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# Relationship Between Survival and Estrogen Receptor Status in Patients With Metastatic Breast Cancer Treated With Capecitabine and Docetaxel: An Exploratory Data Analysis

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## Background

- Women with estrogen receptor-positive (ER+) metastatic breast cancer (mBC) generally have a longer survival time compared with women with ER– tumors.[1-5]
- Addition of capecitabine (C) to docetaxel (D) has been shown to increase time to disease progression, overall survival (OS), and objective tumor response compared with D alone. However, correlation by treatment between outcome and ER status has not been investigated.[6]
- An exploratory analysis was conducted to describe the correlation between survival and ER status among patients with mBC treated with C + D.

## Methods

- This analysis used data from an open-label, randomized, phase III trial of C + D versus D alone in patients with advanced and/or mBC.[6]
- Prior treatment with an anthracycline was required; prior paclitaxel but not docetaxel was permitted.
- Patients were randomized to 21-day cycles of either C 1250 mg/m$^2$ BID on days 1-14 + D 75 mg/m$^2$ on day 1 or D 100 mg/m$^2$ on day 1.
- Survival analysis was used to investigate the effect of baseline ER status of the primary and metastatic tumors on OS.
- ER status was defined as positive if any tumor tested positive, negative if there was at least 1 negative test, or unknown.
- Logistic regression was used to investigate the effect of baseline ER status on clinical benefit and objective response.

## Results

### Demographics

- Among 506 intent-to-treat patients (randomized, received ≥1 dose), ER status was identified in 356: C + D, 90 ER+ and 88 ER–; D alone, 95 ER+ and 83 ER–.
- Groups were generally comparable by ER status and treatment at baseline (Table 1), except that time since diagnosis (median 1414 vs 678 days) and from diagnosis to recurrence (median 888 vs 549 days) were significantly longer in ER+ compared with ER– patients, respectively.

**Table 1. Patient Demographics at Baseline**

| | ER+ | | ER– | |
|---|---|---|---|---|
| | C + D (n = 90) | D (n = 95) | C + D (n = 88) | D (n = 83) |
| Age (y) | | | | |
| Mean ± SD | 53.7 ± 10.6 | 53.1 ± 10.1 | 53.3 ± 10.3 | 51.1 ± 10.34 |
| Range | 27-79 | 28-75 | 28-74 | 29-71 |
| Body mass index (kg/m$^2$) | n = 89 | n = 94 | n = 88 | n = 82 |
| Mean ± SD | 25.9 ± 5.0 | 26.7 ± 6.1 | 26.9 ± 5.4 | 26.6 ± 5.9 |
| Range | 16.1-41.6 | 15.6-50.4 | 16.1-43.4 | 16.2-50.3 |
| Tumor size | | | | |
| <2 cm | 17 (18.9%) | 17 (17.9%) | 9 (10.2%) | 13 (15.7%) |
| 2-5 cm | 43 (47.8%) | 54 (56.8%) | 45 (51.1%) | 48 (57.8%) |
| >5 cm | 11 (12.2%) | 9 (9.5%) | 18 (20.5%) | 11 (13.3%) |
| Not resected | 3 (3.3%) | 7 (7.4%) | 5 (5.7%) | 4 (4.8%) |
| Number of positive axillary lymph nodes | | | | |
| 0 | 21 (23.3%) | 21 (22.1%) | 22 (25.0%) | 20 (24.1%) |
| 1-3 | 27 (30.0%) | 27 (28.4%) | 19 (21.6%) | 25 (30.1%) |
| ≥4 | 29 (32.2%) | 30 (31.6%) | 30 (34.1%) | 28 (33.7%) |
| Predominant site of disease | | | | |
| Bone | 1 (1.1%) | 5 (5.3%) | 3 (3.4%) | 5 (6.0%) |
| Soft tissue | 14 (15.6%) | 18 (18.9%) | 19 (21.6%) | 16 (19.3%) |
| Visceral | 75 (83.3%) | 72 (75.8%) | 66 (75.0%) | 62 (74.7%) |
| Number of metastatic sites | | | | |
| Mean ± SD | 3.7 ± 1.8 | 3.8 ± 1.7 | 3.3 ± 1.7 | 3.7 ± 1.8 |
| Range | 1-9 | 1-9 | 1-8 | 1-8 |
| Time since diagnosis (d) | | | | |
| Median | 1472 | 1328 | 726.5 | 654 |
| Range | 95-7324 | 76-8976 | 86-5898 | 79-5290 |
| Time from diagnosis to recurrence (d) | n = 79 | n = 81 | n = 76 | n = 66 |
| Median | 995.0 | 823.0 | 510.5 | 616.0 |
| Range | 245-5111 | 151-4484 | 79-5168 | 131-4990 |
| Karnofsky score | n = 87 | n = 92 | n = 87 | n = 82 |
| Mean (SD) | 88.0 ± 9.5 | 86.3 ± 9.9 | 88.4 ± 9.6 | 86 ± 10.2 |
| Range | 70-100 | 70-100 | 70-100 | 70-100 |

C, capecitabine; D, docetaxel; ER, estrogen receptor.

### Overall Survival

- In the ER+ group, unadjusted median OS was statistically significantly longer in C + D versus D patients (538.5 vs 379 days) (hazard ratio [HR] = 0.65, 95% confidence interval: 0.47-0.89) (Table 2, Figure).
- In the ER– group, statistical testing between C + D versus D alone was not significant, although numerically, the median OS in C + D patients was longer than in D patients (Table 2, Figure).
- Within the ER+ group, a numerical trend towards longer median OS was seen in C + D patients regardless of progesterone receptor (PR) status (HR = 0.709 for C + D vs D in ER+/PR+ patients; HR = 0.573 in ER+/PR– patients) (Table 3).

**Table 2. Statistical Analysis of Treatment Effect on Overall Survival by Estrogen Receptor (ER) Status**

| | C + D | | | D | | | | |
|---|---|---|---|---|---|---|---|---|
| ER Status | N[a] | n (%) | OS median, d (range) | N | n (%) | OS, median, d (range) | *P* Value[b] | HR[c] (95% CI) |
| ER+ | 90 | 73 (81.1) | 538.5 (450-654) | 95 | 84 (88.4) | 379 (321-441) | 0.007 | 0.65 (0.47-0.89) |
| ER– | 88 | 75 (85.2) | 329 (293-460) | 83 | 71 (85.5) | 301 (234-362) | 0.508 | 0.90 (0.65-1.24) |
| Pooled | 178 | 148 (83.1) | 459 (387-521.0) | 178 | 155 (87.1) | 346.5 (298-381) | 0.023 | 0.77 (0.62-0.97) |

C, capecitabine; CI, confidence interval; D, docetaxel.
[a]N = Total number of patients; n = number of deaths.
[b]*P* value = treatment difference in overall survival (OS) based on log-rank test.
[c]Hazard ratio (HR) based on Cox regression, with D as the reference group.

**Figure. Survival Distribution Function by Treatment**

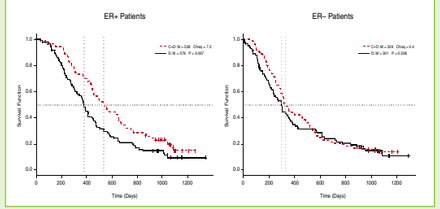


**Table 3. Statistical Analysis of Treatment Effect on Overall Survival (OS) by Progesterone Receptor (PR) Status Stratified by Estrogen Receptor (ER) Status**

| | C + D | | | D | | | | |
|---|---|---|---|---|---|---|---|---|
| PR Status | N | n (%) | OS median, d (range) | N | n (%) | OS, median, d (range) | *P* Value | HR (95% CI)[a] |
| **ER+** | | | | | | | | |
| PR+ | 57 | 48 (84.2) | 501 (442-632) | 59 | 51 (86.4) | 376 (274-458) | 0.087 | 0.709 (0.478-1.053) |
| PR– | 24 | 18 (75.0) | 677.5 (475-876) | 20 | 18 (90.0) | 487 (321-662) | 0.095 | 0.573 (0.296-1.111) |
| Pooled | 81 | 66 (81.5) | 546 (459-657) | 79 | 68 (87.3) | 379 (298-477) | 0.025 | 0.680 (0.485-0.954) |
| **ER–** | | | | | | | | |
| PR+ | 8 | 5 (62.5) | 599.5 (302-N/A) | 13 | 10 (76.9) | 616 (239-1084) | 0.693 | 0.802 (0.268-2.402) |
| PR– | 60 | 50 (83.3) | 349.5 (293-507) | 60 | 52 (86.7) | 300 (198-358) | 0.246 | 0.795 (0.539-1.173) |
| Pooled | 68 | 55 (80.9) | 360 (310-507) | 73 | 62 (84.9) | 304.0 (236-371) | 0.301 | 0.826 (0.574-1.188) |

C, capecitabine; D, docetaxel; HR, hazard ratio.
[a]95% confidence intervals (CI) for Kaplan-Meier estimates are based on a sign test (Brookmeyer and Crowley, 1982).
Cox regression model includes a single covariate for PR status group, stratified by ER status and randomized treatment. Patients with ER status but not PR status are excluded from this analysis.

### Clinical Benefit and Objective Response

- A numerical trend in clinical benefit (complete response + partial response + stable disease) in ER+ and ER– patients favored C + D (Table 4).
- A numerical trend in objective response (complete response + partial response) in ER+ and ER– patients favored C + D. The trend was larger in ER+ patients (Table 5).

**Table 4. Logistic Regression Results Modeling Clinical Benefit by ER Status**

| | | | Clinical Benefit[a] | | | |
|---|---|---|---|---|---|---|
| Covariate | Treatment | N | Yes N (%) | No N (%) | OR (95% CI)[b] | *P* Value[b] |
| **ER+** | C + D | 83 | 75 (90.4) | 8 (9.6) | 1.87 (0.75-4.69) | 0.1785 |
| | D | 90 | 75 (83.3) | 15 (16.7) | | |
| **ER–** | C + D | 84 | 69 (82.1) | 15 (17.9) | 1.76 (0.83-3.72) | 0.1418 |
| | D | 76 | 55 (72.4) | 21 (27.6) | | |

[a]Clinical benefit consists of complete response, partial response, and stable disease. Percentages are out of number of patients within each covariate level.
[b]Odds ratios (OR), confidence intervals (CI), and *P* values are from a logistic regression model by ER status with a single covariate of treatment modeling the probability of clinical benefit. Missing data are excluded.

**Table 5. Logistic Regression Results Modeling Objective Response by Estrogen Receptor (ER) Status**

| | | | Objective Responses[a] | | | |
|---|---|---|---|---|---|---|
| Covariate | Treatment | N | Yes N (%) | No N (%) | OR (95% CI)[b] | *P* Value |
| **ER+** | C + D | 83 | 40 (48.2) | 43 (51.8) | 1.77 (0.96, 3.26) | 0.0673 |
| | D | 90 | 31 (34.4) | 59 (65.6) | | |
| **ER–** | C + D | 84 | 33 (39.3) | 51 (60.7) | 1.32 (0.69, 2.53) | 0.4015 |
| | D | 76 | 25 (32.9) | 51 (67.1) | | |

[a]Objective response consists of complete response and partial response. Percentages are out of number of patients within each covariate level.
[b]Odds ratios (OR), confidence intervals (CI), and *P* values are from a logistic regression model by ER status with a single covariate of treatment modeling the probability of objective response. Missing data are excluded.

### Safety

- An adverse event (AE) was the reason for withdrawal in 25/79 (31.6%) and 20/88 (22.7%) ER+ and 27/92 (29.3%) and 18/79 (22.8%) ER– patients who received C + D versus D, respectively.
- A severe AE occurred in 64/79 (81%) and 64/88 (73%) ER+ and 75/92 (82%) and 51/79 (65%) ER– patients who received C + D versus D, respectively (Table 6).
  - Hand-foot syndrome was the most common AE experienced by patients in the C + D group, while febrile neutropenia was the most common in the D group.

**Table 6. Severe Adverse Events**

| | ER+ | | ER– | |
|---|---|---|---|---|
| Severe Adverse Event | C + D (n = 79) | D (n = 88) | C + D (n = 92) | D (n = 79) |
| Hand-foot syndrome | 25 (32%) | 2 (2%) | 22 (24%) | 0 |
| Febrile neutropenia | 12 (15%) | 20 (23%) | 18 (20%) | 18 (23%) |
| Neutropenia | 14 (18%) | 10 (11%) | 12 (13%) | 11 (14%) |
| Diarrhea | 13 (16%) | 5 (6%) | 11 (12%) | 5 (6%) |
| Stomatitis | 15 (19%) | 3 (3%) | 12 (13%) | 2 (3%) |
| Nausea | 10 (13%) | 1 (1%) | 5 (5%) | 2 (3%) |
| Asthenia | 4 (5%) | 10 (11%) | 7 (8%) | 6 (8%) |

C, capecitabine; D, docetaxel; ER, estrogen receptor.

## Summary

- In the ER+ group, the unadjusted median OS was statistically significantly longer in C + D versus D patients (538.5 vs 379.0 days) and was unaffected by PR status.
- A numerical trend in ER– patients favored the C + D versus D group; however, this effect was not statistically significant and was less pronounced than in ER+ patients.
- Limitations of this trial include:
  - Post-hoc analysis.
  - Treatment groups not randomized by ER status.

## References

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### Acknowledgement

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