PCN290

Use of pCR as a surrogate primary endpoint in drug pivotal trials in neoadjuvant early breast cancer in the EU: **A Perspective from Regulators and Payers**

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Background

- Treating breast cancer at an early stage has the potential to limit the progression of the disease and increases breast conservation rates. Therefore, it has become increasingly common to use neoadjuvant therapy beyond cases of locally advanced or inoperable breast cancer.[1-3]
- Regulatory guidelines state that for neoadjuvant trials, the long-term clinical benefit endpoints should be event-free survival (EFS) or overall survival (OS).[4]
- Performing a large randomized clinical trial (RCT) to assess the clinical benefit of a new treatment of early-stage breast cancer requires a long duration in order to observe sufficient numbers of OS and EFS events to yield reliable conclusions.
- The use of surrogate endpoints (i.e. replacement of the clinical endpoint by providing an indirect measurement of effect in situations where direct measurement of clinical benefit is not feasible or practical endpoints) allows for acceleration of patient access to new innovative drugs.[5]
- Pathologic complete response (pCR) has been a common surrogate endpoint used in many clinical trials for the neoadjuvant setting in patients with early breast cancer.[2]
- European and US regulatory bodies (EMA and FDA) have issued guidance on the use of pCR for regulatory approval in 2014.[4, 6] However, to date, there has not been a uniform definition of pCR, which has made reporting and interpretation of data from neoadjuvant trials challenging.[2, 3] The FDA defines pCR either as the absence of residual invasive cancer, or of both residual invasive and in situ cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0 in the current AJCC staging system).[4]
- Moreover, there is considerable controversy around the prognostic value of achievement of pCR on survival (namely EFS and OS) in the different breast cancer subtypes.[1-2]
- Pertuzumab is the first innovative neoadjuvant therapy for breast cancer approved by the FDA and EMA based on pCR data.[7-11]

Method

- In order to identify drugs that had been approved based on the pCR endpoint, the EMA website was searched (11/06/2018) for breast cancer treatments that were approved since 1995.
- Upon generating a list of approved treatments, EPARs (European Public Assessment Reports) for each of the treatments, were examined to identify which of them were approved based on the pCR endpoint.
- Following this, the websites of national HTA bodies in 5 large European countries (France, Germany, England, Spain and Italy – [EU5]) were examined to determine the reimbursement recommendations of treatments approved based on the pCR endpoint.

Results

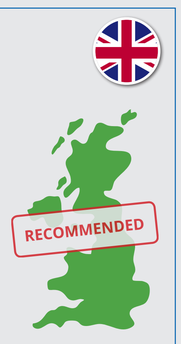
Regulatory approvals of novel drugs based on pCR

- Overall, 30 Marketing Authorizations (MAs) were granted by the EMA for breast cancer drugs, and following the consultation of their respective EPAR, 11 were identified as indicated for eBC and 5 were approved in neoadjuvant treatment of eBC.
- Among the approved treatments in neoadjuvant setting, four drugs were approved based on pCR, one novel drug, pertuzumab, and three trastuzumab biosimilars.[8-11]
- It is important to note that the originator for trastuzumab (Herceptin®) was approved based on disease free survival (DFS) primary endpoint.[12]
- There is a heterogeneous reimbursement landscape for pertuzumab across the EU5 as not all national HTA bodies recognize pCR as a valid surrogate endpoint for EFS, PFS and/or OS.
- In EU countries, once an originator product has recommendation for reimbursement, reimbursement recommendation for the corresponding biosimilar is usually implied if a price has been established.

HTA reimbursement decisions in EU5 countries

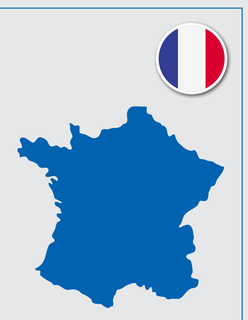
NICE

- Pertuzumab is recommended by NICE for the neoadjuvant treatment of early breast cancer based on the NeoSphere and TRYPHAENA trials which demonstrated induction of pCR following treatment; however, doubts were raised as to the validity of pCR as an indicator for long-term survival.
- The appraisal committee found that there was "considerable uncertainty" as to whether pCR could be viewed as a surrogate for long-term benefit; however, it considered positive results in other indications and EMA and FDA opinion classifying pertuzumab as "reasonably likely" to be linked to improved survival outcomes in making the overall decision to recommend the treatment for use in the NHS.[13]



HAS

- HAS considered pertuzumab to have insufficient clinical benefit in the neoadjuvant setting and therefore did not recommend it for reimbursement.
- The data gathered in a proof of concept study were not considered sufficient to determine the size of the effect of pertuzumab.
- HAS committee opinion specifically criticizes the non-hierarchical nature of the phase II trial and states that it cannot be considered a confirmation trial.
- HAS identified a need for further clinical trials to evaluate the size of the effect of pertuzumab.[17]



AEMPS

- AEMPS has recommended pertuzumab for the neoadjuvant treatment of early breast cancer despite not being able to validate pCR as a predictor of OS and PFS.
- This decision for recommendation is based on EMA criteria for the evaluation of oncology medicines (which includes a section on pCR) all of which were met by pertuzumab. The fulfillment of these criteria indicates a probable association in the view of AEMPS.[14]

G-BA

- The G-BA did not find an additional benefit for pertuzumab in the neoadjuvant setting, therefore did not recommend it for reimbursement above the reference price.
- This is based on the current status of pCR as a surrogate endpoint whose validity is currently unclear. The G-BA notes that pCR has shown a relationship to survival on an individual patient basis; however, this correlation has not been substantiated in a study setting.[15]

AIFA

- AIFA made the decision to recommend against funding for pertuzumab.
- AIFA does not provide the reasons for its decision in public documentation.[16]

Limitations:

- Considering that the study focusses on the examination of the EMA website and did not explore the national regulatory authorities' information, EPARs may not have been captured for products approved via national procedures prior to the use of the centralized procedure since November 2005.
- Local reimbursement information related to biosimilar and generic drugs were often missing and the scope of assessment of these drugs differs from market to market.

Conclusion

- The EMA has been regularly approving new treatments based on pCR demonstration in accordance with its guideline, EMA/CHMP/151853/2014.
- However, HTA bodies in countries throughout Europe have taken a cautious approach to recommending new treatments based on this endpoint with a heterogeneous reimbursement recommendation landscape being present across Europe.
- Despite acknowledging the guidance issued by regulators, HTA bodies do not recognize the validity of pCR as a surrogate endpoint for overall survival, progression-free survival or event-free survival.
- Nevertheless, biosimilars often do not require further HTA assessment and are recommended for reimbursement despite the use of pCR as the primary endpoint.
- Further research will be required if pCR is to be established as a widely accepted surrogate endpoint for novel medicines in early breast cancer.
- The acceptance of pCR will encourage industry innovation and expedite the development of novel therapies in the neoadjuvant setting, enabling patients to access and benefit from the treatment sooner.

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