Case #1 Oncotype Dilemma

42 yo woman with architectural distortion in right breast seen on screening mammogram

- Diagnostic mammogram and US reveal a 9mm density in the 9:30 position, breasts are extremely dense
- Core biopsy reveals a grade 2 IDC with associated high grade DCIS, receptors not reported
- Germline genetic testing panel negative for mutations
- Lumpectomy/SLNBx: 0.9 cm grade 2 IDC, ER positive (95%; strong), PR positive (95%; strong), HER2 negative (IHC 0). No LVI. Intermed grade DCIS. Surgical margins negative. 0/4 LN involved

- Oncotype RS 18
- Patient has been seen at MSKCC, UCSF, AND Stanford to discuss benefit of chemotherapy
Case #1 Oncotype Dilemma

What adjuvant therapy would you recommend for this patient?

A. Tamoxifen alone
B. Ovarian suppression and tamoxifen
C. Ovarian suppression and AI
D. Taxotere and Cytoxan followed by Tamoxifen alone
E. Taxotere and Cytoxan followed by ovarian suppression plus tamoxifen
F. Taxotere and Cytoxan followed by ovarian suppression plus AI

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END OF CASE #1

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Case #2 Multiple Surprises...

- 69 year old healthy woman presents with a left breast mass measuring 2.6 cm on screening mammogram
- Bilateral diagnostic mammogram and left breast US show a 2.6 x 1.6 cm mass at 3:00 in the left breast with at least 3 enlarged lymph nodes in the left axilla
- US guided biopsy of the left breast mass reveals a grade 3 IDC (ER negative/PR negative/HER2/neu 1+ by IHC). Left axillary LN positive for metastatic ductal carcinoma
Baseline breast MRI shows biopsy proven mass measuring 25 x 30 x 37 mm in the outer central left breast. There are multiple small satellite masses and NME extending anteriorly and possibly involving the base of the nipple, with nipple retraction.

PET/CT shows FDG avid left breast mass, FDG avid left axillary lymphadenopathy, 8 mm right lower lobe solid pulmonary nodule, 1 cm FDG avid right thyroid nodule and 1 cm well marginated lytic/cystic lesion of the right ilium without FDG avidity.

Thyroid US/biopsy: 2.7 x 1.6 x 1.3 cm right mid thyroid lobe nodule with mixed solid and cystic components and microcalcifications. No suspicious lymph nodes present.

Pathology: Benign thyroid nodule, involutional type.

MRI pelvic bone: 1 cm well marginated lesion on recent PET/CT scan at right iliac wing is shown to represent intraosseous lipoma.

Outside the context of a clinical trial, what chemotherapy/systemic therapy would you recommend?

A. Neoadjuvant AC‐Taxol
B. Neoadjuvant AC‐Taxol/Carboplatin
C. Neoadjuvant AC‐Taxol and add Carboplatin pre-operatively if poor response
D. Neoadjuvant AC‐Taxol and add Carboplatin or Xeloda post-operatively if path CR not achieved
E. Neoadjuvant AC‐Taxol/Carboplatin and add Xeloda post-operatively if path CR not achieved

<table>
<thead>
<tr>
<th>Study [Reference]</th>
<th>Study design</th>
<th>Chemotherapy regimen</th>
<th>N</th>
<th>PCR (%) Control</th>
<th>PCR (%) Platinum</th>
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<tbody>
<tr>
<td>GeparSixto</td>
<td>Randomized phase II</td>
<td>wp + nPLD 20 mg/m^2 qw + B 15 mg/kg q 3w ± CB AUC 1.5‐2 qw x 18 w</td>
<td>315</td>
<td>ypT0 ypN0</td>
<td>37 53</td>
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<tr>
<td>CALGB 40603</td>
<td>Randomized phase II</td>
<td>wp x 12 ± CB AUC 6 q 3w → ddAC x 4 ± B 10 mg/kg q 2w x 9</td>
<td>433</td>
<td>ypT0/is ypN0</td>
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<tr>
<td>IPIY-2</td>
<td>Randomized phase II</td>
<td>wp x 12 ± CB AUC 6 q 3w x 4 + veliparib → ddAC x 4</td>
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<td>ADAPT</td>
<td>Randomized phase II</td>
<td>weekly nap‐paclitaxel 125 mg/m^2 + CB AUC 2 or gemcitabine 1,000 mg/m^2 on day 1 and 8 q 3w x 4</td>
<td>336</td>
<td>ypT0/is ypN0</td>
<td>28.7 45.9</td>
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<tr>
<td>Sharma et al.</td>
<td>Observational</td>
<td>CB AUC 6 + Docetaxel 75 mg/m^2 x 4‐6 cycles</td>
<td>76</td>
<td>ypT0/is ypN0</td>
<td>na 66</td>
</tr>
</tbody>
</table>

Table from Castrellon et al. Oncol Rev. 2017
Case #2

CALGB 40603
Addition of Carboplatin increased path CR from 41% to 64% (p=0.0029)
Addition of Bevacizumab increased path Cr from 44% to 52% (p=0.059)

- No improvement in EFS (Absolute benefit in 3-year EFS of adding carboplatin was 4.9% [76.5% vs 71.6%; HR, 0.84; 95% P = .36].
- Overall survival differences were also not significant: 81.9% OS in the carboplatin group versus 84.6% without carboplatin (HR, 1.15; P = .53).

- Current raw data:
  - pCR/n [total assigned]
  - Estimated pCR rate (95% prob interval) [equivalent n]
  - Pred prob of success in phase III

<table>
<thead>
<tr>
<th>Signature</th>
<th>Current raw data: pCR/n [total assigned]</th>
<th>Estimated pCR rate (95% prob interval) [equivalent n]</th>
<th>Pred prob of success in phase III</th>
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<tbody>
<tr>
<td>HR+/HER2-</td>
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<td></td>
<td>13/88</td>
<td>13.6% [6.21%]</td>
<td>86.8%</td>
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<tr>
<td>TNBC</td>
<td>15/21</td>
<td>62.4% [19.3%]</td>
<td>&gt;99.9%</td>
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<tr>
<td></td>
<td>16/83</td>
<td>22.3% [12.33%]</td>
<td>99.3%</td>
</tr>
</tbody>
</table>

Nanda et al. J Clin Oncol35, no. 15_suppl (May 20 2017) 506

Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BR):
Results from i-SPY 2.
- 69 pts were randomized to pembro from 12/2015 until it graduated in 11/2016
- 46 pts had undergone surgery
- 5 pts had grade 3 IRAEs:
  - Hypophysitis
  - Adrenal insufficiency
- 4 pts presented after completion of AC (149-179 d after starting pembro)
- 1 presented prior to AC (37 d after starting pembro)
- 7 pts had grade 1-2 thyroid abnormalities

Case #2

Patient is randomized to weekly Taxol x 12 weeks plus Pembrolizumab 8 arm on ISPY2

- 3 week breast MRI shows a good response with dominant left breast mass measuring 22 x 22 x 25 mm (previously 30 x 25 x 37 mm)
- 12 week breast MRI shows interval resolution of mass in LO left breast but 7 cm of residual NME extending from ant aspect of the biopsy-proven IDC to the base of the nipple
  - Satellite lesions decreased in size and enhancement (largest satellite lesion measures 5 mm, previously 7 mm)
  - Interval decrease in size of level 1 and 2 left ALNs. (A low level 1 LN measures 14 x 8 mm, previously 28 x 17 mm)
  - New 4 mm focus of enhancement in the upper central right breast
  - FNA left axillary node after week 12 is still positive for carcinoma

Week 17 MRI breast: Residual NME measuring 10 x 10 mm and below the threshold for kinetic analysis. Satellite mass measuring 8 mm in the central retroareolar left breast. Previously seen NME extending from the biopsy proven IDC to the base of the nipple has essentially resolved. Continued interval decrease in size of level 1 and 2 left axillary lymph nodes

Week 17 FNA of two left axillary nodes: Benign

Completed total of 4 cycles of Pembrolizumab alone
PreOp Breast MRI:
- Susceptibility artifact from a biopsy clip in the central outer left breast at the site of biopsy proven IDC with a few adjacent foci of enhancement spanning 5 mm
- Stable 8 mm mass in the central retroareolar left breast
- No significant remaining enhancement between this mass and the base of the nipple
- Continued decrease in size of left axillary lymph nodes
- No abnormal areas of enhancement or other MRI features of malignancy are identified in the right breast

• Left breast lumpectomy and ALND and right breast reduction
  • Left breast: 0.9 cm of residual grade 3 IDC (75% cellularity) and 6/12 LN+ (largest 1 cm, no ECE). Surgical margins negative.
  • Right breast (from the reduction mammoplasty specimen): 4.5 cm grade 2 ILC (ER+/HER2-). No nodes sampled.

• Completed AC x 4 without difficulty
• Meets with radiation oncology and surgeon to discuss management of radiographically occult right breast cancer and radiation to the left side

How would you manage the radiographically occult RIGHT breast cancer?

A. Mastectomy and SLNBx
B. Attempt at re-excison of margins and SLNBx followed by radiation
C. SLNBx and Radiation alone
D. Other/ No idea.

END OF CASE #2
Case #3 DeNovo Metastatic disease

- 38 yo woman with lump in right LOQ
- Mammogram and US: 1.3 x 0.9 x 1.2 cm hypoechoic mass at 7:00 position
- Right breast core biopsy: Grade 3 IDC, ER+ (1-3+ >95%), PR (1-3+ >95%), Ki67 30%, HER2 1+, FISH 4.9/3.4 = 1.4
- Tumor sent for Neogenomics evaluation: Positive based on HER2/TP53 and HER2/SMSCR ratios

- MRI breasts: Left breast negative. Right breast with at least 2 enhancing spiculated masses (largest 1.4 cm) in the right LOQ and possible small satellite lesions. Enhancement hepatic mass up to 3.4 cm
- CT Abdomen: 4.1 cm hypodense mass in medial segment of left lobe. Additional 1 cm lesion in left lobe, third 9 mm similar focus in posterior subcapsular right lobe
- MRI abdomen: 10 circumscribed masses present in the liver. The largest is 3.6 x 3.0 x 2.8 cm in the medial segment of the left lobe.
- PET/non diagnostic CT: Uptake in breast in several areas, right axillary node, two liver lesions with increased SUV: 3.6 cm with SUV 5.1 in left lobe, and second lesion in right lobe with SUV of 3.2

- Liver core biopsy: Metastatic carcinoma c/w breast primary with neuroendocrine differentiation. ER>95%, PR 90%, Ki67 up to 40%, HER2 2+ by IHC, synaptophysin and chromogranin positive. No evidence of MSI. HER2 equivocal by FISH 4.2/3.2 (ratio 1.3)
- BSO: Pathology benign
- Started letrozole and palbociclib

3 months later (3 months on treatment) CT CAP: Enhancing 8 mm right breast nodule, ill-defined lesions measuring approximately 3.8 x 2.9 cm in hepatic segment 4 and 1.8 x 1.3 cm in segment 6, similar to prior MRI. Additional smaller previously identified hepatic lesions not well seen on CT.

3 months later (6 months on treatment) CT CAP: Interval decrease in size of hepatic metastases. No new lesions identified. Unchanged enhancing 8 mm right breast nodule with adjacent biopsy clip representing patient’s known malignancy. No disease in chest.

3 months later (9 months on treatment) CT CAP: Ill-defined 17 x 16 mm hypodensity in segment 4A is less conspicuous. 8 mm hyperenhancing focus in the anterior right dome was less conspicuous on the prior but is likely unchanged. Previously seen 15 mm lesion in segment 7 is no longer appreciated. 12 x 6 mm hyperenhancing lesion in segment 2 is unchanged and compatible with a portosystemic shunt. No new lesions. No evidence of metastatic disease within the chest.
Breast MRI: RIGHT Breast - Retroareolar mass measuring 8 x 8 x 10 mm (previously 11 x 9 x 10 mm). Two additional enhancing irregular masses located more posteriorly in the slightly lower outer right breast measuring 7 x 7 x 7 mm (previously 14 x 12 x 9 mm) and 5 x 5 x 7 mm (previously 7 x 11 x 10 mm); LEFT Breast – Benign

Referred to breast surgeon to discuss breast surgery and radiation oncology to discuss SRS to metastatic sites

Main Inclusion Criteria
- Controlled primary tumor defined as: at least 3 months since original tumor treated definitively, with no progression at primary site
- Up to 5 hematogenous metastases
- Maximum 3 metastases in any single organ system
- All sites of disease safely treatable

SABR-COMET: Stereotactic Radiation for the Comprehensive Treatment of Oligometastatic Cancers – Results of a Randomized Study

Number of fractions dependent on tumor size and location:
- Lung: 54/3, 55/5, 60/8
- Bone: 35/3, 30/3, 16-20/1
- Brain: SRS (18-24/1) or SABR (40/5), WBRT optional
- Liver: 45-60 Gy in 3-8
- Adrenal: 60/8
Case #4 BRCA2 Mutation Carrier

- 33yo woman with palpable right breast mass
- Mammogram: 3.4 x 3.1 cm mass in RUQ. Left breast benign; US: 2.6 x 2.4 cm irregular hypoechoic mass
- Right breast core bx (outside facility): Grade 3 IDC - ER+(90%), PR+(75%), HER2 1+ by IHC
- PET/CT: FDG avid nodes in the right axilla (levels two and three) with small, subtly positive interpectoral and retropectoral nodes
- Breast MRI: Right upper quadrant cancer measures up to 3.1 cm, extending to the skin and medially. Several satellite lesions, one measuring 0.8 cm. Right axillary adenopathy.

- Core biopsy of right ALN: Metastatic carcinoma, ER+(99%), PR+(59%), HER2 1+ by IHC and negative by FISH (copy number 3, ratio 1.2)
- Bone scan: No evidence of osseous metastatic disease
- Genetic testing reveals a BRCA2 mutation
- Initiated AC-Taxol
- Breast MRI after AC: Decrease in breast mass and right axillary adenopathy

- She completes AC-Taxol and undergoes bilat mastectomies with right ALND
  - RIGHT breast 4.9 cm residual grade 3 IDC ER+ (90%), PR+(20%), HER2 2+ by IHC. Positive by FISH (copy number 4.0 and ratio 2.0). Ki67 <5% Percent cellularity ranging from 1-30% (average 10%) + LVI. Margins negative. 6/9 LN+ (2 with macromets, 4 with micromets, 1 with ITCs) Largest met in node: 0.5 cm. No ENE
  - LEFT breast: benign.
- She initiates post-mastectomy radiation
- She is started on Herceptin
In addition to Herceptin, what other adjuvant therapy would you recommend for this patient?

A. Ovarian suppression plus AI alone
B. Ovarian suppression plus AI plus add Perjeta to Herceptin
C. Ovarian suppression plus AI plus try to secure access to a PARP inhibitor on or off study
D. Ovarian suppression plus AI plus try to secure access to CDK 4/6 inhibitor on or off study
E. Other

END OF CASE #4

Supplemental case

- 74 yo woman with multiple comorbidities including HTN, PE, and second degree heart block requiring pacemaker and defibrillator
- Right breast cancer detected on screening mammogram: 14mm spiculated mass in the right UOQ; US: 1 cm area of shadowing at 10:00. Normal axillary lymph nodes
- US guided core biopsy with clip placement with pathology revealing grade 1 IDC (ER+/PR+/HER2 neg), no LVI
Case #5 Axillary sampling and radiation in the elderly

- Right breast lumpectomy/SLNBx with IORT: 1.3 cm grade 1 IDC, 2 SLN neg but 1 non SLN with micromet (0.8 mm)

Discussion points:
- Who are appropriate candidates for omitting axillary sampling?
- Who are appropriate candidates for shorter radiation courses?
- Who are candidates for omitting XRT entirely?