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Surgical Considerations After Neoadjuvant Treatment

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Primary Analysis of NRG-BR005, a Phase II Trial Assessing Accuracy of Tumor Bed Biopsies in Predicting Pathologic Complete Response (pCR) in Patients with Clinical/ Radiological Complete Response after Neoadjuvant Chemotherapy (NCT) to Explore the Feasibility of Breast-conserving Treatment without Surgery

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San Antonio Breast Cancer Symposium
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Program No. GS5-05

Background

- Pts undergoing neoadjuvant chemotherapy (NAC) have high pCR rates (e.g., up to 66.7% with HER2-directed therapy)
- Very low rates of local recurrence in pCR pts (7% at 10 yrs)
  (Mamounas, et al., *JCO*, 2012)
- Women are asking: Why do I need surgery when the tumor has disappeared?
- Can we define a group who can safely be treated with primary chemo-radiotherapy by developing a tool highly predictive of pCR?
- Imaging is insufficient: MRI accuracy for residual disease ~0.69-0.91
  (De Los Santos, et al., *Cancer*; Marinovich, et al., *JNCI*, 2013)
- What is the additive value of tumor bed/clip biopsy?

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Study Description

- **Phase II trial designed to assess the accuracy of post-neoadjuvant systemic therapy (NST) image-directed tumor bed biopsy for pathologic complete response (pCR = resolution of both invasive disease and DCIS) in cases of clinical and radiological near complete response with tri-modality imaging**
- **This will determine whether post-NST tumor bed needle core biopsies in addition to clinical examination and tri-modality imaging can identify appropriate pts after NST, who are optimal candidates to proceed with radiotherapy treatment without formal breast-conserving surgery (lumpectomy)**

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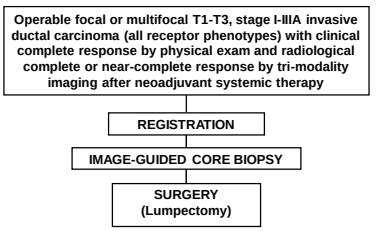
NRG-BR005 Schema



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Primary Endpoint Definitions

Biopsy Negative Predictive Value (NPV):

$$NPV = \frac{\text{number of patients with a negative biopsy and confirmed pCR at surgery}}{\text{total number of patients with a negative biopsy}}$$

Biopsy Sensitivity:

$$Sensitivity = \frac{\text{number of patients with a positive biopsy who had residual tumor at surgery}}{\text{total patients with residual tumor at surgery}}$$

False negative rate (FNR) = 1 - sensitivity

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Secondary Objectives

- Collect axillary pathology results, surgical staging methods (SLNBx and/or ALND), and management (surgery and/or radiation) to determine axillary nodal response to NAC and relationship to breast pCR. Correlate imaging results with pathologic nodal status following NAC for future planning of axillary management in the next study
- To retrospectively assess the negative predictive value (NPV) of a tri-modality imaging algorithm in combination with the tumor bed biopsy for predicting pCR, and to collect all tri-modality imaging data to determine which combination of tri-modality imaging best identifies the group achieving pCR
- To correlate the number of needle cores and tumor bed clip retrievals with the NPV of the tumor site biopsy
- To determine the clinical, imaging, pathological, and molecular tumor factors associated with the highest NPVs of post-NST tumor bed biopsies

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Selected Eligibility Criteria

- Operable (T1-T3, stage I/IIIA) invasive ductal carcinoma
- Completed neoadjuvant chemotherapy
- cCR
- rCR/near rCR by tri-modality imaging:
  - Mammography (mass ≤1 cm and no malignant microcalcifications)
  - Ultrasound (mass ≤2cm)
  - MRI (no mass with rapid rise or washout kinetics)
- Biopsy marker placed within the tumor bed with image confirmation of marker placement
- STEREOTACTIC BIOPSY (mammogram-based)

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Analysis Plan

- A biopsy NPV of ≥90% was chosen *a priori* to support the feasibility of foregoing breast-conserving surgery
- The point estimates and 95% CIs for NPV and Sensitivity were calculated using the exact method
- Planned accrual was 175 pts in order to obtain 35 pts who had residual tumor at surgery
- In accordance with the two-stage design, one interim analysis was planned for the time when 27 pts failed to achieve pCR at surgery

Study Enrollment

- **Opened: June 22, 2017**
- **First patient enrolled: August 25, 2017**
- **As of June 26, 2019, 27 of the 105 enrolled patients reported residual disease at surgery (non-pCR), which triggered a temporary accrual suspension for futility analysis**
- **105 patients enrolled**
  - **4 declined a core biopsy**
  - **3 had not had biopsy or surgery as of 7-31-19**
- **98 evaluable patients**
- **Upon review of all pathology reports, 36 patients had either invasive or DCIS residual disease, which surpassed the required number of non-pCRs for the primary analysis**

Patient Characteristics (cont.)

Tumor Characteristics	Patients (N=98)	
	n	%
Type of Surgery		
Lumpectomy	96	98.0
Mastectomy	2	2.0
Tumor HR/HER2 Status*		
Triple Negative	31	32.3
HR+/HER2−	21	21.9
HER+	44	45.8
Tumor Focality		
Focal	88	89.8
Multifocal	10	10.2

*Two patients with equivocal HER2 are excluded

Results

Biopsy Findings	Residual Disease at Surgery		Total
	Yes (non-pCR)	No (pCR)	
Positive	18	0	18
Negative	18	62	80
Total	36	62	98

Negative Predictive Value (95% CI) = **77.5%** (66.8 to 86.1%)

Sensitivity (95% CI) = **50.0%** (32.9 to 67.1%)

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NPV and Sensitivity of Biopsy by Baseline Tumor Subtype

Baseline Tumor Subtype*	# of Pts	# Patients with Residual Tumor	Negative Predictive Value (95% CI)	Sensitivity (95% CI)
Triple Negative	31	11	**74.1%** (53.7 to 88.9%)	**36.4%** (10.9 to 69.2%)
HR+/HER2−	21	15	**46.2%** (19.2 to 74.9%)	**53.3%** (26.6 to 78.7%)
HER+	44	10	**89.5%** (75.2 to 97.1%)	**60.0%** (26.2 to 87.8%)

*Two patients with equivocal HER2 are excluded

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Biopsy/Surgical Features in non-pCR Patients

Biopsy/Surgical Features	All Non-pCR Patients	False Negative Biopsy	
		n	Row %
Number of Cores			
1 – 5	7	5	71
6 – 13	26	12	46
Unknown	3	1	33
Clip Retrieval at Biopsy Confirmed			
Yes	28	13	46
No	8	5	62
Clip Retrieval at Surgery Confirmed			
Yes	33	15	45
No	3	3	100
Residual Cancer Burden Score			
RCB−0*	8	7	88
RCB−I	4	2	50
RCB−II	10	4	40
RCB−III	2	0	0
Unknown	12	5	42

*RCB-0 includes patients with DCIS only

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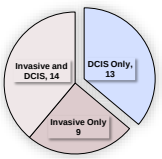
Type of Residual Disease



Comparison of Pathologic Findings from Biopsy and Surgery including only Invasive Disease as a Modified Endpoint for Residual Disease

Biopsy Findings	Residual Disease at Surgery: Yes (non-pCR)	Residual Disease at Surgery: No (pCR)	Total
Positive	14	1	15
Negative	9	74	83
Total	23	75	98

Negative Predictive Value (95% CI) = **89.2%** (80.4 to 94.9%)

Sensitivity (95% CI) = **60.9%** (38.5 to 80.3%)

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Conclusions

- **Biopsy did not achieve an NPV of ≥90%**
- **Biopsy identified 50% of the patients who had residual disease at surgery**
- **The findings do not support breast-conserving treatment without surgery based on these study criteria for cCR, rCR/near rCR, and negative tumor bed biopsies**

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SABCS 2019

- **GS5-03: Diagnosing residual disease and pathologic complete response after neoadjuvantchemotherapy in breast cancer patients by image-guided vacuum-assisted breast biopsy:results of a prospective multicenter trial. Heil J et al (Heidelberg)**
- **GS5-04: Accuracy of post-neoadjuvant chemotherapy image-guided breast biopsy to predict the presence of residual cancer: A multi-institutional pooled analysis. Tasoulis M et al (Royal Marsden, Seoul National UH, MD Anderson)**
- **GS5-06: Toward omitting breast surgery in patients with a pathologic complete response after neoadjuvant systemic treatment: interim analysis of the MICRA trial (Minimally Invasive Complete Response Assessment). Peeters V et al (Netherlands).**

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Heil J et al (RESPONDER trial)

- **Multicentric German trial, n= 595 pts**
- **cCR or PR, image guided VAB (US 79% or stereotaxic 21%), 50% 8G, 31% 10G**
- **Primary endpoint: FNR < 10%**
- **Stopped for futility at 398 pts; FNR= 18% (pCR rate of 48%); NPV: 81%**
- **32% DCIS only; 51% avoidable causes (multicentricity, recurrences, technical failures)**

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Tasoulis M et al

- Pooled data from 3 centers (UK, Korea, USA), n=166
- Partial or complete imaging/clinical response
  - Median tumor size post NAC= 1 cm
- 86% VAB; 78% US
- FNR: primary objective: 19%; NPV= 84%; 86% (HER2+)
- Planned subgroup (n=76): VAB, ≥ 6, ≤ 2 cm imaging: FNR= 3%; NPV=97%

Vrancken Peeters et al (MICRA)

- Prospective study, n=167
- Complete rCR (n=135) or partial response rPR (n=32) on MRI (≤ 2 cm residual or ≥30% tumor shrinkage)
- 8X 14G core needles, in the OR
- Primary outcome = FNR
- pCR rates: rCR 59%; rPR 28%
- FNR= 37%; NPV = 75%
- rCR: FNR = 45%; NPV = 75%
- rPR: FNR = 13%; NPV = 75%

IMAGINE no surgery….

- The findings do not support breast-conserving treatment without surgery based on these study criteria
- All studies revealed limitations
- Refining criteria:
  - ≥ 6 cores
  - clip retrieval
  - BC subtype specific studies?

- Central review of tri-modality imaging and reports