

# Clinics in Oncology and Cancer Therapy

## Research Article

# Comparative Analysis of targeted molecular therapy versus Standard Care in breast cancer

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## Abstract

**Background:** Molecular subtyping of breast cancer by receptor and HER2 status has driven two decades of trials testing whether targeted agents outperform standard chemotherapy or endocrine therapy.

**Objective:** This analysis synthesizes randomized evidence across HER2-positive, hormone receptor-positive, BRCA-mutated, and triple-negative breast cancer to characterize how consistently targeted therapy outperforms standard care.

**Methods:** We compared reported progression-free survival, overall survival, disease-free survival, and pathological complete response from randomized trials of targeted agents added to or substituted for standard-care regimens.

**Results:** HER2-directed antibodies and antibody-drug conjugates produced cumulative survival gains over successive standards; CDK4/6 and PARP inhibitors improved progression-free survival in most but not all settings; and immunotherapy and antibody-drug conjugates improved outcomes in triple-negative disease, while genomic assays identified subsets in whom chemotherapy could be safely omitted.

**Conclusions:** Targeted therapy outperforms standard care across nearly every breast cancer subtype, though benefit magnitude varies by mechanism and setting, supporting subtype-specific individualization over uniform substitution.

**Keywords:** breast cancer; targeted therapy; HER2; CDK4/6 inhibitor; standard care

## 1. Introduction

Breast cancer is no longer treated as a single disease. Routine assessment of estrogen receptor, progesterone receptor, and HER2 status, together with genomic risk assays, separates patients into biologically distinct subtypes that respond very differently to the same cytotoxic backbone, and over the past two decades the field has progressively replaced or supplemented that backbone with agents built around a specific molecular target. The prototype was trastuzumab, a monoclonal antibody against HER2 that, added to chemotherapy in HER2-overexpressing metastatic disease, produced a survival advantage large enough to change first-line practice within a few years of its pivotal trial [1]. That result established a template repeated across hormone receptor-positive, HER2-positive, and triple-negative disease: identify a druggable dependency, pair a targeted agent with or against the existing standard, and test whether the addition or substitution improves outcomes beyond standard cytotoxic or endocrine therapy alone.

Standard care in this context is itself a moving target. For hormone receptor-positive disease it has historically meant endocrine therapy, alone or sequenced with chemotherapy; for HER2-positive disease it has meant anthracycline- or taxane-based chemotherapy; and for triple-negative disease, which lacks a validated receptor target, it has meant chemotherapy as essentially the only systemic option. Targeted therapy has entered each setting differently: HER2-directed antibodies and antibody-drug conjugates in HER2-positive disease, CDK4/6 and PI3K-pathway inhibitors layered onto endocrine therapy in hormone receptor-positive disease, PARP inhibitors in BRCA-mutated disease, and, more recently, immune checkpoint inhibitors and antibody-drug conjugates in triple-negative disease. This comparative analysis synthesizes randomized evidence across these settings to characterize how consistently targeted therapy outperforms standard care.

## 2. Methods

We synthesized results from randomized controlled trials and prospective meta-analyses comparing a targeted molecular agent, alone or added to a chemotherapy or endocrine backbone, against a standard-care comparator in breast cancer, spanning early-stage and metastatic settings. Trials were grouped by molecular subtype: HER2-positive disease (HER2-directed antibodies, antibody-drug conjugates, tyrosine kinase inhibitors), hormone receptor-positive/HER2-negative disease (CDK4/6 inhibitors, mTOR and PI3K-pathway inhibitors, genomic-assay-guided de-escalation), BRCA-mutated disease (PARP inhibitors), and triple-negative disease (checkpoint inhibitors, antibody-drug conjugates). For each trial we extracted the most consistently reported benefit measure, generally progression-free survival, overall survival, invasive disease-free survival, or pathological complete response, with comparator arm and setting. Because designs, comparators, and endpoints differ across this literature, we did not attempt a pooled statistical synthesis; instead we present reported point estimates side by side within each subtype to characterize the consistency and magnitude of benefit, and we note where genomic-assay-guided trials indicate standard chemotherapy can safely be reduced rather than intensified.

## 3. Results

In HER2-positive metastatic disease, adding trastuzumab to chemotherapy improved time to progression and survival relative to chemotherapy alone [1], and in the adjuvant setting trastuzumab added to chemotherapy produced a disease-free survival gain large enough that two adjuvant trials were unblinded early [2,3]. Eleven-year follow-up of the HERA trial confirmed this translated into durable overall survival benefit without excess late cardiac events [4], a joint North American analysis confirmed the overall survival benefit in nearly four thousand patients [5], and a meta-analysis of seven trials and close to fourteen thousand women confirmed reduced recurrence

and mortality across HER2-positive early breast cancer [6].

| Table 1: Randomized trials of HER2-directed targeted therapy versus standard-care comparators in HER2-positive breast cancer [1,2,7,9,10,12,15]. |                                    |                                                                                |                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------|
| Trial                                                                                                                                            | Setting                            | Targeted arm vs comparator                                                     | Reported benefit                               |
| [1]                                                                                                                                              | Metastatic, first-line             | Trastuzumab + chemo vs chemo alone                                             | Improved time to progression and survival      |
| [2]                                                                                                                                              | Adjuvant, early-stage              | Chemo + trastuzumab vs chemo alone                                             | Large absolute gain in disease-free survival   |
| [7]                                                                                                                                              | Metastatic, first-line             | Pertuzumab + trastuzumab + docetaxel vs trastuzumab + docetaxel                | Improved progression-free survival             |
| [9]                                                                                                                                              | Metastatic, second-line            | Trastuzumab emtansine vs lapatinib + capecitabine                              | Improved progression-free and overall survival |
| [10]                                                                                                                                             | Post-neoadjuvant, residual disease | Trastuzumab emtansine vs trastuzumab                                           | ~50% reduction in recurrence or death          |
| [12]                                                                                                                                             | Metastatic, later-line             | Trastuzumab deruxtecan vs trastuzumab emtansine                                | ~75% reduction in progression or death         |
| [15]                                                                                                                                             | Metastatic, later-line             | Tucatinib + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine | Improved progression-free and overall survival |

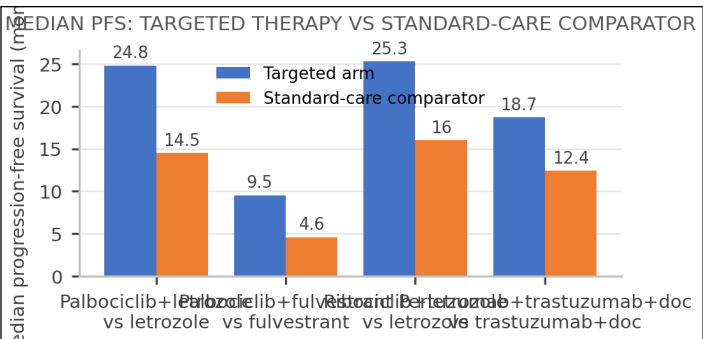


**Figure 1: Median progression-free survival with targeted therapy versus the standard-care comparator across four HER2-positive and hormone receptor-positive metastatic trials [16,17,18,7].**

Later trials tested whether intensifying HER2-directed therapy could outperform trastuzumab-based standard care itself. Adding pertuzumab to trastuzumab and docetaxel improved progression-free survival first-line [7]

and, in final analysis, extended median overall survival to over fifty-six months against low forties for the comparator [8]. Second-line, trastuzumab emtansine outperformed lapatinib plus capecitabine on progression-free and overall survival [9], and post-neoadjuvant, trastuzumab emtansine roughly halved the risk of recurrence or death versus continuing trastuzumab alone in patients with residual disease [10]. Trastuzumab deruxtecan produced a high response rate in heavily pretreated disease [11] and, head-to-head against trastuzumab emtansine, reduced progression or death risk by roughly three-quarters [12]. Earlier regimens showed the same pattern: lapatinib plus capecitabine outperformed capecitabine alone in trastuzumab-pretreated disease [13], dual blockade with lapatinib plus trastuzumab improved survival over lapatinib alone [14], and tucatinib added to trastuzumab and capecitabine improved progression-free and overall survival, including with brain metastases [15].

In hormone receptor-positive, HER2-negative disease, CDK4/6 inhibitors added to endocrine therapy produced consistent benefits: palbociclib plus letrozole roughly doubled median progression-free survival over letrozole alone first-line [16], palbociclib plus fulvestrant markedly improved progression-free survival after prior endocrine therapy [17], and ribociclib plus letrozole produced a comparable first-line benefit [18]. Abemaciclib showed the same pattern with fulvestrant [19] and as initial therapy [20], and adjuvant abemaciclib improved invasive disease-free survival in high-risk, node-positive disease [21]. This benefit was not universal across the class: adjuvant palbociclib failed to improve disease-free survival over endocrine therapy alone in PALLAS [22], contrasting with abemaciclib's positive adjuvant trial. Everolimus added to exemestane improved progression-free survival after prior aromatase-inhibitor exposure [23], and alpelisib added to fulvestrant improved progression-free survival specifically in PIK3CA-mutated tumors [24]. Genomic-assay trials moved in the opposite

direction: the 21-gene assay identified node-negative patients for whom chemotherapy added no benefit over endocrine therapy alone [25], and the 70-gene signature identified a high-clinical/low-genomic-risk subgroup for whom withholding chemotherapy did not compromise outcomes [26], showing standard chemotherapy can be de-escalated, not only augmented.

In BRCA-mutated disease, PARP inhibition outperformed chemotherapy of physician's choice on progression-free survival with olaparib [27] and talazoparib [28], establishing a population where a targeted oral agent replaces chemotherapy as first-choice therapy. In triple-negative disease, lacking a validated receptor target, atezolizumab added to nab-paclitaxel improved progression-free survival in PD-L1-positive metastatic disease [29], pembrolizumab added to neoadjuvant chemotherapy increased pathological complete response and improved event-free survival [30], consistent with pooled evidence that pathological complete response predicts long-term outcome [31], and sacituzumab govitecan improved progression-free and overall survival over single-agent chemotherapy in previously treated triple-negative [32] and hormone receptor-positive, HER2-negative disease [33]. Underlying nearly every comparison is the reference point set by tamoxifen-based endocrine therapy, whose patient-level meta-analysis defined the benefit any newer regimen must now be measured against [34].

4. Discussion

Across every subtype, targeted therapy added to or substituted for standard care produced a measurable improvement, but magnitude and durability varied by mechanism and setting. The largest, most consistent gains cluster in HER2-positive disease, where sequential trials, trastuzumab against chemotherapy, pertuzumab and trastuzumab emtansine against trastuzumab-based care, and trastuzumab deruxtecan against trastuzumab emtansine, produced a stepwise series of new standards

each outperforming the one before, reflecting how tightly HER2 amplification drives tumor dependence. The hormone receptor-positive setting is more heterogeneous: CDK4/6 inhibition delivered a repeated metastatic-setting advantage across three agents, yet one adjuvant trial was negative even as a different agent in the same class succeeded, underscoring that metastatic-setting benefit does not automatically generalize to the adjuvant setting.

| Table 2: Trials of targeted therapy in hormone receptor-positive, BRCA-mutated, and triple-negative breast cancer [17,22,27,28,29,32,25]. |       |                                                             |                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------|-------|-------------------------------------------------------------|------------------------------------------------|
| Subtype                                                                                                                                   | Trial | Targeted arm vs comparator                                  | Reported outcome                               |
| HR+/HER2-, metastatic                                                                                                                     | [17]  | Palbociclib + fulvestrant vs fulvestrant alone              | Improved progression-free survival             |
| HR+/HER2-, adjuvant                                                                                                                       | [22]  | Palbociclib + endocrine therapy vs endocrine therapy alone  | No improvement in disease-free survival        |
| BRCA-mutated, metastatic                                                                                                                  | [27]  | Olaparib vs chemotherapy of physician's choice              | Improved progression-free survival             |
| BRCA-mutated, metastatic                                                                                                                  | [28]  | Talazoparib vs chemotherapy of physician's choice           | Improved progression-free survival             |
| Triple-negative, metastatic                                                                                                               | [29]  | Atezolizumab + nab-paclitaxel vs nab-paclitaxel alone       | Improved progression-free survival (PD-L1+)    |
| Triple-negative, metastatic                                                                                                               | [32]  | Sacituzumab govitecan vs single-agent chemotherapy          | Improved progression-free and overall survival |
| HR+/HER2-, node-negative                                                                                                                  | [25]  | 21-gene assay-guided de-escalation vs standard chemotherapy | Chemotherapy safely omitted in low-risk subset |

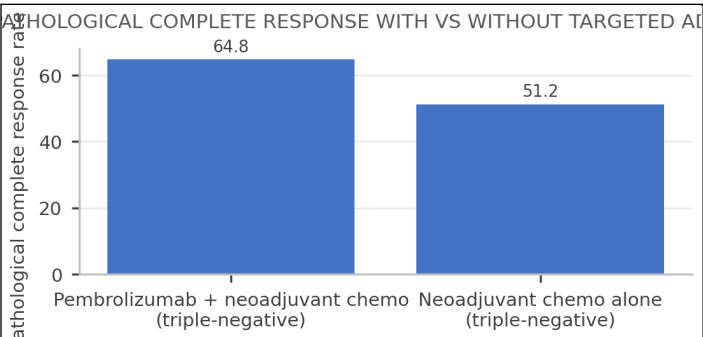


**Figure 2: Pathological complete response rate with targeted therapy added to neoadjuvant chemotherapy versus chemotherapy alone in early-stage triple-negative and HER2-positive breast cancer [30,31].**

A second theme is that "standard care" is not static: several trials reviewed here used a targeted or genomically guided approach to make standard chemotherapy more selective rather than replace it outright. The 21-gene and 70-gene assays tested whether chemotherapy could be safely withheld from patients whose biology predicted minimal added benefit, and both showed it could, sparing many hormone receptor-positive patients from cytotoxic therapy without compromising outcomes. This de-escalation evidence, alongside the intensification evidence from HER2-positive and BRCA-mutated disease, suggests the targeted-therapy era's practical achievement has been precision in both directions.

Several limitations qualify these comparisons. Trials differ in comparator, prior exposure, line of therapy, and endpoint, which precludes formal pooled synthesis and limits comparison to directional consistency rather than precise effect-size ranking. Progression-free survival, the most common endpoint, does not always translate into a comparable overall survival benefit, and some trials report mature survival data while others report only interim endpoints. Triple-negative disease remains the subtype with the fewest validated targets, and its immune checkpoint and antibody-drug conjugate strategies, while practice-changing, still leave many patients without a durable targeted option.

### 5. Conclusion

Targeted molecular therapy has outperformed standard

care across essentially every major breast cancer subtype examined, but the size of that advantage is not uniform. HER2-directed therapy shows the most consistent, cumulative gains; hormone receptor-positive disease shows real but context-dependent benefit including one negative adjuvant trial within a broadly positive drug class; BRCA-mutated disease shows a clean substitution of a targeted oral agent for chemotherapy; and triple-negative disease shows meaningful but incomplete progress. The evidence supports continuing to individualize therapy by molecular subtype, and using genomic risk assays to de-escalate chemotherapy in parallel with using targeted agents to intensify treatment where a druggable dependency has been identified.

### 6. References

1. Slamon, D.J., Leyland-Jones, B., Shak, S., Fuchs, H., Paton, V., Bajamonde, A., et al. (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *New England Journal of Medicine*, 344(11): 783-792.
2. Romond, E.H., Perez, E.A., Bryant, J., Suman, V.J., Geyer, C.E., Davidson, N.E., et al. (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New England Journal of Medicine*, 353(16): 1673-1684.
3. Piccart-Gebhart, M.J., Procter, M., Leyland-Jones, B., Goldhirsch, A., Untch, M., Smith, I., et al. (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New England Journal of Medicine*, 353(16): 1659-1672.
4. Cameron, D., Piccart-Gebhart, M.J., Gelber, R.D., Procter, M., Goldhirsch, A., de Azambuja, E., et al. (2017) 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*, 389(10075): 1195-1205.
5. Perez, E.A., Romond, E.H., Suman, V.J., Jeong, J.H., Sledge, G.,

- Geyer, C.E., et al. (2014) Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *Journal of Clinical Oncology*, 32(33): 3744-3752.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2021) Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13,864 women in seven randomised trials. *Lancet Oncology*, 22(8): 1139-1150.
7. Baselga, J., Cortes, J., Kim, S.B., Im, S.A., Hegg, R., Im, Y.H., et al. (2012) Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *New England Journal of Medicine*, 366(2): 109-119.
8. Swain, S.M., Baselga, J., Kim, S.B., Ro, J., Semiglazov, V., Campone, M., et al. (2015) Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *New England Journal of Medicine*, 372(8): 724-734.
9. Verma, S., Miles, D., Gianni, L., Krop, I.E., Welslau, M., Baselga, J., et al. (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. *New England Journal of Medicine*, 367(19): 1783-1791.
10. von Minckwitz, G., Huang, C.S., Mano, M.S., Loibl, S., Mamounas, E.P., Untch, M., et al. (2019) Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *New England Journal of Medicine*, 380(7): 617-628.
11. Modi, S., Saura, C., Yamashita, T., Park, Y.H., Kim, S.B., Tamura, K., et al. (2020) Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *New England Journal of Medicine*, 382(7): 610-621.
12. Cortes, J., Kim, S.B., Chung, W.P., Im, S.A., Park, Y.H., Hegg, R., et al. (2022) Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *New England Journal of Medicine*, 386(12): 1143-1154.
13. Geyer, C.E., Forster, J., Lindquist, D., Chan, S., Romieu, C.G., Pienkowski, T., et al. (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *New England Journal of Medicine*, 355(26): 2733-2743.
14. Blackwell, K.L., Burstein, H.J., Storniolo, A.M., Rugo, H.S., Sledge, G., Aktan, G., et al. (2012) Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *Journal of Clinical Oncology*, 30(21): 2585-2592.
15. Murthy, R.K., Loi, S., Okines, A., Paplomata, E., Hamilton, E., Hurvitz, S.A., et al. (2020) Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *New England Journal of Medicine*, 382(7): 597-609.
16. Finn, R.S., Martin, M., Rugo, H.S., Jones, S., Im, S.A., Gelmon, K., et al. (2016) Palbociclib and letrozole in advanced breast cancer. *New England Journal of Medicine*, 375(20): 1925-1936.
17. Turner, N.C., Ro, J., Andre, F., Loi, S., Verma, S., Iwata, H., et al. (2015) Palbociclib in hormone-receptor-positive advanced breast cancer. *New England Journal of Medicine*, 373(3): 209-219.
18. Hortobagyi, G.N., Stemmer, S.M., Burris, H.A., Yap, Y.S., Sonke, G.S., Paluch-Shimon, S., et al. (2016) Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *New England Journal of Medicine*, 375(18): 1738-1748.
19. Sledge, G.W., Toi, M., Neven, P., Sohn, J., Inoue, K., Pivot, X., et al. (2017) MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *Journal of Clinical Oncology*, 35(25): 2875-2884.
20. Goetz, M.P., Toi, M., Campone, M., Sohn, J., Paluch-Shimon, S., Huober, J., et al. (2017) MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *Journal of Clinical Oncology*, 35(32): 3638-3646.
21. Johnston, S.R.D., Harbeck, N., Hegg, R., Toi, M., Martin, M., Shao, Z.M., et al. (2020) Abemaciclib combined with

- endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer. *Journal of Clinical Oncology*, 38(34): 3987-3998.
22. Mayer, E.L., Dueck, A.C., Martin, M., Rubovszky, G., Burstein, H.J., Bellet-Ezquerria, M., et al. (2021) Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS). *Lancet Oncology*, 22(2): 212-222.
23. Baselga, J., Campone, M., Piccart, M., Burris, H.A., Rugo, H.S., Sahmoud, T., et al. (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *New England Journal of Medicine*, 366(6): 520-529.
24. Andre, F., Ciruelos, E., Rubovszky, G., Campone, M., Loibl, S., Rugo, H.S., et al. (2019) Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *New England Journal of Medicine*, 380(20): 1929-1940.
25. Sparano, J.A., Gray, R.J., Makower, D.F., Pritchard, K.I., Albain, K.S., Hayes, D.F., et al. (2018) Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *New England Journal of Medicine*, 379(2): 111-121.
26. Cardoso, F., van't Veer, L.J., Bogaerts, J., Slaets, L., Viale, G., Delaloge, S., et al. (2016) 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *New England Journal of Medicine*, 375(8): 717-729.
27. Robson, M., Im, S.A., Senkus, E., Xu, B., Domchek, S.M., Masuda, N., et al. (2017) Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *New England Journal of Medicine*, 377(6): 523-533.
28. Litton, J.K., Rugo, H.S., Ettl, J., Hurvitz, S.A., Goncalves, A., Lee, K.H., et al. (2018) Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *New England Journal of Medicine*, 379(8): 753-763.
29. Schmid, P., Adams, S., Rugo, H.S., Schneeweiss, A., Barrios, C.H., Iwata, H., et al. (2018) Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *New England Journal of Medicine*, 379(22): 2108-2121.
30. Schmid, P., Cortes, J., Puzstai, L., McArthur, H., Kummel, S., Bergh, J., et al. (2020) Pembrolizumab for early triple-negative breast cancer. *New England Journal of Medicine*, 382(9): 810-821.
31. Cortazar, P., Zhang, L., Untch, M., Mehta, K., Costantino, J.P., Wolmark, N., et al. (2014) Pathological complete response and long-term clinical benefit in breast cancer after neoadjuvant chemotherapy. *Lancet*, 384(9938): 164-172.
32. Bardia, A., Hurvitz, S.A., Tolaney, S.M., Loirat, D., Punie, K., Oliveira, M., et al. (2021) Sacituzumab govitecan in metastatic triple-negative breast cancer. *New England Journal of Medicine*, 384(16): 1529-1541.
33. Rugo, H.S., Bardia, A., Marme, F., Cortes, J., Schmid, P., Loirat, D., et al. (2022) Sacituzumab govitecan in hormone receptor-positive/HER2-negative metastatic breast cancer. *Journal of Clinical Oncology*, 40(29): 3365-3376.
34. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*, 378(9793): 771-784.