

# Abstract 547: Impact of CYP2D6 polymorphisms on adverse events in patients with breast cancer treated with tamoxifen: Insights from an early dose escalation trial in CYP2D6 poor metabolizers

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## Background

Tamoxifen is widely used in treating hormone receptor-positive breast cancer. It is primarily metabolized by the CYP2D6 enzyme to yield active metabolites. However, CYP2D6 polymorphisms have been associated with a differential response to tamoxifen. In a clinical trial involving an early dose escalation of tamoxifen in poor metabolizers, we found endoxifen concentration levels similar to those of patients with extensive phenotype, and no long-term survival differences among CYP2D6 phenotypes. However, the impact of that dose escalation on side effect incidence was not addressed.

## Methods

We analyzed the incidence of specific side effects - osteoarticular pain, hot flashes, asthenia, and uterine alterations - in 86 breast cancer patients, differentiated by their CYP2D6 phenotype. In poor metabolizers, the tamoxifen standard dose of 20 mg/day was escalated to 40 mg/day and 60 mg/day for 4 months each, and then treated with 20 mg/day until completing the treatment.

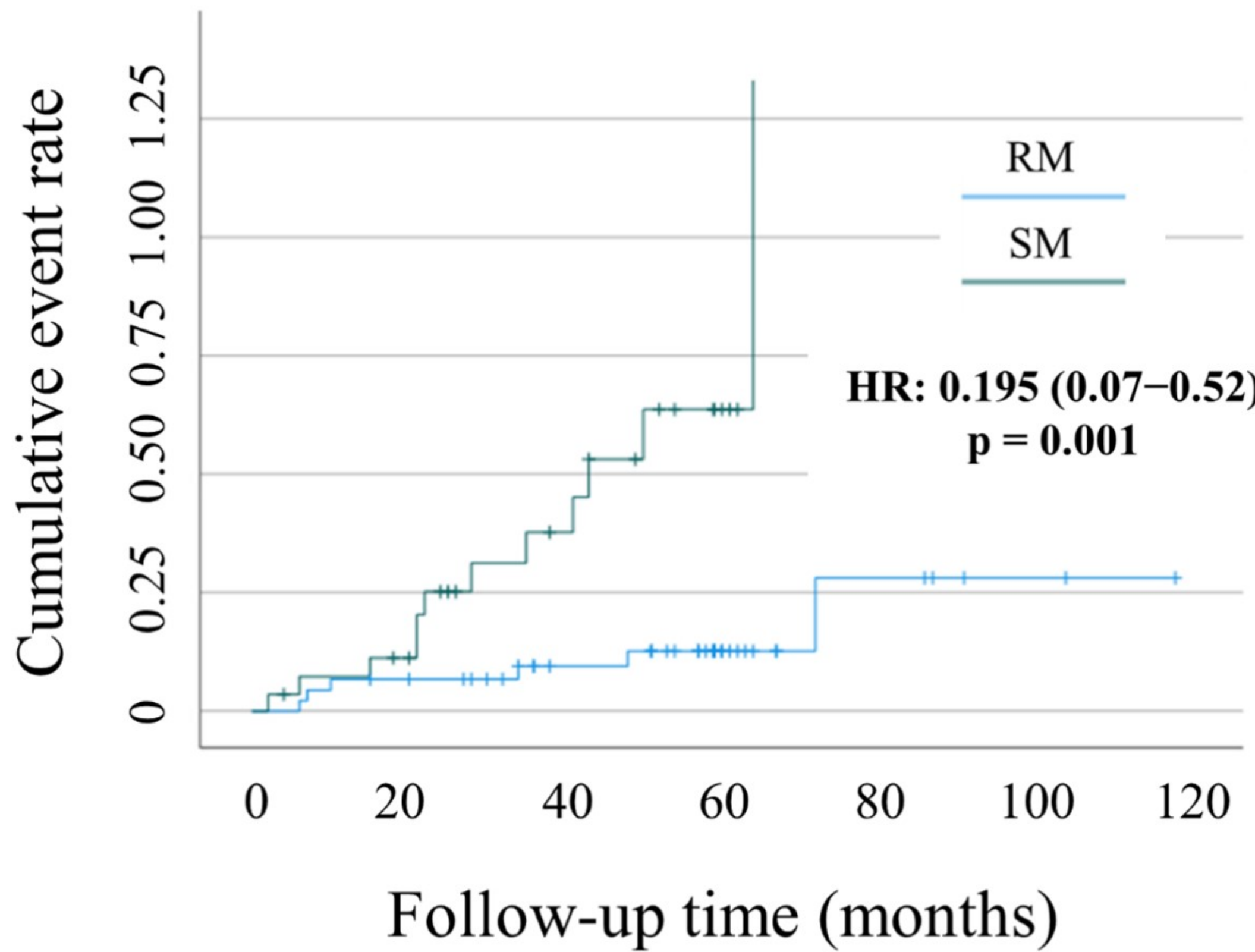
**Table 1.** Comparative Univariable Analysis of Adverse Events in Tamoxifen-treated Breast Cancer Patients: Pre- and Post-Propensity Score Matching Outcomes (PSM)

|                     | All Patients |            |                                 |                    |             |                   | PSM Paired |            |                                 |                   |             |                  |       |
|---------------------|--------------|------------|---------------------------------|--------------------|-------------|-------------------|------------|------------|---------------------------------|-------------------|-------------|------------------|-------|
|                     | N            | Events (%) | Time to Events (months; CI 95%) | P                  | HR (CI 95%) | P                 | N          | Events (%) | Time to Events (months; CI 95%) | P                 | HR (CI 95%) | P                |       |
| Osteoarticular Pain |              |            |                                 |                    |             |                   |            |            |                                 |                   |             |                  |       |
|                     | RM           | 45         | 27 (60)                         | 56.5 (38.3–74.7)   | 0.566       | 1.20 (0.63–2.29)  | 0.571      | 18         | 9 (50)                          | 79.0 (51.0-107.1) | 0.439       | 0.69 (0.27-1.77) | 0.443 |
|                     | SM           | 30         | 15 (50)                         | 37.9 (29.0–46.8)   |             | Reference         |            | 20         | 10 (50)                         | 36.8 (26.8-46.8)  |             | Reference        |       |
| Hot Flashes         |              |            |                                 |                    |             |                   |            |            |                                 |                   |             |                  |       |
|                     | RM           | 46         | 22 (47.8)                       | 83.4 (59.9–106.9)  | 0.526       | 1.26 (0.61–2.62)  | 0.533      | 19         | 10 (52.6)                       | 86.2 (50.4-122.0) | 0.938       | 1.04 (0.41-2.62) | 0.939 |
|                     | SM           | 30         | 11 (36.7)                       | 43.4 (33.3–53.5)   |             | Reference         |            | 20         | 9 (45)                          | 39.2 (26.9-51.4)  |             | Reference        |       |
| Asthenia            |              |            |                                 |                    |             |                   |            |            |                                 |                   |             |                  |       |
|                     | RM           | 45         | 18 (40)                         | 74.2 (58.1–90.2)   | 0.164       | 0.62 (0.31–1.24)  | 0.176      | 17         | 8 (47.1)                        | 72.7 (45.8-99.6)  | 0.245       | 0.58 (0.22-1.49) | 0.256 |
|                     | SM           | 29         | 15 (51.7)                       | 32.7 (22.2–43.2)   |             | Reference         |            | 20         | 11 (55.0)                       | 30.9 (18.7-43.1)  |             | Reference        |       |
| Uterine Changes     |              |            |                                 |                    |             |                   |            |            |                                 |                   |             |                  |       |
|                     | RM           | 46         | 7 (15.2)                        | 113.7 (94.7–132.8) | 0.000       | 0.195 (0.07–0.52) | 0.001      | 19         | 1 (5.3)                         | 87.9 (82.1-93.7)  | 0.001       | 0.07 (0.01-0.54) | 0.011 |
|                     | SM           | 29         | 13 (44.8)                       | 55.3 (38.9–71.8)   |             | Reference         |            | 19         | 9 (47.4)                        | 42.4 (33.3-51.4)  |             | Reference        |       |

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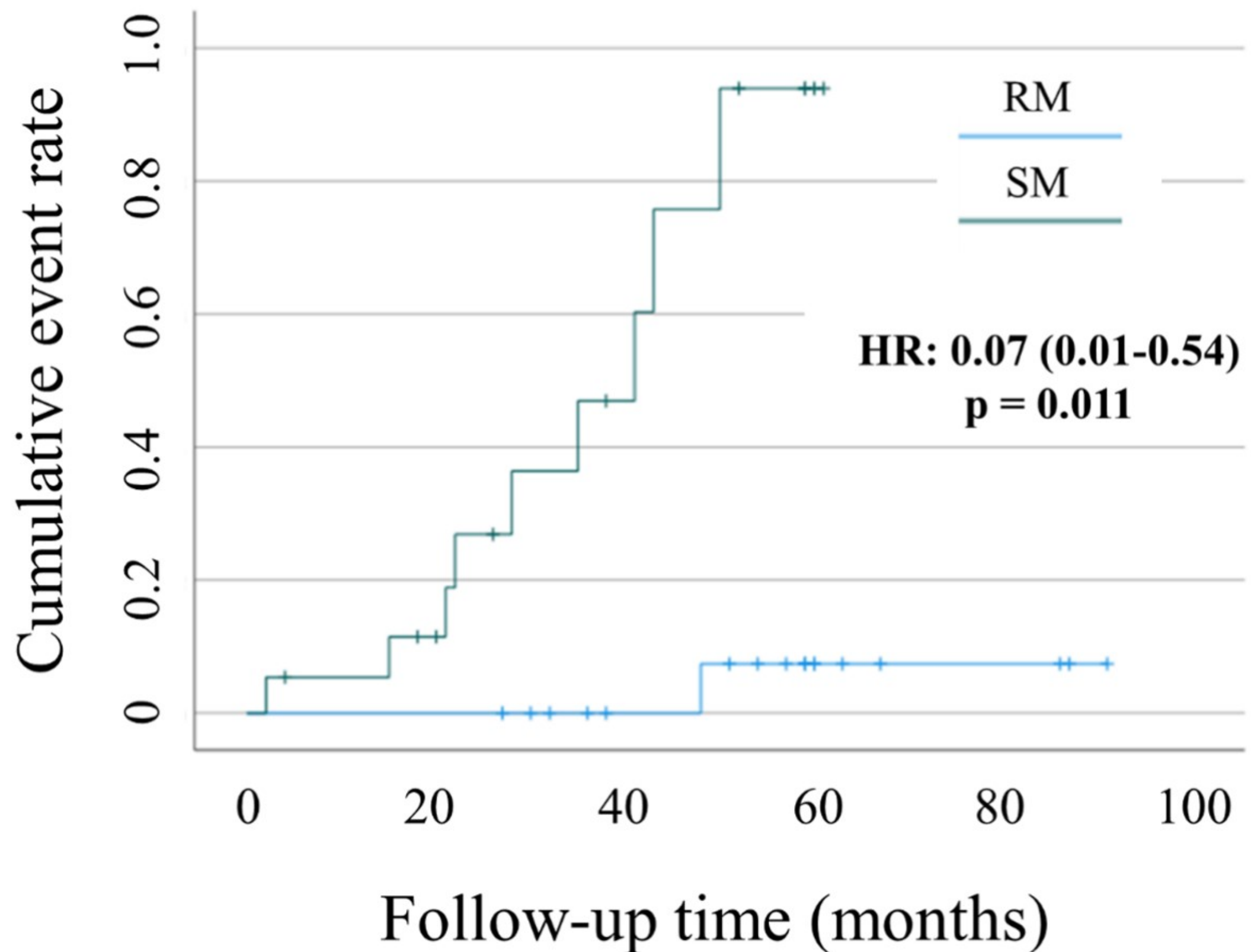


**Table 2.** Multivariate Analysis of Uterine Changes in Tamoxifen-treated Breast Cancer Patients: Adjusted Hazard Ratios Before and After Propensity Score Matching (PSM)

| Multivariate analysis            | All Patients      |              | PSM Paired       |              |
|----------------------------------|-------------------|--------------|------------------|--------------|
|                                  | HR (CI 95%)       | P            | HR (CI 95%)      | P            |
| Uterine Changes                  |                   |              |                  |              |
| CYP2D6 (RM vs <b>SM</b> )        | 0.10 (0.02-0.47)  | <b>0.004</b> | 0.04 (0.00-0.36) | <b>0.004</b> |
| Size (≤ 2 vs <b>&gt;2&lt;5</b> ) | 0.47 (0.11-2.02)  | 0.311        | 0.30 (0.06-1.57) | 0.154        |
| Grade (III vs <b>I</b> )         | 3.68 (0.2-67.39)  | 0.379        | 0.05 (0.00-2.25) | 0.122        |
| Grade (III vs <b>II</b> )        | 2.05 (0.19-21.55) | 0.552        | 0.10 (0.00-2.52) | 0.161        |
| Radiotherapy (No vs <b>Yes</b> ) | 0.83 (0.19-3.54)  | 0.797        | 0.24 (0.03-2.16) | 0.202        |
| Chemotherapy (No vs <b>Yes</b> ) | 0.50 (0.04-5.82)  | 0.583        | 0.87 (0.07-11.2) | 0.913        |
| Nodal (N0 vs <b>N≠0</b> )        | 0.77 (0.19-3.09)  | 0.714        | 0.66 (0.12-3.61) | 0.628        |

The group in bold is the reference for comparison

## Results

Only uterine changes showed significant differences between CYP2D6 phenotypes, with a lower HR for their presentation for rapid metabolizers in univariate (HR 0.195, 95% CI 0.073 - 0.521, P = 0.001) or multivariate analysis (HR 0.098, 95% CI 0.020 - 0.466, P = 0.004) (Tables 1 and 2; Figure 1). Selection of a subgroup through Propensity Score Matching (21 vs 21) corroborated these results. The spectrum of uterine changes and pathologies included endometrial hyperplasia, polyps, adenocarcinoma, myometrial or endometrial thickening, and the presence of multiple myomas.

## Conclusions

Our study indicates that an early increase in tamoxifen dose in poor metabolizer patients according to CYP2D6 polymorphisms may significantly affect the incidence of uterine changes, but not the incidence of osteoarticular pain, hot flashes, or asthenia.

**Figure 1.** Impact of CYP2D6 Phenotype on the Incidence of Uterine Changes in Tamoxifen-treated Breast Cancer Patients Over Time. A) All Patients. B) Propensity Score Matched (PSM) Patients