A PROGNOSTIC FACTOR INDEX FOR OVERALL SURVIVAL IN A HER2-NEGATIVE ENDOCRINE-RESISTANT METASTATIC BREAST CANCER POPULATION: ANALYSIS OF THE ATHENA TRIAL

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INTRODUCTION

- For women with HER2-negative locally recurrent/metastatic breast cancer (LR/mBC), there are no targeted therapies and no gold-standard treatment.[1]
- The impressive gains in progression-free survival (PFS) achieved with the addition of bevacizumab to chemotherapy regimens have been accompanied by a lack of demonstrable overall survival (OS) benefit.[2–4]
- OS varies considerably in this population and is influenced by a wide range of biological and clinical factors, some of which remain unclear.
- Evidence-based definitions of 'poor prognosis' or 'aggressive disease' may help to guide treatment decisions and improve clinical trial design.
- In the multinational ATHENA study, 2264 patients with HER2-negative LR/mBC were treated with first-line bevacizumab in combination with non-anthracycline-containing chemotherapy in the context of routine oncology practice.[5]
  - The ATHENA population provides a rich dataset in which to assess potential prognostic factors.

PATIENTS AND METHODS

- We analyzed prognostic factors for OS in patients with HER2-negative LR/mBC.
  - Patients with disease reported as HER2-positive in the case report form (n=61) were excluded from the present analysis.
- Prognostic factors were selected from a univariate Cox regression analysis.
- Multivariate analysis was performed to explore the strongest prognostic factors further.

RESULTS

Patient population

- The analysis population included 2203 patients (Table 1) with a median age of 53 years (range 22–93 years).
- Bevacizumab was typically administered in combination with single-agent taxane therapy (67% of patients). Approximately one-fifth (22%) received bevacizumab with non-taxane therapy and 11% received bevacizumab with a taxane combination regimen.
- After a median follow-up of 20.1 months, median OS for the entire analysis population was 25.2 months (Table 2).
  - OS was shorter with non-taxane than taxane-containing regimens in combination with bevacizumab, although interpretation is difficult as investigators chose chemotherapy for each individual patient.

Table 1. Baseline characteristics: HER2-negative analysis population (n=2203)

Parameter	No. of patients (%)
ECOG performance status[a]	
0	1263 (57)
1	814 (37)
2	124 (6)
Disease-free interval, months	
≤24	619 (28)
>24	1172 (53)
Metastatic at diagnosis	412 (19)
Number of organs involved[b]	
1	1070 (49)
2	725 (33)
≥3	408 (19)
Metastatic sites[c]	
Bone	1093 (50)
Lung	791 (36)
Liver	790 (36)
Soft tissue	676 (31)
Pleural	119 (5)
Peritoneal	39 (2)
Stage at study entry	
Locally recurrent	163 (7)
Metastatic	2040 (93)
Hormone receptor status	
ER and PgR positive	1096 (50)
ER positive, PgR negative	334 (15)
ER negative, PgR positive	87 (4)
ER and PgR negative (triple negative)	585 (27)
Prior (neo)adjuvant chemotherapy	
Anthracycline and/or taxane	1285 (58)
Non-anthracycline and non-taxane	198 (9)
None	720 (33)
Prior endocrine therapy	
(Neo)adjuvant setting	1069 (49)
Metastatic setting	533 (24)

[a]Missing in one patient, ECOG performance status 3 in one patient. [b]Skin, lymph node, ipsi-/contralateral breast, or other soft tissue involvement was scored as a single organ. [c]More than one answer possible; sites reported in ≤1% of patients not listed. ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; PgR = progesterone receptor.

Table 2. Summary of efficacy: HER2-negative analysis population (n=2203)

Parameter	Value
Response, n (%)	
Objective response rate	1191 (54)
Clinical benefit rate[a]	1908 (87)
Time to disease progression	
Events, n (%)	1592 (72)
Median, months (95% CI)	9.7 (9.4–10.2)
Overall survival	
Events, n (%)	1171 (53)
Median, months (95% CI)	25.2 (23.9–27.0)

[a]Complete or partial response or stable disease. CI = confidence interval.

Prognostic factors

- In a univariate analysis, prognostic factors most closely and robustly associated with worse OS (Figure 1) were:
  - Liver metastases or ≥3 involved organs
  - Disease-free interval (DFI) ≤24 months
  - Prior adjuvant anthracycline and/or taxane therapy
  - Triple-negative breast cancer (TNBC).
- The small subgroup with ECOG performance status 2 also had poor OS expectancy.
- DFI and metastatic organ sites were analyzed further to explore the definition providing the greatest prognostic value (Figure 2; Table 3).
- The overall analysis population was categorized according to the number of risk factors present and a multivariate analysis of OS was performed (Figure 3; Table 4).
  - Half of the population (51%) had one or no risk factors.
  - In 19%, three or four risk factors were present; these patients had a significantly worse OS prognosis than patients with two or fewer risk factors.

- Similar analyses in the subgroup of patients with TNBC and the subgroup with hormone receptor-positive LR/mBC were performed based on the three remaining risk factors (Figures 4 and 5).
  - Within the TNBC population, a small subgroup with no additional risk factors and a relatively good prognosis was identified.
  - Conversely, within the hormone receptor-positive subgroup, a small population of patients with all three remaining risk factors was found to have a prognosis almost as poor as that of the TNBC patients with two or three risk factors (median OS 15.9 vs 13.7 months, respectively).

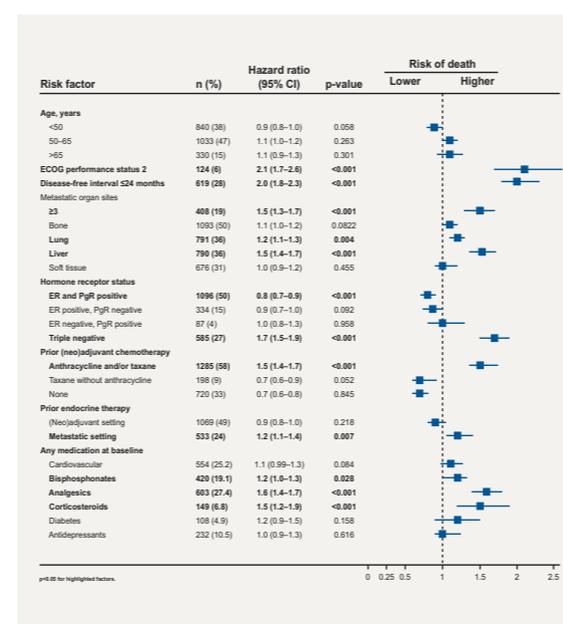**Figure 1.** Cox regression univariate analysis of overall survival

Figure 2. Overall survival according to disease-free interval (HER2-negative population, n=2203)
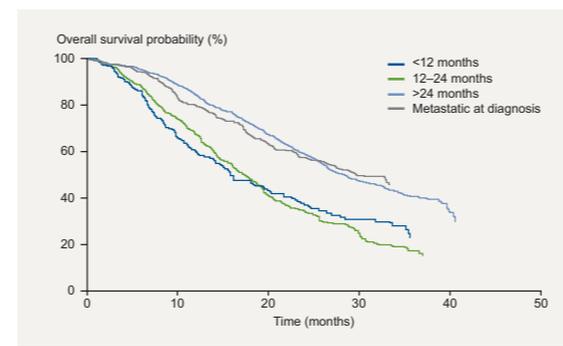

Table 3. Overall survival according to metastatic organ sites (HER2-negative population, n=2203)

Metastatic sites		n (%)	Median OS, months (95% CI)	Hazard ratio (95% CI)	p-value
Liver metastases	Yes	790 (36)	20.0 (18.6–22.0)	1.5 (1.4–1.7)	<0.0001
	No	1413 (64)	28.5 (26.4–30.0)		
≥3 sites	Yes	408 (19)	19.3 (17.2–21.8)	1.5 (1.3–1.7)	<0.0001
	No	1795 (81)	26.5 (25.5–28.5)		
Liver metastases or ≥3 sites	Yes	941 (43)	20.7 (19.5–22.5)	1.5 (1.3–1.7)	<0.0001
	No	1262 (57)	28.6 (26.4–30.1)		

Figure 3. Overall survival according to number of prognostic factors present (HER2-negative population, n=2203)
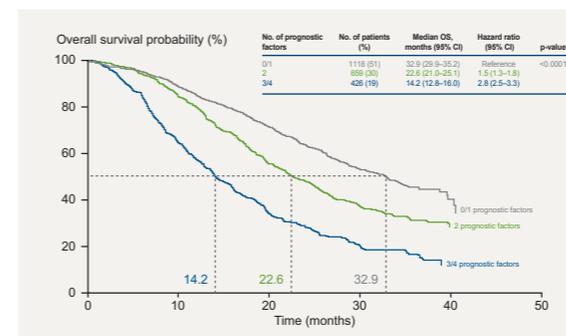

Table 4. Multivariate analysis of overall survival according to prognostic factors (HER2-negative population, n=2203)

Prognostic factor	Hazard ratio (95% CI)
Disease-free interval ≤24 months	1.74 (1.53–1.98)
Liver metastases or ≥3 metastatic organ sites	1.64 (1.46–1.85)
Triple-negative disease	1.56 (1.36–1.78)
Prior (neo)adjuvant anthracycline and/or taxane therapy	1.27 (1.11–1.45)
Model adjustment	
Concordance index	0.631
R²	0.099
Global p-value	p<0.0001

Figure 4. Overall survival in the TNBC subgroup (n=585) according to number of additional prognostic factors present
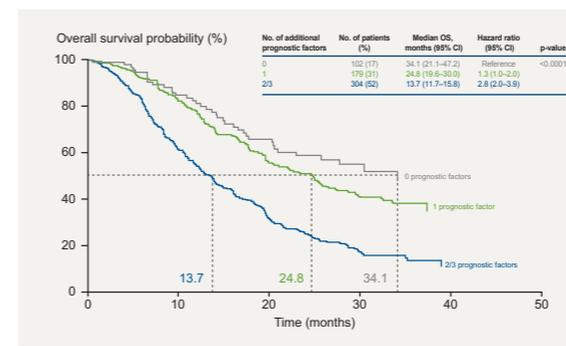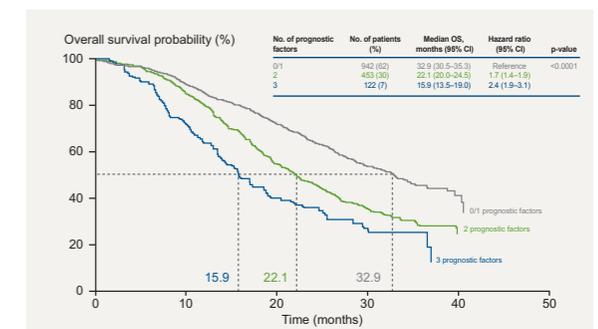

Figure 5. Overall survival in the hormone receptor-positive subgroup (n=1517) according to number of prognostic factors present

CONCLUSIONS

- In this analysis of the ATHENA dataset of >2000 patients with LR/mBC receiving bevacizumab-containing therapy, we identified important prognostic factors for OS (DFI ≤24 months, liver metastases/≥3 metastatic organ sites, TNBC, prior anthracycline/taxane therapy) that could be considered in the design of new trials.
  - The effectiveness of this prognostic index requires validation before extrapolation to nonbevacizumab-containing therapy.
- Importantly, a well-defined population of patients with hormone receptor-positive LR/mBC had a prognosis as poor as that of the subset with high-risk TNBC, with similarly short OS expectancy.
- In the absence of validated biomarkers, application of these simple clinical criteria may enable identification of patients with a poorer prognosis in whom more aggressive systemic regimens may be of interest.

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