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► To cite this version:

Thomas Grinda, Alison Antoine, William Jacot, Paul-Henri Cottu, Thibault de la Motte Rouge, et al.. Real-world clinical and survival outcomes of patients with early relapsed triple-negative breast cancer from the ESME national cohort. *European Journal of Cancer*, 2023, 189, pp.112935. 10.1016/j.ejca.2023.05.023 . hal-04205902

HAL Id: hal-04205902

<https://hal.science/hal-04205902>

Submitted on 16 Nov 2023

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Article type: Original Article**Title: Real-world clinical and survival outcomes of patients with early relapsed triple-negative breast cancer from the ESME national cohort.****Authors list:**

T. Grinda^{1,2}, A. Antoine³, W. Jacot⁴, PH Cottu⁵, T de la Motte Rouge⁶, J-S Frenel⁷, A. Mailliez⁸, F. Dalenc⁹, A. Goncalves¹⁰, F. Clatot¹¹, M-A. Mouret Reynier¹², C. Levy¹³, J-M Ferrero¹⁴, I. Desmoulins¹⁵, L. Uwer¹⁶, T. Petit¹⁷, C. Jouannaud¹⁸, M. Arnedos¹⁹, M. Chevrot²⁰, C. Courtinard^{20,21}, O.Tredan²², E. Brain⁵, D. Pérol³, B. Pistilli¹, S. Delaloge¹.

Affiliations:

1. Department of Cancer Medicine, Gustave Roussy, 114 Rue Edouard Vaillant, 94800 Villejuif, France.
2. Sorbonne University, Medicine, 21 rue de l'École de médecine, 75006 Paris, France.
3. Department of Biostatistics, DRCl, Centre Léon Bérard, 28 Promenade Léa et Napoléon Bullukian, 69008 Lyon, France.
4. Department of Medical Oncology, Institut du Cancer de Montpellier, 208 Rue des Apothicaires, 34298 Montpellier, Montpellier University, INSERM U1194, France.
5. Department of Medical Oncology, Institut Curie, 26 Rue d'Ulm, 75005 Paris & Saint-Cloud, France.
6. Department of Medical Oncology, Centre Eugène Marquis, Avenue de la Bataille Flandres-Dunkerque, 35000 Rennes, France.
7. Department of Medical Oncology, Institut de Cancérologie de l'Ouest Pays de Loire, 15 rue André Boquel, 49055 Angers, France.
8. Medical Oncology Department, Centre Oscar Lambret, 3 Rue Frédéric Combemale, 59000 Lille, France.
9. Department of Medical Oncology, Institut Claudius Regaud – IUCT Oncopole, 1 Avenue Irène-Joliot-Curie, 31059 Toulouse, France.
10. Department of Medical Oncology, Institut Paoli-Calmettes, 232 Boulevard de Sainte-Marguerite, 13009 Marseille, France.
11. Department of Medical Oncology, Centre Henri Becquerel, Rue d'Amiens, 76000 Rouen, France.

12. Department of Medical Oncology, Centre Jean Perrin, 58 Rue Montalembert, 63011 Clermont Ferrand, France.
13. Department of Medical Oncology, Centre François Baclesse, 3 Avenue du Général Harris, 14000 Caen, France.
14. Department of Medical Oncology, Centre Antoine Lacassagne, 06000 Nice, France
15. Department of Medical Oncology, Institut de Cancérologie de Bourgogne, 21079 Dijon, France.
16. Medical Oncology Department, Institut de Cancérologie de Lorraine, Vandoeuvre-lès-Nancy, 6 Avenue de Bourgogne, 54519 Vandœuvre-lès-Nancy, France.
17. Department of Medical Oncology, Centre Paul Strauss, 3 Rue de la Porte de l'Hôpital, 67000 Strasbourg, France.
18. Department of Medical Oncology, Institut de Cancérologie Jean-Godinot, 1 Rue du Général Koenig, 51100 Reims, France.
19. Department of Medical Oncology, Institut Bergonié, 229 Cours de l'Argonne, 33000 Bordeaux, France.
20. Department of Research and Development, R&D Unicancer, 101 Rue de Tolbiac, 75654 Paris, France
21. University of Bordeaux, Inserm, Bordeaux Population Health Research Center, Epicene team, UMR 1219, 33000 Bordeaux, France
22. Department of Medical Oncology, Centre Léon Bérard, 28 Prom. Léa et Napoléon Bullukian, 69008 Lyon, France.

Corresponding author:

Dr Thomas Grinda

Department of Cancer Medicine, Gustave Roussy, 114 Rue Edouard Vaillant, 94800 Villejuif, France.

Tel: +33 1 42 11 64 48 fax: +33 1 42 11 52 74 email: thomas.grinda@gustaveroussy.fr

Keywords: metastatic breast cancer, triple negative breast cancer, early relapse, overall survival, real-world-data,

Database registration: clinicaltrials.gov Identifier NCT032753

Abstract:**Background:**

Early metastatic relapse of triple-negative breast cancer (mTNBC) after anthracyclins and/or taxanes based (A/T) primary treatment represents a highly aggressive cancer situation requiring urgent characterization and handling. ESME-metastatic breast cancer (MBC) database, a multicenter, national, observational cohort (NCT03275311) provides recent data on this entity.

Methods:

All ESME patients diagnosed between 2008 and 2020 with mTNBC occurring as a relapse after a systemic neoadjuvant/adjuvant taxane and/or anthracycline-based chemotherapy were included. Early relapses were defined by a metastatic diagnosis up to 12 months of the end of neo/adjuvant A/T chemotherapy. We assessed overall survival (OS) and progression-free-survival under first-line treatment (PFS1) by early versus late relapse (≥ 12 months).

Results:

Patients with early relapse (N= 881, 46%) were younger and had a larger tumor burden at primary diagnosis than those with late relapses (N=1 045). Early relapse rates appeared stable over time. Median OS was 10.1 months (95%CI 9.3-10.9) in patients with early relapse versus 17.1 months (95%CI 15.7-18.2) in those with late relapse (adjusted Hazard-ratio (aHR): 1.92 (95%CI 1.73-2.13); $p < 0.001$). The median PFS1 was respectively 3.1 months (95%CI 2.9-3.4) and 5.3 months (95%CI 5.1-5.8); (aHR: 1.66; [95%CI 1.50-1.83]; $p < 0.001$). Among early relapsed patients, a higher number of metastatic sites, visceral disease but not treatment types, were independently associated with a poorer OS.

Conclusion:

These real-world data provide strong evidence on the dismal prognosis, higher treatment resistance and major unmet medical need associated with early relapsed mTNBC.

Key words:

breast cancer, triple-negative breast cancer, real-world data, ESME cohort, overall survival, ESME cohort

Article**Introduction**

Breast cancer is currently the leading cause of cancer death among women worldwide (1). While genomics allowed us to enhance our understanding of its biology, the so-called “triple-negative” breast

cancer subtype (TNBC), defined by the lack of expression of the estrogen and progesterone receptors (ER and PgR) as well as absence of HER2 protein overexpression or gene amplification, remains the most aggressive and genomically complex entity (2). One of its major characteristics is the lack of identified recurrent genomic drivers, which comes with lack of common molecular targets for treatment. TNBC is even more worrying as it occurs more often among young and premenopausal women.

While multimodal treatments allows the cure of about 60-65% of early TNBC patients, distant metastases most often occur within three years from diagnosis, particularly in the viscera (brain, lung and liver) with a subsequent median overall survival (OS) of less than 15 months (3–5). Chemotherapy has long been the backbone treatment of advanced/metastatic TNBC (mTNBC). Taxane-based first-line treatment allows an objective response rate (ORR) of approximately 50% and a progression free survival (PFS) of at most 5-6 months among non-exposed patients or late relapsers (6). Many trials tested different approaches and combinations with little or no success (7). However, immune checkpoint inhibitors, antibodies drug conjugates (ADC) and PARP inhibitors have recently brought significant improvements in progression-free survival and, for some of them, overall survival in the treatment of certain mTNBC subsets (8–11).

A clinically defined subgroup of mTNBC stands out for its particularly aggressive course, with rapid progression of metastases and marked treatment resistance. This clinical subgroup consists of patients with an early relapse, occurring up to one year after completion of neo/adjuvant therapy. A disease-free interval of less than one year is a marker of chemotherapy resistance (12,13). In addition, the use of different types of treatment at the localized stage limits treatment options in this subgroup. Several recent pivotal trials in the first metastatic line treatment setting have excluded these patients (6,8,14). Although there are few specific data available, this subgroup may account for 26% to 43% of all patients with mTNBC (15–18), however, a comprehensive description of this population lacks in the literature.

Real-world data help describe patients, treatments and outcomes, especially for populations under-represented in clinical trials but observed in routine practice (19). ESME-MBC (Epidemiology-Strategy-Medico-Economical-Metastatic Breast Cancer) is a large, nationwide, multicenter real-world database of patients with MBC (4,20). In this study, the aim of this study was to describe and compare the characteristics and survival outcomes of women with early relapsed metastatic breast cancer to those with late relapsed metastatic breast cancer in a real-world population of 30,459 women who started treatment for metastatic breast cancer in the ESME cohort between January 1, 2008 and December 31, 2020.

Patients and Methods

Data source and setting

We carried out a retrospective study using the ESME-MBC (NCT03275311) database, a national observational cohort gathering routinely collected real-world data from all consecutive patients aged 18 and over and who initiated treatment for MBC in one of the 18 French Comprehensive Cancer Centers. Data are updated annually and include patient demographics, histopathology, outcomes, and treatment patterns. The information collected integrates patients' data from medical records, hospitalization reports and hospitals' pharmacy records. More details can be found in previously published descriptions of the cohort (4,20,21). For the purpose of reporting this study's results, we followed the STROBE guidelines (22).

Ethics approval and data protection

The present analysis was approved by an independent Ethics Committee (Comité De Protection Des Personnes Sud-Est II- 2015-79). The French data protection authority authorized the ESME MBC database in 2013 (Registration ID 1704113 and authorization NbrDE-2013.-117). In compliance with the applicable European regulations, a complementary authorization was obtained on 14/10/2019 regarding the ESME research Data Warehouse.

Study participants' eligibility

For the present study, we used data from MBC patients who entered the cohort between January 2008 and December 2020. Data were collected until the cut-off date for data extraction, February 2022. The triple negative breast cancer subtype was defined according to locally performed immunohistochemical (IHC) analyses on primary tumour samples. Tumours were considered triple negative if both ER and PgR expression was <10% of tumour cells as standard in France, and HER2 expression was 0 or 1, or 2 with a negative fluorescence or chromogenic in-situ hybridization (FISH/CISH) test (23–25). Patients with early relapsed mTNBC were defined as having a diagnosis of distant metastases up to 12 months of the last dose of neo/adjuvant anthracycline and/or taxane chemotherapy, in patients whose tumor was initially considered as a localized TNBC with an initial stage up to III (12,13). Male patients, those without systemic treatment at metastatic stage with other subtypes or stage 0 or IV disease at initial diagnosis were excluded. Those who had metastatic progression diagnosed more than 12 months after the completion of neo/adjuvant chemotherapy were defined as late relapsed patients. The time to relapse was calculated from the end of the taxane and/or anthracycline-based chemotherapy to the date of metastatic relapse. First-line treatments were separated into monotherapy and combination therapy (combination of agents administered concomitantly or sequentially if started within 2 months of a first agent).

Statistical analyses:

We first described early and late relapsed mTNBC patients' characteristics. Quantitative variables are described using the number of observations, median, first and third quartile values. Qualitative variables are described using number of observations and percentage distribution. The number of missing data are presented but not considered for the percentage calculation. Characteristics were compared using Pearson's Chi-squared and Kruskal-Wallis rank sum tests (no p-value adjustment was performed). The median follow-up time was estimated using the reverse Kaplan-Meier method. OS was defined as the time from the date of metastatic diagnosis to the date of death (any cause) or to the date of last follow-up for censored patients. PFS1 was defined as the time from initiation of the first line treatment in metastatic setting to the date of MBC disease progression or death from any cause, or to the date of last follow-up for censored patients, whichever occurred first. Progression-free survival 2 (PFS2) was defined as the time from initiation of first-line treatment in metastatic setting to the date of disease progression on second-line treatment, the date of death from any cause or the date of last news for censored patients, whichever came first. OS, PFS1 and PFS2 were estimated using the Kaplan-Meier method. A sensitivity analysis was performed using an alternative definition of patients with early relapse, as the presence of metastatic progression diagnosed between 6-18 months from the primary tumour diagnosis or from the diagnosis of a local relapse patients relapsing within 6 months of primary tumor diagnosis are considered de novo metastatic in ESME and therefore excluded from this definition). (5,20). Multivariable Cox proportional hazard models were performed using a backward stepwise selection to identify prognostic factors for OS and PFS1 in early and late relapse mTNBC. Multivariable Cox proportional hazard models were performed using a backward stepwise selection to identify prognostic factors for OS and PFS1 among early and late relapse metastatic TNBC. The covariates were selected using a conservative p value of 0.10 from the univariable analysis, except for certain covariates which were "forced" into either models if not present since strongly recognized as prognostic factors in the literature and/or clinically relevant (taxanes use in early setting, number and sites of metastases at diagnosis of MBC, age groups, time interval from initial diagnosis) (5). The choice of covariates for each multivariable model is described in Supplementary Method 1. A second sensitivity analysis repeated the same analyses among patients with an available performance status at baseline. Both sensitivity analyses were focused on OS. Finally, we performed an analysis of the characteristics of patients excluded because of missing data. The independent prognostic factors included in the final models with a significant *p-value* of 0.05 are presented with their hazard ratios including 95% confidence intervals. All analyses were performed using R Statistical Software version 4.0.0.

Results

Characteristics of patients and tumors by early versus late relapses

Of the 30,459 patients registered in the ESME database, 1,926 women had a relapsed mTNBC following receipt of a neo/adjuvant treatment and were eligible for the present study (whole population) (Figure 1). Of them, 881 (45.7%) and 1,045 (54.3%) had an early and late relapse respectively. The clinical and tumors' characteristics are presented in Table 1. The analysis of the characteristics of the excluded patients is presented in Supplementary Table 1.

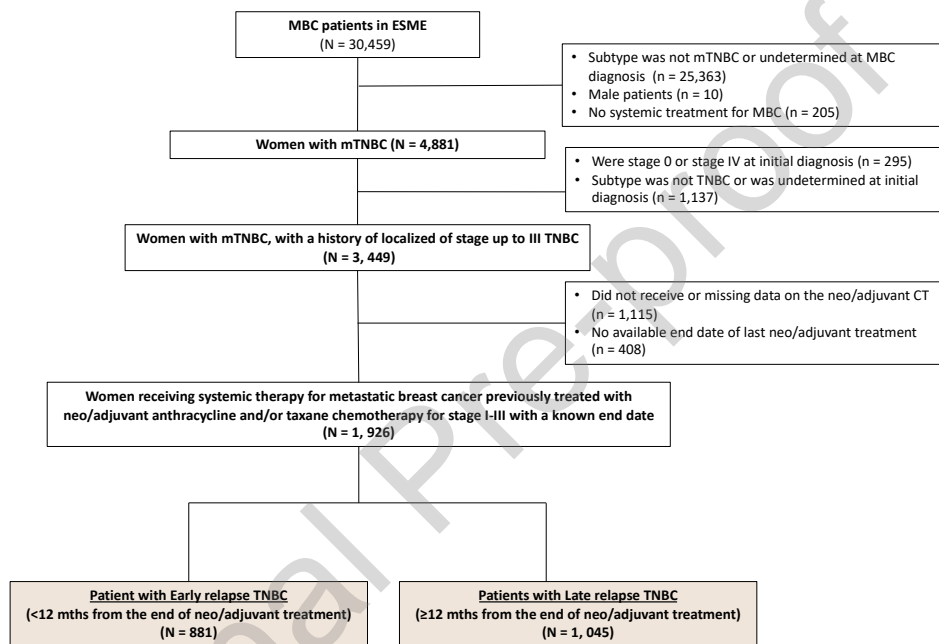


Figure 1: Flow Chart

MBC: Metastatic breast cancer, ESME: Epidemio-Strategy-Medico-Economical-Metastatic Breast Cancer, TNBC: triple negative breast cancer, mTNBC, metastatic TNBC, CT: chemotherapy

Patients with early relapse were significantly younger (median age [q1-q3], 51 [42-60] vs 56 [46-66] years, $p < 0.001$) and had less frequent detection of a *BRCA1/2* germline mutation at metastatic diagnosis (5.6% vs 7.6%, unadjusted $p < 0.001$) compared to patients with late relapse. The primary tumor burden was greater among early relapsers (T3/T4, 49.6% vs 31.5%, lymph node involvement N2/N3, 23.1% vs 8.7%, both unadjusted $p < 0.001$). Although patients with early relapse had slightly significantly less metastatic sites at metastatic diagnosis compared to those with late relapse, type of involvement appeared identical (17% brain metastases, 51-54% visceral metastases excluding CNS involvement). Finally, the proportion of patients per period of diagnosis remained rather similar between early and late relapse groups.

Table 1. Patients and tumors characteristics and description of prior treatments according to the early/late relapse status

	Early relapse (N=881)	Late relapse (N=1045)	Whole study sample (N=1926)	p value
Age at MBC diagnosis (years)				< 0.001²
Median (q1, q3)	51 (42, 60)	56 (46, 66)	53 (44, 63)	
Age groups at MBC diagnosis (years)				< 0.001¹
<50	420 (47.7%)	354 (33.9%)	774 (40.2%)	
>=50	461 (52.3%)	691 (66.1%)	1152 (59.8%)	
Germline <i>BRCA1/2</i> alteration at MBC diag				< 0.001¹
Germline <i>BRCA1/2</i> alteration	49 (5.6%)	79 (7.6%)	128 (6.6%)	
Other germline alteration	1 (0.1%)	1 (0.1%)	2 (0.1%)	
Absence of germline alteration	225 (25.5%)	189 (18.1%)	414 (21.5%)	
No genetic testing	606 (68.8%)	776 (74.2%)	1382 (71.8%)	
Histological type of primary tumour				0.024¹
Invasive ductal carcinoma	780 (88.5%)	879 (84.1%)	1659 (86.1%)	
Invasive lobular carcinoma	22 (2.5%)	48 (4.6%)	70 (3.6%)	
Other	79 (9%)	118 (11.3%)	197 (10.3%)	
HER2 status				0.099 ¹
HER2 0	714 (81.0%)	815 (78.0%)	1529 (79.4%)	
HER2 low (1+ or 2+ but non amplified)	167 (19.0%)	230 (22.0%)	397 (20.6%)	
T status at initial diag.				< 0.001¹
T0/Tis	2 (0.5%)	9 (1.9%)	11 (1.2%)	
T1	54 (12.5%)	95 (20.5%)	149 (16.6%)	
T2	162 (37.4%)	214 (46.1%)	376 (41.9%)	
T3	114 (26.3%)	103 (22.2%)	217 (24.2%)	
T4	101 (23.3%)	43 (9.3%)	144 (16.1%)	
Missing	448	581	1029	
N status at initial diag.				< 0.001¹
N0	156 (37.1%)	227 (50.7%)	383 (44.1%)	
N1	167 (39.8%)	182 (40.6%)	349 (40.2%)	
N2	53 (12.6%)	25 (5.6%)	78 (9.0%)	
N3	44 (10.5%)	14 (3.1%)	58 (6.7%)	
Missing	461	597	1058	
Histological grade at initial diag.				< 0.001¹
I/II	219 (25.9%)	347 (34.2%)	566 (30.4%)	
III	627 (74.1%)	669 (65.8%)	1296 (69.6%)	
Missing	35	29	64	
Year of MBC diagnosis (YOD)				0.372 ¹
2008-2012	350 (39.7%)	409 (39.1%)	759 (39.4%)	
2013-2017	348 (39.5%)	441 (42.2%)	789 (41.0%)	
2018-2020	183 (20.8%)	195 (18.7%)	378 (19.6%)	
MBC diagnosis circumstances				0.014¹
Symptom(s)	415 (47.9%)	548 (53.6%)	963 (51.0%)	
Systematic examination	451 (52.1%)	474 (46.4%)	925 (49.0%)	
Missing	15	23	38	
Performance Status at MBC diag.				0.071 ¹

0	179 (33.8%)	261 (40.3%)	440 (37.4%)	
1	234 (44.2%)	261 (40.3%)	495 (42.1%)	
2-4	116 (21.9%)	125 (19.4%)	241 (20.5%)	
Missing	352	398	750	
Time interval to relapse from the end of neo/adjvant A/T chemotherapy (months)				< 0.001²
Median (q1,q3)	6.31 (3.12, 8.87)	23.92 (16.59, 39.75)	13.14 (6.77, 25.71)	
[0-6[419 (47.6%)	0 (0.0%)	419 (21.8%)	
[6-12[462 (52.4%)	0 (0.0%)	462 (24.0%)	
>=12	0 (0.0%)	1045 (100.0%)	1045 (54.2%)	
No. of metastatic sites at MBC diag.				< 0.001¹
1	441 (50.1%)	454 (43.4%)	895 (46.5%)	
2	227 (25.8%)	253 (24.2%)	480 (24.9%)	
≥3	213 (24.1%)	338 (32.2%)	551 (28.6%)	
Metastatic sites at MBC diag.				0.448 ¹
Non-visceral metastases	280 (31.8%)	305 (29.2%)	585 (30.4%)	
Visceral metastases excluding CNS	454 (51.5%)	564 (54.0%)	1018 (52.8%)	
CNS metastases	147 (16.7%)	176 (16.8%)	323 (16.8%)	
RT in neo/adj. setting				< 0.001¹
Yes	746 (84.7%)	965 (92.3%)	1711 (88.8%)	
No	135 (15.3%)	80 (7.7%)	215 (11.2%)	
Taxanes in neo/adj. setting				< 0.001¹
Yes	823 (93.4%)	870 (83.3%)	1693 (87.9%)	
No	58 (6.6%)	175 (16.7%)	233 (12.1%)	
Anthracyclines in neo/adj. setting				0.128 ¹
Yes	835 (94.8%)	973 (93.1%)	1808 (93.9%)	
No	46 (5.2%)	72 (6.9%)	118 (6.1%)	
Capecitabine in neo/adj. setting				< 0.001¹
Yes	116 (13.2%)	33 (3.2%)	149 (7.7%)	
No	765 (86.8%)	1012 (96.8%)	1777 (92.3%)	

MBC diag.: metastatic breast cancer diagnosis; non-visceral metastasis: bone, skin, and lymph nodes; Visceral metastasis is excluding brain; RT: Radiotherapy; neo/adj.: neo/adjuvant; CNS: Central nervous system metastases; A/T: anthracyclins/taxanes 1. Pearson's Chi-squared test, 2. Kruskal-Wallis rank sum test. No p-value adjustment was performed.

First-line treatments received by the early relapse group

The treatment regimens received by patients with early relapsed mTNBC in first line metastatic disease are shown in Figure 2 and Supplementary Table 2. Of note, 17% of patients were included in a clinical trial as part of their first line metastatic treatment, which was equivalent to late relapsed patients.

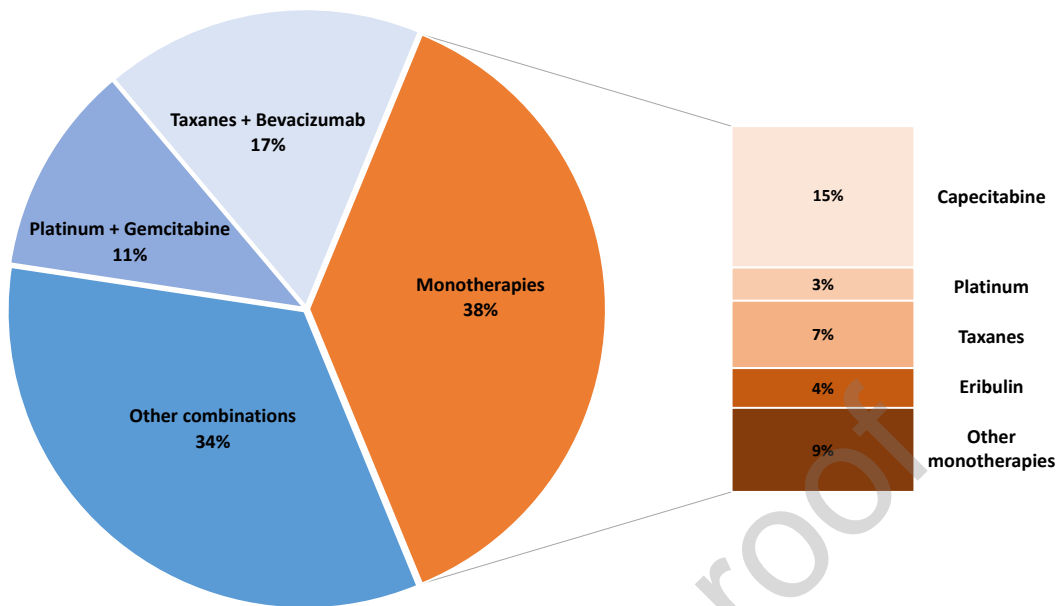


Figure2. Type of first-line metastatic treatments of patients with early relapsed mTNBC

Overall survival and progression-free survival of patients with early or late relapse

The median follow-up duration for the whole study sample was 57.6 months (95% CI 52.3-67.8)). It was 52.3 months (95% CI 49.0-66.3) and 64.4 months (95% CI 53.7-72.2) for the early and late relapse groups, respectively. The median OS of the entire group was 13.5 months (95% CI 12.6-14.1). Median OS was significantly worse in early versus late relapsers (10.1 months [95% CI 9.3-10.9] vs 17.1 months [95% CI 15.7-18.2]; unadjusted Hazard ratio (HR): 1.70; [95% CI 1.54-1.88]; $p < 0.001$ respectively) (Figure 3). Similarly, PFS1 and PFS2 were lower in the early compared to the late relapse group: PFS1 was 3.1 months (95% CI 2.9-3.4) vs 5.3 months (95% CI 5.1-5.8) (HR: 1.60; [95% CI 1.46-1.75]; $p < 0.001$) and PFS2 was 6.3 months (95% CI 6.0-6.7) versus 10.1 months (95% CI 9.4-10.8), respectively (Figure 3 and Supplementary Figure 1).

In a multivariable analysis in the whole (early + late) study sample, age at metastatic diagnosis, number of metastatic sites at metastatic diagnosis, presence of visceral metastases and taxanes exposure in neo/adjuvant setting were independently associated with overall survival. As well, early relapse was associated with OS and PFS1 with an adjusted hazard ratio (aHR) of 1.92 (95% CI 1.73-2.13; $p < 0.001$) and 1.66 (95% CI 1.50-1.83; $p < 0.001$), respectively (Supplementary Table 3).

In a first sensitivity analysis, where early relapse was defined as the presence of metastatic progression within 6-18 months from diagnosis of the primary tumour or local relapse diagnosis, the same OS figures were observed, with a median OS of 10.1 months (95% CI 9.2-10.9) among the 883 such defined patients (Supplementary Figure 2).

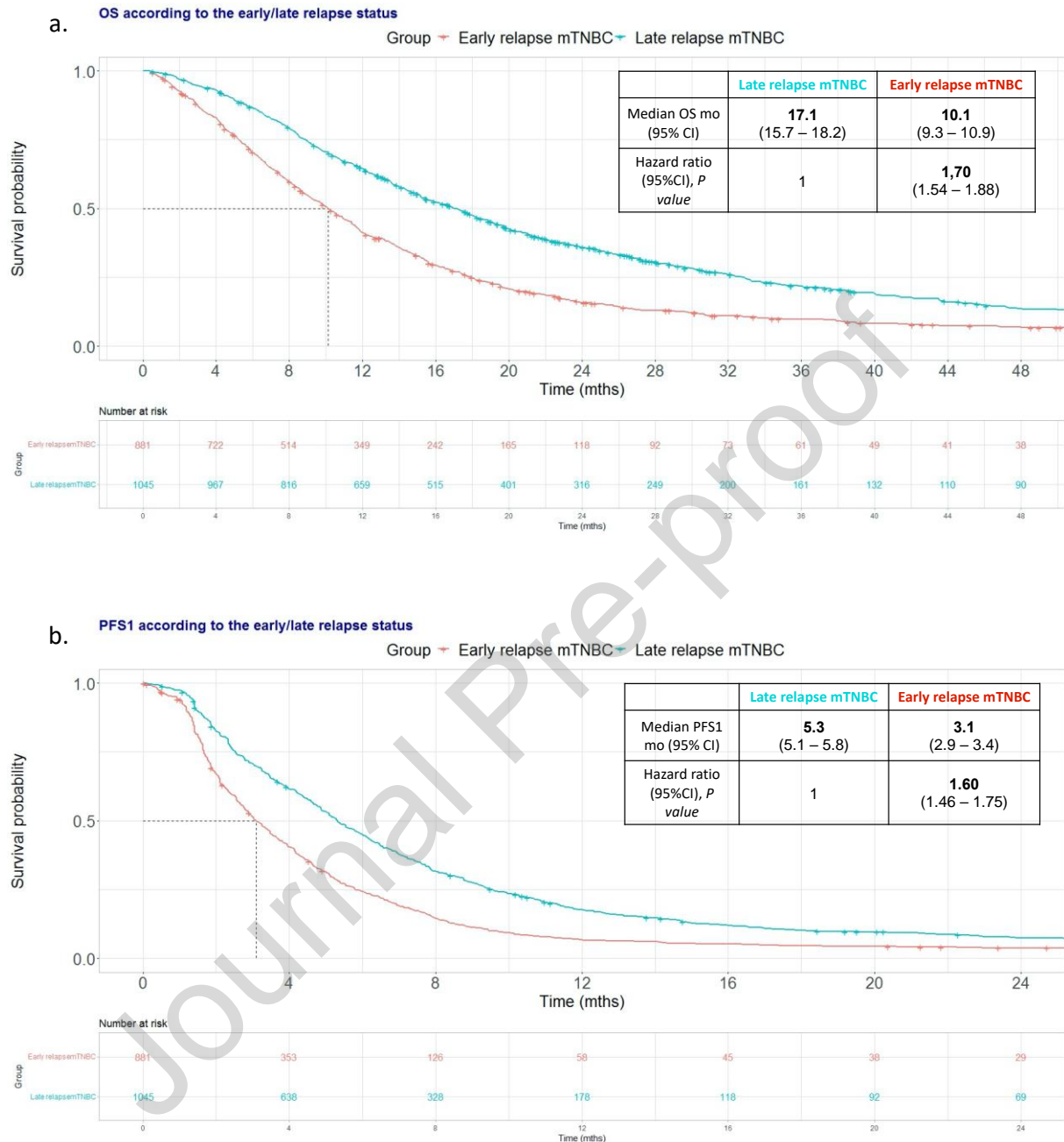


Figure 3: Overall survival (a) and progression-free survival under first line treatment (b) according to early versus late relapse status

Prognostic analyses in patients with early relapsed mTNBC

In multivariable analyses among patients with early relapsed mTNBC, time to relapse [0-6[vs [6-12[and number of metastatic sites were independent prognostic factors of PFS1. Time to relapse, age at metastatic diagnosis, number of metastatic sites and the presence of visceral metastases were independent prognostic factors for OS. Of note, the type of first-line treatment appeared as an

independent factor of both PFS1 and OS: compared to monotherapy, combination therapies were associated with better PFS1 (aHR 0.65 [95%CI 0.56-0.75], $p<0.001$) and OS (aHR 0.78 [95%CI 0.67-0.91], $p=0.001$) (Table 2). However, in a second sensitivity analysis, we repeated the multivariable analysis in patients with early relapsed mTNBC whose performance status was available (N=529). The median OS of this population was 9.3 months (95%CI 8.6-10.3) with a median follow-up time of 49 months (95%CI 42-53.5). Number of metastatic sites and presence of visceral metastases were again independent prognostic factors for OS in this sub-cohort, as was performance status, while combination therapies compared to monotherapy lost significance (aHR of 0.83 [95%CI 0.68-1.01]; $p= 0.063$) (Supplementary Table 4).

Table 2: Multivariable analysis of PFS1 and OS within patients with early relapsed mTNBC (N= 881)

Characteristic	PFS1			OS		
	HR ¹	95% CI ¹	p-value	HR ¹	95% CI ¹	p-value
Time interval to relapse from the end of neo/adjuvant chemotherapy (mo)			0.001			0.012
[0-6[1	—		1	—	
[6-12[0.79	0.69, 0.91		0.83	0.72, 0.96	
Age groups at MBC diag. (yrs)			0.24			0.037
<50	1	—		1	—	
≥50	1.09	0.95, 1.25		1.17	1.01, 1.34	
No. of metastatic sites at MBC diag.			<0.001			<0.001
1	1	—		1	—	
2	1.34	1.13, 1.59		1.62	1.36, 1.94	
≥3	1.90	1.57, 2.29		2.78	2.29, 3.39	
Type of metastatic sites at MBC diag.			0.15			<0.001
Non-visceral metastases	1	—		1	—	
Visceral metastases excluding CNS	1.03	0.87, 1.21		1.18	0.99, 1.40	
CNS metastases	1.22	0.99, 1.51		1.78	1.43, 2.21	
Taxanes use in neo/adj. setting			0.55			0.94
No	1	—		1	—	
Yes	1.09	0.82, 1.44		0.99	0.74, 1.32	
Treatment group in m1L*			<0.001			0.001
Monotherapies	1	—		1	—	
Combinations	0.65	0.56, 0.75		0.78	0.67, 0.91	

MBC diag: metastatic diagnosis, HR = Hazard Ratio, CI = Confidence Interval, non-visceral metastasis: bone, skin, and lymph nodes, Visceral metastasis excluding brain, m1L: metastatic first line treatment, yrs: years, mo: months, mTNBC: metastatic triple negative breast cancer, *This effect disappeared after adjustment on performans status

Discussion

Our analysis of a large, recent, multicenter cohort of mTNBC patients who developed an early relapse provides for the first-time detailed evidence on the dismal prognosis associated with this entity, as well as its clinical characteristics and treatment effect. Our data highlight the major unmet medical

need of this subgroup of patients. However, the rate of early versus late relapses appeared stable over time, which is not in favor of a potential anticipation effect of more aggressive neo/adjuvant treatments.

Among patients with early mTNBC relapse, the factors independently associated with overall survival in our cohort were classical, including number and type of metastatic sites (4,5,21). When first-line treatment type (single-agent versus combination) was included in the models, combination of therapies appeared to be associated with better PFS1 and OS than single agent approaches (aHR 0.65 [95%CI 0.56-0.75], $p < 0.001$ and aHR 0.78 [95%CI 0.67-0.91], $p = 0.001$, respectively). However, these data should be interpreted with caution because of a possible confounding by indication bias. Indeed, this association disappeared when performance status was included in the model (restricted population) revealing a possible prescription bias as more aggressive combination treatments are prescribed to patients in better condition. Since a better general health condition is an independent positive prognostic factor for survival, it can bias the survival outcomes in favor of the combination group. We however tried to eliminate other possible biases by defining treatment combinations as concomitantly initiated (second agent started within 2 months of the first agent), which limits temporal biases by eliminating sequential treatment changes due to toxicity, but also maintenance treatments, linked to more prolonged responses.

The strengths of our analysis are that the ESME cohort has a high level of data quality at the collection and controls levels (20), and a wide national multicenter recruitment in a country where access to care is homogeneous (26). It is the first large cohort of patients with early relapse of mTNBC using time from end of initial anthracyclins and taxanes-based chemotherapy to relapse as a definition. Furthermore, we demonstrated that this definition of early relapse is not biased by the potential missing data for the date of completion of neo/adjuvant therapy, by conducting a sensitivity analysis using an interval of 6 to 18 months from the diagnosis of the primary tumor to the metastatic diagnosis an alternate definition of early relapse (patients who relapsed from 0 to 6 months are excluded as considered de novo metastatic in this case). Although this cohort is retrospective, these data remain relevant and timely as patients with such early relapsed mTNBC were excluded from many recent registration trials (6,8).

Despite our efforts, our study has limitations and biases inherent to the real-world methodology. In the ESME-based analyses, TNBC patients were defined using the threshold of 10% for hormone receptors expression, compared to the North American threshold of 1%. This different classification should not affect survival as patients with low HR (1-10%) were few (0.4% of the cohort, data not

shown) and their prognosis overlaps with TNBC (27,28). The selection criteria of the ESME database included only patients who started a systemic treatment at the metastatic stage. As the ESME cohort focuses on patients with metastatic breast cancer, information on localized stage is often lacking, such as initial staging, specific treatment received such as platinum and biology as well as socioeconomic data, which limits analysis of predictors from early relapse. However, these factors have already been widely demonstrated in two previous cohorts (29,30). Also, several data, especially pathological and biological, are not present in ESME. The lack of genomic data, PDL1 expression, androgen receptor expression, or pathologic response to neoadjuvant therapy (pCR) and the large proportion of patients who did not undergo genetic testing because of the absence of anti-PARP approval during the inclusion period hypothesis generation but would not impact the present findings. In addition, the selection of our population creates a risk of selection bias. Patients for whom the date of completion of neoadjuvant chemotherapy was not specified have similar characteristics to our population and shall not lead to bias. However, patients who did not receive neoadjuvant chemotherapy slightly differ from our population (older, more grades I and II among others), but their small size should not alter our conclusions (Supplementary Table 1). Furthermore, the ESME database, by definition, excludes patients who are not receiving systemic treatment at the metastatic stage and who have a compromised general condition that does not allow for such treatments. This could potentially lead to a slight overestimation of OS without altering our conclusions. Finally, in our analysis, we did not observe any difference in the inclusion of early and late relapsed TNBC patients in first-line metastatic trials. This is likely because modern trials are not accounted for in the inclusion period of our cohort.

Conclusion

In this large-scale real-life study evaluating of 881 women with early relapsed metastatic TNBC, overall survival was less than one year. All survival outcomes were considerably lower than those of women with later relapses, revealing that these patients have highly "difficult-to-treat" disease. Early relapsed metastatic TNBC represents a major unmet medical need for which effective therapeutic strategies and dedicated clinical trials are urgently required.

Acknowledgements

We thank the 18 French Comprehensive Cancer Centers for providing the data and each ESME local coordinator for managing the project at the local level. Moreover, we thank the ESME Scientific Group and Strategic Committee for their ongoing support. 18 Participating French Comprehensive Cancer Centers (FCCC): ; I. Curie, Paris/ Saint-Cloud, G. Roussy, Villejuif, I. Cancérologie de l'Ouest, Angers/Nantes, C. F. Baclesse, Caen, ICM Montpellier, C. L. Bérard, Lyon, C. G-F Leclerc, Dijon, C. H. Becquerel, Rouen; I. C. Regaud, Toulouse; C. A. Lacassagne, Nice; Institut de Cancérologie de Lorraine,

Nancy; C. E. Marquis, Rennes; I. Paoli-Calmettes, Marseille; C. J. Perrin, Clermont Ferrand; I. Bergonié, Bordeaux; C. P. Strauss, Strasbourg; I. J. Godinot, Reims; C. O. Lambret, Lille. The first author would like to thank Lucile Cabanel for her unfailing help.

Funding

The ESME MBC database receives financial support from an industrial consortium (Roche, Pfizer, AstraZeneca, MSD, Eisai and Daiichi Sankyo). Data collection, analysis and publication are managed entirely by UNICANCER independently of the industrial consortium.

Authors contributions

Conceptualization: TG, AA, BP, SD; Formal analysis: TG and AA; Methodology: All authors; Project administration: TG; Software: AA; Supervision: SD; Validation SD; Writing - original draft: TG, AA, SD; Writing - review & editing: All authors

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Author Contribution Statement

Dr Delalogue discloses: Financial interests, all to my institution (advisory boards, speaker activities): AstraZeneca, MSD, Rappta, Besins, Gilead, Elsan. Research and clinical research funding, all to my institution: Sanofi, Pfizer, Novartis, AstraZeneca, Roche Genentech, Lilly, Puma, Orion, Amgen, Servier, MSD, BMS, Pierre Fabre, Seagen, Exact Sciences, Rappta, Taiho, European Commission, French government, Fondation ARC. Recipient, Horizon 2020 grant MyPeBS. Non-financial interests, personal: Pfizer, Novartis, AstraZeneca, Seagen

Dr Frenel reports consulting fees from Pfizer, Lilly, Novartis, Astra Zeneca, Clovis Oncology, GSK, Gilead, Daiichi Sankyo, Seagen; honoraria from Lilly, Novartis, Astra Zeneca, Gilead, Daiichi Sankyo, Seagen; Support for attending meetings and/or travel from Pfizer, Lilly, Novartis, Astra Zeneca, Clovis Oncology, GSK, Gilead, Daiichi Sankyo, Seagen

Dr Jacot reports Grants or contracts from Astra Zeneca and Daiichi Sankyo; Payment or honoraria for lectures from Astra Zeneca, Eisai, BMS, Lilly France, Daiichi Sankyo, MSD, Novartis, Pfizer, Roche, Seagen; Participation on a Data Safety Monitoring Board or Advisory Board from Astra Zeneca Eisai, BMS, Lilly France, Daiichi Sankyo, MSD, Novartis, Pfizer, Roche, Seagen.

Dr Pérol reports Grants or contracts from Roche and ESME, payment or honoraria for lectures from Astrazeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Eli-Lilly, Ipsen, Roche, Novartis, Merck Sharp And Dohme, Takeda, Janssen, Pfizer

Dr Arnedos reports Grants or contracts from Roche and Astrazeneca; Consulting fees from Astra Zeneca, Eli-Lilly, Pfizer; Payment or honoraria for lectures from Gilead and Novartis; Support for attending meetings and/or travel from Astra Zeneca, Daiichi-Sankyo, Eli-Lilly; Participation on a Data Safety Monitoring Board or Advisory Board from Novartis, Astra Zeneca

A Antoine reports a grant from the National French Research and Technology Association (ANRT) and Roche (France) via CIFRE doctoral fellowship no. 2020/1054, outside the submitted work.

All remaining authors have nothing to disclose.

Authors contributions

Conceptualization: TG, AA, BP, SD; Formal analysis: TG and AA; Methodology: All authors; Project administration: TG; Software: AA; Supervision: SD; Validation SD; Writing - original draft: TG, AA, SD; Writing - review & editing: All authors

Journal Pre-proof

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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

Dr Delaloge discloses: Financial interests, all to my institution (advisory boards, speaker activities): AstraZeneca, MSD, Rappta, Besins, Gilead, Elsan. Research and clinical research funding, all to my institution: Sanofi, Pfizer, Novartis, AstraZeneca, Roche Genentech, Lilly, Puma, Orion, Amgen, Servier, MSD, BMS, Pierre Fabre, Seagen, Exact Sciences, Rappta, Taiho, European Commission, French government, Fondation ARC. Recipient, Horizon 2020 grant MyPeBS. Non-financial interests, personal: Pfizer, Novartis, AstraZeneca, Seagen

Dr Frenel reports consulting fees from Pfizer, Lilly, Novartis, Astra Zeneca, Clovis Oncology, GSK, Gilead, Daiichi Sankyo, Seagen; honoraria from Lilly, Novartis, Astra Zeneca, Gilead, Daiichi Sankyo, Seagen; Support for attending meetings and/or travel from Pfizer, Lilly, Novartis, Astra Zeneca, Clovis Oncology, GSK, Gilead, Daiichi Sankyo, Seagen

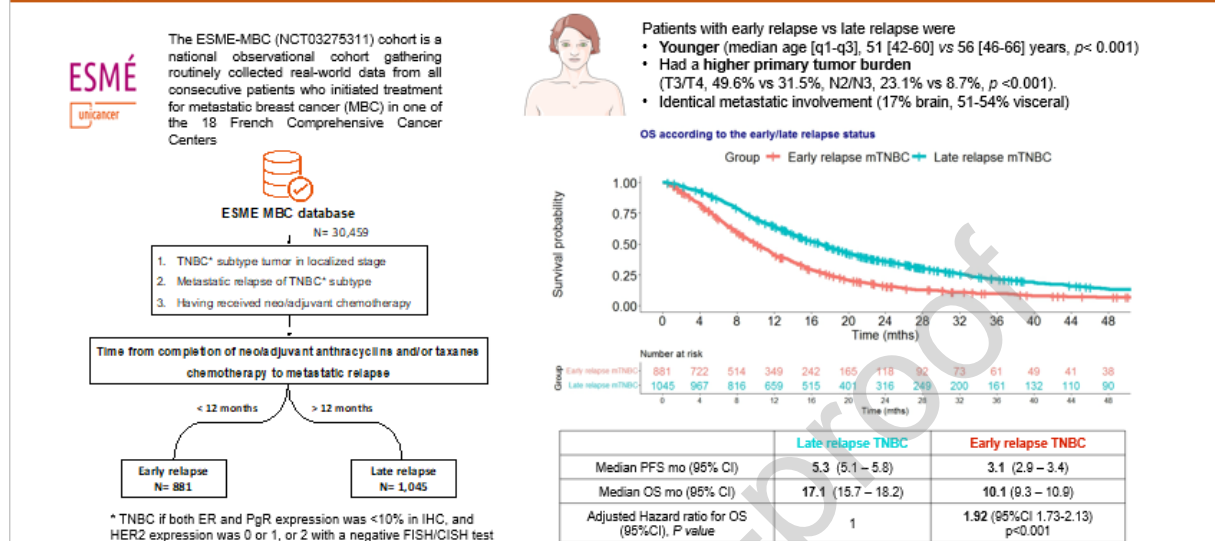
Dr Jacot reports Grants or contracts from Astra Zeneca and Daiichi Sankyo; Payment or honoraria for lectures from Astra Zeneca, Eisai, BMS, Lilly France, Daiichi Sankyo, MSD, Novartis, Pfizer, Roche, Seagen; Participation on a Data Safety Monitoring Board or Advisory Board from Astra Zeneca Eisai, BMS, Lilly France, Daiichi Sankyo, MSD, Novartis, Pfizer, Roche, Seagen.

Dr Pérol reports Grants or contracts from Roche and ESME, payment or honoraria for lectures from Astrazeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Eli-Lilly, Ipsen, Roche, Novartis, Merck Sharp And Dohme, Takeda, Janssen, Pfizer

Graphical abstract

Current and evolutionary analysis of early relapsed metastatic triple negative breast cancer in the Nationwide ESMÉ cohort

T. Grinda, A. Antoine, W. Jacot, PH Cottu, T de la Motte Rouge, J-S Frene, A. Mailliez, F. Dalenc, A. Goncalves, F. Clajot, M-A. Mouret Reynier, C. Levy, J-M Ferrero, I. Desmoulins, L. Ujwer, T. Peiff, C. Jouannaud, M. Amedeos, M. Chevrof, C. Courtinard, O. Tredan, E. Brain, D. Pérof, B. Pistilli, S. Delaloge



Highlights

- Patients with early relapse represent nearly 1/2 of the relapsing metastatic TNBC.
- Early relapsers were younger and had a higher tumor burden at primary diagnosis.
- Median OS of early relapsers was < 1 year (10.1 months vs 17.1 for late relapsers).
- The median PFS1 of early relapsers was lower than late relapsers (3.1 vs 5.3 mo).
- Early relapse is an independent prognostic factor for OS (HR 1.92(1.73-2.13) $p < 0.001$)
- Women with early relapsed metastatic TNBC represent a highly unmet medical need.