
# Treatment outcomes in TNBC patients undergoing neoadjuvant chemotherapy. The importance of Ki-67.


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Personalised Cancer Care

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BREAST CARE CENTRE

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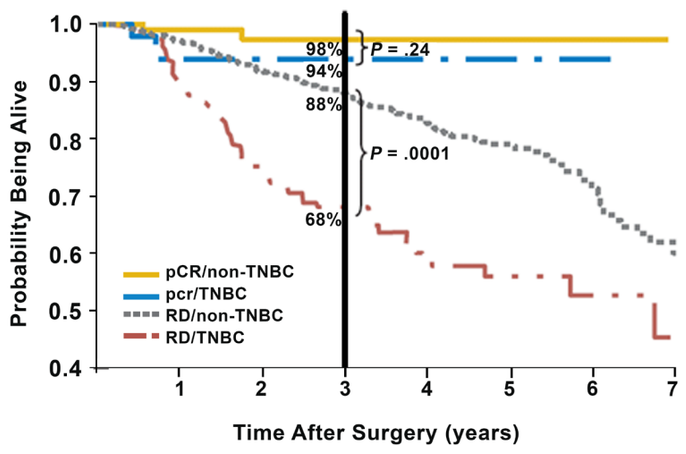
## *Background*

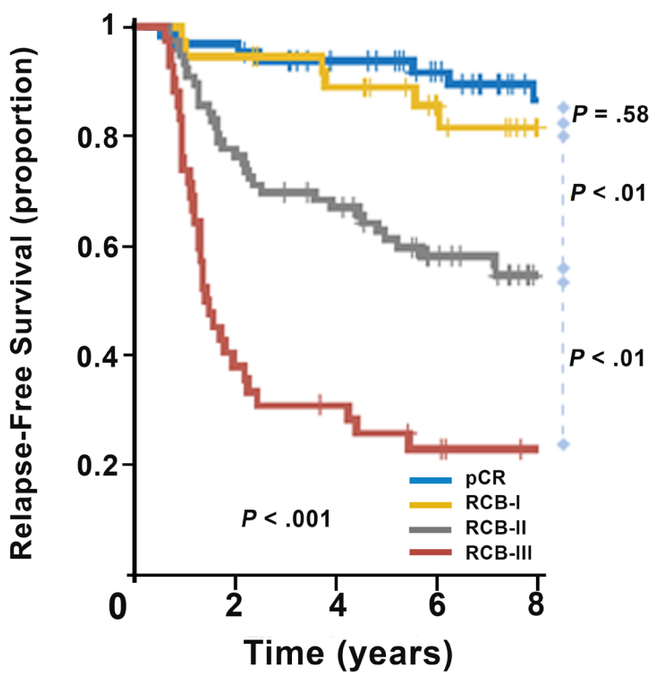
- Neoadjuvant chemotherapy (NAC) is widely used to downstage breast cancers prior to surgery.
- Pathologic complete response (pCR) rate is a strong predictor of outcome for breast cancer.
- TNBC often responsive to conventional NAC with good outcome similar to other subtypes.
- A non-pCR is an indication of a poorer outcome.

**Figure 1. Responsiveness to Neoadjuvant Conventional Chemotherapy.**




Liedtke C, et al. J Clin Oncol. 2008;26:1275-1281.

**Figure 2. TNBC Response Free Survival by Residual Breast Cancer (MD Anderson Data).**




Symmans, et al. J Clin Oncol. 2017, 35 (10): 1049-1060

- The Ki-67: two protein isoforms with molecular weights of 345 and 395 kDa.
- The Ki-67 protein has a half-life of only ~1–1.5 hours.
- 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), there is a sharp decrease in Ki-67 levels.
- The expression of the Ki-67 protein (pKi-67) is associated with the proliferative activity of intrinsic cell populations in malignant tumours.
- Ki-67 is used as a marker of tumour aggressiveness.

## *Methods*

- We analyzed date retrospectively/prospectively on 152 TNBC patients undergoing NAC.
- Outcome assessments: Associations of clinical and pathological characteristics including the Ki-67 with pCR and DFS.
- All patients were treated with anthracycline and/or taxane-based neoadjuvant chemotherapy.
- Immunohistochemical staining was performed for ER, PR, HER-2 and Ki-67.
- Fluoresce in situ hybridization (FISH) was used to confirm HER-2 positivity.
- Clinical assessment was made using bi-dimensional caliper measurements of the primary tumour and axillary lymph nodes.
- Sonographic assessments of the primary tumour and lymph nodes were performed regularly.
- Pathological complete response (pCR) was defined as the complete disappearance of the invasive cancer in the breast and absence of tumour in the axillary lymph nodes.
- Ethics approval was obtained from Pharma-Ethics, Pretoria, South Africa (ethics committee working according to the South African Ethics regulations).

## *Statistical Methods*

- The primary hypothesis was that higher levels of Ki-67 would be associated with a better overall prognosis, independent of anti-cancer therapy.
- 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 ($p < .1$).
- NCSS software version 11 for Windows (USA) was used for statistical analyses.

## *Results*

**Table 1. Patient Characteristics.**

| Patient Characteristics | |
|---|---|
| **Patient Characteristics** | **n (%)** |
| Total (n) | 152 |
| Median Age | 50 (27-85) |
| **Age** | |
| ≤ 50 years | 76 (50%) |
| > 50 years | 76 (50%) |
| **Menopausal Status** | |
| Pre-Menopausal | 51 (37%) |
| Post-Menopausal | 86 (63%) |
| **Tumour Size** | |
| T1 | 35 (23%) |
| T2 | 101 (66%) |
| T3 | 13 (9%) |
| T4 | 3 (2%) |
| **Nodal Status** | |
| Negative | 84 (55%) |
| Positive | 65 (43%) |
| Unknown | 3 (2%) |
| **Stage** | |
| 1A | 19 (13%) |
| 1B | 2 (1%) |
| 2A | 75 (49%) |
| 2B | 41 (27%) |
| 3A | 11 (7%) |
| 3B | 3 (2%) |
| 3C | 1 (1%) |
| **Ethnicity** | |
| Black | 25 (17%) |
| White | 106 (70%) |
| Indian | 15 (10%) |
| Coloured | 5 (3%) |
| **Chemo-Groups** | |
| TAC | 131 (86%) |
| AC + Taxane | 17 (11%) |
| Taxane | 1 (1%) |
| TC | 2 (1%) |
| AC | 1 (1%) |

**Figure 3. Response to neoadjuvant chemotherapy.**

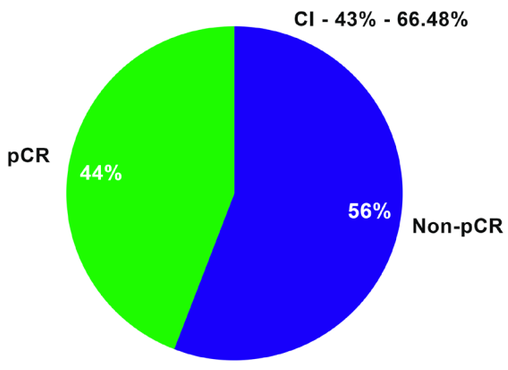



**Figure 4. Frequency of Ki-67 in TNBC (values pre-chemotherapy).**

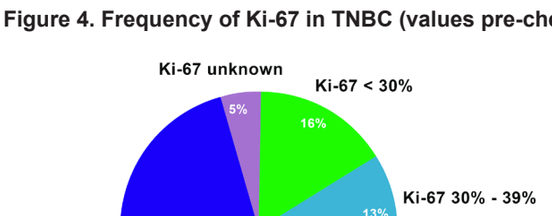



**Figure 5. pCR by stage.**

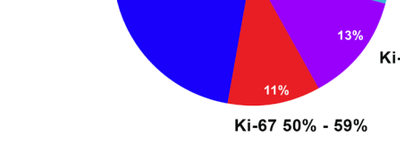



**Figure 6. ROC Curve of Ki-67 for Prediction of pCR.**

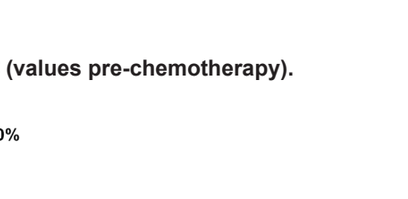
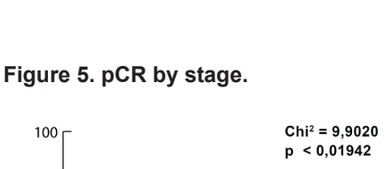



**Figure 7. pCR by tumour size.**




### pCR by Ki-67 at different cut-off levels.

**Figure 8a. Ki-67 cut-off 30%.**

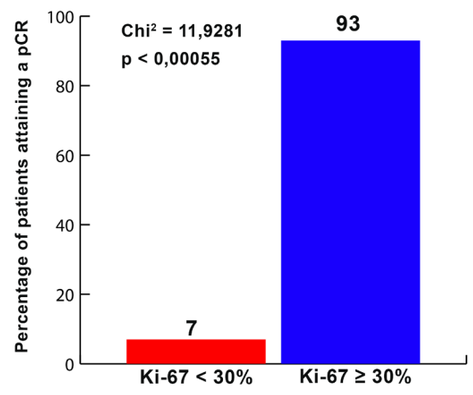



**Figure 8b. Ki-67 cut-off 40%.**

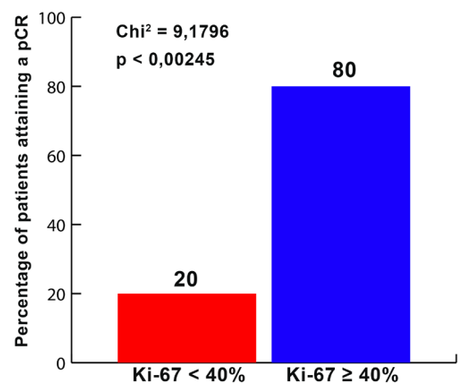



**Figure 8c. Ki-67 cut-off 50%.**

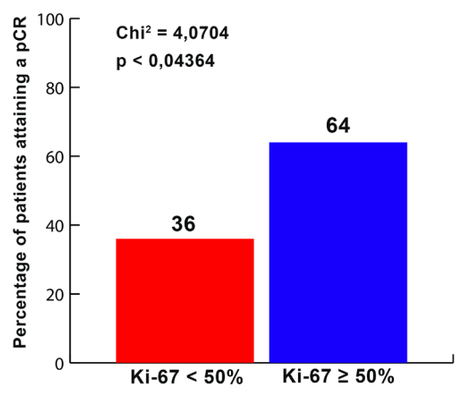
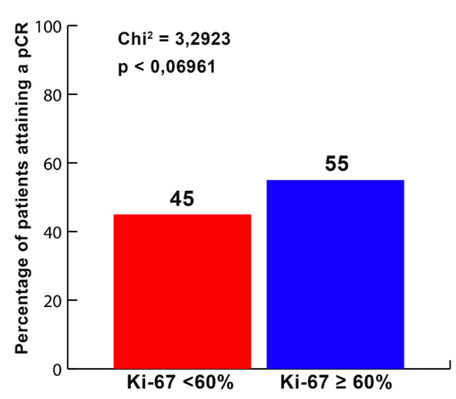



**Figure 8d. Ki-67 cut-off 60%.**




### Univariate Analysis

**Table 2. Univariate Analysis - Variables not significant.**

| Variables not significant | |
|---|---|
| Age | ≤ 50 Years vs. > 50 Years |
| Ethnicity | White vs. Non-White |
| Glands | Positive vs. Negative |

**Figure 9. DFS by Response (pCR vs No pCR).**




### Logistic Regression Analysis

**Table 3. Logistic regression analysis.**

| Logistic regression analysis | | |
|---|---|---|
| **Variables** | **Chi square** | **P-Value** |
| Ki-67 (as a continuous variable) | 8.15692 | 0,00429 |
| T Size (T1 vs T2 vs T3 + T4) | 2.99040 | 0,39311 |
| Stage of Disease (ST1 vs ST2A vs ST2B vs ST3) | 1.59701 | 0.66007 |
| Nodal Status (N0 vs N1 vs N2) | 1.90762 | 0,16723 |

## *Conclusions*

- Ki-67 is an independent prognostic factors of pCR in patients with early TNBC undergoing neoadjuvant chemotherapy.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