



Fulvestrant and trastuzumab in patients with luminal HER2-positive advanced breast cancer (ABC): an Italian real-world experience (HERMIONE 9)

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Abstract

Purpose The most appropriate therapy for HR + /HER2-positive (HER2+) advanced breast cancer (ABC) is a matter of debate. Co-targeting of both receptors represents an attractive strategy to overcome the cross-talk between them.

Methods The HERMIONE 9 is an observational retrospective multicentric study which aimed to describe the clinical outcome of patients with HR + /HER2 + ABC who received the combination of Fulvestrant (F) and Trastuzumab (T) as part of their routine treatment at 10 Italian Institutions.

Results Eighty-seven patients were included. Median age was 63 (range, 35–87) years. The median number of previous treatments was 3 (range, 0–10) and F and T were administered as ≥ 3 rd line in 67 patients. Among the 86 evaluable patients, 6 (6.9%) achieved CR, 18 (20.7%) PR, and 44 (50.6%) had SD ≥ 24 weeks with an overall CBR of 78.2%. At a median follow-up of 33.6 months, mPFS of the entire cohort was 12.9 months (range, 2.47–128.67). No difference was observed in mPFS between patients treated after progression or as maintenance therapy (mPFS 12.9 and 13.9 months in 64 and 23 patients, respectively), neither considering the number of previous treatment lines (≤ 3 or < 3).

Conclusion The combination of F and T was active in this cohort at poor prognosis and deserves further investigations possibly in combination with pertuzumab in patients with high ER expression.

Keywords Trastuzumab · Fulvestrant · Hormone receptor positive · HER2 positive · Advanced breast cancer

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Introduction

Gene expression studies have clearly demonstrated in recent years that HER2-positive (HER2+) breast cancer is a heterogeneous disease [1]. Approximately, 50% of HER2+ tumors are hormone receptor positive (HR+) at immunohistochemistry (IHC) [2]

However, only one half of HER2+ tumors at IHC correspond to the HER2-enriched subtype as defined by gene expression profiling, and within the latter subtype significant molecular differences were observed according to the HR expression [3]

However, these immunohistochemical and molecular differences do not translate in different therapeutic strategies for treatment of HR+/HER2+ tumors which routinely include chemotherapy and anti-HER2 agents [4]. Preclinical evidence suggesting that HER2 overexpression was associated with endocrine resistance [5], further confirmed by the poor results of earlier studies investigating a chemotherapy-free regimen in advanced HR+/HER2+ tumors [6, 7], supported an unique treatment strategy including chemotherapy plus anti-HER2 therapy irrespective of HR status [5]. However, results from neoadjuvant trials and from the advanced setting clearly indicated less sensitivity of luminal HER2+ tumors to this approach probably due to a bidirectional cross-talk between the two driver receptors, estrogen and HER2 [8–11]. Co-targeting of both receptors appears thus an attractive strategy to overcome the resistance due to this cross-talk [12].

The availability of fulvestrant which internalizes ER after binding, leading to a more complete abolishment of the estrogen signaling with respect to aromatase inhibitors, might represent an attractive targeted partner for a full HR/HER2 blockade [13]. A synergistic effect between fulvestrant and trastuzumab in inhibiting growth in cell lines and xenografts has been shown, but only a few *in vivo* data are available on the combination [14].

In the present retrospective observational study we report a real-world series of patients with HR+/HER2+ advanced breast cancer (ABC) treated with the combination of fulvestrant and trastuzumab and analyze possible predictive factors of its effectiveness.

Patients and methods

The HERMIONE 9 is an observational retrospective multicentric study which aimed to describe the clinical outcome of patients with HR+/HER2+ ABC who received the combination of fulvestrant and trastuzumab as part of

their routine treatment at 10 Italian Institutions participating to the HERMIONE platform.

Eligible patients were pre- and postmenopausal women aged ≥ 18 years diagnosed with HR+ (defined as ER and/or PgR $\geq 10\%$) and HER2+ (defined as IHC 3+ or FISH or CISH or SISH positive) inoperable locally advanced and/or metastatic breast cancer. Premenopausal patients received concomitant ovarian suppression with GnRH analogues. Fulvestrant+trastuzumab were administered as any line of treatment. Fulvestrant was administered 500 mg *i.m.* q28 days with loading dose after 14 days; trastuzumab was administered q21 days either as 8 mg/kg loading dose and then 6 mg/kg *i.v.* infusion or 600 mg *s.c.*, according to the internal institutional guidelines.

Patient medical charts were reviewed and tumor response was assessed. Since this is a retrospective study response could not be evaluated according to RECIST 1.1 criteria in all patients, but CT scans and other imaging were reviewed in order to comply with RECIST criteria whenever possible.

Information on age at diagnosis, menopausal status, previous adjuvant therapies, number of previous therapies for metastatic disease, number and response to previous therapies for metastatic disease, pathological features of primary and metastatic tumor if available, sites of metastatic disease, best response, and disease progression if occurred, and last follow-up visit were collected.

This study was approved by the institutional ethical committee of the coordinating center (Humanitas Research Hospital) and of all the other participating Institutions and was conducted in compliance with Helsinki Declaration.

Statistical analysis

Clinical data were summarized as frequencies and proportions or as medians and range. To assess the tumor heterogeneity, we calculated the agreement in the tumor biological profile between primary and metastatic sites in terms of ER, PgR, and HER2 expression using Cohen's K statistics. Response to treatment was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 whenever possible. Clinical Benefit Rate (CBR) was defined as the percentage of patients who achieved CR, PR, and SD ≥ 24 weeks. Survival curves were estimated using the Kaplan–Meier method. Progression-Free Survival (PFS) was defined as the time from the first day of fulvestrant+trastuzumab until disease progression, as shown by radiological or clinical examination, or death from any cause. Patients without any evidence of progressive disease were censored at the date of their last follow-up. PFS curves were analyzed according to disease status at fulvestrant+trastuzumab start, early versus later fulvestrant+trastuzumab line of treatment,

the type of previous therapy, and HR status. Differences among subgroups were evaluated using the log-rank test.

Statistical significance was set at 0.05. Analyses were performed with the STATA software package, version 15 and with STATISTICA version 7, StatSoft, Inc.

Results

From August 2005 to March 2021 a total of 87 patients were treated with the combination of fulvestrant + trastuzumab at the 10 participating Institutions.

Median age was 63 years (range, 35–87). Clinical pathological patients' characteristics are reported in Table 1. Thirty-one percent (27/87) of the patients were diagnosed with de novo metastatic breast cancer; in recurrent ABC (60/87, 69%), median time to metastatic disease was 57.1 months (range, 7.0–330.5).

A biopsy of metastatic site was available in 48 out of 87 patients (45.9%); biological characteristics of metastases were concordant with those of primary tumors except for PgR expression which was significantly lower ($p=0.02$). As a consequence, 59 patients (67.8%) had triple-positive tumors as determined in the primary tumor while in metastatic biopsies only 22 /45 (49%) metastatic tumors were triple positive.

The median number of previous treatments (both chemotherapy ± trastuzumab and endocrine therapy + trastuzumab) for advanced disease was 3 (range, 0–10). Fulvestrant + trastuzumab were administered as ≥ 3 line in 67 patients. All patients had received trastuzumab previously while only 19% of patients had not received prior endocrine therapy for ABC.

Twenty-three patients started fulvestrant + trastuzumab as maintenance treatment while 64 patients had progressed upon the previous regimen (20 patients after endocrine therapy + trastuzumab, 22 after anti-HER2 agents + chemotherapy, and 20 after chemotherapy).

The median duration of fulvestrant + trastuzumab treatment was 11.5 months (range, 2.03–128.67). Trastuzumab was administered i.v. (57/87, 65.52%), or s.c. (15/87, 17.24%), or both (11/87, 12.64%); the data were not available in 4 cases.

Eight-six patients were evaluable for response: 6 patients achieved CR (6.9%), 18 patients (20.7%) PR, and 51 patients (58.6%) SD—of whom 44 patients (50.6%) had SD ≥ 24 weeks. Overall, the CBR was 78.2%. At a median follow-up of 33.6 months (range, 2.47–139.27), mPFS of the entire cohort was 12.9 months (range, 2.47–128.67; Fig. 1). A shorter time to progression (TTP) was observed during the treatment immediately preceding fulvestrant + trastuzumab (7.62 months, range, 2.0–98.9). No statistically significant difference was observed in mPFS in patients treated after

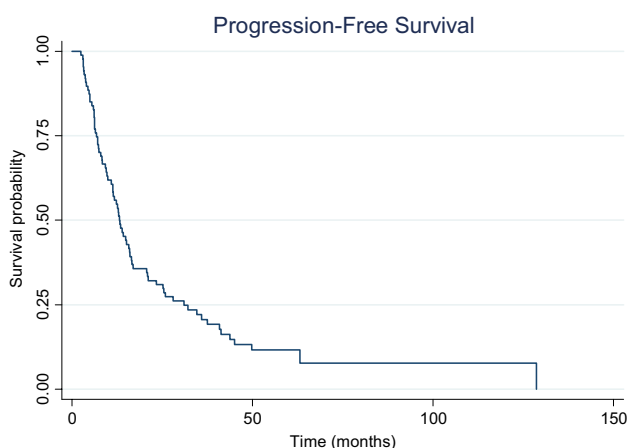
Table 1 Baseline patient and disease characteristics

Median age, years (range)	63 (35–87)
De novo mBC, n (%)	27 (31.03)
Menopausal status, n (%)	
Pre-menopausal	24 (27.59)
Post-menopausal	60 (68.96)
Unknown	3 (3.45)
pT, n (%)	
1	26 (29.88)
2	27 (31.03)
3	7 (8.05)
4	4 (4.60)
x	23 (26.44)
pN, n (%)	
0	18 (20.69)
1	27 (31.03)
2	10 (11.49)
3	10 (11.49)
x	22 (25.30)
HR status, n (%)	
ER +/PgR +	59 (67.81)
ER +/PgR –	24 (27.59)
ER –/PgR +	0 (0.0)
ER –/PgR –	4 (4.60)
Median (range) %ER + staining	70 (20–100)
Median (range) %PgR + staining	50 (10–80)
HER2 status, n (%)	
Positive	82 (94.25)
Negative	4 (4.60)
Unknown	1 (1.15)
Adjuvant CT, n (%)	
Yes	45 (51.72)
No	36 (41.38)
Unknown	6 (6.90)
Adjuvant trastuzumab, n (%)	
Yes	25 (28.73)
No	54 (62.07)
Unknown	8 (9.20)
Adjuvant ET, n (%)	
Yes	52 (59.77)
No	29 (33.33)
Unknown	6 (6.90)
Metastatic sites	
Bone-only	15 (17.24)
Visceral	50 (57.47)
Other	22 (25.29)
Prior lines of therapy CT, n (%)	
0	23 (26.44)
1	20 (22.99)
2	15 (17.24)
≥ 3	29 (33.33)

Table 1 (continued)

Median age, years (range)	63 (35–87)
Prior lines of therapy ET, <i>n</i> (%)	
0	16 (18.39)
1	51 (58.62)
2	17 (19.55)
3	3 (3.44)
Last treatment before F + T, <i>n</i> (%)	
CT + trastuzumab	23 (26.43)
ET + trastuzumab	20 (22.99)
T DM1	8 (9.20)
Lapatinib + capecitabine	4 (4.60)
CT	12 (13.79)
Trastuzumab	1 (1.15)
ET	10 (11.49)
Clinical trial	1 (1.15)
Unknown	8 (9.20)

HR hormone receptor, ER estrogen receptor, PgR progesterone receptor, CT chemotherapy, ET endocrine therapy, F fulvestrant, T trastuzumab

**Fig. 1** Progression-free survival in the overall population

progression to a previous line or as maintenance (mPFS 12.9 and 13.9 months, respectively; $p=0.67$), neither considering the number of previous treatment lines (≤ 3 or < 3) ($p=0.34$), the type of previous therapy (chemotherapy or endocrine therapy), or triple positive vs single HR expression overall ($p=0.22$).

Discussion

In the era of tailored treatments the most appropriate therapy of HR +/HER2 + BC is a matter of debate. While showing less responsiveness to the combination of chemotherapy plus anti-HER2 agents as compared to the HR negative

counterpart, results with the combination of anti-HER2 agents and non-steroidal aromatase inhibitors (NSAI) have been quite disappointing with a mPFS not exceeding 4.8 months with trastuzumab and anastrozole and 8.2 months with lapatinib and letrozole as first-line treatment [6, 7]. The recently updated ALTERNATIVE trial, which investigated the addition of lapatinib, trastuzumab, or both agents to a NSAI, showed a significant improvement in mPFS for the double HER2 blockade vs trastuzumab plus NSAI (11 vs 5.6 months) [15]. On the other hand the PERTAIN trial reported a mPFS of 21.7 months in the arm with the double HER2 blockade with pertuzumab and trastuzumab plus a NSAI, which was not only significantly higher than that reported by the trastuzumab plus NSAI combination but, more importantly, was similar to that reported in patients who had received chemotherapy before endocrine therapy (mPFS = 18.9 months) [16]. The relative small number of patients (54) and the non-randomized assignment to the chemotherapy/no chemotherapy arms leading to a smaller proportion of patients with poor prognostic features in the latter arm, do not allow to qualify the chemotherapy-free combination as a standard first-line treatment for HR +/HER2 + ABC, but clearly represents a strong rationale for further studies to identify which patients may be spared unnecessary chemotherapy [16].

Fulvestrant was proven superior to NSAI in patients with HR +/HER2—ABC [17] and has been considered as favorite anti-ER partner in combination with other targeted therapies in HR +/HER2 + breast cancer (Na-PHer2, MonarcHER), despite the lack of clinical data of the activity of this combination [18, 19]. Fulvestrant monotherapy showed an encouraging activity in a retrospective study in 102 pretreated patients with HR +/HER2 + ABC with a CBR of 42% and a median duration of treatment of 8.1 months, which raised to 14.5 months in patients achieving clinical benefit. Among them only 5 patients had received concurrent trastuzumab [20]. Bartsch et al. reported outcomes of 112 patients with HR + tumors treated with Fulvestrant 20 of whom had HR +/HER2 + tumors and HER2 status did not predict treatment efficacy [21]. Ruzs et al. reported a durable benefit (12, 25, and 28 months) with Fulvestrant monotherapy in 3 pretreated patients with triple-positive ABC [22]. The SystHER, an observational prospective registry study reporting tumor characteristics, treatment patterns, and outcome of patients with HER2 + ABC treated in the USA from 2012 to 2016, included 46 patients who received Fulvestrant but no further information on the setting and outcome is available yet [23].

To our knowledge this is the first report of the combination of fulvestrant + trastuzumab in a clinically relevant number of patients. We observed a mPFS of 12.9 months and a CBR of 78% which favorably compare with those previously reported by the combination of a NSAI and trastuzumab

even when administered in earlier lines [6, 7, 15, 16]. Only the addition of pertuzumab gained a superior mPFS in the PERTAIN study [16]. As expected, our results favorably compare also with those obtained with single agent Fulvestrant, particularly in terms of CBR [20–22].

Remarkably, 77% of our patients had been treated with ≥ 3 previous therapies for metastatic disease, 73% started fulvestrant + trastuzumab after progression to a previous regimen, and more than 50% had visceral disease. The short TTP (7.5 months) observed with the treatment preceding the fulvestrant + trastuzumab combination confirms that our unselected population represented a really poor prognosis cohort.

Fulvestrant was administered as first-line endocrine therapy only in 19% of patients but its activity did not seem to be affected by prior endocrine resistance since the patients (20) who had progressed on endocrine therapy + trastuzumab had a mPFS of 14.26 months (4.37–119.93), thus maintaining responsiveness to a different endocrine manipulation. On the other hand, also patients progressing after a chemotherapy containing regimen experienced an mPFS of 12.73 months (range 3.07–59.57); in both cohorts the mPFS was significantly longer than the TTP obtained with the preceding therapy underlining the activity of the combination irrespective of prior treatments.

Despite the benefit of endocrine maintenance therapy has not been formally investigated in a randomized trial, evidence from PERTAIN and real-world reports support the efficacy of a sustained blockade of the ER signaling in HR + /HER2 + breast cancer [25, 26]. Our results reporting a mPFS of 13.9 months in patients who received maintenance fulvestrant are in line with these reports.

Interestingly, in our study triple-positive tumors did not fare better than single HR-positive tumors. Triple-positive breast cancer, which accounts for 5–10% of all breast cancers, might represent a distinct subtype among luminal HER2 breast cancer with more exquisite endocrine sensitivity. [27]. However, triple-positive breast cancer has been described as a heterogeneous population. A genomic analysis of 5 cohorts of triple-positive breast cancer showed lower levels of HER2 mRNA and protein expression than ER and PgR positive/HER2 + breast cancers. More than 40% of triple-positive breast cancers were classified as the luminal A intrinsic subtype, with an even lower HER2 expression level and were associated with a better prognosis and a reduced benefit from trastuzumab [28]

In a large retrospective series of 872 patients Vici et al. showed a significant interaction between HR expression and trastuzumab benefit since patients with triple positive tumors and HR > 50% gained a modest benefit from adjuvant anti-Her2 treatment [29]. In our series ER status maintained a predictive role, while PgR was not associated with response. The loss of PgR, which may be also attributable to previous

endocrine treatment, apparently did not represent a feature of endocrine resistance, as suggested by its lower expression in metastatic sites without affecting treatment efficacy.

A reduced benefit of the combination of chemotherapy and trastuzumab in the adjuvant setting was shown in a retrospective analysis of the National Cancer Database among 37777 stage I luminal HER2 + breast cancer. A large proportion had received only the combination of endocrine therapy and trastuzumab and had an improved overall survival as compared with patients who were treated with chemotherapy and trastuzumab [30].

Fulvestrant has been chosen as preferred endocrine partner in combination with anti-HER2 agents and CDK4/6 inhibitors either in the early and advanced setting [18, 19]. In the phase II Na-PHER2 study the combination of pertuzumab, trastuzumab, fulvestrant, and palbociclib achieved an objective response and a pathological complete response in 97 and 27% of patients with large HR + /HER2 + tumors, respectively [18].

The MonarcHER study randomized the combination of fulvestrant, trastuzumab and abemaciclib vs trastuzumab, and abemaciclib vs trastuzumab plus chemotherapy in heavily pretreated HR + /HER2 + ABC [19]. The triple targeted regimen resulted in a mPFS of 8.3 months significantly higher than that obtained with chemotherapy, suggesting a benefit of the addition of the blockade of the CDK4/6 pathway. The lack of an arm containing fulvestrant and trastuzumab has represented the major criticism to these results since this did not allow to evaluate the net benefit of the CDK4/6 inhibitor.

These results, along with other indirect evidence, suggest that at least a proportion of luminal HER2 + breast cancer may experience a favorable outcome without chemotherapy.

We are aware of several limitations of our real-world study as compared with prospective trials. First of all the retrospective design which may have not allowed to meet with a strict application of RECIST 1.1 criteria in all the patients. In addition the majority of our patients had not received pertuzumab in earlier lines and this may have led to the inclusion of a relatively less resistant cohort. Finally, given the multicentric design, the sequence of treatments varied among the different Hospitals and might have interfered with the results obtained especially with the definition of predictive factors of efficacy.

Despite these limitations, our results provide a piece of evidence in the refinement of the optimal treatment of HR + /HER2 + breast cancer. Our results suggest that the combination of fulvestrant and trastuzumab is active and may deserve further investigations, possibly in combination with pertuzumab and in patients with high ER expression. Patients with de novo HR + /HER2 + ABC, who represent 30% to 50% of patients receiving first-line treatment, generally experience better outcome as compared with those

with recurrent ABC [24]. For instance, it would be interesting to test this combination \pm CDK4/6 inhibitors vs the chemotherapy containing triplet in this population at better prognosis to understand whether the algorithm of treatment of HER2 + breast cancer may be tailored according to the HR status.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by RT, RP, RdS, PV, GB, LC, VL, RG, AF, MRV, ARG, BT, and LP. The first draft of the manuscript was written by RT and all authors revised all the versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Rosalba Torrisi: Astra Zeneca, Eisai, Pfizer, Eli Lilly, and Gentili. Rita De Sanctis Novartis, Amgen, Kyowa Kirin, and Eisai. Patrizia Vici: Roche, Pfizer, Novartis, Gentili, Eli Lilly, and Eisai. Giulia Valeria Bianchi: Eli Lilly and Novartis. Laura Cortesi: Novartis, Amgen, Astra Zeneca, and Pfizer. Laura Pizzuti Roche, Pfizer, Novartis, Gentili, and Eisai. Marina Elena Cazzaniga: Astra Zeneca, Novartis, Eli Lilly, Eisai Pierre Fabre, and Roche. Armando Santoro BMS, Servier, Gilead, Pfizer, Eisai, Bayer, MSD, Takeda, Roche, Astra Zeneca, Pfizer, Eli Lilly, Novartis, Aqule, Sandoz, and Abb-Vie.

Ethical approval The study was approved by the Ethical Committees of all the participating Institutions. The study was conducted in compliance with Helsinki Declaration.

Consent to participate All patients provided written consent for the use of their anonymized clinical data for scientific purpose.

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