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Adjuvant chemotherapy and HER-2-directed therapy for early-stage breast cancer in the elderly

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There is a lack of sufficient evidence-based data defining the optimal adjuvant systemic therapies in older women. Recommendations are mainly based on retrospective studies, subgroup analyses within larger randomised trials and expert opinion. Treatment decisions should consider the functional fitness of the patient, co-morbidities, in addition to chronological age with the aim to balance risks and potential benefits from treatment(s). In this review, we discuss assessment tools to aid clinicians to select elderly patients who are 'fit' for chemotherapy, and review the literature on the use of chemotherapy and of the anti-HER 2 antibody trastuzumab in this population. We will also review two commonly used prediction models to assess their accuracy in predicting survival outcomes in elderly patients. Ongoing clinical trials specifically focusing on older patients may help to clarify the absolute benefits and risks of adjuvant systemic therapy in this age group.

Breast cancer is the most common female malignancy diagnosed worldwide (Ferlay *et al*, 2015). Women aged 65 and over account for two-fifths of all breast cancer diagnoses (SEER Cancer Statistics Review, 1975-2012, 2015). As the population ages, the number of new breast cancers in older individuals is also expected to increase. Despite this, there is a lack of level I evidence on how to optimally treat early-stage breast cancer in elderly women, owing to relatively poor representation and accrual in clinical trials. There is also no universally defined age cutoff for what constitutes as 'elderly'. Some have considered the age of 70 to be the milestone age, stating that after this age there are significantly increased age-related physiological changes (Pallis *et al*, 2010). Others, such as the European Medicines Agency, consider 65 years old to be the cutoff age (Pallis *et al*, 2010). The aim of this review paper is to summarise available published research and guidelines on chemotherapy and anti-HER 2 therapy in the treatment of elderly women with early-stage breast cancer.

FUNCTIONAL ASSESSMENT

The Society of Geriatric Oncology (SIOG) created a task force in 2007 to provide evidence-based recommendations for the management of breast cancer in elderly patients (Wildiers *et al*, 2007). Recommendations were updated in 2010 (Biganzoli *et al*, 2012). No age cutoff was specified in the 2007 or 2010 guidelines (Wildiers *et al*, 2007; Biganzoli *et al*, 2012). Instead of a strict age cutoff, the committee recommended to assess multiple factors of a patient including life expectancy, risks and benefits of treatment, patient preference, potential treatment barriers, in addition to chronological age (Biganzoli *et al*, 2012). This is mirrored by the St Gallen International Expert Consensus, which also states that the decision for systemic treatment in elderly breast cancer patients should not be based solely on age (Coates *et al*, 2015). The terms 'fit' and 'frail' have been used to distinguish between elderly patients who are independent in activities of daily living with or without minimal co-morbidities *vs* 'frail' patients who have severe co-morbidities and limited functional independence (Balducci and Extermann, 2000).

Clinicians are often thinking in terms of 'fit' or 'frail' when assessing elderly patients in their practice. Clinicians are able to incorporate age-related issues such as co-morbidities and reduced organ function into their decision-making. In fact, a study looking at the impact of patient age on clinical decision-making in oncology showed that oncologists consistently scored age-related

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factors such as co-morbidity and frailty as more important than age itself (Rule *et al*, 2012). Thus, why is chronological age an important issue at all? Interestingly in that same study, when oncologists were presented with case scenarios and asked to make a treatment decision, the most significant influence on the intensity of treatment oncologists would recommend was based on age alone (Rule *et al*, 2012). Chronological age was ranked higher than age-related issues such as co-morbidities, and social needs such as support networks (Rule *et al*, 2012). This is an interesting situation, in that clinicians are aware that chronological age should not guide treatment decisions, but at the time of clinical decision-making, consciously or subconsciously, age becomes a significant factor. Thus, this presents a challenge as how to best manage elderly cancer patients. Assessment tools may be valuable in this setting as a way to help clinicians determine the functional status of a patient with less bias.

There have been many assessment tools that have been developed to help clinicians identify which elderly patients would benefit from adjuvant chemotherapy as opposed to those who would likely have significant toxicities from the treatment. Although there is currently no universally accepted standard method of assessment, the Comprehensive Geriatric Assessment (CGA) has been widely used (Stuck *et al*, 1993). The CGA contains multiple domains assessing function, co-morbidity, nutrition, medication, socio-economic issues and geriatric syndromes (Stuck *et al*, 1993). There is some evidence for its use in cancer patients. One study investigated whether CGA or clinical judgment was more effective at identifying diffuse large B-cell lymphoma patients that could benefit from curative chemotherapy (Tucci *et al*, 2009). The study enrolled 84 patients >65 years old, and they were classified as 'fit' or 'unfit' by CGA, but had curative or palliative treatment based on the clinical judgment alone (Tucci *et al*, 2009). The results showed that the patients who were classified as 'unfit' by CGA, but 'fit' by the clinical judgment had poor outcomes, and patients who were classified as 'fit' by CGA and were treated with curative intent had the best survival outcomes (Tucci *et al*, 2009). However, CGA can be time-consuming, requiring up to 45 min to administer and is usually carried out by a geriatrician (Biganzoli *et al*, 2012). Thus, this method of assessment is generally not feasible to implement in routine clinical practice.

Therefore, shorter screening tools have been developed to allow for a more feasible assessment to be conducted in the clinic setting. One such tool is the G8 screening test, which has been studied in cancer patients and found to have a sensitivity of 77% compared with the CGA (Soubeyran *et al*, 2014). The G8 screening tool consists of eight items relating to the categories of nutrition, motor skills, psychological status, medications and age (Bellera *et al*, 2012). The SIOG recommends using a screening tool such as the G8, but it does not replace the CGA (Biganzoli *et al*, 2012). If a screening tool is abnormal, the patient should be referred on to have a CGA (Biganzoli *et al*, 2012).

A question that remains unanswered is whether these assessment tools have a meaningful clinical impact on breast cancer outcomes. For example, the G8 screening test did not predict for serious adverse events or treatment discontinuations in the ICE II-GBG 52 study (von Minckwitz *et al*, 2015). This study compared adjuvant chemotherapy consisting of epirubicin and cyclophosphamide, or cyclophosphamide, methotrexate and 5-fluorouracil (CMF), with nab-paclitaxel and capecitabine for fit elderly patients (von Minckwitz *et al*, 2015). However, a criticism is that patients in this study who had an abnormal G8 did not go on to have a CGA, as recommended by the SIOG (Biganzoli *et al*, 2012). A small pilot study of 15 early-stage breast cancer patients aged 70 and older who received formal CGA testing, over a third of the patients, had their treatment altered following the formal geriatric testing (Girre *et al*, 2008). However, whether the changes improved relevant clinical outcomes of these patients is unknown (Girre *et al*, 2008). More studies are clearly needed to further characterise the clinical impact of these geriatric assessment tools in breast cancer patients.

ADJUVANT CHEMOTHERAPY

It is difficult to determine the magnitude of benefit elderly cancer patients derive from the adjuvant chemotherapy owing to the lack of level I evidence. This is because elderly patients are either often excluded and/or under-represented in the randomised clinical trials of adjuvant chemotherapy ± the targeted therapy. A meta-analysis looking at the trend of chemotherapy benefit in breast cancer patients by age group showed that there was a survival advantage from chemotherapy for patients up to the age of 69 years old (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005). After age 70, the benefit of chemotherapy was no longer statistically significant (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005). Of note, however, is that only a small proportion (4.1%) of the total number of patients were aged 70 years or older, thus limiting the statistical power and ability to detect an actual difference (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005).

There are a limited number of adjuvant chemotherapy trials that have focused specifically on an elderly breast cancer patient population. A CALGB study that included 633 women aged 65 years and older showed that there was a benefit from combination chemotherapy (Muss *et al*, 2009). The study randomised patients to either CMF or cyclophosphamide plus doxorubicin (AC) *vs* capecitabine (Muss *et al*, 2009). The aim of the study was to test for non-inferiority of capecitabine, which is potentially a more tolerable oral agent than poly-chemotherapy. The study showed that at 3 years, capecitabine was in fact inferior to poly-chemotherapy for both disease-free survival (DFS) and for overall survival (OS; Muss *et al*, 2009). The toxicity profile showed that fewer patients on the capecitabine arm had grade 3 or higher adverse events, although there were two deaths from treatment-related complications in the capecitabine arm (Muss *et al*, 2009). Assuming that capecitabine does not have a detrimental effect on DFS, this study would suggest that adjuvant poly-chemotherapy does in fact have an adjuvant impact in elderly patients with early-stage breast cancer.

The futility of capecitabine as adjuvant therapy for elderly patients with breast cancer was further confirmed by the ICE (Ibandronate with or without Capecitabine in Elderly Patients with Early Breast Cancer) study (von Minckwitz *et al*, 2014). This study enrolled 1358 elderly women over the age of 65 with moderate to high-risk breast cancer to either ibandronate alone or in combination with capecitabine (von Minckwitz *et al*, 2014). After 61 months of follow-up, both groups had a similar DFS and OS (von Minckwitz *et al*, 2014). These two studies support the use of combination chemotherapy as standard of care for elderly patients, as opposed to single-agent capecitabine.

Though an advantage of combination chemotherapy over single-agent chemotherapy appears clear, the optimal chemotherapy combination is unknown. The ELDA (Elderly Docetaxel Adjuvant) trial randomised 299 women aged 65 and older to either CMF or weekly docetaxel (Punglia *et al*, 2015). The results showed that there was no DFS difference between the two arms, but the docetaxel arm had more toxicities and an associated worse quality of life (Gori *et al*, 2015). In the US Oncology Research Trial 9735 comparing AC *vs* docetaxel and cyclophosphamide (DC), DFS and OS were superior in the DC arm (Jones *et al*, 2009). Subgroup analysis of patients aged 65 and older showed that older patients derived the same benefit from DC, but had more febrile

neutropenia and anaemia with treatment (Jones *et al*, 2009). This conclusion is limited, in that only a small proportion of patients in the study (16%) were 65 years or older (Jones *et al*, 2009). Table 1 lists the adjuvant clinical trials that have been conducted focusing on an elderly breast cancer patient population.

Adjuvant chemotherapy is feasible in fit elderly patients. However, when selecting a chemotherapy regimen for older patients, there is no 'one size fits all'. A taxane-based treatment may have improved outcomes (analogous to younger patients), but appears to come at a cost of increased toxicity. An anthracycline regimen may put elderly patients at increased cardiac toxicity especially if there is pre-existing heart disease (Aapro *et al*, 2011). CMF may be an option if patients are unable to tolerate a taxane or anthracycline treatment. There are no studies on the use of sequential anthracycline–taxane regimen specifically in elderly patients. Therefore, clinicians should base the choice of the chemotherapy regimen on the patient's co-morbidities, risk of disease recurrence, risk for toxicities, patient preference and functional status – preferably following some form of formal functional assessment.

ADJUVANT TRASTUZUMAB

Trastuzumab, a monoclonal antibody against HER-2, added to chemotherapy increases OS and DFS in patients with early-stage HER-2-positive breast cancer, as evidenced in the landmark trials of HERA, NSABP B31, NCCTG N9831 and BCIRG006 (Piccart-Gebhart *et al*, 2005; Romond *et al*, 2005; Perez *et al*, 2011; Slamon *et al*, 2015). However, these trials had less than one-fifth of patients aged 60 and above (Piccart-Gebhart *et al*, 2005; Romond *et al*, 2005; Perez *et al*, 2011). A systemic review of prospective randomised trials in patients aged 60 years and older showed a 47% relative risk reduction in elderly patients receiving trastuzumab compared with chemotherapy alone – a similar magnitude of benefit as seen in younger patients (Brollo *et al*, 2013). Therefore, the use of trastuzumab should be considered standard of care for elderly patients with HER-2-positive disease that warrant systemic and targeted treatment similar to younger patients. The challenges are the increased toxicities that are unfortunately experienced in older patients.

The major toxicity associated with trastuzumab is the risk of cardiotoxicity, especially in older patients who are also more likely to have pre-existing cardiac disease. An independent review of the NSABP B31 and NCCTG N9831 trials showed that age >50 was one of the independent predictor for cardiac events, defined as heart failure, myocardial infarction or primary arrhythmias that resulted in death, or decline of at least 10 percentage points (absolute) from baseline left ventricular ejection fraction and a decline to $<50\%$ (Russell *et al*, 2010). However, this result was not seen in the HERA trial that showed no difference in cardiac events in patients over and under 60 years old (de Azambuja *et al*, 2014).

A cohort study of elderly patients (age 66 and over) looked at the rate of cardiotoxicity in patients who received trastuzumab and chemotherapy (anthracycline and/or taxane) compared with chemotherapy alone (Chavez-MacGregor *et al*, 2013). The study showed a 10% increase in congestive heart failure in the group treated with trastuzumab and chemotherapy compared with the chemotherapy alone group (Chavez-MacGregor *et al*, 2013). Among trastuzumab-treated patients, older age (age >80 years old) was one of the factors that increased the risk of congestive heart failure (Chavez-MacGregor *et al*, 2013). Another retrospective study of elderly women aged 67–94 years of age compared different permutations of trastuzumab and chemotherapy ($\pm$ trastuzumab $\pm$ anthracycline/non-anthracycline chemotherapy; Chen *et al*, 2012). Results showed that the addition of an anthracycline to trastuzumab was associated with the highest rate of cardiotoxicity (Chen *et al*, 2012).

This finding was also seen in the BCIRG006 trial, although this study did not focus on older patients and had an upper age cutoff of 70 years old. This trial compared docetaxel, carboplatin and trastuzumab (TCH) with an anthracycline–taxane–trastuzumab regimen (AC-TH) for early-stage HER-2-positive breast cancer (Slamon *et al*, 2015). The ten-year follow-up results show similar efficacy between the two arms; however, AC-TH had a five-fold increase in clinical congestive heart failures (Slamon *et al*, 2015). Therefore, the use of a non-anthracycline chemotherapy and trastuzumab should be considered as an alternative regimen in elderly patients with either significant cardiac risk factors or underlying cardiac disease.

Another non-anthracycline regimen that may be more tolerable than TCH is weekly paclitaxel and trastuzumab (Tolaney *et al*, 2015). This regimen has been studied in node-negative, HER-2-positive breast cancer with a primary tumour size of 3 cm or less, and demonstrated very favourable early clinical outcomes (3 year DFS of 98.7%; 95% CI 97.6–99.8%). Although this study did not focus on elderly patients, it may be an option for older patients with node-negative tumours who are otherwise not suitable for more aggressive chemotherapy. Currently, there are no clinical data on the use of monotherapy, trastuzumab alone, as treatment in elderly patients.

PREDICTION MODELS

Outcome prediction tools have been developed to help guide treatment decisions, and predict expected benefits to systemic and targeted therapy for individual breast cancer patients. Adjuvant! Online is a popular assessment programme that is available free online and provides information on breast cancer relapse and

Table 1. Elderly breast cancer adjuvant chemotherapy clinical trials

Clinical trial	Sample size	Age criteria	Follow-up period	Treatment	Result
CALGB 49907 (Muss *et al*, 2009)	633	65 and older	3 years	CMF or AC *vs* capecitabine	Decreased DFS and OS in capecitabine arm
ICE (von Minckwitz *et al*, 2015)	1358	65 and older	5 years	Ibandronate *vs* Ibandronate + capecitabine	No difference in DFS and OS between the two arms
ELDA (Punglia *et al*, 2015)	299	65 and older	5 years	CMF *vs* weekly docetaxel	No DFS difference; more toxicities in docetaxel arm
US Oncology Research Trial 9735 (Jones *et al*, 2009)	160 (subgroup analysis)	65 and older (subgroup analysis)	7 years	AC *vs* DC	Increased DFS and OS in DC arm; more febrile neutropenia and anaemia in DC arm

Abbreviations: AC = doxorubicin and cyclophosphamide; CMF = cyclophosphamide, methotrexate and fluorouracil; DC = docetaxel and cyclophosphamide; DFS = disease-free survival; OS = overall survival.

Table 2. International Guidelines on Adjuvant Systemic Treatment of Elderly Breast Cancer Patients

Consensus panel (update year)	Recommendations
SIOG/EUSOMA (2010)	Decision to treat with chemotherapy should not be based on age alone AC and CMF are preferred to monotherapy capecitabine Anthracycline-containing regimen is preferred to CMF Taxane can be added to anthracycline in high-risk healthy elderly patients or substituted for anthracycline to decrease cardiac risk HER2-positive tumours should be treated with trastuzumab + chemotherapy in patients without cardiac disease
St Gallen (2015)	No age cutoff Treatment should be based on disease characteristics, co-morbidity, life expectancy and patient preference
ASCO (2015)	Consider life expectancy, risks and benefits of the treatment, and patient preference Systemic therapy should be offered to patients with life expectancy >5 years HER2-positive small node-negative tumours: consider paclitaxel and trastuzumab HER2-positive larger tumours: consider TCH that has more favourable toxicity profile compared with anthracycline, taxane and trastuzumab combination

Abbreviations: AC = doxorubicin and cyclophosphamide; CMF = cyclophosphamide, methotrexate and fluorouracil; SIOG = International Society of Geriatric Oncology; EUSOMA = European Society of Breast Cancer Specialists; St Gallen = St Gallen International Expert Consensus; ASCO = American Society of Clinical Oncology; TCH = docetaxel, carboplatin and trastuzumab.

mortality (Ravdin *et al*, 2001). This programme was developed in a population of women aged 69 years and younger (Ravdin *et al*, 2001). A validation study was conducted to see if Adjuvant! Online could accurately predict outcomes for older patients (de Glas *et al*, 2014). This study was tested in 2012 patients older or equal to 65 years old (de Glas *et al*, 2014). The results showed that Adjuvant! Online overestimated the 10-year OS and recurrence-free survival by 9.8% and 8.7%, respectively, for older patients when co-morbidity was selected as average for age (de Glas *et al*, 2014).

The PREDICT tool is another computerised assessment tool used to calculate the 5- and 10-year outcomes from early-stage breast cancer (Wishart *et al*, 2010). PREDICT included a cohort of almost 5700 women, of which a third were aged 65 years or over (Wishart *et al*, 2010). When PREDICT was tested in the same population of 2012 older patients, the results showed that PREDICT had similar 5-year OS with a difference of 1.7%, but 10-year OS was overestimated, with a difference of 4.5% (de Glas *et al*, 2016). The largest differences were observed in the oldest patients (>85 years old) and in patients with multiple co-morbidities (de Glas *et al*, 2016). These results demonstrated that PREDICT appears to be a better prediction tool than Adjuvant! Online, however, it is still not perfect for elderly patients. New or improvements to existing models designed specifically for older patients are needed, and should incorporate functional assessment and elderly specific end points, such as risk for toxicity to treatment in addition to relapse and mortality risks.

ONGOING CLINICAL TRIALS

A few ongoing trials may help to improve upon our current evidence. The ASTER 70 s (GERICO, UCBG) is a multicentre phase III trial evaluating whether adjuvant chemotherapy increases survival in women over the age of 70 who are at high risk of relapse according to Genomic Grade (ClinicalTrials.gov identifier NCT01564056). RESPECT is a Japanese phase III trial in women over the age of 70, comparing monotherapy trastuzumab with trastuzumab + chemotherapy with HER-2-positive early-stage disease (ClinicalTrials.gov identifier NCT01104935). The results from this study may be useful for elderly patients who are not candidates for chemotherapy, but whose tumours express the HER-2 proto-oncogene.

CONCLUSION

The adjuvant treatment of breast cancer in the elderly population is complex with lack of clear level I evidence with regard to selection of specific chemotherapy regimens and defined magnitude of benefit relative to rates of significant adverse events. Major issues include the lack of clinical trial inclusion specifically for elderly breast cancer patients and also differing upper age cutoffs used in the various studies. Selection bias of elderly patients enrolled onto clinical trials creates a challenge when attempting to extrapolate to routine clinical practice where the majority of the patients are not likely to be the 'fit of the fit'.

On the basis of the available evidence, fit elderly patients should be treated the same as their younger counterparts. Table 2 lists the current recommendations from three international consensus panels – SIOG/EUSOMA, St Gallen and ASCO – on the use of adjuvant systemic therapy in elderly breast cancer patients (Biganzoli *et al*, 2012; Coates *et al*, 2015). The recommendation from the consensus groups is that, in clinical practice, clinicians should avoid using chronological age alone to make treatment decisions. This should also be applied to patient selection criteria in clinical trials. Eliminating upper age cutoffs from clinical trial design would be more in keeping with real-world practice and may potentially help to increase enrolment of fit elderly patients onto clinical trials. Furthermore, having a universal definition for the terms elderly and frailty would be valuable for consistency purposes moving forward.

Research is needed in this field to assess both pharmacogenomic and physiological factors to predict for greater toxicity in elderly patients relative to specific treatments received. In addition, more research is needed to assess the clinical impact of geriatric assessment tools in breast cancer outcomes as the data are lacking. However, the SIOG currently supports performing a screening test, such as the G8 screening test, in women aged 65 years or older in whom adjuvant chemotherapy ± trastuzumab is contemplated. If the G8 is abnormal, the patient should then be referred on to have a more formal geriatric assessment such as the CGA as performed by a geriatrician.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Aapro M, Bernard-Marty C, Brain EG, Batist G, Erdkamp F, Krzemieniecki K, Leonard R, Lluch A, Monfardini S, Ryberg M, Soubeyran P, Wedding U (2011) Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. *Ann Oncol* **22**: 257–267.

Balducci L, Extermann M (2000) Management of cancer in the older person: a practical approach. *Oncologist* **5**: 224–237.

Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck M, Soubeyran PL (2012) Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol* **23**: 2166–2172.

Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, Reed M, Ciatto S, Voogd AC, Brain E, Cutuli B, Terret C, Gosney M, Aapro M, Audisio R (2012) Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol* **13**: e148–e160.

Brollo J, Curigliano G, Disalvatore D, Marrone BF, Criscitiello C, Bagnardi V, Kneubil MC, Fumagalli L, Locatelli M, Manunta S, Goldhirsch A (2013) Adjuvant trastuzumab in elderly with HER-2 positive breast cancer: a systematic review of randomized controlled trials. *Cancer Treat Rev* **39**: 44–50.

Chavez-MacGregor M, Zhang N, Buchholz TA, Zhang Y, Niu J, Elting L, Smith BD, Hortobagyi GN, Giordano SH (2013) Trastuzumab-related cardiotoxicity among older patients with breast cancer. *J Clin Oncol* **31**: 4222–4228.

Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP (2012) Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Coll Cardiol* **60**: 2504–2512.

Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, Thurlimann B, Senn HJ (2015) Tailoring therapies–improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol* **26**: 1533–1546.

de Azambuja E, Procter MJ, van Veldhuisen DJ, Agbor-Tarh D, Metzger-Filho O, Steinseifer J, Untch M, Smith IE, Gianni L, Baselga J, Jackisch C, Cameron DA, Bell R, Leyland-Jones B, Dowsett M, Gelber RD, Piccart-Gebhart MJ, Suter TM (2014) Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin Adjuvant trial (BIG 1-01). *J Clin Oncol* **32**: 2159–2165.

de Glas NA, Bastiaannet E, Engels CC, de Craen AJ, Putter H, van de Velde CJ, Hurria A, Liefers GJ, Portielje JE (2016) Validity of the online PREDICT tool in older patients with breast cancer: a population-based study. *Br J Cancer* **114**: 395–400.

de Glas NA, van de Water W, Engelhardt EG, Bastiaannet E, de Craen AJ, Kroep JR, Putter H, Stiggelbout AM, Weijl NI, van de Velde CJ, Portielje JE, Liefers GJ (2014) Validity of Adjuvant! Online program in older patients with breast cancer: a population-based study. *Lancet Oncol* **15**: 722–729.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* **365**: 1687–1717.

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* **136**: e359–e386.

Girre V, Falcou MC, Gisselbrecht M, Gridel G, Mosseri V, Bouleuc C, Poinsot R, Vedrine L, Ollivier L, Garabige V, Pierga JY, Dieras V, Mignot L (2008) Does a geriatric oncology consultation modify the cancer treatment plan for elderly patients? *J Gerontol A Biol Sci Med Sci* **63**: 724–730.

Gori S, Colantuoni G, Barni S, Riccardi F, De Maio E, Montanino A, Morabito A, Daniele G, Di Maio M, Piccirillo MC, Signoriello S, Gallo C, de Matteis A (2015) Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III ELDA trial. *Ann Oncol* **26**: 675–682.

Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ, Pippen JE, Bordelon JH, Kirby RL, Sandbach J, Hyman WJ, Richards DA, Mennel RG, Boehm KA, Meyer WG, Asmar L, Mackey D, Riedel S, Muss H, Savin MA (2009) Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol* **27**: 1177–1183.

Muss HB, Berry DA, Cirrincione CT, Theodoulou M, Mauer AM, Kornblith AB, Partridge AH, Dressler LG, Cohen HJ, Becker HP, Kartcheske PA, Wheeler JD, Perez EA, Wolff AC, Gralow JR, Burstein HJ, Mahmood AA, Magrinat G, Parker BA, Hart RD, Grenier D, Norton L, Hudis CA, Winer EP (2009) Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med* **360**: 2055–2065.

Pallis AG, Fortpied C, Wedding U, Van Nes MC, Penninckx B, Ring A, Lacombe D, Monfardini S, Scalliet P, Wildiers H (2010) EORTC elderly task force position paper: approach to the older cancer patient. *Eur J Cancer* **46**: 1502–1513.

Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer Jr CE, Martino S, Mamounas EP, Kaufman PA, Wolmark N (2011) Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol* **29**: 3366–3373.

Punglia RS, Hughes KS, Muss HB (2015) Management of older women with early-stage breast cancer. In *American Society of Clinical Oncology Educational Book*, Dizon DS (ed) pp 48–55. American Society of Clinical Oncology: Alexandria, VA, USA.

Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD. Herceptin Adjuvant (HERA) Trial Study Team (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* **353**: 1659–1672.

Ravdin PM, Siminoff LA, Davis GJ, Mercer MB, Hewlett J, Gerson N, Parker HL (2001) Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol* **19**: 980–991.

Romond EH, Perez EA, Bryant J, Suman VJ, Geyer Jr CE, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* **353**: 1673–1684.

Rule J, Birtwistle M, Day R, Holding J, Matarredona A, Zeiderman M, Redfern N, Richards M, Audisio RA (2012) The impact of patient age on clinical decision-making in oncology. *J Geriatr Oncol* **3**: S24–S25.

Russell SD, Blackwell KL, Lawrence J, Pippen Jr JE, Roe MT, Wood F, Paton V, Holmgren E, Mahaffey KW (2010) Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant Breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. *J Clin Oncol* **28**: 3416–3421.

SEER Cancer Statistics Review, 1975-2012 (2015) Available at http://seer.cancer.gov/csr/1975_2012 (accessed 4 July 2016).

Slamon DJ, Eirmann W, Robert NJ, Giermek J, Martin M, Jasiowka M, Mackey JR, Chan A, Liu MC, Pinter T, Valero V, Falkson C, Fornander T, Shiftan TA, Bensfia S, Hitier S, Xu N, Bee-Munteanu V, Drevot P, Press MF, Crown J (2015) Ten year follow-up of the BCIRG-006 trial comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer patients. In: *Proc 38th Annu San Antonio Breast Cancer Symp*; 8–12 December; San Antonio, TX, USA. Abstract no. S5-04.

Soubeyran P, Bellera C, Goyard J, Heitz D, Cure H, Rousselot H, Albrand G, Servent V, Jean OS, van Praagh I, Kurtz JE, Perin S, Verhaeghe JL, Terret C, Desauw C, Girre V, Mertens C, Mathoulin-Pelissier S, Rainfray M (2014) Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study. *PLoS One* **9**: e115060.

Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ (1993) Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* **342**: 1032–1036.

Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, Albain KS, Rugo HS, Ellis M, Shapira I, Wolff AC, Carey LA, Overmoyer BA,

Partridge AH, Guo H, Hudis CA, Krop IE, Burstein HJ, Winer EP (2015) Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* **372**: 134–141.

Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G (2009) A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. *Cancer* **115**: 4547–4553.

von Minckwitz G, Conrad B, Reimer T, Decker T, Eidtmann H, Eiermann W, Hackmann J, Mobus V, Marme F, Potenberg J, Stickeler E, Simon E, Thomssen C, Huober J, Denkert C, Alfer J, Jackisch C, Nekljudova V, Burchardi N, Loibl S (2015) A randomized phase 2 study comparing EC or CMF versus nab-paclitaxel plus capecitabine as adjuvant chemotherapy for nonfrail elderly patients with moderate to high-risk early breast cancer (ICE II-GBG 52). *Cancer* **121**: 3639–3648.

von Minckwitz G, Reimer T, Potenberg J, Conrad B, Schurer U, Eidtmann H, Just M, Paepke S, Stickeler E, Heinrich G, Untch M, Moebus V, Tomssen C, Jackisch C, Huober J, Loibl S, Nekljudova V, Nitz U (2014) The phase III ICE study: adjuvant ibandronate with or without capecitabine in elderly patients with moderate or high risk early breast cancer. In: *Proc 37th Annu San Antonio Breast Cancer Symp*; 9–13 December; San Antonio, TX, USA. Abstract no. S3-04.

Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C, Hurria A, Extermann M, Girre V, Brain E, Audisio RA, Bartelink H, Barton M, Giordano SH, Muss H, Aapro M (2007) Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. *Lancet Oncol* **8**: 1101–1115.

Wishart GC, Azzato EM, Greenberg DC, Rashbass J, Kearins O, Lawrence G, Caldas C, Pharoah PD (2010) PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer. *Breast Cancer Res* **12**: R1.