Rocky Road to the Acceptance of Pathological Complete Response (pCR) as Predictor of Improved Disease-Free Survival by HTA agency in Czech Republic

Šárka Motylová, Jakub Novák, Jan Doležel, Martin Pour, Kateřina Kříhová, David Skalický

ROCHE Czech Republic

ISPOR Europe 2023
Nov 14 2023

*"**pCR is not included** among the parameters on the **basis of which** it would be possible to **state** a significantly higher **effectiveness of therapy**..."*

- State Institute for Drug Control (SUKL), Dec 2016

*"The **effectiveness of the therapy** ... was primarily **evaluated** in the subject indication after completion of NAT, **based on the frequency** of achieving a **pathological complete response** (pCR)"*

- State Institute for Drug Control (SUKL), Feb 2023

Pathological complete response (pCR)

Definition

Disappearance of all invasive cancer in the breast after completion of neoadjuvant chemotherapy
(some authors require clearance of residual disease in axillary nodes as well.)[1]

1) von Minckwitz G, Untch M, Blohmer J-U, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012;30:1796–804.

pCR Allows Early Assessment of Efficacy of Therapies for Patients with Early Breast Cancer

"Approval based on pCR may be acceptable for a medicinal product as add-on to an established (neo)adjuvant regimen for the treatment of patients with high-risk early stage breast cancer..." (EMA 2015)[2]

2) EMA (2015) - guideline on the evaluation of anticancer medicinal products in man - Appendix 4

Early Access Imperative Drives Need for Alternative Endpoints in Drug Approvals

- between 2015-2020, pharmacokinetics, ORR, and pathological complete response (pCR) represented 22 % of primary end-points for all oncology drug approvals[3]

- only 8 % of solid-tumor early stage drug approvals by EMA were based on overall survival (OS)[3]

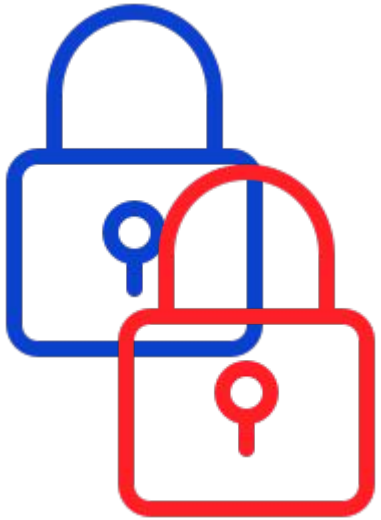
3) Falcone et al. (2022) https://doi.org/10.3390/cancers14040889;

Clash Between Two Gatekeepers Begins

- regulator
  - Is it safe?
  - Is it effective?

- HTA agency/payer
  - Is it effective?
  - What price for the effect?
  - Often preference for (mature) OS data

- in oncology - two conflicting concerns[5]
  - delay in patient access?
  - uncertainty in clinical and/or long-term benefit

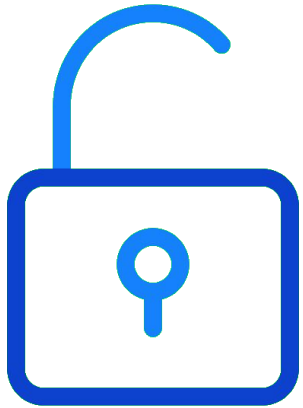


5) Lux, M. et al., Cancer management and research, 13, 8457–8471. https://doi.org/10.2147/CMAR.S328058

Clash Between Two Gatekeepers Begins

EMA Approval (July 2015)

Pertuzumab is indicated for use in combination with trastuzumab and chemotherapy in the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence



- extension of indication was based on two phase II studies
  - NEOSPHERE (WO20697)
    - pCR
    - CRR, TTCR, BCSR, DFS, PFS
  - TRYPHAENA (BO22280)
    - tolerability (related to cardiac functions)
    - pCR, CRR, BCSR, TTCR, OS, DFS, PFS

Different HTA Agency, Different Approach

Recommendations of national HTA agencies

Inconsistent consideration of level of evidence and statistical validation among different HTA agencies.[6]

SMC update: Dec 2018, accepted under PAS

Technology	Indication	Clinical Area	Main Surrogate Endpoint(s) [Patient-Centered Endpoint Substituted for]	NICE	HIS/ SMC	HAS	PBAC/ MSAC	CADTH	IQWiG/ G-BA	ZiN	NIPN
Pertuzumab	Neoadjuvant treatment of HER2-positive breast cancer	Cancer	Pathological complete response Invasive disease-free survival Progression-free survival [overall survival]	✓	✓	✓	✓[b]	✓[b]	✓	—	✓

[a]■, approved for reimbursement; ■, restricted reimbursement (either restricted prescription or subject to a price change); ■, rejected.
[b]Multiple evaluations available.

6) Ciani O et al., Medical Decision Making. 2021 May;41(4):439-52.

Czech Gatekeeper - State Institute for Drug Control (SÚKL)

- HTA approaches in evaluation of medicinal products implemented in CR since 2008[7]

- generally accepted endpoints: OS, PFS, EFS, and DFS

- no guidelines or recommendations regarding surrogate endpoints

7) Vostalova et al., 2017, doi:10.1017/S0266462317000204

2015

2018

2022

Unlocking of pCR Surrogacy

First attempt from 2015

- NEOSPHERE (WO20697)[8] + pooled analysis CTNeoBC[9]
  - "certain benefit" for pCR patients BUT:
  - problematic design of NEOSPHERE trial
  - inconsistent results when compared to CTNeoBC
    => unacceptable uncertainty
- negative positions of SMC or IQWiG (but recommended by NICE)

-> **ASSESSMENT: insufficient evidence on therapeutic efficacy**

8) Gianni et al., Lancet Oncol. 2012 doi: 10.1016/S1470-2045(11)70336-9
9) Cortazar et al., 2014 http://dx.doi.org/10.1016/S0140-6736(13)62422-8

...Took Time and Required Patience

Second attempt from 2018

- updated results of NeoSphere study[8]
  - 15% diff in pCR -> 5% diff in PFS and 3% diff in EFS

- CTNeoBC pooled analysis[9]
  - not relevant - trastuzumab only
  - trial-level association between increase in frequency of pCR and EFS was low

- Cherny et al., **ESMO- Magnitude of Clinical Benefit Scale - level C**[10]

- EMA: "*Currently available data **do not allow a prediction of DFS/OS** effect from a certain pCR effect.*"[11]

-> ASSESSMENT: insufficient evidence on therapeutic efficacy

8) Gianni et al., Lancet Oncol. 2012 doi: 10.1016/S1470-2045(11)70336-9, Gianni et al., Lancet Oncol. 2016 doi: 10.1016/S1470-2045(16)00163-7
9) Cortazar et al., 2014 http://dx.doi.org/10.1016/S0140-6736(13)62422-8
10) Cherny et al., ESMO- Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 0: 1-27, 2017
11) EMA, 2014 - The role of the pathological Complete Response as an endpoint in neoadjuvant breast cancer studies EMA/CHMP/151858/2014

The Right Key Was Made of...

Third attempt from 2022

- additional studies + updates of existing studies[11,12,13,14,15]
- guidelines - pCR became decision point in clinical practice
- support from the Czech Society for Oncology (CSO)
  - consolidation of NAT + AT into a single therapeutic unit
  - pCR is significant prognostic factor for PFS/OS determination

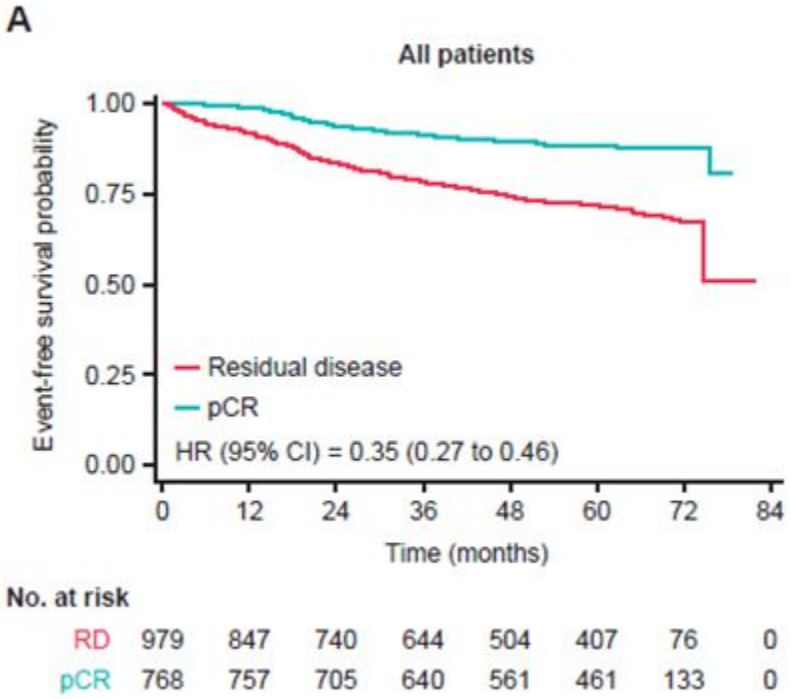
11) Loibl et al., Cancer Res (2020) 80 (4_Supplement): P5-06-02. https://doi.org/10.1158/1538-7445.SABCS19-P5-06-02
12) Spring et al., Clinical cancer research : an official journal of the American Association for Cancer Research (2020), https://doi.org/10.1158/1078-0432.CCR-19-3492
13) Dang, C., et al., Pertuzumab/trastuzumab in early stage HER2-positive breast cancer: 5-year and final analysis of the BERENICE trial. Annals of Oncology (2021) 32 (suppl_2): S37-S47. 10.1016/annonc/annonc504
14) Cortazar et al., 2014 http://dx.doi.org/10.1016/S0140-6736(13)62422-8
15) Broglio et al., JAMA Oncol. 2016;2(6):751-760. doi:10.1001/jamaoncol.2015.6113

Pooled analysis by Swain et al. 2022[16]

- 5 studies:
  - HannaH (NCT00950300)
  - NeoSphere (NCT00545688)
  - TRYPHAENA(NCT00976989)
  - BERENICE (NCT02132949)
  - KRISTINE (NCT02131064)

- Median follow-up > 5 yrs

A **pCR was associated** with a substantially **decreased risk of an EFS** event irrespective of baseline clinical stage and nodal status, as well as HR status and HER2-regimen.



16) Swain et al., Cancers 2022, 14(20), 5051; https://doi.org/10.3390/cancers14205051

Take-Home Message & Outlook

- Czech HTA agency accepts survival endpoints (OS, PFS, EFS,DFS) in oncology

- in 2023 SUKL accepted pCR as a surrogate for improved survival (EFS) based mainly on:
  - multisource evidence
  - repeated and consistent support from the medical society

- accelerated regulatory approval did not translate into reduced time to reimbursement (2015-2023), but this **decision opens door to other similar cases** as there is **no national guidance available on surrogate endpoints** yet

Doing now what patients need next