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The role of the pathological Complete Response as an endpoint in neoadjuvant breast cancer studies

Condition - specific guidance, Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man

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Comments should be provided using this template. The completed comments form should be sent to ONCWPsecretariat@ema.europa.eu

Keywords	Breast cancer, pCR, neoadjuvant treatment, surrogate endpoint

Background	Concept paper on the need to revise Condition – Specific guidance, Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man

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Introduction

Neoadjuvant chemotherapy is commonly used in locally advanced breast cancer (LABC) patients to facilitate breast conserving surgery (*Romero et al. Annals of Oncology 24: 655-661, 2013*). Currently, disease-free survival (DFS) is considered to be an appropriate endpoint for treatment effect and as a surrogate endpoint for overall survival (OS) (*EMA/CHMP/205/95/Rev.4*). As new therapies have emerged, the DFS and ultimately the OS of patients with breast cancer has increased, and thereby the time needed to procure confirmatory data. A new surrogate endpoint for efficacy that would allow the assessment of time-to-event for a given therapy at an earlier point in time would therefore be valuable, as it could potentially bring novel therapies faster to the market for the benefit of the patients and society in general.

Definition of pCR

Pathologic complete response (pCR) has been proposed as a surrogate endpoint for the evaluation of the efficacy of novel therapies for invasive breast cancer without distant metastasis. pCR is defined 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 (ypT0/cis ypN0). 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)**.

The relationship between pCR and OS/EFS

Recently a number of randomised trials have shown that pCR in relation to primary chemotherapy was associated with long-term survival. Consequently, it has been proposed that pCR in the neoadjuvant setting could serve as a surrogate endpoint for treatment effect in neoadjuvant trials (*Romero et al. Annals of Oncology 24: 655–661, 2013*). However, it seems that the pCR rate differs according to molecular subtypes. A meta-analysis of neoadjuvant studies in breast cancer has shown, that pCR was uncommon in patients with low-grade hormone receptor-positive (HR+) tumours, and more common in the following tumour subtypes in increasing order: high-grade HR+, HR+/HER2+, triple negative, and hormone receptor-negative (HR–)/HER2+. Thus, patients with more aggressive tumour subtypes who achieved pCR seems to have greater EFS compared to patients who did not achieve pCR as follows: HR+ high grade, HR+/HER2+, HR-/HER2+ and triple negative. 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 72, Issue 24, Supplement 3*).

pCR as endpoint in neoadjuvant breast cancer studies from a licensure perspective

Currently available data do not allow a prediction of DFS/OS effect from a certain pCR effect.

From an efficacy perspective it is therefore foreseen that only add-on randomised trials to established neoadjuvant treatment regimens will provide sufficiently convincing data. 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 data.

As the magnitude of the effect in terms of DFS/OS cannot be estimated, only minor add-on changes in toxicity are acceptable. In addition there should be no concerns related to an increased risk for secondary tumours on theoretical grounds. The safety data base should therefore be sufficiently large to capture relevant increases in common adverse reactions and follow-up should be sufficiently long to assess reversibility of known side effects, such as neuropathy and cardiomyopathy.

Studies conducted with the regimen in the metastatic setting may provide important safety data and supportive evidence of efficacy.

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.

Therefore, approval based on pCR may be acceptable for patients with aggressive (high-risk) early stage breast cancer as add-on to an established (neo) adjuvant regimen, if there is a well-characterised mechanism of action and provided the results show major increase in pCR with only minor changes in toxicity. Such results may lead to an approval with agreed conditions for confirmatory study data in terms of DFS/OS.