# Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial

*Ian E Krop, Sung-Bae Kim, Antonio González-Martín, Patricia M LoRusso, Jean-Marc Ferrero, Melanie Smitt, Ron Yu, Abraham C F Leung, Hans Wildiers, on behalf of the TH3RESA study collaborators**

## Summary

**Background** Patients with progressive disease after two or more HER2-directed regimens for recurrent or metastatic breast cancer have few effective therapeutic options. We aimed to compare trastuzumab emtansine, an antibody–drug conjugate comprising the cytotoxic agent DM1 linked to trastuzumab, with treatment of physician's choice in this population of patients.

**Methods** This randomised, open-label, phase 3 trial took place in medical centres in 22 countries across Europe, North America, South America, and Asia-Pacific. Eligible patients (≥18 years, left ventricular ejection fraction ≥50%, Eastern Cooperative Oncology Group performance status 0–2) with progressive HER2-positive advanced breast cancer who had received two or more HER2-directed regimens in the advanced setting, including trastuzumab and lapatinib, and previous taxane therapy in any setting, were randomly assigned (in a 2:1 ratio) to trastuzumab emtansine (3·6 mg/kg intravenously every 21 days) or physician's choice using a permuted block randomisation scheme by an interactive voice and web response system. Patients were stratified according to world region (USA *vs* western Europe *vs* other), number of previous regimens (excluding single-agent hormonal therapy) for the treatment of advanced disease (two to three *vs* more than three), and presence of visceral disease (any *vs* none). Coprimary endpoints were investigator-assessed progression-free survival (PFS) and overall survival in the intention-to-treat population. We report the final PFS analysis and the first interim overall survival analysis. This study is registered with ClinicalTrials.gov, number NCT01419197.

**Findings** From Sept 14, 2011, to Nov 19, 2012, 602 patients were randomly assigned (404 to trastuzumab emtansine and 198 to physician's choice). At data cutoff (Feb 11, 2013), 44 patients assigned to physician's choice had crossed over to trastuzumab emtansine. After a median follow-up of 7·2 months (IQR 5·0–10·1 months) in the trastuzumab emtansine group and 6·5 months (IQR 4·1–9·7) in the physician's choice group, 219 (54%) patients in the trastuzumab emtansine group and 129 (65%) of patients in the physician's choice group had PFS events. PFS was significantly improved with trastuzumab emtansine compared with physician's choice (median 6·2 months [95% CI 5·59–6·87] *vs* 3·3 months [2·89–4·14]; stratified hazard ratio [HR] 0·528 [0·422–0·661]; p<0·0001). Interim overall survival analysis showed a trend favouring trastuzumab emtansine (stratified HR 0·552 [95% CI 0·369–0·826]; p=0·0034), but the stopping boundary was not crossed. A lower incidence of grade 3 or worse adverse events was reported with trastuzumab emtansine than with physician's choice (130 events [32%] in 403 patients *vs* 80 events [43%] in 184 patients). Neutropenia (ten [2%] *vs* 29 [16%]), diarrhoea (three [<1%] *vs* eight [4%]), and febrile neutropenia (one [<1%] *vs* seven [4%]) were grade 3 or worse adverse events that were more common in the physician's choice group than in the trastuzumab emtansine group. Thrombocytopenia (19 [5%] *vs* three [2%]) was the grade 3 or worse adverse event that was more common in the trastuzumab emtansine group. 74 (18%) patients in the trastuzumab emtansine group and 38 (21%) in the physician's choice group reported a serious adverse event.

**Interpretation** Trastuzumab emtansine should be considered as a new standard for patients with HER2-positive advanced breast cancer who have previously received trastuzumab and lapatinib.

**Funding** Genentech.

*Lancet Oncol* 2014; 15: 689–99

Published Online
May 2, 2014
http://dx.doi.org/10.1016/S1470-2045(14)70178-0

See Comment page 668

See Online for an audio interview with Ian Krop

*Collaborators are listed in the appendix

**Dana-Farber Cancer Institute, Harvard University School of Medicine, Boston, MA, USA** (I E Krop MD); **Asan Medical Center, University of Ulsan College of Medicine, Songpa-gu, Seoul, South Korea** (Prof S-B Kim MD); **MD Anderson Cancer Center, Madrid, Spain** (A González-Martín MD); **Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA** (Prof P M LoRusso DO); **Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France** (Prof J-M Ferrero MD); **Genentech, South San Francisco, CA, USA** (M Smitt MD, R Yu PhD, A C F Leung MD); **and Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium** (Prof H Wildiers MD)

Correspondence to:
Dr Ian E Krop, Dana-Farber Cancer Institute, Harvard University School of Medicine, 450 Brookline Avenue, Boston, MA 02215, USA
**ikrop@partners.org**

See Online for appendix

## Introduction

HER2 is overexpressed in about 15–20% of invasive breast cancers and is associated with poor clinical outcome in the absence of systemic therapy.[1] The addition of trastuzumab to standard chemotherapy improves survival in patients with HER2-positive metastatic breast cancer.[2,3] However, despite the efficacy of trastuzumab, trastuzumab treatment, and additional intervention is required. In view of the evidence that HER2 overexpression persists and remains relevant beyond progression,[4–6] strategies to overcome insensitivity to treatment have involved changing the HER2-directed agent or switching chemotherapies in subsequent lines of treatment.[7,8] Moreover, combination treatment with

therapy, has been shown to improve overall survival compared with lapatinib alone in patients with heavily pretreated metastatic breast cancer.[6] However, few clinical studies have been done in patients with progressive disease who have already received both trastuzumab and lapatinib, and re-treatment with trastuzumab-containing regimens seems to have only moderate activity in this population.[9,10]

Antibody–drug conjugates, comprising a potent cytotoxic molecule linked to a target-specific antibody, are a class of therapeutic agents that potentially reduce systemic toxicities and enhance antitumour activity by specifically directing cytotoxic compounds to tumours. Trastuzumab emtansine is an antibody–drug conjugate that delivers the microtubule-inhibitory agent DM1 directly to HER2-expressing tumour cells, where it is internalised by lysosomes and promotes apoptosis upon intracellular release.[11] In binding HER2, trastuzumab emtansine, like trastuzumab, inhibits cell signalling through the PI3K/AKT pathway, inhibits HER2 shedding, and induces antibody-dependent cellular cytotoxicity.[12] Trastuzumab emtansine was recently approved in several countries and regions, including the USA and the European Union, as a single-agent treatment for patients with HER2-positive metastatic breast cancer who have previously received trastuzumab and a concurrent or sequential taxane in any setting, on the basis of results from the phase 3 EMILIA trial.[13] In EMILIA, use of trastuzumab emtansine was associated with significant reductions in both the risk of disease progression (hazard ratio [HR] 0·65, 95% CI 0·55–0·77) and death (HR 0·68, 0·55–0·85), with lower grade 3 or worse toxicity when compared with lapatinib plus capecitabine.[13]

Although all patients in EMILIA had previously received trastuzumab, previous lapatinib was an exclusion criterion. Data from phase 2 clinical trials have shown the single-agent activity of trastuzumab emtansine in heavily pretreated patients with previous exposure to trastuzumab and lapatinib,[14,15] but there are no definitive studies in this population and no clear standard of care exists for these patients.[7] Therefore, new treatment options are needed. TH3RESA is the second phase 3 study of trastuzumab emtansine done in the metastatic breast cancer population and was designed to compare trastuzumab emtansine with treatment of physician's choice in a population with progressive disease who had received both trastuzumab-containing and lapatinib-containing regimens for advanced breast cancer.

## Methods

### Study design and patients

The TH3RESA study is a randomised, multicentre, open-label, phase 3 trial with enrolment in 22 countries across Europe, North America, South America, and Asia-Pacific. Eligible patients had HER2-positive, unresectable locally cancer (hereafter termed advanced breast cancer), had previously received both trastuzumab and lapatinib in the advanced setting and a taxane in any setting, and had documented investigator-assessed progression after treatment with two or more HER2-directed regimens for advanced breast cancer. Disease progression had to have occurred during both trastuzumab-containing and lapatinib-containing regimens, with at least 6 weeks of exposure to each agent, except when intolerance to lapatinib was identified. HER2-positive status of tumour tissue, defined as in-situ hybridisation positivity or 3+ by immunohistochemical analysis, was prospectively confirmed by a central laboratory. Patients with non-measurable or measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were enrolled.[16] Additional eligibility criteria included age of 18 years or older, a left ventricular ejection fraction (LVEF) of 50% or higher as measured by echocardiography or multiple-gated acquisition scanning, an Eastern Cooperative Oncology Group performance status of 0–2, adequate organ function (including platelet count >100 000 cells per μL and aspartate aminotransferase and alanine aminotransferase ≤2·5×upper limit of normal), and provision of written informed consent.

Major exclusion criteria were previous enrolment in a clinical trial of trastuzumab emtansine, grade 3 or worse peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0,[17] symptomatic or untreated CNS metastases or treatment for such metastases within 1 month of randomisation, a history of symptomatic congestive heart failure, and a history of myocardial infarction or unstable angina within 6 months of enrolment.

The trial protocol was approved by the relevant institutional review boards of each study centre, and the trial was done in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local laws. All patients provided written informed consent.

### Randomisation and masking

Study investigators enrolled patients, who were randomised to the trial with use of an interactive voice and web response system. A permuted block randomisation scheme, with a block size of six, was used to ensure an approximate 2:1 allocation of patients to receive trastuzumab emtansine or treatment of physician's choice, respectively, with stratification according to world region (USA, western Europe, or other), number of previous regimens (excluding single-agent hormonal therapy) for advanced breast cancer (two to three *vs* more than three), and presence of visceral disease (any *vs* none). Neither patients nor investigators were masked to treatment assignment in

### Procedures

Patients randomly assigned to trastuzumab emtansine received a dose of 3·6 mg/kg intravenously every 21 days. If a patient needed a dose reduction, the dose was reduced first from 3·6 mg/kg to 3·0 mg/kg and then from 3·0 mg/kg to 2·4 mg/kg. Patients given trastuzumab emtansine 2·4 mg/kg who developed an adverse event necessitating dose reductions were withdrawn from the study. Dose interruptions for up to 42 days from the last treatment dose were permitted for trastuzumab-emtansine-related thrombocytopenia, hepatotoxicity, neurotoxicity, cardiotoxicity, infusion-related reactions or hypersensitivity, pulmonary toxicity, or any other clinically significant treatment-related toxicity that did not recover to grade 1 or baseline. The requirements for trastuzumab emtansine dose delays, reductions, and discontinuations owing to toxicities were protocol-defined and in keeping with current prescribing information.[18]

Patients randomly assigned to treatment of physician's choice were given an approved systemic therapy administered as per local practice at the investigator's discretion and according to the needs of each patient. Treatment options were restricted to chemotherapy (any single agent), hormonal therapy for hormone-receptor-positive disease (single-agent or dual therapy), or HER2-directed therapy (single-agent, dual HER2-targeted therapy, or combination with either single-agent chemotherapy or single-agent hormonal therapy). Best supportive care alone, including palliative radiotherapy in the absence of systemic therapy, was not permitted. Treatment with trastuzumab emtansine or physician's choice was continued until progressive disease or unmanageable toxicity. From September, 2012, onwards, after EMILIA data were reported,[13] patients who had progressive disease while receiving treatment of physician's choice were eligible to cross over to trastuzumab emtansine treatment, starting at 3·6 mg/kg.

Tumour assessments were done every 6 weeks for the first 54 weeks and every 12 weeks thereafter, irrespective of dose delays or interruptions, until investigator-assessed progressive disease or death. LVEF was measured by means of echocardiography (preferred method) or multiple-gated acquisition scanning at screening, week 6 (ie, end of cycle 2), every 12 weeks thereafter until study discontinuation, and 30 days after the last treatment dose. Local laboratory assessments were done at baseline, on day 1 of each treatment cycle, and 30 days after the last treatment dose. Patients were continuously monitored for adverse events, which were graded using NCI CTCAE (version 4.0). A serious adverse event was any adverse event that was fatal, life threatening, led to inpatient hospital admission (or an extended hospital stay), resulted in persistent or clinically significant disability or incapacity, resulted in a congenital anomaly or birth defect in a neonate or infant born to a mother exposed to the investigational product, or was considered to be a

Data for patient-reported outcomes were obtained using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30). Patients completed the EORTC QLQ-C30 on day 1 of each treatment cycle until study treatment discontinuation or investigator-assessed disease progression (whichever occurred later).

### Outcomes

The coprimary endpoints were investigator-assessed progression-free survival (PFS) and overall survival in the intention-to-treat population, which consisted of all randomly assigned patients, irrespective of whether they received study treatment. PFS was defined as the interval from randomisation to first documented disease progression according to RECIST or death from any cause, whichever occurred first. Overall survival was defined as the interval from randomisation to death from any cause. Secondary endpoints were investigator-assessed objective response according to RECIST, duration of objective response, 6-month survival, 1-year

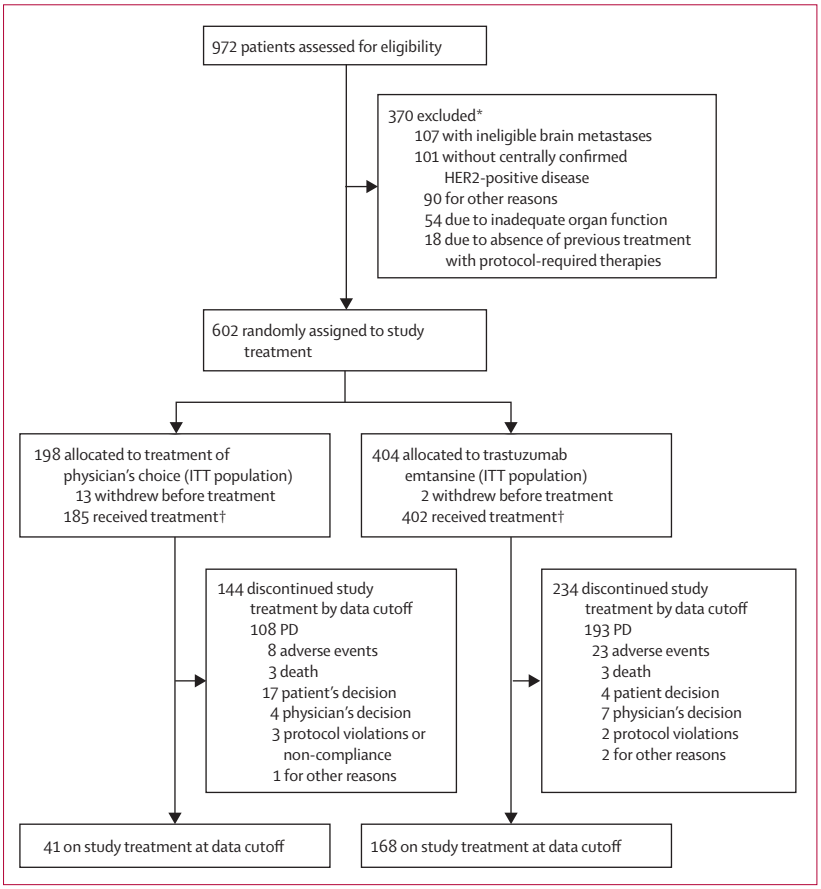


***Figure 1:*** **Trial profile**

ITT=intention-to-treat. PD=progressive disease. *Reasons for patient ineligibility comprising 5% or more of the total number of screen failures are presented; all other reasons for ineligibility have been grouped under "other", with each individual reason representing 2% or less of the total number of screen failures. †One patient randomised to the physician's choice group received two cycles of trastuzumab emtansine by mistake; this patient

survival, and safety. The safety population included all randomly assigned patients who received study treatment. Further secondary endpoints were general health status or quality of life and health-related quality of life, symptom severity and interference, and pain ratings as assessed by EORTC QLQ-C30.

### Statistical analysis

The overall 5% type I error rate was split asymmetrically between the coprimary endpoints, with 0·5% allocated to PFS and 4·5% allocated to overall survival. We calculated that a sample size of about 600 patients would provide 80% power to detect an HR of 0·65 for PFS (a 54% improvement in median PFS from 4 months in the physician's choice group to 6·15 months in the trastuzumab emtansine group) at a two-sided significance level of 0·5% and an HR of 0·76 for overall survival (a 32% improvement in median overall survival from 12 months in the physician's choice group to 15·8 months in the trastuzumab emtansine group) at a two-sided significance level of 4·5%.[15,19] The primary PFS analysis was to be done when about 324 PFS events had occurred and only after all patients had enrolled and had the opportunity for at least one post-baseline tumour assessment. We planned two formal interim overall survival analyses (to be done at the time of the primary PFS analysis and at about 330 deaths, respectively) and one final overall survival analysis (at about 492 deaths). The overall type I error was to be controlled at 0·045 for the formal overall survival interim analyses and final overall survival analysis using the Lan-DeMets alpha-spending function with an O'Brien-Fleming boundary. The boundaries used at each interim and final overall survival analysis depend on the actual number of observed deaths at each analysis. If either PFS or overall survival were statistically significant at any analysis, the secondary endpoints were to be tested in a prespecified order.

For PFS and duration of objective response, we censored patients who had neither disease progression nor death at the date of the last tumour assessment in which an overall response other than unknown or unevaluable was recorded on or before the cutoff date.

| | Physician's choice (n=198) | Trastuzumab emtansine (n=404) |
|---|---|---|
| Age (years) | 54 (28–85) | 53 (27–89) |
| <65 | 164 (83%) | 345 (85%) |
| 65–74 | 28 (14%) | 46 (11%) |
| ≥75 | 6 (3%) | 13 (3%) |
| World region | | |
| USA | 48 (24%) | 99 (25%) |
| Western Europe | 85 (43%) | 171 (42%) |
| Other | 65 (33%) | 134 (33%) |
| Race | | |
| White | 161 (81%) | 325 (80%) |
| Asian | 24 (12%) | 57 (14%) |
| Other* | 13 (7%) | 22 (5%) |
| ECOG PS† | | |
| 0 | 82 (41%) | 180 (45%) |
| 1 | 101 (51%) | 200 (50%) |
| 2 | 15 (8%) | 22 (5%) |
| Hormone receptor status‡ | | |
| ER positive and/or PR positive | 103 (52%) | 208 (51%) |
| ER negative and PR negative | 85 (43%) | 185 (46%) |
| Unknown | 10 (5%) | 11 (3%) |
| Visceral disease involvement | 150 (76%) | 302 (75%) |
| Disease extent | | |
| Metastatic | 187 (94%) | 391 (97%) |
| Unresectable locally advanced or recurrent | 11 (6%) | 13 (3%) |
| Measurable disease | 163 (82%) | 345 (85%) |
| Number of previous regimens for advanced breast cancer§¶ | 4 (1–19) | 4 (1–14) |
| ≤3 | 78 (39%) | 131 (33%) |
| 4–5 | 65 (33%) | 149 (37%) |
| >5 | 55 (28%) | 122 (30%) |
| Previous exposure to HER2-directed therapy | | |
| Trastuzumab | 198 (100%) | 404 (100%) |
| Duration (months) | 23·7 (0·7–508·8) | 24·3 (1·4–140·5) |
| Lapatinib | 198 (100%) | 404 (100%) |
| Duration (months) | 7·62 (0·1–48·0) | 7·98 (0·1–71·2) |
| Previously treated asymptomatic brain metastasis | 27 (14%) | 40 (10%) |

Data are median (range) or number (%). ECOG PS=Eastern Cooperative Oncology Group performance status. ER=oestrogen receptor. PR=progesterone receptor. *Includes multiracial patients. †Two patients in the trastuzumab emtansine group had missing ECOG PS scores; proportions are calculated out of a population of 402 patients. ‡At initial diagnosis of breast cancer. §Excluding hormonal treatment. ¶Two patients in the trastuzumab emtansine group had missing information; proportions are calculated out of a population of 402 patients.

| | Physician's choice (n=185) |
|---|---|
| **Treatment category** | |
| Single-agent trastuzumab emtansine | 1 (<1%)* |
| Combination with HER2-directed agent | 153 (83%) |
| Trastuzumab plus chemotherapy | 126 (68%) |
| Trastuzumab plus lapatinib | 19 (10%) |
| Trastuzumab plus hormonal therapy | 3 (2%) |
| Lapatinib plus chemotherapy | 5 (3%) |
| Single-agent chemotherapy | 31 (17%) |
| **Chemotherapy agents†** | |
| Vinorelbine | 59 (32%) |
| Gemcitabine | 29 (16%) |
| Eribulin | 16 (9%) |
| Paclitaxel | 16 (9%) |
| Docetaxel | 10 (5%) |
| Other | 32 (17%) |

Data are number (%). Further details can be found in the appendix. *One patient randomised to the physician's choice group (whose planned treatment was trastuzumab plus gemcitabine) received two cycles of trastuzumab emtansine by mistake. †With or without HER2-directed therapy.

***Table 2:*** **Type of treatment in patients who received treatment of**

For the analysis of overall survival, we censored patients who were alive at the time of data cutoff at the last date they were known to be alive on or before the cutoff date. Patients with no post-baseline information were censored at the date of randomisation plus 1 day. For the analysis of overall response, we regarded patients with measurable disease at baseline who had no post-baseline record of tumour assessment as non-responders.

We estimated median time-to-event outcomes and corresponding 95% CIs for each treatment group using Kaplan-Meier methods. We used the two-sided log-rank test, stratified by the protocol-defined randomisation factors, to compare time-to-event outcomes between treatment groups. The unstratified log-rank test was done as a sensitivity analysis. HRs and corresponding 95% CIs were estimated using Cox proportional hazards models, stratified by the protocol-defined randomisation factors. Overall response data were compared between treatment groups using a stratified Mantel-Haenszel $\chi^2$ test. Statistical analyses were done with SAS (version 9.2).

This study is registered with ClinicalTrials.gov, number NCT01419197.

## Role of funding source

The TH3RESA study was designed by the funder, Genentech, in collaboration with the study steering committee. Two non-Roche steering committee members and authors of this Article, IEK and PML, reviewed and approved the statistical analysis plan before finalisation of the original protocol. All steering committee members discussed and agreed to any protocol amendments, including changes to the statistical analysis after data from the EMILIA study became available. Employees of the funder managed the data and did the statistical analyses. Steering committee members reviewed the tables, listings, and graphs during the development of this manuscript and could have had access to the primary database, if requested. The Article's senior author, HW, provided his sign-off on the clinical study report. Moreover, the study's independent data monitoring committee, which provided external oversight, had access to all primary data throughout the course of the trial. All authors were involved in data analysis and interpretation, manuscript writing, and final approval of the manuscript. The manuscript was also reviewed by the funder. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

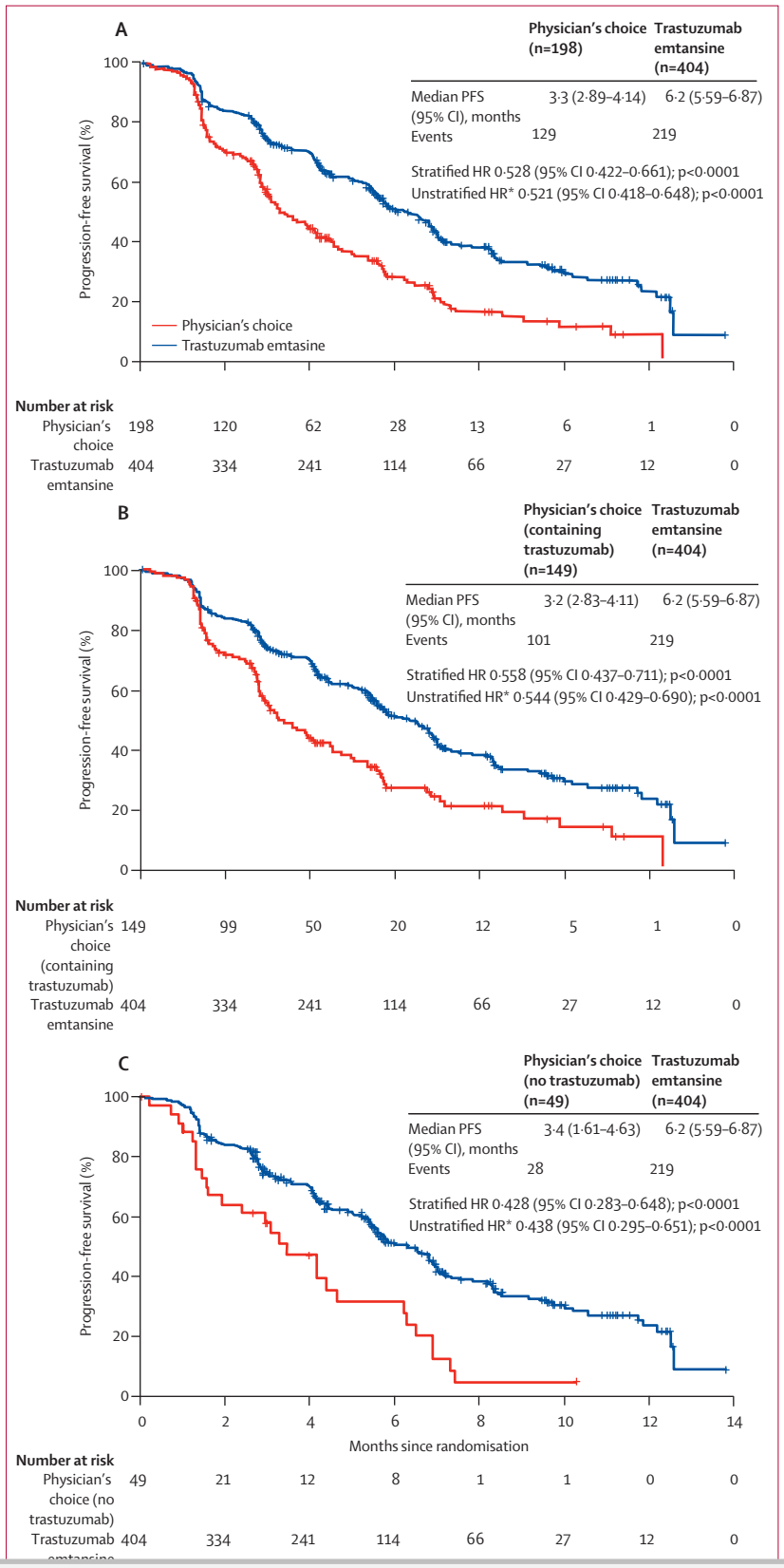


***Figure 2:*** **Kaplan-Meier curves of progression-free survival**
Probability of progression-free survival in all randomised patients in each treatment group (A), in all randomised patients in the trastuzumab emtansine group and those in the physician's choice group who received a trastuzumab-containing regimen as study medication (B), and in all randomised patients in the trastuzumab emtansine group and those in the physician's choice group who received a study medication regimen that did not contain trastuzumab (C)

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.