Early and locally advanced breast cancer: diagnosis and management - Neoadjuvant chemotherapy and ovarian function suppression (update)

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Association of Clinical Psychologists UK	Guideline	General	General	ACP-UK comments that there are no considerations of the psychological and psychosocial impacts of the treatments offered, and how these may positively or negatively impact on patients. Considering that this may be outside of the scope of the current document, we would suggest signposting to any NICE guidelines that do contain this information is included within the final guidance.	Thank you for your comment. How to address the psychological and psychosocial impacts of treatments were not within the scope of the current update. However, the new recommendations made as part of this update will be published as part of the full NG101 guideline. There is a section on providing information and psychological support within the NICE guideline NG101 on early and locally advanced breast cancer: diagnosis and management. There is a recommendation that covers offering people with breast cancer access to specialist psychological support and, where appropriate, psychiatric services. We have also added a cross reference to the NICE guideline on Depression in adults with a chronic physical health problem, which covers identifying, treating and managing depression in people aged 18 and over who also have a chronic physical health problem such as cancer.

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BASO - The Association for Cancer Surgery	Guideline	009	1.11.2	We do not agree that HER2-positive breast cancer patients should be recommended to have neo-adjuvant chemotherapy for the following reasons: 1. As per the GMC guidance and the UK Law (esp Montgomery vs Lancashire health board, 2015) the patient should be the ultimate decision maker for their treatment and they cannot give their full consent without being advised the accurate estimate of the benefit from the chemotherapy before surgery compared with after surgery. Where this data is not available, such lack should be highlighted as an urgent research need rather than embracing the use of such drugs without establishing safety and efficacy of delaying surgery. Furthermore, given neoadjuvant chemotherapy is known to increase local recurrence, the guideline should mandate the summary of data from	Thank you for your comment. Please see our responses to your earlier comment in addition to our responses below. NICE strongly advocates that patients should be actively involved in any decision-making around their care and have entire guidelines dedicated to helping ensure this happens. (See CG138 Patient experience in adult NHS services: improving the experience of care for people using adult NHS services and NG197 Shared decision-making.) The committee agreed that the person with breast cancer is the ultimate decision maker for their treatment. In all cases the patient has the opportunity to accept or decline recommended treatment options. The committee highlighted the importance of having a conversation with the person about all suitable treatment options when planning systemic anticancer therapy. This is reflected in recommendations in the section of the guideline on Systemic anticancer therapy planning which have

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				publications listed below should be shared with patients. 2. The benefit is directly dependent on the risk of relapse, which can only be **accurately** estimated with full pathological examination of the post-surgical histological specimen. Therefore, stipulating "where chemotherapy is indicated" is an inappropriate because comprehensively ascertaining indication of chemotherapy is only possible after surgery. Therefore, neither the clinician or patient cannot take part in the process of a fully informed consent before the cancer is taken out and tissues examined under the microscope (exact tumour size, number of lymph nodes involved, extra-nodal involvement, lympho-vascular invasion, grade of the whole tumour (not just of the core biopsy), receptor status and any heterogeneity of the tumour in terms of	been expanded to cover all SACT and not just adjuvant therapy. These include a recommendation cross referring to the NICE guidelines mentioned above (CG138 and NG197). The current update to the HER2 positive breast cancer neoadjuvant chemotherapy recommendations was focused around comparing two different neoadjuvant chemotherapy regimens and any other issues relating to whether neoadjuvant chemotherapy should be used and the role of any anti-HER2 therapy in the neoadjuvant setting is therefore out of scope of this piece of work. We have not looked at whether neoadjuvant chemotherapy should be used (comparing the clinical and cost effectiveness of neoadjuvant chemotherapy compared to no neoadjuvant chemotherapy) as part of this work and therefore cannot respond to your comment about local recurrence in point 1. We are unable to respond to the clinical details in your comment 2, and comments

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				ER, PR HER2, etc) – if they are forced to give consent to chemotherapy before surgery such a consent is without having all information necessary for the decision. 3. There is no proven improvement in quality of life by using neoadjuvant chemotherapy other than downsizing the tumour and less extensive surgery which is also proven to increase local relapse. 4. The basis of using chemotherapy for HER2-positive breast cancer is to use patient's tumour in the breast as a test bed for drugs and use another drug if there is no response. It has been shown in many studies that testing a drug by assessing pathological complete response (pCR) is an unreliable approach and improvement in pCR usually does not translate into a survival benefit. Therefore, FDA has	3 and 5 for the same reason. Please see the evidence reviews for neoadjuvant treatment (review J) from the 2018 update for more details of why the committee made their recommendations in favour of using neoadjuvant chemotherapy. In relation to comment 4, the committee did not review the evidence on trastuzumab emtansine for treating HER2-positive early breast cancer as the Katherine trial did not meet the inclusion criteria for our review comparing types of neoadjuvant chemotherapy for people with HER2 positive breast cancer. We are therefore unable to comment on the results of this trial. The Katherine trial was used as evidence in the NICE TA632 on Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer. Please see this document for how this evidence was used to reach the recommendation for the use of Trastuzumab emtansine. Any feedback on technology appraisals should be sent to NICE using

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				stopped approving drugs using such an approach ([1 2]. The results of the Katharine trial are used to justify use of chemotherapy before surgery. In the Katherine trial, if HER2-directed therapy (trastuzumab) did not achieve pCR then patients were found to benefit from T-DM1. There are several substantial logical and scientific errors in using the Katharine trial results to justify use of chemotherapy + HER2 directed therapy. a. Most patients in the trial had big cancers (25% had inoperable cancer, 90% patients were >=T2, 85% patients were node positive). So the results are not applicable with smaller tumours:	the suggest a topic for guidance development form. See the page on Prioritising our guidance topics for more information. The topic in comment 6 is similarly out of scope and we are therefore unable to respond.

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				b. Most patients receiving anti-HER2 treatment today receive trastuzumab + pertuzumab. As there were only a few such patients in the trial (<300), the results of Katherine trial are not applicable. Therefore, there is no evidence or justification to use T-DM1 in the absence of pCR of such patients. Therefore, when pertuzumab is used, there cannot be any basis for giving chemotherapy before surgery (neoadjuvant) c. The trial excluded patients if they had a pCR. Therefore, such patients who clearly have a chemo-sensitive tumour (but a high 20% mortality) are denied treatment with T-DM1.	

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				d. Despite such high background risk, the survival benefit was small (4.7% 89.1% vs 84.4% at 7 years [3] e. Patients need to be informed that adverse events of grade 3 or higher were noted in 26.1% of the patients in the T-DM1 group and 15.7% of those in the trastuzumab group. [3]. When there is such a high increase in grade 3 adverse events, it is important to recognise that with long term follow up, a drug class that was commonly used for breast cancer – anthracyclines – the deaths due to adverse events – from non-breast cancer causes and leukemia completely cancelled out any survival benefit leading to zero survival benefit when followed up for long time [4]	

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				5. Patients with ER positive HER2 positive tumour cancers have poor response rates to neoadjuvant chemotherapy and will not usually benefit patients. 6. Addition of anti-her2 therapy does not improve breast conserving surgery rates as per the meta-analysis below.	

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				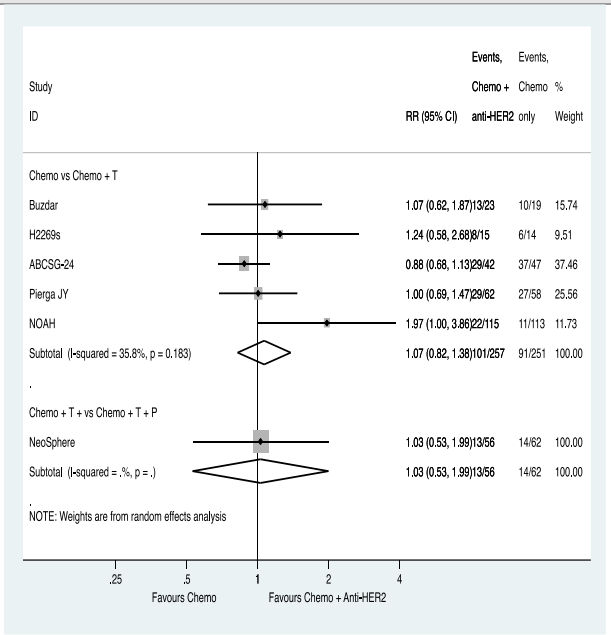 Therefore, current evidence does not give any reason to start using NACT for all patients with	

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				HER2 positive breast cancer. It will lead to many more patients receiving chemotherapy and they will have received it without full informed consent about its benefits vs harms. Such practice not only goes against the GMC guidance and the UK Law but also is unnecessarily expensive to the NHS.	
BASO - The Association for Cancer Surgery	Guideline	009	1.11.3	The use of pertuzumab in the neoadjuvant setting is invalidated as per the points made above (under section 1.11.2) The use of pertuzumab in combination with trastuzumab in the adjuvant setting is being justified only for node positive patients. This justification has several weaknesses: a) there is no survival benefit b) the benefit in terms of invasive disease-free survival is only in a subgroup analysis.	Thank you for your comment. NICE is working on bringing guidance together by topic. As part of the guideline update, all relevant NICE technology appraisals will be incorporated into the guideline unchanged without any further review of the evidence. We are therefore unable to respond to the specific points in your comment. The process through which NICE technology appraisals will be incorporated is explained in the Interim process and

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				The side effects of pertuzumab may be unacceptable to patients when considered with the fact that it does not lead to an overall survival benefit[5] and increase in cardiac toxicity, despite long follow up of a large number of patients.	methods statement for bringing together NICE guidance. Any feedback on technology appraisals or requests for future work should be sent to NICE using the suggest a topic for guidance development form. See the page on Prioritising our guidance topics for more information.
BASO - The Association for Cancer Surgery	Guideline	009	1.11.4	We believe that there is no supportive evidence/ rationale or patient benefit for recommending neoadjuvant chemotherapy for patients with triple negative breast cancer (TNBC) 1. As per the GMC guidance and the UK Law (esp Montgomery vs Lancashire health board, 2015) the patient should be the ultimate decision maker for their treatment, and they cannot give their full consent without knowing the a proper estimate of the benefit from the chemotherapy before surgery.	Thank you for your comment. Please see our responses to your earlier general comment about neoadjuvant chemotherapy in addition to our responses below. NICE strongly advocates that patients should be actively involved in any decision-making around their care and have entire guidelines dedicated to helping ensure this happens. (See CG138 Patient experience in adult NHS services: improving the

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				7. The risk of relapse can only be **accurately** estimated with full pathological examination of the post-surgical histological specimen. Therefore, stipulating "where chemotherapy is indicated" is an inappropriate because comprehensively ascertaining indication of chemotherapy is only possible after surgery. Therefore, neither the clinician or patient cannot take part in the process of a fully informed consent before the cancer is taken out and tissues examined under the microscope (exact tumour size, number of lymph nodes involved, extra-nodal involvement, lympho-vascular invasion, grade of the whole tumour (not just of the core biopsy), receptor status and any heterogeneity of the tumour in terms of ER, PR HER2, etc) – if they are forced to give consent to chemotherapy before surgery such a consent is without having all information necessary for the decision.	experience of care for people using adult NHS services and NG197 Shared decision-making.) The committee agreed that the person with breast cancer is the ultimate decision maker for their treatment. In all cases the patient has the opportunity to accept or decline recommended treatment options. The committee highlighted the importance of having a conversation with the person about all suitable treatment options when planning systemic anticancer therapy. This is reflected in recommendations in the section of the guideline on Systemic anticancer therapy planning which have been expanded to cover all SACT and not just adjuvant therapy. These include a recommendation cross referring to the NICE guideline mentioned above (CG138 and NG197). In addition, the specific recommendation for platinum based neoadjuvant chemotherapy for people with triple negative breast cancer (TNBC) highlights the need for the clinician to discuss the benefits and

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				2. The reason given for using neoadjuvant chemotherapy (vs adjuvant chemotherapy) in patients with triple negative breast cancer is the possible benefit of capecitabine if there is no pCR. However, Capecitabine is of benefit to patients with TNBC in adjuvant setting as well[6] therefore using neoadjuvant chemotherapy is not necessary to make decision about capecitabine and such an approach will deny capecitabine to patients who achieve pCR. 3. There is no evidence of improved quality of life by giving chemotherapy before surgery in TNBC patients. 4. Use of platinum-based chemotherapy leads to overall survival benefit whether it is given either in the adjuvant or the neo-	risks of this approach taking into account the person's circumstances, needs and preferences. The committee have included a table of the benefits and risks of adding a platinum to neoadjuvant chemotherapy for TNBC to help with decision making. The current update to the recommendations for neoadjuvant chemotherapy for people with TNBC was focused around comparing two different neoadjuvant chemotherapy regimens (with or without platinum chemotherapy) and any other issues relating to whether neoadjuvant chemotherapy should be used are therefore out of scope of this piece of work. We have not looked at whether neoadjuvant chemotherapy should be used (comparing the clinical and cost effectiveness of neoadjuvant chemotherapy compared to no neoadjuvant chemotherapy) or when chemotherapy should be used (in the neoadjuvant or adjuvant setting) as part

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				adjuvant setting. Therefore, there is no need to force the patient to have chemotherapy before surgery just so that they receive platinum. (https://www.thebreastonline.com/article/S0960-9776(24)00043-2/fulltext)[7]	of this work and therefore cannot respond to your comments in points 7, 2, 3 or 4 that relate to these issues.
BASO - The Association for Cancer Surgery	Guideline	009	References	References 1. Early Breast Cancer Trialists Collaborative Group EBCTCG, Asselain B, Barlow W, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. The Lancet Oncology 2018;19(1):27-39. doi: 10.1016/S1470-2045(17)30777-5 2. Vaidya JS, Massarut S, Vaidya HJ, et al. Rethinking neoadjuvant chemotherapy for breast cancer. *BMJ* 2018;360:j5913. doi:	Thank you for your comment. The aim of this update to the neoadjuvant chemotherapy section of the guideline was to determine whether there was evidence to support recommending one neoadjuvant chemotherapy regimen over another for people with HER2 positive or triple negative breast cancer. The full Cochrane review by Mason et al. in 2023 (your reference number 8 is a summary of Mason et al. 2023) was already included as evidence in review S: platinum based neoadjuvant chemotherapy. The rest of referenced articles do not meet the inclusion criteria to be included in review S or evidence review T: neoadjuvant chemotherapy for people with HER2

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				10.1136/bmj.j5913 [published Online First: 2018/01/13] 3. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *The Lancet* 2014;384(9938):164-72. doi: 10.1016/s0140-6736(13)62422-8 4. Geyer CE, Jr., Untch M, Huang CS, et al. Survival with Trastuzumab Emtansine in Residual HER2-Positive Breast Cancer. *N Engl J Med* 2025;392(3):249-57. doi: 10.1056/NEJMoa2406070 5. Geyer CE, Jr., Blum JL, Yothers G, et al. Long-Term Follow-Up of the Anthracyclines in Early Breast Cancer Trials (USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 [NRG Oncology]). *J Clin Oncol* 2024;42(12):1344-49. doi: 10.1200/JCO.23.01428 [published Online First: 20240209]	positive breast cancer. These are the reasons for not including your references: 1. EBCTCG 2018 – this meta-analysis of individual patient data compares neoadjuvant and adjuvant chemotherapy. This was not the aim of this update. 2. Vaidya et al. 2018 – analysis article questioning the rationale behind neoadjuvant chemotherapy in breast cancer. This was not the focus of this update. 3. Cortazar et al. 2014 – pooled analysis to investigate pathological complete response as a surrogate endpoint for improved event-free survival and overall survival. This was not the focus of this update. 4. Geyer et al. 2025 – longer follow-up of KATHERINE trial used as evidence for technology appraisal TA632 and is out of scope of this update. 5. Geyer et al. 2024 – long-term follow-up of 3 anthracyclines trials as adjuvant treatment- out of scope for this update. 6. Piccart et al. 2021 – longer follow-up of APHINITY trial used as evidence for technology appraisal TA569 that is out of scope of this update.

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				6. Piccart M, Procter M, Fumagalli D, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. *J Clin Oncol* 2021;39(13):1448-57. doi: 10.1200/JCO.20.01204 [published Online First: 20210204] 7. Natori A, Ethier JL, Amir E, et al. Capecitabine in early breast cancer: A meta-analysis of randomised controlled trials. *Eur J Cancer* 2017;77:40-47. doi: 10.1016/j.ejca.2017.02.024 [published Online First: 20170327] 8. Mason SR, Willson ML, Egger SJ, et al. Platinum chemotherapy for early triple-negative breast cancer. *Breast* 2024;75:103712. doi: 10.1016/j.breast.2024.103712 [published Online First: 20240312]	7. Natori et al. 2017 – meta-analysis of trials with capecitabine in early breast cancer. Capecitabine was not a treatment that we reviewed in this update. 8. Mason et al. 2024 – we already included the main publication: Mason et al. 2023. Any feedback on technology appraisals or requests for future work should be sent to NICE using the suggest a topic for guidance development form. See the page on Prioritising our guidance topics for more information.

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BASO - The Association for Cancer Surgery	Guideline	General	General	BASO~ACS representing all cancer surgery in the UK for over 50 years, is a key stakeholder of NICE but we only found out about this consultation today. It is essential that key stakeholders are briefed rather than register their interest of each individual guidance. We submit that the recommendation to administer chemotherapy before surgery ('neoadjuvant') in newly diagnosed breast cancer is not evidence-based for several reasons: published evidence, scientific rationale, and patient's perspective. The published evidence does not support neo-adjuvant chemotherapy over adjuvant chemotherapy for any survival benefit in any breast cancer subtype[1]. The level-1 evidence only demonstrates that one can reduce the extent of surgery in a small proportion of patients (15%) at the cost of increasing local recurrence rates. Delayed and inadequate of surgery (after neoadjuvant chemotherapy it is practically impossible to remove residual tumour precisely	Thank you for your comment. We're sorry to hear you found about the consultation at the last moment. We're looking at our registration processes to try to simplify them and support stakeholder engagement. The 2018 update of the NICE guideline NG101 on early and locally advanced breast cancer looked at whether or not to recommend the use of neoadjuvant chemotherapy and for which groups of people. As part of that update the committee made several recommendations about the use of neoadjuvant chemotherapy. Building on the previous recommendations the aim of our current update was to review whether evidence supported recommending one specific neoadjuvant chemotherapy regimen over another for people with triple negative breast cancer (TNBC) or HER2 positive breast cancer. Therefore, we did not look again at the evidence considered in 2018 about whether to use neoadjuvant therapy or not or the

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				and completely) is responsible for increase in local recurrence and based on current evidence must have a detrimental effect on overall survival. If this guidance is intent on encouraging clinicians to further neoadjuvant chemotherapy recommendations, and providing patients with access to drugs that have no proven efficacy in the adjuvant setting, then it is very likely to increase cost of care (a prime example is approval of pertuzumab for all HER2 positive patients in neoadjuvant setting when there was zero survival advantage in adjuvant setting)	timing of when to give chemotherapy (before or after breast surgery). However, in response to your comments, as part of the current update to this guideline the committee has expanded the section on systemic anti-cancer therapy (SACT) planning in both the neoadjuvant and adjuvant settings. These recommendations are intended to support clinicians and people with breast cancer to choose the most suitable treatment options for the individual and when they should be delivered. This guideline is not advocating the use of neoadjuvant chemotherapy (or other neoadjuvant drug treatments) over adjuvant chemotherapy (or other adjuvant drug treatments) and recommendations highlight the importance of multidisciplinary team discussions with individual treatment decisions made with the person with breast cancer.

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					The committee have taken note of your comments and revised the wording of the consultation draft recommendation for people with HER2 positive breast cancer to be offered neoadjuvant chemotherapy, where chemotherapy is indicated. They have amended this recommendation to clarify their meaning by referring instead to where neoadjuvant chemotherapy is indicated. The committee declined to provide more detail about what these criteria entail because this is a complex clinical decision based on individual patient factors that cannot be captured well in a recommendation. They agreed that the suitability of neoadjuvant chemotherapy for the person should be determined by multidisciplinary team assessment as covered in recommendations on systemic anticancer therapy planning. We have added a sentence to the rationales for both the triple negative and HER2 neoadjuvant chemotherapy recommendations to emphasise this and cross refer to the SACT planning section.

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					In addition, NICE is working on bringing guidance together by topic. As part of the current guideline update, all relevant NICE technology appraisals (TAs) will be incorporated into the guideline unchanged without any further review of the evidence. The process through which NICE technology appraisals will be incorporated is explained in the Interim process and methods statement for bringing together NICE guidance. To facilitate TA incorporation and better reflect current practice the full guideline has been rearranged to cover SACT by receptor subtype thus grouping all neoadjuvant and adjuvant SACT options together to make it easier for the clinician and patient to make treatment decisions. NICE strongly advocates that patients should be able to actively participate in their care and be involved in any decision-making process. The committee have added a recommendation in the SACT planning section of the guideline to cross-refer to NICE guidance on these topics:

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					• CG138 Patient experience in adult NHS services: improving the experience of care for people using adult NHS services • NG197 Shared decision-making The clinical effectiveness and cost effectiveness of pertuzumab for breast cancer in the neoadjuvant setting was not in the scope of this update and has been previously reviewed as part of the NICE Technology appraisal programme. Any feedback on technology appraisals or requests for future work should be sent to NICE using the suggest a topic for guidance development form. See the page on Prioritising our guidance topics for more information.
BASO - The Association for Cancer Surgery	Recommendations for Research	011	General	**Suggestions for Research Questions:** 1. What is the survival benefit of adjuvant immunotherapy? 2. What is the survival benefit of (any new drug) in the adjuvant setting? – New drugs	Thank you for your comment. NICE research recommendations can only be made if evidence has been searched for and a gap in the evidence has been identified. Adjuvant therapy and neoadjuvant therapy versus adjuvant therapy were not considered as part of this update. Therefore, we were unable to add your suggestions as

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				should not be only tested in the neo-adjuvant setting. 3. Is delaying effective surgical treatment in early breast cancer truly safe?	recommendations for research within this guideline update.
Breast Cancer Now	Guideline	004	General	We are pleased that NICE has adopted more inclusive and specific language as part of this update by referring to 'women, trans men and non-binary people who currently have ovaries'	Thank you for your comment and support.
Breast Cancer Now	Guideline	004	1.7.3	Rec 1.7.3 – It's our understanding that using tamoxifen without ovarian function suppression is most common for premenopausal women with a lower risk of recurrence. Those with a higher risk of recurrence may be offered an aromatase inhibitor with ovarian suppression, or tamoxifen with ovarian suppression depending on the risk. This decision will depend on clinical expertise and decisions made at the MDT. The guideline does not provide any explanation as to why someone may/may not be offered ovarian function	Thank you for your comment. The committee discussed the use of ovarian function suppression (OFS) in depth. The intention of the recommendation is that all of the treatments (tamoxifen alone, tamoxifen with OFS and aromatase inhibitors with OFS) are available as options to all premenopausal and perimenopausal people with female reproductive organs who have ER positive breast cancer to give everyone the same opportunity to benefit from these treatments.

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				suppression, for example what risk considerations may feed into that decision. It would be helpful to include some more detail for people to understand why they've been offered something specifically.	They intended for the choice of treatment to be based on a shared decision-making process, weighing up the benefits and harms of each option and taking the individual patient's clinical circumstances into account. The committee acknowledged that the use of OFS may be most beneficial for people who are at higher risk of disease recurrence but also noted in the rationale that: "… some people at lower risk would also choose to accept this treatment [OFS with tamoxifen or OFS with an aromatase inhibitor], and other people at low or high risk may choose to take tamoxifen instead." The committee declined to add more information about the clinical decision making process as this is a complex decision that takes multiple factors into account and is tailored to individual needs. It is not something that can be captured in a recommendation without oversimplification.
Breast Cancer Now	Guideline	004	1.7.3	Rec 1.7.3 – The use of ovarian function suppression may have an impact on a patient's	Thank you for your comment. The committee highlighted that the recommendation focuses on a

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				quality of life due to menopausal symptoms and/or joint pain. These side-effects should be discussed with the patient. Side effects may impact on treatment adherence by the patient. Therefore, it would be helpful to include a suggestion for the patient to be referred to a specialist, or to other support to manage side effects like menopausal symptoms and/or joint pain.	shared decision-making process which includes discussing the benefits and risks (which would include side effects) of the treatment options. The recommendation also includes a bullet point about the provision of information about the possible side effects of each treatment option (ovarian function suppression being one of the options in combination with tamoxifen or an aromatase inhibitor) and how the side effects could be managed if they develop. Based on your comment, the committee decided to expand the recommendation to include consideration of referral to support services if they are needed. The recommendation is supplemented by a table listing the common side effects of each treatment option. In addition, there is a section on Management of treatment side effects and menopausal symptoms with recommendations on how to treat menopausal symptoms associated with breast cancer treatment (section on menopausal symptoms) within the NICE guideline NG101 on early and locally advanced

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					breast cancer: diagnosis and management. The new recommendations made at this update will be published as part of the full NG101 guideline. There is also a section on people with a personal history of breast cancer within the NICE guideline NICE guideline NG23 menopause: identification and management. This section has recommendations on treatments to manage menopausal symptoms in people with a personal history of breast cancer.
Breast Cancer Now	Guideline	007	1.7.6	Rec 1.7.6 – It would be useful to have clarification on why testicular function suppression is needed if tamoxifen is not suitable. The guidance could make reference to the relevant evidence to help the patient understand the rationale behind this.	Thank you for your comment. We do not provide details of the evidence base in the recommendations or rationale. The evidence for this recommendation can be seen in evidence review R: testicular function suppression along with the committee's discussion of how they reached these recommendations. In summary, the committee acknowledged the lack of the evidence around using aromatase inhibitors and TFS for people with ER-positive invasive breast cancer who have male reproductive organs. They used their own expertise and evidence from healthy men and people with ER-positive invasive breast

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					cancer who have female reproductive organs to try to fill the gaps in the evidence base. The committee summarised their decision making in the rationale that accompanies the recommendations. Based on your feedback we have now added some additional information to explain why TFS with an aromatase inhibitor could be beneficial if tamoxifen is not suitable or not tolerated. For people with ER-positive invasive breast cancer tamoxifen blocks the oestrogen receptor within tumour cells with the aim of reducing the risk of the tumour recurring, but if patients are unable to take tamoxifen then they could be considered for other endocrine treatment options that may have a similar effect on reducing the risk of recurrence. The committee were aware of indirect evidence from studies in healthy people with male reproductive organs showing that an aromatase inhibitor alone does not suppress oestrogen effectively and would

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					be unlikely to lower oestrogen levels sufficiently to reduce tumour growth. However, extrapolating from the evidence for people with ER-positive invasive breast cancer who have female reproductive organs, a combination of an aromatase inhibitor with TFS could have a similar effect on suppressing tumour growth in people with male reproductive organs. Therefore, the committee recommended considering TFS in combination with an aromatase inhibitor if tamoxifen is not suitable or not tolerated. They also recommended that an aromatase inhibitor should not be used alone in people with male reproductive organs who have ER positive invasive breast cancer.
Breast Cancer Now	Guideline	007	1.7.6	Rec 1.7.6 - It would be useful to have clarity on what testicular function suppression will be used. We understand that GNRH antagonists are currently offered to patients.	Thank you for your comment. The committee discussed your comment and agreed to add the term 'gonadotrophin-releasing hormone receptors (GNRH)' to the rationale related to this recommendation.
Breast Cancer Now	Guideline	007	1.7.7	Rec 1.7.7 – It would be useful to understand the evidence behind suggesting to not use an aromatase inhibitor alone in this particular group of patients. The guidance could make reference	Thank you for your comment. The evidence for this recommendation can be seen in evidence review R: testicular function suppression. It is not NICE practice to refer to the evidence in any detail in the

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				to the relevant evidence to help the patient understand the rationale behind this.	recommendations or rationale. The committee also described this in the rationale that accompanies the recommendation. In summary, the committee acknowledged the uncertainty of the evidence in people with ER-positive invasive breast cancer who have male reproductive organs and they used their own expertise to address this uncertainty. They were aware of indirect evidence from studies in healthy people with male reproductive organs showing that an aromatase inhibitor alone does not suppress oestrogen effectively and would be unlikely to lower oestrogen levels sufficiently to reduce tumour growth in people with male reproductive organs who have breast cancer. Taking this into account, the committee recommended that an aromatase inhibitor should not be used alone in people with male reproductive organs who have ER positive invasive breast cancer.
Breast Cancer Now	Guideline	007	1.7.8	Rec 1.7.8 – If a patient is dealing with erectile dysfunction, this may impact on their adherence to treatment. As well as impacting adherence to treatment, this may impact on the patient's quality	Thank you for your comment. The committee agreed that it was important to discuss with the person how to access support if side effects specific to people

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				of life. It would be helpful to include a suggestion for the patient to be referred to a specialist, or to support.	with male reproductive organs develop. They amended the recommendation to say this.
Breast Cancer Now	Guideline	009	1.11.2	Rec 1.11.2 – It would be useful for the guidance to be clearer on which patients with HER2-positive invasive breast cancer would fit the criteria for needing chemotherapy.	Thank you for your comment. The committee decided that clarification was required as the consultation version of the recommendation talked about 'where chemotherapy is indicated' rather than 'where neoadjuvant chemotherapy is indicated' as intended. This has been amended in the current version of the recommendation. As you note, not all people with HER2-positive invasive breast cancer meet the criteria to receive neoadjuvant chemotherapy. The committee declined to provide more detail about what these criteria entail because this is a complex clinical decision based on individual patient factors that cannot be captured well in a recommendation. They agreed that the suitability of neoadjuvant chemotherapy for the person should be determined by multidisciplinary team assessment as covered in recommendations on systemic anticancer therapy planning.

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Breast Cancer Now	Guideline	009	1.11.3	Rec 1.11.3 – It would be helpful for the guideline to offer more detail on what constitutes high risk of recurrence.	Thank you for your comment. The committee did not review the evidence on pertuzumab in combination with trastuzumab for treating HER2-positive breast cancer as this is subject to a separate technology appraisal (TA424). This recommendation was added as part of the process of bringing technology appraisal (TA) recommendations into guidelines. (The process through which NICE technology appraisals will be incorporated is explained in the Interim process and methods statement for bringing together NICE guidance.) The wording for the TA recommendations in guidelines is intended to be brief and more detail can be found in the full TA document.
Breast Cancer Now	Guideline	009	1.11.4	Rec 1.11.4 – It would be helpful for the guideline to suggest that treatment teams should discuss the likely side effects, as these may be increased with platinum-based chemotherapy.	Thank you for your comment. The recommendation covers discussing the benefits and risks (which would include side effects) and is supplemented by a table listing the common side effects that may be experienced more frequently when taking platinum-based neoadjuvant chemotherapy.
Breast Cancer Now	Guideline	009	1.11.4	Rec 1.11.4 - The guideline should take the use of immunotherapies into consideration. TA851	Thank you for your comment. NICE is working on bringing guidance together by topic. As part of the

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				recommends use of pembrolizumab for neoadjuvant and adjuvant treatment of triple-negative early or locally advanced breast cancer	guideline update, all relevant NICE technology appraisals will be incorporated into the guideline unchanged without any further review of the evidence. This will include technology appraisal TA851. The process through which NICE technology appraisals will be incorporated is explained in the Interim process and methods statement for bringing together NICE guidance.
Breast Cancer Now	Guideline	General	General	If a patient, whether female or male, is on an aromatase inhibitor, they should be offered a bone density scan. This is mentioned within the recommendations on bone health, but it is important to include this within the guideline. Additionally, some patients have previously been offered ADcalD3. There needs to be consistency in what is recommended as best practice for patients.	Thank you for your comment. The new recommendations made as part of this update will be fully integrated with the rest of the NG101 recommendations at publication. The existing recommendations on bone health cover bone density scans for women who are starting adjuvant aromatase inhibitor treatment. We have also included a new recommendation as part of this update that covers assessing bone mineral density in people with ER-positive invasive breast cancer who have male reproductive organs if they start

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					taking testicular function suppression in combination with an aromatase inhibitor. We did not look at the evidence for treatments such ADcalD3 (calcium and vitamin D supplement for bones and teeth) or bisphosphonates to help treat or prevent bone health problems as part of our current work. Therefore, the committee was unable to recommend the use of calcium and vitamin D supplements for people with breast cancer on aromatase inhibitor treatment. The bone health section of the guideline referred to above does cover offering bisphosphonates to women at risk of treatment induced bone loss and there is a separate section on the use of adjuvant bisphosphonate therapy**.** However, if you think that this section or the one on bone health is out of date and there is evidence to support changing the recommendations or adding new ones then you can suggest a topic for us to address (please see the page on Prioritising our guidance topics where you can suggest a topic for guidance development).

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British Nuclear Medicine Society	Guideline	General	General	BNMS supports the recommendations. Baseline assessment of bone health and ongoing monitoring in patients undergoing ovarian or testicular function suppression is welcomed as part of reducing health inequalities.	Thank you for your comment and support of the recommendations.
Merck Sharp & Dohme	Appendix O - Platinum based neoadjuvant chemotherapy	Search strategy results	General	We note the research question for Appendix O: "*What is the clinical and cost effectiveness of adding a platinum to a taxane based neoadjuvant chemotherapy regimen with or without an anthracycline in people with invasive breast cancer that is either: triple negative, or of any receptor subtype with a BRCA germline mutation?*" Having looked at the search strategies for clinical and cost-effectiveness we would anticipate that recent studies such as that of KEYNOTE-522 (Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer | New England Journal of Medicine), whilst not focusing explicitly in the clinical effectiveness of taxanes in neoadjuvant interventions alone, should have	Thank you for your comment. KEYNOTE-522 (Schmid et al. 2024) was picked up by the search strategy results. This study was excluded using the information provided in the published abstract. The reason for exclusion was that all participants in the study received carboplatin and paclitaxel. The addition of a platinum to a taxane based neoadjuvant chemotherapy regimen could not be evaluated because there was not a group of participants without a platinum and a taxane based neoadjuvant chemotherapy regimen. Therefore, the study did not meet the eligibility criteria for inclusion in this review.

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				been picked up by the SLR and /or justification for their inclusion/exclusion should had been provided. Please do review and provide supplementary text.	
NHS England	Guideline	004, 008, 016	General	There is reference to a recommendation on bone health but this link doesn't seem to work or lead to anywhere. Is this in development?	Thank you for your comment. The link will be fixed before final publication of this guideline update.
NHS England	Guideline	General	General	May want to consider acknowledging for the Neo adjuvant Her 2 and TNT patients that some may be eligible for R444.1 testing	Thank you for your comment. The committee have added a cross reference to section R444 in the Rare and Inherited disease eligibility criteria from the National Genomic Test Directory to the sections of the guideline covering systemic anti-cancer therapy for people with triple negative or HER2 positive breast cancer as requested.
The Mens VMU	Guideline	004	1.7.3	1.7.3 - 3rd paragraph - Aromatase Inhibitor should be defined as AI as AI is used multiple times later in the document	Thank you for your comment. We usually avoid abbreviations within recommendations to follow the guide on writing for NICE. However, we have now defined this abbreviation in the supporting table and in the rationale section that accompanies the recommendations.

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The Mens VMU	Guideline	007	1.7.6	1.7.6 2nd paragraph - I don't understand what is meant by "this was an off-label use for testicular function suppression"	Thank you for your comment. Sometimes NICE recommends a medicine for a particular condition or patient group when this is not within the medicine's marketing authorisation. This is known as 'off-label'. For more details on what NICE means with off-label use of medicines, see information about making decisions using NICE guidelines.
The Mens VMU	Guideline	007	1.7.7	Why?	Thank you for your comment. The evidence for this recommendation can be seen in evidence review R: testicular function suppression. The committee also described this in the rationale that accompanies the recommendation. In summary, the committee acknowledged the uncertainty of the evidence in people with ER-positive invasive breast cancer who have male reproductive organs and they used their own expertise to address this uncertainty. They were aware of indirect evidence from studies in healthy people with male reproductive organs showing that an aromatase inhibitor alone does not suppress oestrogen effectively and would be unlikely to lower oestrogen levels sufficiently to reduce tumour growth in people with male reproductive organs who have

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					breast cancer. Taking this into account, the committee recommended that an aromatase inhibitor should not be used alone in people with male reproductive organs who have ER positive invasive breast cancer.
The Mens VMU	Guideline	016 & 017	General	Last paragraph on page 16 and 1st paragraph on page 17 there are links to research recommendations but I can't get the links to work. NB other links in the document seem to work ok.	Thank you for your comment. The links will be fixed before final publication of this guideline update.
The Mens VMU	Guideline	019	General	There are two links to research recommendations but again I can't get the links to work.	Thank you for your comment. The links will be fixed before final publication of this guideline update.
The Mens VMU	Guideline	General	General	Having personally suffered Pulmonary embolisms due to taking Tamoxifen and a raised risk of clotting being listed as a side effect of tamoxifen, I believe it is important that the raised risk of clotting should be mitigated. There should be a recommendation that patients should be tested to see whether they have a raised propensity for clotting. this could be a cholesterol test, blood pressure testing or any other suitable test.	Thank you for your comment. The committee acknowledged that blood clots are a known side-effect with the use of tamoxifen. Whilst there is no routine testing for increased clotting risk for people being offered tamoxifen, the committee highlighted that clinicians weigh up pros and cons of any medications before prescribing including known risks and side effects. Where there is an increased risk of clotting, clinicians consider options to mitigate this risk (for example, with the use of anticoagulants). The committee agreed that the recommendations

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					could not cover all potential side effects and how to mitigate them. They agreed that clinicians are expected to consult the British National Formulary (**BNF**) and the Summary of product characteristics (SmPC) that accompanies each drug for information about side effects. They therefore decide against adding the requested recommendation.
The Mens VMU	Guideline	General	General	I see no recommendation to discover the appropriate dose of tamoxifen for patients. It may be for women a standard dose is appropriate and is tried and tested. the Cancers identified in men may be Estrogen positive but what evidence says that Men should be taking the same dose of tamoxifen as women?	Thank you for your comment. We do not routinely include dosages into NICE guidelines and are therefore unable to comment on what dose of tamoxifen men should take. Please see the NICE guidance on Making decisions using NICE guidelines.
UK Charity for Triple Negative Breast Cancer	Evidence review O	050	041	We note that there was "No evidence at all on quality of life" and consider this a significant omission. In that context, we hope our survey of 43 women with triple negative breast cancer who were asked about initial diagnosis and treatment of their	Thank you for your comment. Please see our response to your first comment about the survey. The review did not include any evidence on quality of life because the included clinical trials did not report data on this. However, they reported extensive information about side effects. The committee therefore used their clinical experience and the

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				TNBC detailed in our response to Table 2 of the Guidelines is helpful.	experiences of the patient committee members to try to link the risk and types of side effects to effects on quality of life. The points you have raised were consistent with their discussions.
UK Charity for Triple Negative Breast Cancer	Evidence review O	055	038 - 039	We note that there was no quality of life data so the committee used their own expertise and experience to fill the gap. In that context, we hope our survey of 43 women with triple negative breast cancer who were asked about initial diagnosis and treatment of their TNBC detailed in our response to Table 2 of the Guidelines is especially helpful.	Thank you for your comment. Please see our response to your first comment about the survey. The points you have raised were consistent with the committee discussions.
UK Charity for Triple Negative Breast Cancer	Guideline	010	Table 2	**Effect on survival/disease free survival** Most patients prioritise efficacy over tolerability. In a survey of 43 women with triple negative breast cancer who were asked about initial diagnosis and treatment of their TNBC, 75% of whom had received neo-adjuvant chemotherapy including platinum, they opted for efficacy over tolerability.	Thank you for your comment. The committee agreed that the results of your survey were in line with their experiences as clinicians or patients and supported our recommendation to offer patients a platinum containing regimen even if this meant that they had a higher risk of having side effects. This would be part of a shared decision-making process allowing the individual to decide whether they were willing to accept these risks of

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				Most responders (62.5%) preferred "stronger" chemotherapy with more side effects but which is also more effective in preventing the cancer coming back, others (37.5%) would follow medical advice of my medical team; none opted for chemotherapy, with fewer side effects but less efficacy.	side effects to have possible improvements in their oncological outcomes. We were unable to include your survey as part the body of evidence for this update because it didn't meet the inclusion criteria for the review. We were also unable to refer to it in the discussion section of the evidence review as part of other evidence that the committee were aware of because we were unable to find a published version that we could refer readers to.
UK Charity for Triple Negative Breast Cancer	Guideline	010	Table 2	**Side effects** Although recognising the toxicities of chemotherapy, for most patients this was not a major obstacle to treatment. In a survey of 43 women with triple negative breast cancer who were asked about initial diagnosis and treatment of their TNBC, 75% of whom had received neo-adjuvant chemotherapy including platinum.	Thank you for your comment. Please see our response to your first comment about the survey. This information provides further support for our recommendations allowing the individual to choose whether to accept a higher risk of certain side effects to have possible improvements in their oncological outcomes. As you note, the increased risk of side effects was for specific side effects classified as 'short term' by our committee as opposed to those that they classified as 'longer term' and this may

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				The most difficult part of treatment was side effects of chemotherapy. • For many responders (33%) this was the worst part of their initial diagnosis and treatment; similar numbers found being told that TNBC was more aggressive or coping at the end of treatment the most difficult part. Nevertheless, most found treatment toxicities manageable. • For some responders it was "difficult but bearable" (33%) but most found it "not too bad" (66%); none described chemotherapy as "dreadful" or "OK" • This is relevant as from the evidence review, we note that there was a higher incidence of treatment cessation with the more "effective" platinum-based regimens	increase people's willingness to accept a potentially more toxic treatment if the side effects are shorter term.

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				Most also said the risk of hospital admission due to neutropaenia/infection would not make treatment unacceptable. • Many responders (66%) said would take the advice of their clinical team and the remainder found that risk acceptable (33%); none said the risk was unacceptable • This is especially relevant as the more "effective" platinum-based regimens are recognised as increasing the risk of haematological adverse events and febrile neutropaenia Interestingly, patients were more concerned about potential long term, than short term, side effects. • Half (50%) were most concerned about side effects that persisted after chemotherapy; the remainder were most	

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				concerned about side effects during treatment (25%) or did not know (25%). We note that the evidence review did not identify a higher incidence of longer-term side effects with the more "effective" platinum based regimens	

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*