

17th Multidisciplinary Management of Cancers: A Case-based Approach

Breast Tumor Board 2017

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Case 1

- A healthy 28 y/o woman presents with a palpable left breast mass.
- A diagnostic mammogram reveals a 1.4 cm lobulated, irregular mass with pleomorphic calcifications, corresponding to the palpable mass.
- Ultrasound confirms the breast mass and reveals a 1.8 cm suspicious left axillary lymph node.

Case 1

- Core biopsy of the left breast reveals a high-grade infiltrating ductal carcinoma. There is no staining for estrogen or progesterone receptors. There is no staining for HER-2 and no amplification by fluorescent in situ hybridization (FISH). The Ki-67 index was 90%.
- Fine needle aspiration of the axillary lymph node confirms metastatic carcinoma.

Case 1

- She has a clinical stage II, T1C N1, high grade, triple negative breast cancer.
- A urine test the same day confirms a 6 week 4 day desired pregnancy.

1.1 As a next step you recommend

1. Lumpectomy and sentinel lymph node biopsy
2. Lumpectomy and axillary lymph node dissection
3. Neoadjuvant chemotherapy
4. No surgery or systemic therapy until she's in the 2nd trimester of pregnancy
5. Termination of the pregnancy, followed by chemotherapy and surgery

Case 1

- The patient undergoes a lumpectomy and axillary lymph node dissection at 12 weeks of pregnancy.
- Pathology reveals a 2.1 cm high grade, infiltrating ductal carcinoma with lymphovascular space invasion and accompanying high-grade ductal carcinoma in situ of 9 mm. All margins of resection are negative. One of 11 lymph nodes is positive for metastatic disease.
- She has a pathological stage IIB, T2 N1, triple negative breast cancer.

1.2 What staging studies would you recommend?

1. CT chest, abdomen and pelvis and bone scan
2. PET/CT
3. Chest X-ray with abdominal shielding and abdominal ultrasound
4. None

Case 1

- Chest X-ray and abdominal ultrasound are unremarkable.
- Family history is significant for a paternal aunt and grandmother with breast cancers in their 40's and 50's, respectively.
- She is found to carry a *BRCA1* mutation.

1.3 Which adjuvant chemotherapy do you recommend now?

1. Standard doxorubicin/cyclophosphamide (A/C) → weekly paclitaxel (T)
2. Dose dense A/C → T
3. Dose dense A/C → T + carboplatin
4. Standard A/C → delivery then T
5. Standard A/C → delivery then T + carboplatin

Breast cancer during pregnancy

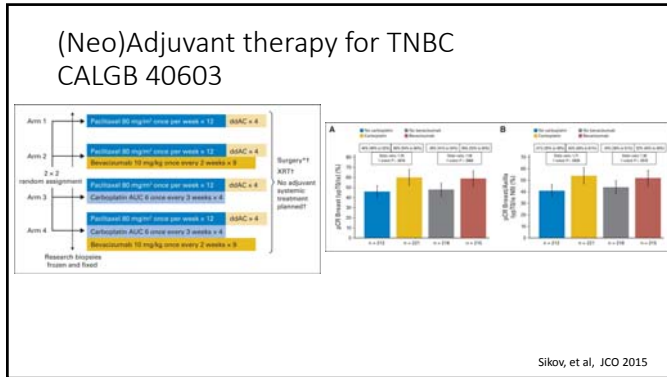
- Staging studies should minimize radiation to the fetus (CXR, mammogram with shielding, ultrasound).
- Surgery is safe at any time but less risk of miscarriage after 1st trimester.
- Radiation therapy should be deferred until after delivery.

ESMO Guidelines Working Group
Annals of Oncology 2013

Breast cancer during pregnancy

- Anthracycline-based chemotherapy can be given after 1st trimester.
- No data on dose-dense schedule, although growth factors are safe during pregnancy.
- Very limited data on the taxanes.

ESMO Guidelines Working Group
Annals of Oncology 2013



Case 1

- She receives 4 cycles of standard A/C starting at 15 weeks gestation.
- She delivers a healthy boy at 34 weeks.
- She receives weekly paclitaxel and q 3 week carboplatin at AUC 5. Her course is complicated by neutropenic fevers, requiring growth factors and dose reduction of carboplatin to AUC 4 with C3.

Case 1

- CT chest, abdomen and pelvis and bone scan after delivery reveal no metastases.

1.4 Regarding her *BRCA1* mutation, what are your further recommendations?

1. Bilateral mastectomies
2. Annual mammogram and MRI breast screening

1.5 Regarding her *BRCA1* mutation, what are your further recommendations?

1. Bilateral salpingo-oophorectomies
2. Pelvic ultrasound and CA-125 levels every 6 months

Case 1

- At the completion of chemotherapy, she undergoes bilateral skin-sparing mastectomies. Pathology reveals no malignancy.
- She is undergoing q 6 month pelvic ultrasound and CA-125 levels

1.6 Do you recommend post-mastectomy XRT?

1. Yes
2. No

Case 1: Take Home Points

- Local and systemic treatment options for breast cancer in pregnancy
- Adjuvant chemotherapy for triple negative breast cancer
- Genetic counseling for triple negative breast cancer (diagnosed \leq age 60)

End of Case 1

Case 2

- A 68 y/o woman presents with a right breast mass.
- On exam, she has a palpable, mobile mass encompassing her entire right breast with peau d'orange and palpable right axillary adenopathy.
- A biopsy reveals a low grade infiltrating ductal carcinoma. There is no staining for estrogen or progesterone receptors. HER2 is amplified.

Case 2

- Imaging reveals 2 hypodense, ill-defined lesions in the liver. The largest measures 1.6 cm.
- Image-guided fine needle aspiration of the larger liver lesion confirms metastatic carcinoma, hormone receptor negative and HER2 amplified.
- She has a stage IV, T4d N1 M1, breast cancer.

Case 2

- She has a history of coronary artery disease, s/p stent placement; hypertension; and hyperlipidemia on medical management.
- Echocardiogram shows normal LV wall motion and LVEF of 70%.

2.1 As a next step you recommendation?

1. Taxane + trastuzumab and pertuzumab
2. Docetaxel, carboplatin + trastuzumab and pertuzumab
3. Doxorubicin/cyclophosphamide → taxane + trastuzumab and pertuzumab
4. Taxane chemotherapy without HER-2 directed antibodies?

Case 2

- She receives 6 cycles of weekly paclitaxel and trastuzumab, which she tolerates well.
- She has a dramatic response in her breast and after 4 cycles, her liver lesions cannot be detected by imaging.

2.2 As a next step you recommend

1. Continued paclitaxel and trastuzumab until disease progression
2. Continued trastuzumab alone until disease progression

2.3 What local therapy do you recommend?

1. Right mastectomy
2. Right mastectomy and axillary lymph node dissection
3. Right mastectomy and chest wall/regional radiation
4. Right mastectomy, axillary lymph node dissection, and chest wall/regional radiation

Case 2

- After 6 cycles, the patient is treated with trastuzumab alone.
- She undergoes right mastectomy and ALND.
- Pathology reveals no residual disease in the breast and 2/11 axillary nodes contain metastatic disease.
- She receives right chest wall and supraclavicular field irradiation.

Case 2

- She continues on single agent trastuzumab and remains without radiographic evidence of disease.
- Regular echocardiograms reveal no decrease in LVEF.
- Although she is tolerating trastuzumab, after 3 years, she asks to go off therapy.

2.4 As a next step you recommend

1. Continue trastuzumab, as she is without measurable disease nearly 4 years since diagnosis.
2. Provide a treatment holiday with serial imaging. Restart trastuzumab if recurrent/progressive disease.

Case 2

- The patient remains on trastuzumab, but self discontinues after 4 and ½ years of single agent therapy.
- She remains without evidence of disease more than 3 years later.

Case 2: Take Home Points

- Treatment options for metastatic, HER2 positive breast cancer
- Management of long-term survivors with HER2 positive metastatic disease

End of Case 2

Case 3

- A 39 y/o healthy woman presents with a left breast mass.
- Exam reveals a large left breast mass and skin thickening, and left axillary adenopathy.
- Family history reveals no breast or ovarian cancer. Father had colon cancer and melanoma.

Case 3

- Left breast ultrasound is unremarkable.
- Diagnostic mammogram reveals a large, asymmetric density in the left breast, confirmed by magnification views.
- Stereotactic biopsy reveals a grade 2 infiltrating ductal carcinoma with associated grade 2 ductal carcinoma in situ. Invasive cancer stains 99% for ER, 0% for PgR. Her2 is negative by IHC at 1+ staining and non-amplified.

Case 3

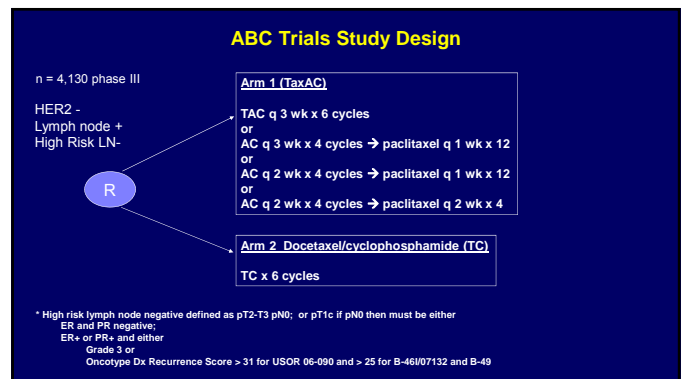
- Breast MRI reveals a 9.6 x 7.5 cm left lateral breast mass with extension to the nipple, abnormal left axillary adenopathy up to 1.6 cm and abnormal skin thickening.
- Skin biopsy was unremarkable.
- Biopsy of the left axillary lymph node reveals poorly differentiated carcinoma consistent with a breast primary.

Case 3

- Further imaging reveals the left breast mass, left axillary adenopathy and a left subpectoral lymph node. There is no distant disease.
- She has a stage III, cT4b pN1 M0, breast cancer.

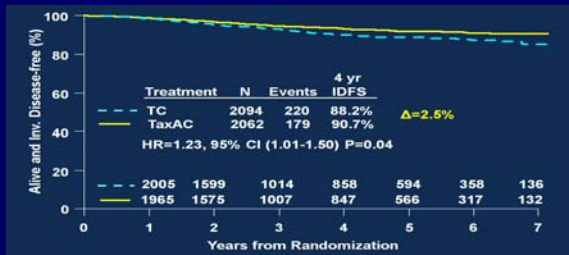
3.1 What neoadjuvant therapy do you recommend?

1. Doxorubicin/cyclophosphamide x 4 → taxane x 4 (AC → T)
2. Docetaxel/doxorubicin/cyclophosphamide (TAC) x 6
3. Docetaxel/cyclophosphamide (TC) x 4
4. TC x 6



ABC Trials: Invasive Disease Free Survival

The primary aim: Determine if invasive disease free survival with TC is non-inferior compared to TaxAC, defined by HR of less than 1.18



Blum JL et al, ASCO 2016, abstract 1000

ABC Trials: IDFS by Hormone and Nodal Status Exploratory Analysis

	Pts		Events		4 yr IDFS		4 yr IDFS	HR (95% CI)
	TaxAC	TC	TaxAC	TC	TaxAC	TC	Delta	
ER/PgR (-)								
N-	459	488	37	52	89.5	87.0	2.5%	1.31 (0.86-1.99)
1-3 N+	153	119	21	28	85.5	74.6	10.9%	1.58 (0.90-2.79)
4+ N+	42	40	11	16	71.8	60.8	11.0%	1.34 (0.62-2.91)
ER or PgR (+)								
N-	358	378	29	22	91.5	94.2	-2.7%	0.69 (0.39-1.19)
1-3 N+	771	789	46	53	94.3	92.3	2.0%	1.14 (0.77-1.69)
4+ N+	279	280	35	49	87.2	81.4	5.8%	1.46 (0.95-2.26)

Blum JL et al, ASCO 2016, abstract 1000

Case 3

- She receives 4 cycles of dose dense AC followed by paclitaxel with resolution of her breast mass and axillary adenopathy.
- She undergoes a left modified radical mastectomy.
- Pathology reveals a grade 2 IDC scattered over 8.5 cm with associated high grade DCIS. Lymphovascular invasion is present; margins are negative. 4 of 11 axillary lymph nodes are positive; the largest 1.7 cm. Pathology notes that there is "treatment effect in the breast mass but not in the lymph nodes".

Case 3

- The residual breast cancer stains 100% for ER, 0% for PgR and is negative for HER2 expression by IHC.
- The lymph node(s) stain 100% for ER, 0% for PgR, but is HER2 amplified (HER2/CEP17 2.7).

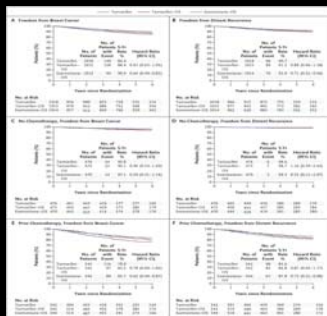
3.2 In addition to adjuvant endocrine therapy, you recommend

1. Trastuzumab x 1 year
2. Capecitabine x 8 cycles per CREATE
3. Enrollment in the PALLAS trial of adjuvant palbociclib
4. Enrollment in S1207 of adjuvant everolimus
5. No additional treatment

3.3 Your choice of initial adjuvant endocrine therapy is

1. Tamoxifen
2. Ovarian function suppression + tamoxifen
3. Ovarian function suppression + aromatase inhibitor

Kaplan–Meier Estimates of Freedom from Recurrence of Breast Cancer and Freedom from the Recurrence of Breast Cancer at a Distant Site after a Median Follow-up of 67 Months, According to Treatment Assignment.



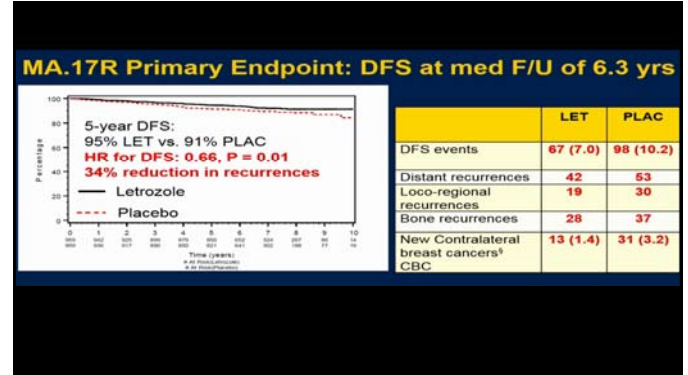
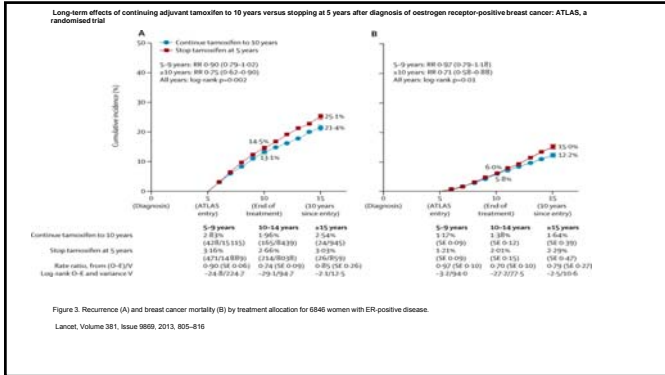
Francis PA et al. N Engl J Med 2015;372:436-446



THE NEW ENGLAND JOURNAL OF MEDICINE

3.4 The duration of adjuvant endocrine therapy you recommend is

1. 5 years
2. 10 years
3. Greater than 10 years



Case 3: Take Home Points

- Importance of anthracyclines and taxanes in high risk breast cancer
- Tumor heterogeneity
- Optimal endocrine therapy in premenopausal women

End of Case 3

Case 4

- A 62 y/o healthy woman has a new, irregular, 6 mm ill-defined mass in her right breast on screening mammogram.
- Ultrasound confirms an irregular, hypoechoic 6 mm mass with no abnormalities in the axillary lymph nodes.
- An ultrasound-guided biopsy reveals a low grade invasive mammary carcinoma with tubular and lobular features. There is no staining for estrogen or progesterone receptors. HER2 was non-amplified. Ki-67 index was 5%.

Case 4

- The patient undergoes lumpectomy and sentinel lymph node biopsy revealing a low grade 9 mm invasive mammary carcinoma with features of tubular carcinoma. 2 sentinel nodes are negative for metastases.
- This tumor stains 25% for ER, 0% for PgR. HER2 is nonamplified.
- She has a stage I, T1B N0, low grade tumor.

4.1 Besides post-lumpectomy radiation, you recommend

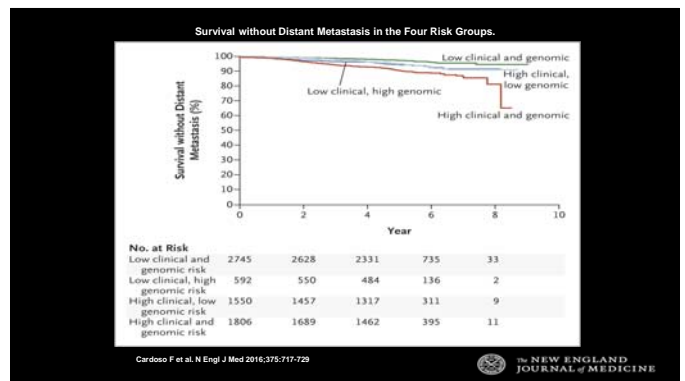
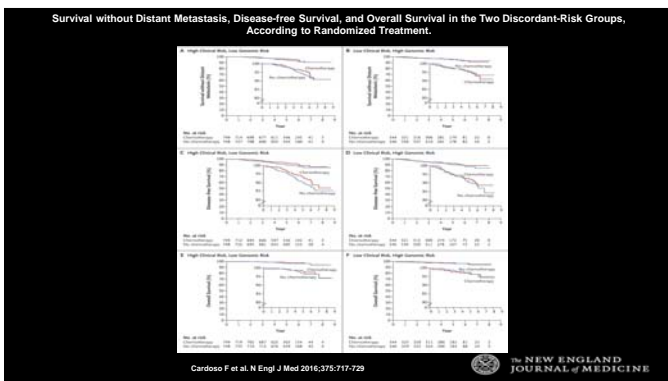
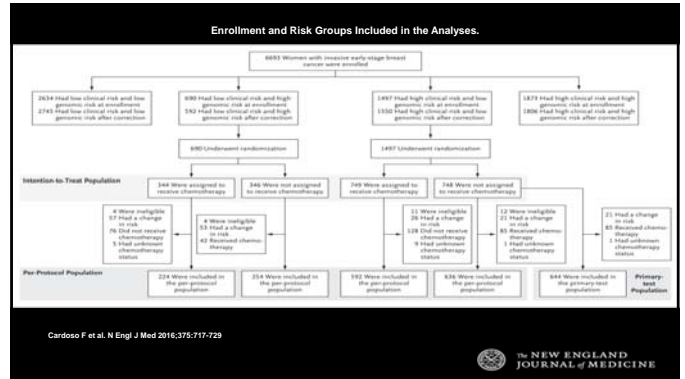
1. Aromatase inhibitor x 5 years
2. Aromatase inhibitor x 10 years
3. Gene tumor expression assay in addition to endocrine therapy
4. Adjuvant docetaxel/cyclophosphamide (TC) x 4 cycles followed by endocrine therapy

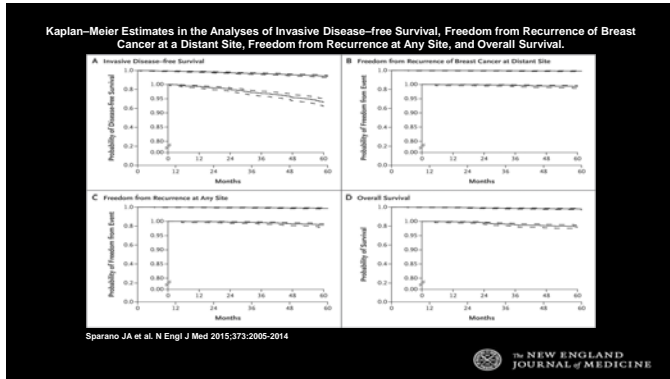
Case 4

- A Mammaprint assay reveals a high risk luminal B profile.

4.2 As a next step you recommend

1. Aromatase inhibitor x 5 years
2. Aromatase inhibitor x 10 years
3. Adjuvant docetaxel/cyclophosphamide (TC) x 4 cycles followed by endocrine therapy
4. Adjuvant A/C→T followed by endocrine therapy



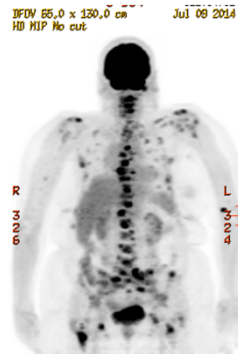


Case 4

- She receives TC x 4 cycles followed by 5 years of endocrine therapy.
- 5 years after completion of adjuvant endocrine therapy, she presents with low back pain.

Case 4

- Imaging reveals diffuse bony metastases.
- Biopsy of a spinal lesion is consistent with metastatic breast cancer, which stains 50% for ER, 10% for PgR and is HER2 non-amplified.



4.3 As a next step you recommend

1. Aromatase inhibitor
2. Fulvestrant
3. 1 or 2 and palbociclib
4. Taxane chemotherapy

4.4 Do you utilize molecular profiling of the metastatic lesion, eg Foundation One?

1. Yes
2. No

Case 4

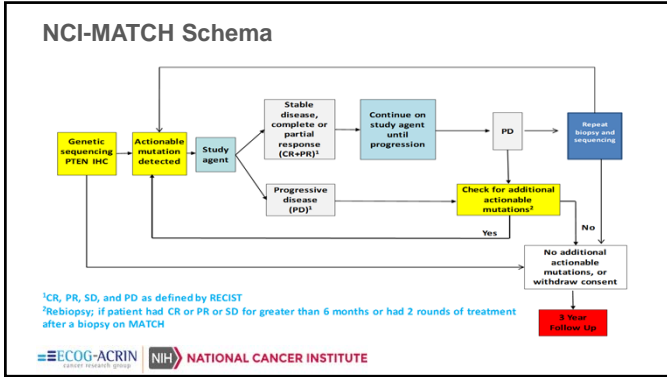
- The patient's tumor is sent for Foundation One analysis. Her tumor has genetic alterations including loss of PTEN, among others.

Case 4

- Consideration for NCI MATCH trial.

NCI MATCH Eligibility Defined Molecularly

- Initial tumor biopsy to identify mutations/amplifications/ translocations
- Patients can be screened with local NGS but results must be confirmed on NCI-MATCH assay
- Patient assignment to relevant agent(s)/subprotocol
- Perform tumor biopsies and sequencing at progression to illuminate resistance mechanisms
 - Submit de-identified samples to central labs
 - Conduct whole-exome, mRNA sequencing (research purposes)



- ### NCI-MATCH Eligibility
- Patients with solid tumors or lymphomas whose disease has progressed following at least one line of standard systemic therapy – or with tumors that do not have standard therapy
 - Exclude histologies that had been approved by the FDA or had shown lack of efficacy with an agent
 - Tumor accessible to biopsy and patient willing to undergo biopsy
 - Adults ≥ 18 year of age
 - ECOG performance status ≥ 1
 - Adequate organ function
- ECOG-ACRIN NATIONAL CANCER INSTITUTE

NCI-MATCH Subprotocols

Molecular Target	Estimated % Prevalence	Agent(s) for Molecular Target	Subprotocol ID
EGFR activating mutations	1 - 4	Afatinib	EAY131-A
HER2 activating mutations	2 - 5	Afatinib	EAY131-B
EGFR T790M mutations and rare activating mutations of EGFR	1 - 2	AZD9291	EAY131-E
ALK translocations	4	Crizotinib	EAY131-F
ROS1 translocations	5	Crizotinib	EAY131-G
BRAF V600E or V600K mutations	7	Dabrafenib and trametinib	EAY131-H
HER2 amplification	5	Ado-trastuzumab emtansine	EAY131-Q
BRAF fusions, or non-V600E, non-600K BRAF mutations	2.8	Trametinib	EAY131-R
NF2 loss	2	Defactinib	EAY131-U
ckIT mutations	4	Sunitinib	EAY131-V

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NCI-MATCH Subprotocols

Molecular Target	Estimated % Prevalence	Agent for Molecular Target	Subprotocol ID
PIK3CA mutations or amplifications, but without RAS mutations or PTEN loss	17-18	Taselisib	EAY131-I
MET ex 14 sk		Crizotinib	EAY131-C2
NRAS mutation		Binimetinib	EAY131-21A
PTEN mutations or deletions, with PTEN expression on IHC	11	GSK2636771	EAY131-N
PTEN loss by IHC	11	GSK2636771	EAY131-P
NF1 mutations	7.7	Trametinib	EAY131-S1
GNAQ or GNA11 mutations	2 and 1.6	Trametinib	EAY131-S2
Smoothed (SMO) or patched 1 (PTCH1) mutations	2.6 - 3.8	Vismodegib	EAY131-T
DDR2 mutations	2	Dasatinib	EAY131-X

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NCI-MATCH Subprotocols

Molecular Target	Estimated % Prevalence	Agent for Molecular Target	Subprotocol ID
MET amplifications	4	Crizotinib	EAY131-C
Aberrations in FGFR pathway	5	AZD4547	EAY131-W
AKT mutations	1 - 10	AZD5363	EAY131-Y
CCND1, 2, 3 amplification		Palbociclib	EAY131-Z1B
dMMR		Nivolumab	EAY131-Z1D

<https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match#9>



Case 4: Take Home Points

- Tumor gene expression and prognostic or predictive value
- Endocrine therapy duration in postmenopausal women
- NCI MATCH trial in metastatic disease

End of Case 4

Case 5

- A 69 y/o healthy woman has a 6 mm asymmetry of her right breast on screening mammogram.
- Ultrasound confirms a 5 mm hypoechoic, irregular density.
- Ultrasound-guided biopsy reveals a grade 2 invasive mammary carcinoma NOS, ER 99%, PgR 0%, HER2 non-amplified.

Case 5

- She undergoes right lumpectomy and sentinel lymph node biopsy, which reveals a 4 mm, grade 2 invasive mammary carcinoma with negative margins.
- Three sentinel lymph nodes are identified and one contains 1 mm metastasis, without extracapsular extension.
- She has a stage II, T1A N1, breast cancer.

Case 5

- She undergoes right lumpectomy and sentinel lymph node biopsy, which reveals a 4 mm, grade 2 invasive mammary carcinoma with negative margins.
- Three sentinel lymph nodes are identified and one contains 1 mm metastasis, without extracapsular extension.
- She has a stage II, T1A N1, breast cancer.

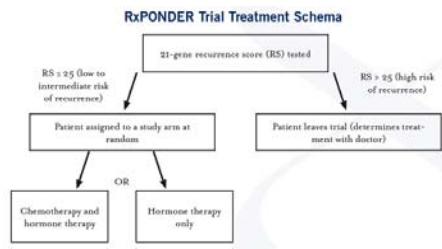
5.1 What further local therapy do you recommend?

1. Axillary lymph node dissection and breast irradiation
2. Breast irradiation
3. Breast and axillary irradiation

5.2 Regarding systemic therapy, you recommend

1. Tumor gene expression profile
2. Docetaxel/cyclophosphamide (TC) x 4 followed by endocrine therapy
3. TC x 6 followed by endocrine therapy
4. Dose dense doxorubicin/cyclophosphamide → paclitaxel followed by endocrine therapy
5. Endocrine therapy alone

NCI RxPONDER Trial



Case 5: Take Home Points

- Optimal management of lower-risk node positive disease

End of Case 5