23 July 2015
EMA/94983/2015
Oncology Working Party (ONCWP)

Overview of comments received on “Guideline on the role of the pathological Complete Response (pCR) as an endpoint in neoadjuvant breast cancer studies” (EMA/CHMP/151853/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	MEB, The Netherlands
2	IQWIG
3	EFPIA
4	ROCHE
5	EORTC
6	TEVA

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	We fully agree with the proposed text and have no further comments.	
2 (IQWIG)	The draft guidance describes that "Eradication of tumour from both breast and lymph nodes has been shown to be associated with better event-free survival (EFS) and overall survival (OS) compared with eradication in only the breast (*Cortazar et al. Cancer Research: December 15, 2012; Volume 72, Issue 24, Supplement 3*) and (*Von Minckwitz et al. Journal of Clinical Oncolog:* May 20, 2012 vol. 30 no. 15 1796-1804)." Furthermore, the draft guidance states that "In conclusion, there seems to be a stronger association between pCR and EFS in patients with aggressive tumour subtypes compared to patients with less aggressive tumours (*Cortazar et al. Cancer Research: December 15, 2012; Volume* 49 *72, Issue 24, Supplement 3*)." From our point of view the literature cited in this context does not seem to be adequate to support pCR as a surrogate for DFS/OS. None of the studies used an adequate method to validate pCR as a surrogate. Validity relies on high correlation of treatment effects on surrogate and true endpoints, especially on the trial level, and requires appropriate meta-analyses of randomised controlled trials. The approach has first been outlined by Buyse et al. (2000) [Buyse, M, Molenberghs, G, et al.; The validation of surrogate endpoints in meta-analyses of randomized experiments; Biostatistics, 2000, 49-67] and is more extensively described in Burzykowski et al. (2005) [Burzykowski, T., Molenberghs, G., Buyse, M., The Evaluation of Surrogate Endpoints, Springer, 2005]	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	In addition, the guidance states “Currently available data do not allow a prediction of DFS/OS effect from a certain pCR effect”, which clearly emphasizes the uncertain surrogate status of pCR. However, we support EMA’s goal to find and use valid surrogate endpoints for regulatory and clinical decision making. We therefore would like to suggest, that before using pCR as a new endpoint for decision making, EMA undertakes a validation study of pCR as a surrogate for patient-relevant endpoints in breast cancer. We would like to suggest that EMA requests the required patient-level data from sponsors of breast cancer studies and uses these data to perform appropriate analyses for surrogate validation. From our point of view EMA is in the position to facilitate the required analyses pooling study data from various sponsors.	
3 (EFPIA)	EFPIA welcomes the opportunity to comment on the draft condition-specific guidance on the role of pathological Complete Response as an endpoint in neoadjuvant breast cancer studies. The proposed EMA guidance approving pCR as valuable surrogate endpoint to OS in neo-adjuvant breast cancer studies is welcomed and represents a major step for Europe. EMA and FDA final guidance should wherever possible be aligned with regard to all aspects that are not dependent on different regulatory procedures between EU and USA, i.e. Biological and clinical aspects such as definition of endpoint, high risk populations etc., in order to facilitate global development programmes. The guidance should consider evolving changes in the surgical management of early-stage BC (Ref.: ESMO Clinical Practice Guideline: Senkus et al. Annals of Oncology 24 (Supplement 6): vi7–	This guideline has been aligned with the FDA draft guidance from the beginning.

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	vi23, 2013; ASCO Clinical Practice Guideline: Lyman et al. J Clin Oncol 32, 2014) and address how results of sentinel lymph node biopsy should be used for evaluation of pCR. Also, the guidance should talk to presence of residual ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) at the time of surgery. From a licensure perspective, the guidance should enable any adequate and well controlled clinical trials using pCR as the surrogate endpoint. The premise of evaluation of pCR does not hinge upon the type of trial, but rather the ability to accurately assess pCR. Therefore, we agree with the EMA in that approval based on pCR should involve a product with a well-characterized mechanism of action and major increase in pCR with acceptable changes in toxicity, compared to the reference product, but believe that such trials may involve a landscape that would include new active substances, products already on the market, head to head trials and "add on trials." Approval based on pCR as a surrogate endpoint, potentially with agreed conditions for confirmatory study data in terms of DFS/OS is encouraged and should not be restricted to new active substances that can take advantage of the formal "conditional marketing authorisation" pathway, i.e. an approval based on pCR should be available to products already on the market in other indications.	The text has been revised to reflect these points. The guidance is flexible and there are no restrictions in our opinion.
4 (Roche)	F. Hoffmann-La Roche Ltd welcomes the publication of this important draft guidance on pCR and the opportunity to comment on the use of pathologic complete response (pCR) as a primary endpoint in a potentially curable early breast cancer population treated with a neoadjuvant approach in addition to current adjuvant standard of care (including surgery, systemic therapy and radiotherapy).	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
6 (TEVA)	This guidance provides specific scenarios where a pCR can be used as a surrogate marker for DFS and OS to get a new drug approval in neoadjuvant and adjuvant settings in locally advanced breast cancer patients, therefore, is very useful.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Pre line 18-19	4	Comment: The guidance does not currently describe that patients could potentially achieve a cure if effective treatments are given in the early breast cancer setting (including surgery, systemic therapy and radiotherapy). This potential for cure emphasises the unmet need in this setting even further. It is proposed to add a sentence to highlight this point as follows: ***'Availability of new effective treatments in the early breast cancer setting is important in a population where there is curative potential.'***	The proposed sentence is considered not crucial for the understanding of this guideline. Not accepted.
18	5	Comment: Neoadjuvant chemotherapy is more and more often used for initially operable tumours as well, in order to check in vivo chemosensitivity of the tumour. Therefore, the statement that neoadjuvant chemotherapy is commonly used in locally advanced breast cancer to facilitate breast conserving surgery is not accurate. Besides it is not always chemotherapy, as monoclonal antibodies and	The proposed changes are accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		endocrine agents have been used in neoadjuvant setting. Proposed change (if any): EORTC suggest the term “neoadjuvant chemotherapy” is replaced by “neoadjuvant treatment”.	
18-19	3	**Comment:** This opening sentence suggests that neoadjuvant therapy is appropriate only for LABC and that this document is concerned with LABC only. The following patient groups should be mentioned: LABC that is inoperable, early breast cancer with operable tumours where breast conserving surgery may be an option and inflammatory breast cancer (a subtype of LABC for whom primary systemic therapy is essential). We have also added proposed wording to cover some of the advantages of the neoadjuvant approach. **Proposed changes:** *Neoadjuvant chemotherapy is commonly used in locally advanced breast cancer (LABC) patients* ***or in selected patients with operable tumours*** *to facilitate breast surgery (Romero et al. Annals of Oncology 24: 655-661, 2013).* ***Additional advantages include the ability to directly assess response to therapy and change treatment if needed. Neoadjuvant therapy is essential for patients with inflammatory breast cancer, an aggressive sub-type of LABC (Robertson et al. CA Cancer J Clin; 60:351–375, 2010).***	The proposed changes are not accepted. It is ONCWP’s opinion that we shouldn’t define different (sub)types of breast cancer. Instead, only “early breast cancer” is mentioned, which includes the proposed types of breast cancer.
18-19	4	Comment: This opening sentence suggests that neoadjuvant therapy is appropriate only for LABC and that this document is concerned with LABC only. The following patient	Similar comment as EFPIA’s (see above)

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		groups should be mentioned: LABC that is inoperable , early breast cancer with operable tumours where breast conserving surgery may be an option, and inflammatory breast cancer (a subtype of LABC for whom primary systemic therapy is essential). We have also added proposed wording to cover some of the advantages of the neoadjuvant approach. Proposed changes: ***Neoadjuvant chemotherapy is commonly used in locally advanced breast cancer (LABC) patients to enable mastectomy or in selected patients with operable tumours to facilitate breast conserving surgery (Romero et al. Annals of Oncology 24: 655-661, 2013). Additional advantages include the ability to directly assess response to therapy and change treatment if needed. Neoadjuvant therapy is essential for patients with inflammatory breast cancer, an aggressive sub-type of LABC (Robertson et al. CA Cancer J Clin ;60:351–375, 2010)."***	
19-20	3	Comment: DFS is an appropriate endpoint for adjuvant studies. EFS is more appropriate for neoadjuvant studies Proposed change for clarity: Suggest expand as follows: *"Currently, disease-free survival (DFS) is considered to be an appropriate* ***primary*** *endpoint and surrogate for overall survival (OS)* ***in adjuvant studies*** *(EMA/CHMP/205/95/Rev.4).* ***For neoadjuvant studies, event-free survival (EFS) is preferred to DFS since it includes progression on therapy (prior to surgery) as an event"***	The comment is endorsed. The guidance has been revised to reflect this issue.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
19-20	4	Comment: DFS is an appropriate endpoint for adjuvant studies. EFS is more appropriate for neoadjuvant studies Proposed change for clarity: Suggest expand as follows: ***"Currently, disease-free survival (DFS) is considered to be an appropriate primary endpoint and surrogate for overall survival (OS) in adjuvant studies (EMA/CHMP/205/95/Rev.4). For neoadjuvant studies, event-free survival (EFS) is preferred to DFS since it includes progression on therapy (prior to surgery) as an event"***	Similar comment as EFPIA's (see above)
20	5	Comment: This sentence is too strong. DFS has been validated for adjuvant chemotherapy for colo-rectal cancer and some evidence exists for early- breast cancer. Proposed change: EORTC suggest this sentence is re-formulated to read as "DFS is an accepted endpoint for treatment effect"	The proposed changes are not accepted. DFS is an appropriate and recognised endpoint.
23-25	3	Comment: This sentence is confusing, see suggested revision Proposed change: *"A new surrogate endpoint for* ***long-term outcomes (EFS, OS)*** ~~***efficacy***~~ *that would allow the assessment of* ***efficacy*** ~~***time-to-event for a given therapy***~~ *at an earlier point in time would therefore be valuable…"*	Partially accepted. Sentence slightly reworded for clarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
23-25	4	Comment: This sentence is confusing, see suggested revision Proposed change for clarity: ***"A new surrogate endpoint for long-term outcomes (EFS, OS) that would allow the assessment of efficacy at an earlier point in time would therefore be valuable …" (delete "time to event for a given therapy")***	Similar comment as EFPIA's (see above)
27-28	3	Comment: Suggest giving a reason early on in the document why pCR has been proposed as a surrogate endpoint. This will allow for clearer context in the guidance. For example: Proposed change for clarity: ***"Based on data from several meta-analyses and clinical trials pathologic complete response (pCR) has been shown to have an association with long term outcomes.*** *pCR has therefore been proposed as a surrogate endpoint for the evaluation of the efficacy of novel therapies for invasive breast cancer without distant metastasis."*	The comment is endorsed. The guidance has been revised.
27-28	4	Suggest giving a reason early on in the document why pCR has been proposed as a surrogate endpoint. This will allow for clearer context in the guidance. For example: ***"Based on data from several meta-analyses and clinical trials pathologic complete response (pCR) has been shown to have an association with long term outcomes. As there are no reports of spontaneous remissions between diagnosis and surgery of early breast cancer, the effect of the***	Similar comment as EFPIA's (see above)

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		neoadjuvant treatment is directly linked to achieving pCR. pCR has therefore been proposed as a surrogate endpoint for the evaluation of the efficacy of novel therapies for invasive breast cancer without distant metastasis."	
29	3	Comment: Suggest the removal of the word "novel" as pCR can be used to evaluate comparative efficacy of existing therapies. Proposed change: *"… (pCR) has been proposed as a surrogate endpoint for the evaluation of the efficacy of* ~~***novel***~~ *therapies for invasive breast cancer without distant metastasis."*	The proposed changes are accepted.
29	3	Comment: Given the reference to "invasive breast cancer without distant metastasis": it would be useful to provide the correspondence with the classification of stages of breast cancer.	Not accepted. It is clear in the guidance. There is no need to summarise the different stage.
30	3	Comment: In the definition, the designation "sampled ipsilateral lymph nodes" brings flexibility in terms of surgical approach. The surgical approach can potentially impact the interpretation of pCR, guidance on the surgical management of the primary tumour and axilla should follow standard algorithms and should be clearly referenced / explained in the protocol.	The comment is relevant. Additional text has been added to reflect this issue.
27-36		Comment: Only one definition of pCR is provided. There are at least two others in common	

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		use. For clarity, we suggest that that the other two definitions are provided as well as the recommended definition. To facilitate comparison with other studies, we suggest that data for all three definitions are prospectively collected where possible. Proposed change: ***"There are three main definitions of pCR in common use:*** ***Eradication of invasive cancer from the breast and lymph nodes (ypT0/is ypN0, also known as tpCR [total pCR])*** ***Eradication of invasive cancer from the breast (ypT0/is, also known as bpCR [breast pCR])*** ***Eradication of invasive and in situ disease from breast and lymph nodes (ypT0 N0, also known as German Breast Group [GBG] pCR)*** ***The preferred definition for registration-directed neoadjuvant trials is tpCR, defined in full as: the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of the neoadjuvant systemic therapy.*** It is also noted above that the definition of pCR in the draft guidance is stated (ypT0/cis ypN0). The standard abbreviation is "is" for in situ disease without the "c" (AJCC staging handbook). There is no comment on the presence or absence of in situ disease in the definition of pCR. Suggest adding the following wording after line 36: ….***Presence or absence of ductal carcinoma in situ does not appear to***	The proposed changes are partially accepted. The text has been revised. It is now mentioned that there are several definitions of pCR, but the preferred definition is total pCR (ypT0/is N0)

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		affect long-term outcomes (Cortazar et al. The Lancet. 14 Feb 2014). It is therefore not recommended that the definition of pCR should include presence or absence of in situ disease. To facilitate comparison with historical studies data for all three should be prospectively collected where possible."	Accepted. It has been corrected. (cis = carcinoma in situ). The first sentence is accepted, but the last two sentences are not. The text has been revised.
27-36	4	Comment: Only one definition of pCR is provided. There are at least two others in common use. For clarity, we suggest that that the other two definitions are provided as well as the recommended definition. To facilitate comparison with other studies, we suggest that data for all three definitions are prospectively collected where possible. Proposed change: ***" There are three main definitions of pCR in common use:*** • ***Eradication of invasive cancer from the breast and lymph nodes (ypT0/is ypN0, also known as tpCR [total pCR])*** • ***Eradication of invasive cancer from the breast (ypT0/is, also known as bpCR [breast pCR])*** • ***Eradication of invasive and in situ disease from breast and lymph nodes (ypT0 N0, also known as German Breast Group [GBG] pCR)***	Similar comment as EFPIA's (see above)

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		Achieving a pCR is associated with better long-term outcomes, regardless of the definition used. The preferred definition for registration-directed neoadjuvant trials is tpCR, defined in full as: the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of the neoadjuvant systemic therapy. There is no comment on the presence or absence of in situ disease in the definition of pCR. Suggest adding the following after line 36: ….***Presence or absence of ductal carcinoma in situ does not appear to affect long-term outcomes (Cortazar et al. The Lancet. 14 Feb 2014). It is therefore not recommended that the definition of pCR should include presence or absence of in situ disease. To facilitate comparison with historical studies data for all three should be prospectively collected where possible."***	
38-39	3	Comment: Suggest to provide references; add meta-analyses and systematic reviews; delete "recently"; and change "chemotherapy" to "systemic therapy" Proposed change for clarity: *"****~~Recently a number of~~*** *Many randomised trials****, systematic reviews and meta-analyses*** *have shown* ***~~that~~****a consistent association between achievement of a pCR following primary* ***~~chemotherapy~~*** *systemic therapy and better overall survival* ***(Fisher et al, 1998, Bear et al, 2006; Wapnir et al, 2006; Mieog et al, 2007; Mazouni et al, 2007; Kong et al, 2011; Berruti et al, 2011; Mamounas et al, 2012; Esserman et al,***	The proposed changes are endorsed. The guidance has been updated.

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		2012; von Minckwitz et al, 2012; Cortazar et al, 2014; Bonnefoi et al, 2014).”	
38-39	4	Comment: suggest to provide references; add meta-analyses and systematic reviews; delete “recently”; and change “chemotherapy” to “systemic therapy” Proposed change for clarity: ***“Many randomised trials, systematic reviews and meta-analyses have shown a consistent association between achievement of a pCR following primary systemic therapy and better overall survival (Fisher et al, 1998, Bear et al, 2006; Wapnir et al, 2006; Mieog et al, 2007; Mazouni et al, 2007; Kong et al, 2011; Berruti et al, 2011; Mamounas et al, 2012; Esserman et al, 2012; von Minckwitz et al, 2012; Cortazar et al, 2014; Bonnefoi et al, 2014).”***	Similar comment as EFPIA’s (see above)
43	5	Comment: Re-phrasing suggested below Proposed change: “A meta-analysis of neo-adjuvant studies in breast cancer has shown that p CR rates ***were lower*** in patients with low-grade hormone-receptor positive tumors ***and higher*** in the following subtypes in increasing order….”	The proposed changes are accepted.
47	3	Comment: Clarification would be helpful on the breast cancer sub-population to be included in these types of studies, or cancer subtypes (e.g. HER2-enriched, triple-negative, hormone receptor-positive, etc.) where the role of pCR could be used as a potential surrogate endpoint in neoadjuvant for an approval, instead of overall survival.	This is not accepted. It would decrease the flexibility of the guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
47-50	3	Comment: We agree with this statement but think that pCR may still be an appropriate primary endpoint for neoadjuvant studies in less aggressive tumour types, in certain circumstances. Perhaps the pCR rate increments in such patient groups would need to be larger than in patients with less aggressive tumours. Proposed changes: ***"Consideration should be given to less aggressive tumour types"*** (see also later proposal after line 71 from a licensure perspective).	The proposed changes are not acceptable. There is very little evidence to support this statement.
47-50	4	Comment: We agree with this statement but think that pCR may still be an appropriate primary endpoint for neoadjuvant studies in less aggressive tumour types, in certain circumstances. Perhaps the pCR rate increments in such patient groups would need to be larger than in patients with less aggressive tumours. Proposed changes: ***"Consideration should be given to less aggressive tumour types"*** (see also later proposal after line 71 from a licensure perspective).	Not accepted. Similar comment as EFPIA's (see above)
50	3	Comment: If the treatment is based on a predictive biomarker derived from archival tissue at diagnosis prior to surgery/adjuvant treatment, EFS and OS may depend more on the degree of oncogene addiction to that target, than on the aggressiveness of the underlying tumour.	This comment is relevant. The text has been revised to reflect this issue.

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		For this kind of treatment, the use of pCR as surrogate endpoint could be discussed and could not be considered appropriate. Discussion about the treatment considered eligible for this approach to use pCR as endpoint would be helpful for the applicant.	
53	5	Comment: The meaning of the phrase is not clear. EORTC would interpret it in a way that the magnitude of p CR required to predict an improvement in longer-term outcomes has not been defined yet. Please re-phrase for clarification Proposed change: Not being sure of the meaning, it is unfortunately not possible to provide a constructive suggestion.	The comment is well-taken. The text has been revised to make this issue more clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
54-55	3	Comment: This statement does not follow logically from the previous statement ("Currently available data do not allow a prediction of DFS/OS effect from a certain pCR effect"). Furthermore, requiring effective new agents to be evaluated as "add-ons" seems unnecessarily restrictive. If the efficacy of a new agent is sufficiently promising to be evaluated as an alternative to standard therapy, this should be allowed if there is a positive benefit/risk. Proposed change: Insert a more logical follow-on sentence after line 53 e.g. ***"Therefore, a substantial increase in pCR is required for there to be a reasonable likelihood that this will translate into a clinically meaningful improvement in long-term outcomes*** Change the next sentence to ***"Due to the established efficacy of current neoadjuvant regimens for breast cancer, randomised trials in which the new agent is added to an established neoadjuvant treatment regimen are likely to be required"*** In addition, it would be increasingly difficult to continuously add on therapy to an existing regimen as eventually there will be multiple drugs in the regimen, at the likely cost of a high burden of toxicity. Although it is understood that the EMA wishes to start cautiously with this new endpoint, this may not be in the best interests of the patients being able to receive a very efficacious agent in the neoadjuvant setting when there is the best chance of a cure. In order to open further dialogue with the Agency on other potential options, the following wording is suggested:	The proposed changes are endorsed. The guidance has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"In cases where it is not possible to add therapy onto an existing regimen, (for example due to overlapping toxicity) or when a favourable benefit/risk has been established in a pivotal study, (for example replacing standard of care in the MBC setting), and superiority is expected in the neoadjuvant setting, it may not be necessary for the new agent to be an add-on to established therapy. The sponsor is advised to present the case for CHMP scientific advice."	
54-55	4	Comment: This statement does not follow logically from the previous statement ("Currently available data do not allow a prediction of DFS/OS effect from a certain pCR effect"). Furthermore, requiring effective new agents to be evaluated as "add-ons" seems unnecessarily restrictive. If the efficacy of a new agent is sufficiently promising to be evaluated as an alternative to standard therapy, this should be allowed if there is a positive benefit/risk. Proposed change: Insert a more logical follow-on sentence after line 53 eg. ***"Therefore, a substantial increase in pCR is required for there to be a reasonable likelihood that this will translate into a clinically meaningful***	Similar comment as EFPIA's (see above)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		improvement in long-term outcomes and change the next sentence to ***"Due to the established efficacy of current neoadjuvant regimens for breast cancer, randomised trials in which the new agent is added to an established neoadjuvant treatment regimen are likely to be required"*** In addition, it would be increasingly difficult to continuously add on therapy to an existing regimen as eventually there will be multiple drugs in the regimen, at the likely cost of a high burden of toxicity. Although it is understood that the EMA wishes to start cautiously with this new endpoint, this may not be in the best interests of the patients being able to receive a very efficacious agent in the neoadjuvant setting when there is the best chance of a cure. In order to open further dialogue with the Agency on other potential options, the following wording is suggested: ***"In cases where it is not possible to add therapy onto an existing regimen, (for example due to overlapping toxicity) or when a favourable benefit/risk has been established in a pivotal study, (for example replacing standard of care in the MBC setting), and superiority is expected in the neoadjuvant setting, it may not be necessary for the new agent to be an add-on to established therapy. The sponsor is advised to present the case for CHMP scientific advice."***	
56	3	Comment: Clarification on the following sentence "*there should be no reason to suspect an adverse interactions with the established treatment regimen based on PK/PD data*" would be useful, if it means that a dedicated trial phase I on the combination is suggested.	The comment is relevant. The guidance has been revised. Only PK studies and additional studies may be required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
55-57	3	Comment: Need to add “or safety” to this sentence Proposed change: *The mechanism of action should be well-known and there should be no reason to suspect an adverse interaction with the established treatment regimen based on PK/PD* ***or safety*** *data*	The proposed changes are accepted. The guidance has been revised.
55-57	4	Comment: Need to add “or safety” to this sentence Proposed change: The mechanism of action should be well-known and there should be no reason to suspect an adverse interaction with the established treatment regimen based on PK/PD ***or safety*** data	Similar comment as EFPIA’s (see above)
58-59	3	Comment: An add-on chemotherapy agent, such as carboplatin, may result in significant acute toxicity that is acceptable because it is reversible and manageable with routine measures. It seems reasonable to assess the benefit/risk for each agent/trial on a case by case basis. Recommended change: *“As the magnitude of the effect in terms of DFS/OS cannot be estimated, only minor add-on changes in toxicity,* ***or add-on changes in toxicity that are reversible and manageable with routine measures,*** *are acceptable.”*	The proposed changes are not accepted. The suggested revision doesn’t make the text more clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
58-59	4	Comment: It seems reasonable to assess the benefit/risk for each agent/trial on a case by case basis. Proposed change: Suggest change to ***"In general, only minor increments in toxicity are likely to be acceptable in neoadjuvant trials which have a pCR primary endpoint. However if an exceptional improvement in efficacy is observed, a larger increment in toxicity may be acceptable"***	Not accepted. Similar comment as EFPIA's (see above)
59-60	3	General comment: Almost all cytotoxic agents and many targeted agents are genotoxic, meaning they pose a theoretical increased risk for secondary tumours. Therefore, this position is overly restrictive. In fact, current standard regimens all pose a real increased risk of secondary tumours: the rate of increased AML/MDS with current standard therapy is approximately 0.5% at ten years post treatment (Karp et al., SABCS 2013). An increased risk of this magnitude (therefore doubling the overall treatment risk) is small, and would not be detected during a pivotal trial of neoadjuvant or adjuvant therapy. Post-approval monitoring of such risk is required regardless of approval pathway. Thus, conditional approval should not be discouraged based on a theoretical risk. More appropriate is to assure that any conditional approval would include plans for long-term risk monitoring in the pivotal neoadjuvant trial, in the pivotal confirmatory trial, and according to the RMP at the time of approval. Recommended change to text: *"In addition, **agents which pose a theoretical increased risk of secondary***	The proposed changes are endorsed. The guidance has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		tumors must include appropriate patient monitoring and follow up in the pivotal and confirmatory trials to asses and report such risks" ~~there should be no concerns related to an increased risk for secondary tumours on theoretical grounds.~~"	
59-60	4	Comment: Many effective drugs used in oncology are associated with second malignancies but the risks of second malignancies are generally small compared with the risk of disease progression/relapse in a patient receiving neoadjuvant therapy for breast cancer. This statement seems too restrictive therefore. Proposed change: ***"In general, the risk of secondary malignancies with a new agent evaluated in the neoadjuvant setting should be small and outweighed by the likely benefits of this treatment"***	Similar comment as EFPIA's (see above).
63-64	3	Comment: The sentence should be expanded to allow for other scenarios (e.g. where the MBC regimen is very different from the proposed EBC regimen). Proposed change: *"Studies conducted with the regimen in the metastatic setting may provide important safety data and support evidence of efficacy****; however this may not be appropriate or necessary in all cases and should be determined on a case by case basis. The totality of the data available will determine the benefit:risk****."*	The proposed changes are accepted. The guidance has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
65	5	Comment: This cannot globally be accepted and cannot be considered as a rule. Recent example is the ALTTO trial and results announced during ASCO 2014. This trial was in adjuvant setting and the combination of trastuzumab plus lapatinib proved to be insufficient. However, the p CR rates in NeoALLTO (that was conducted before) were almost doubled. Therefore in the absence of ALTTO study according to this line the combination would be considered beneficial for the adjuvant setting which is questionable. Proposed change (if any): -	This comment is reasonable and was supported by many members of the ONCWP. Thus, this paragraph has been deleted.
65-66	3	Comment: Clarification is requested on the following statement: “Extrapolation from the neoadjuvant setting to an indication of use as adjuvant therapy is considered acceptable provided that the background regimen is an established adjuvant regimen”. Does this mean that a marketing authorisation or new indication for the adjuvant treatment of breast cancer could be obtained solely based on the pCR and safety results from a neoadjuvant study (with agreed conditions for confirmation)?	In light of the recent results from the ALTTO study, this extrapolation may be associated with some uncertainty. Thus, this paragraph has been deleted.
65		Comment: The conditions of extrapolation from the neoadjuvant setting to an indication of use as adjuvant therapy need to be developed there.	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
65-71		Comment: Use of term “early breast cancer”. The draft guideline appears to describe an experimental agent, studied for registration purposes as an add-on to an established regimen. If the established regimen includes treatments administered as neoadjuvant and adjuvant, then there can be utility to support ‘indication of use’ to include the term “early breast cancer”. For example, the situation may arise when a regimen is adapted by the prescribing oncologist due to bedside considerations, which may modify any sharp divisions between neoadjuvant vs. adjuvant setting. In the context of product labeling, indication statement limited to “neoadjuvant” and/or “adjuvant therapy” may lead to confusion by patients, prescribers, and may impede appropriate reimbursement by payers.	Considering the ALTTO results and the lack of solid evidence to extrapolate form neo-adjuvant to adjuvant, this point cannot be supported
67	3	Comment: Patients with LABC/IBC should be explicitly included in this recommendation. As mentioned earlier, there seems no reason to mandate add-on studies if the new agent were sufficiently efficacious. In addition, there seems no reason not to allow approval based on pCR for less aggressive breast cancer if sufficient improvement in efficacy can be achieved. The chances of achieving this sort of improvement may be different (lower) to those for aggressive subtypes; this can be covered with a caveat. Proposed changes: *“Therefore, approval based on pCR may be acceptable for patients with aggressive (high-risk)* ***locally advanced, inflammatory or*** *early stage breast cancer if there is a well-characterised mechanism of action and provided* ***there is***	The proposed changes are not accepted. It is ONCWP’s opinion that we shouldn’t define different (sub)types of breast cancer. Instead, only “early breast cancer” is mentioned, which includes the proposed types of breast cancer.

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		a favourable benefit/risk ~~***the results show major increase in pCR with only 69 minor changes in toxicity***~~.	
67	4	Comment: Patients with LABC/IBC should also be explicitly included in this recommendation. As mentioned earlier, there seems no reason to mandate add-on studies if the new agent were sufficiently efficacious. In addition, there seems no reason not to allow approval based on pCR for less aggressive breast cancer if sufficient improvement in efficacy can be achieved. The chances of achieving this sort of improvement may be different (lower) to those for aggressive subtypes, this can be covered with a caveat. Proposed changes: The following modifications are proposed to the sentence starting on line 67: "Therefore, approval based on pCR may be acceptable for patients with aggressive (high-risk) ***locally advanced, inflammatory or*** early stage breast cancer if there is a well-characterised mechanism of action and provided there is a favourable benefit/risk.	Similar comment as EFPIA's (see above).
70-71	3	Comment: Propose to add EFS to allow multiple trial designs that contribute to the confirmatory data. Proposed change: *"Such results may lead to an approval with agreed conditions for confirmatory study data in terms of DFS/****EFS/****OS"* An additional sentence is also proposed to be added at the end of line 71:	The proposed changes are accepted. The guidance has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"Approval based on pCR may also be acceptable for patients that are candidates for neoadjuvant therapy with less aggressive, locally advanced or early stage breast cancer if there is a well-characterised mechanism of action and provided that there is a favourable benefit/risk (Kaufmann et al. Ann Surg Oncol 19:1508–1516, 2012)"	Not accepted. There is no solid evidence to support this statement.
70-71	4	Comment: Propose to add EFS to allow multiple trial designs that contribute to the confirmatory data. Proposed change: ***"Such results may lead to an approval with agreed conditions for confirmatory study data in terms of DFS/EFS/OS"*** ***An additional sentence is also proposed to be added at the end of line 71: "Approval based on pCR may also be acceptable for patients that are candidates for neoadjuvant therapy with less aggressive, locally advanced or early stage breast cancer if there is a well-characterised mechanism of action and provided that there is a favourable benefit/risk (Kaufmann et al. Ann Surg Oncol 19:1508–1516, 2012)***	Same comment as EFPIA's. (see above)
70-71	6	Comment: The sentence 'Such results may lead to an approval with agreed conditions for confirmatory study data in terms of DFS/OS.' is not clear if it means that pCR can be used as the primary endpoint, therefore, can be used for sample size calculation, and the approval is a full approval, or the approval using pCR is just for an accelerated approval with condition that the trial will still need to use time	This remark is irrelevant. There is no mentioning of conditional approval in the draft. It is clearly stated that pCR may lead to early approval (not accelerated or conditional approval) with agreed conditions for confirmatory study data.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to event variables (DFS or OS) as the primary endpoint for final approval. Proposed change: Please add more sentences to clarify so that the pharmaceutical companies can design a trial per the guidance.	