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SUPPLEMENTARY INFORMATION

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Breast cancer drug approvals by the US FDA from 1949 to 2018

Chandra P. Leo[1], Cornelia Leo[2] and Thomas D. Szucs[3]*

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[1]*HBM Partners, Zug, Switzerland.*
[2]*Interdisciplinary Breast Center, Kantonsspital Baden, Baden, Switzerland.*
[3]*European Center for Pharmaceutical Medicine, University of Basel, Basel, Switzerland.*
**e-mail: chandra.leo@hbmpartners.com*

Supplementary Box 1 | **Data and analysis**

For the first part of our analysis, we identified all oncology drugs approved by the US Food and Drug Administration (FDA) between January 1949 and December 2018, and marketed in the United States as of December 2018, from the GlobalData drug database. We removed duplicates (including generic and biosimilar versions), combinations of drugs previously approved as monotherapies and cancer supportive care medicines, yielding 203 unique cancer drugs (Supplementary Table 1). These drugs were further categorized regarding their approval status for breast cancer and other common solid tumors, using documents on the websites of the FDA and the National Cancer Institute (NCI). The approval numbers per tumour entity are mutually non-exclusive since many oncology drugs are approved for more than one cancer type.

For each medicine in the subset of FDA-approved breast cancer drugs, we verified that the treatment of breast cancer was explicitly mentioned in the "Indications and Usage" section of the most recent prescribing information.

The following medicines were excluded from our analysis:

- drugs that are clinically applied in the treatment of breast cancer but do not have an FDA label specifying this use (e.g. carboplatin, vinorelbine)
- drugs that historically received an FDA approval for breast cancer, but are no longer used in this indication (e.g. fluoxymesterone, methyltestosterone)
- the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, which received an accelerated FDA approval for breast cancer in 2008 that was subsequently withdrawn in 2011
- the selective estrogen receptor modulator (SERM) raloxifene, which is indicated for the risk reduction in women at high risk for breast cancer, but not for the treatment of breast cancer
- the RANKL inhibitor denosumab, which is indicated to increase bone mass in women receiving adjuvant aromatase inhibitor therapy for breast cancer

The resulting list consists of 34 medicines (Supplementary Table 2), from methotrexate (approved in 1953) to talazoparib (approved in 2018). For each drug, we reviewed documents on the FDA server and other publicly available sources to extract information about the first (initial or supplemental) approval date for breast cancer, the first approval date in any indication and various other characteristics (Supplementary Table 3). In cases of accelerated approval, the date of the initial decision is given as the approval date. For the five drugs approved prior to 1970, the exact sequence of approvals for different tumour entities could not be ascertained, so the date of the first-ever FDA approval was used instead. Moreover, these five drugs were included under the "advanced/metastatic" indication despite their broad labels for "breast cancer", since their approvals predated the introduction of adjuvant chemotherapy. Mechanisms of action were classified as "cytotoxic" (including cytostatic agents), "endocrine" or "targeted" based on FDA prescribing information and the published literature.