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Performance of Time to Discontinuation and Time to Next Treatment as Proxy Measures Compared with Direct Observation of Progression-Free Survival

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BACKGROUND

- Overall survival (OS) is the gold standard efficacy outcome in prospective oncology research, but progression-free survival (PFS) is a widely used alternative, favored because it requires shorter follow-up. Real-world studies typically examine these priority endpoints and permit evaluation of real-world outcomes using the same metric as prospective studies.
- PFS requires information about both death and disease progression. However, some real-world data sources provide limited access to information about the occurrence of disease progression. These include claims data and most structured electronic medical record (EMR) data.
- Research with sources that do not provide direct access to information about disease progression may adopt proxy indicators of PFS, such as time to discontinuation (TTD) or time to next treatment (TTNT).
- In contrast, EMR data that include both structured and unstructured content (i.e., provider progression notes, lab reports, path reports, radiology scan reports) may permit curation that directly identifies disease progression. This makes it possible to calculate PFS based on directly observed disease progression events.
- The performance of proxy indicators of PFS, such as TTD and TTNT, is not yet clear, but is critical to interpreting research that may rely on these measures.
- The current study sought to investigate the performance of both the proxies and the directly-observed PFS measures, using data from an existing study of metastatic breast cancer (mBC).

OBJECTIVES

- To describe the demographic and clinical characteristics of eligible mBC patients in a real-world community setting.
- To describe the treatment patterns from the qualifying diagnosis through the start of the second line (2L) of therapy or until the end of the record, whichever occurs first.
- To compare TTD and TTNT values with PFS as determined directly from curated progression data.
- To describe and compare treatment effect sizes observed for treatment-based groups on the endpoints of TTD, TTNT, and PFS.

METHODS

- **Study Design:** Retrospective, observational
- **Data source:** Previously curated EMR data from Concerto's Definitive Oncology Dataset[1]
- **Eligibility:**
  - Female patients age ≥18 years old at mBC diagnosis
  - Diagnosis of mBC in 2008 or later and record of systemic therapy for treatment of mBC
  - Hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) status
- **Sample Size:** 378 patients
- **Statistical Methods:**
  - Kaplan-Meier methods were used to estimate PFS, TTD, and TTNT for first line (1L) therapy based on direct observation of the respective events. Cox regression analysis was conducted to examine differences in effectiveness outcomes among the treatment groups under the proportional hazard assumption.
  - The time origin, terminal event, and censoring rules employed for calculation of endpoints are shown in **Table 1**.
  - The sensitivity of the findings to modifications in the definitions of the above endpoints was evaluated.
  - Patients were classified as to receipt vs. non-receipt of an aromatase inhibitor (AI) in the first regimen of 1L. The source study for these data did not investigate outcomes based on this classification[1], but the sample divided almost evenly on this treatment component and permitted an exploratory investigation of variation of treatment effect size across the endpoints.

Table 1. Endpoint Definitions

Outcome	Time Origin	Terminal Event*	Censoring
Time to Discontinuation (TTD)	Start of 1L therapy	• Start of a new regimen, indicated by introduction of a new drug > 30 days after start of the regimen, with or without discontinuation of existing drugs • Discontinuation of the regimen without start of a new regimen, indicated by the beginning of a gap of systemic therapy of > 63 days • Death	Censored at last office visit
Time to Next Treatment (TTNT)	Start of 1L therapy	• Introduction of any new agent > 30 days after the start of 1L therapy • Resumption after a hold of the existing regimen for > 63 days • Death	Censored at last office visit
Progression-Free Survival (PFS)	Start of 1L therapy	• Disease progression as documented through human curation of the medical record • Death	Censored at last office visit

*Terminal event is the earliest of the bulleted events applicable to each outcome.

RESULTS

- The study included a total of 378 patients, of which 138 (36.51%) were de novo stage IV or metastatic. The mean patient age was 60.30 (SD 13.30), 57.14% were White, and 68.25% were perimenopausal/ postmenopausal. More than half of patients (n=206, 54.50%) had an ECOG of 0 or 1. **(Table 2)**
- The majority of patients in the AI treatment group received AI monotherapy (n=104, 58.10%). Over half of patients in the non-AI treatment group received chemotherapy (n=100, 50.25%). The majority of patients went on to receive 2L. **(Table 3)**
- Censoring of endpoints occurred in a minority of patients, with 307 (81.22%) PFS events, 342 (90.48%) TTD events, and 336 (88.89%) TTNT events. **(Table 4)**
- The median PFS in the sample was 9.11 months [95% CI 7.89, 10.68], compared to a much shorter median TTD of 5.56 months [5.00, 6.48] and TTNT of 5.95 months [5.26, 6.94]. **(Table 4)**
- Patients who received an AI had significantly longer TTD and TTNT than patients who did not receive an AI. However, there was no significant difference in PFS across the groups. **(Table 4)**
- The treatment hazard ratio (HR) based on PFS was 0.942 [0.751, 1.181] but statistically insignificant (p=0.602). The HR based on TTD was 0.703 [0.567, 0.871] (p=0.001). The HR based on TTNT was very similar: 0.722 [0.581, 0.896] (p=0.003).
- The effect of modification to the definitions of the endpoints during sensitivity analysis appeared negligible.

Table 2. Summary Demographic and Clinical Characteristics

Variable / Statistic	Aromatase Inhibitor Yes (N=179)	Aromatase Inhibitor No (N=199)	Overall
Mean Age (SD)*	63.0 (12.2)	57.8 (13.9)	60.3 (13.3)
Race			
Black or African American	72 (40.22%)	81 (40.70%)	153 (40.48%)
White	102 (56.98%)	114 (57.29%)	216 (57.14%)
Other	5 (2.79%)	4 (2.01%)	9 (2.38%)
Stage at Initial Diagnosis			
0	3 (1.68%)	1 (0.50%)	4 (1.06%)
I	22 (12.29%)	19 (9.55%)	41 (10.85%)
II	46 (25.70%)	54 (27.14%)	100 (26.46%)
III	27 (15.08%)	39 (19.60%)	66 (17.46%)
IV	65 (36.31%)	73 (36.68%)	138 (36.51%)
Other/Unknown/Undocumented	16 (8.94%)	13 (6.53%)	29 (7.67%)
ECOG Performance Status			
0	64 (35.75%)	70 (35.18%)	134 (35.45%)
1	42 (23.46%)	30 (15.08%)	72 (19.05%)
2+	12 (6.70%)	12 (6.03%)	24 (6.35%)
Undocumented	61 (34.08%)	87 (43.72%)	148 (39.15%)
Menopausal Status*			
Premenopause	17 (9.50%)	41 (20.60%)	58 (15.34%)
Perimenopause/Postmenopause	131 (73.18%)	127 (63.82%)	258 (68.25%)
Unknown	31 (17.32%)	31 (15.58%)	62 (16.40%)

*denotes p<0.05

Table 3. Summary of Treatment Patterns

Patients with Aromatase Inhibitor in 1L (N=179)		Patients without Aromatase Inhibitor in 1L (N=199)	
Distribution of First Regimens*			
AI Monotherapy	104 (58.10%)	CDK4/6 Inhibitor + Fulvestrant	16 (8.04%)
AI + CDK4/6 Inhibitor-containing regimen	46 (25.70%)	CDK4/6 Inhibitor-containing regimen	2 (1.01%)
AI + Fulvestrant-containing regimen	10 (5.59%)	Fulvestrant-containing regimen	43 (21.61%)
AI + Chemotherapy-containing regimen	3 (1.68%)	Chemotherapy	100 (50.25%)
AI + Other	16 (8.94%)	Other Non-AI	38 (19.10%)
Number of Patients Receiving 2L	125 (69.83%)		156 (78.39%)

*Classifications are mutually exclusive and assigned in the order presented here.

Table 4. Description of Kaplan-Meier Treatment Effects Results for PFS, TTD, and TTNT for mBC Sample

Statistic	Aromatase Inhibitor Yes	Aromatase Inhibitor No	Overall	Log Rank
PFS				Log Rank X^2 (1, 378) = 0.27, p=0.6033
No. of Events / No. of Patients	137 / 179	170 / 199	307 / 378	
Median	9.9	7.89	9.11	
95% CI of Median	8.35, 12.62	6.77, 11.54	7.89, 10.68	
Quartiles	4.24, 20.94	3.65, 19.92	3.91, 20.48	
Minimum, Maximum	0.46, 64.31	0.39, 106.36	0.39, 106.36	
TTD				Log Rank X^2 (1, 378) = 10.39, p=0.0013
No. of Events / No. of Patients	152 / 179	190 / 199	342 / 378	
Median	8.12	4.77	5.56	
95% CI of Median	5.79, 9.53	4.18, 5.42	5, 6.48	
Quartiles	2.89, 16.04	2.79, 8.35	2.83, 12.46	
Minimum, Maximum	0.85, 64.31	1.02, 76.01	0.85, 76.01	
TTNT				Log Rank X^2 (1, 378) = 8.73, p=0.0031
No. of Events / No. of Patients	147 / 179	189 / 199	336 / 378	
Median	8.28	5.03	5.95	
95% CI of Median	6.51, 10.45	4.27, 5.75	5.26, 6.94	
Quartiles	3.25, 16.67	2.79, 10.26	2.86, 14.17	
Minimum, Maximum	0.85, 64.31	1.02, 76.01	0.85, 76.01	

Figure 1. Kaplan-Meier Plot of PFS, TTD, and TTNT for mBC Sample

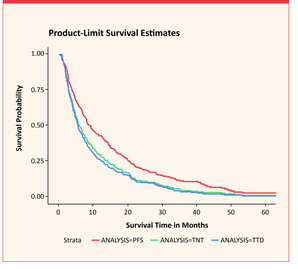


Figure 2. Kaplan-Meier Plot of Treatment Group Comparison based on PFS for mBC Sample

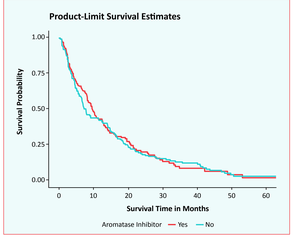


Figure 3. Kaplan-Meier Plot of Treatment Group Comparison based on TTD for mBC Sample

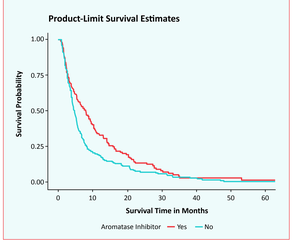
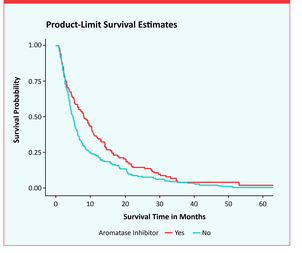


Figure 4. Kaplan-Meier Plot of Treatment Group Comparison based on TTNT for mBC Sample



LIMITATIONS

- The analysis was conducted in findings from a single tumor type, from a single study. The relationship among TTD, TTNT, and PFS should be examined in other tumors and in additional studies.
- The analysis was conducted using study data with a high proportion of observed events. Understanding whether the patterns would remain consistent in more heavily censored data would be important to understanding the relationship of censoring to these findings.
- The analysis of the hazard ratio within Cox models was based on a proportional hazard assumption, which was not further tested. In addition, the only covariate included in the Cox analysis was the treatment group, with no additional controls. The objective of this analysis was not to make a definitive clinical statement about treatment effects of AI in the mBC setting, but to illustrate the consistency of findings across analytical models.
- Patient data evaluated in this study was drawn from records of treatment in community oncology settings in the USA. Findings from other treatment settings or in other geographic locations may differ.
- The endpoints evaluated in this study can be defined in different ways. Although our analysis did examine alternative constructions of some endpoints, this examination was not exhaustive. Other definitions of the endpoints may influence the pattern of findings described in this study.

CONCLUSIONS

- Estimates of TTD and TTNT aligned closely, suggesting that nearly all patients who discontinued initial therapy received subsequent treatment.
- PFS based on directly observed progression was markedly longer than TTD and TTNT. Use of these endpoints as proxy indicators of PFS may therefore lead to underestimate of PFS in this tumor. TTD and TTNT events likely occur earlier than PFS events for several patients. The mechanism by which this occurs was not directly explored in this study, but plausibly occurs through treatment switching associated with treatment toxicity.
- Outcomes such as TTD, TTNT, and PFS may have differential sensitivity to the effects of treatment toxicities or other drivers of treatment change. As a result, treatment effects measured by these outcomes may vary across the outcomes, and effect sizes measured in TTD and TTNT may not reflect the corresponding effects that would be measured by PFS.
- The analysis showed limited censoring. Although higher rates of censoring may be observed in many studies, this condition of the data strengthens the findings about the underlying relationship among the endpoints in this tumor.

REFERENCES

1. Saverno K, Cuyun Carter G, Dufour R, et al. Outcomes among metastatic breast cancer patients with characteristics that confer a less favorable prognosis (P2-08-66). *San Antonio Breast Cancer Symposium*. 2018 Available at https://www.abstracts2view.com/sabcs/view.php?nu=SABCS18L_879. Accessed May 11, 2020.

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