

Real-world Evidence of clinical and survival outcomes of patients with early relapsed triple-negative breast cancer from the ESME national cohort.

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Supplementary data

Supplementary Method 1

Selection of the covariates of the multivariate models:

Multivariable Cox proportional hazard models were performed using a backward stepwise selection to identify prognostic factors for OS and PFS1 early and late relapse metastatic TNBC. The covariates were selected using a conservative p value of 0.10 from the univariable analysis, except for covariate which was added because it is strongly recognized as a prognostic factor in the literature and/or is clinically relevant (5).

1- Multivariable analysis for PFS1 and OS in early relapsed mTNBC (Table 2)

The following covariates were selected using a conservative p value of 0.10 from the univariable analysis: Number and sites of metastases at diagnosis and treatment group in metastatic first-line. Taxanes use in neo/adjuvant setting and age groups at metastatic diagnosis were “forced” into PFS1 and OS models. Time interval to relapse from the end of neo/adjuvant chemotherapy was “forced” into OS model.

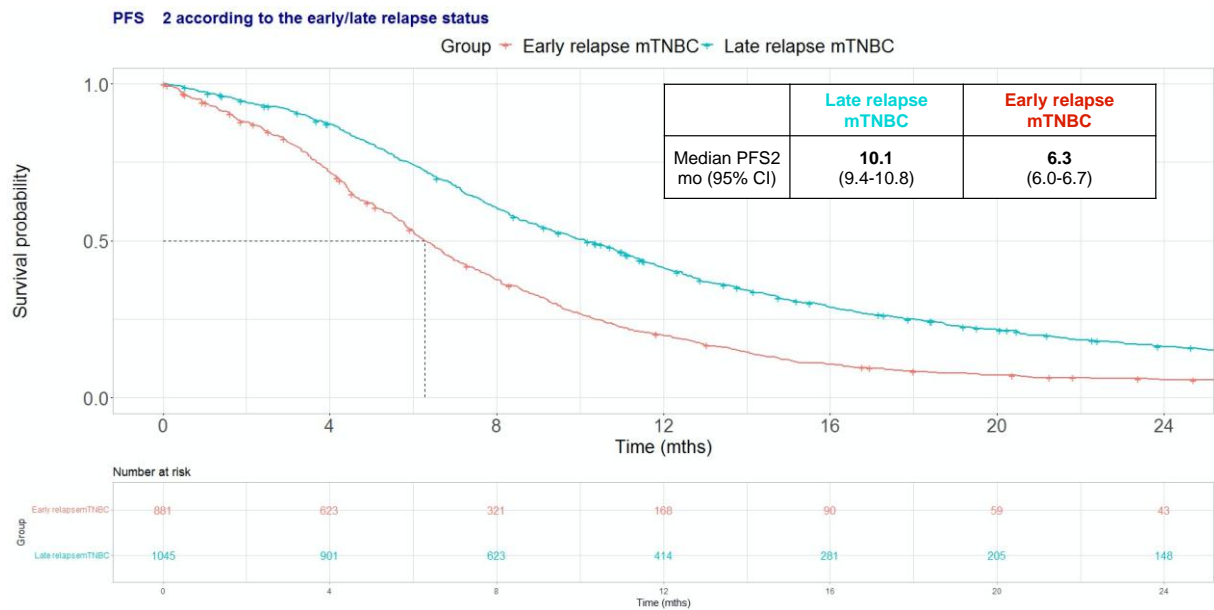
2- Multivariable analysis for PFS1 and OS in the whole sample (early + late relapsed mTNBC), (Supplementary Table 2)

The following covariates were selected using a conservative p value of 0.10 from the univariable analysis: time to relapse after completion of last neo/adjuvant therapy, number of metastatic sites at diagnosis, taxanes in neo/adjuvant setting. Age groups at metastatic diagnosis and capecitabine in neo/adjuvant setting was “forced” for OS and PFS1 models.

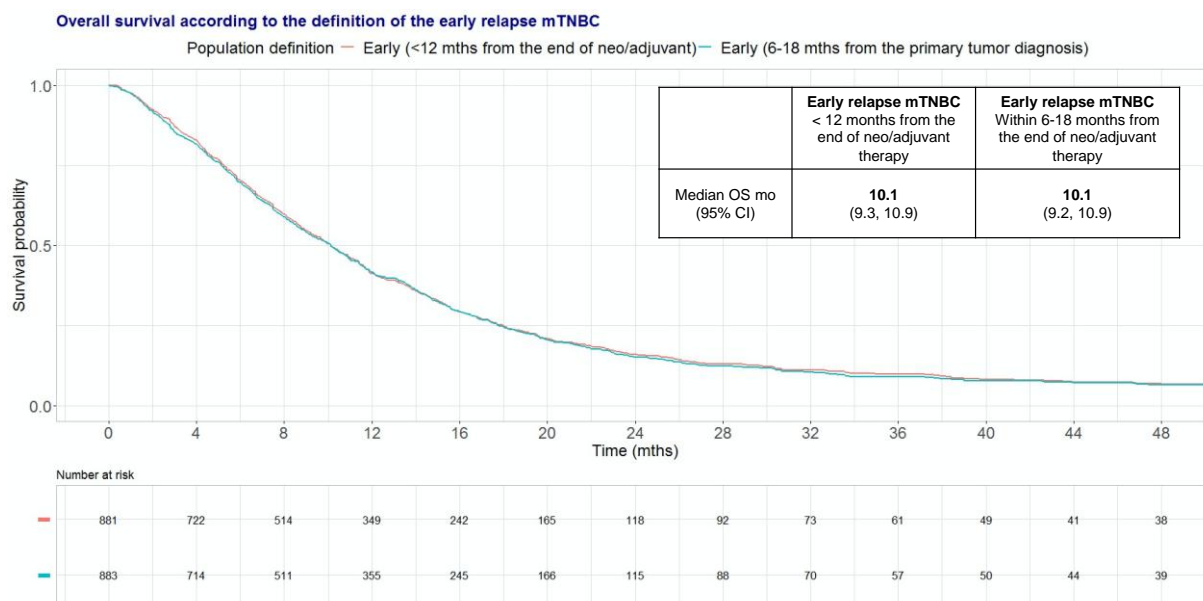
3- Multivariable analysis for OS within patients with early relapse mTNBC whose PS was available (Supplementary Table 3)

The following covariates were selected using a conservative p value of 0.10 from the univariable analysis: Number and sites of metastases at diagnosis and treatment group in metastatic first-line. Taxanes use in neo/adjuvant setting, age groups at metastatic diagnosis and time interval to relapse from the end of neo/adjuvant chemotherapy were “forced” into OS models.

Supplementary Figures



Supplementary Figure 1: Progression-free survival 2 by early versus late relapse



Supplementary Figure 2: Sensitivity analysis comparing OS using two definitions of early relapse: one by the time from last neo/adjuvant treatment (<12 months the other by the time elapsed between primary diagnosis and metastatic relapse (< 18 months)

As the two definitions are not exclusive, patients can be present in both curves.

Supplementary Tables

Supplementary Table 1 – Patients and tumors characteristics and description of prior treatments according to the study group and excluded patients' group

	Included sample (N=1,926)	No end date (N=350)	No neo/adjuvant CT (N=206)	p value
Age at MBC diag. (yrs)				< 0.001
N	1926	350	206	
Median (q1,q3)	53 (44, 63)	53 (45, 63)	73 (59, 80)	
Age groups at MBC diag. (yrs)				< 0.001
<50	774 (40.2%)	134 (38.3%)	22 (10.7%)	
>=50	1152 (59.8%)	216 (61.7%)	184 (89.3%)	
Year of M+ diagnosis (YOD)				< 0.001
2008-2012	759 (39.4%)	242 (69.1%)	103 (50.0%)	
2013-2017	789 (41.0%)	86 (24.6%)	74 (35.9%)	
2018-2020	378 (19.6%)	22 (6.3%)	29 (14.1%)	
Performance Status at M+ diag.				0.18
0	440 (37.4%)	38 (43.2%)	34 (30.4%)	
1	495 (42.1%)	35 (39.8%)	46 (41.1%)	
2-4	241 (20.5%)	15 (17.0%)	32 (28.6%)	

Supplementary Table 1 – Patients and tumors characteristics and description of prior treatments according to the study group and excluded patients' group

	Included sample (N=1,926)	No end date (N=350)	No neo/adjuvant CT (N=206)	p value
Missing	750	262	94	
No. of metastatic sites at M+ diag.				0.49
1	895 (46.5%)	167 (47.7%)	102 (49.5%)	
2	480 (24.9%)	97 (27.7%)	51 (24.8%)	
>=3	551 (28.6%)	86 (24.6%)	53 (25.7%)	
Metastatic sites at M+ diag.				0.007
Non-visceral metastases only	585 (30.4%)	112 (32.0%)	69 (33.5%)	
Visceral metastases excluding CNS	1018 (52.9%)	191 (54.6%)	122 (59.2%)	
CNS metastases	323 (16.8%)	47 (13.4%)	15 (7.3%)	
Histological type of initial diag.				< 0.001
Invasive ductal carcinoma (IDC)	1659 (86.1%)	307 (87.7%)	158 (76.7%)	
Other	267 (13.9%)	43 (12.3%)	48 (23.3%)	
Histological grade (SBR) at initial diag.				0.001
I/II	566 (30.4%)	84 (25.9%)	77 (41.2%)	
III	1296 (69.6%)	240 (74.1%)	110 (58.8%)	
Missing	64	26	19	
RT in (neo)adj setting				< 0.001
Yes	1711 (88.8%)	307 (87.7%)	138 (67.0%)	
No	215 (11.2%)	43 (12.3%)	68 (33.0%)	

Supplementary Table 2 – Description of first-line metastatic treatments in early relapsed mTNBC patients

Treatment	N	% (total)
Monotherapies	331	38.0%
Capecitabine	128	14,5%
Platinum salts	30	3,4%
Taxanes	61	6,9%
Eribuline	36	4,1%
Other	76	8,6%
Combinations	550	62.4%
Platinum + Gemcitabine	101	11.5%
Taxanes + Bevacizumab	152	17.3%
Other combinations	297	33.6%
----- Taxanes-based	92	10.4%
----- Platinum-based	141	15.9%
----- EC/FEC	20	2.2%
Anti-PD1/PDL1-based	23	2.6%
Included in clinical trial in mL1	150	17.0%

mTNBC: metastatic Triple negative breast cancer, E: Epirubicine, C: Cyclophocphamide, F: fluorouracil mL1: metastatic first line treatment, yrs: years, mo: months

Supplementary Table 3 - Multivariable analysis for PFS1 and OS in the whole sample (N= 1926)

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			<0.001
>=12	—	—		—	—	
<12	1.66	1.50, 1.83		1.92	1.73, 2.13	
Age groups at MBC diag. (yrs)			0.80			0.030
<50	—	—		—	—	
>=50	1.01	0.92, 1.11		1.12	1.01, 1.24	
No. of metastatic sites at MBC diag.			<0.001			<0.001
1	—	—		—	—	
2	1.38	1.22, 1.56		1.53	1.35, 1.74	
>=3	1.82	1.61, 2.07		2.41	2.11, 2.75	
Metastatic sites at MBC diag.			<0.001			<0.001
Non-visceral metastases only	—	—		—	—	
Visceral metastases excluding CNS	0.98	0.87, 1.11		1.14	1.00, 1.29	
CNS metastases	1.29	1.11, 1.50		1.63	1.40, 1.91	
Taxanes in neo/adj. setting			0.048			0.020
No	—	—		—	—	
Yes	1.16	1.00, 1.38		1.20	1.03, 1.40	
Capecitabine in neo/adj setting			0.37			0.057
No	—	—		—	—	
Yes	1.09	0.91, 1.29		1.20	1.00, 1.44	

MBC diag: metastatic diagnosis, HR = Hazard Ratio, CI = Confidence Interval, non-visceral metastasis: bone, skin, and lymph nodes, Visceral metastasis excluding brain, mL1: metastatic first line treatment, yrs: years, mo: months, mTNBC: metastatic triple negative breast cancer,

Supplementary Table 4 - Multivariable analysis for OS within patients with early relapse mTNBC whose PS was available (n=529)

Characteristic	HR	95% CI	p-value
<i>Time interval to relapse from the end of neo/adjuvant chemotherapy (mo)</i>			0.057
[0-6[—	—	
[6-12[0.83	0.69, 1.01	
<i>Age groups at MBC diag. (yrs)</i>			0.22
<50	—	—	
≥50	1.13	0.93, 1.36	
<i>No. of metastatic sites at MBC diag.</i>			<0.001
1	—	—	
2	1.49	1.18, 1.87	
≥3	2.40	1.87, 3.08	
<i>Metastatic sites at MBC diag.</i>			0.022
Non-visceral metastases only	—	—	
Visceral metastases excluding CNS	1.09	0.87, 1.37	
CNS metastases	1.50	1.12, 2.01	
<i>Performance Status at MBC diagnosis</i>			<0.001
0	—	—	
1	1.57	1.26, 1.96	
2-4	3.00	2.30, 3.90	
<i>Taxanes in neo/adjuvant setting</i>			0.79
No	—	—	
Yes	1.06	0.71, 1.58	
<i>Treatment group in mL1</i>			0.063
Monotherapies	—	—	
Combinations	0.83	0.68, 1.01	

mTNBC: metastatic triple negative breast cancer, PS: Performance status, HR: Hazard Ratio, CI: Confidence Interval, MBC diag: metastatic breast cancer diagnosis, non-visceral metastasis: bone, skin, and lymph nodes, Visceral metastasis is excluding brain, mL1: metastatic first line treatment, yrs: years, mo: months,