

# Relationship between effects on time-to-disease progression and overall survival in studies of metastatic breast cancer

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The relationship between overall survival (OS) and disease progression end points has been demonstrated in colorectal, colon, and non-small cell lung cancers. We assessed the association between OS and time-to-progression (TTP) or progression-free survival (PFS) in metastatic breast cancer (MBC) studies. A literature search retrieved all randomised controlled trials since 1994 in patients with MBC in which OS and either TTP or PFS were reported. Summary data on trial and patient characteristics were abstracted. Study effect sizes were derived as the ratio of median progression (or survival) times, which approximates the hazard ratio. Effects were centred at zero for regression analyses weighted by sample size. Numerous treatments were represented in 67 studies (17 081 patients). Modeling showed a positive association between outcomes for progression and survival ( $R^2 = 0.30$ ) with a slope of 0.32 ( $P < 0.001$ ) and a non-significant intercept. Thus, a treatment effect on TTP/PFS translated into a concordant effect on OS, but with attenuated effect size. Similar results were found in models of subsets and sensitivity analyses. These results demonstrate that treatment effects on progression end points in MBC trials are expected to result in treatment differences on OS that are smaller yet consistently in the same direction.

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Most studies of anticancer agents are designed and powered to show differences between groups on disease progression end points such as response rates, time-to-progression, time-to-recurrence or disease-free survival. Although increased survival time is clearly an implicit goal, it is difficult to establish in randomised studies when standard clinical practise is to change treatments at the onset of new progressive events. Especially in the metastatic setting, where expected survival time may be very short, the use of drug combinations or sequential use of multiple drug classes is commonplace. Increasingly, patients in clinical trials are offered alternate treatment upon progression. Consequently, few studies actually demonstrate an unequivocal survival benefit using intent-to-treat analysis approaches.

In several tumour types, efforts have been made to justify the use of alternate, more easily established end points by showing how well they are correlated with survival. Several meta-analyses have been published (Table 1) that show a link between time-to-progression (TTP) or progression-free survival (PFS) with overall survival (OS) in metastatic colorectal or non-small cell lung cancer (Johnson *et al*, 2006) and colon cancer in the adjuvant setting (Sargent *et al*, 2005). For breast cancer, a moderately strong

correlation between 2-year disease-free survival and 5-year overall survival was observed in the adjuvant setting (Ng *et al*, 2008). A meta-analysis of metastatic breast cancer studies found a positive relationship between objective response and overall survival on an individual patient basis, but the relationship was less clear when treatment regimens were compared (Bruzzi *et al*, 2005). The authors questioned whether the relationship was strong enough to support objective response rate as a valid surrogate of survival when comparing treatments. Articles by two groups (Hackshaw *et al*, 2005; Burzykowski *et al*, 2008) examined the association with survival of several potential surrogate end points, specifically in studies of anthracyclines for advanced or metastatic breast cancer.

We performed a broad-based structured review and meta-analysis of randomised controlled trials in metastatic breast cancer. The objective of this research was to document and model the relationship between time-to-disease progression and OS in metastatic breast cancer studies across the literature.

## METHODS

### Study selection

Inclusion criteria for studies were determined prior to starting the literature search. Published articles of randomised controlled trials (RCTs) of patients with metastatic breast cancer were considered for inclusion if they were published in English after 1994 and reported both TTP (or PFS) and OS. Only studies in which the entire population had metastatic breast cancer (MBC) were

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**Table 1** Published meta-analyses in multiple tumour types

Tumour type	Studies included	Reference	Relationship analysed	Number of studies	Slope coefficient	R <sup>2</sup>
Breast: metastatic	All randomised studies reporting progression and survival times by treatment	Current analysis	Ratio of median progression and ratio of median survival times (centred at zero)	67	0.32	0.30
Breast: metastatic	Studies of anthracyclines and taxanes with individual patient data	Burzykowski <i>et al</i> (2008)	Log hazard ratio for progression and log hazard ratio for survival	11	Not provided	0.23
Breast: metastatic	Studies of epirubicin regimens with individual patient data	Bruzzi <i>et al</i> (2005)	Log hazard ratio for response and log odds ratio for survival	10	Not provided	0.10
Breast: advanced	Studies of first-line treatments using FAC or FEC	Hackshaw <i>et al</i> (2005)	Log hazard ratio for time-to-progression and log hazard ratio for survival	17 before 1990 9 after 1990	0.58 before 1990 0.40 after 1990	0.67 before 1990 0.41 after 1990
Breast: adjuvant	Studies reporting 2- to 3-year disease-free survival and 5-year overall survival (N ≥ 100)	Ng <i>et al</i> (2008)	Difference in proportion with disease-free survival at 2 years and difference in proportion surviving > 5 years	126	Not provided	0.38
Colorectal: advanced	Studies of FU+leucovorin with individual patient data	Buyse <i>et al</i> (2007)	Log hazard ratio for progression-free survival and log hazard ratio for survival	10	0.81	0.98
Colorectal: metastatic	Studies with 'mature data' (N ≥ 100)	Tang <i>et al</i> (2007)	Hazard ratio for progression and hazard ratio for survival	39	Not provided	0.55 (PFS) 0.27 (TTP)
Colorectal: metastatic	Studies of first-line treatments	Johnson <i>et al</i> (2006)	Difference in months-to-progression and difference in survival months	146	0.096	0.33
Colorectal: metastatic	Studies of first-line treatments (N ≥ 100 per arm)	Louvet <i>et al</i> (2001)	Median months progression-free survival and median months survival by treatment group	29	0.68	0.23
Colon: adjuvant	Studies selected based on 'relevance, maturity and data availability' (individual patient data)	Sargent <i>et al</i> (2005)	Hazard ratio for disease-free survival and hazard ratio for survival	18	0.89	0.90
Lung (non-small-cell)	Studies reporting hazard ratios since 1977	Johnson <i>et al</i> (2004)	Log hazard ratio for time-to-progression and log hazard ratio for survival	48	Not provided	0.42
Lung: metastatic	Studies of first-line treatments	Johnson <i>et al</i> (2006)	Difference in months-to-progression and difference in survival months	191	0.62	0.19

R<sup>2</sup> = coefficient of determination for multivariate analysis or derived as squared correlation coefficient.

included; studies that included patients with locally advanced breast cancer were not included to avoid potential confounding. PubMed searches were conducted using the terms 'breast cancer,' 'metastatic,' and 'survival' combined with recognised search terms to identify randomised controlled trials. In addition to the electronic literature search, we reviewed bibliographic reference lists of included studies and key review articles to identify other studies. Titles were initially reviewed for relevance. For those potentially meeting the inclusion criteria, the abstract was then reviewed. Finally, for those abstracts that appeared eligible for inclusion, full-text articles were retrieved and further examined.

### Data abstraction

Data were abstracted from studies where estimates were provided for both progression and survival outcomes. In addition to the summary data, we abstracted definitions of the primary outcomes in each trial. Distinctions between definitions for TTP and PFS were not consistent. Many trials included all deaths as events for the TTP outcome, which is more typically done for the PFS outcome. For this reason and considering the similarity in summary data, we combined results for the outcomes of TTP or PFS.

The methodological quality of each trial was assessed by confirming randomisation and allocation concealment, identifying whether the trial was blinded, and whether intention-to-treat analyses were available. After review of abstracted data, items were grouped or redefined to combine and use data from the most studies possible. Ratings for disease severity using Eastern Cooperative Oncology Group or Karnofsky scales were converted

to the World Health Organization (WHO) scale. Where possible, studies were characterised as to whether patients were identified as ER+ and/or PR+, and also HER2+ (ER/PR = oestrogen receptor/progesterone receptor; HER2 = human epidermal growth factor receptor-2). Treatments were characterised as first-line or subsequent (if any prior treatments for MBC) and grouped by drug class. For simplicity, only two treatment groups were used from each study. For studies that included three treatment groups, the group with the highest efficacy compared with control or the highest group from dose-ranging studies was included. Treatment groups were reviewed by two clinicians and identified, to the best extent possible, as an experimental treatment or a more standard treatment.

All studies provided at least the median overall survival and median TTP/PFS per study arm. We abstracted effect sizes and variances, where available. Hazard ratios and s.e. were not consistently available, and variances could not be calculated for all studies. For this reason, we show regression models weighted by sample size.

### Data analysis

Although few studies reported hazard ratios (HR), we derived it as the ratio of median times to event for the two treatment groups, under the assumption that survival follows an exponential distribution (Hackshaw *et al*, 2005). HRs were computed for experimental treatment vs standard treatment. The estimates for HR<sub>TTP</sub> and for HR<sub>OS</sub> were each centred at unity, so that the treatment effects for each outcome were defined as:

$$\text{Effect}_{\text{TTP}} = \text{HR}_{\text{TTP}} - 1$$

$$\text{Effect}_{\text{OS}} = \text{HR}_{\text{OS}} - 1$$

Using traditional meta-regression techniques, each study was analysed as a unit. Modeling by study provides a test for the association between each effect size for progression and effect size for survival. In other words, the model tests whether a study that shows differentiation between groups on the progression outcome is expected to show differentiation between groups on survival.

The basic model structure for the meta-regression is:

$$\text{Effect}_{\text{OS } i} = \beta_1 \times \text{Effect}_{\text{TTP } i} + \varepsilon$$

where each study ( $i$ ) contributed one observation to the meta-regression, weighted by sample size. Note that the intercept is forced to equal zero to reflect the plausible assumption that treatments with no effect on TTP will have no effect on survival. Preliminary modeling justified the choice of no intercept. For computing prediction intervals associated with different values of  $\text{Effect}_{\text{TTP}}$ , an intercept term was included so that perfect prediction at the no effect point was not assumed. Average survival time was considered as a covariate, but it was not significant, did not affect inferences, and was removed for ease of presentation. Exclusion of outliers did not affect inferences, so all studies were retained in the analyses. Subgroups of clinical interest were modeled separately for ease of interpretation. All analyses were performed using SAS version 9.1.

## RESULTS

The electronic literature search was conducted using PubMed on 11 October 2007. Data flow is shown in Figure 1 and study data is presented in Appendix 1. Two articles represented data from the same clinical trial (Eiermann, 2001; Slamon *et al*, 2001), and three of the 71 abstracted articles were subsequently excluded because they used high-dose chemotherapy, which has limited application to current clinical practise (Lotz *et al*, 2005; Schmid *et al*, 2005; Kröger *et al*, 2006). The resulting 67 clinical trials represent 17 081 patients. All trials were randomised. One trial was placebo-controlled and two allocated the control group to observation or usual care. Blinding was identified for only two trials. In 37 trials, analyses were identified as intent-to-treat; other trials did not specifically state intent-to-treat approach.

Most trials required patients at entry to be rated as WHO Grade 2 or below for performance status; 11 studies allowed up to Grade 3 performance status. Median age was 55 years (range: 50–75 years).

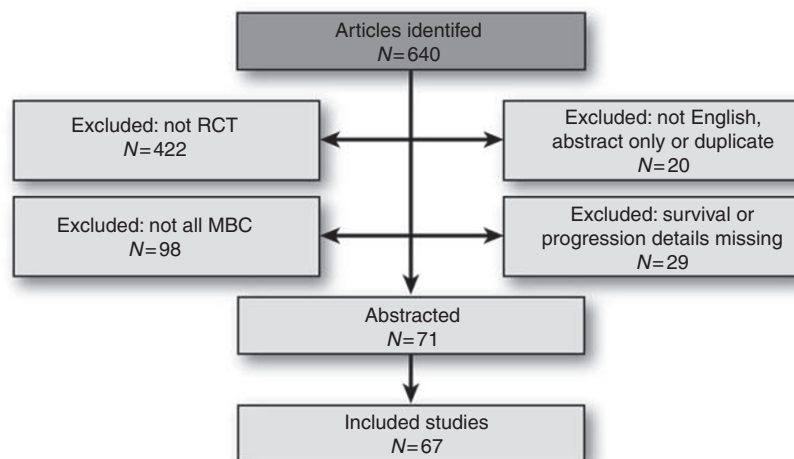
Hormone status for patients was presented for 46 studies, ranging from 14 to 84% oestrogen and/or progesterone receptor (ER/PR) positive. Only six studies provided HER2 (human epidermal growth factor receptor-2) status, four of which included only HER2+ patients. Most studies were of first-line treatment for MBC (46 studies); some of these studies allowed prior adjuvant treatment, but not prior chemotherapy for MBC. A range of drug classes were represented in 28 studies of monotherapies and 39 studies of combination regimens as shown in Tables 2 and 3.

The unweighted median TTP/PFS averaged across all treatment groups was 7 months (range, 2–15 months), and the average survival time was 20 months (range, 8–38 months). Correlation was 0.38 between time-to-progression and survival in the separate treatment groups (that is, ignoring trial comparisons).

Of 31 studies that provided tests of treatment differences for both TTP/PFS and OS, there was a moderate agreement between outcomes (Kappa test for agreement = 0.47,  $P < 0.05$ ). About half of these studies (48%) had a significant effect on progression, but only 23% had a significant effect on survival. None of the studies reported a significant effect on survival if there was not a significant effect on progression.

Figure 2 shows  $\text{HR}_{\text{OS}}$  vs  $\text{HR}_{\text{TTP}}$  for all studies with the radius of the bubbles representing relative study sample sizes. The range of  $\text{HR}_{\text{TTP}}$  for comparing experimental to standard treatments was 0.5–1.9;  $\text{HR}_{\text{OS}}$  ranged from 0.4 to 1.6. Minimal effects on both progression and survival were seen in 13% of studies; that is, the hazard ratio for both end points was close to one ( $0.9 < \text{HR} < 1.1$ ). In 39% of studies, treatment effects on both progression and survival were greater than 10% and in the same direction. Other within trial treatment comparisons gave mixed results on the two end points. In many studies, the hazard ratios showed a treatment effect on progression with minimal effect on survival (30%); fewer studies resulted in hazard ratios representing a minimal effect on progression with a more pronounced effect on survival (13%). In the very few studies with discordant results on treatment effect (that is,  $\text{HRR}_{\text{TTP}}$  and  $\text{HRR}_{\text{OS}}$  in opposite directions, shown in upper left and lower right quadrants of Figure 2), no pattern was apparent in terms of treatment or patient types. The unweighted Pearson correlation between  $\text{HR}_{\text{TTP}}$  and  $\text{HR}_{\text{OS}}$  across trials was 0.46.

The regression line shown in Figure 2 corresponds to the primary model results shown in Table 4. If the slope coefficient in this model equals zero ( $\beta = 0$ ), then the treatment effect on progression is not expected to affect treatment difference in survival; if  $\beta = 1$ , treatment effects on survival are expected to mirror treatment effects on progression end points. For  $0 < \beta < 1$ , we would expect that a treatment effect on progression is



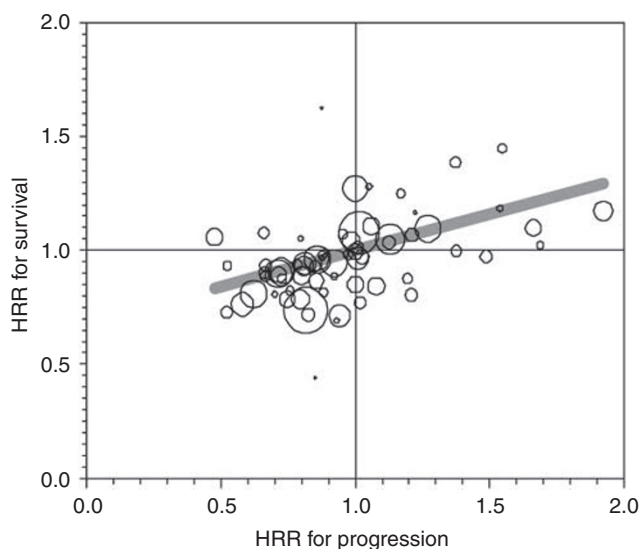
**Figure 1** Flow diagram of literature search.

**Table 2** Treatment types in included studies of monotherapies (n = 28)

Comparator	Experimental monotherapy					
	Anthracycline	Chemotherapy	Hormonal agent	Taxane	Biologic	Other
Anthracycline	4					
Chemotherapy		1				
Hormonal agent			10			
Taxane				3		
Biologic					1	
Placebo or usual care			1	1		1

**Table 3** Treatment types in included studies of combination therapies (n = 39)

Comparator	Experimental combination regimens							
	Anthracycline+taxane	Anthracycline+chemotherapy	Anthracycline+hormonal agent or biologic	Multiple anthracyclines	Multiple chemotherapies	Chemotherapies+Other	Multiple hormonal agents	Biologic+Chemotherapy or taxane
Anthracycline+taxane	4							
Anthracycline+chemotherapy	6	5	1		2			
Anthracycline+other						1		
Anthracycline		3	1	2				
Chemotherapy		4			3	2		1
Hormonal agent							1	
Taxane	1							1
Biologic+taxane								1



**Figure 2** Plot of HR for survival vs HR for progression by study size regression line: Effect<sub>OS</sub> = 0.32 × Effect<sub>TTP</sub> where Effect is the HR centred at unity. Bubbles show relative sample sizes from each study.

concordant but not as large for the OS outcome. In this meta-analysis, we found  $\beta_1 = 0.32$  (95% CI: 0.20, 0.43) supporting the last interpretation ( $R^2 = 0.30$ ). Results did not suggest curvature in the relationship (quadratic term,  $P = 0.16$ ). Adding an intercept term had only a minor effect on the slope parameter. The model predicts that a treatment effect on HR for progression equal to 0.70 would translate into a hazard ratio for survival of 0.88 (Table 5). Note that the confidence intervals shown in Table 5 are based on

modelling the meta-analysis data and are not intended for trial planning purposes; the width of the interval will be dependent on the sample size of future trials.

In studies of hormonal agents, the regression had a steeper slope with a wide CI encompassing one ( $\beta_1 = 0.58$ ; 95% CI: 0.001, 1.17; Table 4). Results in subsets of anthracycline studies, first-line treatments and later treatments were similar to the overall analysis. In four studies in which all patients were identified as HER2+, the slope was 0.50 but the CI did not encompass one. In this group of studies, the correlation between end points was particularly strong ( $R^2 = 0.93$ ).

Several additional subset analyses were performed in an effort to determine if patient characteristics or study type affected results. Studies in which progression was delayed by at least 6 months in the standard group might represent patients with better prognosis than in the overall group of studies. However, analysis of this group of studies and analysis of studies with at least 100 patients per group were very similar to the overall analysis.

We also reran the overall analysis with indicators for blinding and availability of ITT results. Neither had a significant effect on the regression ( $P = 0.77$  and 0.36 respectively), nor did the parameter estimate for the slope of the progression end point change appreciably. The fact that a study reported HRs is another potential indicator for study quality. HRs from proportional hazards modeling properly account for censored data and may have incorporated additional covariate effects; the reported values provide the best effect estimates from each study. For the 10 studies that reported hazard ratios, the reported HR<sub>TTP</sub> corresponded more closely with HR<sub>OS</sub> (slope = 0.52) than in the overall analysis using derived HRs and more of the variability was accounted for by the model ( $R^2 = 0.52$ ).

Additional exploratory analyses using different configurations of the outcome variable (difference in survival months, logarithm of the hazard ratio, analysis on survival months from separate

**Table 4** Summary of regression analyses<sup>a</sup>

	Number of studies	Slope parameter estimate (95% CI)	R <sup>2</sup> (adjusted)
Primary model – all studies	67	0.32 (0.20, 0.43)	0.30
Studies of hormonal treatments	12	0.58 (0.001, 1.17)	0.24
Studies of anthracyclines	36	0.32 (0.19, 0.43)	0.43
Studies of first-line treatments for MBC	46	0.29 (0.15, 0.42)	0.28
Studies of non first-line treatments	21	0.38 (0.14, 0.62)	0.32
Studies with only HER2+patients	4	0.50 (0.28, 0.71)	0.93
Studies which reported HRs	10	0.52 (0.18, 0.86)	0.52
Studies where TTP in standard group ≥ 6 months	37	0.32 (0.18, 0.47)	0.35
Studies with N per group ≥ 100	36	0.31 (0.16, 0.47)	0.31

CI = confidence interval. <sup>a</sup>Models without intercept and weighted by sample size.

**Table 5** Predicted HR<sub>OS</sub> based on observed HR<sub>TTP</sub>

Observed HR <sub>TTP</sub>	Predicted* HR <sub>OS</sub>
0.5	0.82 (0.76, 0.88)
0.6	0.85 (0.80, 0.90)
0.7	0.88 (0.84, 0.92)
0.8	0.91 (0.87, 0.95)

<sup>a</sup>Using model Effect OS = -0.03+(0.30 \*Effect TTP).

treatment groups) provided results and inferences consistent with the models shown here.

## DISCUSSION

These results demonstrate a clear positive association between effects on progression and survival in MBC patients, which is statistically significant. The analyses suggest that a treatment that prolongs time-to-progression will likely also have a longer overall survival time than the alternate treatment, although the relative effect will be substantially smaller. The analysis suggests that additional survival time seems to occur prior to progression and be a direct result of delaying this event; however, we did not have adequate data to look specifically at survival after progression.

The plot of effects on progression and survival illustrates the wide heterogeneity of results across studies conducted in metastatic breast cancer patients. In our analyses, we saw the highest level of predictability when analysing only the small subset of studies, which were conducted in HER2+ patients. Whether this finding is because of the similar design, homogeneous patients or treatment comparisons in these four studies remains in question. We note that the R-squared term (coefficient of determination) represents the amount of variance explained by the regression model and provides a measure of how reliably progression effects can predict survival effects. In other words, it measures the reproducibility of the relationship and is dependent both on the validity of the model and the sample size of the individual studies. On the other hand, the slope parameter (beta estimate) from the model quantifies the size of the effect, allowing one to ascertain how changes in progression effects will translate into changes in survival effects. In all the analyses presented here, we found a slope parameter that is statistically greater than zero (lower bound of CI is greater than zero). The relative survival effect is expected to be about one-third of the relative effect on progression.

Conducting a meta-analysis of time-to-event data from published reports is difficult as appropriate summary statistics are not always available in the publications. In practise, meta-analysis is

constrained by data availability, often suffers from lack of power, and may not adequately capture the effects of patient characteristics. For this analysis, we made decisions regarding outcome selection, weighting and model building that allowed us to incorporate the most studies. Results should be viewed as hypothesis-generating, rather than confirmatory. Specific limitations related to reporting include the following:

- Inclusion criteria and individual patient characteristics of prognostic importance may have varied across studies. Thus, homogeneous groups or subgroups of patients cannot be readily identified.
- Studies had somewhat inconsistent definitions for progression end points. Methods of assessing progression and specifics about how progression itself was defined were not examined.
- Consistent summary statistics (for example, hazard ratios and variance) were not available for all trials making more detailed analyses impossible.
- Few studies clearly identified treatment options such as crossover after progression.

Although it seems almost obvious that progression-free survival should be correlated with overall survival, the link between delayed progression of MBC from anticancer drugs and survival benefit is not well established. The goal of this investigation was to explore the extent to which progression end points can provide a reliable surrogate for OS in trials conducted in women with metastatic breast cancer. Although reducing death from breast cancer must be the primary goal of clinical trials, use of OS as a primary end point has several problems. In particular, (1) there is no control of treatment options after progression has taken place, (2) survival results are delayed as progression precedes death by several years on average even in metastatic breast cancer, and (3) deaths from causes other than breast cancer may occur. All of these factors can dilute real treatment effects on breast cancer survival in these women. These diluting factors make it hard to confirm the link between effects on progression and effects on survival.

Results presented here are generally consistent with findings in other tumour types (Table 1), although the different analysis approaches and inclusion criteria make it difficult to compare results across the literature. In breast and other tumour types, the highest predictive power was achieved when meta-analyses were performed using individual patient data on a small group of trials (Sargent *et al*, 2005; Buyse *et al*, 2007). Hackshaw *et al* (2005) noted an association between treatment effects on progression and survival when comparing anthracycline-based regimens in advanced breast cancer and suggested use of time-to-progression as a surrogate marker for survival. Interestingly, they found a stronger relationship between the end points in studies performed prior to 1990 when second-line therapies for metastatic cancer were not commonly used. More recently, a meta-analysis of 11 studies in

metastatic breast cancer comparing anthracyclines to taxanes examined the association of several end points with survival (Burzykowski *et al*, 2008). The researchers found tumour response to be more highly associated with overall survival than was progression-free survival. However, that meta-analysis appears to be unweighted. Our weighted analysis of anthracycline studies produced an  $R^2$  value almost double that reported by Burzykowski *et al* (2008). Using sample sizes as weights, we show a moderately strong linear correlation between progression-free survival and survival, in a large group of studies covering many treatment types. We find it intriguing that the strength of the relationship between end points may vary by tumour and/or treatment types and by line of therapy.

The consistency of findings in this comprehensive meta-analysis shows that we can expect overall survival with metastatic breast cancer to be extended when tumour progression is delayed,

although the effect size will typically be smaller. The attenuated effect is due at least partly to the diluting factors indicated above and suggests that overall survival itself is not a perfect end point for assessing the value of a treatment. We do not believe that the current findings are sufficient for accepting time-to-progression as a fully validated surrogate marker for overall survival in MBC, as the variance in the relationship is not fully explained. Factors that could improve the prediction remain under investigation. Nonetheless, the evidence suggests that progression is a useful early end point that should feature prominently in assessments of treatment efficacy for MBC. Further work is needed to better understand what determinants are associated with the link between disease progression and breast cancer survival and whether some tumour and/or treatment subgroups experience a more substantial survival benefit from delayed progression.

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Appendix

Appendix I Table of studies and treatments showing median months to progression (TTP or PFS) and overall survival (OS)

First author	Reference	Standard treatment	N	TTP	OS	Experimental treatment	N	TTP	OS
Abrams	<i>J Clin Oncol</i> 1999;17:64–73.	Megestrol acetate 160 mg/d	124	8.3	27.8	Megestrol acetate 800 mg/d	120	8.1	28.6
Ackland	<i>J Clin Oncol</i> 2001;19:943–53.	CMF	223	6.3	18.2	CEF	237	8.7	20.1
Alba	<i>J Clin Oncol</i> 2004;22:2587–93.	Concomitant doxorubicin+docetaxel 6 cycles	69	9.2	21.8	Sequential doxorubicin -> docetaxel 3 cycles each	75	10.5	22.3
Bastholt	<i>J Clin Oncol</i> 1996;14:1146–55.	Epirubicin 40	76	4.4	13.6	Epirubicin 90	71	8.4	14.6
Batist	<i>J Clin Oncol</i> 2001;19:1444–54.	Doxorubicin+cyclophosphamide	142	5.5	16	Myocet (liposome encapsulated doxorubicin)	155	5.1	19
Becher	<i>Semin Oncol</i> 1996;23:28–33.	Continued epirubicin/fluorouracil	63	5.4	13.5	Discontinued	60	3.2	13.2
Beex	<i>Eur J Cancer</i> 2006; 42: 3178–3185	Continuous tamoxifen	94	11	35.1	Intermittent tamoxifen	93	8	35.2
Berruti	<i>J Clin Oncol</i> 2002;20:4150–9.	Epirubicin+cisplatin	185	10.9	28.8	Epirubicin+ionidamine	186	10.8	29.8
Bezwodna	<i>Oncology</i> 1998;55:416–20.	megestrol acetate 40 mg qid	46	4.18	26.18	Fadrozole	50	3.98	20.46
Biganzoli	<i>J Clin Oncol</i> 2002;20:3114–21.	Doxorubicin+cyclophosphamide	138	6	20.5	Doxyrubicin+paclitaxel	135	6	20.6
Bishop	<i>J Clin Oncol</i> 1999;17 :2355–64.	Cyclophosphamide	107	6.4	13.9	Paclitaxel	102	5.3	17.3
Bonnerterre	<i>Br J Cancer</i> 2004;91:1466–71.	Epirubicin 75+5-FU 500+cyclophosphamide 500	70	5.9	28	Epirubicin 75+docetaxel 75	72	7.8	34
Bonnerterre	<i>Br J Cancer</i> 2002;87:1210–5.	5-FU 750+vinorelbine 25	88	5.1	15	Docetaxel 100	90	6.5	16
Bontenbal	<i>J Clin Oncol</i> 2005;23:7081–8.	FAC	109	6.6	16.2	Doxyrubicin+docetaxel	107	8	22.6
Bontenbal	<i>Br J Cancer</i> 1997;77:2257–63.	Doxorubicin 75	118	5.75	11.75	Epirubicin 90	114	4.75	11
Brufman	<i>Ann Oncol</i> 1997;8:155–62.	Standard FEC (epi 50)	214	7	17	Intensive FEC (epi 100)	242	7.6	18
Byrne	<i>J Clin Oncol</i> 1997;15:3141–8.	Tamoxifen+medroxy progesterone	109	3	17.2	Medroxyprogesterone only	106	4.5	18.4
Capotorto	<i>J Chemother</i> 2003;15:184–91.	FEC	45	12.7	23.3	MMM-G (time intensified)	46	14.5	24.1
Chan	<i>Ann Oncol</i> 2004;15:1527–34.	Epirubicin+C	80	5.6	16	Myocet(liposome-encapsulated doxorubicin)+C	80	7.7	18.3
Chan	<i>Breast Cancer Res Treat</i> 2004;86:197–206.	Doxorubicin 50	161	5.25	14	Docetaxol 100	165	6.5	15
Cocconi	<i>Am J Clin Oncol</i> 1999;22:593–600.	CONVENTIONAL CMF (cyclophosphamide, methotrexate, 5-FU)	53	15	27.25	Rotational crossing program	53	9.75	23
Conte	<i>Ann Oncol</i> 1996;7:487–90.	CEF	128	9.4	17.3	Diethylstilbestrol +CEF	130	11	20
Conte	<i>Cancer</i> 2004;101:704–12.	Concomitant epirubicin and paclitaxel	106	11	20	Sequential epirubicin and paclitaxel	92	10.8	26
Dogliotti	<i>J Clin Oncol</i> 1996; 14:1165–72.	Epirubicin	104	10.6	25.3	Epirubicin+ionidamine	103	10.5	25
Ejlertsen	<i>J Clin Oncol</i> 2004;22:2313–20.	Epirubicin	194	8.2	18	Epirubicin+vinorelbine	193	10.1	19.1
Elmmaa	<i>Ann Oncol</i> 2003;14:699–703.	Vinorelbine 20 (+methotrexate and fluorouracil)	26	7	26	Vinorelbine 30 +MF	10	8	16
Estaban	<i>Breast Cancer Res Treat</i> 1999;58:141–50.	Cyclophosphamide+fluorouracil+epirubicin (CEF)	76	12.75	18.6	Cyclophosphamide+fluorouracil+mitoxantrone (CNF)	75	8.25	12.85
Fountzilas	<i>J Clin Oncol</i> 2001;19:2232–9.	Epirubicin +paclitaxel	93	8.5	20	Epirubicin x 4cycles THEN paclitaxel x 4cycles	90	10	21.5
Fountzilas	<i>Ann Oncol</i> 1997;8:1213–20.	Epirubicin every 4 weeks+filgastim	81	7.2	14.6	Epirubicin every 2 weeks+filgastim	86	7.4	14.9
French Epirubicin Study Group	<i>J Clin Oncol</i> 2000;18:3115–24.	FEC 75 x 11 cycles	139	10.3	17.9	FEC 100 x 4 cycles+FEC 50 x 8 cycles	133	6.2	16.3
Gennari	<i>J Clin Oncol</i> 2006; 24: 3912–3918	Control	109	9	29	Paclitaxel	106	8	28
Gershonovich	<i>Ann Oncol</i> 1998;9:639–45.	Aminoglutethimide 250 mg	192	3.2	20	Letrozole 2.5 mg OD	178	3.4	28
Goss	<i>J Clin Oncol</i> 1999;17:52–63.	Megestrol acetate 40 mg QID	225	3.3	28.8	Vorozole 2.5 mg OD	227	2.6	26.3
Gregory	<i>Eur J Cancer</i> 1997;33:2194–7.	Stop current treatment (VAC, VEC or MMM) after six courses	52	7	10.5	Continue current treatment for 12 courses	48	10	13
Hausmaninger	<i>Eur J Cancer</i> 1995;31A:2169–73.	Epirubicin – vindesine	149	5.4	14.7	Mitoxantrone – vindesine	146	5.1	13.3
Hayes	<i>J Clin Oncol</i> 1995;13:2556–66.	Toremifene 60 mg/d	212	5.6	38.3	Toremifene 200 mg/d	221	5.6	30.1
Heidemann	<i>Ann Oncol</i> 2002;13:1717–29.	Mitoxantrone 12	127	4.4	14.1	Fluorouracil 500+epirubicin 50+cyclophosphamide 500 (FEC)	133	6.15	15.8
Ingle	<i>Cancer</i> 1994;73:2337–43.	CMF	80	4.1	13.3	CMF preceded by diethylstilbestrol	83	4.3	12.4
Jaassem	<i>J Clin Oncol</i> 2001;19:1707–15.	FAC	134	6.2	18.3	Doxorubicin+paclitaxel	133	8.3	23.3
Joensuu	<i>J Clin Oncol</i> 1998;16:3720–30.	Epirubicin 20 weekly then mitomycin every 4 weeks	153	8	16	CEF 3 x week then mitomycin+vinblastin	150	10	18
Jones	<i>J Clin Oncol</i> 1995;13:2567–74.	Alkeran (melphalan)	115	2	7.75	Navelbine (vinorelbine)	64	3	8.75
Kaufman <sup>a</sup>	<i>Clin Breast Cancer</i> 2000;1 Suppl 1:S15-S18.	Megestrol acetate 40 mg/d	366	4.15	13.75	Exemestane 25 mg/d	403	5.08	18.65
Kloke	<i>Breast Cancer Res Treat</i> 1999;55:51–9.	No treatment	46	3.9	18.3	Medroxy progesterone acetate	44	4.9	17.4
Langley	<i>J Clin Oncol</i> 2005;23:8322–30.	Epirubicin+cyclophosphamide	353	7.1	14	Epirubicin+paclitaxel	352	7	13
Marty	<i>J Clin Oncol</i> 2005;23:4265–74.	Docetaxel	94	6.1	22.7	Trastuzumab+docetaxel	94	11.7	31.2
Miller	<i>J Clin Oncol</i> 2005; 23:792–9.	Capecitabine alone	230	4.17	14.5	Capecitabine 2,500 bd+bevacizumab 15 mg/kg	232	4.86	15.1
Muss	<i>J Clin Oncol</i> 1994;12:1630–8.	Medroxy progesterone acetate	91	8.1	33	Tamoxifen 20 mg/d	91	5.9	23.8
Nabholtz	<i>J Clin Oncol</i> 1999;17:1413–24.	Mitomycin 12+vinblastine 6	203	2.75	8.7	Docetaxel 100	189	4.75	11.4
Nabholtz	<i>J Clin Oncol</i> 2003;21:968–75.	Doxorubicin 60+cyclophosphamide 600	214	7.98	21.7	Doxorubicin 50+docetaxel 75	215	9.325	22.5
Nabholtz	<i>J Clin Oncol</i> 1996;14:1858–67.	Paclitaxel 135	235	3	10.5	Paclitaxel 175	236	4.2	11.7
Namer	<i>Eur J Cancer</i> 2001;37:1132–40.	Mitoxantrone+vinorelbine	138	7	17	FAC or FEC	142	7	20
Nooij	<i>Eur J Cancer</i> 2003;39:614–21.	Continue CMF	97	5.2	14	Stop CMF (and restart in the case of progression)	107	3.5	14.4
Norris	<i>J Clin Oncol</i> 2000;18:2385–94.	Doxorubicin alone	151	6.1	14.4	doxorubicin+vinorelbine	149	6.2	13.8
O'Brien	<i>Ann Oncol</i> 2004;15:440–9.	Doxorubicin	254	7.8	22	Caelyx (PLD)	255	6.9	21
Pacilio	<i>Br J Cancer</i> 2006;94:1233–6.	Docetaxel 100	25	11	21	Docetaxel 80+epirubicin 75	26	9	18
Paridaens	<i>J Clin Oncol</i> 2000;18:724–33.	Doxorubicin	166	7.5	18.3	Paclitaxel	165	3.9	15.6
Pavesi	<i>Anticancer Res</i> 1995;15:495–501.	FNC	78	7.5	15.5	FEC	74	8.5	19
Peethambaram	<i>Breast cancer Res Treat</i> 1999;54:117–22.	Diethylstilbestrol	69	6.9	36	Tamoxifen	74	5.9	28.8
Perez	<i>Ann Oncol</i> 2002;13:1225–35.	AC THEN docetaxel	17	10.2	13.2	Docetaxel THEN AC	16	12	30
Robert	<i>J Clin Oncol</i> 2006;24:2786–92.	TP (trastuzumab and paclitaxel)	98	7.1	32.2	TPC (trastuzumab, paclitaxel and carboplatin)	98	10.7	35.7
Rose	<i>Breast Cancer Res Treat</i> 2000;61:103–10.	Tamoxifen+fluoxymesterone	86	9.2	21.1	Tamoxifen+aminoglutethimide+hydrocortisone	86	7.7	24.1
Sjostrom	<i>Eur J Cancer</i> 1999;35(8):1194–1201.	Sequential methotrexate and 5-FU	143	3	11	Docetaxel 100	140	6.3	10.4
Slamon	<i>N Engl J Med</i> 2001;344:783–92.	Standard chemotherapy	234	4.6	20.3	Standard chemotherapy+trastuzumab	235	7.4	25.1
Sparano	<i>J Clin Oncol</i> 2004;22:4683–90.	Placebo	69	3.1	26.6	Marimastat	120	4.7	24.7
Taberner	<i>Ann Oncol</i> 2004;15:1358–65.	Docetaxel 3-weekly	41	5.3	20.1	Docetaxel weekly	42	5.7	29.1
Vogel	<i>J Clin Oncol</i> 2002;20:719–26.	Trastuzumab 4 mg/kg loading+2 mg/kg weekly	59	3.5	22.9	Trastuzumab 8 mg/kg loading+4 mg/kg weekly	55	3.8	25.8
Winer	<i>J Clin Oncol</i> 2004;22:2061–8.	Paclitaxel 175	158	3.9	11	Paclitaxel 210	155	4.9	14

Abbreviations for treatments: A = Adriamycin (doxorubicin); C = Cytoxan (cyclophosphamide); E = epirubicin; D = docetaxel; F = 5-FU; V = vinorelbine. Acronyms for combination regimens: AC = doxorubicin+cyclophosphamide; CMF = cyclophosphamide+methotrexate+5-FU; FAC = 5-FU+doxorubicin+cyclophosphamide; FEC = 5-FU+epirubicin+cyclophosphamide(also called CEF); FNC = 5-FU+novantrone+cyclophosphamide; MMM = mitoxantrone+methotrexate+mitomycin-C; TP = trastuzumab+paclitaxel. <sup>a</sup>OS provided at 25th percentile.