Pathological complete response in early breast cancer patients undergoing neoadjuvant chemotherapy. Focus on Ki-67 and molecular subtypes.

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Background

- Neoadjuvant chemotherapy is widely used to downstage breast cancers prior to surgery.
- Pathologic complete response (pCR) rate is a strong predictor of outcome for breast cancer.
- The Ki-67 antigen, which encodes two protein isoforms with molecular weights of 345 and 395 kDa; was originally identified by Scholzer and Gerdes in the early 1980s.
- The Ki-67 protein has a half-life of only ~1–1.5 h. Ki-67 is present during all active phases of the cell cycle (G1, S, G2 and M), but is absent in resting cells (G0). In later phases of mitosis (during anaphase and telophase), a sharp decrease in Ki-67 levels occurs.
- Expression of the Ki-67 protein (pKi-67) is associated with the proliferative activity of intrinsic cell populations in malignant tumors, allowing it to be used as a marker of tumor aggressiveness.
- The prognostic value of pKi-67 has been investigated in a number of studies with its potential as a reliable marker having been shown in cancers of the breast, soft tissue, lung, prostate, cervix and central nervous system.
- Ki-67 immuno-histochemical determination is a widely used biomarker of cell proliferation in patients undergoing endocrine treatment for breast cancer. The role of Ki-67 in patients undergoing neoadjuvant chemotherapy for early breast cancer remains controversial.

Methods

Table 1. Patient Characteristics.

Patient Characteristics (n=208)	
Age (median = 53 [26-90])	
Age ≤ 50	80 (38%)
Age > 50	128 (62%)
Ki-67 PreCT (median = 40 [5-90])	
Ki-67 > 20%	158 (76%)
Ki-67 ≤ 20%	40 (19%)
Unknown	10 (5%)
Menopausal Status	
Pre-Menopausal	80 (38%)
Post-Menopausal	128 (62%)
Tumor Size	
T1	45 (22%)
T2	133 (64%)
T3	19 (9%)
T4	11 (5%)
Nodal Status	
Negative	93 (45%)
Positive	110 (53%)
Unknown	5 (2%)
Stage	
1	20 (10%)
2A	91 (44%)
2B	65 (31%)
3	32 (15%)
Molecular Type	
Luminal A & B	54 (26%)
TNBC	116 (56%)
HER-2 Positive ER- & PR-	12 (6%)
HER-2 Positive ER+ &/or PR+	26 (13%)

Study Population

- We analyzed retrospectively data on 208 patients undergoing taxane and/or anthracycline, transtuzumab based NAC.
- Patients received neo-adjuvant therapy including TAC, AC & Taxane, Taxane, TC, AC, Taxane & Adriamicin, AC & Taxane & Herceptin, or Taxane & Herceptin.

Ethics approval

- Ethics approval was obtained from Pharma-Ethics, Pretoria, South Africa (ethics committee working according to the South African Ethics regulations).

Clinical and pathological assessment

- Clinical assessment of the primary tumor and lymph nodes was made using bi-dimensional caliper measurements of the primary tumor and axillary nodes.
- Sonographical assessments of the primary tumor and lymph nodes were performed regularly.
- Immunohistochemical staining was performed for ER, PR, Her-2 and Ki-67.
- Fluoresce in situ hybridization (FISH) was used to confirm Her-2 positivity.
- Pathological complete response (pCR) was defined as the complete disappearance of the invasive cancer in the breast and absence of tumor in the axillary lymph nodes examined by axillary clearance.

Statistical Analysis

- The primary hypothesis was that higher levels of Ki-67 would be associated with a better prognosis overall, independent of anti-cancer therapy.
- The distribution of all demographic and clinical variables by study group was tabulated.
- Receiver-operating characteristic (ROC) curve analysis was used to determine the optimal cut point for Ki-67.
- DFS was calculated from the time of diagnosis to first date of any documented disease recurrence, death, or date of last follow-up. DFS were estimated using the Kaplan-Meier method and compared using the log-rank test.
- Fisher's exact or Chi squared tests were used for the analysis of categorical variables.
- Multivariate models included only variables that exhibited a univariate association with the dependent variable, pCR ($p < .05$).
- NCSS software version 11 for Windows (USA) was used for statistical analyses.

Results

- The results of the statistical analysis are depicted in the tables and figures as follows:

Figure 1. ROC Curve of Ki-67 for Prediction of pCR.

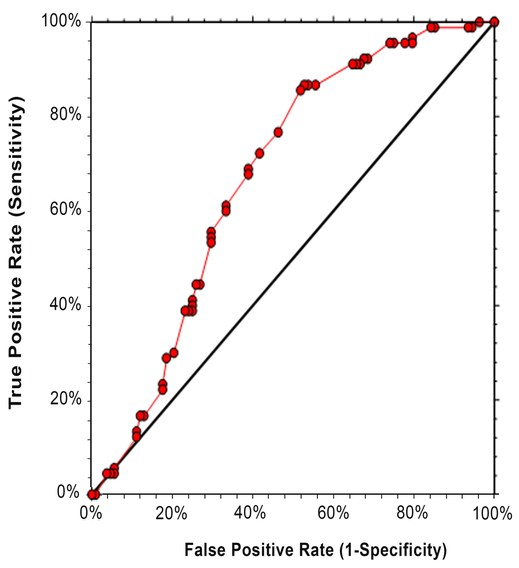
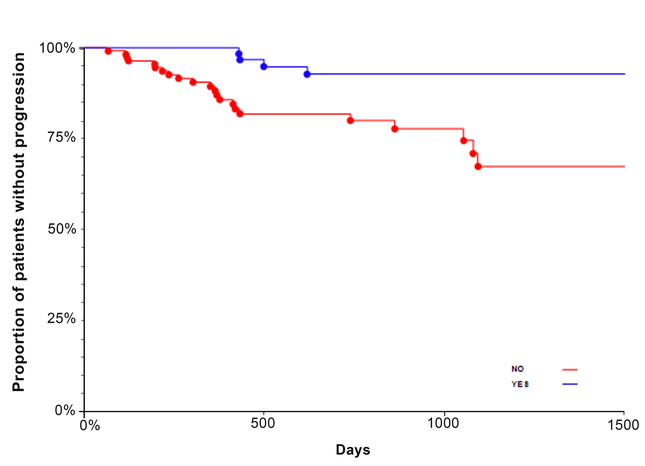


Figure 2. Progression Free Survival by PCR.



At 4 years 95% of pts who attained a pCR were disease free compared to 78% of pts who did not attain a pCR (log rank test Chi square=10.775, p < 0.01).

Figure 3. Response by Age.

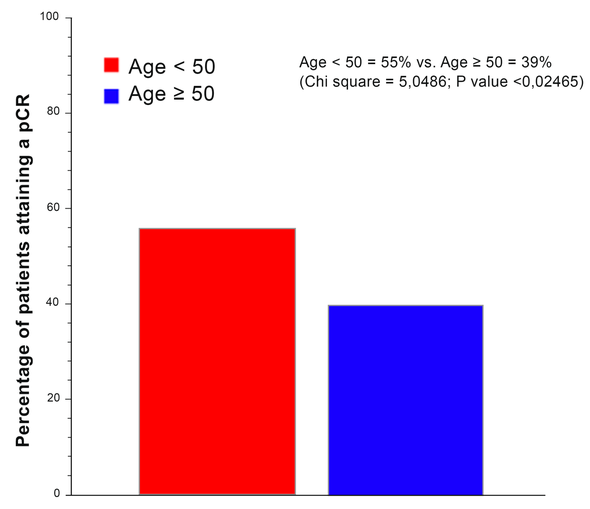


Figure 4. Response by Primary Tumour Size.

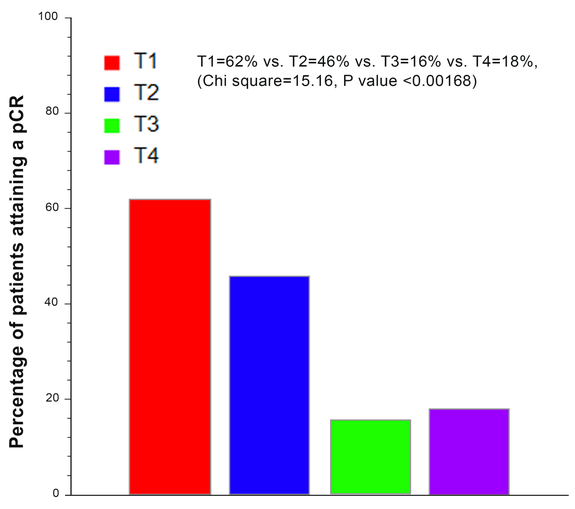


Figure 5. Response by Nodal Status.

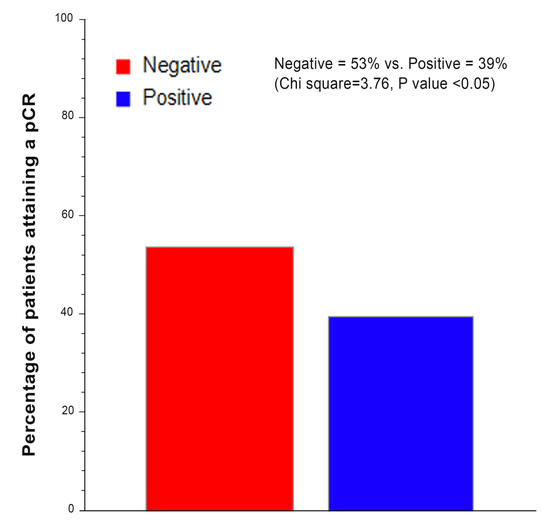


Figure 6. Response by ER.

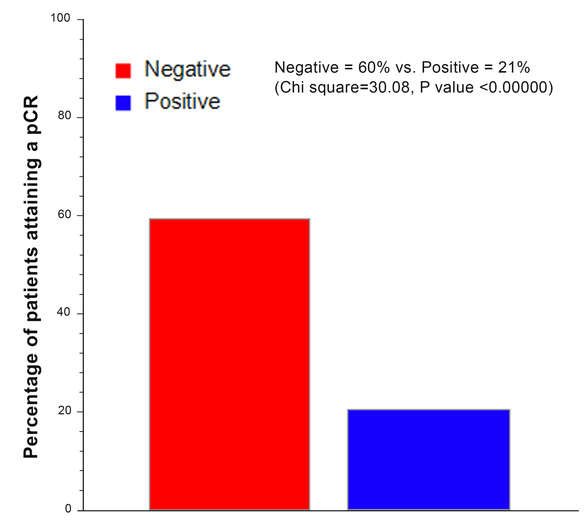


Figure 7. Response by PR.

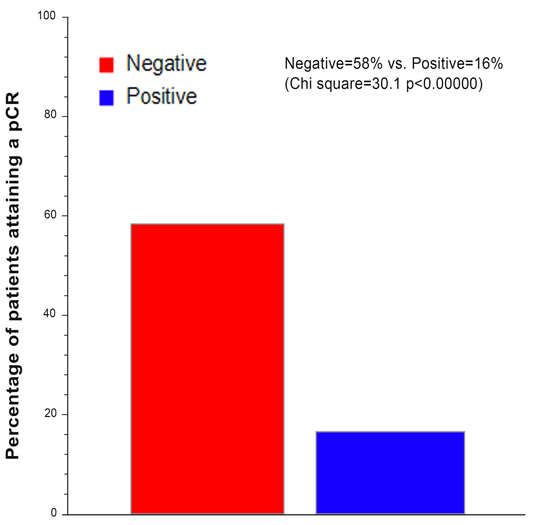


Figure 8. Response by Stage.

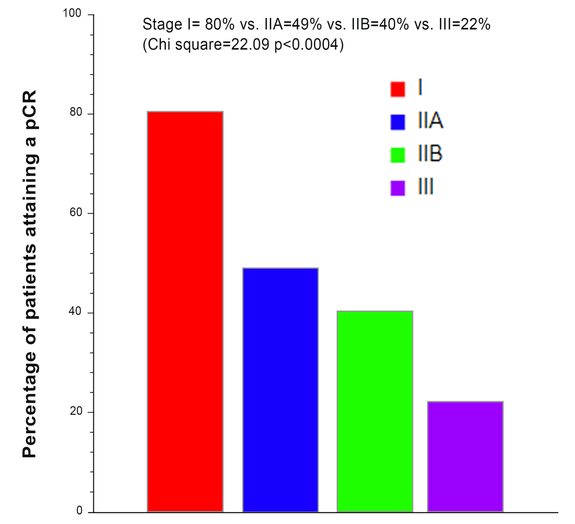


Figure 9. Response by Ki-67.

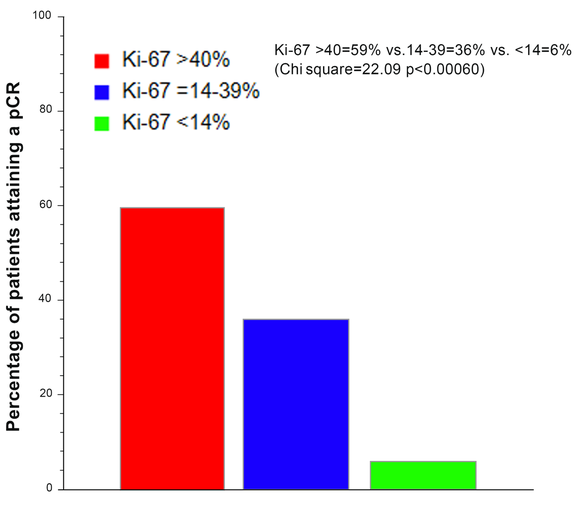


Figure 10. Response by Molecular Subtype.

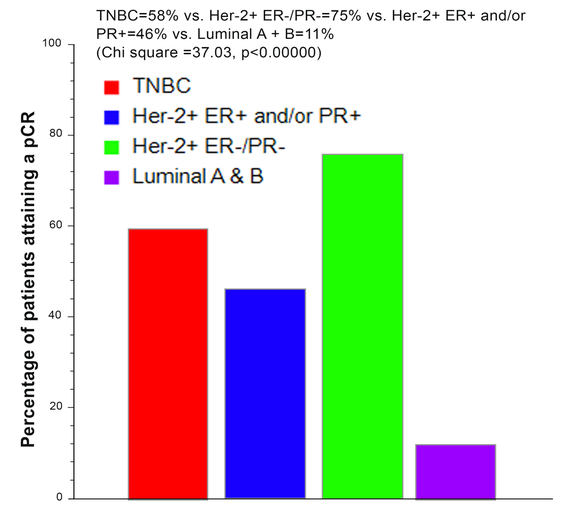


Table 2. Logistic Regression Analysis.

Logistic Regression Analysis		
Variables	**Chi square**	**P-Value**
Ki-67 (as a continuous variable)	12,75101	0,00036
Molecular Subtype	19,74867	0,00019
Nodal Status	0,97675	0,61362
Stage	2,65892	0,44725
Age < 50 vs. Age ≥ 50	0,00861	0,92607
Tumor Size	0,82810	0,84273

Conclusions

- TNBC and Her-2 positive molecular subtype and high Ki-67 are associated with a higher pCR rate in early breast cancer patients undergoing neo-adjuvant chemotherapy.

ESMO Breast Cancer Annual Congress; May 2 - 4 2019; Berlin, Germany

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