18th Multidisciplinary Management of Cancers: A Case-based Approach

Breast Tumor Board 2018

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18th Multidisciplinary Management of Cancers: A Case-based Approach

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Case 1: Locally advanced breast cancer

- A 52-year-old premenopausal woman with a history of rheumatoid arthritis presents to you with a self detected large left axillary mass and pain radiating down the left arm
- On exam, her breasts are symmetrical with no skin changes. No masses are palpable in the left breast and the nipple areolar complex is normal. There is left infraclavicular fullness. In the left axilla, matted nodes are palpable measuring 5 x 5 cm. There is no left arm edema. The right breast is unremarkable.

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Case 1: Locally advanced breast cancer

- Mammography reveals a 5.5 cm lobulated calcified mass in the left axillary tail
- Ultrasound of the left breast and axilla reveals a 4.9 cm lobulated vascular mass at the site of the lump in the axillary tail, and abnormal left axillary lymph nodes with the largest measuring 3 cm

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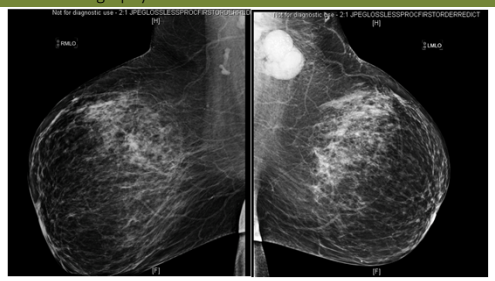
Case 1: Mammography



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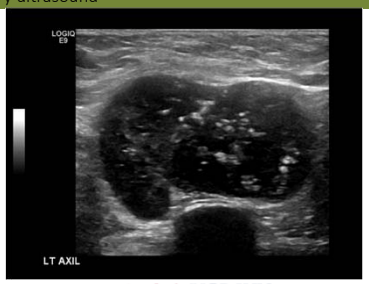
Case 1: Axillary ultrasound



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Case 1: Locally advanced breast cancer

- A breast MRI is ordered and reveals multiple left axillary masses, infraclavicular and supraclavicular nodes. No abnormal enhancement is seen in left breast. Right breast is benign.
- It is favored that the 4.7 cm dominant axillary mass at 2:30, 15cm from the nipple, represents the primary breast carcinoma.
- A staging PET/CT scan reveals:
  - Bulky FDG avid nodes in left axilla, subpectoral, and supraclavicular areas
  - Primary breast cancer not visualized
  - No distant metastases

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Case 1: Locally advanced HER2-positive breast cancer

- A core biopsy of axillary mass is pursued and reveals:
  - Poorly differentiated metastatic carcinoma most c/w breast origin in an axillary lymph node
  - ER 2%, PR 2%, HER2 3+ via IHC
  - Ki-67 = 40%
- She is staged as having TX N3c M0 Clinical Stage IIIC disease

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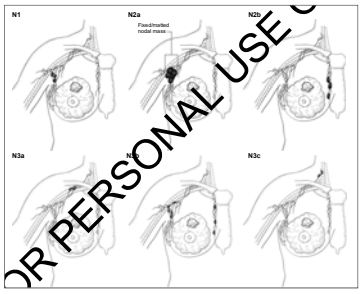
Case 1: Anatomic nodal stage is N3c



AJCC Staging Manual 8th edition, 2017
Breast chapter
Hortobagyi et al.

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Case 1: Treatment of locally advanced HER2-positive breast cancer

- She is treated with neoadjuvant docetaxel, carboplatin, trastuzumab and pertuzumab (TCH+P) for 6 cycles
- Palpable residual disease remains after chemotherapy clinically.
- A repeat breast MRI reveals:
  - The largest axillary lesion decreased from 49 to 23 mm
  - All lesions decreased in size consistent with treatment response
  - No new lesions
  - No left breast primary tumor identified

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Case 1: For surgical management, you recommend:

1. Mastectomy and ALND
2. ALND only
3. Lumpectomy and ALND

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Case 1: Surgery

- She undergoes bilateral breast reduction with left axillary nodal dissection
- Pathology reveals:
  - No evidence of carcinoma or treatment effect in the breast
  - 25/33 nodes involved with residual carcinoma
  - Extensive extra-capsular extension
  - ER-negative, PR-negative
  - HER2-positive (IHC 2+, FISH ratio 1.42, HER2 copies/cell = 7.4, AMPLIFIED)
  - Ki-67 40%

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Case 1: Regarding adjuvant radiotherapy, you recommend:

1. Whole breast and regional nodal irradiation
2. Regional nodal irradiation only

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Case 1: Regarding adjuvant systemic therapy, you recommend:

1. Adjuvant trastuzumab
2. Adjuvant trastuzumab + pertuzumab
3. Adjuvant capecitabine + trastuzumab
4. Adjuvant capecitabine + trastuzumab + pertuzumab
5. Adjuvant trastuzumab followed by adjuvant neratinib for one year

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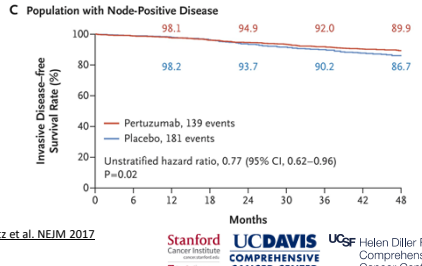
Case 1: APHINITY adjuvant HER2+ (trastuzumab + pertuzumab/placebo for 1 year)



von Minckwitz et al. NEJM 2017

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Case 1: ExteNET – Study Design

Early Stage Breast Cancer
HER2+

Stratification Factors:
- Nodes 0, 1-3, vs 4+
- ER/PR status
- Concurrent vs sequential trastuzumab

1:1 RANDOMIZATION
N=2840

Neratinib x 1 yr
240 mg/day
N=1420

Placebo x 1 yr
N=1420

Primary Analysis
2-year follow-up for IDFS

Exploratory Analysis
5-year follow-up for IDFS

Overall survival

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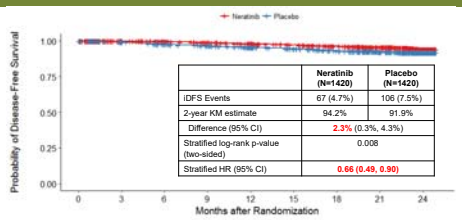
Case 1: ExteNET primary analysis



	Neratinib (N=1420)	Placebo (N=1420)
iDFS Events	67 (4.7%)	106 (7.5%)
2-year KM estimate	94.2%	91.9%
Difference (95% CI)	2.3% (0.3%, 4.3%)	
Stratified log-rank p-value (two-sided)	0.008	
Stratified HR (95% CI)	0.66 (0.49, 0.90)	

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Case 1: Adjuvant treatment

- She completes whole breast and regional nodal irradiation with concurrent capecitabine
- She completes 6 months of adjuvant capecitabine and one year of trastuzumab + pertuzumab
- She declines endocrine therapy and neratinib
- She remains NED

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Case 1:

END OF CASE 1

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Case 2: Male Breast Cancer

- A 72-year-old man presents with a lump in the right breast and skin changes involving the nipple and areola.
- Family history is significant for ovarian cancer in his mother at age 80 and early onset breast cancer in a maternal first cousin at age 30.
- On exam, he has a 4 x 5 cm right retroareolar mass with nipple retraction and matted right axillary nodes measuring 4 cm. Dermal involvement by carcinoma is noted.
- An ultrasound is ordered and reveals:
  - 3.9 cm retroareolar mass at 2 o'clock
  - Multiple right axillary nodes up to 2.9 cm

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Case 2: Male Breast Cancer

- Right breast core biopsy is pursued and reveals:
  - IDC grade 3
  - ER 99%
  - PR 99%
  - HER2 negative (DISH ratio 1.2)
- Right axillary node core biopsy reveals metastatic carcinoma
- CT CAP and bone scan negative for distant metastases
- Clinical stage: cT4 N2 M0 -- Stage IIIB

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Case 2: Male Breast Cancer -- RISK FACTORS

- 0.7% of all breast cancer diagnoses
- Testicular dysfunction (crytporchidism, orchitis, infertility)
- Klinefelter's syndrome (XXY): 3-7% (50-fold increase)
- Family history of female breast cancer (2.5-fold increase risk)
- Prior radiation therapy to the chest
- Genetic predisposition

Giordano SH *The Oncologist* 2005

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Case 2: Male Breast Cancer

- He declines genetic testing
- Neoadjuvant chemotherapy is pursued with doxorubicin and cyclophosphamide (AC) x 4 followed by paclitaxel weekly x 12

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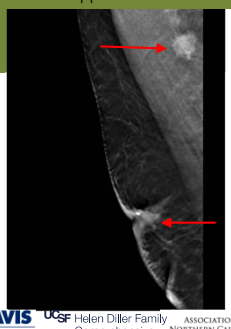
Case 2: Male Breast Cancer

- Mammogram post-neoadjuvant chemotherapy reveals interval decrease in the size of breast mass and axillary disease
  - Mass 3.6 -> 3.2 cm
  - Largest axillary node 2.8 -> 1.7 cm
- Clinically, the NAC is retracted with no dominant mass and he no longer has palpable axillary adenopathy



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Case 2: The next best step in management is:

1. Modified radical mastectomy
2. Simple mastectomy + SLNB
3. Lumpectomy + SLNB

Case 2: Male Breast Cancer

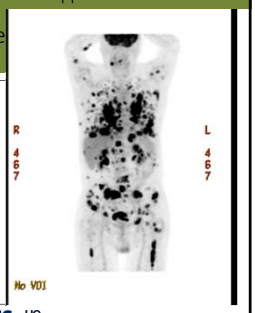
- He undergoes right simple mastectomy + SLNB
- Pathology reveals:
  - IDC, grade 3, multiple residual foci spanning 2.1 x 1.6 cm (cellularity 10%)
  - 1/6 SLNs positive with a 4 mm deposit and no ECE
  - No LVI, no nipple involvement, no skeletal muscle involvement, margins negative
  - ypT2 ypN1a
  - Estrogen Receptor POSITIVE (>95%, 3+)
  - Progesterone Receptor: POSITIVE (50%, 1-3+)
  - HER2 negative
  - Ki67: 1-5%

Case 2: Male Breast Cancer

- Post-mastectomy chest wall and regional nodal radiation is pursued:
  - 50 Gy in 25 fractions to the right chest wall and right supraclavicular fossa
  - Boost to the mastectomy scar given his initial T4 disease
- Tamoxifen is started

Case 2: Male Breast Cancer - relapse

- 2 years later he presents with dyspnea, failure to thrive, unintentional weight loss and hypercalcemia
- He is admitted, fluid resuscitated, and given zoledronic acid
- He agrees to genetic testing and tests positive for a germline mutation in BRCA2



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Case 2: The next best step in management is:

1. AI + LHRH analog
2. AI + LHRH analog + CDK4/6 inhibitor
3. Chemotherapy
4. PARP inhibitor

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Phase III OLympiAD Trial
(Olaparib in Advanced Disease)

Metastatic germline BRCA+ breast cancer

Prior anthracycline/taxane

0-2 prior tx for mBC

No prior platinum

→ Physician's choice (capecitabine, vinorelbine, eribulin)

→ Olaparib

Primary endpoint: PFS (no cross-over)

Secondary: OS, PFS2

Planned sample size: 310 patients

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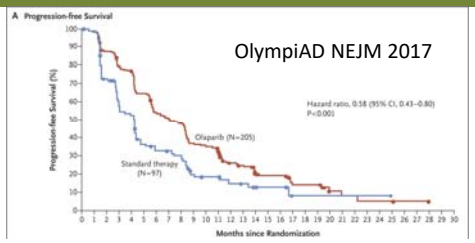
Case 2: Olaparib for MBC with BRCA mutations



OlympiAD NEJM 2017

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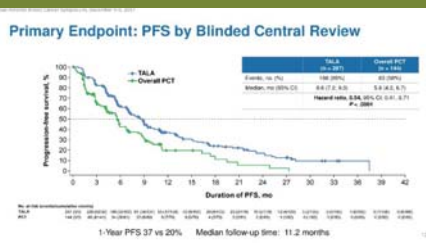
Case 2: EMBRACA: Talazoparib for MBC with BRCA mutations



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Case 2: Male Breast Cancer - relapse

- He was given a single dose of carboplatin with improvement of symptoms
- He then started single agent olaparib with excellent response

Case 2: At the time of progression on PARPi which would be relatively contraindicated?

1. Capecitabine
2. Endocrine therapy
3. Platinum-based chemotherapy
4. Taxanes

Case 2

END OF CASE 2

Case 3: Early stage ER+/HER2- breast cancer

- A 52-year-old postmenopausal woman with a strong family history of breast cancer is noted to have a palpable right upper inner breast mass during a routine clinical breast exam without axillary lymphadenoathy
- Diagnostic mammography reveals a spiculated lesion in the RUIQ with associated calcifications. On ultrasound, the mass measures 2 x 1.9 cm. No suspicious axillary nodes are noted.

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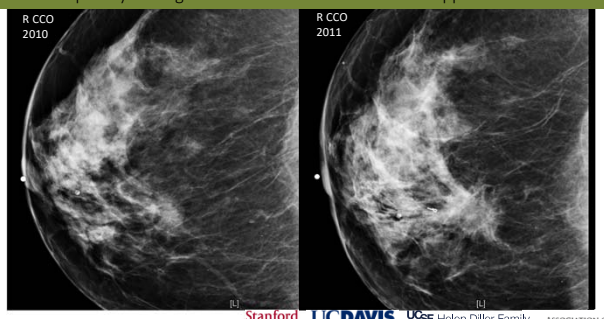

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Case 3: Early stage ER+/HER2- breast cancer

- Core biopsy
  - IDC, grade 2
  - ER/PR both 3+ (95%)
  - HER2 negative (0 by IHC)
- She tests negative for mutations in BRCA1 and BRCA2
- She undergoes lumpectomy and SLNB
  - 4 cm grade 2 IDC, SLNB 0/1 – All margins greater than 5 mm
  - High-grade DCIS – 1 mm anterior margin

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Case 3: Based on the reported pathological findings you recommend:

1. Re-excision
2. No further surgery
3. Mastectomy

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Case 3: ER+ breast cancer with DCIS (Margins)

- SSO & ASTRO Guidelines 2013 invasive carcinoma
  - "NO TUMOR ON INK"
- SSO/ASCO/ASTRO Guidelines 2016 Pure DCIS (Rx BCT + WBRT)
  - For DCIS 2 mm margin is adequate
  - >2 mm does not improve IBTR
  - <2 mm may be okay if other risk factors low
  - DCIS with micro-invasion (<1 mm) treat as pure DCIS
- Invasive cancer + DCIS = NO TUMOR ON INK

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Case 3: Early stage ER+/HER2- breast cancer

- She undergoes re-excision with no residual disease
- Pathologic Anatomic Stage IIA, T2 N0 M0
  - If she were diagnosed today her Pathologic Prognostic Stage would be IA
- She receives adjuvant docetaxel and cyclophosphamide x 4 cycles
- She completes whole breast radiation

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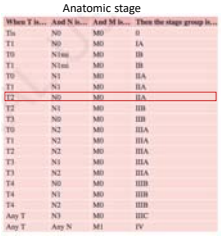
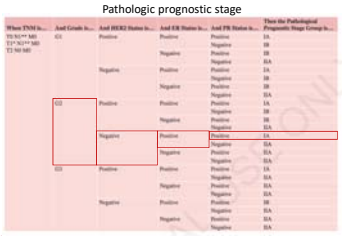
Case 3: Early stage ER+/HER2- breast cancer

Anatomic stage



Pathologic prognostic stage



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Case 3: ER+ breast cancer

- She begins anastrozole
- However, she discontinues after 6 months due to significant joint pain and is lost to follow up

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Case 3: Recent phase III data shows improvement of AI-related joint pain with which of the following:

1. Glucosamine chondroitin sulfate
2. Weight-bearing exercise
3. Acetaminophen
4. Acupuncture

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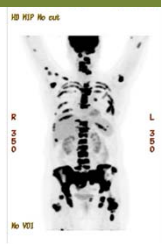
Case 3: Accupuncture improved AI-related joint pains

- **Phase III SWOG S1200 trial (SABCS 2017; Hershman et al)**
  - 226 patient Randomized (2:1:1) Acupuncture : Sham : Nothing
  - Acupuncture – Bi-weekly x 6 weeks, then weekly x 6 weeks
  - Brief Pain Inventory – Short Form (14 questions)
  - Acupuncture led to significantly significant decrease in pain
  - Major decreases in pain in 58% : 33% : 31% for Acupuncture : Sham : Nothing

Case 3: ER+ breast cancer -- Relapse

- She is lost to follow-up for 3 years and then presents with back pain
- PET/CT shows diffuse FDG avid bone metastases as well as hilar and internal mammary nodes



Case 3: For first line metastatic treatment, you recommend:

1. Single agent aromatase inhibitor
2. Letrozole + CDK4-6 inhibitor
3. Fulvestrant
4. Fulvestrant + CDK4-6 inhibitor

Case 3: CDK4/6 inhibitors – A new paradigm in ER+ HER2- MBC

	Palbociclib	Ribociclib	Abemaciclib
1st line studies:	**Paloma-2**	**Monaleesa-2**	**Monarch-3**
Endocrine Partner:	Letrozole	Letrozole	Letrozole/Anastrozole
PFS (months):	24.8 vs 14.5 HR = 0.58	25.3 vs 16.0 HR = 0.556	NR vs 14.7 HR = 0.53
		Monaleesa-7 Tam/NSAI + OS 23.8 vs 13.0 HR = 0.553	
Prior endocrine tx:	**Paloma-3**	**Monaleesa-3**	**Monarch-2**
Endocrine Partner:	Fulvestrant	Fulvestrant	Fulvestrant
PFS (months):	11.2 vs 4.6 HR = 0.5	Pending	16.4 vs 9.3 HR = 0.55

Case 3: CDK4/6 inhibitor toxicity

Drug	Dosing	Neutropenia Grade 3/4	Diarrhea Grade 3/4	QTc	Hepatotoxicity Grade 3/4	VTE	CNS penetration
Palbociclib	125 mg QD 3/1 wks	66%	1%	n/a	n/a	n/a	? (less)
Ribociclib	600 mg QD 3/1 wks	59%	1%	⇧ 22.9 ms EKG C1D0, C1D15	11% LFTs q2w x2m	n/a	?
Abemaciclib	150/200 mg (combo/mono) BID continuous	22-32%	13%/20% loperamide required	n/a	2-4% LFTs q2w x2m	5%	Yes

Adapted from Castrellon AB et al. 2017

Case 3: Recurrent ER+ breast cancer

- She starts letrozole + palbociclib with significant improvement in pain, ambulation
- After 2 years, she progresses with multiple areas of visceral involvement

Case 3: Recurrent ER+ breast cancer

- She undergoes expanded germline testing and tests positive for a deleterious PALB2 mutation
- She is now being treated on a clinical trial of talazoparib (PARPi) for patients with beyond BRCA homologous recombination pathway gene mutations

Case 3:

END OF CASE 3

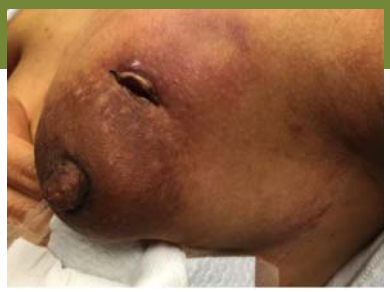
Case 4:

- A 34 woman notes a left breast mass while breast feeding that is increasing in size
- She is referred for ultrasound which reveals a 5.4 cm mass in the superior left breast and left axillary LAD
- US-guided core biopsy is pursued: 5 cores, 14 G needle
  - "Marked lymphocytic infiltrate with atypia, favor chronic mastitis"
  - Axillary node with benign lymphoid tissue

Case 4:

- Now 3 months after initial detection, the mass continues to increase in size with new pain and erythema of the overlying skin
- She undergoes incision and drainage of a suspected abscess vs cyst
  - Pathology showed crushed epithelial proliferation consistent with invasive mammary carcinoma
  - ER negative, PR negative, HER 2 negative by IHC
  - Ki-67 >95%

Case 4:



Case 4: Post-partum locally advanced TNBC

- Staging CT CAP is performed showing left breast skin thickening and multiple enlarged left axillary nodes. No distant metastases are noted.
- BRCA1/2 testing is negative.

Case 4: For initial management, you recommend:

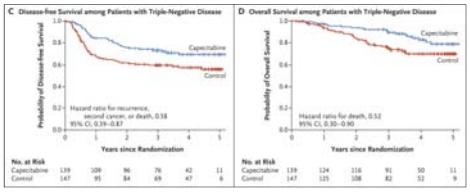
1. Mastectomy and ALND
2. Neoadjuvant dose dense AC followed by paclitaxel (AC-T)
3. Neoadjuvant docetaxel + cyclophosphamide (TC)
4. Neoadjuvant dose dense AC followed by paclitaxel + carboplatin (AC-TP)

Case 4: Post-partum locally advanced TNBC

- She is treated with preoperative dose dense AC followed by 4 cycles of paclitaxel
- She undergoes lumpectomy and SLNB that reveals:
  - Multiple small foci of invasive carcinoma within the tumor bed with the largest focus measuring 3 mm (total tumor bed 32 x 23 mm; 30% cellularity: 90% in situ + 10% invasive)
  - Extensive high-grade DCIS
  - 0/6 LNs
  - ypT1a ypN0
  - Residual Cancer Burden = 1.352, RCB-I
- She completes radiation (50 Gy to breast and regional nodes with 10 Gy boost to lumpectomy cavity)

Case 4: Post-partum locally advanced TNBC

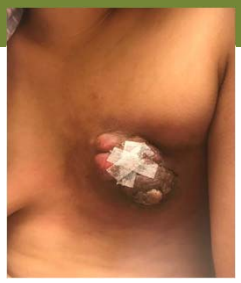
- She declines adjuvant capecitabine (CREATE-X)



Masuda et al. NEJM 2017

Case 4: One year later . .

- She presents with multiple skin/subcutaneous masses in the upper inner left breast
- Biopsy confirms TNBC involving dermis
- Staging PET/CT shows a single FDG avid contralateral axillary node concerning for metastasis
  - She declines biopsy

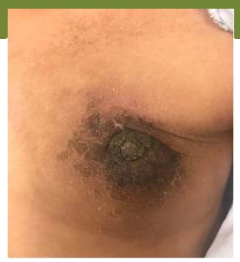


Case 4: At this point, you recommend

1. Mastectomy
2. Chemotherapy without locoregional intervention
3. Repeat chemotherapy followed by left mastectomy and radiation

Case 4:

- She is treated with single agent carboplatin with rapid response in the left breast disease
- She proceeds with left mastectomy and bilateral axillary sampling that reveals:
  - Two areas of residual invasive carcinoma 2.4 and 1.2 cm (5% cellularity)
  - 0/2 left and 0/1 right axillary nodes
- Repeat irradiation and capecitabine are planned

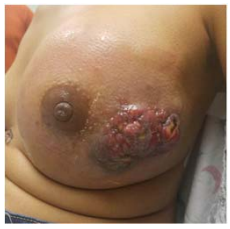


Case 4:

END OF CASE 4

Case 5:

- A 35-year-old premenopausal woman presents with a left breast mass that has been enlarging for the last 8 months
- She also endorses low back and right hip pain as well as unintentional weight loss
- On exam, the entire breast is firm and replaced by tumor with skin nodules in the lateral breast.
- She has a palpable 3.5 cm infraclavicular node and matted left axillary nodes



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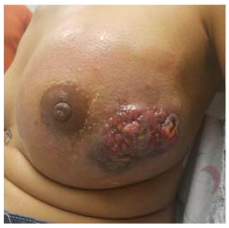
Case 5:

- Biopsy reveals invasive ductal carcinoma
  - Histologic grade 3
  - ER 0%, PR 0%, HER2 negative
  - Ki-67 60-70%



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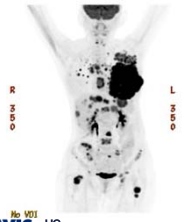
Case 5: Metastatic Breast Cancer

- Staging PET/CT scan shows widely disseminated lung, liver and bone disease including a T12 vertebral fracture
- She receives palliative XRT to spine and right hip
- She begins zoledronic acid
- Expedited germline panel testing is negative



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Case 5:

- She is recommended for carboplatin + taxane combination chemotherapy, but declines taxane therapy due to concerns about toxicity.
- After struggling to decide if she wants any treatment at all, she agrees to single agent carboplatin

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Case 5:

- She receives carboplatin AUC 6 for 2 cycles with clinical disease progression
- Combination chemotherapy with AC or TC is recommended.
- She initiates AC with partial response to treatment after 4 cycles, but disease progression is noted clinically during cycle 5

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Case 5: At this point, you recommend:

1. Palliative care / hospice
2. Taxane chemotherapy
3. Eribulin
1. Pursuit of a clinical trial

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Case 5: Additional interrogation of her tumor is pursued to evaluate for possible clinical trial/therapy options

TUMOR TYPE: BREAST INVASIVE DUCTAL CARCINOMA (IDC)

Genomic Alterations Identified†

AKT1 E17K
AR amplification – equivocal*
NF1 loss exons 12-29
RAF1 amplification
CCNE1 amplification
CRK1 amplification – equivocal*
TP53 V173L

Additional Findings†

Microsatellite status MS-Stable
Tumor Mutation Burden TMB-Intermediate; 6 Muts/Mb

Additional Disease-relevant Genes with No Reportable Alterations Identified†

ERBB2

- Androgen receptor = IHC 3+, 95%
- Mismatch repair (MMR) IHC = intact
- Somatic tumor profiling reveals an AKT1 E17K mutation

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Case 5: At this juncture, you recommend:

1. Sacituzumab govitecan (antibody drug conjugate to Trop-2) on a clinical trial
2. AKT inhibitor on a clinical trial
3. Anti-PD-1/PD-L1 inhibitor monotherapy
4. Novel immunotherapy clinical trial
5. Androgen receptor antagonist
6. Cytotoxic chemotherapy

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Case 5: Refractory TNBC

- She elects to participate in a phase II trial of intratumoral plasmid IL-12 with electroporation
- She completes this therapy and then enrolls on a phase II trial of pembrolizumab and imprime PPG (dual immunotherapy approach)

Case 5:

END OF CASE 5