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Original article

A real-life study on the implementation and effectiveness of exemestane plus everolimus per hospital type in patients with advanced breast cancer. A study of the Southeast Netherlands Advanced Breast Cancer registry.

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ABSTRACT

Purpose: We aimed to assess the implementation and effectiveness of exemestane plus everolimus treatment per hospital type in real-life, shortly after approval of everolimus.
Methods: Advanced breast cancer patients treated with exemestane plus everolimus in 2012–2014 were included from the SONABRE registry. Progression-free survival (PFS) and a 12-week conditional PFS (post-hoc) were estimated by Kaplan-Meier method. The multivariable Cox proportional hazards model was performed by type of hospital and adjusted for patient, tumour and treatment characteristics.
Results: We included 122 patients, comprising 48 patients treated in academic ($N = 1$), 56 in teaching ($N = 4$), and 18 in non-teaching ($N = 2$) hospitals. The median PFS was 6.3 months (95% Confidence Interval (CI) 4.0–8.6) overall, and 8.5 months (95% CI 7.7–9.3), 4.2 months (95% CI 2.0–6.3), and 5.5 months (95% CI 4.2–6.7) for the patients treated in academic, teaching and non-teaching hospitals, respectively. The adjusted Hazard Ratio (HR) for PFS-events was 1.5 (95% CI 1.0–2.2) and 1.0 (95% CI 0.5–1.9) respectively for patients treated at teaching and non-teaching hospitals versus the academic hospital. The adjusted HR for 12-week conditional PFS-events was not different between hospital types. In the first 12-week treatment period, treatment was discontinued due to early progression in one out of 48 patients in the academic versus nine out of 74 patients in the non-academic hospitals, confirmed by imaging in one and two patients, respectively.
Conclusions: In our study, the median PFS was borderline significantly different between hospital types, possibly the result of a different assessment approach in the first 12-week treatment period.

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Abbreviations

ABC	advanced breast cancer
CA 15-3	cancer antigen 15-3
CI	confidence interval
HER2-negative	human epidermal growth factor receptor-2-negative
HR	hazard ratio
HR-positive	hormone-receptor-positive
KM	Kaplan-Meier
mTOR	mammalian target of rapamycin
PFS	progression-free survival
OS	overall survival
SONABRE	SOutheast Netherlands Advanced BREast cancer

1. Introduction

Advanced breast cancer (ABC) is a major cause of death among women worldwide. The median overall survival (OS) of patients diagnosed with ABC irrespective of their breast cancer subtype is ~2–3 years and the 5-year survival is only ~25% [1]. The hormone-receptor-positive/human epidermal growth factor receptor-2-negative (HR-positive/HER2-negative) subtype is the leading subtype of ABC, accounting for 60–70% of all patients with ABC [2]. In recent years, progress has been made in the treatment of these patients by the introduction of new therapeutic drugs [3,4]. Everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR) that targets the oncogenic PI3K-AKT-mTOR driver pathway, is one of these agents [3,5].

Everolimus in combination with exemestane was evaluated in the BOLERO-2 trial in patients who had recurrence or progression on a non-steroidal aromatase inhibitor [3]. Progression-free survival (PFS) was significantly longer for exemestane plus everolimus as compared with exemestane plus placebo, with a median of 7.8 months versus 3.2 months (hazard ratio (HR) 0.45) [6]. No statistically significant difference in overall survival (OS) was detected (31.0 months for exemestane plus everolimus versus 26.6 months for exemestane alone; HR 0.89) [7]. It should be noted, however, that there was a small imbalance in post-study use of chemotherapy (53% versus 63%, respectively), which may partly explain the lack of an improved OS besides a lack of power for this secondary study endpoint [7]. The results of the BOLERO-2 phase 3 trial were in line with previous phase 2 trials [5].

Randomised controlled trials offer the highest level of evidence on efficacy of a particular treatment, but in real-life the situation may be different. The use of a drug in a population with generally more co-morbidities than in a trial setting may lead to more dose reductions or earlier treatment cessation. Ultimately, patient selection and delivered treatment modifications impact effectiveness, as shown in previous phase IIIb studies on everolimus [8–10]. In addition, the implementation of new anti-cancer drugs in real-life is often slow and a large variation between different hospital types has actually been shown for a number of systemic therapies [11,12]. For that reason real-life data may not only support future reimbursement decisions and shared decision making in real-life. It may also improve the quality of delivered care when using the data per hospital type as mirror information for daily practice.

Therefore, the objective of our study was to investigate the PFS duration of ABC patients treated with exemestane plus everolimus in the Southeast of the Netherlands shortly after registration of everolimus (i.e. the period 2012–2014) and, foremost, whether implementation and PFS was associated with hospital type.

2. Material and Methods

2.1. SOutheast Netherlands Advanced BREast cancer (SONABRE) registry

Data for this study were obtained from the SONABRE registry of the Southeast Netherlands Breast Cancer Consortium (NCT03577197), which is currently running in seven hospitals and shortly extending to another seven hospitals in the Netherlands. In line with Dutch practice, the hospitals were classified as academic, teaching, or non-teaching hospitals. The treatment of patients with ABC in the Netherlands is not centralized and thus performed at all hospitals. The SONABRE registry is an ongoing observational cohort study aimed at the inclusion of all patients diagnosed with ABC since 2007, irrespective of received treatment and irrespective of date of primary breast cancer diagnosis. Specially trained registration clerks collect the data retrospectively from medical files. The data concerns patient, treatment, and tumour characteristics, hospitalization, and outcomes (progression and death). The SONABRE registry has already been effectively used to perform real-life studies on safety and effectiveness of various treatments used in ABC patients [13,14]. The Medical Research Ethics Committee of Maastricht University Medical Center approved the registry (no. 15-4-239).

2.2. Study population

The European Medicines Agency approved exemestane plus everolimus on 31 July 2012. We selected patients from the SONABRE registry when treatment was started before 31 December 2014, which we had defined as 'the implementation phase' (Supplementary Fig. 1). Data lock was on July 25th, 2017.

2.3. Endpoints and statistical analyses

The endpoint of the study was the PFS of ABC patients treated with exemestane plus everolimus in the implementation phase and, foremost, per hospital type (academic, teaching and non-teaching). PFS was defined as the interval between start of treatment with exemestane plus everolimus and the earliest date of progression or death from any cause, whichever came first. Dates for censoring included last update in case of ongoing treatment, date of next treatment in case of switching to a different therapy without progression, or last date of exemestane plus everolimus treatment in case of no further treatment and no information on progression. PFS was estimated using the Kaplan-Meier (KM) method and compared between hospital types using the log-rank test. Based on the observation that the number of PFS-events mainly differed between hospital types in the first 12-week treatment period, we additionally performed a post-hoc 12-week conditional analysis for patients who used exemestane plus everolimus treatment for longer than 12 weeks. The multivariable Cox proportional hazards model was performed by type of hospital and adjusted for potential confounding factors at start of exemestane plus everolimus treatment. Factors considered in the model were age (<65 versus ≥65 years), metastatic-free interval (de novo, 3–24 months versus >24 months), visceral disease (yes versus no), number of metastatic sites (1, 2 versus ≥3), prior (neo)adjuvant endocrine therapy (yes versus no), prior (neo)adjuvant chemotherapy (yes versus no), number of previous systemic therapies (1, 2 versus ≥3), and start dose everolimus (<10 mg versus ≥10 mg). Performance status was not included in the model, because of the high number of missing items and also considered to be related to the other included factors. Factors with a *P*-value below 0.25 in the univariable model were included in the multivariable model.

To evaluate the implementation of exemestane plus everolimus treatment, we additionally assessed treatment duration for exemestane -irrespective of everolimus-, exemestane plus everolimus treatment duration, and for exemestane plus everolimus dosed at 10 mg using the KM method and log-rank tests. Further, we assessed the reasons for treatment discontinuation (i.e. progression, toxicity or other reasons).

Baseline characteristics of the patients between hospital types were compared using Pearson's chi-squared tests for categorical variables and the nonparametric Kruskal-Wallis test for median age. Overall follow-up time was estimated using the reverse KM method.

3. Results

3.1. Study population

At time of data lock, we registered 244 patients who were treated for HR-positive/HER2-negative ABC in 2012–2014 in the SONABRE registry, of whom 65, 123, and 56 patients were treated in the academic ($N = 1$ hospital), teaching ($N = 4$ hospitals) and non-teaching hospitals ($N = 2$ hospitals), respectively. A total of 122 patients started treatment with exemestane plus everolimus, of whom 48 patients were treated in an academic, 56 in teaching and 18 in non-teaching hospitals. The first patient started treatment on August 28th, 2012 (Supplementary Fig. 1). The majority of patients were female (99.5%). The median age was 64 years (range 32–89) (Table 1). The majority had a metastatic-free interval of >24 months (75%), visceral disease (66%), and ≥3 lines of previous systemic therapy in the (neo)adjuvant and/or palliative setting (68%). No statistically significant differences in baseline characteristics were found between hospital types, apart from performance status which was often missing from the patient files. The median follow-up time after start of treatment was 40 months (95% Confidence Interval (CI) 35–45).

3.2. The effectiveness of exemestane plus everolimus

The median PFS was 6.3 months (95% CI 4.0–8.6) for the total population, and for the patients treated in academic, teaching and non-teaching hospitals respectively 8.5 months (95% CI 7.7–9.3), 4.2 months (95% CI 2.0–6.3), and 5.5 months (95% CI 4.2–6.7) (log-rank $P = 0.20$) (Fig. 1).

In the multivariable analysis, we found that patients treated in teaching hospitals had a borderline significant shorter PFS (adjusted Hazard Ratio (HR) 1.5; 95% CI 1.0–2.3, $P = 0.08$) and that patients treated in non-teaching hospitals had a comparable PFS (adjusted HR 1.0; 95% CI 0.5–1.9, $P = 0.98$) as compared with patients treated in the academic hospital (Table 2). When looking at the PFS figures, we noted a clear PFS difference in the first 12-week treatment period, for which we next performed a post-hoc 12-week conditional analysis, showing that the difference in PFS between hospital types disappeared (adjusted HR 1.2; 95% CI 0.7–2.1, $P = 0.42$, and adjusted HR 1.3; 95% CI 0.7–2.5, $P = 0.49$, respectively) (Table 2).

We decided to look more into depth in the patient files as an attempt to find the underlying explanation for the clear difference in PFS in the first 12-week treatment period. Early progression was

Table 1
Patient, tumour and treatment characteristics at start of exemestane plus everolimus treatment for advanced breast cancer in 2012–2014.

Characteristic	Total	Type of hospital			*P*-value
	N = 122 (%)	Academic *N* = 48 (%)	Teaching *N* = 56 (%)	Non-teaching *N* = 18 (%)	
Age					
Median (years, range)	64 (32–87)	65 (32–87)	63 (44–80)	64 (50–84)	0.62
Comorbidities					
Any	61 (50)	22 (46)	27 (48)	12 (67)	0.30
Infections	1 (1)	1 (2)	0 (0)	0 (0)	0.46
Respiratory system abnormalities	8 (7)	5 (10)	3 (5)	0 (0)	0.28
Vascular disorders	43 (35)	15 (31)	20 (36)	8 (44)	0.60
Metabolic and nutritional disorders	10 (8)	3 (6)	5 (9)	2 (11)	0.79
Performance status					0.01
0-1	51 (42)	24 (50)	26 (46)	1 (6)	
≥2	9 (7)	4 (8)	4 (7)	1 (6)	
Unknown	62 (51)	20 (42)	26 (46)	16 (89)	
Metastatic-free interval					0.54
De novo (<3 months)	26 (21)	13 (27)	10 (18)	3 (17)	
3–24 months	4 (3)	1 (2)	3 (5)	0 (0)	
>24 months	92 (75)	34 (71)	43 (77)	15 (83)	
Visceral disease	81 (66)	29 (60)	42 (75)	10 (56)	0.17
No. of metastatic sites					0.63
1	32 (26)	13 (27)	12 (21)	7 (39)	
2	34 (28)	12 (25)	17 (30)	5 (28)	
≥3	56 (46)	23 (48)	27 (48)	6 (33)	
Prior NSAI use	116 (95)	46 (96)	53 (95)	17 (94)	0.95
Prior (neo)adjuvant endocrine therapy	64 (53)	26 (54)	27 (48)	11 (61)	0.60
Prior lines of endocrine therapy for ABC, median (range)	2 (0–5)	1.5 (0–4)	2 (0–5)	2 (0–4)	0.53
Prior (neo)adjuvant chemotherapy	48 (39)	19 (40)	22 (39)	7 (39)	1.00
Prior lines of chemotherapy for ABC, median (range)	0 (0–11)	0 (0–4)	0 (0–11)	0 (0–4)	0.89
No. of previous systemic therapies[a]					0.36
1	14 (12)	7 (15)	6 (11)	1 (6)	
2	25 (21)	13 (27)	10 (18)	2 (11)	
≥3	83 (68)	28 (58)	40 (71)	15 (83)	

Data are number (%) of patients, unless otherwise stated.
Abbreviation: ABC, advanced breast cancer; NSAI, non-steroidal aromatase inhibitor.
Visceral disease was defined as lung, liver, brain, pleural or peritoneal involvement.
Metastatic-free interval was defined as the time between primary breast cancer diagnosis and the detection of distant recurrence.
[a] Previous systemic therapies include those used in the (neo)adjuvant setting or to treat metastatic disease and include chemo- and endocrine therapy.

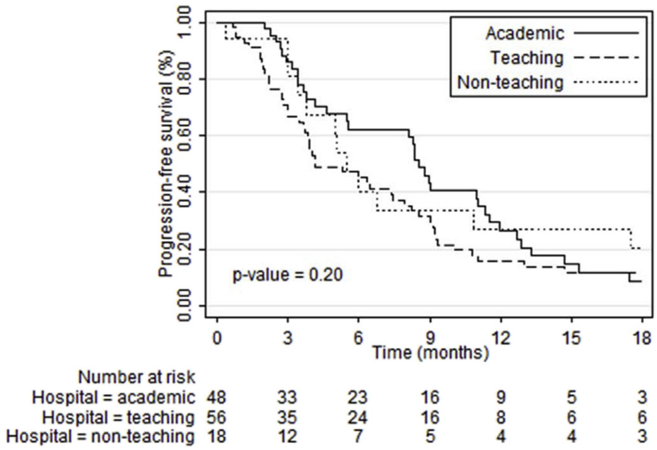

Fig. 1. Progression-free survival for exemestane plus everolimus treatment in 2012–2014 by type of hospital (i.e. academic, teaching or non-teaching).

reported in one out of 48 patients in the academic as compared to nine out of 74 patients in the non-academic hospitals. In the academic hospital, progression was confirmed by imaging. In the non-academic hospitals, early progression was confirmed by imaging in two patients, indicated by a rise in the cancer antigen 15-3 (CA 15-3) in four patients, by symptomatic deterioration in two patients and by unknown reason in one patient.

3.3. Delivered everolimus treatment

Everolimus was started at a 10 mg dose in 81%, 84% and 67% of the patients treated in the academic, teaching and non-teaching hospitals, respectively (Supplementary Fig. 2A-C).

In the first 12-week treatment period, 2% of patients in the academic versus 14% of patients in teaching and 11% of patients in non-teaching hospitals had stopped treatment because of progressive disease, whereas respectively 8%, 5%, and 11% of patients had stopped treatment because of toxicity (Supplementary Fig. 2D-F).

There were no significant differences in median treatment durations between hospital types (Supplementary Table 1).

4. Discussion

Here, we present real-life data of patients with HR-positive/HER2-negative ABC, who started treatment with exemestane plus everolimus from August 2012 till December 2014 to assess the implementation and effectiveness of everolimus treatment per hospital type. The real-life median PFS was 6.3 months overall, with a borderline significant difference in PFS between hospital types, due to a difference in number of reported PFS-events in the first 12 weeks of treatment. In the first 12-week treatment period, treatment was discontinued due to early progression in one out of 48 patients in the academic versus nine out of 74 patients in the non-academic hospitals, confirmed by imaging in one and two patients, respectively.

The overall median PFS observed in our real-life study (6.3 months) was slightly shorter as seen in the BOLERO-2 trial (7.8 months) [6]. Our real-life population was more heavily pretreated and in a more severe state of disease as compared with the patient population in the BOLERO-2 trial. For instance, our patients had received more often ≥3 lines of systemic treatment (68% versus 54%) and had more often visceral involvement (66% versus 58%) than in the BOLERO-2 trial [3,6]. Several phase IIIb studies reported on the efficacy and safety of everolimus, showing that PFS depends on patient selection and everolimus starting dose [8–10]. Although these studies report on real-life data, we note that most studies used eligibility criteria and study treatment protocols, and/or included only patients from dedicated cancer centers. In contrast, in our study the patient selection and the decisions on everolimus dosing were fully left to the local oncologist. Knowledge on parameters that are related to treatment outcome is of relevance when informing future patients on the benefits that can be expected, in that way providing a more realistic, individualized prospect.

As far as we know, our real-life study is the first study ever reported assessing everolimus effectiveness per hospital type. We observed that patients treated in teaching hospitals had a borderline significant shorter PFS as compared to those treated in the academic hospital (median 4.2 months versus 8.5 months, adjusted HR 1.5). There seemed to be a small, statistically non-significant, imbalance in number of previous systemic treatment lines between hospital types, but this did not change the HR in the adjusted analysis. By the post-hoc analysis, we showed that the difference in PFS originated from the first 12-week treatment period which seemed to be the result of a different assessment approach. The assessment was not always based on imaging, but also on a rise in CA 15-3. However, caution is needed when interpreting a rise in CA 15-3, especially in the first weeks after treatment initiation, since an initial rise in CA 15-3 may be followed by a decline with longer treatment duration in ~25% of the patients [15,16]. Therefore, we stress not to use tumour markers as sole criterium for determining progression, especially not in the initial treatment period [15].

The implementation of exemestane plus everolimus among hospitals types was assessed by determining the number of patients treated with exemestane plus everolimus divided by the

Table 2
The adjusted hazard ratios for PFS events for exemestane plus everolimus treatment in 2012–2014 performed by type of hospital, from start and after 12 weeks of treatment.

	Number ($N = 122$)	Events ($N = 102$)	Unadj. HR (95% CI)	Adjusted HR (95% CI)[a]	P-value
From start of treatment					
Academic hospital	48	37	Reference	Reference	Reference
Teaching hospitals	56	51	1.4 (0.9–2.2)	1.5 (1.0–2.3)	0.08
Non-teaching hospitals	18	14	1.0 (0.6–1.9)	1.0 (0.5–1.9)	0.98
After 12 weeks of treatment	Number ($N = 87$)	Events ($N = 80$)	Unadj. HR (95% CI)	Adjusted HR (95% CI)[a]	P-value
Academic hospital	37	32	Reference	Reference	Reference
Teaching hospitals	36	35	1.2 (0.7–1.9)	1.2 (0.7–2.1)	0.42
Non-teaching hospitals	14	13	1.1 (0.6–2.1)	1.3 (0.7–2.5)	0.49

Abbreviations: adj., adjusted; CI., confidence interval; HR., hazard ratio; unadj., unadjusted.

[a] Adjusted for potential confounders at start of treatment, i.e., age, metastatic-free interval, visceral disease, number of metastatic sites, prior (neo)adjuvant endocrine therapy, prior (neo)adjuvant chemotherapy, number of previous systemic therapies, start dose everolimus. Factors with a P-value below 0.25 in the univariable model were included in the multivariable model.

number of patients registered and newly diagnosed with HR-positive/HER2-negative ABC in the first 29 months after registration. We had expected to find a similar overall distribution rate of exemestane plus everolimus use among the hospitals types. However, we found that in total only 50% of patients (122/244 patients) initiated treatment with exemestane plus everolimus, these proportions were 74% (48/65), 46% (56/123) and 32% (18/56) in the academic, teaching and non-teaching hospitals, respectively. These numbers suggest that the implementation of exemestane plus everolimus was not optimal, and lower in the non-academic hospitals when compared with the academic hospital. Of note, these proportions need to be interpreted with caution as for some patients exemestane plus everolimus may not be indicated, while for other patients a catch-up may have occurred as exemestane plus everolimus could be provided as third-line treatment and beyond in the first period after approval by the EMA. These two phenomena may have resulted in respectively an under- and overestimation of our results, of which its size is unknown, but expected to be similar between hospital types. An alternative explanation for the lower implementation rate could be that patients diagnosed in non-academic hospitals had more serious co-morbidities. However, as the academic hospital has also a local function (i.e. the only hospital in a large city) and referral for ABC is not frequently done in the region, we do not think this is a major reason for the observed differences. The difference in the implementation rate of exemestane plus everolimus by hospital type may also be explained by a difference in experience in prior clinical trials. The implementation may be improved when discussing the best treatment strategies in ABC patients in a team of breast cancer specialists, sharing specific knowledge about the new drug among breast cancer specialists who work at different hospitals.

The present study has a number of strengths. The data were collected by specially trained registration clerks. A thorough data cleaning further contributed to the high quality of the data. Furthermore, we had almost complete exemestane plus everolimus treatment and follow-up data for the patients included due to the long observation period. Last, no exclusion criteria were defined, which makes our study a real-life cohort of patients with ABC treated with exemestane plus everolimus.

Our study also has some limitations which are inherent to the observational design of this study, such as the potential of information bias due to physicians' way of documentation and different assessment schedules. Further, some missing data could not be retrieved. Due to the ongoing nature of our registry, hospitals had different levels of patient inclusion at time of data lock. Patient registration was, however, performed at random, leaving our findings unbiased. Last, we included in total seven hospitals in the implementation phase, which comprised one academic, four teaching and two non-teaching hospitals. The results by type of hospital are therefore indicators for variation between hospitals rather than a comparison between hospital types in the Netherlands and the results should be interpreted accordingly.

5. Conclusions

In our real-life implementation-phase study, the median PFS was slightly shorter as compared with the BOLERO-2 trial, as is also reported with other treatments and in other tumour types. We observed a difference in the adjusted HR for PFS between hospital types, which was due to a difference in PFS in the first 12-week treatment period. In real-life, the assessment of progressive disease may be more pragmatic and not always based on imaging. As in the first months of treatment the tumour markers may not be a reliable indicator for disease status and toxicity may be more pronounced, we caution to be careful in concluding too early that a treatment is failing. We recommend physicians to broadly share treatment protocols and treatment experience to improve the implementation of therapies.

Ethical approval

This study utilizes retrospective, de-identified information. Informed consent was not necessary.

Conflicts of interest

S.M.E. Geurts: Netherlands Organization for Health Research and Development (ZonMw: 80-82500-98-8003); Novartis BV; Roche; Pfizer.

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M. de Boer: Netherlands Organization for Health Research and Development (ZonMw: 80-82500-98-8003); Novartis BV; Roche; Pfizer; Eisai.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.01.001.

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