**Supplementary Material**

In the ***intermediate risk (RS 11-25) node negative population***, there were 66/106 patients (62%) in A and 58/97 (60%) in B. No significant differences were noted in demographics and therapy administration, except from a mean dose of radiotherapy applied, which was relevantly higher (p=0.021) in cohort A (54.15 Gy, SD 6.8) vs. in cohort B (50.31 Gy, SD 7.14) (Supplemental Table 3).

In terms of treatment, in the intermediate node negative subgroup, the majority underwent conservative breast surgery (76% in A and 64% in B, p=0.114), with 58% cases of reconstruction in A and 50% in B (p=0.69). Radiotherapy was administered in 70% of women in A and 69% in B (p=0.969). Only 6 patients in A had CHT, after 5 refused. In cohort B, 3 patients had CHT (p=0.49) with no refusal being registered. There was only one major therapy associated side effect, which was registered in A and required treatment interruption. There are 4 cases of relapse in A and 2 in B (p=0.516) with two BC related deaths in A. However, due to study design implying later enrollment for patients in cohort B, these data should not be taken into consideration.

In the intermediate RS (11-25) there were 10 cases of relapse in A (9.4%), of which only one patient received CHT. Three patients in this category had an RS <16, with the rest having higher RS. There were 3 registered death events, of which one BC related.

In the same category in B there relapse was reported in 4 patients (4%), none of which received CHT and of which 3 had an RS >16. There were no deaths recorded in this group.

In the intermediate RS node negative group however, there were 4 cases of relapse (40%) with 2 death events which were not related to BC in A, while in B there were 2 cases of relapse (50%) and no death events. In cohort A, all relapses occurred in patients with RS>16, who did not receive CHT. In B these cases were of patients who did not have CHT and had an RS of 13 and 16, respectively.

In the intermediate node negative population, TB decision was implemented in 76% of cases in A and 83% in B (p=0.919). In A there were 7/15 premenopausal patients with RS >16, of which only one received CHT. In B there were 13/20 patients with RS >16, of which 4 received CHT. There was only one refusal of CHT in A and none in B. In A 15 women were under 50 years of age, of which 9 with RS >16, but only one received CHT. In B, from the 21 young women, of which 14 with RS >16, 3 received CHT.

Details relaying therapy administration and outcome in the intermediate node negative population before and after TAILORx publication are summarized in Table S5.

In the intermediate RS (11-25), CHT administration remains almost unchanged (14/106 cases in A and 13/97 in B). Interestingly to discuss, **in the intermediate RS node negative group**, which included 66 patients, only one patient receiving CHT in A was premenopausal and <50 years of age, although there were 6 other premenopausal, younger women with an RS >16. In the same group in B, which included 13 premenopausal, younger (<50 years old) patients with RS>16, only two patients had CHT. These differences were not deemed statistically relevant (p=0.951). It is also important to mention that among these women the refusal rate is relatively low in A (n=2) and none in B. One can safely conclude from the rate of TB decision implementation (76% in A and 83% in B p=0.522) that these women were excluded from CHT according to TB decision, and that RS was not significant when assigning CHT for pre-menopausal younger women with RS >16. However, given there are so few instances we cannot infer that these findings are relevant enough.

**Table S1. Main differences in treatment administration and therapy-associated complications, in the two populations, before (A) and after (B) publication of TAILORx study**

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| --- | --- | --- | --- |
| **Table S1. Treatment in the two cohorts** | | | |
|  | **Cohort A** | **Cohort B** | **p-value** |
| **Treatment administration** |
| Surgery | 165 | 161 | 0.352 |
| Breast Conservative | 113 (68%) | 108 (67%) |
| Mastectomy | 47 (32%) | 53 (33%) |
| Postoperative Complications | 21 (13%) | 18 (11%) | 0.764 |
| Reconstruction | 28/47 (60%) | 29/53 (55%) | 0.679 |
|  |  |  |  |
| Radiotherapy (RT) | 128 (78%) | 123 (76%) | 0.223 |
| RT Complications | 3 (2%) | 1 (0.8%) | 0.86 |
| Dose RT | 54.99 (SD 8.31) | 52.35 (SD 7.88) | 0.417 |
|  | | | |
| **TB Treatment Recommendation according to RS** | | | |
| ET+CHT total (%) | 51 (31%) | 48 (30%) | 0.865 |
| ET+CHT (RS >26) | 28 | 27 |  |
| CHT+ET TB Recommendation in RS 11-25 | 23/106 (22%) | 16/97 (17%) |  |
| CHT+ET TB Recommendation in RS 0-10 | 1/31 (3%) | 0/37 (0%) |  |
| ET alone TB Recommendation | 116 (70%) | 117 (73%) | 0.712 |
| ET | 155 (94%) | 152 (94%) | 0.229 |
| ET Refusal | 6 (3.8%) | 9 (5.6%) | 0.429 |
|  |  |  |  |
| Adjuvant CHT | 31 (19%) | 35 (22%) | 0.763 |
| CHT in patients ≤ 50 years old | 7/40 (17.5%) | 16/53 (30%) | <0.001 |
| CHT in patients ≥ 51 years old | 24/125 (19%) | 20/108 (19%) | 0.664 |
| CHT in patients with RS 11-20 | 5 (6%) | 9 (13%) | 0.449 |
| CHT in patients with RS 21-25 | 9 (35%) | 4 (17%) | 0.743 |
| CHT in patients with RS 26-30 | 9 (75%) | 7 (78%) | 0.284 |
| CHT in patients with RS >30 | 8 (57%) | 14 (78%) | 0.252 |
| CHT Refusal | 15 (9%) | 6 (3.7%) | 0.042 |
| Osteo-oncologic Treatment | 67 (41%) | 72 (45%) | 0.695 |

RS = Recurrence Score; ET = Endocrine Therapy; TB = Tumor Board; RT = Radiotherapy; CHT = Chemotherapy; SD = Standard Deviation. Note: Percentages were rounded.

**Table S2. Administration of CHT+ET vs. ET alone before TAILORx (cohort A) and after TAILORx (cohort B)**

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| --- | --- | --- | --- | --- | --- | --- |
| **Table S2. Application of CHT+ET and ET alone in A vs. B** | | | | | | |
|  | **CHT+ET Administration** | | | **ET Administration** | | |
|  | A (%) | B (%) | **Change** (%) | A (%) | B (%) | **Change** (%) |
| Total | 31 (19%) | 35 (22%) | + 3% | 158 (96%) | 152 (94%) | -2% |
| Age ≤ 50 years old | 7 (17.5%) | 16 (30%) | +12.5% | 38 (95%) | 53 (98%) | +3% |
| Age ≥ 51 years old | 24 (19%) | 20 (19%) | 0% | 121 (96%) | 99 (93%) | -3% |
| N0 | 14 (15%) | 16 (17%) | +3% | 90 (95%) | 89 (95%) | 0% |
| N1 | 17 (25%) | 19 (28%) | +3% | 67 (100%) | 64 (96%) | -4% |
| Grade 3 | 18 (29%) | 20 (31%) | +2% | 21 (42%) | 50 (100%) | 58% |
| Lobular | 4 (14%) | 6 (24%) | +10% | 26 (90%) | 23 (92%) | +2% |
| Ki-67 | 16 (31%) | 20 (31%) | 0% | 50 (96%) | 61 (95%) | -1% |

CHT = Chemotherapy; ET = Endocrine Therapy. Note: Percentages were rounded.

**Table S3. Logistic Regression model for association of patient, tumor, and treatment characteristics with chemoendocrine therapy in cohort A (before TAILORx) and cohort B (after TAILORx)**

|  |  |  |
| --- | --- | --- |
| **Cohort A** | | |
|  | OR (95% CI) | p-Value |
| Age | 1.05 (1.01 – 1.11) | 0.03 |
| Age <50/>50 | 0 | 0.998 |
| N0/+ | 3.32 (1.09 – 10.06) | 0.034 |
| Grade 3 vs. G1/2 | 0.4 (0.14 – 1.12) | 0.082 |
| Ki-67% high/low (<20% vs. ≥ 20%) | 2.15 (0.74 – 6.29) | 0.162 |
| Tumor stage (T2/3 vs. T1) | 0.97 (0.95 – 1) | 0.043 |
| RS 18-30 | 0.12 (0.03 – 0.43) | 0.001 |
| RS>31 | 0.04 (0.01 – 0.21) | <0.001 |
| **Cohort B** | | |
|  | OR (95% CI) | p-value |
| Age | 0.89 (0.84 – 0.94) | <0.001 |
| Age <50/>50 | 0.79 (0.11 – 5.92) | 0.818 |
| N0/+ | 3.31 (1.29 – 8.53) | 0.013 |
| Grade 3 vs. G1/2 | 0.79 (0.27 – 2.26) | 0.654 |
| Ki-67 high/low (<20% vs. ≥ 20%) | 1.1 (0.39 – 3.13) | 0.853 |
| Tumor Size (T2/3 vs. T1) | 0.99 (0.96 – 1.01) | 0.357 |
| RS 11-25 | 0.76 (0.21 – 2.76) | 0.678 |
| RS >26 | 1.31 (0.36 – 4.76) | 0.678 |

CHT = Chemotherapy; RS = Recurrence Score; N0/+ = nodal status; SD = Standard Deviation; OR = Odds Ratio; CI = Confidence Interval

**Table S4. Chemotherapy administration in the whole study population according to patients and tumor characteristics.**

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| --- | --- | --- | --- | --- |
| **Table S4. Logistic regression analysis of chemotherapy (CHT) administration in the entire population according to demographic and tumor characteristics** | | | | |
|  | **SD** | **p-Value** | **Odds Ratio (OR)** | **95% Confidence Interval** |
| **Age** | 0.02 | 0.001 | 0.93 | 0.89-0.97 |
| **Age ≤50 />50 years old** | 0.33 | 0.367 | 1.35 | 0.7 - 2.59 |
| **Cohort A/Cohort B** | 0.46 | 0.102 | 0.47 | 0.19-1.16 |
| **Comorbidities Yes/No** | 0.45 | 0.626 | 1.24 | 0.52-2.99 |
| **pT** | 0.35 | 0.086 | 1.81 | 0.92-3.56 |
| **pN** | 0.44 | <0.001 | 4.77 | 2.03-11-22 |
| **Lobular/Ductal Histology** | 0.32 | 0.12 | 0.61 | 0.33-1.14 |
| **Ki-67 ≤20%/>20%** | 0.49 | 0.291 | 0.6 | 0.23-1.55 |
| **Grade 2** | 0.46 | 0.376 | 0.67 | 0.27-1.63 |
| **Grade 3** | 0.45 | 0.473 | 1.39 | 0.57 - 3.38 |
| **Oncotype RS low (0-10)** | 1.2 | <0.001 | 0 | 0-0.02 |
| **Oncotype RS intermediate (11-25)** | 0.58 | <0.001 | 0.02 | 0.01-0.07 |
| **Oncotype RS high (≥26)** | 1.21 | <0.001 | 617.93 | 57.97 - 6587.16 |

CHT = Chemotherapy; RS = Recurrence Score; N0/+ = nodal status; SD = Standard Deviation; OR = Odds Ratio; CI = Confidence Interval

**Table S5. Main treatment strategies and outcomes in the intermediate RS (11-25) node negative population before and after publication of TAILORx study**

|  |  |  |  |
| --- | --- | --- | --- |
| **Table S5. Treatment administration and outcomes in the intermediate RS (11-25) node negative BC population** | | | |
|  | **Cohort A** | **Cohort B** | **p-value** |
| Number of patients | 66 (62%) | 58 (60%) |  |
| **Menopause** | 51 (77%) | 38 (66%) | 0.206 |
| Age ≤ 50 years old | 15 (23%) | 19 (33%) | 0.338 |
| Age ≥ 51 years old | 51 (77%) | 39 (67%) | 0.205 |
| Surgery |  | | |
| Breast conservative | 50 (76%) | 37 (64%) | 0.114 |
| No surgical reconstruction | 28 (42%) | 29 (50%) | 0.69 |
| **CHT** | 6 (9%) | 3 (5%) | 0.49 |
| CHT refusal | 5 (45%) | 0 (0%) |  |
| CHT in premenopausal women with RS >16 | 1 (16%) | 2 (67%) |  |
| RT | 46 (70%) | 40 (69%) | 0.969 |
| RT refusal | 4 (8%) | 2 (5%) | 0.904 |
| Mean RT Dose | 54.14 (SD 6.8, IQR 9.52) | 50.31 (SD 7.16, IQR 2.8) | 0.021 |
| ET | 62 (94%) | 52 (90%) | 0.326 |
| ET refusal | 3 (5%) | 6 (10%) |  |
| Osteo-oncologic treatment | 29 (44%) | 23 (40%) | 0.91 |
| **Relapse** | 4 (6%) | 2 (3%) | 0.516 |
| Death | 2 (3%) | 0 (0%) |  |
| Mean Follow-up (months) | 60.52 (SD 22.03, IQR 27)  Range: [4-108]  Median: 61 | 18.5 (SD 11.47, IQR 16.5)  Range: [1-41]  Median: 17 | <0.001 |
| TB Implementation | 50 (76%) | 48 (83%) | 0.919 |

CHT = Chemotherapy; RS = Recurrence Score; RT = Radiotherapy; ET = Endocrine Therapy; TB = Tumor Board; SD = Standard Deviation. Note: Percentages were rounded.

**Table S6. Association of chemotherapy administration according to age and RS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table S6.a. Relationship between CHT Administration, Age and RS in A** | | | | |
|  | **SD** | **p-Value** | **OR** | **95% CI** |
| Age ≤ 50 years old | 0.11 | 0.835 | 1.02 | 0.83 – 1.26 |
| RS for Patients ≤ 50 years old | 0.13 | 0.009 | 0.75 | 0.56 – 0.92 |
| Age ≥ 51 years old | 0.05 | 0.006 | 1.13 | 1.04 – 1.24 |
| RS for Patients ≥ 51 years old | 0.04 | <0.001 | 0.81 | 0.74 – 0.88 |
| **Table 9.b. Relationship between CHT Administration, Age and RS in B** | | | | |
|  | SD | p-Value | OR | 95% CI |
| Age ≤ 50 years old | 0.07 | 0.552 | 0.96 | 0.84 – 1.1 |
| RS for Patients ≤ 50 years old | 0.08 | 0.001 | 1.29 | 1.11 – 1.49 |
| Age ≥ 51 years old | 0.05 | <0.001 | 0.81 | 0.74 – 0.89 |
| RS for Patients ≥ 51 years old | 0.04 | 0.132 | 1.06 | 0.98 – 1.14 |

CHT = Chemotherapy; RS = Recurrence Score; SD = Standard Deviation; OR = Odds Ratio; CI = Confidence Interval