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Original article

Primary predictors of survival outcomes for HER2-positive advanced breast cancer patients initiating ado-trastuzumab emtansine

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ABSTRACT

Objectives: Common therapies for HER2-positive advanced breast cancer (ABC) are associated with heterogeneity in prognosis and treatment benefit. Prognostic models of survival outcomes with ado-trastuzumab-emtansine (T-DM1) have not been evaluated.

Material and methods: A pre-treatment prognostic model for overall survival (OS) and progression-free survival (PFS) based on clinicopathological factors was developed for HER2-positive ABC patients initiating second-line and later T-DM1 using data from the randomised clinical trials EMILIA and TH3RESA (n = 893). Pre-treatment prognostic groups were identified via recursive partitioning analysis.

Results: The most significant OS/PFS pre-treatment risk predictors were metastatic sites count (≤2 versus > 2) and ECOG performance-status (0 versus ≥ 1) ($P < 0.05$). Based on these two factors, patients can be characterised as one of three prognostic groups (good = 0 factors; intermediate = 1 factor; poor = 2 factors). The prognostic groups were identified as significantly associated with OS ($P < 0.001$) and PFS ($P < 0.001$). Median OS for the good, intermediate and poor prognostic groups were 40 (95%CI: 36–48), 25 (23–30) and 16 (14–19) months, respectively, and median PFS was 12 (10–15), 8 (7–9) and 6 (4–7) months.

Conclusion: Pre-treatment prognostic groups with significant differences in OS and PFS for HER2-positive ABC patients initiating second-line and later T-DM1 were identified. For HER2-positive ABC patients considering initiating second-line and later T-DM1, the prognostic groups enable more personalized expectations of disease control, survival and absolute treatment benefit.

Introduction

Trastuzumab-emtansine (T-DM1) is a recommended second-line and later treatment option for human epidermal growth factor receptor 2 (HER2) positive advanced breast cancer (ABC) [1–3]. These recommendations are largely based upon the randomised control trials EMILIA and TH3RESA, which demonstrated improved overall survival (OS) and progression-free survival (PFS) for T-DM1 compared to lapatinib plus capecitabine [2,3] or physicians choice [4,5] in this setting. While T-DM1 is an important treatment option, there is substantial heterogeneity in patient prognosis and treatment benefit.

Multivariable risk prediction tools integrate information from multiple patient and tumour characteristics to identify patient subgroups with different prognosis [6]. Additionally, such risk prediction tools can utilise pre-treatment characteristics to help identify patient subgroups with greater and lesser absolute treatment benefits (i.e. heterogeneity of treatment effect) [7,8]. Thereby, clinical risk prediction tools may facilitate improved decision making by providing patients with personalized expectations of prognosis and treatment benefit [6–8]. Although a number of individual prognostic factors have been associated with survival outcomes in HER2-positive ABC patients [9–12], there are no validated clinical risk prediction tools applicable to HER2-positive ABC patients who are considering initiating second-line and later T-DM1 treatment.

The objectives of this study were to (1) identify pre-treatment prognostic groups with distinct OS and PFS outcomes in HER2-positive ABC patients initiating second-line and later T-DM1; and

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(2) evaluate the heterogeneity of treatment benefit between the pre-treatment prognostic groups for T-DM1 compared to lapatinib plus capecitabine or physician's choice.

Materials and methods

Analysis population

Individual-participant data (IPD) from 2 randomised clinical trials sponsored by Roche (EMILIA [NCT00829166] [2,3], and TH3RESA [NCT01419197] [4,5]) were accessed via clinicalstudydatarequest.com. Secondary analysis of anonymised participant-level trial data was approved by the Southern Adelaide Clinical Human Research Ethics Committee.

Development data for the identification of pre-treatment prognostic groups consisted of HER2-positive advanced breast cancer patients treated with T-DM1, with available OS and PFS data from EMILIA and TH3RESA.

EMILIA included HER2-positive, unresectable, locally advanced or metastatic breast cancer patients with documented disease progression to previous trastuzumab and a taxane [2,3]. Patients were excluded if they had received prior T-DM1, lapatinib or capecitabine [2,3]. Participants were randomly assigned in a 1:1 ratio to 1250 mg daily oral lapatinib plus 1000 mg/m^2 twice daily oral capecitabine on days 1 through 14 of a 21-day cycle, or to 3.6 mg/kg of intravenous T-DM1 every 21 days [2,3]. Crossover from control to trastuzumab-emtansine did occur [2,3].

TH3RESA included HER2-positive, unresectable, locally advanced, recurrent or metastatic breast cancer patients with documented disease progression to previous trastuzumab and lapatinib in the advanced setting and had received a taxane in any setting [4,5]. Participants were randomly assigned in a 1:2 ratio to a treatment of physician's choice (restricted to any single chemotherapy, single/dual hormonal therapy for hormone-receptor-positive disease, or single/dual HER2-directed therapy ± single-agent chemotherapy/hormonal therapy), or to 3.6 mg/kg of intravenous T-DM1 every 21 days [4,5]. Crossover from control to trastuzumab-emtansine did occur [4,5].

Predictors and outcomes

Analysed covariates were prespecified based upon availability, prior evidence [9–12] and biological plausibility. Analysed pre-treatment covariates included sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS; 0 or ≥1), weight, race, estrogen and progesterone receptor status, time since diagnosis (<6 month, ≥6 months), any prior trastuzumab, anthracycline or taxane in all settings, count of metastatic sites, and albumin below the lower limit of normal (<LLN).

OS was defined from the time of randomization to the last follow-up or death from any cause [2–5]. EMILIA defined PFS from the time of randomization to disease progression or death from any cause, with progression independently assessed using a modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 [2,3]. TH3RESA defined PFS from the time of randomization to disease progression or death from any cause, with progression assessed by the investigators using RECIST version 1.1 [4,5].

Recursive partitioning analysis

Pre-treatment prognostic groups for each of OS and PFS were identified via a recursive partitioning analysis. Subsequently, simplification of the developed PFS and OS models were explored. To facilitate clinical translation (i.e. minimise computation), a single model with maintained predictive performance for both PFS and OS was to be preferred.

The recursive partitioning analysis uses a unified conditional inference framework to avoid bias in the selection of covariates and minimise overfitting of the data [13]. This approach ensures a rightsized tree with no need for pruning or cross-validation. The recursive partitioning analysis tests the global null hypothesis of independence between the prespecified input variables and outcome variables. If the null hypothesis cannot be rejected, the analysis is stopped; otherwise, the covariate most strongly associated with the outcome variable is identified based on univariate P values. These steps are repeated until no further covariates with a significant association with the outcome variable can be distinguished. The stop criterion was set at a multiplicity-adjusted univariate P value of less than 0.05, with no subgroup size below 150 in the development data.

Discriminative performance of defined pre-treatment prognostic groups was assessed via the concordance statistic. Kaplan-Meier analysis was used for plotting and estimating probabilities.

Data analysis was conducted using R version 3.3.0, and the package *partykit* was used to conduct the recursive partitioning analysis [14,15].

Heterogeneity of treatment effect by prognostic group

Heterogeneity of treatment effect (absolute and proportion scale [7]) by prognostic group was evaluated in the intention to treat populations of EMILIA (n = 991) and TH3RESA (n = 602). Kaplan-Meier analysis was used to plot and estimate the absolute difference in OS and PFS for participants randomised to T-DM1 versus control for the identified prognostic groups. Cox proportional hazard analysis was used to assess the difference in OS and PFS for T-DM1 compared to control across the identified prognostic groups on the proportional scale. Prognostic groups were assessed using a treatment-by-biomarker interaction term in a Cox proportional regression model.

Results

Patient population

Supplementary Table 1 provides a summary of the patient characteristics for the 1593 participants in this study. The model development dataset included 893 HER2-positive ABC patients treated with second-line and later T-DM1 from EMILIA and TH3RESA. Median follow-up was 47 [95% CI 45–48] months within the EMILIA subset of the model development data, and 35 [34–35] months within the TH3RESA subset.

Pre-treatment prognostic groups

The analysis identified four pre-treatment prognostic groups for OS including (1) metastatic sites count ≤ 2, and ECOG PS = 0, (2) metastatic sites count ≤ 2, and ECOG PS ≥ 1, (3) metastatic sites count > 2, and ECOG PS = 0, and (4) metastatic sites count > 2, and ECOG PS ≥ 1. The discriminative performance (*c*-statistic) of these pre-treatment prognostic groups were 0.62 for OS. Supplementary Fig. 1 presents the Kaplan-Meier plot of OS for these pre-treatment prognostic groups.

The analysis identified four pre-treatment prognostic groups for PFS including (1) ECOG PS = 0 and metastatic sites count ≤ 2, (2) ECOG PS = 0 and metastatic sites count > 2, (3) ECOG PS ≥ 1 and metastatic sites count ≤ 2, and (4) ECOG PS ≥ 1 and metastatic sites count > 2. The discriminative performance (*c*-statistic) of these pre-treatment prognostic groups were 0.59 for PFS. Supplementary Fig. 2 presents the Kaplan-Meier plot of PFS for these pre-

treatment prognostic groups.

Metastatic sites count (≤2 versus > 2), and ECOG PS (0 versus ≥ 1) were the two most significant prognostic factors for both OS and PFS (P < 0.05). Subsequently, categorising participants as one of three prognostic groups was assessed (good = 0 factors [neither metastatic sites count > 2 or ECOG PS ≥ 1]; intermediate = 1 factor [one of metastatic sites count > 2 or ECOG PS ≥ 1]; poor = 2 factors [both metastatic sites count > 2 and ECOG PS ≥ 1]). The intermediate and poor prognostic groups were significantly associated with worse OS (HR [95%CI]: intermediate = 1.61 [1.31–1.97]; poor = 2.94 [2.35–3.69]; P < 0.001) and PFS (HR [95% CI]: intermediate = 1.62 [1.36–1.94]; poor = 2.33 [1.90–2.86]; P < 0.001) compared to the good prognostic group. The discriminative performance (*c*-statistic) of the pre-treatment prognostic groups were 0.62 for OS and 0.58 for PFS, maintaining the performance of the original models. Fig. 1 presents the median OS, 3-year OS probability, median PFS and 2-year PFS probability for the pre-treatment prognostic groups for participants who received T-DM1 therapy. Fig. 2 presents the Kaplan-Meier plots of OS and PFS for the pre-treatment prognostic groups for participants who received T-DM1 therapy. Supplementary Table 2 and Supplementary Fig. 3 presents OS and PFS estimates for the pre-treatment prognostic groups independently for participants who received T-DM1 therapy within EMILIA and TH3RESA.

Heterogeneity of treatment effect by prognostic group

Cox proportional hazard analysis identified no relative difference (interaction) between treatment and pre-treatment prognostic groups on OS (P = 1.00 and P = 0.30) and PFS (P = 0.30 and P = 0.96) within EMILIA and TH3RESA, respectively (Supplementary Table 3). Indicative that the prognostic groups are not specific to T-DM1 therapy, and that the benefit of T-DM1 compared to comparator treatments does not change statistically on a relative scale across prognostic groups. While there is no relative difference, the absolute benefit of treatments can differ across prognostic groups which may be important to patients and clinicians considering therapies [7,8]. Supplementary Figs. 4 and 5 present the observed absolute improvement in OS and PFS for study participants randomised to T-DM1 compared to control arms (lapatinib plus capecitabine, and physicians' choice) of EMILIA and TH3RESA, respectively, by pre-treatment prognostic groups.

Discussion

A pre-treatment risk prediction tool for OS and PFS in HER2-positive ABC patients initiating second-line and later T-DM1, was developed based on large (n = 893) and high-quality data, and to the best of the authors knowledge is the first study to present a risk prediction tool for this patient group. The risk prediction tool was able to clearly distinguish pre-treatment prognostic groups with distinct OS and PFS outcomes.

The most significant pre-treatment predictors identified for each of PFS and OS were metastatic sites count (≤2 versus > 2) and ECOG PS (0 versus ≥ 1). These predictors are in concordance with previous literature, where high pre-treatment metastatic burden [11,12], and worsening performance status [12,16] have been associated with poor outcomes in ABC.

The developed pre-treatment risk prediction tool allows the simultaneous interpretation of both OS and PFS prognostic risk for HER2-positive ABC patients who are considering second-line and later T-DM1. The presented OS and PFS estimates are applicable to HER2-positive ABC patients who align with the inclusion criteria of EMILIA and TH3RESA. Notably this study observed a difference of 24 (40 versus 16) months in median OS and 36% (55 versus 19) in 3-year OS probability between the good and poor prognostic groups for patients who received T-DM1 therapy. Furthermore, a difference of 6 (12 versus 6) months in median PFS and 28% (34 versus 6) in 2-year PFS probability was observed between the good and poor prognostic groups. Such large and significant discrimination between prognostic groups indicates a potential for the developed tool to provide more realistic treatment expectations to patients considering T-DM1 therapy.

This study was conducted with a focus on developing a pre-treatment risk prediction tool practical for clinical use. This included using routinely available clinic data, a single model for OS and PFS, and avoiding complex numerical derivations. While more complex development techniques for risk prediction models (e.g. least absolute shrinkage and selection operator (LASSO) analysis) may result in greater prediction performance, simplicity of model use was prioritised to facilitate clinical use.

Prognostic tools can be used to explore treatment effect heterogeneity and absolute treatment benefit [7,8]. No relative difference (interaction) between treatment effect (T-DM1 versus control arms) and pre-treatment prognostic group was observed on OS or PFS within EMILIA or TH3RESA (Supplementary Table 3). While no relative difference was identified, the absolute benefit of treatments can differ across prognostic groups which may be important to patients and clinicians considering therapies [7,8]. Within EMILIA the improvement in median OS for participants randomised to T-DM1 (compared to lapatinib plus capecitabine) within the good, intermediate and poor pre-treatment prognostic groups was 8 (41

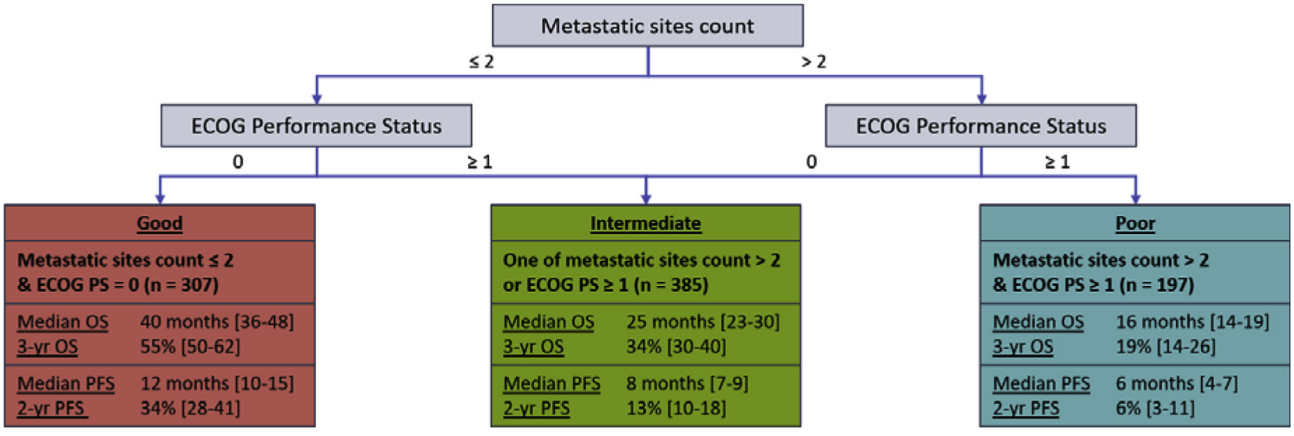

Fig. 1. Decision tree and OS/PFS estimates [95%CI] by pre-treatment prognostic group for participants who received T-DM1 therapy.

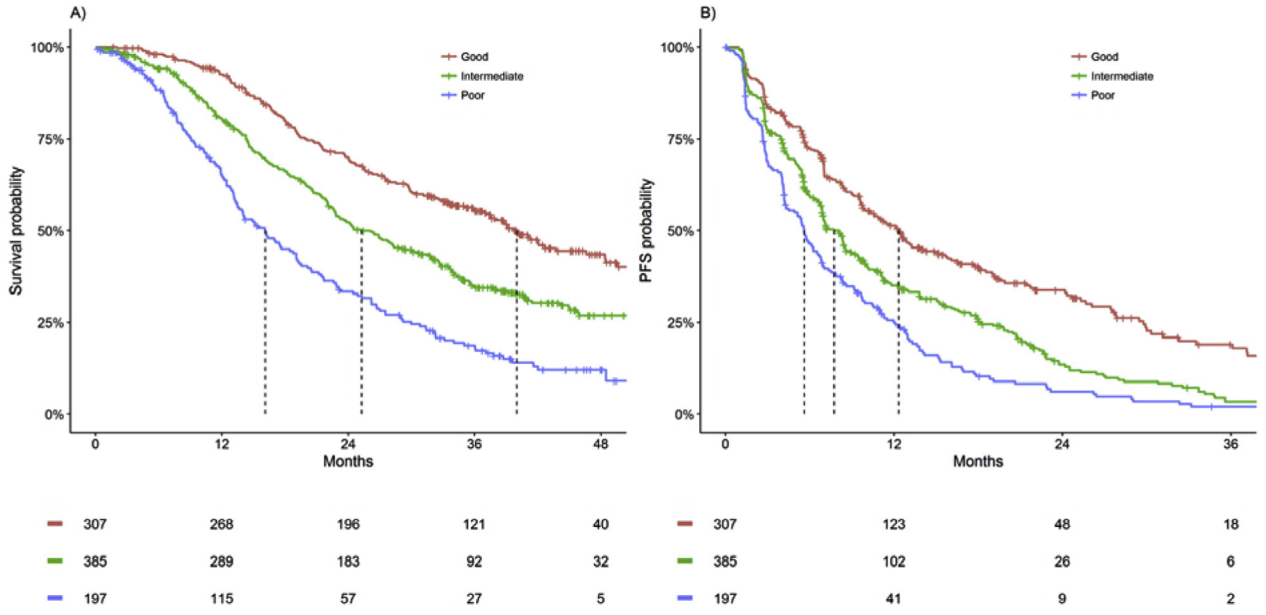

Fig. 2. Kaplan Meier estimates of OS and PFS by pre-treatment prognostic group for participants who received T-DM1 therapy.

vs 33), 6 (29 vs 23) and 4 (19 vs 15) months, respectively, and the improvement in median PFS was 10 (18 vs 8), 3 (10 vs 7), and 2 (6 vs 4) months (Supplementary Fig. 4). Furthermore, within TH3RESA the improvement in median OS for participants randomised to T-DM1 (compared to physicians' choice) within the good, intermediate and poor pre-treatment prognostic groups was 12 (39 vs 27) months, 6 (22 vs 16) months and no observed benefit (14 vs 16), respectively, and the improvement in median PFS was 3 (8 vs 5), 4 (7 vs 3), and 2 (5 vs 3) months (Supplementary Fig. 5). Outlining the potential for the pre-treatment prognostic tool to provide information on the absolute benefit of T-DM1 compared to lapatinib plus capecitabine or physician's choice across prognostic groups.

At the centre of evidence-based medicine are randomised trials, however due to inclusion and exclusion criteria their generalisability to the real-world population can be limited [17]. In this study, IPD from EMILIA and TH3RESA were used, increasing study power and generalisability to present OS and PFS predictions for a diverse range of patients considering T-DM1 therapy. Disease control is an important outcome to patients and PFS data is often not collected within real-world databases, providing additional strength to the data source used here. The discriminative performance of the prognostic groups for OS were consistent with a moderately well performing model ($c > 0.6$). Ideally the discriminative performance of the prognostic groups for PFS would have a concordance statistic greater than 0.6, albeit a significant association between prognostic groups and PFS was identified ($P < 0.001$). Differences in inclusion criteria (e.g. prior treatments received) and nuances of disease progression definitions between EMILIA and TH3RESA may have contributed to the poorer prediction of the PFS outcome. Ideally in the future the developed pre-treatment risk prediction tool will be validated and recalibrated, if necessary, using real-world population data, which will increase generalisability and performance.

In conclusion a pre-treatment risk prediction tool for OS and PFS in HER2-positive ABC patients initiating second-line and later T-DM1 was developed from previously completed clinical trials. The selected variables were in concordance with the previous literature and are routinely available in the clinic. The pre-treatment prognostic groups displayed significant difference in OS and PFS outcomes. There is the potential for the developed pre-treatment risk prediction tools to help inform treatment decisions and provide more realistic treatment expectations to patients considering T-DM1 therapy.

Declarations

Ethics approval and consent to participate

Secondary analysis of anonymised participant-level trial data was approved by the Southern Adelaide Clinical Human Research Ethics Committee.

Consent for publication

Not applicable.

Availability of data and materials

Individual-participant data utilised in this study is available for request to access at clinicalstudydatarequest.com.

Declaration of interests

M.J.S. and A.R. report investigator-initiated project grants from Pfizer, outside the scope of the submitted work. A.M.H and J.M.L have no conflicts of interest to disclose.

Conflicts of interest

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Authors' contributions

All authors were involved in analysis and manuscript preparation for this project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.05.011.

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