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Therapeutic Patterns and Survival Outcomes in 939 HER2-Negative Metastatic Breast Cancer Patients: 10-Year Results from the Italian GIM 13-AMBRA Cohort

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ABSTRACT

The GIM 13-AMBRA project is a longitudinal cohort investigation designed to report on treatment patterns and associated outcome metrics in 939 patients with HER2-negative metastatic breast cancer (MBC). In both Luminal (30.2%) and TNBC (33.3%) groups, first-line care most often involved taxane-based therapy, either alone or with targeted agents—most commonly Bevacizumab. The median PFS1 reached 12.5 months (95% CI 16.79-19.64), showing no subtype-related differences. In contrast, the median TTC1 was markedly shorter in the TNBC cohort (7.7 months, 95% CI 5.7-9.2) compared with Luminal A (13.2 months, 95% CI 11.7-15.1) and Luminal B (11.8 months, 95% CI 10.3-12.8). PFS2 was also reduced in TNBC (5.5 months, 95% CI 4.3-6.5) versus Luminal A (9.4 months, 95% CI 8.1-10.7) and Luminal B (7.7 months, 95% CI 6.8-8.2; F-ratio 4.30, p = 0.014). TTC2 followed the same pattern, with shorter intervals observed in TNBC. Median OS1 for Luminal A patients was 35.2 months (95% CI 30.8-37.4), surpassing Luminal B (28.9 months, 95% CI 26.2-31.2) and TNBC (18.5 months, 95% CI 16-20.1; F-ratio 7.44, p = 0.0006). As one of the most extensive Italian datasets, GIM 13-AMBRA provides valuable real-world evidence concerning timing outcomes across multiple chemotherapy lines in HER2- MBC.

Keywords: Metastatic breast cancer, HER2-negative, Progression-free survival, Time to treatment change, Overall survival

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Introduction

Breast cancer (BC) remains the primary cause of cancer mortality among women globally [1]. Data on stage and regional distribution [2] indicate that, in Italy, around 55, 000 new cases and 13, 000 deaths occur annually [3]. Even with advances in management of localized disease, approximately 30% of BC patients eventually experience distant spread [4, 5]. The clinical evolution of MBC varies greatly in growth kinetics and responsiveness to systemic therapy, and treatment is palliative, with median survival for certain subgroups approaching 2 years. No uniform chemotherapy approach exists for HER2-negative tumors, which account for 80-85% of BC cases [5]. The only prior Italian real-world analysis—the IRIS project [6]—monitored 539 metastatic cases treated between 1999 and 2001. Although randomized clinical trials (RCTs) define the effectiveness and safety of emerging regimens, their strict inclusion rules limit applicability to the broader MBC population. Standard endpoints such as Progression-Free Survival (PFS) rely on predetermined assessment moments and therefore are not directly suited for observational research. The GIM 13-AMBRA cohort was established to document real-world management of HER2- MBC across Italy. Its principal goal was to outline systemic therapy choices across first and later chemotherapy (CHT) lines and to analyze associated timing variables—including Time to Treatment Change (TTC)—as potential pragmatic alternatives to PFS in observational settings.

Materials and Methods

Study design

GIM 13-AMBRA is a longitudinal cohort that enrolled the first 50 consecutive HER2- MBC patients initiating first-, second-, or later-line CHT between January 2012 and December 2016. Forty-two sites were chosen from 192 national oncology units listed in the Libro Bianco 2012 of the Italian Association of Medical Oncology (AIOM), with selection based on institutional characteristics and geographic representation. Eligible participants were women aged 18+ with newly diagnosed MBC who provided written informed consent. All centers obtained approval from their respective Ethical Committees following authorization by the Coordinating Center EC (CE Brianza).

Objectives

The main aim was to summarize therapeutic decisions across first and subsequent chemotherapy lines in patients receiving at least one CHT course, along with the associated outcomes. Secondary aims included:

1. Examining relationships between treatment selection—either in the adjuvant or metastatic setting—and patient factors (age, menopausal status, comorbidities);
2. Characterizing recurrence features and key clinical endpoints (TTC, PFS, OS);
3. Assessing alignment with published guidance on treatment sequencing.

This report presents findings related to the primary objective.

Definitions

HER2 and hormone-receptor (HR) status were taken from pathology evaluations of the primary tumor or, for de novo cases, from metastatic tissue. Intrinsic subtypes followed classifications described by Prat *et al*. [7, 8].

Statistical analysis

The primary endpoint involved describing regimen selection; categorical variables were expressed as frequencies and percentages. Clinical outcomes included Disease-Free Survival (DFS)—time from initial diagnosis to death—and PFS1/PFS2, defined as the interval from start of first- or second-line therapy to documented progression or latest follow-up. TTC1/TTC2 represented the period from initiation of first or second-line therapy to commencement of the next treatment line, with no fixed assessment time due to the study's observational structure. OS was measured from the date of metastatic diagnosis to death from any cause or last contact. Kaplan-Meier methods were used for time-to-event estimation, with Fisher's exact test applied where required. Analyses were performed using NCSS® 12 (2018). Continuous variables were summarized via standard descriptive metrics (n, mean, SD, median, minimum, 25th/75th percentiles, maximum). The F-ratio—between-group variance divided by within-group variance—was applied to evaluate group differences. All data, including demographics, tumor features, outcomes, and treatments, were recorded on a dedicated electronic platform. With roughly 15, 000 new MBC diagnoses annually in Italy, a cohort of 1000 cases is sufficient to mirror national patterns; one year of follow-up was expected to capture both primary and secondary outcomes.

Results and Discussion

From May 2015 to September 2020, the study accrued 1071 participants, but 132 (12.3%) could not be analyzed due to missing first-line treatment details or other exclusion conditions. At the time of initial breast cancer diagnosis, the median age was 51.9 years (range 50.6-52.9).

Across the three molecular groups, age at presentation and stage distribution showed no relevant variations. A substantial proportion underwent adjuvant chemotherapy (71.8%), most commonly anthracycline combined with taxanes (305; 31.5%) or anthracycline paired with non-taxane agents (266; 28.3%). Among Luminal A cases, 261 (67.6%) received adjuvant CHT, usually an anthracycline-based regimen (125; 32.4%), whereas TNBC cases most often received anthracycline-taxane schedules (305; 31.5%) **(Table 1)**.

Table 1. Adjuvant treatments by subtype.

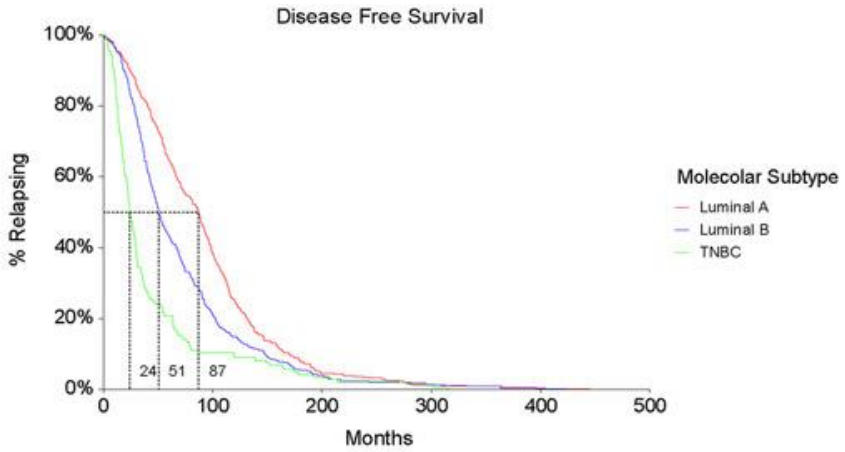
	Luminal A (N = 386)	**Luminal B (N = 408)**	**TNBC (N = 145)**	**All Patients (N = 939)**
None	13 (3.4%)	13 (3.2%)	14 (9.6%)	939

Endocrine therapy alone	112 (29.0%)	91 (22.3%)	0	203 (20.7%)
CHT + ET	245 (63.5%)	279 (68.4%)	4 1	528 (53.9%)
CHT regimens				
Anthracycline-based	125 (32.4%)	109 (26.7%)	32 (22.1%)	266 (28.3%)
Anthracycline + Taxanes	93 (24.1%)	137 (33.6%)	75 (51.7%)	305 (31.5%)
taxanes 2	4 (1.0%)	16 (3.9%)	7 (4.8%)	27 (2.9%)
CMF	38 (9.8%)	40 (9.8%)	16 (11.0%)	94 (10.0%)
Others	1	2	1	4

[1] Four individuals with ER/PgR <5% received ET.

[2] Taxane-containing regimens are grouped separately from anthracycline-based ones.

The overall median DFS was 57.2 months (95% CI 53.2-63.8). DFS reached 87 months in Luminal A (95% CI 75.3-91.7), notably longer than in Luminal B (50.7 months, 95% CI 46.4-56.5; HR 0.71 (0.62-0.82)) and in TNBC (24.3 months, 95% CI 21.6-29.2; TNBC vs Luminal A HR 2.22 (1.74-2.83); TNBC vs Luminal B HR 1.74 (1.39-2.17)) **(Figure 1; Table 2)**.



Months -> Nr at risk	30	60	90	120	150	180	210	240	270	300	330	360	390
Lum A	334	250	182	97	53	31	18	13	9	5	3	3	2
Lum B	315	176	110	60	38	22	11	10	9	5	4	3	2
TNBC	57	30	15	13	11	6	4	3	3	2	0	0	0

Figure 1. DFS by subtype.

Table 2. DFS hazard ratios/log-rank outcomes.

	Cox Mantel HR (95% CI)	**Cox Mantel Logrank Test Chi²**
Luminal A vs. Luminal B	0.71 (0.62-0.82)	23.15
TNBC vs. Luminal A	2.22 (1.74-2.83)	70.59
TNBC vs. Luminal B	1.74 (1.39-2.17)	33.62

Information on initial recurrence sites was available for 922 of 939 (98.2%) individuals. Luminal A predominantly relapsed in the bone (31.9%), whereas Luminal B showed a more dispersed pattern involving bone (24.0%), bone + visceral sites (20.8%), and viscera alone (23.5%) **(Table 3)**.

Table 3. Relapse distributions by subtype.

	Luminal A (N = 386)	**Luminal B (N = 408)**	**TNBC (N = 145)**	**All Patients (N = 939)**
Bone	123 (31.9%)	98 (24.0%)	9 (6.2%)	230 (30.4%)
Bone + soft tissue	21 (5.4%)	22 (5.4%)	7 (4.8%)	50 (6.6%)
Viscera	84 (21.8%)	96 (23.5%)	39 (26.9%)	219 (28.9%)
Viscera + soft tissue	29 (7.5%)	33 (8.1%)	23 (15.9%)	85 (11.2%)
Viscera + bone	68 (17.6%)	85 (20.8%)	13 (8.9%)	166 (17.7%)

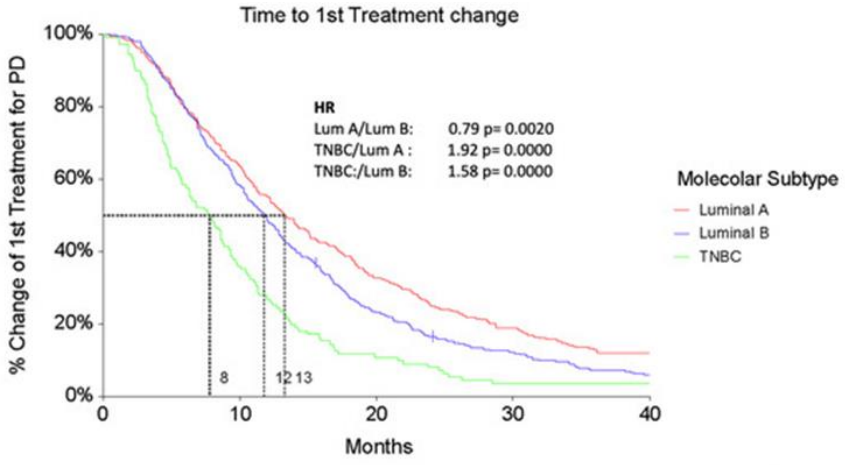
Soft tissue	53 (13.7%)	62 (15.2%)	46 (31.7%)	161 (21.3%)
Other	4 (1.0%)	3 (0.7%)	1 (0.6%)	4 (0.5%)
Not specified	17			

For first-line metastatic therapy, most Luminal patients received endocrine therapy alone (42%) or CHT followed by ET (29.2%). Taxane-centered regimens, with or without targeted drugs (most often Bevacizumab), were the leading option in both Luminal (30.2%) and TNBC (33.3%) **(Table 4)**.

Table 4. First-line approaches across subtypes.

	Luminal A & B (N = 460) (%)	**TNBC (N = 141) (%)**
ET alone	334 (42%)	0
Chemo + ET	232 (29.2%)	0
Chemotherapy regimens		
Capecitabine +/− Vinorelbine	82 (17.8)	24 (17.02)
Paclitaxel + Bevacizumab	139 (30.2)	47 (33.33)
Platinum-based	23 (5)	25 (17.7)
Anthracycline-based	44 (9.5)	5 (3.5)
Anthracycline + Taxanes	19 (4.13)	2 (1.4)
Taxanes	133 (28.9)	22 (15.6)
CMF	4 (0.8)	7 (4.9)
Other	16 (3.4)	9 (6.3)

Regarding toxicity, Grade 3 AEs peaked during the initial cycle (11.0%) and declined thereafter. Grade 4 events were uncommon, with a maximum incidence of 0.72% among patients treated for more than six cycles.
The median PFS1 was 12.5 months (95% CI 16.79-19.64), with no subtype-related difference (Luminal A 18.03 months, Luminal B 15.95 months, TNBC 14.04 months). In contrast, TTC1 was markedly shorter in TNBC (7.7 months, 95% CI 5.7-9.2) than in Luminal A (13.2 months, 95% CI 11.7-15.1) or Luminal B (11.8 months, 95% CI 10.3-12.8) **(Figure 2)**.

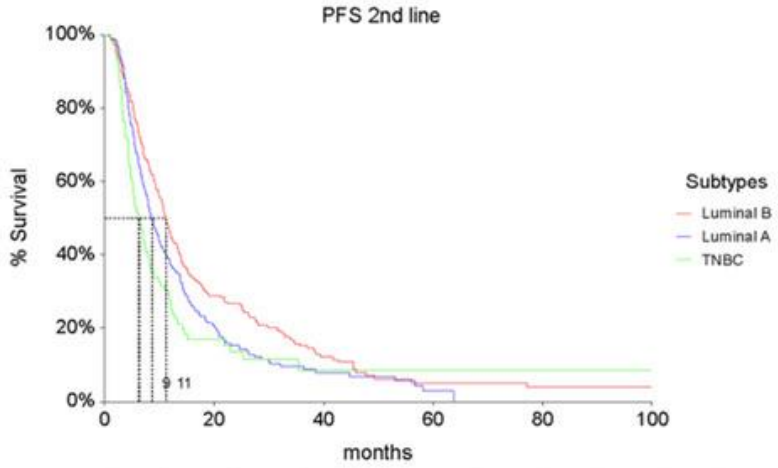


Months -> Nr at risk	9	18	27	36	45	54	63	72	81	90	99	108	117
Lum A	213	123	69	41	32	24	17	14	12	12	12	10	7
Lum B	217	92	44	24	15	9	4	3	3	3	3	2	2
TNBC	46	13	5	4	4	2	2	2	1	1	1	1	0

Figure 2. TTC1 across subtypes.

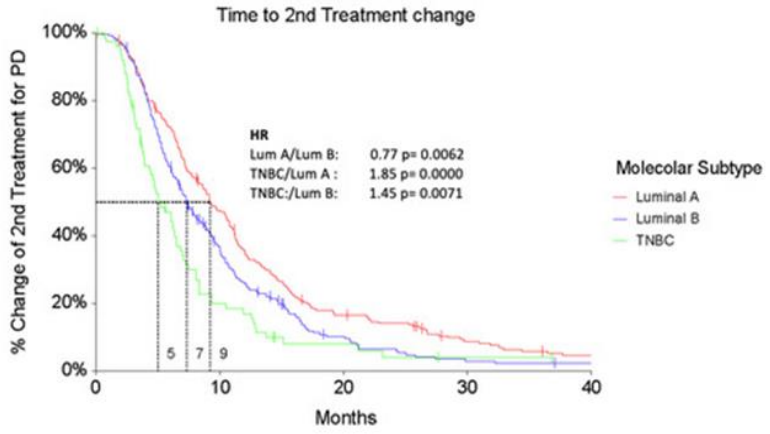
Second-line treatment patterns diverged considerably: Luminal A/B cases frequently received endocrine therapy (29%) or, if given chemotherapy, Capecitabine ± Vinorelbine. TNBC, on the other hand, was mainly treated with

platinum-based options (22.4%) or Capecitabine ± Vinorelbine (21%). PFS2 was shortest for TNBC (5.5 months, 95% CI 4.3-6.5) versus Luminal A (9.4 months, 95% CI 8.1-10.7) and Luminal B (7.7 months, 95% CI 6.8-8.2) (F-ratio 4.30, p = 0.014). TTC2 demonstrated the same pattern **(Figures 3-4)**.



Months -> Nr at risk	9	18	27	36	45	54	63	72	81	90	99	108	117
Lum A	174	78	42	23	12	7	5	4	2	2	2	2	2
Lum B	148	54	23	13	6	5	1	0	0	0	0	0	0
TNBC	32	11	6	3	2	2	2	1	1	1	1	1	0

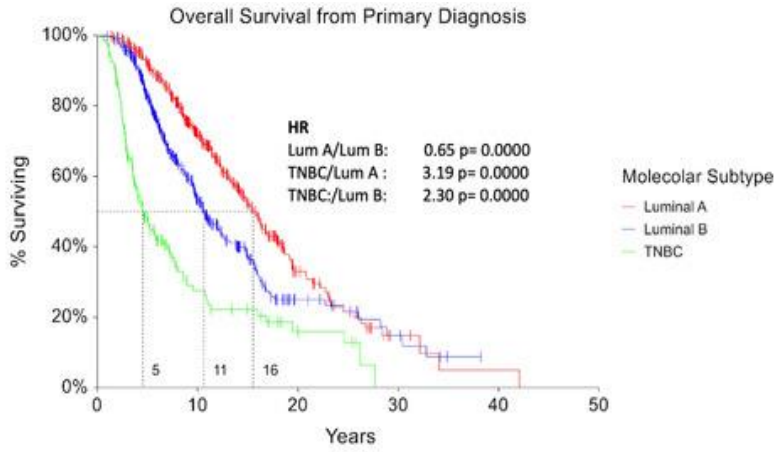
Figure 3. PFS2 by subtype.



Months -> Nr at risk	4	8	12	16	20	24	28	32	36	40	44	48	52
Lum A	185	127	77	48	35	29	18	13	10	7	5	3	1
Lum B	183	98	52	30	17	11	6	5	4	3	2	1	1
TNBC	44	21	12	4	4	2	1	1	1	0	0	0	0

Figure 4. TTC2 by subtype.

Median overall survival from initial diagnosis was 10 years for Luminal A, 7 years for Luminal B, and 3.6 years for TNBC (p = 0.0006) **(Figure 5)**.



Years -> Nr at risk	3	6	9	12	15	18	21	24	27	30	33	36	39
Lum A	371	305	221	146	94	50	27	16	10	4	2	1	1
Lum B	377	246	221	81	52	25	17	13	9	6	3	1	0
TNBC	87	40	21	15	13	8	5	5	1	0	0	0	0

Figure 5. OS according to subtype.

Median OS1 (survival from first progression) reached 35.2 months (95% CI 30.8-37.4) in Luminal A, exceeding values in Luminal B (28.9 months, 95% CI 26.2-31.2) and TNBC (18.5 months, 95% CI 16-20.1; F-ratio 7.44, p = 0.0006) **(Figure 6)**.

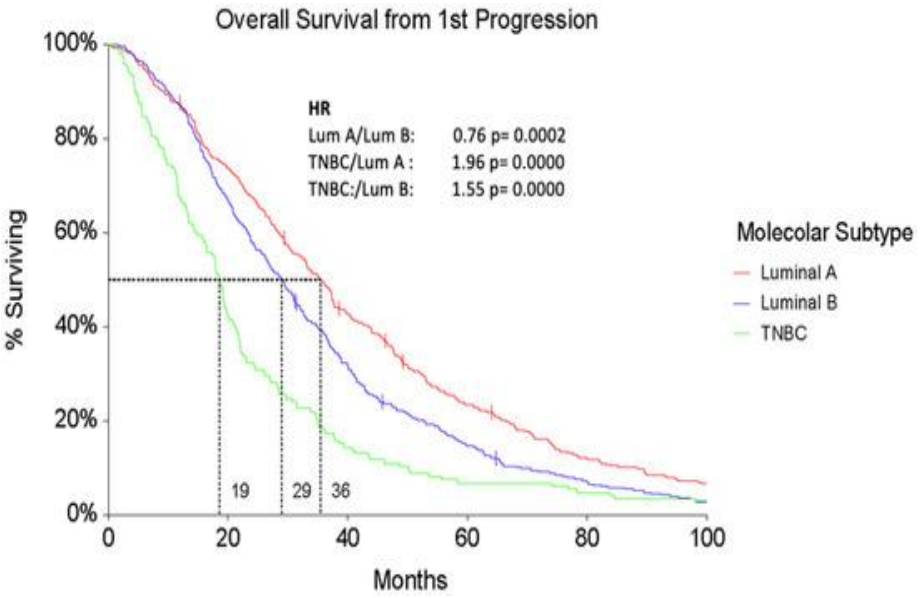


Figure 6. OS1 across subtypes.

The GIM 13-AMBRA project represents an extensive Italian real-life cohort analyzing therapies for HER2-metastatic breast cancer (MBC), offering a rare chance to observe "pre-CDK4/6 inhibitor era'' PFS patterns across routinely used first-, second-, and later-line chemotherapy strategies. Given the study framework and eligibility criteria, the cohort reflects a population with substantial baseline risk, which is supported by the high proportion of node-positive cases (61.76%) and Grade 3 tumors (50.47%) at diagnosis.

Across the study timeframe, more than 70% of participants received adjuvant chemotherapy, independent of subtype. The particularly high usage in Luminal A disease (67.6%) highlights the previous absence of predictive genomic tools capable of distinguishing those who would inevitably require chemotherapy to prevent relapse [7]. Anthracycline-based regimens—frequently paired with 5-Fluorouracil and Cyclophosphamide (44.2%)—were

the most common choice in the Luminal A group, though findings from the GIM 2 study [8] no longer endorse anthracyclines in this setting due to lack of demonstrated benefit.

For median first-line PFS (PFS1), our results align closely with ESME data in Luminal patients, where PFS under initial systemic therapy was reported as 9.6 months (95% CI 9.4-9.9) overall and 10.7 months (95% CI 10.5-11.0) in HR+/HER2- disease. The introduction of CDK4/6 inhibitors—Palbociclib, Abemaciclib, Ribociclib—combined with Aromatase Inhibitors for endocrine-responsive tumors has profoundly modified outcomes, with median PFS1 now approaching 25 months [9-11], effectively pushing back chemotherapy requirements. Ribociclib plus letrozole additionally improved OS to 63.9 months (95% CI 52.4-71.0) in the MONALEESA-2 study [9]. Whether this drug class will reshape the long-term trajectory of Luminal cancers remains unresolved; early, smaller studies [12] show that no sequence currently holds category-1 recommendation. Large randomized studies are ongoing, and new therapies will be applied once progression occurs under CDK4/6 inhibitor + endocrine therapy. The ByLieve trial (phase 2) showed approximately 7 months of PFS for alpelisib after CDK inhibitor therapy, suggesting benefit for PIK3CA-mutated tumors when combined with fulvestrant [13].

By contrast, therapeutic advances for TNBC have been minimal over the past decade. In our dataset, median PFS1 was 8.8 months (95% CI 6.7-10.2), compared with 4.8 months (95% CI 4.6-5.1) reported in ESME. Lack of detailed chemotherapy data in ESME limits direct interpretation.

Median OS from initial diagnosis in our study was 10 years for Luminal A, 7 years for Luminal B, and 3.6 years for TNBC ($p = 0.0006$). Since 2008, only a few treatments—eribulin among them—have shown OS gains in HER2-negative MBC [14]. In the ESME cohort, median OS was 37.22 months (95% CI 36.3-38.04) overall and 14.52 months (95% CI 13.70-15.24) for TNBC. The authors emphasized a lack of major progress for HR+/HER2-negative and TNBC groups between 2008 and 2014, perhaps due to the late availability or limited effectiveness of newer options. In our population, targeted therapies such as bevacizumab were used in 20% of Luminal and 25% of TNBC cases. Although RCTs did not show OS improvement with bevacizumab [15], several real-world analyses suggested different findings: economic modeling indicated that bevacizumab plus paclitaxel was likely cost-effective versus paclitaxel alone in first-line HER2-negative MBC [16], and the ATHENA study reported a median TTP of 9.5 months (95% CI 9.1-9.9) [17].

A deeper molecular separation of TNBC subtypes proposed by Lehmann *et al*. [18] has more recently promoted subtype-specific therapy, including immunotherapy for PD-L1-positive tumors. In IMpassion130 [19], atezolizumab plus nab-paclitaxel achieved longer median PFS than placebo (ITT: 7.2 vs. 5.5 months, HR 0.8; PD-L1+: 7.5 vs. 5.0 months, HR 0.62), though OS improvement was statistically meaningful only in the PD-L1+ group. Pembrolizumab + chemotherapy produced comparable trends: median PFS 9.7 vs. 5.6 months (HR 0.65), and median OS 23.0 vs. 16.1 months (HR 0.73). When contrasted with our earlier-period results, these data underscore the ongoing unmet needs in mTNBC.

A secondary goal of this analysis was to assess whether TTC could serve as a real-world proxy for PFS. Median PFS1 and TTC1 were nearly identical across the cohort. For Paclitaxel + Bevacizumab (PB), used as a case example of TTC utility, median TTC was 9.36 months (40.67 weeks) and median PFS was 10.8 months (46.92 weeks). The 6.2-week gap was not statistically significant (Wilcoxon test, $\alpha = 0.050$, $p = 0.089$) and was inside the predefined acceptable window. PFS1 for PB was roughly one month shorter than in ECOG 2100 [15], which is plausible given the different patient populations. These results support TTC as a credible surrogate endpoint for RWS and justify its future use in observational designs.

The GIM 13-AMBRA cohort offers national and international oncology groups a real-world reference set of survival outcomes that can anchor future clinical studies and provide clearer benchmarks for the added value of newer agents.

This analysis carries several limitations: (1) its retrospective design, (2) constraints in subtype classification, (3) retrospective timing and treatment-decision documentation, (4) limited representation of the full Italian MBC population, and (5) lack of patient-reported outcomes.

Conclusion

The GIM 13-AMBRA dataset represents one of the most extensive Italian real-world collections to date and delivers valuable information regarding time-to-event outcomes for first and later treatment lines in HER2-negative MBC. Repeating this assessment with more contemporary cohorts would allow evaluation of the impact of newly integrated therapies on everyday clinical practice.

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Conflict of Interest: None

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Ethics Statement: None

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