Dual Therapy in SOFT: 5-Yr Breast Cancer–Free Interval With and Without Chemotherapy

Regimen, %	No Chemotherapy		Chemotherapy		Women < 35 Yrs of Age (94% Received Chemo)	
	5-Yr Breast Cancer Incidence	Relative Improvement	5-Yr Breast Cancer Incidence	Relative Improvement	5-Yr Breast Cancer Incidence	Relative Improvement
Tam	4.2		22.0		32.3	
OFS + Tam	4.9	5	17.5	22	21.1	---
OFS + AI	2.9	41	14.3	35	16.6	---

- Higher-risk pts received chemotherapy and benefited from its addition to OFS
- Pts who did not receive chemotherapy had such a low baseline risk that efficacy is difficult to assess

Francis PA, et al. N Engl J Med. 2015;372:436-446.

Case #2

- 60 y/o obese WF
- Menarche 16 y/o, G4 P4, menopause 45 y/o
- BCP X 3yrs, no HRT
- PMHx: bipolar, hypothyroidism
- FHx: neg.

Case #2

- PE: RB, 10:00, 2.3 X 2.0cm mobile mass, cN0
- Mam: RB, 10:00, 2.6 X 1.8 ill-defined stellate mass (BIRADS 4)
- Sono: RB, 10:00, 2.4 X 2.0 X 1.6 ill-defined hypo echoic irregularly shaped mass with posterior shadowing (BIRADS 4)
- Core biopsied

Case #2

- Path: IDC, Gr 1 , ER=100%, PR=100%, Her-2=neg. (IHC), Ki-67=10%
- cStage IIA (cT2 cN0 cM0)
- Large breast amenable to breast conserving surgery which pt. desired

Margins in Breast Conserving Therapy for Infiltrating Carcinoma

- SSO and ASTRO Consensus Guidelines for margins in Stage I & II cancer patients undergoing breast conserving surgery and WBI (2014)
- Meta-analysis on ~28,000 pts. with min. median follow up of 4 years in studies from 1965-2013
- No neo-adj. or pure DCIS in these guidelines

- J Clin Oncol. 2014 May 10;32(14):1507-15

Importance of Margins in Breast Conserving Therapy

- Pos. margin = ink on tumor (inv. or DCIS) at edge of resected tissue in breast conserving surgery
  - 2 fold increase in IBTR (regardless of XRT boost, ca. biology or systemic therapy)
- Neg. margin = NO ink on tumor at edge of resected tissue
  - Lowest risk of IBTR
  - Increase width doesn't lower risk

J Clin Oncol. 2014 May 10;32(14):1507-15

Importance of Margins in Breast Conserving Therapy

- Systemic therapy lowers IBTR
  - If not received, there is no evidence that wider margins add benefit compared with negative margins
- Women <40 y/o have increased IBTR regardless of width of negative margin
- EIC has no increased risk of IBTR if neg. margins

J Clin Oncol. 2014 May 10;32(14):1507-15

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MARGIN STATUS IN INFILTRATING CARCINOMA

The use of breast-conserving therapy is predicated on achieving a pathologically negative margin of resection. The NCCN Panel accepts the definition of a negative margin as "No ink on the tumor," from the 2014 Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guidelines on Margins.[1] Cases where there is a positive margin should generally undergo further surgery, either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to allow for breast-conserving therapy, this can be done with resection of the involved margin guided by the orientation of the initial resection specimen or re-excision of the entire original excision cavity.

It may be reasonable to treat selected cases with breast-conserving therapy with a microscopically focally positive margin in the absence of an extensive intraductal component (EIC).[2] For these patients, the use of a higher radiation boost dose to the tumor bed should be considered. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical doses are 10–16 Gy at 2 Gy/fx.

Margins should be evaluated on all surgical specimens from breast-conserving surgery. Requirements for optimal margin evaluation include:
- Orientation of the surgical specimens
- Description of the gross and microscopic margin status
- Reporting of the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin

[1]Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol. 2014 May 10;32(14):1507-15.
[2]An extensive intraductal component is defined as an infiltrating ductal cancer where greater than 25% of the tumor volume is DCIS and DCIS extends beyond the invasive cancer into surrounding normal breast parenchyma.

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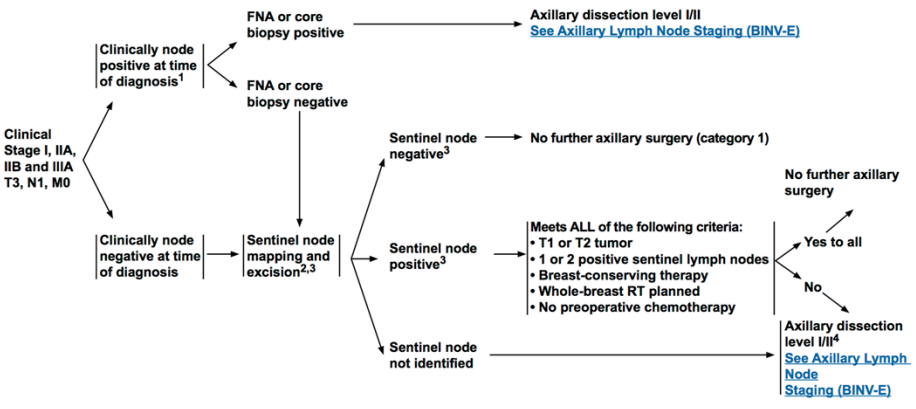
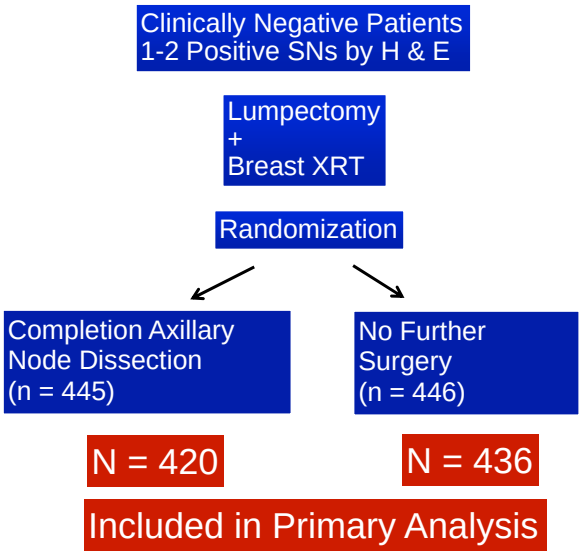
SURGICAL AXILLARY STAGING - STAGE I, IIA, IIB and IIIA T3, N1, M0



[1]Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound-guided FNA or core biopsy in determining if a patient needs axillary lymph node dissection.
[2]Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal.
[3]Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision making.
[4]For patients with clinically negative axillae who are undergoing mastectomy and for whom radiation therapy is planned, axillary radiation may replace axillary dissection level I/II for regional control of disease.

ACOSOG Z0011



Target Accrual: 1900 women (500 deaths)
Actual Accrual: 891 pts (94 deaths)

Giuliano AE, et al. *JAMA.* 2011;305(6):569-575.

ACOSOG Z0011

Endpoint	SNB Alone	Completion AND	*P* value
Additional Positive Nodes on AND	N/A ??	27.3% 97 pts	
5-Year In-Breast Recurrence	2.1%	3.7%	0.16
5-Year Axillary Nodal Recurrence	1.3%	0.6%	0.44
5-Year Overall Survival	92.5% (90-95.1)	91.8% (89.1-94.5)	HR: 0.87 .25
5-Year DFS	83.9% (80.2-87.9)	82.2% (78.3-86.3)	HR: 0.88 .14

Giuliano AE, et al. *JAMA.* 2011;305(6):569-575.

ACOSOG Z0011: Conclusions

- T1-2, cN0 BC pts undergoing lumpectomy and XRT
  - cN0 = non-palpable
- If 1-2 SLN+ for macromets., no ALND or additional radiation fields needed
- No difference in L/R recur, DFS or OS in ALND vs No ALND group (6.3 yr F/U)

Giuliano AE, et al. JAMA. 2011;305(6):569-575.

Recommendations for SLN+

- SLN-, don't do ALND
- SLN+ (micromets), don't do ALND whether lumpectomy or mastectomy
  - Don't do routine IHC to find micromets
- SLN+ (macromets), don't do ALND if only 1-2 + nodes, having lumpectomy and receiving WBI and systemic tx
  - 2/3 of all node + pts. have only 1-2 nodes pos.

When is ALND required ?

- cN pos
- IBC
- >2 + SLN (macromet)
- Gross extra-nodal tumor extension
- Resid. palp nodes after SLN bx
- SLN + (macromet) having mastectomy
- SLN + (macromet) not receiving XRT or systemic tx

Case #2

- Surgery: partial mastectomy with SLN bx converted to ALND. Several (4) nodes clinically pos. during surgery led to conversion
- Path:
  - Breast: IDC 3.2cm, biology unchanged, LVI+, EIC+, closest margins 2mm for IDC and 1mm for DCIS others widely clear
  - LN: 5/11 pos. nodes, largest 1.8cm with extra-nodal extension
  - pStage IIIA (pT2 pN2 M0)

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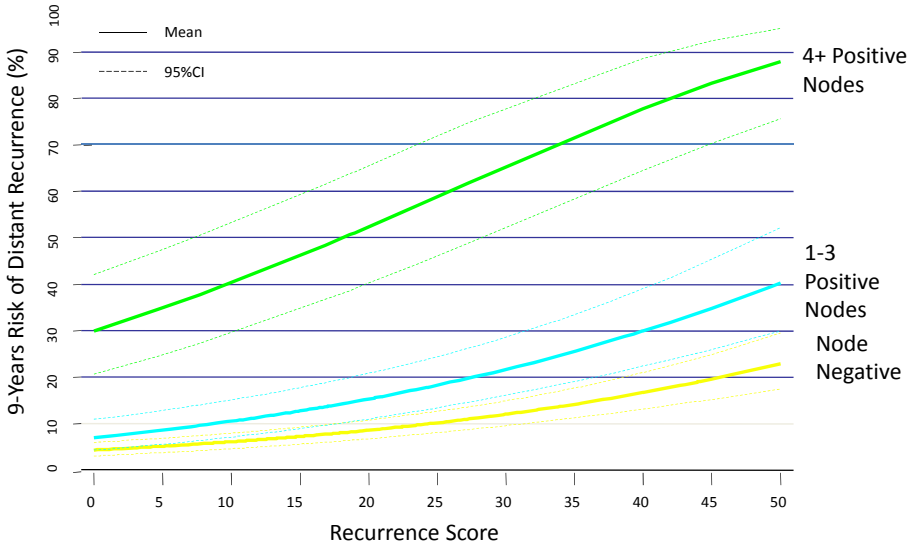
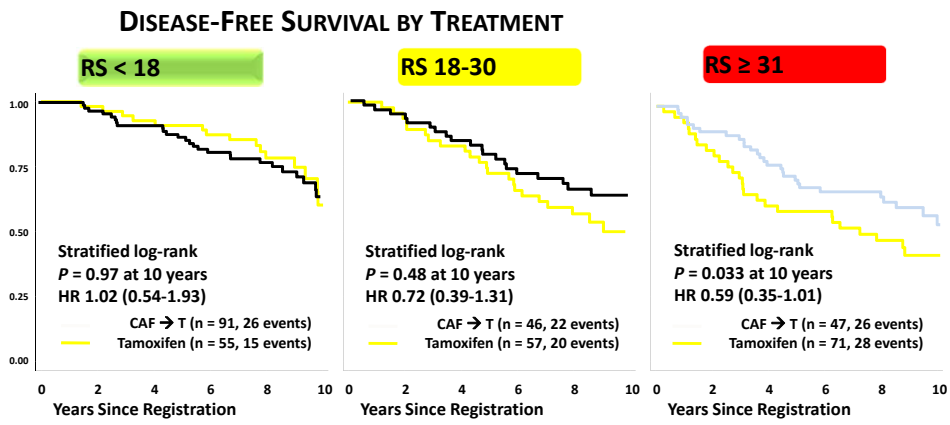
Results: For Any Recurrence Score the Rate of Distant Recurrence Increases with the Number of Positive Nodes



Dowsett et al., SABCS 2008, Abstract # 53

Does chemotherapy help all node positive patients?
Biology may play a larger role than anatomy



Albain KS, et al. *Lancet Oncol*. 2010;11(1):55-65.

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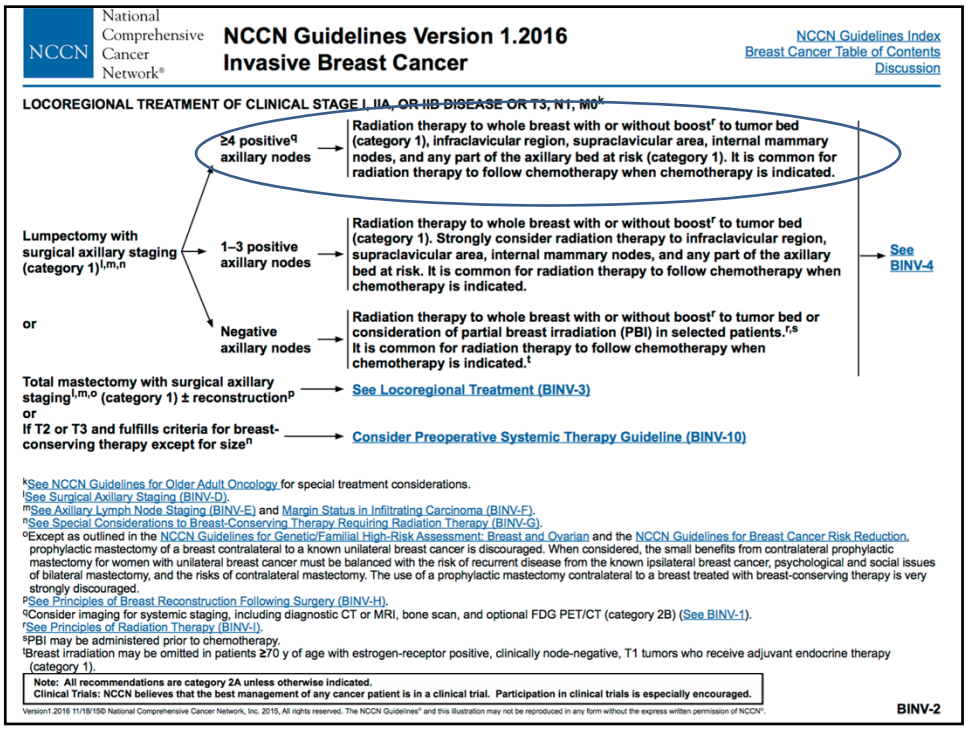

Case # 3

- 79 yo WF presented in 2009 with breast mass
- Core biopsy showed ILC with ductal component, grade 2 ER+PR+Her2-. Palpable axillary LN +
- Underwent bilat mastectomies:
  - Left 7.4 cm infiltrating ductal cancer with associated comedo DCIS 13/19 LNs positive
  - Right, 2 cm intracystic papillary cancer with negative margins, 6 LNs negative
  - PET/CT scan internal mammary nodes +

Intracystic Papillary Carcinoma (IPC)

- <1% of breast cancers
- Pure form or associated with IDC or DCIS
- Dx: Micro: IHC for absence of intact myoepithelial cell layer
  - Present=benign
  - Absent=malignant

YA Bndkaddour, et al Obstet Gynecol. 2012; 2012: 979563

Intracystic Papillary Carcinoma (IPC)

- Treatment:
  - Pure form: surgical resection alone, no data to support any additional therapy
  - Associated with IDC or DCIS: target adjuvant XRT or endocrine based on this component
- Prognosis:
  - Pure form: Excellent with exc. alone
  - Associated IDC or DCIS: determines prognosis

YA Bndkaddour, et al Obstet Gynecol. 2012; 2012: 979563

Case #3

- Adjuvant TC X 6
- RT to chest wall, SCLNs and IM LNs
- Began letrozole 10/09
- Tolerated it well with good adherence
- 11/15 presented with mild-mod pain in lower back x 2 months, not precipitated by trauma or movement, slowly worse
- Obtained laboratory showed increase tumor marker

Case #3

- Bone scan: Extensive osseous disease in calvarium, multiple levels thoracic and lumbar spine, most pronounced in L1, pelvic, L distal humerus
- CT CAP: No definite disease, questionable lesion L1, no vertebral compression
- CA15-3 974; CEA 99

What 1st line therapy should the patient begin?

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Invasive Breast Cancer

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ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Premenopausal patients with hormone-receptor positive disease should have ovarian ablation/suppression and follow postmenopausal guidelines

Postmenopausal Patients
- **Non-steroidal aromatase inhibitor (anastrozole, letrozole)**
- **Steroidal aromatase inactivator (exemestane)**
- **Exemestane + everolimus[1]**
- **Palbociclib + letrozole[2]**
- **Palbociclib + fulvestrant (category 1)[3]**
- **Fulvestrant[4]**
- **Tamoxifen or toremifene**
- **Megestrol acetate**
- **Fluoxymesterone**
- **Ethinyl estradiol**

[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).
[2]Palbociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.
[3]For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on endocrine therapy.
[4]A single study (S0226) in women with hormone receptor-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.

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.

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PALOMA3 Study Design

Double blind Phase 3

- HR+, HER2– ABC
- Pre-/peri-* or post-menopausal
- Progressed on prior endocrine therapy:
  - On or within 12 mo adjuvant
  - On therapy for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

*All received goserelin.

2:1 Randomization

N=521

Stratification:
- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-/peri- vs Post-menopausal

n=347 → **Palbociclib (125 mg QD; 3 wks on/1 wk off) + Fulvestrant† (500 mg IM q4w)**

n=174 → **Placebo (3 wks on/ 1wk off) + Fulvestrant† (500 mg IM q4w)**

- ***Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.***

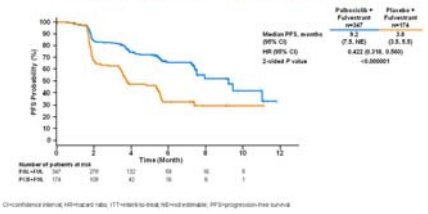
†administered on Days 1 and 15 of Cycle 1.

Primary endpoint: PFS

Clinicaltrials.gov NCT01942135

PALOMA-3:
Efficacy and safety

Primary Endpoint: PFS (ITT Population)



Adverse Events—All Cause

AE, %	Palbociclib + Fulvestrant (n=345)			Placebo + Fulvestrant (n=172)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE	98	59	11	89	16	2
Neutropenia	79	53	9	3	0	1
Leukopenia	46	25	1	4	0	1
Anemia	26	3	0	10	2	0
Thrombocytopenia	19	2	1	0	0	0
Fatigue	38	2	0	27	1	0
Nausea	29	0	0	26	1	0
Headache	21	<1	0	17	0	0
Upper respiratory infection[a]	19	<1	0	16	0	0
Diarrhea	19	0	0	17	1	0
Constipation	17	0	0	14	0	0
Alopecia	15	0	0	6	0	0

Turner NC, et. al. NEJM 2015

Case #3

- Letrozole D/C
- Began Fulvestrant/Palbociclib 12/15
- Also began denosumab
- Good tolerance; mild neutropenia
- Initial tumor markers at 6 weeks were CA15-3 686, CEA 65

Three Identical International, Randomized, Double-Blind, Active-Controlled Trials

Enrollment Criteria

- Adults with breast, prostate, or other solid tumors and bone metastases or multiple myeloma
- No current or prior IV bisphosphonate administration for treatment of bone metastases

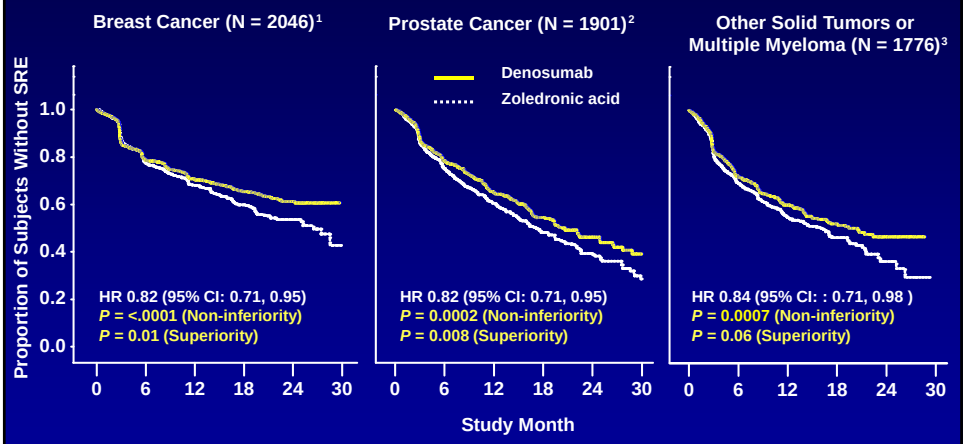
Denosumab 120 mg SC and Placebo IV* every 4 weeks (N = 2862)

Supplemental Calcium and Vitamin D Recommended

Zoledronic Acid 4 mg IV* and Placebo SC every 4 weeks (N = 2861)

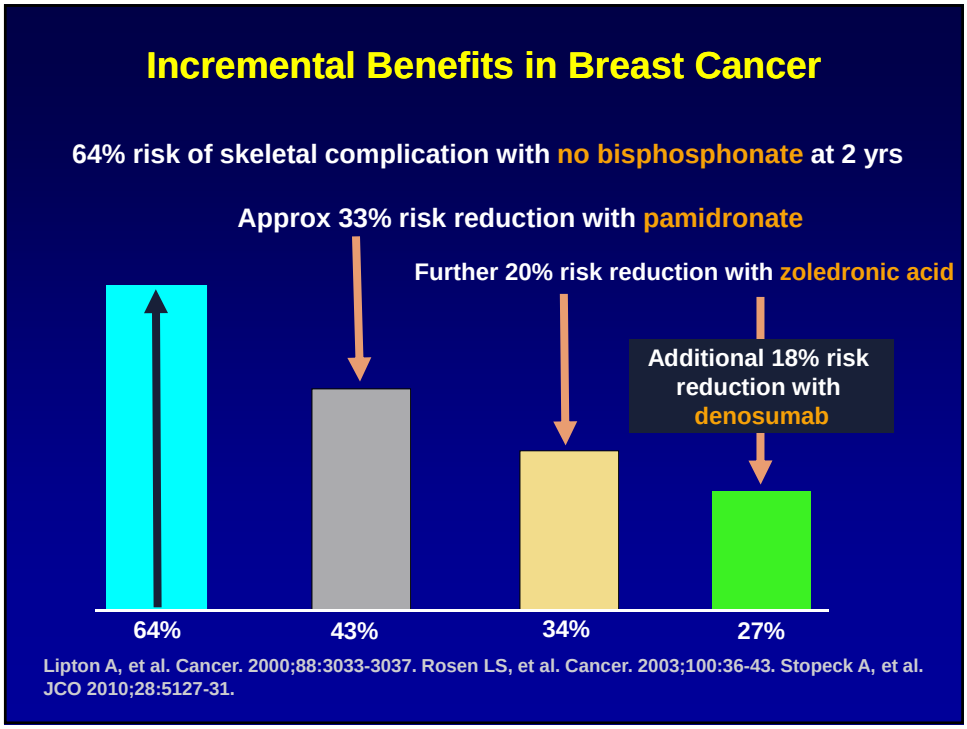
1° Endpoint	•Time to first on-study SRE (non-inferiority)
2° Endpoints	•Time to first on-study SRE (superiority) •Time to first and subsequent on-study SRE (superiority)

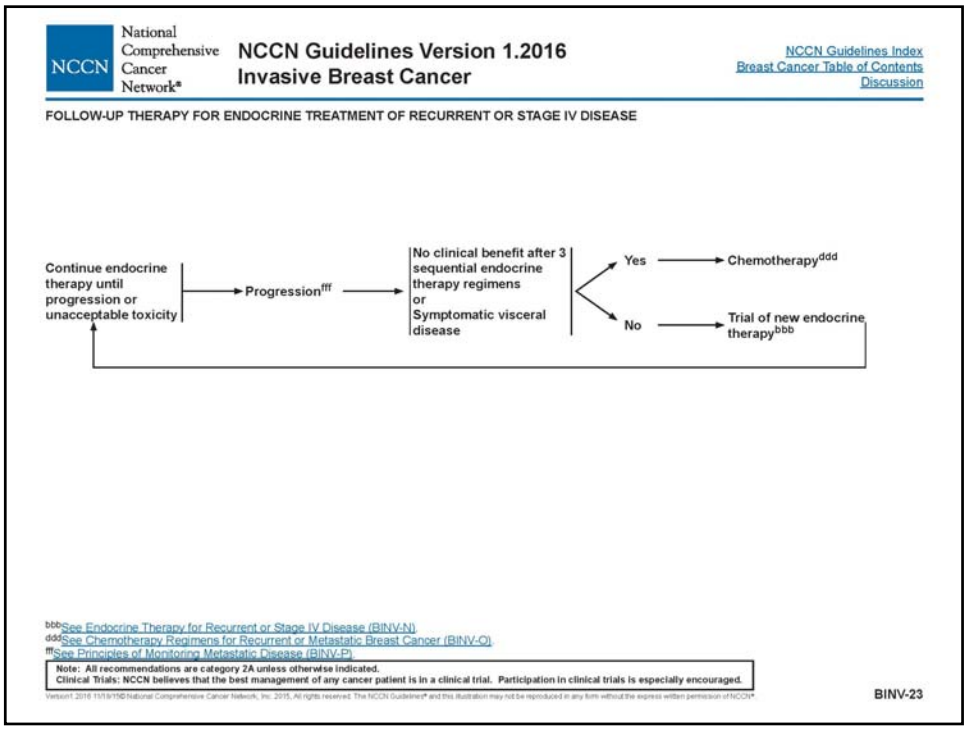
Primary Endpoint: Time to First On-Study SRE



* All data come from the primary analysis phase of these studies

[1]Stopeck A et al. *Eur J Cancer Suppl.* 2009;7:2(Abs 2LBA); [2]Fizazi K, et al. *J Clin Oncol.* 2010; 28:18s, (Abs LBA4507); [3]Henry D, et al. *Eur J Cancer Suppl.* 2009;7:11(Abs 20LBA)





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