Impact of antibiotics on residual cancer burden and pathologic response rates during neoadjuvant Pembrolizumab in breast cancer

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BACKGROUND

- Achieving pathologic complete response (pCR) following neoadjuvant chemotherapy is associated with significantly better event free survival (EFS) and overall (OS), particularly for triple negative and HER2+ breast cancer [1]
- Addition of immunotherapy to neoadjuvant chemotherapy in early stage breast cancer has been shown to improve pCR rates over chemotherapy alone [2]
- Clinical factors affecting pCR rates in the context of immunotherapy are not well understood
- Antibiotic exposure during immunotherapy has been shown to negatively affect clinical outcomes in renal cell cancer, metastatic melanoma and non-small cell lung cancer [3-8]
- We tested whether antibiotics exposure during neoadjuvant pembrolizumab affects residual cancer burden (RCB) and pathologic complete response rate (pCR) in the pembrolizumab-4 arm of the ISPY-2 trial

METHODS

- I-SPY2 is an adaptively-randomized, phase II platform trial for high-risk, stage II/III breast cancer
- Women with HER2-negative breast cancer were eligible for randomization to standard of care taxane and anthracycline-based chemotherapy with or without pembrolizumab. The primary endpoint was pathologic complete response (pCR). Secondary endpoints were residual cancer burden (RCB) and 3-year event and distant recurrence free survival.
- In Pembrolizumab-4 arm of ISPY-2 trial, patients received neoadjuvant pembrolizumab 200mg every 3 weeks for four cycles concurrently with 80mg/m2 paclitaxel weekly for 12 weeks, followed by four cycles of 60mg/m2 doxorubicin plus 600mg/m2 cyclophosphamide every 2 weeks.
- Data on antibiotic use during neoadjuvant pembrolizumab was reviewed
- Patients who received at least one dose of systemic antibiotics were included in the antibiotic exposure group (ATB+). All other patients were included in the no exposure group (ATB).
- RCB index was used to evaluated as a continuous variable where a higher RCB index indicated higher RCB
- RCB index and pCR rates were compared between ATB+ and ATB- groups
- Association of antibiotic use with RCB and pCR rates was evaluated using linear regression and logistic regression respectively
- Clinical variables for adjustment were age, stage and hormone receptor (HR) status.
- SAS 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses

RESULTS

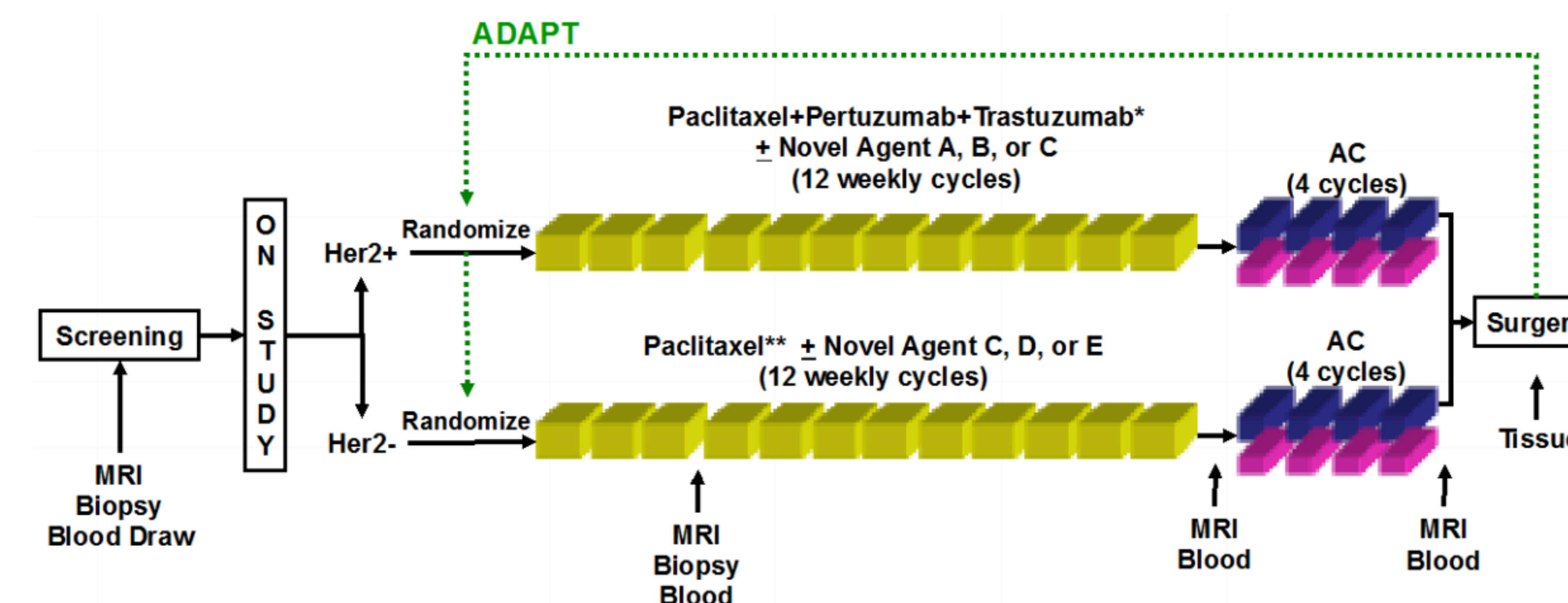### Figure 1. Overall study design schema of ISPY-2 trial

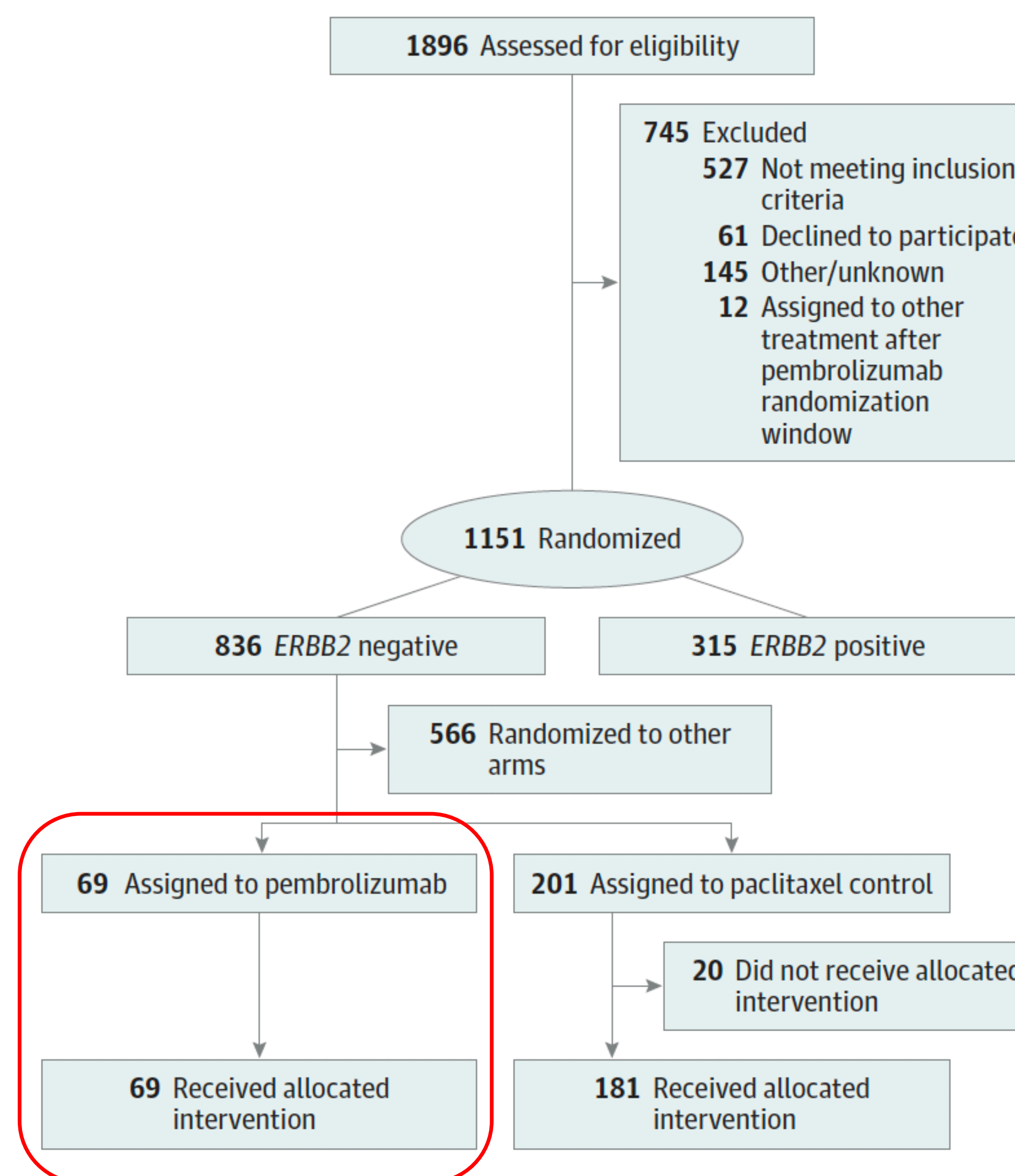### Figure 2. Consort diagram for ISPY-2 clinical trial and pembrolizumab-4 arm

1896 Assessed for eligibility

745 Excluded
- **527** Not meeting inclusion criteria
- **61** Declined to participate
- **145** Other/unknown
- **12** Assigned to other treatment after pembrolizumab randomization window

1151 Randomized

836 ERBB2 negative **315** ERBB2 positive

566 Randomized to other arms

69 Assigned to pembrolizumab **201** Assigned to paclitaxel control

20 Did not receive allocated intervention

69 Received allocated intervention **181** Received allocated intervention

Table 1. Clinical characteristics of patients in pembrolizumab-4 arm

Variable	With Antibiotic use		Without antibiotic use		P-value
	N	Median (range)	N	Median (range)	
Age	19	46 (27-69)	49	50 (29-71)	0.58
Hormone receptor (HR) status					0.23
Negative	10	52.6 %	18	36.7%	
Positive	9	47.4%	31	63.3%	
Stage					0.02
Stage I, II (%)	6	42.9%	27	77.1%	
Stage III (%)	8	57.1%	8	22.9%	

Figure 3. Comparison of RCB index and pCR rates between ATB+ and ATB-

RCB index — pCR rates
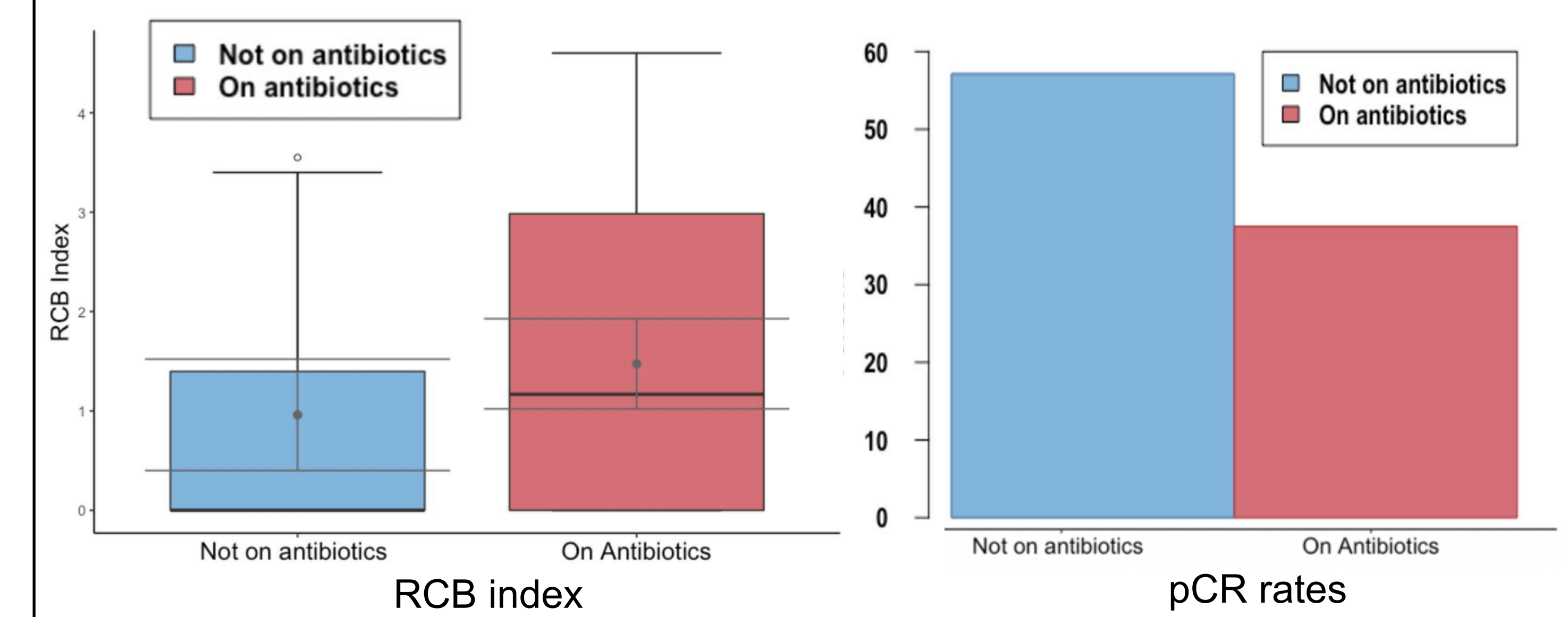
Results Summary

- Sixty-nine patients received neoadjuvant pembrolizumab with chemotherapy
- Forty patients were hormone receptor (HR)-positive and 29 triple-negative
- One patient was excluded due to missing data on antibiotics
- Sixty-eight patients were included in the final analysis
- 19/68 (28%) patients were in the ATB+ group
- Antibiotic use in HR+ and HR- patients were 9/19 (47%) and 31/49 (63%) respectively (P=0.23)
- Compared to ATB- group, patients in the ATB+ group had **higher mean RCB index** (1.05 vs 1.80, P=0.04)
- Compared to ATB- group, patients in the ATB+ group had **lower pCR rate** (53.1% vs 26.3%, P=0.05)
- **Antibiotic use was associated with higher probability of RCB in univariate analysis (Coefficient estimate CE: 0.75, 95% CI 0.01-1.48, P=0.04)** and multivariable analysis (CE: 0.89, 95% CI 0.11-1.65, P=0.02)
- HR positivity was independently associated with higher probability of RCB (CE: 1.07, 95% CI 0.38-1.77 P=0.002)
- **Antibiotic use was associated with higher probability of not having pCR (Odds ratio 3.17, 95% CI 0.99-10.15, P=0.05).**

DISCUSSION

- Patients with antibiotic exposure during neoadjuvant pembrolizumab in early stage breast cancer were associated with higher RCB and lower pCR rates
- Further validation in a larger independent cohort is needed to confirm these findings.

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