

Article

Not peer-reviewed version

---

# Overall Survival and Prognostic Factors in Metastatic Triple-Negative Breast Cancer: an NCDB Analysis

---

[Meghana Kesireddy](#)<sup>\*</sup>, Lina Elsayed, Valerie K Shostrom, Priyal Agarwal, [Samia Asif](#), Amulya Yellala, Jairam Krishnamurthy

Posted Date: 17 April 2024

doi: 10.20944/preprints202404.1138.v1

Keywords: metastatic triple negative breast cancer; overall survival; prognostic factors



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Article

# Overall Survival and Prognostic Factors in Metastatic Triple-Negative Breast Cancer: An NCDB Analysis

Meghana Kesireddy, M.D <sup>1,\*</sup>, Lina Elsayed, MBBch <sup>1</sup>, Valerie K. Shostrom, M.S <sup>2</sup>, Priyal Agarwal, M.D <sup>1</sup>, Samia Asif, M.D <sup>1</sup>, Amulya Yellala, M.D <sup>1</sup> and Jairam Krishnamurthy M.D <sup>1</sup>

<sup>1</sup> Division of Oncology and Hematology, Department of Internal Medicine, University of Nebraska Medical Center  
<sup>2</sup> Department of Biostatistics, University of Nebraska Medical Center.  
\* Correspondence: meghana.kesireddy@unmc.edu

**Simple Summary:** This should be written in one paragraph before the Abstract in layman’s terms, to explain why the research is being suggested, what the authors aim to achieve, and how the findings from this research may impact the research community. Please use as few abbreviations as possible and do not cite references in the Simple Summary. The Simple Summary should 100–150 words. Submissions without a simple summary will be returned directly. An example can be found at <https://www.mdpi.com/2072-6694/12/9/2424>.

**Abstract: Background:** Metastatic triple-negative breast cancer (TNBC) is aggressive with a poor median overall survival (OS), ranging from 8 to 13 months. There exists considerable heterogeneity in the survival at the individual patient level. To better understand the survival heterogeneity and improve risk stratification, our study aims to identify the factors influencing survival utilizing a large patient sample in the National Cancer Database (NCDB). **Methods:** Women diagnosed with metastatic TNBC from 2010 to 2020 in the NCDB were included. Demographic, clinic-pathological, treatment data, and overall survival (OS) outcomes were collected. Kaplan-Meier curves were used to estimate OS. The log-rank test was used to identify OS differences between groups for each variable in the univariate analysis. For the multivariate analysis, the Cox proportional hazard model with backward elimination was used to identify factors affecting OS. Adjusted hazard ratios and 95% confidence intervals are presented. **Results:** 2,273 women had a median overall survival of 13.6 months. Factors associated with statistically significantly worse OS included older age, higher comorbidity scores, specific histologies, higher number of metastatic sites, presence of liver or other site metastases in those with only one metastatic site (excluding brain metastases), presence of cranial and extra-cranial metastases, lack of chemotherapy, lack of immunotherapy, lack of surgery to distant sites, lack of radiation to distant sites, and receipt of palliative treatment to alleviate symptoms. In the multivariate analysis, comorbidity score, histology, number of metastatic sites, immunotherapy, and chemotherapy had a statistically significant effect on the OS. **Conclusions:** Through NCDB analysis, we have identified prognostic factors for metastatic TNBC. These findings will help improve prognostication at diagnosis, optimize treatment strategies, and facilitate patient stratification in future clinical trials.

**Keywords:** metastatic triple-negative breast cancer; overall survival; prognostic factors; national cancer database; demographic factors; clinic-pathological factors; treatment factors; cox proportional hazard model; multivariate analysis

## 1. Introduction

Breast cancer is the most commonly diagnosed cancer globally, surpassing lung cancer[1]. Triple-negative breast cancer (TNBC) accounts for 15-20% of all breast cancers[2]. TNBCs are estrogen and progesterone receptor-negative: <1% by immunohistochemistry (IHC) and human epidermal growth factor receptor 2 (HER2) negative (0-1+ by IHC or 2+ by IHC with FISH negative). TNBC is more commonly diagnosed in women younger than 40 (odds ratio of 2.13, 95% CI 1.34- 3.39) and

African-American women (odds ratio 2.41, 95% CI 1.81- 3.21) compared to those over 50 and Caucasian women respectively[3].

Compared to hormone receptor-positive or HER2-positive breast cancers, TNBC is known for its aggressiveness with larger tumor size, lymph node involvement, higher tumor grade, higher relapse rate of localized TNBC to metastatic TNBC, and a propensity for younger patients [3-5]. Individuals with TNBC experience an increased likelihood of distant recurrence within 5 years of diagnosis with a predilection for visceral as opposed to bony sites of relapse[6-9]. Due to the lack of biomarkers for targeted therapies like hormone receptor or HER-2 expression, there are only a few approved agents for TNBC, and the treatment mainly involves cytotoxic agents[10,11]. All these factors contribute to reduced overall survival in TNBC compared to other types of breast cancer, in both localized and metastatic settings. The 5- year overall survival (OS) for metastatic TNBC is around 11% with a median OS of around 11 to 13 months [5,12]. Despite this bleak prognosis, considerable prognostic heterogeneity exists at the individual patient level, with a wide range of OS of 0.8 months to 99.8 months [5,13].

To better understand this survival heterogeneity and improve risk stratification within de novo metastatic TNBC, our study aims to explore the impact of demographic factors, clinicopathological factors, and treatment factors on OS, utilizing a large patient sample in the National Cancer Data Base (NCDB).

## 2. Methods

This study utilized the National Cancer Database (NCDB) which includes over 1500 Commission on Cancer (CoC) programs that treat approximately 70% of all newly diagnosed cancers in the United States [14,15]. A retrospective review of de-identified patient data adhering to the established procedures for NCDB analyses was conducted and hence was exempt from our institutional review board. A total of 2,273 women diagnosed with metastatic TNBC between 2010 and 2020, each with all the required data, were included in our study.

Demographics (age, race, and Charlson-Deyo comorbidity score); clinico-pathological variables (histology, HER2 IHC expression, number of metastatic sites, and sites of metastases); and treatment variables (first-line chemotherapy, immunotherapy, days from diagnosis to systemic therapy, distant site surgery, distant site radiation, and palliative treatment to alleviate symptoms) were collected. Charlson-Deyo comorbidity scores were divided into 4 groups: score 0, score 1, score 2, and score 3 or more. Histology included invasive ductal carcinoma, invasive lobular carcinoma, adenocarcinoma with metaplasia, adenocarcinoma not otherwise specified (NOS), and other carcinomas. Other carcinomas included carcinoma NOS, small cell carcinoma, neuroendocrine carcinoma, non-small cell carcinoma, and inflammatory carcinoma predominantly; along with adenoid cystic and cribriform carcinoma and mucoepidermoid carcinoma. The number of metastatic sites refers to the number of organs involved with metastatic cancer. Time to initiation of systemic therapy initiation was categorized as < 2 weeks, 2-4 weeks, >4 weeks, and no systemic therapy. Palliative treatment was referred to as any treatment aimed to relieve symptoms and may involve surgery, radiation, systemic therapy, and/or other pain management. The overall survival (OS) was defined as the time from the diagnosis of metastatic TNBC until death.

Demographic, clinico-pathological data, and treatment data were described using frequencies and percentages. Kaplan-Meier (KM) curves were used to estimate the OS for each variable of interest. The log-rank test was used to identify OS differences between groups for each variable in the univariate analysis. The Cox proportional hazard model with backward elimination was used to identify factors affecting the OS in the multivariate analysis. The median OS in months, adjusted hazard ratios, and 12- month survival estimates with 95% confidence intervals (CI) were reported. PC SAS version 9.4 was used for all analyses. The statistical significance level was set at 0.05 for all analyses.

## 3. Results

A total of 2,273 women diagnosed with de novo metastatic TNBC had a median OS of 13.6 months (95% CI 12.81- 14.65). Table 1 details demographic, clinico-pathologic, and treatment variables. Most women were aged 41-70 (63.1%), Caucasian (67.4%), and had the Charlson-Deyo comorbidity score 0 (76.2%). The majority had invasive ductal carcinoma (81%), HER-2 IHC expression of 0 (53.5%), extra-cranial metastases only (89%), and a single metastatic site (49.7%). The majority of women received multi-agent chemotherapy as first-line therapy (41.6%), no immunotherapy (80.4%), had > 4 weeks from diagnosis to initiation of systemic therapy (49.8%), no surgery or radiation to the distant lymph node or metastatic site (93.9% and 70.5% respectively), and no palliative treatment to alleviate symptoms (75.7%).

**Table 1.** Univariate analysis of demographic, disease, and treatment characteristics on OS.

	No. of patients (% of total patients)	Median OS in months (95% CI)	Logrank p-value	Hazard Ratio (95% CI)	12-month survival estimates
Demographic Characteristics					
Age					
19-40	179 (7.9)	15.5 (13.2-	<0.0001	Reference	0.64 (0.57-0.72)
41-70	1435 (63.1)	18.2)		1.05 (0.87-1.27)	0.58 (0.55-0.60)
71-90	659 (29)	15.6 (14.2-16.7)		1.52 (1.24-1.85)	0.44 (0.41-0.48)
		9.6 (8.0-11.4)			
Race					
Caucasian	1532 (67.4)	13.6 (12.7-	0.2033	Reference	0.54 (0.52-0.57)
African-American	638 (28.1)	14.8)		1.02 (0.91-1.14)	0.54 (0.5-0.58)
Other	103 (4.5)	13.4 (11.9-15.2)		0.8 (0.62-1.03)	0.6 (0.51-0.71)
		16.9 (12.3-28.3)			
Charlson-Deyo score					
0	1732 (76.2)	15.3 (14.3-	< 0.0001	Reference	0.59 (0.56-0.61)
1	339 (14.9)	16.3)		1.22 (1.06-1.41)	0.46 (0.41-0.52)
2	118 (5.2)	10.4 (9.1-13.1)		1.8 (1.47-2.22)	0.35 (0.27-0.45)
3 or more	84 (3.7)	6.9 (5.2-9.6)		2.46 (1.94-3.12)	0.25 (0.17-0.36)
		4.6 (2.9- 6.9)			
Clinicopathologic/ Cancer Characteristics					
Histology					
Invasive ductal carcinoma	1840 (81)	15.2 (14.1-16.3)	< 0.0001	Reference	0.58 (0.56-0.60)
Invasive lobular carcinoma	79 (3.5)	12 (8.5-16.0)		1.23 (0.95 - 1.60)	0.49 (0.39-0.61)
Adenocarcinoma with metaplasia	64 (2.8)	14.0 (8.9-20.3)			0.54 (0.43-0.68)
Adenocarcinoma NOS	105 (4.6)	4.0 (2.9-8.1)		1.0 (0.73-1.4)	0.33 (0.25-0.44)
Other carcinoma	185 (8.1)	6.7 (5.2-9.3)		1.89 (1.51-2.37)	0.35 (0.29-0.43)
				1.83 (1.55-2.17)	
HER-2 IHC expression					
0	1217 (53.5)		0.3099	Reference	0.53 (0.50-0.56)

1+	634 (27.9)	13.1 (12.2-		0.95 (0.84-1.07)	0.55 (0.51-0.59)
2+	422 (18.6)	14.5)		0.91 (0.79-1.04)	0.57 (0.53-0.62)
		14.2 (12.5-			
		16.1)			
		14.7 (12.8-			
		17.2)			
No. of metastatic sites					
1	1129 (49.7)	19.8 (18.1-		Reference	0.67 (0.65-0.70)
2	603 (26.5)	22.2)		1.72 (1.53-1.94)	0.47 (0.43-0.51)
3	328 (14.4)	11 (9.8-12.3)	< 0.0001	1.99 (1.72-2.30)	0.43 (0.38-0.49)
4	157 (6.9)	9.1 (6.9-11.2)		3.16 (2.62-3.80)	0.24 (0.18-0.32)
5 and 6	56 (2.4)	4.6 (3.5-5.6)		4.61 (3.47-6.13)	0.17 (0.10-0.31)
		2.6 (2.2- 5)			
Site of metastatic involvement (subgroup analysis in those with single metastatic site only after excluding brain metastases )					
	233	24.4 (21.8-		Reference	0.8 (0.75-0.85)
LN only	317	33.5)	0.0001	1.36 (1.08-1.72)	0.67 (0.61-0.72)
Bone only	165	18.9 (16.6-		1.67 (1.29-2.17)	0.61 (0.54-0.69)
Liver only	286	24.7)		1.23 (0.97-1.56)	0.7 (0.65-0.76)
Lung only	83	15.6 (13.3-		1.85 (1.34-2.55)	0.5 (0.41-0.63)
Other only		19.4)			
		22.8 (17.6-			
		26.5)			
		12.3 (10.2-			
		23.0)			
Location of metastases					
Cranial only	45 (2)	11.8 (7.2-19.8)		Reference	0.47 (0.34-0.64)
Cranial +extra-cranial	204 (9)	5.3 (4.5-7.2)	< 0.0001	1.7 (1.16-2.49)	0.32 (0.26-0.4)
Extra-cranial only	2024 (89)	14.6 (13.6-15.8)		0.86 (0.60-1.22)	0.57 (0.55-0.59)
Treatment characteristics					
First-line chemotherapy					
None	613 (27)	2.9 (2.6-3.3)		Reference	0.18 (0.15-0.22)
Single-agent	714 (31.4)	16.4 (14.6-	< 0.0001	0.29 (0.25-0.33)	0.61 (0.58-0.65)
Multi-agent	946 (41.6)	18.4)		0.23 (0.21-0.26)	0.71 (0.68-0.74)
		19.9 (18.1-22)			
Immunotherapy					
No	1827 (80.4)	11.5 (10.9-	< 0.0001	Reference	0.49 (0.47-0.51)
Yes	446 (19.6)	12.6)		0.49 (0.42-0.56)	0.76 (0.72-0.80)

		25.6 (22.3-29.1)			
<b>Time from Dx to systemic therapy</b>					
<b>None</b>					
< 2 weeks	579 (25.5)	2.7 (2.4-3.1)		Reference	0.47 (0.39-0.56)
2-4 weeks	138 (6.1)	10.8 (9.2-15)	< 0.0001	0.34 (0.28-0.43)	0.61 (0.57-0.66)
>4 weeks	425 (18.7)	15.6 (14.2-16.8)		0.26 (0.23-0.31)	0.71 (0.68-0.73)
	1131 (49.8)	20.6 (19.3-22.6)		0.21 (0.18-0.23)	0.17 (0.14-0.2)
<b>Surgery of distant site (LN or other site)</b>					
No	2134 (93.9)	13.1 (12.5-14.1)	< 0.0001	Reference	0.53 (0.51-0.55)
Yes	106 (4.7)	29.2 (23.0-NE)		0.50 (0.38-0.66)	0.76 (0.69-0.85)
<b>Radiation to the distant site</b>					
No	1603 (70.5)	12.6 (11.5-13.6)	0.0204	Reference	0.51 (0.49-0.54)
Yes	482 (21.2)	14.7 (12.7-17.5)		0.86 (0.76-0.98)	0.57 (0.53-0.61)
<b>Palliative treatment (to alleviate symptoms)</b>					
No	1721 (75.7)	14.5 (13.5-15.6)	0.0037	Reference	0.56 (0.54-0.59)
Yes	552 (24.3)	11.3 (10.0-12.9)		1.18 (1.06-1.32)	0.48 (0.44-0.53)

Table 1 and 3 detail the median OS, Log rank p-value, Hazard ratio (HR), and the 12-month survival estimates of different groups for each demographic, clinico-pathologic, and treatment variable in the univariate analysis; and the results of the multi-variate analysis.

In the demographic variables, the OS was significantly worse for the 71-90 age group with the shortest median OS of 9.6 months compared to the 19-40 age group (HR 1.52, 95% CI 1.24- 1.85); the OS was similar in the 19-40 (median OS 15.5 months) and 41-70 age groups (median OS 15.6 months). The Charlson-Deyo comorbidity score groups of 1 (HR 1.22, 95% CI 1.06-1.41), 2 (HR 1.8, 95% CI 1.47-2.22), and 3 or more (HR 2.46, 95% CI 1.94-3.12) were associated with statistically significantly worse OS compared to the score 0 group, demonstrating a clear trend of decreasing survival as the comorbidity score increased. Women with a score of 3 or more had the shortest median OS of 4.6 months compared to the longest median OS of 15.3 months in the score 0 group. No significant differences were observed in the OS based on race (p= 0.2033).

Within the cancer related/ clinico-pathologic variables, OS was significantly worse for adenocarcinoma NOS with a median OS of 4 months (HR 1.89, 95% CI 1.51-2.37) and the other carcinoma group with a median OS of 6.7 months (HR 1.83, 95% CI 1.55-2.17) compared to the invasive ductal carcinoma group. However, OS was similar among invasive ductal carcinoma (median OS 15.2 months), invasive lobular carcinoma (median OS 12 months), and adenocarcinoma with metaplasia (median OS 14 months) groups. The number of metastatic sites of 2 (HR 1.72, 95% CI 1.53-1.94), 3 (HR 1.99, 95% CI 1.72-2.3), 4 (HR 3.16, 95% CI 2.62-3.8), 5 or 6 (HR 4.61, 95% CI 3.47-6.13) had statistically significantly worse OS compared to only 1 metastatic site, with a clear trend of decreasing survival as the metastatic sites increased. Women with 5 or 6 metastatic sites had the

shortest median OS of 2.6 months compared to the longest median OS of 19.8 months in the 1 metastatic site group. In the subgroup analysis of those with only single metastatic site (excluding brain-only metastases due to their known worse prognosis), women with bone only metastases (HR 1.36, 95% CI 1.08-1.72), liver only metastases (HR 1.67, 95% CI 1.29-2.17), other site only metastases (HR 1.85, 95% CI 1.34-2.55) had worse OS compared to those with lymph node only metastases; while the OS was similar in those with lymph node only metastases and lung only metastases. The OS was statistically significantly worse in those with both cranial and extra-cranial metastases with the shortest median OS of 5.3 months compared to cranial only metastases (HR 1.7, 95% CI 1.16-2.49), and OS was similar in the cranial only metastases (median OS 11.8 months) and extra-cranial only metastases (median OS 14.6 months). No significant differences were observed in the OS based on HER2 IHC expression (p= 0.3099).

In the treatment variables, OS was statistically significantly better for women who received either single agent first-line chemotherapy with a median OS of 16.4 months (HR 0.29, 95% CI 0.25-0.33) or multi-agent first-line chemotherapy with a median OS of 19.9 months (HR 0.23, 95% CI 0.21-0.26) compared to no chemotherapy with a median OS of 2.9 months. This improvement in OS with first-line chemotherapy remained consistent across all the Charlson-Deyo comorbidity score groups in the sub-group analysis, refer to table 2 for details. Women who received immunotherapy had a better OS with a median OS of 25.6 months compared to the median OS of 11.5 months in no immunotherapy group (HR 0.49, 95% CI 0.42-0.56). Regarding the time from diagnosis to initiation of systemic therapy, women with > 4 weeks had a better median OS of 20.6 months (HR 0.21, 95% CI 0.18-0.23), followed by those with 2-4 weeks who had a median OS of 15.6 months (HR 0.26, 95% CI 0.23-0.31) and those with < 2 weeks with a median OS of 10.8 (HR 0.34, 95% CI 0.28-0.43) compared to women with no systemic therapy who had a median OS of 2.7 months.

**Table 2.** Sub-group analysis of first-line chemotherapy receipt in each Charlson-Deyo comorbidity score groups.

	No. of patients	Median OS in months (95% CI)	Logrank p-value	Hazard Ratio (95% CI)	12-month survival estimates
Charlson-Deyo comorbidity score 0; no. of patients= 1732 (76.2%)					
First-line chemotherapy					
None	401	3.3 (2.9-4.0)	<0.0001	Reference	0.22 (0.18-0.27)
Single-agent	550	17.3 (15.5-19.7)		0.31 (0.27-0.36)	0.65 (0.61-0.69)
Multi-agent	781	20.1 (18.4-22.4)		0.26 (0.23-0.3)	0.72 (0.69-0.75)
Charlson-Deyo comorbidity score 1; no. of patients= 339 (14.9%)					
First-line chemotherapy					
None	111	2.4 (1.7-3.3)	<0.0001	Reference	0.15 (0.09-0.24)
Single-agent	112	13.1 (9.6-17.7)		0.28 (0.21-0.38)	0.51 (0.43-0.62)
Multi-agent	116	19.9 (16.4-29.1)		0.19 (0.14-0.26)	0.7 (0.62-0.79)
Charlson-Deyo comorbidity score 2; no. of patients= 118 (5.2%)					
First-line chemotherapy					
None	52	2.2 (1.4-3.4)	< 0.0001	Reference	0.08 (0.03-0.21)
Single-agent	31	13.2 (10.9- NE)		0.19 (0.11-0.33)	0.57 (0.41-0.77)
Multi-agent	35	16.8 (8.6-25.2)		0.21 (0.13-0.35)	0.54 (0.4-0.74)
Charlson-Deyo comorbidity score=3 or more; no. of patients= 84 (3.7%)					
First-line chemotherapy					
None	49	2.2 (1.5-3.7)		Reference	

**Commented [M1]:** Please cite the table in the text and ensure that the first citation of each table appears in numerical order.



Single-agent	21	10.9 (5.3-21.2)	< 0.0001	0.3 (0.16-0.54)	0.1 (0.04-
Multi-agent	14	12.1 (7.5- NE)		0.28 (0.14-0.56)	0.24)
					0.41 (0.24-0.7)
					0.5 (0.3-0.84)

Surgery of the distant lymph node or distant metastatic site was associated with significantly better OS with a median OS of 29.2 months compared to no surgery with a median OS of 13.1 months (HR 0.5, 95% CI 0.38-0.66). Similarly, women who received radiation to distant site had a significantly better OS with a median OS of 14.7 months compared to no radiation with a median OS of 12.6 months (HR 0.86, 95% CI 0.76-0.98). However, the receipt of palliative treatment to alleviate symptoms was associated with significantly worse OS with a median of 11.3 months compared to no palliative treatment with a median OS of 14.5 months (HR 1.18, 95% CI 1.06-1.32).

Based on the results from the univariate analysis, the following variables were included in the final multivariate analysis: age, Charlson-Deyo comorbidity score group, histology, number of metastatic sites, site of metastases: cranial only/ cranial and extra-cranial/ extra-cranial only, receipt of first line chemotherapy, receipt of immunotherapy, and receipt of palliative treatment to alleviate symptoms. In the multi-variate cox proportional hazard analysis; the Charlson-Deyo comorbidity score, histology, number of metastatic sites, receipt of first-line chemotherapy and receipt of immunotherapy were identified as the five factors independently influencing OS, as detailed in Table 3. Figure 1 displays the univariate Kaplan-Meier survival curves for these five prognostic factors. Surgery and radiation of the distant site variables were excluded from multi-variate analysis, despite significance in the univariate analysis, due to missing information in some patients. Similarly, the time from diagnosis to initiation of systemic therapy variable was also excluded due to its overlapping subgroups with first-line chemotherapy variable.

Table 3. Multi-variate Cox proportional Hazard analysis.

	Hazard ratio (95% CI)	Overall p-value
<b>Charlson-Deyo score</b>		
0	Reference	
1	1.23 (1.07-1.42)	
2	1.57 (1.27-1.93)	< 0.0001
3	1.97 (1.55- 2.51)	
<b>Histology</b>		
Invasive ductal carcinoma	Reference	
Invasive lobular carcinoma	1.04 (0.80-1.35)	
Adenocarcinoma with metaplasia	0.83 (0.60-1.14)	
Adenocarcinoma NOS	1.29 (1.03-1.62)	< 0.0001
Other carcinoma	1.54 (1.29-1.82)	
<b>No. of metastatic sites</b>		
1	Reference	
2	1.90 (1.69-2.15)	
3	2.16 (1.86-2.5)	< 0.0001
4	3.58 (2.96-4.33)	
5 and 6	4.81 (3.61-6.42)	
<b>First-line chemotherapy</b>		
None	Reference	
Single-agent and Multi-agent	0.28 (0.25-0.32)	< 0.0001
<b>Immunotherapy</b>		
No	Reference	
Yes	0.56 (0.49-0.65)	< 0.0001



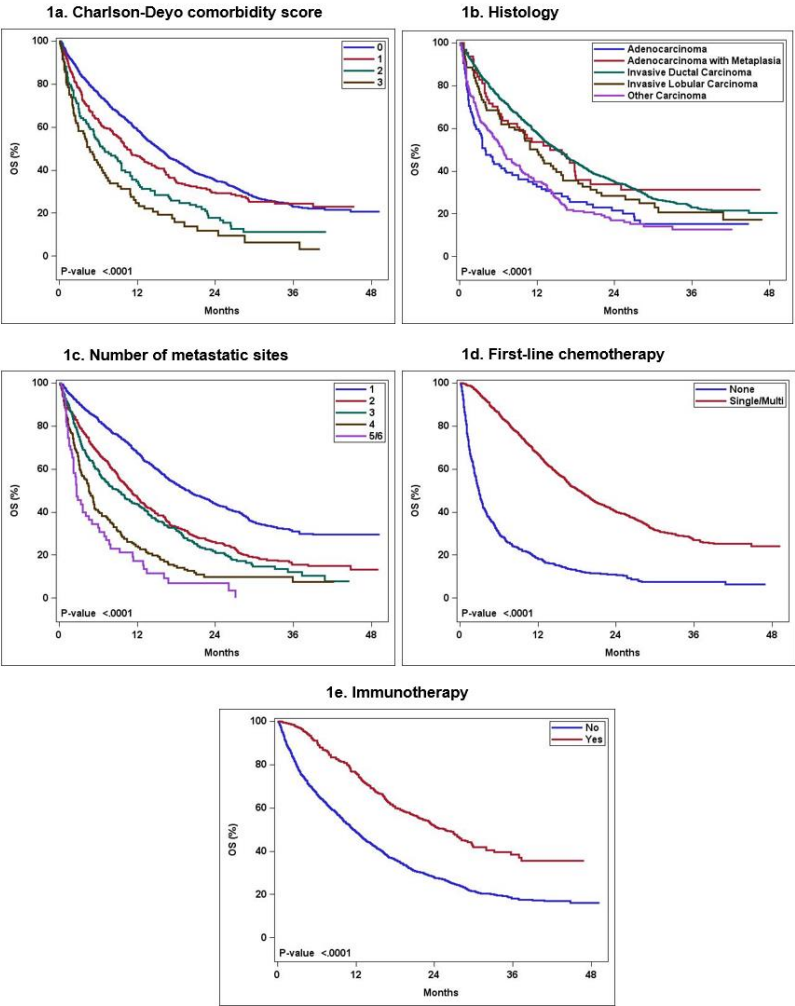


Figure 1. Kaplan-Meier survival curves of the five significant variables in the multi-variate analysis.

4. Discussion

Prognostication based on the results observed in therapeutic clinical trials may not realistically estimate prognosis in the real-world. Fewer comorbidities and better functional status due to stringent eligibility criteria, lower cancer burden without visceral crisis or severe symptoms, better treatment compliance, and increased access to health care and other supportive resources typically seen in participants leads to longer OS in clinical trials [16-18]. A meta-analysis of three phase III trials of first line treatment in metastatic TNBC reported a median OS of 17.5 months, surpassing the real-world OS estimates of 11 to 13 months [5,12,18,19]. These reported real-world studies, with limited sample size and selective representation, may not accurately reflect the diverse TNBC patient population in the United States. Our study, the largest to date, included 2,273 metastatic TNBC women from the NCDB, encompassing data from multiple institutions treating over 70 percent of all

cancer patients in the United States. It revealed a median OS of 13.6 months, consistent with prior reports.

We identified 5 independent prognostic variables for survival in metastatic TNBC in the multivariate analysis: Charlson-Deyo comorbidity score, histology, number of metastatic sites, receipt of first-line chemotherapy and receipt of immunotherapy. Affirming the crucial role of overall health in prognosis, there was an inverse correlation between Charlson-Deyo comorbidity score and OS. This finding was consistent with a prior study in non-metastatic TNBC that showed those with a Charlson comorbidity index score of  $\geq 3$  had a significantly higher risk of death compared to those without comorbidities in African-American patients, and comorbidities at diagnosis increased risk of death independent of TNBC [20]. In the metastatic setting, our study demonstrated that histology is an independent prognostic factor. Invasive ductal carcinoma, invasive lobular carcinoma, and adenocarcinoma with metaplasia had similar OS, while the adenocarcinoma NOS and other carcinoma (encompassing aggressive histologies like inflammatory carcinoma, neuroendocrine carcinoma, small cell carcinoma) exhibited worse OS. In non-metastatic TNBC, prior studies showed that invasive lobular carcinoma and metaplastic carcinoma were associated with worse OS compared to invasive ductal carcinoma [21,22]. However, another study, adjusting for tumor stage and demographics, found similar OS between invasive lobular carcinoma and invasive ductal carcinoma [23], highlighting the potential OS differences between invasive lobular carcinoma and invasive ductal carcinoma in previous studies due to selection bias and inadequate adjustment for clinically relevant covariates. In our study, there was an inverse correlation between the number of metastatic sites and OS suggesting that the number of metastatic sites may reflect disease burden. This finding was consistent with a prior study that showed higher risk of death for those with more than one metastatic site compared to those with only one metastatic site in TNBC [12]. Receipt of first-line chemotherapy, either single agent or multi-agent, the primary backbone of treatment for metastatic TNBC, was an independent prognostic factor for OS, as those not receiving experienced worse OS likely due to faster cancer progression. Receipt of immunotherapy was also an independent prognostic factor, associated with better OS, consistent with the results from Impassion 130 and Keynote 522 trials. In 2019, Atezolizumab, a PD-L1 inhibitor, was approved as a first line treatment in combination with chemotherapy for PD-L1  $\geq 1\%$  tumors based on the Impassion130 trial but was later withdrawn in 2021 due to a lack of PFS and OS improvement in the Impassion 131 trial [24,25]. In 2020, Pembrolizumab, a PD-1 inhibitor was approved as first line treatment in combination with chemotherapy in PD-L1  $\geq 10\%$  tumors based on the Keynote 355 trial [26]. PD-L1 positivity in TNBC is approximately 20-47% [27,28]. In our study, which included patients from 2010-2020, 19.6% of total patients received immunotherapy, some likely in later lines after having received other treatments before the immunotherapy approval.

In our study, poor OS was observed in the 71-90 age group in univariate analyses, but age was not an independent prognostic factor in multi-variate analyses. A prior study on metastatic TNBC surprisingly revealed a poor prognosis in those under 50 years old [5]. Studies in non-metastatic TNBC examining the impact of age at diagnosis on OS yielded conflicting results [29-31]. Age itself may not be an independent prognostic factor, but advanced age is usually linked to a higher burden of comorbidities, poor overall health, and potentially lower chemotherapy uptake, adversely affecting OS [16]. Thus, treatment decisions should consider functional age over chronological age [32]. While OS was worse for those with both cranial and extra-cranial metastases in the univariate analyses, the location of metastases (cranial only Vs. cranial and extra-cranial Vs. extra-cranial only) has lost significance in the multi-variate analyses. TNBC typically has a higher incidence of brain metastases at 30% with a median OS of 5 months after brain metastases [33,34]. Factors impacting mortality in brain metastases include having more than 3 brain lesions, symptomatic brain metastases, lack of brain metastases directed treatment, and uncontrolled extracranial metastases [35]. It is possible that the location of metastases did not emerge as an independent prognostic factor in our study due to smaller number of patients with cranial metastases (only 2% had cranial only metastases and 9% had both cranial and extra-cranial metastases). Alternatively, it is possible that overall cancer burden and ability to receive treatment (both systemic therapy and brain metastases

directed local treatments like radiation) are the clinically relevant confounding covariates impacting OS rather than the presence of brain metastases itself. Palliative treatment (to alleviate symptoms), despite showing an association with poor OS in the univariate analysis, was not identified as an independent prognostic factor in the multi-variate analysis, as it likely reflects higher disease burden rather than treatment impact.

In the subgroup analysis of patients with a single metastatic site (excluding brain-only metastases due to their known worse prognosis) [33,35], those with lung only metastases or distant lymph node only mets demonstrated better OS, indicating potential prognostic implications of the site of metastatic disease in this subgroup that warrants further evaluation in future studies. Additionally, the sub-group analysis of first line chemotherapy across all Charlson-Deyo score groups showed that, despite an increased percentage of patients not receiving chemotherapy with higher Charlson-Deyo scores, those who received chemotherapy had better OS in all score groups. This suggests that a higher comorbidity score itself should not automatically deter chemotherapy administration unless there are contra-indications or concerns about serious toxicity.

Receiving chemotherapy more than 4 weeks after diagnosis showed better OS in the univariate analysis, indicating that a delay in chemotherapy initiation by a few weeks may not harm OS in metastatic TNBC. This contrasts with non-metastatic TNBC, where a delay in adjuvant chemotherapy initiation by  $\geq 30$  days after surgery was associated with worse OS and recurrence free survival [36,37]. The better OS associated with surgery or radiation to the distant metastatic site in the univariate analysis may be due to selection bias; as these patients are likely to be younger, healthier, and have less metastatic burden to be considered for locoregional treatments. The role of these variables could not be assessed in the multivariate analyses due to missing information in some study patients whether they received surgery or radiation to the distant site. Currently, there is no compelling prospective evidence supporting surgery or radiation to distant metastatic site in TNBC management. The SABR COMET study showed an OS advantage with stereotactic radiation in oligometastatic cancer (only 18 out of the 99 patients had breast cancer), but the NRG BR-00213 study done exclusively in breast cancer patients showed no OS benefit [38]. Similarly, randomized controlled data for surgery of the primary tumor have not demonstrated an OS benefit, and there are no randomized trials examining surgery of the distant metastatic sites[39].

Previous studies on racial disparities in TNBC OS outcomes yielded inconsistent results [11,12,40-42]. Disparities in comorbidities and care may have contributed to worse OS outcomes for African-Americans in some studies as no racial differences in TNBC survival were observed when they received similar treatment under comparable conditions [20,40,41]. In our study, OS did not significantly differ among races, indicating metastatic TNBC behaves biologically similarly across all racial groups and equitable access to health care are likely to result in similar OS. HER-2 expression level in TNBC does not influence biology or gene expression [43], hence HER-2 expression level itself did not influence OS in our study, aligning with findings in other studies [44]. However, with the newer treatment option, Trastuzumab deruxtecan, approved for metastatic HER-2 low ( IHC 1+ or IHC 2+ with negative FISH) TNBC in 2022 based on the DESTINY BREAST-04 trial, patients with HER-2 low TNBC are likely to have better OS than those with HER-2 zero TNBC in the future[45].

One limitation of our study is that the newer FDA-approved treatments like Olaparib/ Talazoparib (PARP inhibitors), Atezolizumab (PD-L1 inhibitor, later withdrawn from the market in 2021), Pembrolizumab (PD-1 inhibitor), Sacituzumab govitecan (Trop-2 directed antibody drug conjugate), and Trastuzumab deruxtecan (HER-2 directed antibody drug conjugate), introduced mainly after 2018, have resulted in slightly improved OS for metastatic TNBC, which is not completely reflected in our 2010-2020 data [26,45-49]. While these new treatments demonstrated improved OS in clinical trials, it is important to note that the absolute difference in OS ranged only from 0 to 6 months compared to control arms. In the real world, this OS difference may be even smaller, as patients tend to experience better outcomes in clinical trials than in real-world settings. Our study results will serve as a benchmark for assessing progress in treatment of metastatic TNBC in future decades.

Our study's limitations stem from the NCDB, a hospital-based data collection system that pools data from multiple centers, which may introduce variations in data collection due to possible distinct data collection standards at each center, alongside potential errors during data abstraction and entry from the medical records. The NCDB also lacks information about relapsed metastatic TNBC, response to first-line therapy, longitudinal treatment data (provides only first line treatment without subsequent treatment information), patient reported outcomes like quality of life, and cause of death.

## 5. Conclusions

In conclusion, our study on OS in metastatic TNBC is the largest of its kind to comprehensively explore the impact of various factors on OS to better understand the survival heterogeneity. These findings empower clinicians to offer personalized prognostic information at diagnosis and tailor treatment strategies. This may involve considering options of aggressive systemic therapy versus focusing on comfort/quality of life based on expected prognosis, and the consideration for more frequent scans to assess response to treatment given short window for therapeutic interventions, especially in those with poor prognostic factors. Our study highlights the clear unmet need for newer therapeutic options to improve outcomes particularly for those with poor prognostic factors and can aid in the development of prognostic groups for use in future clinical trials.

**Author Contributions:** For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis, X.X.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing—original draft preparation, X.X.; writing—review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript." Please turn to the [CRediT taxonomy](#) for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

**Funding:** Please add: "This research received no external funding" or "This research was funded by NAME OF FUNDER, grant number XXX" and "The APC was funded by XXX". Check carefully that the details given are accurate and use the standard spelling of funding agency names at <https://search.crossref.org/funding>. Any errors may affect your future funding.

**Institutional Review Board Statement:** In this section, you should add the Institutional Review Board Statement and approval number, if relevant to your study. You might choose to exclude this statement if the study did not require ethical approval. Please note that the Editorial Office might ask you for further information. Please add "The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of NAME OF INSTITUTE (protocol code XXX and date of approval)." for studies involving humans. OR "The animal study protocol was approved by the Institutional Review Board (or Ethics Committee) of NAME OF INSTITUTE (protocol code XXX and date of approval)." for studies involving animals. OR "Ethical review and approval were waived for this study due to REASON (please provide a detailed justification)." OR "Not applicable" for studies not involving humans or animals.

**Informed Consent Statement:** Any research article describing a study involving humans should contain this statement. Please add "Informed consent was obtained from all subjects involved in the study." OR "Patient consent was waived due to REASON (please provide a detailed justification)." OR "Not applicable." for studies not involving humans. You might also choose to exclude this statement if the study did not involve humans. Written informed consent for publication must be obtained from participating patients who can be identified (including by the patients themselves). Please state "Written informed consent has been obtained from the patient(s) to publish this paper" if applicable.

**Data Availability Statement:** In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Please refer to suggested Data Availability Statements in section "MDPI Research Data Policies" at <https://www.mdpi.com/ethics>. If the study did not report any data, you might add "Not applicable" here. "Not applicable." can only be used in Review type. For most of the articles Article/Brief Report/Communication etc (research article types), data are actually included. If the authors state the DAS as "Not applicable.", please use "Data are contained within the article." or "Data are contained within the article and supplementary materials."

**Commented [M2]:** There is our template, please provide information here in all back part, following highlights are the same

**Acknowledgments:** In this section, you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

**Conflicts of Interest:** Declare conflicts of interest or state “The authors declare no conflict of interest.” Authors must identify and declare any personal circumstances or interest that may be perceived as inappropriately influencing the representation or interpretation of reported research results. Any role of the funders in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript, or in the decision to publish the results must be declared in this section. If there is no role, please state “The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results”.

## References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: a cancer journal for clinicians* **2021**, *71*, 209-249, doi:10.3322/caac.21660.
2. Foulkes, W.D.; Smith, I.E.; Reis-Filho, J.S. Triple-negative breast cancer. *N Engl J Med* **2010**, *363*, 1938-1948, doi:10.1056/NEJMra1001389.
3. Trivers, K.F.; Lund, M.J.; Porter, P.L.; Liff, J.M.; Flagg, E.W.; Coates, R.J.; Eley, J.W. The epidemiology of triple-negative breast cancer, including race. *Cancer Causes Control* **2009**, *20*, 1071-1082, doi:10.1007/s10552-009-9331-1.
4. Nam, Y.H. A Study on the Factors and Prediction Model of Triple-Negative Breast Cancer for Public Health Promotion. *Diagnostics (Basel)* **2023**, *13*, doi:10.3390/diagnostics13223486.
5. Kassam, F.; Enright, K.; Dent, R.; Dranitsaris, G.; Myers, J.; Flynn, C.; Fralick, M.; Kumar, R.; Clemons, M. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. *Clin Breast Cancer* **2009**, *9*, 29-33, doi:10.3816/CBC.2009.n.005.
6. Rodriguez-Pinilla, S.M.; Sarrio, D.; Honrado, E.; Hardisson, D.; Calero, F.; Benitez, J.; Palacios, J. Prognostic significance of basal-like phenotype and fascin expression in node-negative invasive breast carcinomas. *Clin Cancer Res* **2006**, *12*, 1533-1539, doi:10.1158/1078-0432.CCR-05-2281.
7. Therasse, P.; Arbuck, S.G.; Eisenhauer, E.A.; Wanders, J.; Kaplan, R.S.; Rubinstein, L.; Verweij, J.; Van Glabbeke, M.; van Oosterom, A.T.; Christian, M.C., et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* **2000**, *92*, 205-216, doi:10.1093/jnci/92.3.205.
8. Dent, R.; Hanna, W.M.; Trudeau, M.; Rawlinson, E.; Sun, P.; Narod, S.A. Pattern of metastatic spread in triple-negative breast cancer. *Breast Cancer Res Treat* **2009**, *115*, 423-428, doi:10.1007/s10549-008-0086-2.
9. Mandapati, A.; Lukong, K.E. Triple negative breast cancer: approved treatment options and their mechanisms of action. *J Cancer Res Clin Oncol* **2023**, *149*, 3701-3719, doi:10.1007/s00432-022-04189-6.
10. Banerjee, S.; Reis-Filho, J.S.; Ashley, S.; Steele, D.; Ashworth, A.; Lakhani, S.R.; Smith, I.E. Basal-like breast carcinomas: clinical outcome and response to chemotherapy. *J Clin Pathol* **2006**, *59*, 729-735, doi:10.1136/jcp.2005.033043.
11. Bauer, K.R.; Brown, M.; Cress, R.D.; Parise, C.A.; Caggiano, V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. *Cancer* **2007**, *109*, 1721-1728, doi:10.1002/cncr.22618.
12. Skinner, K.E.; Haiderali, A.; Huang, M.; Schwartzberg, L.S. Real-world effectiveness outcomes in patients diagnosed with metastatic triple-negative breast cancer. *Future Oncol* **2021**, *17*, 931-941, doi:10.2217/fon-2020-1021.
13. Dent, R.; Trudeau, M.; Pritchard, K.I.; Hanna, W.M.; Kahn, H.K.; Sawka, C.A.; Lickley, L.A.; Rawlinson, E.; Sun, P.; Narod, S.A. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res* **2007**, *13*, 4429-4434, doi:10.1158/1078-0432.CCR-06-3045.
14. Bilimoria, K.Y.; Stewart, A.K.; Winchester, D.P.; Ko, C.Y. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol* **2008**, *15*, 683-690, doi:10.1245/s10434-007-9747-3.
15. Boffa, D.J.; Rosen, J.E.; Mallin, K.; Loomis, A.; Gay, G.; Palis, B.; Thoburn, K.; Gress, D.; McKellar, D.P.; Shulman, L.N., et al. Using the National Cancer Database for Outcomes Research: A Review. *JAMA Oncol* **2017**, *3*, 1722-1728, doi:10.1001/jamaoncol.2016.6905.
16. Batra, A.; Kong, S.; Cheung, W.Y. Eligibility of real-world patients with metastatic breast cancer for clinical trials. *Breast* **2020**, *54*, 171-178, doi:10.1016/j.breast.2020.10.005.

17. Gong, I.Y.; Yan, A.T.; Earle, C.C.; Trudeau, M.E.; Eisen, A.; Chan, K.K.W. Comparison of outcomes in a population-based cohort of metastatic breast cancer patients receiving anti-HER2 therapy with clinical trial outcomes. *Breast Cancer Res Treat* **2020**, *181*, 155-165, doi:10.1007/s10549-020-05614-5.
18. Li, C.H.; Karantz, V.; Aktan, G.; Lala, M. Current treatment landscape for patients with locally recurrent inoperable or metastatic triple-negative breast cancer: a systematic literature review. *Breast Cancer Res* **2019**, *21*, 143, doi:10.1186/s13058-019-1210-4.
19. Celik, A.; Berg, T.; Jensen, M.B.; Jakobsen, E.; Nielsen, H.M.; Kümler, I.; Glavicic, V.; Jensen, J.D.; Knoop, A. Real-World Survival and Treatment Regimens Across First- to Third-Line Treatment for Advanced Triple-Negative Breast Cancer. *Breast Cancer (Auckl)* **2023**, *17*, 11782234231203292, doi:10.1177/11782234231203292.
20. Swede, H.; Sarwar, A.; Magge, A.; Braithwaite, D.; Cook, L.S.; Gregorio, D.I.; Jones, B.A.; R Hoag, J.; Gonsalves, L.; L Salner, A., et al. Mortality risk from comorbidities independent of triple-negative breast cancer status: NCI-SEER-based cohort analysis. *Cancer Causes Control* **2016**, *27*, 627-636, doi:10.1007/s10552-016-0736-3.
21. Montagna, E.; Maisonneuve, P.; Rotmensz, N.; Cancelli, G.; Iorfida, M.; Balduzzi, A.; Galimberti, V.; Veronesi, P.; Luini, A.; Pruneri, G., et al. Heterogeneity of triple-negative breast cancer: histologic subtyping to inform the outcome. *Clin Breast Cancer* **2013**, *13*, 31-39, doi:10.1016/j.clbc.2012.09.002.
22. Balkenhol, M.C.A.; Vreuls, W.; Wauters, C.A.P.; Mol, S.J.J.; van der Laak, J.A.W.M.; Bult, P. Histological subtypes in triple negative breast cancer are associated with specific information on survival. *Ann Diagn Pathol* **2020**, *46*, 151490, doi:10.1016/j.anndiagpath.2020.151490.
23. Joshi, U.; Budhathoki, P.; Gaire, S.; Yadav, S.K.; Shah, A.; Adhikari, A.; Choong, G.; Couzi, R.; Giridhar, K.V.; Leon-Ferre, R.A., et al. Clinical outcomes and prognostic factors in triple-negative invasive lobular carcinoma of the breast. *Breast Cancer Res Treat* **2023**, *200*, 217-224, doi:10.1007/s10549-023-06959-3.
24. Miles, D.; Gligorov, J.; André, F.; Cameron, D.; Schneeweiss, A.; Barrios, C.; Xu, B.; Wardley, A.; Kaen, D.; Andrade, L., et al. Primary results from IMPassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. *Ann Oncol* **2021**, *32*, 994-1004, doi:10.1016/j.annonc.2021.05.801.
25. Schmid, P.; Adams, S.; Rugo, H.S.; Schneeweiss, A.; Barrios, C.H.; Iwata, H.; Diéras, V.; Hegg, R.; Im, S.A.; Shaw Wright, G., et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* **2018**, *379*, 2108-2121, doi:10.1056/NEJMoa1809615.
26. Cortes, J.; Rugo, H.S.; Cescon, D.W.; Im, S.A.; Yusuf, M.M.; Gallardo, C.; Lipatov, O.; Barrios, C.H.; Perez-Garcia, J.; Iwata, H., et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. *N Engl J Med* **2022**, *387*, 217-226, doi:10.1056/NEJMoa2202809.
27. Mittendorf, E.A.; Phillips, A.V.; Meric-Bernstam, F.; Qiao, N.; Wu, Y.; Harrington, S.; Su, X.; Wang, Y.; Gonzalez-Angulo, A.M.; Akcakanat, A., et al. PD-L1 expression in triple-negative breast cancer. *Cancer Immunol Res* **2014**, *2*, 361-370, doi:10.1158/2326-6066.CIR-13-0127.
28. Zhou, T.; Xu, D.; Tang, B.; Ren, Y.; Han, Y.; Liang, G.; Wang, J.; Wang, L. Expression of programmed death ligand-1 and programmed death-1 in samples of invasive ductal carcinoma of the breast and its correlation with prognosis. *Anticancer Drugs* **2018**, *29*, 904-910, doi:10.1097/CAD.0000000000000683.
29. Kaplan, H.G.; Malmgren, J.A.; Atwood, M.K. Triple-negative breast cancer in the elderly: Prognosis and treatment. *Breast J* **2017**, *23*, 630-637, doi:10.1111/tbj.12813.
30. Rayson, D.; Payne, J.I.; Michael, J.C.R.; Tsuruda, K.M.; Abdolell, M.; Barnes, P.J. Impact of Detection Method and Age on Survival Outcomes in Triple-Negative Breast Cancer: A Population-Based Cohort Analysis. *Clin Breast Cancer* **2018**, *18*, e955-e960, doi:10.1016/j.clbc.2018.04.013.
31. Zhu, W.; Perez, E.A.; Hong, R.; Li, Q.; Xu, B. Age-Related Disparity in Immediate Prognosis of Patients with Triple-Negative Breast Cancer: A Population-Based Study from SEER Cancer Registries. *PLoS One* **2015**, *10*, e0128345, doi:10.1371/journal.pone.0128345.
32. Maltoni, R.; Ravaioli, S.; Bronte, G.; Mazza, M.; Cerchione, C.; Massa, I.; Balzi, W.; Cortesi, M.; Zanoni, M.; Bravaccini, S. Chronological age or biological age: What drives the choice of adjuvant treatment in elderly breast cancer patients? *Transl Oncol* **2022**, *15*, 101300, doi:10.1016/j.tranon.2021.101300.
33. Morris, P.G.; Murphy, C.G.; Mallam, D.; Accordino, M.; Patil, S.; Howard, J.; Omuro, A.; Beal, K.; Seidman, A.D.; Hudis, C.A., et al. Limited overall survival in patients with brain metastases from triple negative breast cancer. *Breast J* **2012**, *18*, 345-350, doi:10.1111/j.1524-4741.2012.01246.x.
34. Venkitaraman, R.; Joseph, T.; Dhadda, A.; Chaturvedi, A.; Upadhyay, S. Prognosis of patients with triple-negative breast cancer and brain metastasis. *Clin Oncol (R Coll Radiol)* **2009**, *21*, 729-730, doi:10.1016/j.clon.2009.07.002.
35. Jin, J.; Gao, Y.; Zhang, J.; Wang, L.; Wang, B.; Cao, J.; Shao, Z.; Wang, Z. Incidence, pattern and prognosis of brain metastases in patients with metastatic triple negative breast cancer. *BMC Cancer* **2018**, *18*, 446, doi:10.1186/s12885-018-4371-0.



36. Cai, L.; Tong, Y.; Zhu, X.; Shen, K.; Zhu, J.; Chen, X. Prolonged Time to Adjuvant Chemotherapy Initiation Was Associated with Worse Disease Outcome in Triple Negative Breast Cancer Patients. *Sci Rep* **2020**, *10*, 7029, doi:10.1038/s41598-020-64005-4.
37. Morante, Z.; Ruiz, R.; Araujo, J.M.; Pinto, J.A.; Cruz-Ku, G.; Urrunaga-Pastor, D.; Namuche, F.; Flores, C.; Mantilla, R.; Luján, M.G., et al. Impact of the Delayed Initiation of Adjuvant Chemotherapy in the Outcome of Triple Negative Breast Cancer. *Clin Breast Cancer* **2021**, *21*, 239-246.e234, doi:10.1016/j.clbc.2020.09.008.
38. Burgaleta, A.M.; Burguete, A.B.; Gutiérrez, L.R.; Nuín, E.B.; Felipe, G.A.; de la Vega, F.A. Local treatment in oligometastasis from breast cancer: an overview. *Clin Transl Oncol* **2023**, *25*, 2861-2867, doi:10.1007/s12094-023-03170-0.
39. Cardoso, M.J.; Mokbel, K. Locoregional therapy in de novo metastatic breast cancer. The unanswered question. *Breast* **2021**, *58*, 170-172, doi:10.1016/j.breast.2021.05.002.
40. Pacheco, J.M.; Gao, F.; Bumb, C.; Ellis, M.J.; Ma, C.X. Racial differences in outcomes of triple-negative breast cancer. *Breast Cancer Res Treat* **2013**, *138*, 281-289, doi:10.1007/s10549-012-2397-6.
41. Dawood, S.; Broglio, K.; Kau, S.W.; Green, M.C.; Giordano, S.H.; Meric-Bernstam, F.; Buchholz, T.A.; Albarracín, C.; Yang, W.T.; Hennessy, B.T., et al. Triple receptor-negative breast cancer: the effect of race on response to primary systemic treatment and survival outcomes. *J Clin Oncol* **2009**, *27*, 220-226, doi:10.1200/JCO.2008.17.9952.
42. O'Brien, K.M.; Cole, S.R.; Tse, C.K.; Perou, C.M.; Carey, L.A.; Foulkes, W.D.; Dressler, L.G.; Geradts, J.; Millikan, R.C. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. *Clin Cancer Res* **2010**, *16*, 6100-6110, doi:10.1158/1078-0432.CCR-10-1533.
43. Schettini, F.; Chic, N.; Brasó-Maristany, F.; Paré, L.; Pascual, T.; Conte, B.; Martínez-Sáez, O.; Adamo, B.; Vidal, M.; Barnadas, E., et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer* **2021**, *7*, 1, doi:10.1038/s41523-020-00208-2.
44. Gampenrieder, S.P.; Dezentjé, V.; Lambertini, M.; de Nonneville, A.; Marhold, M.; Le Du, F.; Cortés Salgado, A.; Alpuim Costa, D.; Vaz Batista, M.; Chic Ruché, N., et al. Influence of HER2 expression on prognosis in metastatic triple-negative breast cancer-results from an international, multicenter analysis coordinated by the AGMT Study Group. *ESMO Open* **2023**, *8*, 100747, doi:10.1016/j.esmoop.2022.100747.
45. Modi, S.; Jacot, W.; Yamashita, T.; Sohn, J.; Vidal, M.; Tokunaga, E.; Tsurutani, J.; Ueno, N.T.; Prat, A.; Chae, Y.S., et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med* **2022**, *387*, 9-20, doi:10.1056/NEJMoa2203690.
46. U.S. Food & Drug administration. Oncology (Cancer)/ Hematologic Malignancies Approval Notifications. <https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications>, 2023.
47. Robson, M.E.; Im, S.A.; Senkus, E.; Xu, B.; Domchek, S.M.; Masuda, N.; Delaloge, S.; Tung, N.; Armstrong, A.; Dymond, M., et al. OlympiAD extended follow-up for overall survival and safety: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Eur J Cancer* **2023**, *184*, 39-47, doi:10.1016/j.ejca.2023.01.031.
48. Litton, J.K.; Hurvitz, S.A.; Mina, L.A.; Rugo, H.S.; Lee, K.H.; Gonçalves, A.; Diab, S.; Woodward, N.; Goodwin, A.; Yerushalmi, R., et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. *Ann Oncol* **2020**, *31*, 1526-1535, doi:10.1016/j.annonc.2020.08.2098.
49. Bardia, A.; Hurvitz, S.A.; Tolane, S.M.; Loirat, D.; Punie, K.; Oliveira, M.; Brufsky, A.; Sardesai, S.D.; Kalinsky, K.; Zelnak, A.B., et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *N Engl J Med* **2021**, *384*, 1529-1541, doi:10.1056/NEJMoa2028485.

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.