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PROGNOSTIC RELEVANCE OF PRIOR ENDOCRINE TREATMENTS IN OVERALL SURVIVAL (OS) AT THE TIME OF FIRST LINE CHEMOTHERAPY IN ER[+]/HER2[-] ADVANCED BREAST CANCER (ABC) PATIENTS

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BACKGROUND

- International consensus stresses a preference for endocrine therapies (ET) for the ER[+]/HER2[-] ABC population[1].
- However, in real-world clinical practice, chemotherapy (CT) administration is common practice long before depleting endocrine options[2]. There is little knowledge on the prognostic factors that drive OS in the ER[+]/HER2[-] population at the time of first-line CT for ABC, and particularly on the influence of endocrine therapies on post-progression.
- The updated ESMO – ABC2 guidelines[1] for advanced breast cancer introduced clinical criteria to establish endocrine sensitivity / resistance potentials.
- 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[3].
- The ATHENA population provides a rich dataset in which to assess potential prognostic factors[4].

METHODS

- The Athena trial assessed safety of different first-line CT & bevacizumab regimens in 2.264 patients (pts) treated between 2006 and 2009 over 34 countries.
- We adapted the ESMO 2013 (ABC2) guidelines of endocrine resistance[1] to the data collected, considering 5 years to be the median duration of (neo)adjuvant ET. Endocrine Sensitive Status (ESS) at the time of inclusion was characterized by:

  (1) Progression on ET for Early stage (EEP) [on or within the first year of], and

  (2) Prior ET for ABC (AEP), whatever the duration or number of endocrine lines.

  Three ESS subgroups were pre-defined:

  - Low Endocrine Sensitive (LES): patients with both EEP and AEP criteria
  - Moderately Endocrine Sensitive (MES): either EEP or AEP criteria, and
  - Highly Endocrine Sensitive (HES): No EEP and AEP criteria.
- Other risk factors (RF) identified in a prior analysis were incorporated[4] in a multivariate Cox proportional-hazard model.

RESULTS

Patient population:

- The analysis population included 1.492 confirmed ER/PgR[+] and HER2[-] pts, as well as 585 triple negative breast cancer patients (TNBC) (control arm). The baseline characteristics in ESS and TN subgroups are described in **table 1**.

Table 1. Baseline characteristics: endocrine sensitive subgroups (HS, MS and LS) in ER[+]/HER2[-] ABC population (n=1492) and triple negative population (N=585).

	Highly Sensitive (N = 492)	Medium Sensitive (N = 755)	Low Sensitive (N = 245)	Triple negative (N = 585)
Median age, years. Median (range)	53 (22 to 83)	53 (28 to 93)	55 (32 to 86)	52 (24 to 85)
Follow-up time, months. Median (range)	24.6 (0.1 to 43.2)	22.1 (0.1 to 43.6)	18.1 (0.2 to 41.1)	14.7 (0.3 to 43.5)
ECOG performance status, n (%)				
0	284 (57.7)	440 (58.3)	134 (54.7)	341 (58.3)
1	178 (36.2)	280 (37.1)	96 (39.2)	208 (35.6)
2	30 (6.1)	35 (4.6)	15 (6.1)	36 (6.2)
Disease-free interval (months), n (%)				
≤24	61 (12.4)	183 (24.2)	73 (29.8)	285 (48.7)
>24	215 (43.7)	500 (66.2)	172 (70.2)	199 (34)
Metastatic de novo	216 (43.9)	72 (9.5)	0 (0)	101 (17.3)
Number of organs involved, n (%)*				
1	239 (48.6)	331 (43.8)	95 (38.8)	339 (57.9)
2	163 (33.1)	266 (35.2)	92 (37.6)	164 (28)
≥3	90 (18.3)	158 (20.9)	58 (23.7)	82 (14)
*Skin, lymph node, ipsi-/contra- breast, or other soft tissue involvement was scored as a single organ				
Metastasic sites, n (%)				
Bone	246 (50)	422 (55.9)	185 (75.5)	186 (31.8)
Lung	176 (35.8)	261 (34.6)	71 (29)	232 (39.7)
Liver	150 (30.5)	342 (45.3)	110 (44.9)	149 (25.5)
Soft tissue	164 (33.3)	215 (28.5)	56 (22.9)	207 (35.4)
Pleural	31 (6.3)	40 (5.3)	15 (6.1)	26 (4.4)
Peritoneal	7 (1.4)	17 (2.3)	6 (2.4)	6 (1)
Current stage, n (%)				
Locally recurrent	41 (8.3)	29 (3.8)	8 (3.3)	77 (13.2)
Metastasic	451 (91.7)	726 (96.2)	237 (96.7)	508 (86.8)
Hormonal status, n (%)				
ER+	451 (91.7)	719 (95.2)	238 (97.1)	0 (0)
PR+	370 (75.2)	576 (76.3)	188 (76.7)	0 (0)
Prior (neo)adjuvant chemotherapy, n (%)				
Anthracycline and/or taxanes	135 (27.4)	502 (66.5)	190 (77.6)	411 (70.3)
Non anthracycline nor taxanes	51 (10.4)	65 (8.6)	22 (9)	37 (6.3)
No (neo)adjuvant chemotherapy	306 (62.2)	188 (24.9)	33 (13.4)	137 (23.4)
Endocrine therapy, n (%)				
(Neo) adjuvant	117 (23.8)	612 (81.1)	245 (100)	35 (6)
Prior metastasic	0 (0)	229 (30.3)	245 (100)	19 (3.2)
(Neo) adjuvant & Prior metastasic	0 (0)	86 (11.4)	245 (100)	6 (1)
Nor (Neo) adjuvant & nor Prior metastasic*	375 (76.2)	0 (0)	0 (0)	537 (91.8)
Nr of prior endocrine therapy agents,				
0	375 (76.2)	0 (0)	0 (0)	537 (91.8)
1	85 (17.3)	425 (56.3)	0 (0)	37 (6.3)
2	26 (5.3)	218 (28.9)	108 (44.1)	5 (0.9)
≥3	6 (1.2)	112 (14.8)	137 (55.9)	6 (1)
1rst regimens used in combination with beva, n (%)				
Taxane single agent	323 (65.7)	513 (67.9)	181 (73.9)	382 (65.3)
Taxane combination	70 (14.2)	58 (7.7)	20 (8.2)	70 (12)
Non Taxane	99 (20.1)	184 (24.4)	44 (18)	133 (22.7)
Medical History at study entry (active), n (%)				
Cardiovascular	163 (33.1)	210 (27.8)	75 (30.6)	168 (28.7)
Respiratory	61 (12.4)	81 (10.7)	21 (8.6)	70 (12)
Psychological / Neurological	49 (10)	116 (15.4)	42 (17.1)	76 (13)
Endocrine	76 (15.4)	113 (15)	43 (17.6)	78 (13.3)
Gastrointestinal / Hepatic	92 (18.7)	87 (11.5)	37 (15.1)	82 (14)
Renal	19 (3.9)	24 (3.2)	10 (4.1)	23 (3.9)
Skin and musculoskeletal	61 (12.4)	94 (12.5)	40 (16.3)	77 (13.2)
Concomitant medication, n (%)				
Cardiovascular	129 (26.2)	183 (24.2)	73 (29.8)	133 (22.7)
Bisphosphonates	62 (12.6)	176 (23.3)	108 (44.1)	58 (9.9)
Analgesics	126 (25.6)	210 (27.8)	95 (38.8)	150 (25.6)
Corticosteroids	37 (7.5)	55 (7.3)	13 (5.3)	38 (6.5)
Diabetes	34 (6.9)	37 (4.9)	13 (5.3)	18 (3.1)
Antidepressants	45 (9.1)	89 (11.8)	32 (13.1)	53 (9.1)

RESULTS

- Bevacizumab was typically administered in combination with single-agent taxane therapy (68.2% of patients). Approximately one-fifth (22%) received bevacizumab with non-taxane therapy and 10% received bevacizumab with a taxane combination regimen.
- Patients were previously exposed to anthracyclines (53.5%) and taxanes (21.4%) for early stage BC. Prior endocrine therapy in the (neo)adjuvant and the metastatic settings were (65.3%) and (31.8%), respectively. Pts with de novo metastatic disease represented 19.3%, and the median DFI in pts progressing from an early stage was 43.2 mo. Liver involvement was observed in 40.3% of pts and 20.5% presented ≥3 organs involved. The ESS of the population were HES: 492 pts (33%), MES: 755 pts (50.6%) and LES: 245 pts (16.4%).
- Median follow-up was 22.6 months (range: 0.1 to 43.6) and 752 OS events (50.4% of pts) were observed.
- The percentage of HES patients previously exposed to anthracyclines and taxanes or with liver metastasis was significantly lower than the MES and LES subgroups. No significant differences were observed for any other risk factors.

Prognostic significance of endocrine sensitive status:

- Both EEP, progression on endocrine therapy for early stage Breast Cancer **(Figure 1)**; and AEP, prior endocrine therapy for advanced disease **(Figure 2)** were strong and independent prognostic markers for OS at the time of inclusion in the study.
- Median OS since study initiation for HES, MES, LES and TNBC groups were >40 mo. (median not achieved), 26.3 (95%CI: 24.5–28.4), 20.1 (95%CI: 17.8–23.9) and 18.3 (95%CI: 16.3–19.7) respectively **(Figure 3)**. 3-year OS survival rates for HES, MES, LES and TNBC were 53.5%, 34.8%, 23.9% and 26.6%, respectively.
- Median OS since advanced breast cancer diagnosis for HES was higher than MES, LES and TNBC subgroups **(Table 2)**.
- Multivariate-adjusted hazard ratios of OS since study initiation for (HES vs LES) and (HES vs MES) were 2 (IC95%: 1.6–2.5) and 1.5 (IC95%: 1.2–1.8). The other risk factors related to OS were: ECOG≥2 or analgesics or corticosteroids 1.6 (IC95%: 1.4–1.8); liver mets or>2 involved organs 1.4 (IC95%: 1.2–1.6) and adjuvant anthracylines and/or taxanes 1.2 (IC95%: 1–1.4) **(Table 3)**.
- The overall analysis population was categorized according to the number of risk factors present and a multivariate analysis of OS since study initiation was performed **(Figure 4)**.
  - About 30% of population had one or no risk factors.
  - In 43%, three or more risk factors were present; these patients had a significantly worse OS prognosis than patients with two or fewer risk factors.
  - The percentage of HES patients classified in the best prognostic category of multivariate analysis (0-1 RF) was 72.7%. The percentage of LES patients classified as worse prognostic (3-5 RF) was 92.7%. Therefore, about 80% of patients classified by ESS alone in best and worse prognostic groups will be in accordance with multivariate analysis.

Table 2. Summary of efficacy: endocrine sensitive subgroups (HES, MES and LES) in ER[+]/HER2[-] ABC population (n=1492) and triple negative population (N=585)

	Highly Sensitive (N = 492)	Medium Sensitive (N = 755)	Low Sensitive (N = 245)	Triple negative (N = 585)
Overall survival since chemo initiation, n (%)				
Events, n (%)	178 (36.2)	411 (54.4)	163 (66.5)	362 (61.9)
Median 95%CI, months	Not achieved	26.3 (24.5 to 28.4)	20.1 (17.8 to 23.9)	18.3 (16.4 to 19.7)
Overall survival since ABC diagnosis, n (%)				
Events, n (%)	178 (36.2)	411 (54.4)	163 (66.5)	362 (61.9)
Median 95%CI, months	42.6 (36.7 to 48.5)	34 (30.9 to 38.6)	36.1 (31.6 to 44.1)	20.2 (17.8 to 21.6)

Figure 1. Overall survival according to progression on ET for Early stage (EEP) [on or within the first year of] in ER[+]/HER2[-] ABC population (n=1492).

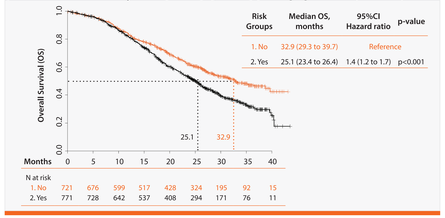


Figure 2. Overall survival according to prior ET for ABC (AEP), independent of the duration or number of endocrine lines in ER[+]/HER2[-] ABC population (n=1492).

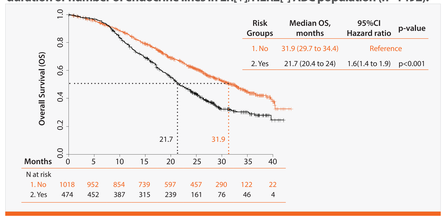


Figure 3. Summary of efficacy: endocrine sensitive subgroups (HES, MES and LES) in ER[+]/HER2[-] ABC population (n=1492) and triple negative population (N=585).

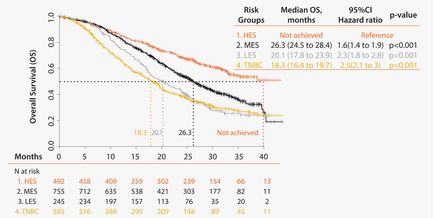
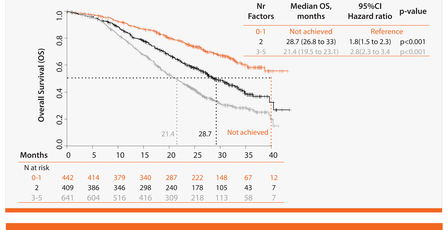


Table 3. Multivariate analysis of overall survival according to presence of risk factors (ER[+]/HER2[-] ABC population, n=1492).

Prognostic Factor	Hazard Ratio (95%CI)
High sensitive vs. low sensitive	2 (1.6 to 2.5)
vs. medium sensitive	1.5 (1.2 to 1.8)
ECOG performance status 2 and/or prior analgesic treatment and/or prior corticosteroid treatment	1.6 (1.4 to 1.8)
Liver metastases or >3 metastatic organ sites	1.4 (1.2 to 1.6)
Prior (neo)adjuvant anthracycline and/or taxane therapy	1.2 (1 to 1.4)

Figure 4. Overall survival according to number of risk factors present (ER[+]/HER2[-] ABC population, n=1492).



CONCLUSIONS

- One third of ER[+]/HER2[-] ABC pts included in the ATHENA first-line CT trial was precluded as Highly Endocrine Sensitive (HES) given the absence of endocrine resistance criteria (ABC-2).
- Baseline characteristics for the HES population were not considerably different from the moderate (MES) or the low endocrine sensitive (LES) subgroups with regards to prior endocrine and cytotoxic therapy exposition and liver involvement.
- Endocrine Sensitive Status was the most important factor influencing OS. The best and worse prognosis populations may be stratified based on the Endocrine Sensitive Status.
- The HES subgroup achieved a median OS that almost doubled the MES and LES subgroups. The OS for the LES subgroup was very similar to the TNBC subgroup.
- This study requires confirmatory studies as the absence of post-progression treatment information does not allow to correlate OS gains to specific endocrine treatments.
- As for the need for a survival signal, future large phase III trials exploring the role of chemotherapy in the ABC ER[+]/HER2[-] population should appropriately stratify or select patients based on the Endocrine Sensitive Status.

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