

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 Breastconserving Treatment without Surgery

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San Antonio Breast Cancer Symposium December 13, 2019 Program No. GS5-05

San Antonio Breast Cancer Symposium Dec. 10-14, 2019

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 chemoradiotherapy 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?



San Antonio Breast Cancer Symposium Dec. 10-14, 2019 **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) NRG NRG-BR005 Schema Operable focal or multifocal T1-T3, stage I-IIIA invasive ductal carcinoma (all receptor phenotypes) with clinical complete response by physical exam and radiological complete or near-complete response by tri-modality imaging after neoadjuvant systemic therapy REGISTRATION IMAGE-GUIDED CORE BIOPSY SURGERY (Lumpectomy) NRG **Primary Endpoint Definitions Biopsy Negative Predictive Value (NPV):** number of patients with a negative biopsy and confirmed pCR at surgery total number of patients with a negative biopsy

Biopsy Sensitivity:

Sensitivity =

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number of patients with a positive biopsy who had residual tumor at surgery

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



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



NRG • STEREOTACTIC BIOPSY (mammogram-based)

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

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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



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Patient Characteristics (cont.)

Tumor Characteristics	Patients (N=98)		
Tullion Characteristics	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	

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*Two patients with equivocal HER2 are excluded

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Results

	Residual Dis		
Biopsy Findings	Yes (non-pCR)	No (pCR)	Total
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%)



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	False Negative Biopsy	
	Patients	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

	Residual Disc		
Biopsy Findings	Yes (non-pCR)	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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Primary endpoint: FNR < 10%

Allegheny Health Network

Stopped for futility at 398 pts; FNR= 18% (pCR rate of 48%); NPV: 81% 32% DCIS only; 51% avoidable causes (multicentricity, recurrences, technical failures)

Tasoulis M	et	al
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- 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

