City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Tumor Board: Difficult Cases to Manage

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Panel & Disclosures

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This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Ribociclib will be addressed.

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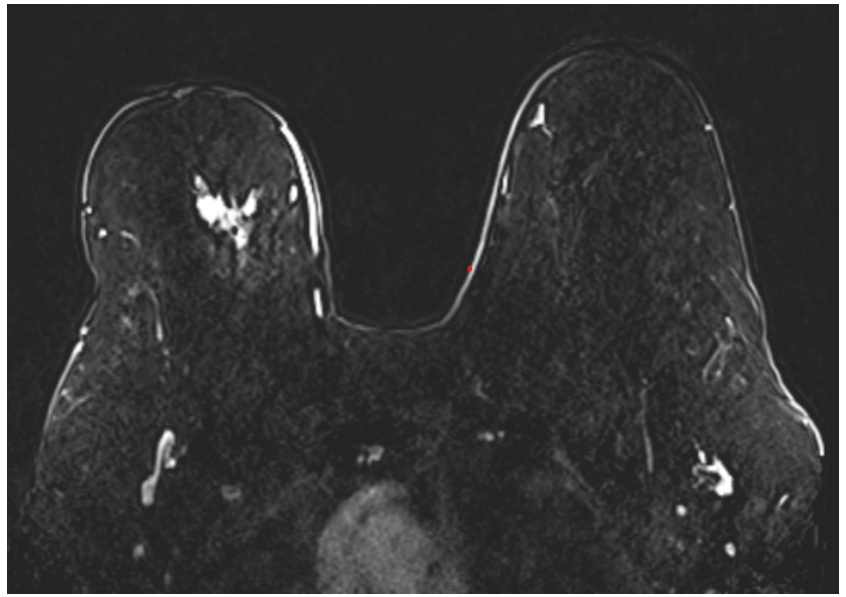
Case #1

Early Breast Cancer, cN+: Clinical Information

58 yo postmenopausal woman presenting with screening detected RIGHT breast cancer

- 2.6cm index mass at 12:00: IDC, grade 2, ER 90% PR 90% HER2 0, Ki-67 10%
- Right axillary LN + for metastatic carcinoma
- Patient factors:
  - PMH: BMI 43, GERD
  - Strong family history of breast cancer



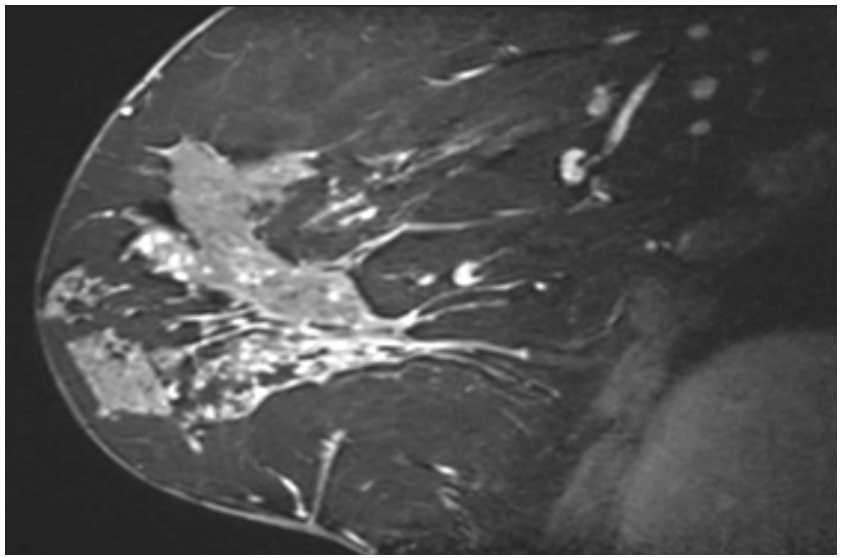
Surgery or Neoadjuvant Systemic Therapy Upfront?

Case #1

Early Breast Cancer, cN+: Treatment Options

58 yo postmenopausal woman: cT2N1 ER+PR+HER2- Ki-67 10%

- Additional helpful testing?
- Benefits of
    - Surgery upfront? What surgery?
    - Neoadjuvant upfront? What regimen?



What if TNBC or HER2+ disease?
What if premenopausal patient?

Case #1

Early Breast Cancer, cN+: Take Home Points

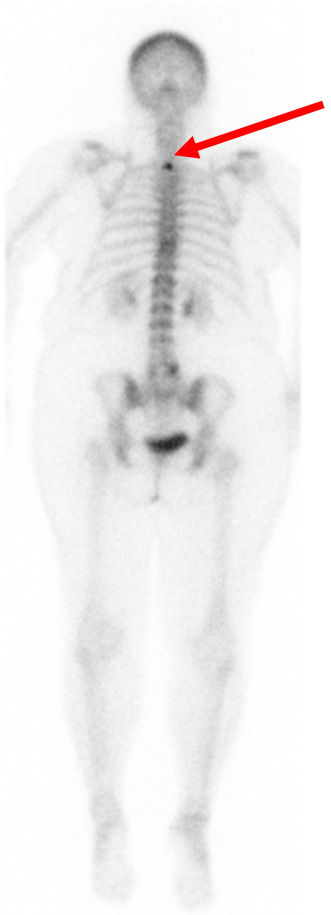
- cN+ ≠ cALND in all patients, can consider TAD (low threshold for cALND for high-risk patients)
- Neoadjuvant systemic therapy should be carefully considered in HR+HER- patients
    - HR+HER- patients who benefit from cytotoxic therapy: Consider upfront genomic testing
    - Neoadjuvant endocrine therapy: Clinical trial
- High-risk patients (genomic testing confirmed, cT2N0-1 TNBC/HER2+) can be considered for upfront systemic therapy
- Preop Radiation Oncology consultation if consideration of de-escalation of axillary surgery and/or plan for immediate reconstruction

Case #2a: Oligometastatic Breast Cancer

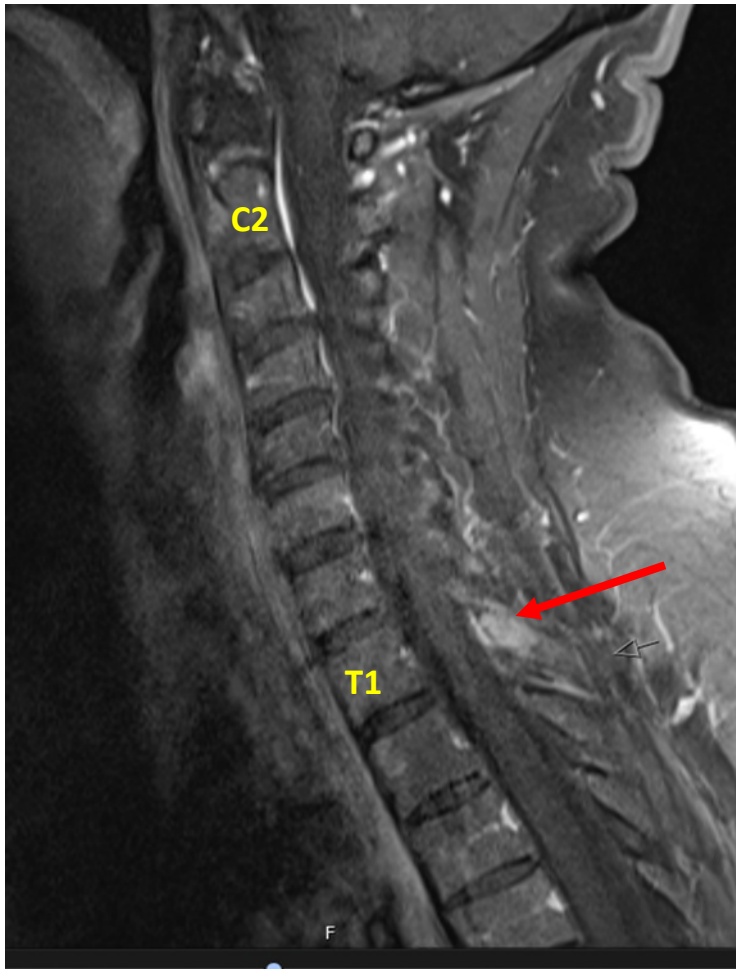
- 55 y/o woman presents with palpable RIGHT breast mass
- Breast imaging (dx mammogram, US, MRI) shows a 3cm breast mass with calcifications and non-mass enhancement spanning ~11 cm as well as suspicious axillary adenopathy
- US-guided core biopsy of the breast mass and axilla shows:
    - Breast: IDC, grade 2, ER+(100%), PR+(70%), HER2-, Ki67=10%
    - Axilla: metastatic carcinoma c/w breast primary, ER+ (95%), PR+ (70%), HER2-, Ki67=20%
- Patient undergoes right modified radical mastectomy without reconstruction with pathology showing:
    - IDC, 2.4 cm, grade 2, associated DCIS (2.4 cm), negative margins, no LVSI
    - Axilla: 18 of 27 nodes involved with macrometastases up to 1.8 cm with extrapsular extension

Case #2a: Oligometastatic Breast Cancer

- Patient undergoes CT chest, abdomen, pelvis with contrast and bone scan for staging showing focal uptake at T1 on bone scan without any CT correlate and no other sites of disease



- MRI thoracic spine wwo contrast performed confirms suspicious enhancement at T1



- Patient asymptomatic
- IR unable to biopsy

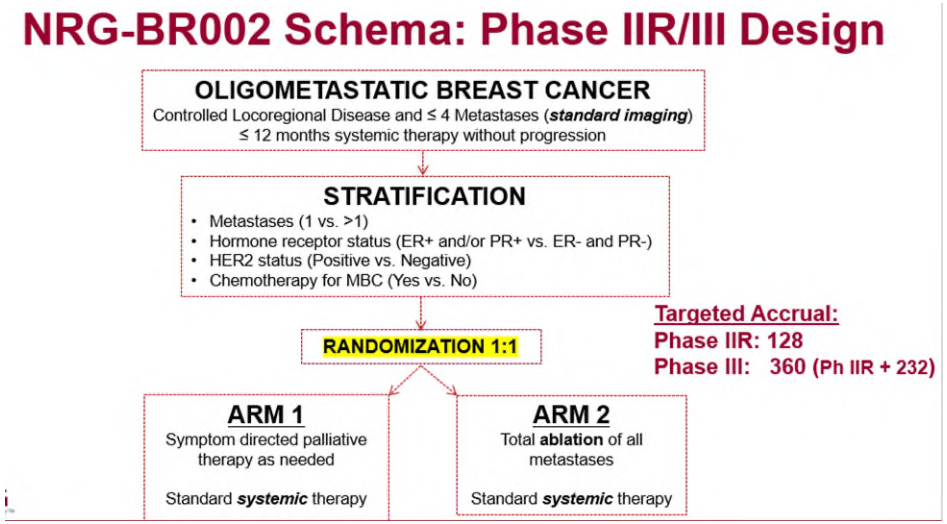
Case #2a: Oligometastatic Breast Cancer Questions

- Should the patient proceed with standard adjuvant chemotherapy (ddAC-ddT) or should the patient be started on 1st line metastatic therapy with ET+CDK4/6 inhibitor?

- Should the patient receive postmastectomy radiation therapy to the right chestwall and regional lymphatics?

- Should the patient receive radiation therapy to the oligometastatic site at T1?

Case #2a: Oligometastatic Breast Cancer



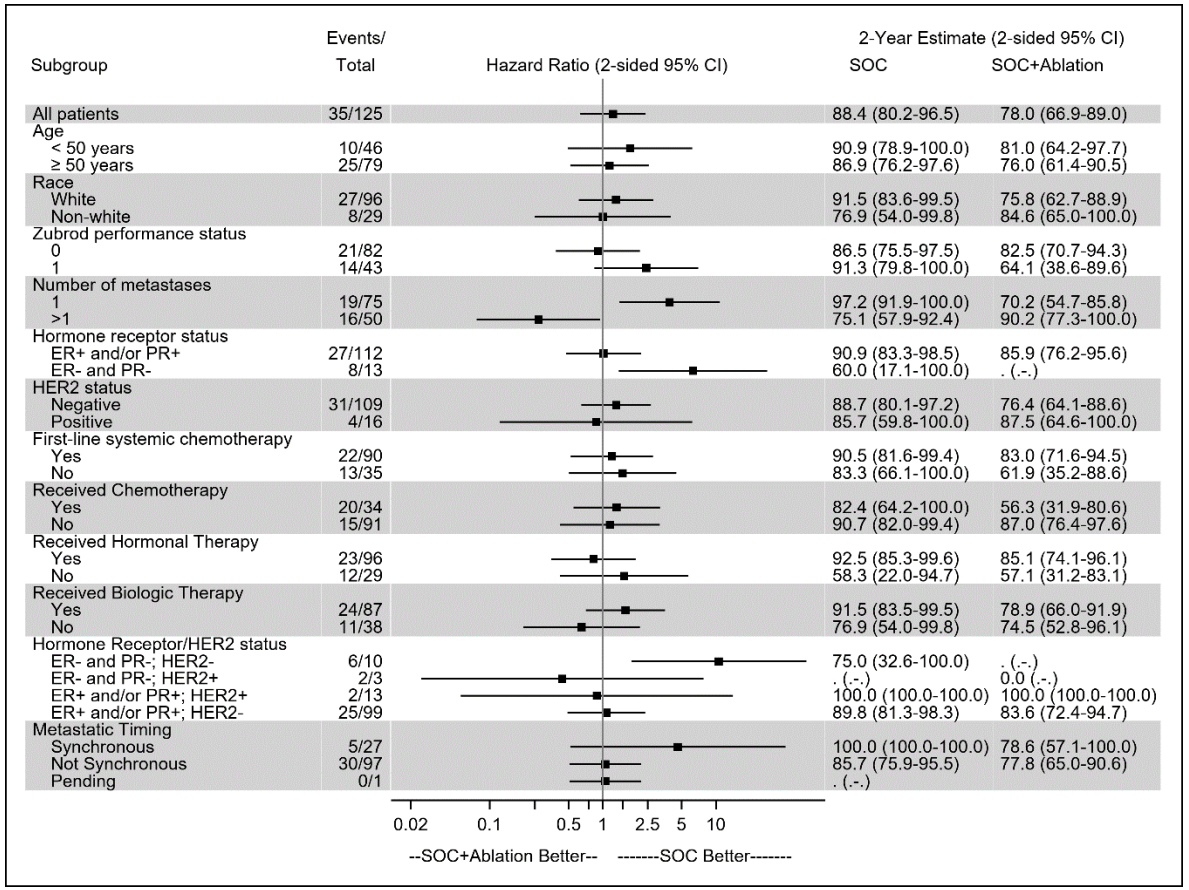
Phase IIR:

- **Hypothesis**: Metastasis-directed therapy of all ***VISIBLE*** lesions with systemic therapy will provide a **signal** for improved ***PFS*** (hazard ratio [HR]=0.55, corresponding to median PFS from 10.5 to 19 months).
  - → Failure defined as: progression of metastases, new metastases, or death
  - → Log-rank test statistic; 1-sided significance level = 0.15 (70% CI); 92% power; 69 events
  - → If PFS "Go Signal", trial continues to answer Ph III overall survival (OS)

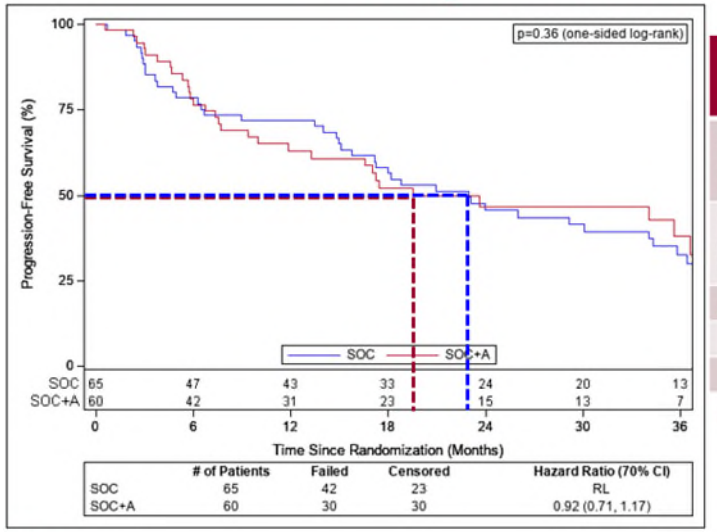
	Standard of Care (n=65)	Standard of Care + Ablation (n=60)	Total (n=125)
Age (years)			
Median	53	55.5	54
Performance Status (Zubrod)			
0	41 (63%)	41 (68%)	82 (66%)
1	24 (37%)	19 (32%)	43 (34%)
Patient Metastasis Count			
1	39 (60%)	36 (60%)	75 (60%)
>1	26 (40%)	24 (40%)	50 (40%)
Hormone Receptor/HER2 Status			
ER and PR-; HER2-	5 (8%)	5 (8%)	10 (8%)
ER and PR-; HER2+	2 (3%)	1 (2%)	3 (2%)
ER and/or PR+; HER2+	6 (9%)	7 (12%)	13 (10%)
ER and/or PR+; HER2-	52 (80%)	47 (78%)	99 (79%)
Metastatic Timing			
Synchronous	12 (18%)	15 (25%)	27 (22%)
Not synchronous	52 (80%)	45 (75%)	97(78%)
Pending	1 (2%)	0 (0%)	1 (1%)

NRG BR002, Chmura S, ASCO 2022 Oral Presentation
https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.1007

Case #2a: Oligometastatic Breast Cancer: NRG BR002 Results



PFS by Treatment Arm

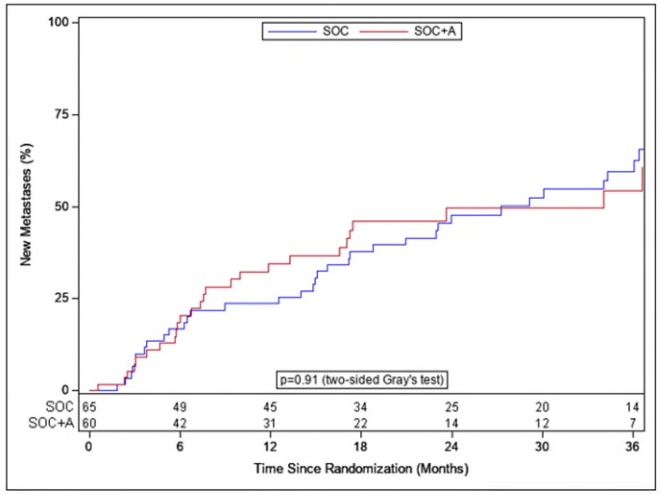


	SOC (n=65)	SOC+A (n=60)
24-month estimate (70% CI)	45.7% (38.9%, 52.5%)	46.8% (39.2%, 54.3%)
36-month estimate (70% CI)	32.8% (26.0%, 39.5%)	38.1% (29.7%, 46.6%)
mPFS		
Design	10.5 months	19 months
Observed	23 months	19.5 months

HR [SOC+A/SOC] (70% CI): 0.92 (0.71, 1.17)

Median Follow-up = 35 months
(min-max: 0.03-62.74)

New Metastases & Patterns of 1st Failure



Analysis of first failure:

- New mets *outside* index area (Arm 1) /RT field (Arm 2)
  - Developed similarly in both arms (~40%)
- New mets *inside* index area (Arm 1) /RT field (Arm 2)
  - Fewer for SOC+A: 7% vs. 29%

NRG BR002, Chmura S, ASCO 2022 Oral Presentation
https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.1007

Case #2b: Oligoprogressive Breast Cancer

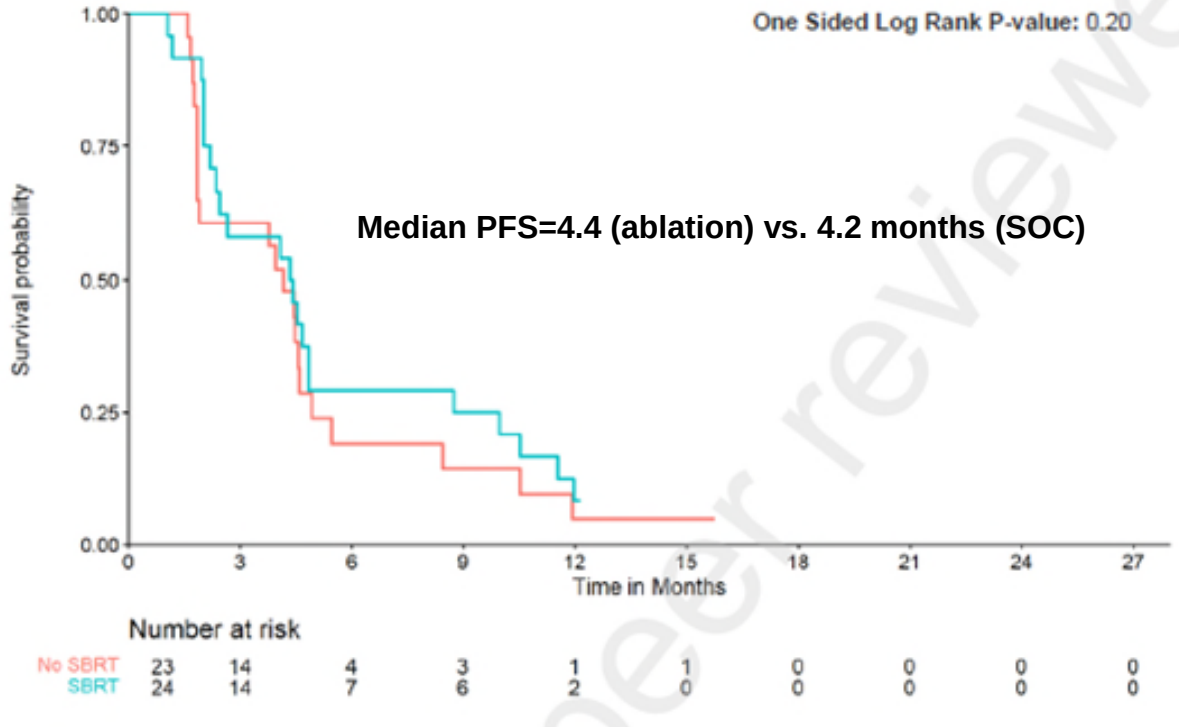
- 32 y/o woman presents with palpable right breast masses and axillary adenopathy with biopsy consistent with ER-/PR-/HER2+ breast cancer
- Staging workup to evaluate abdominal pain identifies numerous liver lesions (>4). Biopsy of the liver demonstrates metastatic breast cancer consistent with breast primary that is ER-/PR-/HER2+
- She receives 6 cycles of pertuzumab+trastuzumab+paclitaxel with significant decrease in size of the breast lesions and liver lesions followed by maintenance pertuzumab+trastuzumab with stable disease for >2 years
- She then develops right breast pain and dedicated breast imaging shows a new breast lesion at 12-1:00 that is 1.5 cm in size. Restaging studies show stability of liver lesions and no new sites of disease

Case #2b: Oligoprogressive Breast Cancer

- Should a biopsy be performed of the new lesion in the breast?
- The biopsy shows ER-/PR-/HER2+ breast cancer. Is there a role for local therapy (surgery or radiation) in this case?

Case #2b: CURB Trial

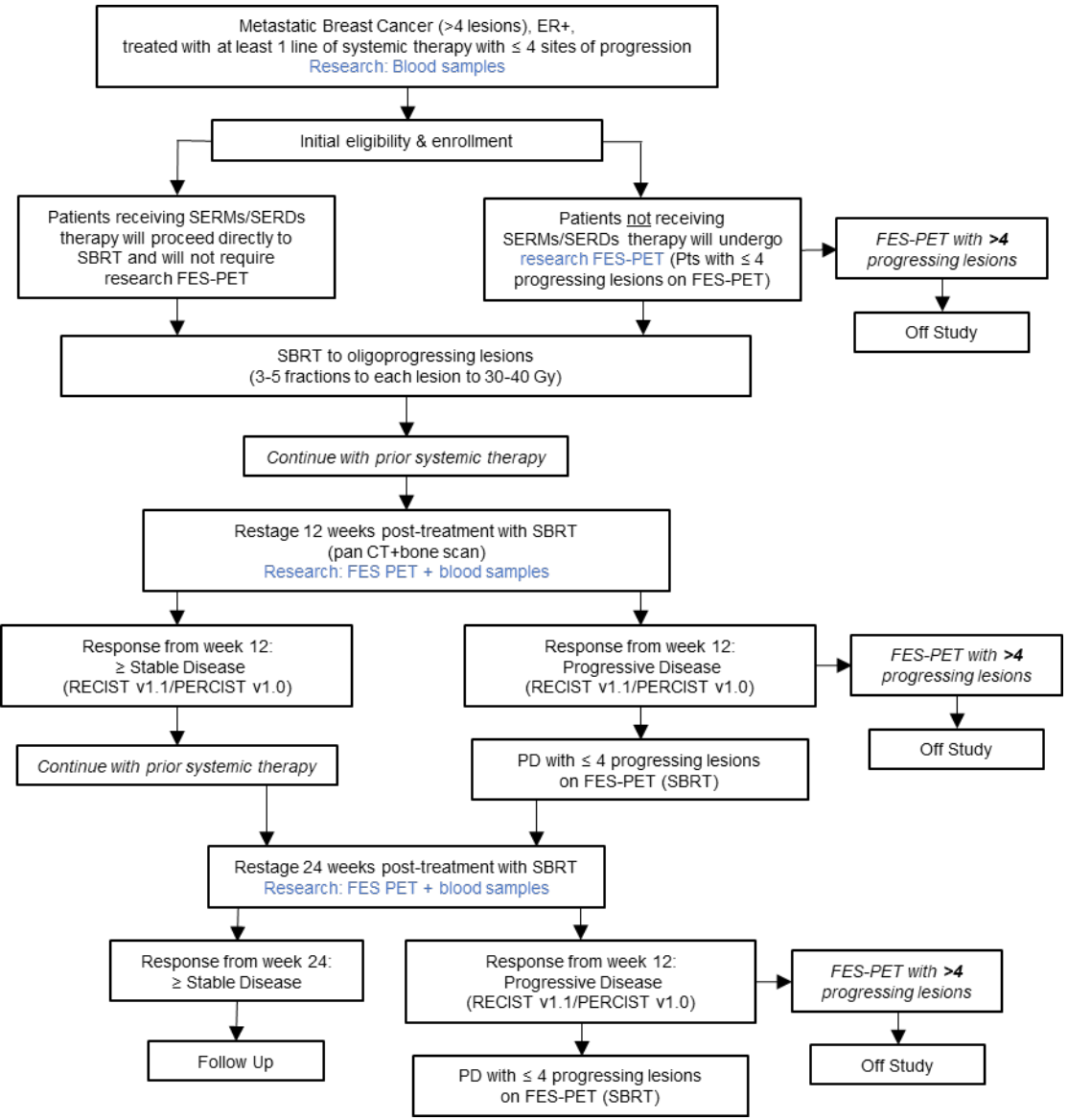
Figure 2B. Progression-Free Survival (Breast)

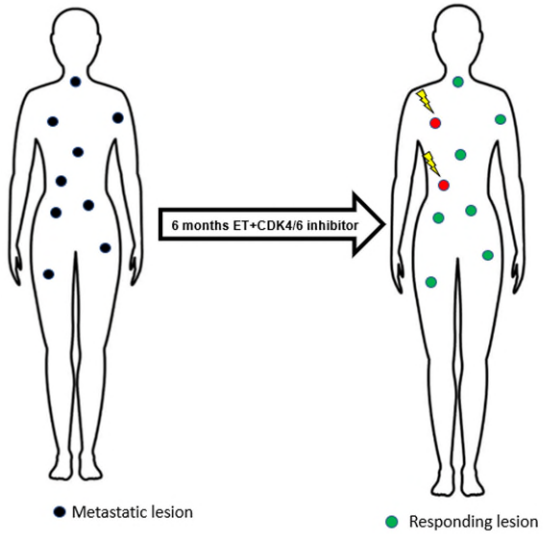


- 16 of 47 had TNBC
- >80% had SBRT to 2-5 lesions
- Median number of prior lines of therapy was 4 in SOC group and 3 in the SBRT group (versus 1 in the NSCLC patients in both groups)
- Need better patient selection!

Tsai J, *Lancet Oncology*, *in press*.

COH 23353 (PI: Bazan): A Phase II Trial of SBRT+FES PET Scans in Patients with Oligoprogressive ER+ Metastatic Breast Cancer





Simon 2 Stage Design

- H_0: Proportion that stay on ST is 20%
- H_a: Proportion that stay on ST is 50%
- Stage 1: 8 patients (if 2+ responses seen)
- Stage II: 10 additional patients
- Null rejected if 6 or more responses are seen

Inclusion

- Age ≥18 years old
- Males or Females
- Zubrod performance status ≤ 2
- Histologically documented metastatic breast cancer
- Metastatic breast cancer with progression of 1-4 extracranial lesions as defined by RECIST v1.1 or PERCIST v1.0 (including new lesions)*
- All progressing lesions amenable to stereotactic body radiation therapy in 3-5 fractions
- Patients with prior treated brain metastases are allowed (patients must not have intracranial disease progression)

Exclusion

- Has received at least one line, but not more than two lines, of systemic therapy for metastatic disease
- Metastases with indistinct borders making targeting not feasible
- Intracranial metastases
- Metastases located within 3cm of the previously irradiated critical structures (cord, brachial plexus, brainstem, stomach, bowel)
- Patients with progression in >4 lesions are not allowed.
- Patients with current progression of malignant pleural effusions, malignant ascites, abdominal carcinomatosis, and/or lymphangitic pulmonary involvement are considered to have >4 metastases (Note that patients with a history of these conditions earlier in the disease course with no evidence of progression of these conditions are eligible).

Primary Hypothesis: In patients with OP ER+ breast cancer that receive SBRT to the OP lesions, at least 50% will remain on their original systemic therapy after 2 sets of re-imaging studies

Exploratory Hypothesis: Use of FES PET in addition to standard imaging at baseline and in follow-up will help confirm patients have OP disease and will help assess for new lesions on restaging

Case #3.

- 87 yo female with Alzheimer's disease who presented with
- Left invasive ductal carcinoma
- ER 0% PR 0% HER2 1+ FISH negative; Ki67-80%
  cT4bN1
- MRI breast: 4.6 x 3.3 x 2.6cm abut lateral and inferior skin surface. Single abnormal left axillary LN
- PET/CT negative for distant metastasis
- Germline genetic testing: VUS in FH, RINT1

Case 3. Continued

- Neoadjuvant chemotherapy was recommended
- Paclitaxel + carboplatin weekly x 12 with pembrolizumab q3 weekly x 4 cycles
- Interval imaging suggesting excellent response. US and MMG suggesting decreasing size; MRI showing resolution of prior mass and lymph node
- Left lumpectomy and sentinel lymph node biopsy: ypTisN0
  5% tumor viable as only DCIS (ER 95%PR0%), fibrotic change in previously biopsied LN suggesting treatment effect
- Adjuvant radiation: left breast and axilla/supraclav + L breast boost (total 52.56 Gy)
- Patient and family opted for no further adjuvant therapy

Case 3. Regimens for TNBC

- Keynote 522: pCR 65% (Schmidt et al. NEJM 2020)
- AC-T: pCR 35-45% (Sikov et al JCO 2015 CALGB40603, Esserman et. al JCO 2012 ISPY-1)
- Docetaxel/Carboplatin x 6 cycles: pCR 55% (Sharma et al. CCR 2017)
- Oral Paclitaxel, Carboplatin, Dostarlimab (PD-1 inhibitor): pCR 48% (Yeung et al. JCO ISPY-2)
- NeoPACT: Phase II Study of Pembrolizumab and Docetaxel/Carboplatin x 6 cycles (Sharma et al ASCO 2022)
    - pCR 58% (95% CI 48%-67%)
    - RCB 0+1 rates 69% (95% CI 60%-78%)
    - 3-year EFS 86%

Case 3. Continued

- Therapy must be individualized for older individuals
- Imaging is helpful in predicting response
- De-escalation Trials:
  - SWOG 2212: **SCARLET Shorter Anthracycline-Free Chemo Immunotherapy Adapted to Pathological Response in Early Triple Negative Breast Cancer (SCARLET), a Randomized Phase III Study**
  - ALLIANCE: **Pembrolizumab vs. Observation in People With Triple-negative Breast Cancer Who Had a Pathologic Complete Response After Chemotherapy Plus Pembrolizumab** NCT05812807