Translational Oncology 72 (2026) 102960

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Original Research

# Time-varying hazard rates reveal patterns of progression in HR+/HER2– metastatic breast cancer: Towards risk-adapted monitoring

Linda Cucciniello [a], Fabiola Giudici [b], Lorenzo Foffano [a,c], Alessandra Franzoni [d], Brenno Pastò [a,c], Elisabetta Molteni [c], Serena Della Rossa [a,c], Gaetano Pascoletti [e], Simon Spazzapan [a], Lorena Musco [f], Gabriele Di Giustino [f], Lucia Da Ros [a], Riccardo Vida [a,c], Elena Poletto [e], Elena Nascimbeni [g], Marta Bonotto [e], Alessandro Marco Minisini [e], Barbara Belletti [f], Giuseppe Damante [c,d], Lorenzo Gerratana [a,c,1,*], Fabio Puglisi [a,c,1]

[a] Department of Medical Oncology, CRO di Aviano, National Cancer Institute, IRCCS, 33081 Aviano, Italy
[b] Unit of Cancer Epidemiology, CRO Aviano National Cancer Institute, IRCCS, Aviano, Italy
[c] Department of Medicine, University of Udine, 33100 Udine, Italy
[d] Institute of Human Genetics, Santa Maria della Misericordia University Hospital, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), 33100 Udine, Italy
[e] Department of Oncology, Santa Maria della Misericordia University Hospital, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), 33100 Udine, Italy
[f] Division of Molecular Oncology, CRO di Aviano, National Cancer Institute, IRCCS, 33081 Aviano, Italy
[g] Clinical Trial Office, CRO di Aviano, National Cancer Institute, IRCCS, 33081 Aviano, Italy

ARTICLE INFO

*Keywords:*
Breast cancer
Monitoring strategies
Precision medicine

ABSTRACT

*Background:* optimal imaging intervals for patients with hormone receptor-positive/HER2-negative metastatic breast cancer (MBC) remains undefined. Aim of this study was to analyze the temporal patterns of disease progression to identify high risk subgroups that may benefit from intensified monitoring.
*Methods:* we analyzed 149 hormone receptor-positive/HER2-negative MBC patients prospectively enrolled in the MAGNETIC.1 trial (NCT05814224) and treated with first line endocrine therapy. Hazard rates (HR) for disease progression were determined according to clinico-pathological and liquid biopsy features.
*Results:* in the overall population, two distinct progression-risk peaks emerged at 2–3 months (32.9/1000 person-months) and at 24 months (28.0/1000). Higher risk of progression was observed in lobular carcinoma (61.1) [HR 61.12 per 1000 person month (pm)], progesterone receptor-negative status (HR 39.07), fulvestrant-based treatment (HR 46.88), liver metastases (HR 59.00), and presence of $\geq$ 3 metastatic sites (HR 40.10).
*Conclusions:* Hazard distribution in hormone receptor-positive/HER2-negative MBC is biphasic and modulated by readily available clinical variables. High-risk subgroups may benefit from intensified radiologic and liquid-biopsy surveillance during the first three months and around two years after treatment start.

## Background

Breast cancer (BC) represents the most common neoplasia diagnosed in the female population and the leading cause of cancer-related death worldwide [1]. In about 10% of the cases, BC is diagnosed as *de novo* metastatic disease, whilst about 30% of patients initially diagnosed with early stage BC, will later develop distant metastases [2]. The expression of estrogen and/or progesterone receptors (ER and PR), evaluated through immunohistochemistry (IHC) performed on tissue biopsy or on the surgical sample, is observed in about 70% of the cases and defines the disease as "luminal-like" [3]. In particular, according to international guidelines, BC is considered as hormone receptor-positive with $\geq$ 1% of tumor cell nuclei staining ER and/or PR positive [4].

Endocrine therapy (ET) represents the mainstay for the management of early and metastatic luminal-like BC [5,6]. The combination of ET with a cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6 inhibitor), is the current standard first line treatment for luminal-like metastatic BC (MBC), considering the significant survival benefit reported with this combination with respect to ET alone [7–9]. In particular, the addition of palbociclib, ribociclib or abemaciclib to standard ET has determined a

* Corresponding author at: Department of Medical Oncology, CRO di Aviano, National Cancer Institute, IRCCS, 33081 Aviano, Italy.
*E-mail address:* lorenzo.gerratana@outlook.com (L. Gerratana).
[1] Contributed equally.

https://doi.org/10.1016/j.tranon.2026.102960
Received 6 July 2026; Received in revised form 24 July 2026; Accepted 26 July 2026
Available online 28 July 2026

significant shift in the first line treatment strategy [7–12].

In clinical practice, treatment response is typically monitored through clinico-radiological assessments, generally programmed at 2–3 month intervals, a schedule largely extrapolated from clinical trials, rather than individualized patient needs [13].

Currently, monitoring strategies for MBC are not standardized. Time intervals as well as the imaging modalities for disease re-evaluation are influenced by different variables, including but not limited to serum tumor biomarkers, alterations in blood works and signs/symptoms suggestive of disease progression [13].

The latest ESMO guidelines recommend radiological re-evaluations every 2 to 4 months during treatment [14]. NCCN guidelines offer more specific recommendations, suggesting that imaging studies should be repeated every 2 to 4 treatment cycles for patients undergoing chemotherapy and/or intravenous targeted therapy, and every 2 to 6 months for patients receiving ET alone or combined to a CDK4/6 inhibitor or other kinds of oral targeted therapy [15]. However, a study from Accordino et al., demonstrated how more than one-third-of patients diagnosed with MBC undergo more frequent monitoring, receiving more than four imaging studies per year [16].

To date, no definite clinical or liquid biopsy-based feature seems to help in defining the optimal timings of imaging schedule.

The aim of this study is to analyze the role of clinical and liquid biopsy (LB) characteristics in patients with hormone receptor-positive/HER2-negative MBC receiving a first line ET-based therapy to analyze the different timings of disease progression and thus identify the optimal intervals for scheduling radiological re-evaluations.

## Materials and methods

### *Study design and population*

A cohort of 149 patients was enrolled from January 2018 to January 2023 in the MAGNETIC.1 trial (NCT05814224), a pragmatic multicenter liquid biopsy-based clinical trial designed to evaluate if circulating tumor DNA (ctDNA)- detected genetic and epigenetic *ESR1* alterations could be integrated to conventional radiological re-evaluations in monitoring treatment response.

All patients enrolled in the trial had a histologically proven diagnosis of hormone receptor-positive HER2-negative breast cancer with radiological evidence of metastatic spreading and received a first line therapy with either an aromatase inhibitor (AI) or fulvestrant [± a luteinizing hormone releasing hormone analogue (LHRHa) if in pre-menopause] alone or in combination with a CDK4/6 inhibitor according to clinical practice.

Clinico-pathological characteristics included demographic characteristics, tumor histology, hormone receptor expression, HER2 status, type of treatment received, number and sites of distant metastases, as well as liquid biopsy features.

In detail, hormone receptor expression was assessed by IHC with ER and/or PR-positive disease being defined as $\geq$1% of tumor cell nuclei staining. Metastatic sites included bone, liver, lung, lymph nodes, central nervous system (CNS) and other visceral locations and were categorized as 1, 2 or $\geq$ 3 according to the baseline disease spreading assessed by imaging studies at metastatic diagnosis.

Baseline imaging [either computed tomography (CT) scan or positron emission tomography (PET)] had to be performed up to 28 days prior to treatment start. The first imaging re-evaluation was performed after 8 weeks, and the subsequent ones were scheduled every 12 weeks according to study protocol.

Liquid biopsy (LB) samples were collected at baseline before treatment start. The first interim LB was scheduled after 4 weeks from the beginning of the therapy. All the subsequent LB were planned in concomitance to and in between the radiological re-evaluations.

### *Circulating cell free DNA extraction and next generation sequencing (NGS)*

Maxwell® RSC ccfDNA plasma kit (Promega) was used for automated purification of circulating cell-free DNA (ccfDNA) from patients' plasma. Plasma was obtained by centrifuging whole blood from EDTA tubes 1X for 10 min at 2000 g and 2X for 10 min at 4000 g. A pre-established volume of 7ul of DNA from liquid biopsies was used for subsequent analysis by NGS using an amplicon-based strategy, as previously described [17,18]. Primers aimed at covering the hotspot mutation regions of human *ESR1, PIK3CA, AKT1* and *ERBB2* genes were designed and modified adding specific 5′-adapter sequences (Merck). To prepare the NGS libraries, two consecutive rounds of PCR with Phusion Hot Start II High- Fidelity DNA Polymerase (Thermo Fisher Scientific) were performed. First, regions of interest were amplified, then, after a 1:100 dilution from previous round, barcodes (index primers, IDT) were added to the samples for unique identification. Next, fragments were purified using Wizard R© SV Gel and PCR Clean-Up System (Promega), quantified using QuantiFluor® ONE dsDNA System (Promega) and normalized to 2nM to create the final library. Libraries were then sequenced using the Miseq sequencing platform (Illumina) at a minimum depth of 5000X. Sequencing data were exported as BAM and VCF files and analyzed using VariantStudio™ software (Illumina) and Integrative Genomics Viewer (IGV) software, respectively. After quality checks and filtering, Catalogue of Somatic Mutations in Cancer (COSMIC, https://cancer.sanger.ac.uk/cosmic) and International Cancer Genome Consortium (ICGC, https://dcc.icgc.org/) data portals were interrogated and variants with possible clinical significance annotated.

### *Statistical analysis*

Clinico-pathological variables were reported through descriptive analysis.

Hazard rates (HR) were used to characterize the first progression dynamics. HR in this study were measured monthly. The HR of the first progression was defined as the conditional probability of progression in a time interval, given that patients were free of progression at the beginning of the interval. Time-varying HR were estimated using the nonparametric method proposed by Rebora et al. which performs a likelihood-based smoothing in a mixed model framework using the Poisson structure of the data: the number of events in each increment of time is modelled as a Poisson-distributed variable whose mean is the expected number of events [19]. We generated HR estimates of varying degrees of smoothness: estimates that are less smooth emphasize local features of the hazard function, whereas smoother estimates emphasize more global features.

The smoothed hazard and confidence intervals (CI) are presented graphically. All analyses were conducted in R statistical software version 4.2.3 (2023).

Progression-free survival was defined as the time from first line treatment start to disease progression or death from any cause.

### *Ethics*

The study was approved by the ethical committee under the CEUR-2018-Sper-056-CRO-protocol and was carried out in accordance with Good Clinical Practice guidelines and the Helsinki Declaration.

Before enrolling, all patients provided written informed consent.

## Results

### *Clinico-pathological and LB characteristics of the analyzed cohort*

Amongst the 149 enrolled patients, 45 (30%) had *de novo* MBC and most cases (101, 68%) were invasive ductal carcinoma (IDC) (Table 1).

Median age at MBC diagnosis was 61 years [interquartile range (IQR)

**Table 1**
clinico-pathological and liquid biopsy characteristics of study population.

| Variable | N° patients (total = 149) | Percentage (100%) |
|---|---|---|
| Histotype | | |
| Lobular | 18 | 12 |
| Ductal | 101 | 68 |
| Missing | 30 | 20 |
| MBC diagnosis | | |
| De novo | 45 | 30 |
| Recurrent | 81 | 54 |
| Missing | 23 | 16 |
| ER status | | |
| Positive | 143 | 96 |
| Negative | 0 | 0 |
| Missing | 6 | 4 |
| PR status | | |
| Negative | 32 | 21 |
| Positive | 110 | 74 |
| Missing | 7 | 5 |
| ET | | |
| SERD/SERM | 39 | 26 |
| AI | 110 | 74 |
| Bone | | |
| No | 39 | 26 |
| Yes | 107 | 72 |
| Missing | 3 | 2 |
| Node | | |
| No | 66 | 44 |
| Yes | 80 | 54 |
| Missing | 3 | 2 |
| Lung | | |
| No | 109 | 73 |
| Yes | 37 | 25 |
| Missing | 3 | 2 |
| Liver | | |
| No | 96 | 64 |
| Yes | 43 | 29 |
| Missing | 10 | 7 |
| CNS | | |
| No | 142 | 95 |
| Yes | 4 | 3 |
| Missing | 3 | 2 |
| N° Metastases | | |
| 1 | 21 | 14 |
| 2 | 76 | 51 |
| ≥3 | 49 | 33 |
| Missing | 3 | 2 |
| *ESR1* | | |
| Wild Type | 116 | 78 |
| Mutated | 8 | 5 |
| Missing | 25 | 17 |
| *PIK3CA* | | |
| Wild Type | 98 | 66 |
| Mutated | 26 | 17 |
| Missing | 25 | 17 |
| *AKT1* | | |
| Wild Type | 118 | 79 |
| Mutated | 6 | 4 |
| Missing | 25 | 17 |
| *ERBB2* | | |
| Wild Type | 119 | 80 |
| Mutated | 5 | 3 |
| Missing | 25 | 17 |
| CDK4/6i | | |
| Palbociclib | 59 | 40 |
| Ribociclib | 49 | 33 |
| Abemaciclib | 17 | 11 |
| No CDK4/6i | 24 | 16 |

Abbreviations: MBC=metastatic breast cancer; ER=estrogen receptor; PR=progesterone receptor; ET=endocrine therapy; SERD=selective estrogen receptor degrader; SERM=selective estrogen receptor modulator; AI=aromatase inhibitor; CDK4/6i=CDK4/6 inhibitor.

51–70)].

Most patients (143, 96%) had ER-positive disease, and 32 patients (21%) had PR-negative disease (Table 1).

Bone was the most common metastatic site (107, 72%), followed by lymph nodes (80, 54%), liver (43, 29%) and lung (37, 25%) (Table 1). Only 4 patients (3%) presented central nervous system (CNS) spreading (Table 1).

Twenty-one patients (14%) had a single metastatic site, while 76 (51%) had 2 metastatic sites and 49 (33%) had metastatic lesions in 3 or more organs (Table 1).

All patients were treated with a first line therapy encompassing an endocrine agent. In particular, 110 patients (74%) received an aromatase inhibitor, and 39 patients (26%) received fulvestrant (Fulvestrant). Out of these 149 patients, only 24 received ET alone in the first line setting, while 125 received ET in association with a CDK 4/6 inhibitor. In particular, 59 patients (40%) received ET + palbociclib, 49 (33%) received ribociclib and 17 (11%) were treated with abemaciclib (Table 1).

All patients underwent the baseline LB sample collection. At the time of data cut-off (March 4th, 2025), baseline LB data were available for the first 134 patients enrolled in the study.

At baseline LB, 8 patients (6%) presented *an ESR1* mutation, 26 patients (19%) had a *PIK3CA* mutation, 6 (5%) had an *AKT1* mutation and 5 (4%) harbored an *ERBB2* mutation.

### *Patterns of disease progression in the overall population*

Considering the overall patient population, significant temporal variations in the hazard of disease progression were observed. In particular, a high risk of disease progression was observed within the first 2–3 months from treatment start, with a peak hazard rate of 32.85 per 1000-person months (pm) (Fig. 1). This was followed by a gradual decline in risk up to 18 months, followed by a second peak at 24 months with a hazard rate of 28.03 per 1000 pm (Fig. 1). Then, another risk reduction was observed, followed by a potential increase after 40 months of treatment, although the interpretation might be limited by the dwindling number of patients still at risk during this prolonged period of follow up (Fig. 1).

### *Patterns of disease progression according to clinico-pathological and LB characteristics*

Significant differences in hazard rates were noted amongst histological subtypes, as patients with invasive lobular carcinoma (ILC) had a substantially higher overall hazard rate compared to those with IDC (HR

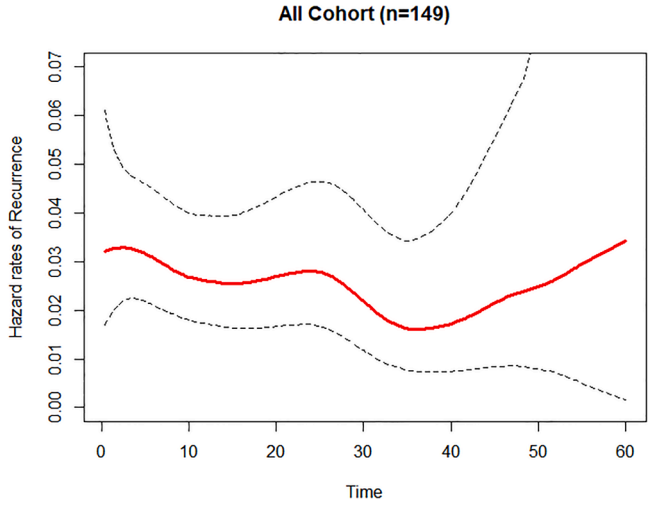


**Fig. 1.** Smoothed hazard functions for breast cancer progression in all patients.

61.12 per 1000 pm for ILC versus 22.66 per 1000 pm for IDC) (Table 2).

Notably, PR expression substantially affected the risk of disease progression. In fact, patients with PR-negative disease presented a higher risk of disease progression in the first 1–2 months from treatment start with a peak hazard of 70.55 per 1000 pm. Then, a decline was noted until 10 months, followed by another peak of risk at about 20 months (41.67 per 1000 pm). Notably, after 35 months of follow up the hazard rate in PR-negative patients became lower than that of PR-positive ones (Fig. 2A, 2B). Moreover, the overall HR was higher in PR-negative cases as compared to the PR-positive ones (HR for PR-negative 39.07 per 1000 pm versus 23.15 per 1000 pm for PR-positive) (Table 2).

The type of ET administered deeply impacted upon the progression risk. In fact, with respect to patients treated with aromatase inhibitors, those treated with fulvestrant exhibited a higher risk of disease progression within the first 1–2 months from metastatic diagnosis with a peak hazard of 71.94 per 1000 pm, followed by a gradual decline over the subsequent 46 months (Fig. 2C, 2D). Also, overall hazard rates markedly varied within the two groups (HR for fulvestrant 46.88 per 1000 pm versus 22.26 per 1000 pm for AIs) (Table 2).

Instead, with regards to the type of CDK4/6 received in association to ET, abemaciclib was associated with the lowest progression risk, followed by ribociclib and palbociclib (HR for abemaciclib 18.26 per 1000 pm versus HR for ribociclib 25.06 per 1000 pm versus HR for palbociclib 28.05 per 1000 pm) (Table 2).

Another relevant determinant of the risk of disease progression was the number of metastatic sites, as patients with a higher disease burden, defined by the presence of $\geq$ 3 metastatic sites, showed a higher risk of early disease progression at 1–2 months from treatment start with a peak hazard of 64.62 per 1000 pm, followed by a gradual decrease over the subsequent months, whilst no clear peak was identified for patients with 1 or 2 metastatic sites (Fig. 2E, 2F). Accordingly, a lower risk of progression was reported for patients with a single metastatic site (HR 13.16 per 1000 pm) compared to those with two metastatic sites (HR 24.61 per 1000 pm) and to those with $\geq$3 metastatic locations (HR 40.10 per 1000 pm) (Table 2).

Patients with liver metastases displayed a sharp 1–2 month hazard spike (91.34 per 1000 pm), a transient decline by month 18, and a secondary peak at month 30 (58.64 per 1000 pm) (Fig. 3A, 3B). Moreover, this was the variable associated with the most pronounced increase in the risk of disease progression amongst all the ones analyzed, with an overall HR of 59.00 per 1000 pm compared to 19.39 per 1000 pm for

**Table 2**
Overall Hazard Rate for progression according to prognostic factors.

| Variable | N° patients | N° events | Total person-months | Overall Hazard Rate | Overall Hazard Rate per 1000 person-months |
|---|---|---|---|---|---|
| Histotype | | | | | |
| Lobular | 18 | 15 | 245.43 | 0.061 | 61.12 |
| Ductal | 101 | 56 | 2471.49 | 0.023 | 22.66 |
| Missing | 30 | | | | |
| PR status | | | | | |
| Negative | 32 | 23 | 588.75 | 0.039 | 39.07 |
| Positive | 110 | 60 | 2592.31 | 0.023 | 23.15 |
| Missing | 7 | | | | |
| ET | | | | | |
| SERD/SERM | 39 | 29 | 618.58 | 0.047 | 46.88 |
| AI | 110 | 59 | 2650.53 | 0.022 | 22.26 |
| Bone | | | | | |
| No | 39 | 19 | 870.65 | 0.022 | 21.82 |
| Yes | 107 | 67 | 2353.47 | 0.028 | 28.47 |
| Missing | 3 | | | | |
| Node | | | | | |
| No | 66 | 36 | 1529.09 | 0.024 | 23.54 |
| Yes | 80 | 50 | 1695.02 | 0.029 | 29.50 |
| Missing | 3 | | | | |
| Lung | | | | | |
| No | 109 | 66 | 2435.06 | 0.027 | 27.10 |
| Yes | 37 | 20 | 789.05 | 0.025 | 25.35 |
| Missing | 3 | | | | |
| Liver | | | | | |
| No | 96 | 51 | 2630.86 | 0.019 | 19.39 |
| Yes | 43 | 35 | 593.25 | 0.059 | 59.00 |
| Missing | 10 | | | | |
| N° Metastases | | | | | |
| 1 | 21 | 7 | 532.05 | 0.013 | 13.16 |
| 2 | 76 | 46 | 1869.20 | 0.025 | 24.61 |
| $\geq$3 | 49 | 33 | 822.87 | 0.040 | 40.10 |
| Missing | 3 | | | | |
| *PIK3CA* | | | | | |
| Wild Type | 98 | 59 | 2252.64 | 0.026 | 26.19 |
| Mutated | 26 | 18 | 646.33 | 0.028 | 27.85 |
| Missing | 25 | | | | |
| *ESR1* | | | | | |
| Wild Type | 116 | 70 | 2728.91 | 0.0257 | 25.65 |
| Mutated | 8 | 7 | 170.06 | 0.0412 | 41.17 |
| Missing | 25 | | | | |
| CDK4/6i | | | | | |
| Palbociclib | 59 | 42 | 1497.35 | 0.028 | 28.05 |
| Ribociclib | 49 | 27 | 1077.38 | 0.025 | 25.06 |
| Abemaciclib | 17 | 7 | 383.34 | 0.018 | 18.26 |
| Missing | 24 | | | | |

Abbreviations: PR=progesterone receptor; ET=endocrine therapy; SERD=selective estrogen receptor degrader; SERM=selective estrogen receptor modulator; AI=aromatase inhibitor; CDK4/6i=CDK4/6 inhibitor.

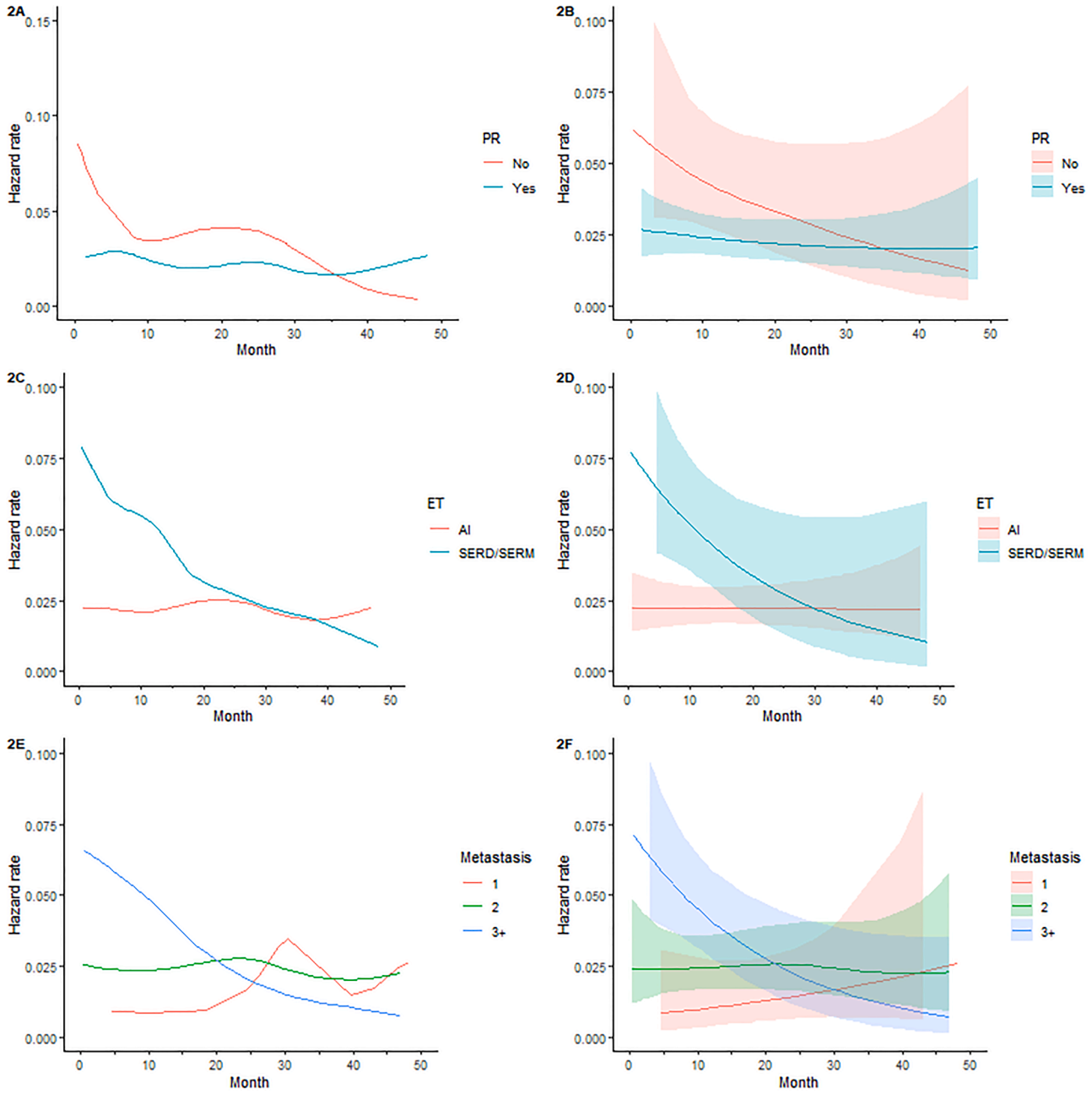


**Fig. 2.** A-F: Hazard estimates for breast cancer progression stratified according to progestertone receptor status (2A, 2B), type of endocrine therapy (2C, 2D) and number of metastatic sites (2E, 2F).
Abbreviations: PR=progesterone receptor; ET=endocrine therapy; AI=aromatase inhibitor; SERD=selective estrogen receptor degrader; SERM=selective estrogen receptor modulator.

patients without liver metastases, thus indicating a three-fold higher risk (Table 2).

No significant differences in overall hazard rates were noted according to other metastatic sites, including bone, lung and lymph nodes (Fig. 3C-3H).

With regards to LB features, the presence of a *PIK3CA* mutation at baseline was associated with a slightly higher risk of disease progression (HR 28.05 per 1000 pm) compared to *PIK3CA* wild type (HR 26.19 per 1000 pm) (Table 2). In detail, *PIK3CA*-mutated cases had a peak hazard of 52.38 per 1000 pm for disease progression in the first 2 months from treatment start, followed by a gradual decline with a stable HR of 29.54 per 1000 pm, then decreasing until the end of the follow up. In non-mutated cases, instead, the risk of disease progression remained constant with slight fluctuations along the observation period (Fig. 4A, 4B).

Finally, although limited by the small sample size, cases with baseline *ESR1* mutation presented a higher risk of disease progression (HR 41.17 per 1000 pm) compared to the non-mutated ones (HR 25.65 per 1000 pm) (Table 2). In particular, a higher risk was noted in the first 3-4 months, followed by a progressive decline along the follow up in the *ESR1*-mutated group, while the non-mutated cases presented a constant risk with few oscillations over time (Fig. 4C, 4D).

## Discussion

The present study evaluated a cohort of patients with hormone receptor-positive/HER2-negative MBC treated with first line ET, with the aim of assessing whether the integration of clinicopathological and liquid biopsy features could help anticipate the timing of disease

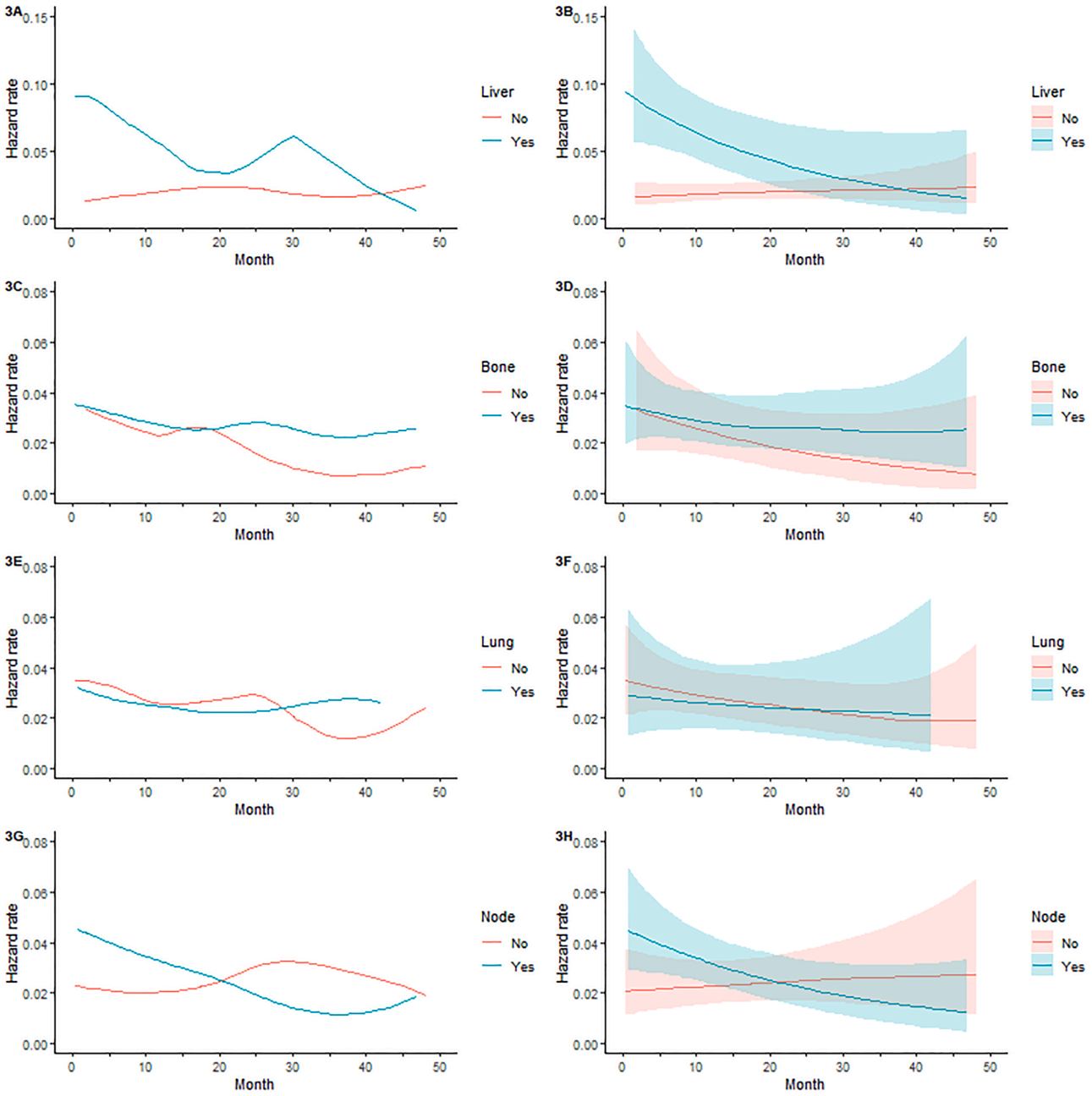


**Fig. 3.** A-H: Hazard estimates for breast cancer progression stratified according to metastatic site (liver: 3A, 3B; bone: 3C, 3D; lung 3E, 3F; lymph nodes 3 G, 3H).

progression and improve the scheduling of radiologic reassessments.

Lobular histology was independently associated with an increased risk of early disease progression compared to ductal histology. A higher risk was also observed in patients with PR–negative tumors or those receiving first line fulvestrant. Moreover, liver involvement conferred a threefold greater risk of progression relative to other metastatic sites. Finally, a high metastatic burden, with three or more metastatic sites, was linked to a significantly increased hazard of early progression compared to involvement of one or two sites.

Consistently, a French retrospective study by Dalenc et al. evaluated the prognostic role of lobular versus ductal histology in a cohort [20], showing how patients with ILC presented a significantly worse PFS (HR 1.15, 95% CI 1.07–1–22, *p-value*<0.0001) and OS (HR 1.31, 95% CI 1.20–1.42, *p-value*<0.0001) compared to those with IDC, regardless of hormone receptor and HER2 expression [20]. These unfavorable outcomes observed for the lobular histology could be related to the higher odds of metastatic spreading to multiple variable sites including the peritoneum, the retroperitoneum and abdominal organs [21–23].

Similarly to what observed in our study, also in another work by Chen et al., patients with ILC had a poorer OS after 5 years from the diagnosis with respect to patients with IDC and, in particular, patients with ER-positive but PR-negative ILC were the ones with the worse OS outcome (p-value<0.0001) [24]. Indeed, the prognostic role of PR expression is well established. The absence of PR expression has been associated with more aggressive features including larger tumor size, presence of lymph node metastasis or distant metastatic spreading and, consequently, worse survival outcomes [25,26]. Interestingly, our data showed a lower risk of disease progression in PR-negative cases after 35 months of follow, potentially embodying the cured fraction principle utilized in BC survival modeling [27]. This concept was further investigated by Dignam et al., who demonstrated that patients with aggressive tumor characteristics, who survive the initial high-risk period, have

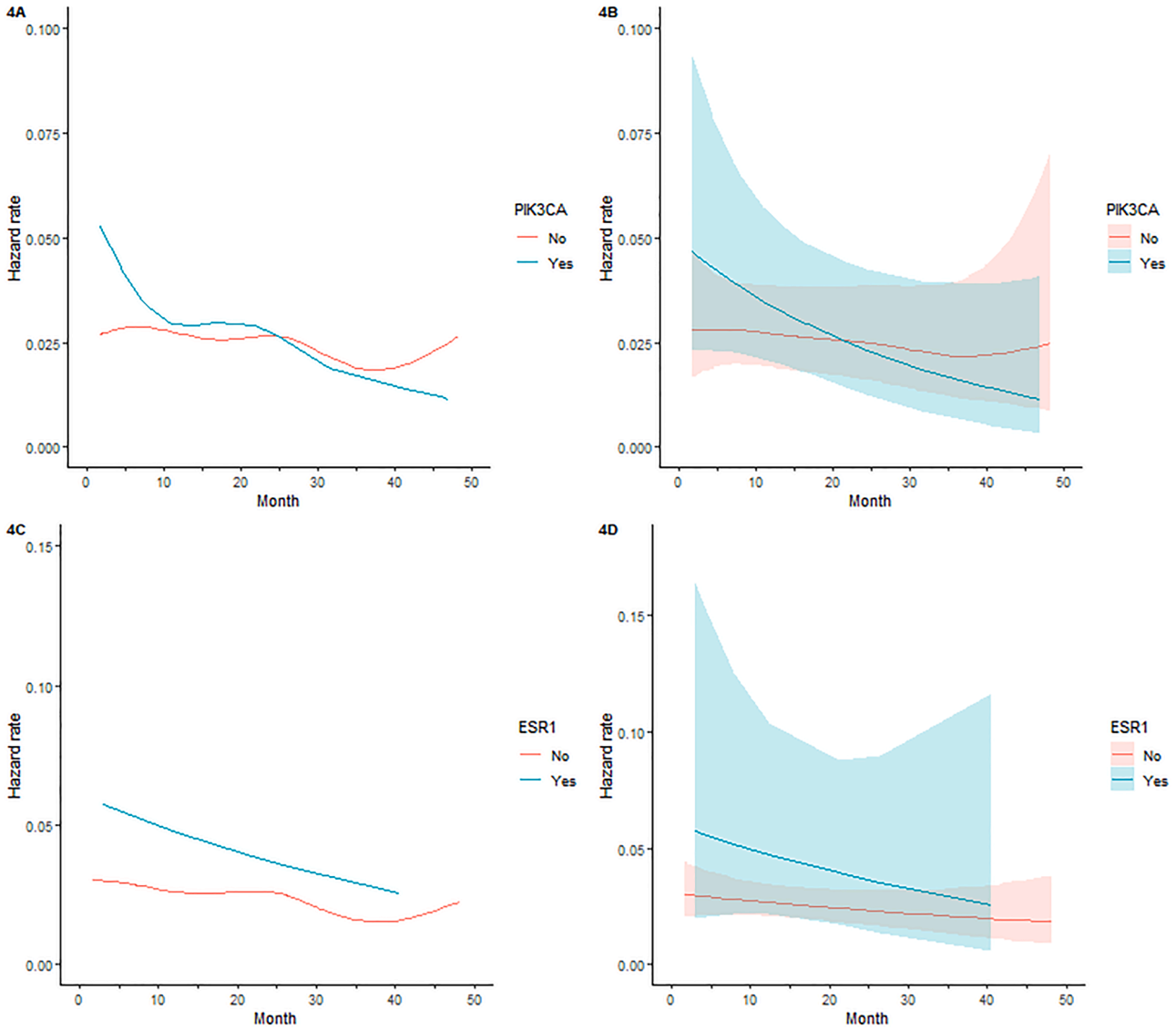


**Fig. 4.** A-D: Hazard estimates for breast cancer progression stratified according to *PIK3CA* mutational status (4A, 4B) and *ESR1* mutational status (4C, 4D).

unexpectedly longer long-term survival [28].

We also reported a higher risk of disease progression for patients treated with fulvestrant compared to those treated with AIs. Given that fulvestrant is typically employed in the first line setting for the treatment of patients with endocrine resistant disease, this finding could reflect a more intrinsic aggressiveness of these cases [29].

In clinical trials, response assessments are performed at predefined intervals—typically every 8 to 12 weeks—according to the study protocol. In routine clinical practice, however, imaging schedules are less standardized and generally occur every 2 to 3 treatment cycles, corresponding to intervals of approximately 10 weeks to 3 months. The timing of these evaluations is often influenced by clinical factors, including the patient's overall condition, laboratory abnormalities, or a sudden increase in tumor-associated serum biomarkers [13].

Currently, there is no evidence supporting the routine use of intensive imaging monitoring in patients with metastatic breast cancer (MBC), as this approach has proven neither cost-effective nor beneficial in terms of quality of life, often increasing patient anxiety [16,30]. Moreover, imaging schedules in clinical practice are not dynamically tailored to individual clinical features or biomarker profiles. However, our findings suggest that patients with lobular histology, PR–negative status, fulvestrant-based treatment, liver metastases, and a high metastatic burden are at increased risk of early disease progression. In these high-risk subgroups, a more personalized and intensified monitoring strategy may facilitate the early detection of progression and support timely therapeutic optimization. In this context, the use of minimally invasive techniques such as liquid biopsy could pave the way for biomarker-driven surveillance approaches.

In this light, the PADA-1 randomized clinical trial introduced a biomarker-driven treatment optimization approach to MBC. PADA-1 enrolled patients with hormone receptor-positive/HER2-negative MBC treated with first line AI in combination with palbociclib, longitudinally characterized through ctDNA every 2 months to detect emerging *ESR1* mutations [31]. Patients with emergent *ESR1* mutations without evidence of radiological disease progression were randomly assigned to either switch the ET backbone to fulvestrant or maintain AI [31]. After a median follow up of almost 35 months, switching the treatment before the evidence of clinical progression, led to a statistically significant improvement in median PFS [median PFS 11.0 months (95% CI 9.1–13.6) for patients treated with fulvestrant and palbociclib versus 5.7 months (95% CI 3.9–7.5) with AI and palbociclib group (stratified HR 0.61, 95% CI 0.43–0.86; p-value=0·0040) [31]. Consistently, the recently published results of the SERENA-6 trial align with this evidence.

In SERENA-6, patients with hormone receptor-positive/HER2-

negative MBC who had received a first line treatment with an AI plus a CDK4/6 inhibitor for at least six months underwent *ESR1* monitoring through ctDNA assessments every 2 to 3 months—to monitor for *ESR1* mutations in ctDNA [32]. Similarly to PADA-1, patients underwent a ctDNA-guided randomization to either continuing AI or to early switch to the nex-generation oral SERD camizestrant, leading to a significant improvement in PFS, with a median PFS of 16.0 months (95% CI, 12.7–18.2) in the group treated with camizestrant group versus 9.2 months (95% CI, 7.2 to 9.5) in the group treated with AIs (HR for progression or death, 0.44; 95% CI, 0.31 to 0.60; *p-value*<0.0001) [32].

Although both studies demonstrated the potential of ctDNA monitoring to support proactive and personalized treatment strategies, their implementation in real-world settings may require improved coordination between liquid biopsy sampling and imaging assessments. Notably, in our experience, a clear second peak of disease progression was identified at 24 months of follow up, prompting for an integration of liquid biopsy sampling at this timepoint to anticipate the clinical outcome. A transition from fixed schedules to risk-adapted strategies is therefore essential to optimize resource utilization and enhance patients' quality of life.

Finally, several limitations should be acknowledged. Although the study was based on a prospective cohort evaluated using a strict and homogeneous schedule, the analysis of specific subgroups may have been limited by small sample sizes, potentially affecting the precision of the reported hazard estimates. In addition, the decreasing number of patients remaining on treatment over time may have reduced the reliability of hazard rates during prolonged follow-up, and thus long-term trends should be interpreted with caution. Furthermore, patients enrolled in the MAGNETIC.1 trial were managed with a homogeneous and strictly scheduled imaging follow-up. Although this design maximized the internal consistency of hazard rate estimates, it might limit the direct application of these findings to community oncology practice where surveillance timings are more heterogeneous and often adapted to different needs, including patients' clinical conditions and tumor biomarkers alterations. Additionally, alternative monitoring intervals could reveal different distributions of progression risk over time, potentially anticipating or smoothing the peaks described in our paper. Moreover, beyond imaging- and ctDNA-based approaches, emerging bioelectronic platforms able to characterize the electrophoretic and dielectrophoretic behavior of cancer cells could complement this risk-adapted monitoring framework, further supporting this shift toward dynamic, patient-tailored monitoring [33].

## Conclusions

The present study highlighted how hazard rates of disease progression in metastatic breast cancer may vary significantly over time and across distinct clinico-pathological subgroups. Recognizing these temporal dynamics and identifying high-risk patient profiles may support the development of individualized monitoring strategies. Specifically, lobular histology, progesterone receptor–negative status, fulvestrant-based treatment, liver metastases, and a high metastatic burden were associated with an increased risk of early progression. For patients presenting these features, an intensified schedule of radiological and ctDNA assessments could be considered to enable timely therapeutic interventions, while balancing the need to preserve quality of life.

## Funding declaration

This study was supported by AstraZeneca, Italian Ministry of Health – Ricerca Corrente, Italian Ministry of Health RF-2021-12-371-961 to FP and BB, Associazione Italiana per la Ricerca sul Cancro (AIRC) IG#20-061 to BB and CRO Intramural Research Grant 5 × 1000 2017 MdS-BrCaCuRe to BB.

The Funding Organizations enabled the conduct of this study, but had no role in its design, patient recruitment, data collection, data analyses, interpretation or writing of the present paper.

## CRediT authorship contribution statement

**Linda Cucciniello:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. **Fabiola Giudici:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **Lorenzo Foffano:** Conceptualization, Data curation, Methodology, Resources, Writing – review & editing. **Alessandra Franzoni:** Investigation, Methodology, Validation, Writing – review & editing. **Brenno Pastò:** Resources, Writing – review & editing. **Elisabetta Molteni:** Resources, Writing – review & editing. **Serena Della Rossa:** Resources, Writing – review & editing. **Gaetano Pascoletti:** Resources, Writing – review & editing. **Simon Spazzapan:** Resources, Writing – review & editing. **Lorena Musco:** Conceptualization, Resources, Writing – review & editing. **Gabriele Di Giustino:** Conceptualization, Resources, Writing – review & editing. **Lucia Da Ros:** Resources, Writing – review & editing. **Riccardo Vida:** Resources, Writing – review & editing. **Elena Poletto:** Resources, Writing – review & editing. **Elena Nascimbeni:** Project administration, Resources, Writing – review & editing. **Marta Bonotto:** Resources, Writing – review & editing. **Alessandro Marco Minisini:** Resources, Writing – review & editing. **Barbara Belletti:** Data curation, Resources, Writing – review & editing. **Giuseppe Damante:** Methodology, Resources, Writing – review & editing. **Lorenzo Gerratana:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Fabio Puglisi:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Resources, Writing – review & editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

**M.B.** reports advisory/consultancy fee from AstraZeneca, Lilly, MSD, Novartis, Pfizer, SeaGen; travel grants from Lilly, Roche. **A.M.M.** reports advisory/consultancy fee from Novartis, MSD, BMS, Merk, Sunpharma, PierreFabre, Gilead, Seagen, Genomic Health; invited speech from Novartis, MSD, BMS, Merk, Sunpharma, Sanophi, PierreFabre, AstraZeneca, Daiichi Sankyo; travel grants from Gilead, PierreFabre; other familial: MSD, AstraZeneca, Pharmamar, GSK. **L.G.** reports advisory/consultancy fee from AstraZeneca, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Incyte, Novartis, Pfizer, Merck Sharp & Dohme, Menarini Stemline, Abbvie; research funding from Menarini Silicon Biosystems. **F. P.** reports honoraria for advisory boards, activities as a speaker, travel grants, research grants from Amgen, AstraZeneca, Daiichi Sankyo, Celgene, Eisai, Eli Lilly, Exact Sciences, Gilead, Ipsen, Italfarmaco, Menarini, MSD, Novartis,Pierre Fabre, Pfizer, Roche, Seagen, Takeda, Viatris; Research funding from AstraZeneca – Eisai – Roche.

## Data availability

The datasets analyzed for the current study are available upon reasonable request to the first author at linda.cucciniello@cro.it.

## References

[1] H. Sung, J. Ferlay, R. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, et al., Global Cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021) 209–249, https://doi.org/10.3322/caac.21660.

[2] M. Bonotto, L. Gerratana, E. Poletto, P. Driol, M. Giangreco, S. Russo, et al., Measures of outcome in metastatic breast cancer: insights from a real-world scenario, Oncologist 19 (2014) 608–615, https://doi.org/10.1634/theoncologist.2014-0002.

[3] A. Goldhirsch, W. Wood, R. Gelber, A. Coates, B. Thürlimann, H.-J. Senn, Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007, Ann. Oncol. 18 (2007) 1133–1144, https://doi.org/10.1093/annonc/mdm271.
[4] K. Allison, M. Hammond, M. Dowsett, S. McKernin, L. Carey, P. Fitzgibbons, et al., Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update, J. Clin. Oncol. 38 (2020) 1346–1366, https://doi.org/10.1200/JCO.19.02309.
[5] L. Cucciniello, L. Gerratana, L. Del Mastro, F. Puglisi, Tailoring adjuvant endocrine therapy in early breast cancer: when, how, and how long? Cancer Treat. Rev. 110 (2022) 102445 https://doi.org/10.1016/j.ctrv.2022.102445.
[6] F. Cardoso, S. Paluch-Shimon, E. Senkus, G. Curigliano, M. Aapro, F. André, et al., 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5), Ann. Oncol. 31 (2020) 1623–1649, https://doi.org/10.1016/j.annonc.2020.09.010.
[7] H. Rugo, R. Finn, V. Diéras, J. Ettl, O. Lipatov, A. Joy, et al., Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up, Breast. Cancer Res. Treat. 174 (2019) 719–729, https://doi.org/10.1007/s10549-018-05125-4.
[8] G. Hortobagyi, S. Stemmer, H. Burris, Y. Yap, G. Sonke, S. Paluch-Shimon, et al., Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer, Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 29 (2018) 1541–1547, https://doi.org/10.1093/annonc/mdy155.
[9] M. Goetz, M. Toi, J. Huober, J. Sohn, O. Tredan, I. Park, et al., LBA15 MONARCH 3: interim overall survival (OS) results of abemaciclib plus a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+, HER2- advanced breast cancer (ABC), Ann. Oncol. 33 (2022) S1384, https://doi.org/10.1016/j.annonc.2022.08.009.
[10] R. Finn, H. Rugo, V. Dieras, N. Harbeck, S. Im, K. Gelmon, et al., Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2− ABC): analyses, J. Clin. Oncol. 40 (2022), https://doi.org/10.1200/JCO.2022.40.17_suppl.LBA1003. LBA1003–LBA1003.
[11] G. Hortobagyi, S. Stemmer, H. Burris, Y. Yap, G. Sonke, L. Hart, et al., Overall survival with Ribociclib plus letrozole in advanced breast cancer, N. Engl. J. Med. 386 (2022) 942–950, https://doi.org/10.1056/NEJMoa2114663.
[12] M. Goetz, M. Toi, J. Huober, J. Sohn, O. Trédan, I. Park, et al., Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2− advanced breast cancer: final overall survival results of MONARCH 3, Ann. Oncol. 35 (2024) 718–727, https://doi.org/10.1016/j.annonc.2024.04.013.
[13] M. Bonotto, D. Basile, L. Gerratana, M. Bartoletti, C. Lisanti, G. Pelizzari, et al., Clinico-radiological monitoring strategies in patients with metastatic breast cancer: a real-world study, Futur. Oncol. 16 (2020) 2059–2073, https://doi.org/10.2217/fon-2020-0020.
[14] A. Gennari, F. André, C. Barrios, J. Cortés, E. de Azambuja, A. DeMichele, et al., ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer, Ann. Oncol. 32 (2021) 1475–1495, https://doi.org/10.1016/j.annonc.2021.09.019.
[15] W. Gradishar, M. Moran, J. Abraham, et al., NCCN Guidelines Index table of Contents DIscussion, Breast. Cancer Version 4 (2025) n.d.;NCCN Guide.
[16] M. Accordino, J. Wright, S. Vasan, A. Neugut, G. Hillyer, J. Hu, et al., Use and costs of disease monitoring in women with metastatic breast cancer, J. Clin. Oncol. 34 (2016) 2820–2826, https://doi.org/10.1200/JCO.2016.66.6313.
[17] L. Gerratana, D. Basile, A. Franzoni, L. Allegri, D. Viotto, C. Corvaja, et al., Plasma-based longitudinal evaluation of ESR1 epigenetic status in hormone receptor-positive HER2-negative metastatic breast cancer, Front. Oncol. 10 (2020), https://doi.org/10.3389/fonc.2020.550185.
[18] D. Viotto, F. Russo, I. Anania, I. Segatto, G. Rampioni Vinciguerra, A. Dall'Acqua, et al., <scp>*CDKN1B* </scp>mutation and copy number variation are associated with tumor aggressiveness in luminal breast cancer, J. Pathol. 253 (2021) 234–245, https://doi.org/10.1002/path.5584.
[19] P. Rebora, A. Salim, M. Reilly, Bshazard: A flexible tool for nonparametric smoothing of the hazard function, R. J. 6 (2014) 114, https://doi.org/10.32614/RJ-2014-028.
[20] F. Dalenc, A. Lusque, T. De La Motte Rouge, B. Pistilli, E. Brain, D. Pasquier, et al., Impact of lobular versus ductal histology on overall survival in metastatic breast cancer: a French retrospective multicentre cohort study, Eur. J. Cancer 164 (2022) 70–79, https://doi.org/10.1016/j.ejca.2021.12.031.
[21] Y. Wong, P. Jagmohan, Y. Goh, T. Putti, S. Ow, Y. Thian, et al., Infiltrative pattern of metastatic invasive lobular breast carcinoma in the abdomen: a pictorial review, Insights. ImAging 12 (2021) 181, https://doi.org/10.1186/s13244-021-01120-4.
[22] U. Petrausch, B.C. Pestalozzi, Distinct clinical and prognostic features of invasive lobular breast cancer, Breast. Dis. 30 (2009) 39–44, https://doi.org/10.3233/BD-2009-0280.
[23] D. Lobbezoo, R. van Kampen, A. Voogd, M. Dercksen, F. van den Berkmortel, T. Smilde, et al., Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-positive subtype is associated with the most favorable outcome, Breast. Cancer Res. Treat. 141 (2013) 507–514, https://doi.org/10.1007/s10549-013-2711-y.
[24] Z. Chen, J. Yang, S. Li, M. Lv, Y. Shen, B. Wang, et al., Invasive lobular carcinoma of the breast: a special histological type compared with invasive ductal carcinoma, PLoS One 12 (2017) e0182397, https://doi.org/10.1371/journal.pone.0182397.
[25] K. Van Asten, L. Slembrouck, S. Olbrecht, L. Jongen, O. Brouckaert, H. Wildiers, et al., Prognostic value of the progesterone receptor by subtype in patients with estrogen receptor-positive, HER-2 negative breast cancer, Oncologist 24 (2019) 165–171, https://doi.org/10.1634/theoncologist.2018-0176.
[26] Y. Li, D. Yang, X. Yin, X. Zhang, J. Huang, Y. Wu, et al., Clinicopathological characteristics and breast cancer–Specific survival of patients with single hormone receptor–Positive breast cancer, JAMA Netw. Open. 3 (2020) e1918160, https://doi.org/10.1001/jamanetworkopen.2019.18160.
[27] A. Mariotto, A. Noone, N. Howlader, H. Cho, G.E. Keel, J. Garshell, et al., Cancer survival: an overview of measures, uses, and interpretation, JNCI Monogr. 2014 (2014) 145–186, https://doi.org/10.1093/jncimonographs/lgu024.
[28] J. Dignam, L. Huang, L. Ries, M. Reichman, A. Mariotto, E. Feuer, Estimating breast cancer-specific and other-cause mortality in clinical trial and population-based cancer registry cohorts, Cancer 115 (2009) 5272–5283, https://doi.org/10.1002/cncr.24617.
[29] R. Clarke, J.J. Tyson, J.M. Dixon, Endocrine resistance in breast cancer–an overview and update, Mol. Cell Endocrinol. 418 (Pt 3) (2015) 220–234, https://doi.org/10.1016/j.mce.2015.09.035.
[30] J. Bauml, A. Troxel, C. Epperson, R. Cohen, K. Schmitz, C. Stricker, et al., Scan-associated distress in lung cancer: quantifying the impact of "scanxiety, Lung Cancer 100 (2016) 110–113, https://doi.org/10.1016/j.lungcan.2016.08.002.
[31] F. Bidard, A. Hardy-Bessard, F. Dalenc, T. Bachelot, J. Pierga, T. de la Motte Rouge, et al., Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial, Lancet Oncol. 23 (2022) 1367–1377, https://doi.org/10.1016/S1470-2045(22)00555-1.
[32] F. Bidard, E. Mayer, Y. Park, W. Janni, C. Ma, M. Cristofanilli, et al., First-line camizestrant for emerging ESR1 -mutated advanced breast cancer, N. Engl. J. Med. 393 (2025) 569–580, https://doi.org/10.1056/NEJMoa2502929.
[33] S. Moharamipour, M. Aminifar, M. Foroughi-Gilvaee, P. Faranoush, R. Mahdavi, H. Abadijoo, et al., Hydroelectric actuator for 3-dimensional analysis of electrophoretic and dielectrophoretic behavior of cancer cells; suitable in diagnosis and invasion studies, Biomater. Adv. 151 (2023) 213476, https://doi.org/10.1016/j.bioadv.2023.213476.