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**Evolution in the real-world therapeutic strategies in more than 20,000 breast cancer women having received HER2 targeted treatments. Results from the French PRM database (2011-2018).**

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## **Abstract**

### *Background*

There is a growing need for real-world data on cancer treatments usage, especially to assess compliance with recommendations. We developed a French project using hospital data to analyze evolution in the therapeutic strategies implemented in patients with HER2-overexpressed (HER2+) breast cancer (BC) and exposed to injectable HER2 targeted therapies, *i.e.* trastuzumab, pertuzumab or trastuzumab emtansine (T-DM1).

### *Patients and methods*

Data from 26,350 women with BC were extracted in September 2018 from the Electronic Pharmacy Record systems of 120 French randomly recruited hospitals. Evolution in the treatments used and combination regimens were described from 2011, according to BC stage and treatment line.

### *Results*

Overall, 21,119 patients treated since 2011 were analyzed: 16,398 patients with early BC (eBC) and 6,030 patients with metastatic BC (mBC) including patients treated at both stages. In eBC, 89.2% of patients received trastuzumab combined with at least taxanes (trastuzumab-taxane-anthracycline: 62.6%). Patients with mBC were respectively treated in first-line (80.3%) and/or second-line (40.1%) and/or  $\geq$ third-line (28.3%). After its approval in 2014, pertuzumab was first used in first line therapy combinations in 67.4% of the total cases, while trastuzumab-taxane decreased from 47.2% to 9.2%. Similarly, T-DM1 was used as second-line treatment in 53.8% of cases.

### *Conclusions*

Given recent changes in available treatments for HER2+ BC patients, this large French project provides robust information on real-world evolution in therapeutic strategies. Our data

suggest there is room for significant improvement in optimal drug utilization. Such data will be useful to build drug-related indicators for future value-based pricing solutions.

**Key words:** breast cancer; HER2; retrospective real world data study; pertuzumab; trastuzumab; trastuzumab emtansine.

## **Highlights**

- There is a growing need for real-world data on how cancer treatments are used
- Use of therapies for early or advanced HER2+ breast cancer have changed over time
- Cancer treatments were captured in electronic pharmacy systems in French hospitals
- We provide real-world data on 2011-2018 evolution in injectable HER2 treatments.
- Results suggest that improvement is necessary for an optimal use.
- Drug-related indicators will be further built for value-based pricing solutions

## Introduction

The human epidermal growth factor receptor 2 (HER2) gene is amplified, overexpressed, or both in approximately 15% of breast cancers (BC), and is associated with aggressive disease (1,2). The first approved HER2-targeted therapy (trastuzumab, Herceptin®, a humanized monoclonal antibody that targets the extracellular domain of the HER2 receptor) has proven an outstanding clinical benefit in both advanced and early disease when combined with cytotoxic chemotherapy (3–5). However, patients with HER2+ BC may still experience relapse and/or progressive disease, and new targeted therapies, *i.e.* pertuzumab (6,7) and trastuzumab emtansine (T-DM1)(8), were developed to improve patient outcomes in first- and second-line advanced or metastatic setting (mBC).

These recent changes in HER2-targeted therapies have led to a refinement of treatment strategies in HER2+ BC. Recent international guidelines have established the level of evidence and recommendations for use of new intravenous and oral HER2 targeted therapies in mBC (9), and have strengthened the recommendations for HER2+ eBC (10). Within this context, there is a real need for real-world data accurately describing the use of these treatments and its evolution over time, as well as compliance with current recommendations.

Two large ongoing French real-world studies aim to fill this gap: the Epidemiological Strategy and Medical Economics (ESME) research program compiling data on a retrospective then prospective basis in mBC patients since 2014 (11), and the prospective 10-year CANTO (CANcer TOxicities) study focusing on the toxicity of drug and non-drug cancer therapies in patients with early BC stage (eBC) (12). However, both studies are conducted mainly in comprehensive cancer centers and focus on either mBC or eBC, but not both. Within this context, the Personalized Reimbursement Model (PRM) nationwide French project involving 132 French hospitals (including cancer centers, university and community public and non-public hospitals) was developed by Roche, in order to generate consistent real-world data over

time in patients with early or advanced breast cancer treated with trastuzumab, pertuzumab or T-DM1, and to ultimately propose new reimbursement models. The present report describes the 2011-2018 evolution of the hospital use of these drugs in HER2+ BC patients according to BC stage and metastatic treatment line.

### **Patients and methods**

PRM is a retrospective, non-interventional study based on secondary use of patient data, conducted in French public and non-public hospitals usually dealing with patients with HER2+ BC and exposed to a treatment including trastuzumab, pertuzumab, or T-DM1 at least once since January 2011. According to French legislation, patients received written information about the study. All included patients had no objection to sharing their data. Only anonymized data were used for analysis.

#### *Procedures*

Retrospective data on eligible patients were extracted two times a year from the chemotherapy Electronic Pharmacy Record (EPR) systems of participating centers, which include all patients exposed to injectable cancer treatments. Within ~300 French centers treating BC patients [1], random recruitment of 132 hospitals was performed after double stratification including types of hospitals (university hospital, community hospital, comprehensive cancer center, and private clinic) and French regions ( $N=6$ ). Among these 132 hospitals, 120 centers participated in the present study. Eligible patients were women having received anti-HER2 therapy (princeps drugs trastuzumab, pertuzumab or T-DM1) at least once between January 1<sup>st</sup>, 2011 and September 30<sup>th</sup>, 2018. Use of biosimilars was not recorded per protocol. Data collection was securely performed by an health data accredited hosting provider, from hospital EPR systems in which useful data are already available. No study-related involvement from pharmacists, physicians or study nurses was necessary at any time during data extraction process.



After extraction and anonymization, data from non-eligible patients were removed from the analysis, as well as data from patients with unavailable or inconsistent BC stage(s) over time. More specifically, the different steps between data transmission by hospitals and definition of the PRM analysis population were as follows. After files with raw data sent by the participating centers had been integrated into a dedicated database without any transformation (source files), a first data mapping was built for standardization of data formats (dates and numeric or text fields). Diagnoses, disease stages, treatments and treatment lines were then extracted and coded for each captured administration. Filters were then applied to identify inconsistent or out of scope data (patients who did not meet PRM selection criteria, inadequate data such as non-chemotherapy treatments, duplicates or lack of treatment dose) before defining the eligible patient population. Using algorithms and rules validated by the independent PRM scientific committee, last controls aimed to complete disease stages on the basis of stages identified before and/or after the time of the missing information, to assign disease stages using therapeutic patterns prescribed (standard protocols for early or advanced breast cancer, immunotherapy given for metastatic disease...), and to finally validate sequential treatment lines (i.e treatment sequences). Once these rules and algorithms were applied, the last patients with missing/ incomplete/ inconsistent disease stage were excluded before defining the PRM analysis population.

All results reported here are based on the data extraction performed in September 2018.

Roche had access only to aggregated results.

### *Assessments*

Extracted data included demographic, clinical patient characteristics (year of birth, height and weight), disease stage assessment, treatments received for eBC and mBC (treatment line,

systemic and anti-HER2 treatments, dates of administration and doses), and participation in an interventional study assessing injectable cancer treatments.

### *Statistical methods*

The representativeness of the 132 initial participating centers was ensured, overall and according to center type and geographical location, on the basis of data using the national public hospital database (<https://www.atih.sante.fr/>; see Supplementary material, Table S1). Among the 60,204 BC patients with at least one infusion of chemotherapy in French hospitals in 2017 (at project implementation), 30,009 patients (49.8%) were treated in the PRM centers including 10,211 patients treated at least with an anti-HER2 drug, confirming the good representativeness of our sample.

Descriptive analyses were performed on the use of targeted treatments, including trastuzumab, pertuzumab, and T-DM1 (evolution of the use of treatments, combined therapies, and treatment duration), in the overall analysis population, and according to disease stage and treatment line. For pertuzumab and T-DM1, treatment use was analyzed according to three periods: 2011-2013 (before both treatments were available), 2014-2016 (after approval), and 2017-2018 (current period). We also analyzed the treatment duration of pertuzumab and T-DM1 according selection criteria closed to those used in CLEOPATRA and EMILIA studies in order to compare data between real-life and clinical trials data (6,8). Successive treatment lines were also described.

Analyses were carried out using Apache Spark 2.1.0, PostgreSQL 8.5.6, and Python 2.7.5 softwares.

## Results

As of September 30, 2018, data from 26,350 patients were extracted from the EPR systems of 120 centers and 21,119 of them (80%) with available and consistent BC stage(s) over time were retained for analysis.

### *Stages of breast cancer and treatment lines*

Over the 2011-2018 period, 27,428 treatment sequences were documented for the 21,119 analyzed patients. From 2011, 16,398 (77.7%) patients (median age: 56 years; range: 21-99) received injectable treatment(s) for eBC (Figure 1). Taking into account that a single patient could present with early and then metastatic disease stages between 2011 and 2018, 6,030 (28.6%) patients were treated at least once for mBC during this period: 4,841 (80.3%) of them in first-line, and/or 2,471 (40.1%) in second-line, and/or 1,707 (28.3%) in at least third-line. At the start of these metastatic treatment lines, the respective median ages of patients were similar: 59 years (range: 49-69), 60 years (range: 50-68), and 59 years (range: 50-62), respectively.

### *Treatments at early stage of breast cancer*

Between 2011 and 2018, trastuzumab was combined with at least one taxane for eBC in 14,634/16,398 (89.2%) patients (with both taxane and anthracycline: 10,262/16,398, 62.6%) (Figure 2). No major changes were observed over time regarding these combinations: between 876/1,389 (63.1%) patients in 2011 and 900/1,753 (51.3%) patients in 2018 for the trastuzumab-taxane-anthracycline combination, and between 315/1,389 (22.7%) and 674/1,753 (38.4%) patients for the trastuzumab-taxane anthracycline-free combination. In adjuvant setting, median duration of trastuzumab was 54.0 weeks (interquartile range, IQR: 35.0-55.3; mean duration: 46.0±24.3 weeks).

### *First line therapy in metastatic breast cancer*

Prior to 2014, pertuzumab was used in clinical trials in 71/1,227 (5.8%) patients having received a 1<sup>st</sup>-line metastatic therapy. The prescription of pertuzumab increased as soon as during the 2014-2017 period until it was used in 940/1,395 (67.4%) patients between 2017 and 2018 (Figure 3). Pertuzumab-trastuzumab-taxane was the most frequently reported combination over this last period (826/1,395, 59.2%), in particular in patients younger than 70 years (644/1,016, 63.4% *versus* 182/379, 48.0% in older patients). From 2011-2013 to 2017-2018, the use of the trastuzumab-taxane combination decreased from 579/1,227 (47.2%) to 128/1,395 (9.2%) patients. The median treatment duration of pertuzumab was 18.1 months (IQR: 8.3-28.9; mean: 20.4±14.8 months).

### *Second line therapy in metastatic breast cancer*

Prior to its approval in 2014, T-DM1 was used in clinical trials in 40/647 (6.2%) patients having received a second-line metastatic therapy (see Supplementary material, Figure S2). It was used in only 372/691 (53.8%) patients during the 2017-2018 period. During the same two periods, the use of trastuzumab-vinorelbine and trastuzumab-taxane combinations decreased dramatically in second line setting, from 193/647 (29.8%) to 10/691 (1.5%) patients and from 188/647 (29.1%) to 47/691 (6.7%), respectively. The median duration of T-DM1 was 7.6 months (IQR 4.1-15.8; mean: 11.5±10.6 months).

### *Successive metastatic lines of treatment*

Figures 4 and 5 show how successive therapeutic strategies have evolved between the 2011-2013 and the 2017-2018 periods. In 2011-2013, when trastuzumab based therapy was used as first line treatment (1,010/1,227, 82.3%), it was usually continued as treatment backbone in

further lines: as second-line treatment in 156/212 (73.6%) patients, and as third-line treatment in 96/159 (60.4%) patients treated after second-line trastuzumab (Figure 4). During the most recent period (2017-2018), new targeted anti-HER2 treatments, *i.e.* pertuzumab and T-DM1, were more frequently used. We observed that the majority of patients received first-line treatment with the combination of pertuzumab-trastuzumab-chemotherapy (785/1,185, 66.2%), and then received a further second-line therapy ( $N=114$ ) with T-DM1 ( $N=76$ , 66.7%). After second-line T-DM1 (326/605, 53.9%), the 86 patients who received a further third-line therapy were mostly treated with trastuzumab ( $N=66$ , 76.7%). (Figure 5). Taken together, these data suggest that implementation in the routine practice of major drugs such as pertuzumab and T-DM1 is quick and efficient. However, it also appears from figures 4 and 5 that substantial subsets of patients received these drugs off label (e.g. pertuzumab after the first line), or conversely were not exposed at all. More than 35% of patients did not receive pertuzumab as first line treatment, and more than 45% of patients did not received T-DM1 as second line treatment.

## **Discussion**

There is a growing need for real-world data on use of cancer treatments, notably to (i) assess compliance with recommendations, (ii) confirm in a real-life setting previous results from interventional studies, and (iii) follow the evolution of patient management over time. The PRM project, based on data from French hospitals, was thus designed to provide consistent real-world data over time on the therapeutic strategies implemented in HER2+ BC patients. We developed an original method based on regular, automated extractions from electronic pharmacy records. Our analysis led to robust data, notably thanks to data controls and corrections performed after data extraction. The quick, automated data collection process we have developed led to project sustainability and made possible data extractions on a regular basis, thus able to generate accurate and updated analyses that can be repeatedly performed

within only two months of time. Based on data extraction performed in September 2018, the present report assessed evolution in injectable cancer treatments used in hospitals according to BC stage and treatment line in 21,119 patients exposed to either trastuzumab, pertuzumab or T-DM1 at least once from 2011. Use of biosimilars was not recorded per protocol.

In patients with early breast cancer, trastuzumab was used accordingly to the French Haute Autorité de Santé and the European Medicines Agency recommendations, in combination with at least one taxane in most cases, and a median treatment duration of one year.

In patients with metastatic BC, treatment strategies have evolved considerably in France since pertuzumab (in December 2013) and T-DM1 (in July 2014) became available. The proportion of patients treated with first-line pertuzumab increased to 67% (in combination with trastuzumab and taxane: 59%) during the 2017-2018 period, as well as second-line T-DM1 (up to 57%) decreasing the use of trastuzumab-vinorelbine and trastuzumab-taxane combinations. These evolutions are in accordance with the 2017 European guidelines for mBC, prevailing at the time of data extraction (13) and suggest that physicians tend to prescribe new treatments as soon as available when possible, especially in the metastatic setting. However, our results also strikingly suggest that important proportions of patients are not given access to state-of-the-art therapies, with potential and presently non-evaluable medical consequences for individual patients. In our study, we observed the non-use of first-line pertuzumab in around 30% of patients. As drug access is fortunately not an issue in France, reasons for this underuse of key medications have to be explored. It might be hypothesized that indeed about 30% of patients are primarily resistant to conventional trastuzumab based combinations as evidenced in populations with short delay relapses in the CLEOPATRA and PERUSE studies (6,14). Another possibility is the use of double HER2

blockade with non-approved drugs in this setting. For instance, capecitabine therapy as used in the PHEREXA trial (15) is not recorded in our system. Finally, in some patients, chemotherapy-free regimens might have been used, according to residual side effects from prior treatments, or in combination with endocrine treatment. In addition, pertuzumab-trastuzumab-taxane was less frequently prescribed in patients over 70 years (48.0% *versus* 63.4% in younger patients). One likely reason for the under-use in elderly could be their frequent comorbidities and potential drug toxicities. Finally, some patients received T-DM1 in the first line setting, probably based on the non-inferiority re-analysis of the MARIANNE trial (16).

Treatment durations with pertuzumab and T-DM1 were described in patients with a first injection at least 18 months before data extraction, and with characteristics close to those of previous clinical trials. The respective median treatment durations were strikingly similar to the median progression-free survival observed in the CLEOPATRA study (6) for pertuzumab (18.0 and 18.7 months, respectively), and in the EMILIA study (8) for T-DM1 (7.6 and 9.6 months, respectively), indirectly confirming the efficacy of both drugs in routine medical practice.

One limitation of the PRM project is that no clinical data, such as tumor characteristics, response to treatment or drug toxicity, are entered into the hospital EPR systems. In addition, oral cancer therapies prescribed at the hospital, as well as combined non-cancer therapies, are not tracked by hospitals. Use of biosimilars, which have now entered common practice, will be captured in future data extractions. This may lead to incomplete treatment history. To fill this gap, matching with other medical databases, such as electronic medical records, existing clinical registries or databases, or national public health databases could be an opportunity.

## **Conclusions**

The PRM project is the first program providing consistent real-world information over time on the therapeutic strategies implemented in a large and representative population of French HER2+ BC patients. In addition to a better knowledge of present patient management and how treatments evolution are implemented in routine care, such data will be useful to build medico-economic models or new value-based pricing solutions in a real-life setting. This project is currently extended to lung cancer, and could be enlarged to other cancers and pathologies.



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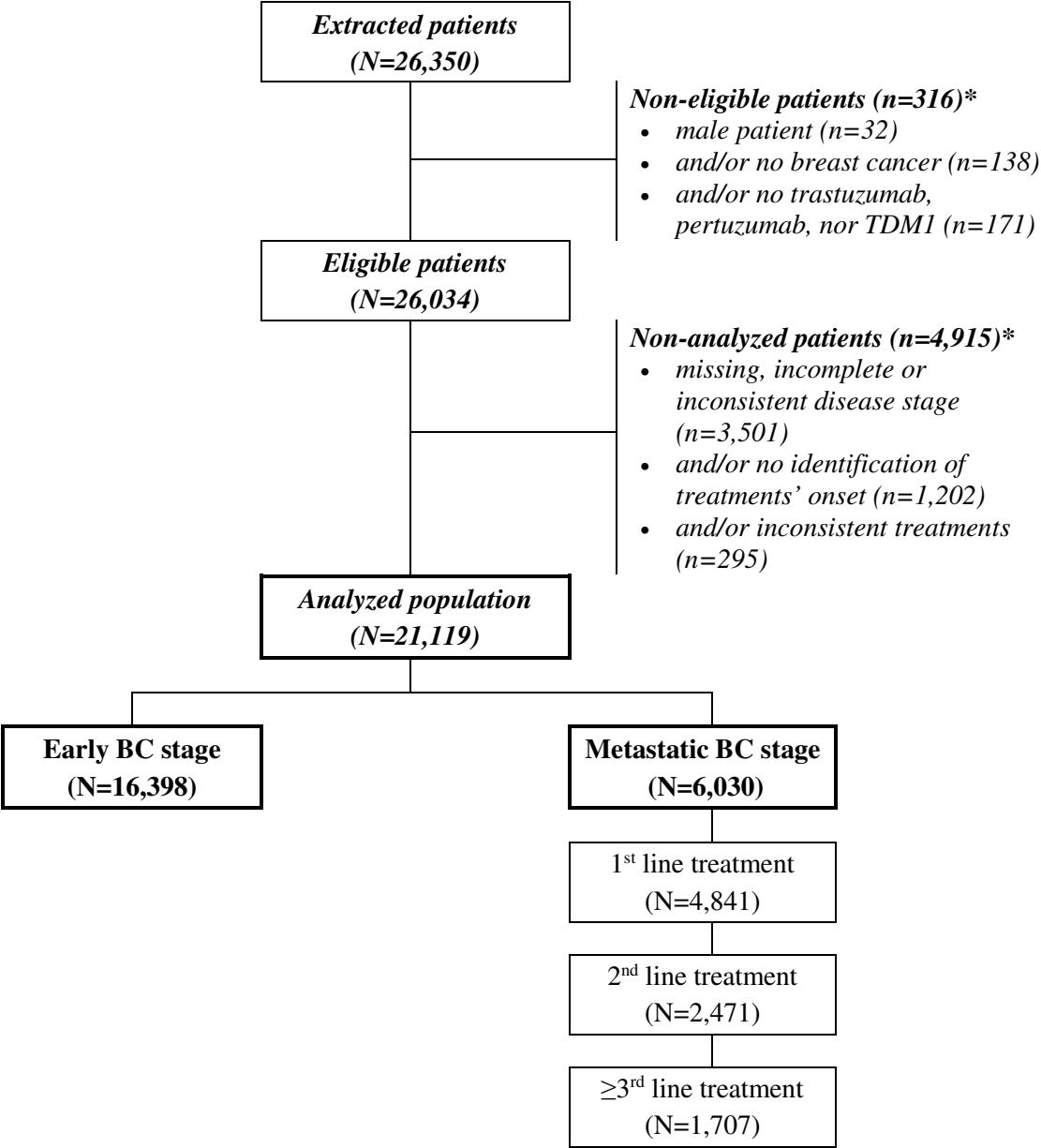
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## **Conflict of interest**

This work was supported by Roche. PC, BC, DP, AD, JM, OA, HB and XP received institutional funding for the study. NC and LS are Roche employees.

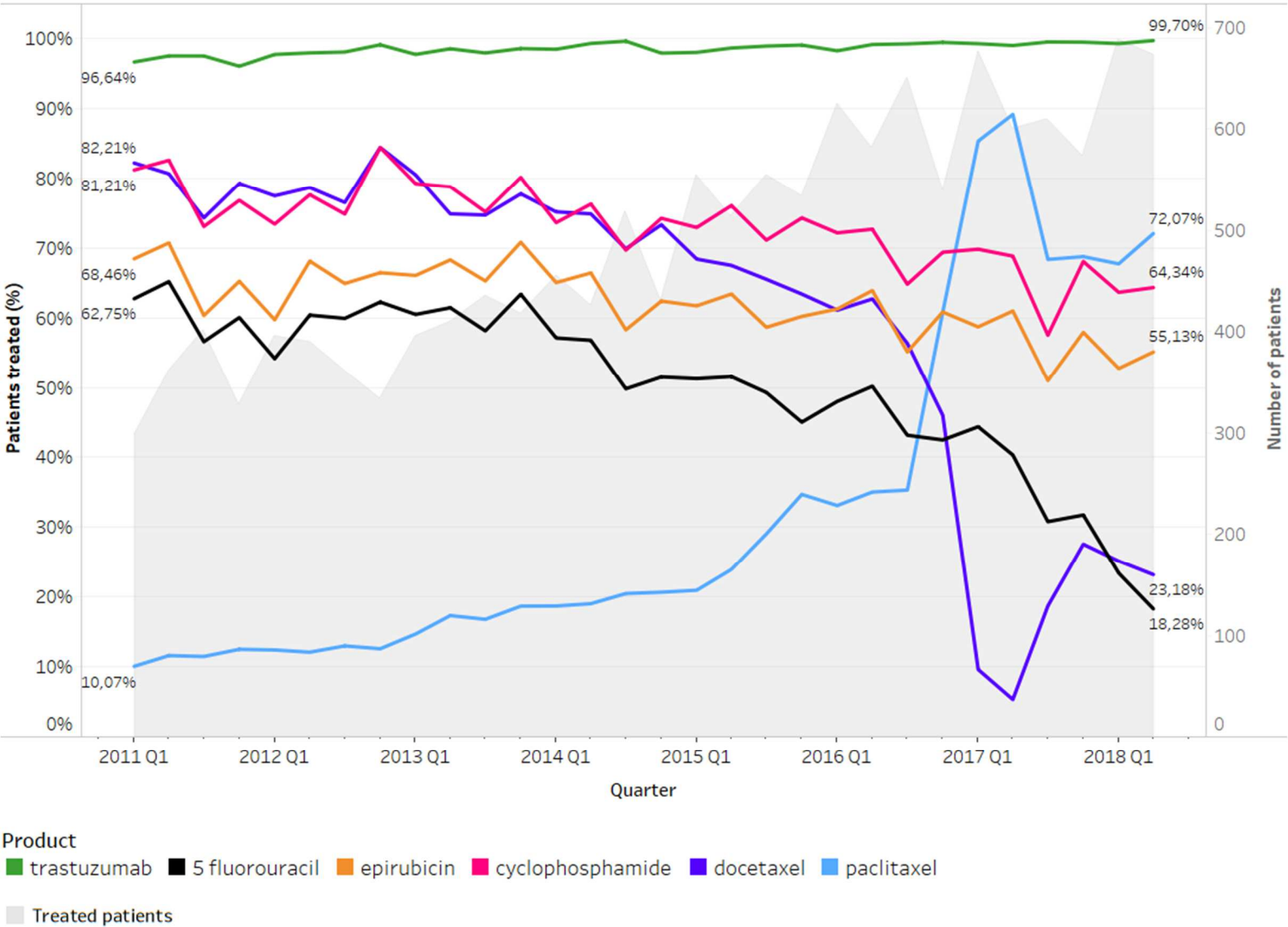
**Figure 1: Disease stages and treatment lines in patients with HER2-positive breast cancer (BC), exposed to either trastuzumab, pertuzumab, or trastuzumab-emtansine (T-DM1) treatment at least once since 2011**



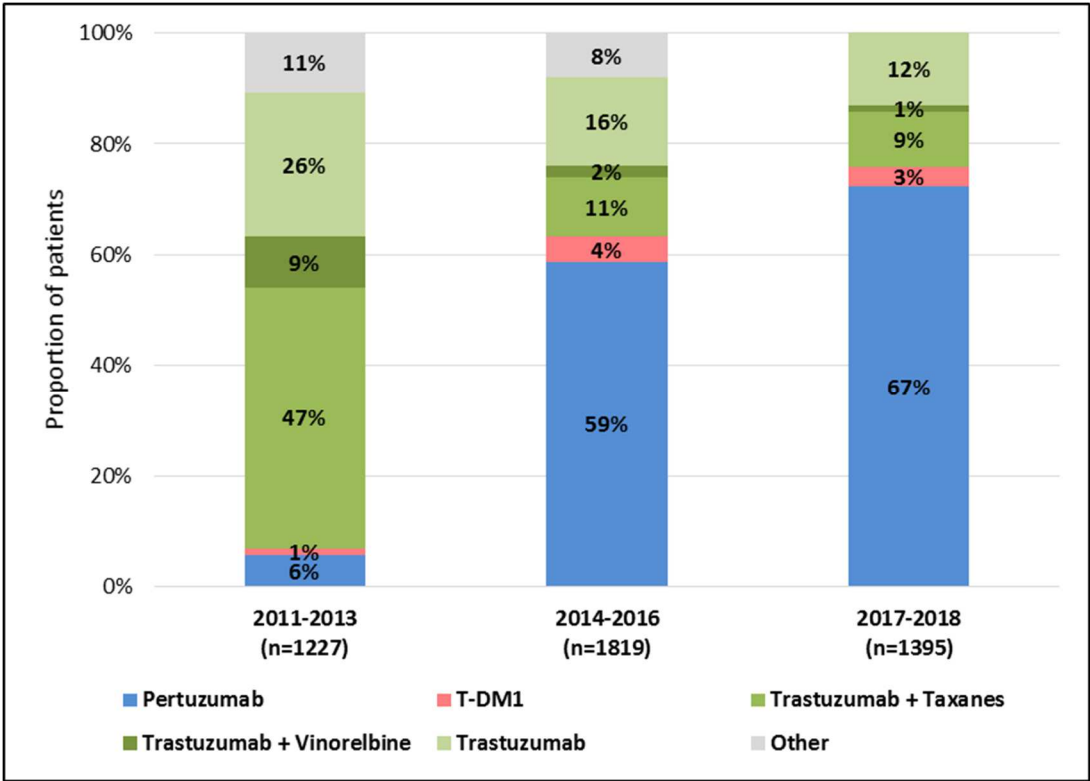
\* Several reasons possible for a same patient

A same single patient could receive different lines of treatments and could have early and then metastatic BC stages during follow-up (N=1,309).

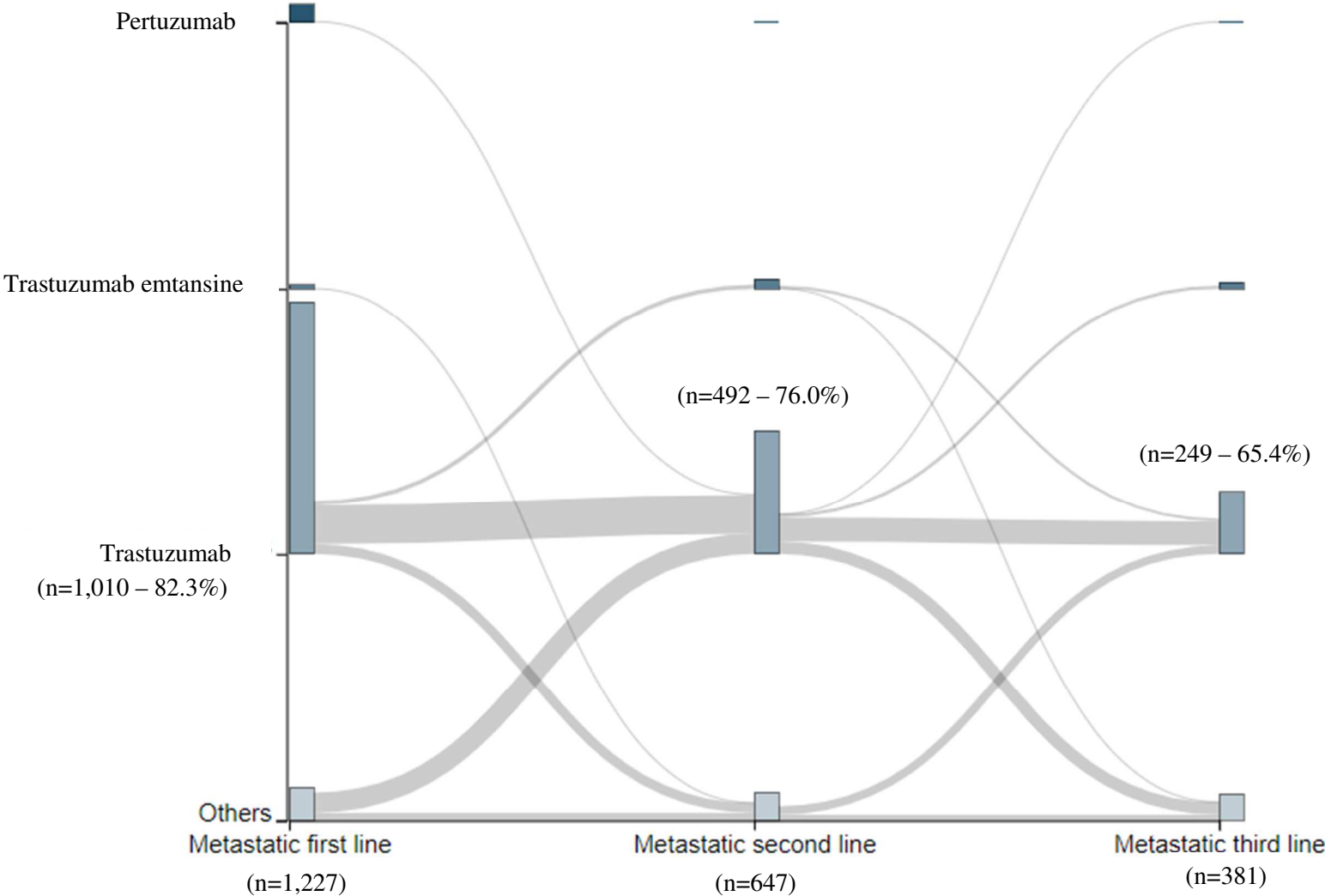
**Figure 2: Evolution in HER2+ targeted treatments used in early stage breast cancer – 2011-2018 period**



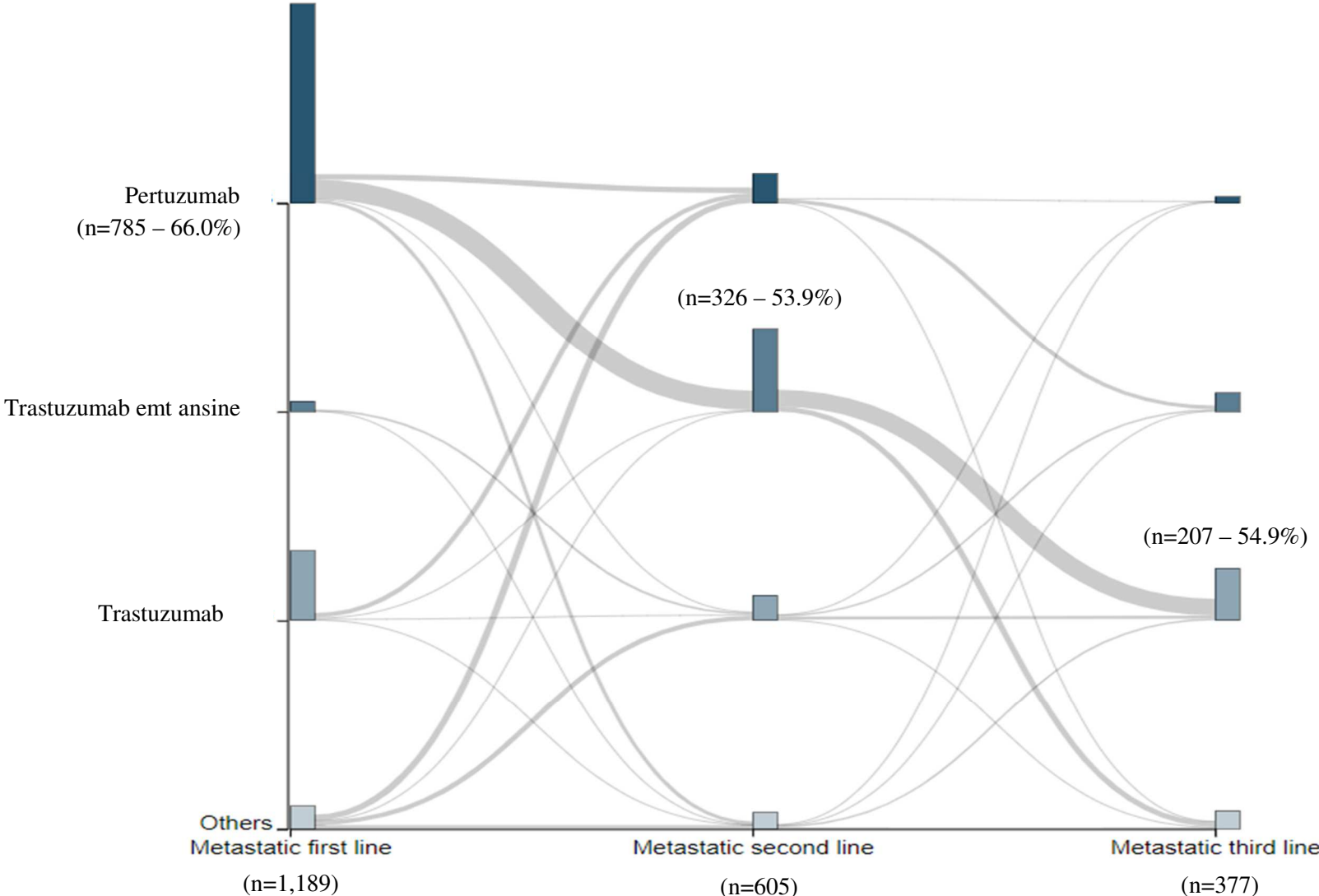
**Figure 3: Evolution in HER2+ targeted treatments used in first-line metastatic breast cancer – 2011-2013, 2014-2016, and 2017-2018 periods**



**Figure 4: Therapeutic strategies used in patients with HER2+ metastatic breast cancer – 2011-2013 period**



**Figure 5: Therapeutic strategies used in patients with HER2+ metastatic breast cancer – 2017-2018 period**



## REFERENCES

1. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 9 janv 1987;235(4785):177-82.
2. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. *J Clin Oncol Off J Am Soc Clin Oncol*. 1 janv 2010;28(1):92-8.
3. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol Off J Am Soc Clin Oncol*. 1 juill 2005;23(19):4265-74.
4. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 6 oct 2011;365(14):1273-83.
5. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet Lond Engl*. 25 mars 2017;389(10075):1195-205.
6. Baselga J, Cortés J, Kim S-B, Im S-A, Hegg R, Im Y-H, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 12 janv 2012;366(2):109-19.
7. Swain SM, Baselga J, Kim S-B, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 19 févr 2015;372(8):724-34.
8. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 8 nov 2012;367(19):1783-91.
9. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. *Ann Oncol Off J Eur Soc Med Oncol*. 1 août 2018;29(8):1634-57.
10. Burstein HJ, Curigliano G, Loibl S, Dubsy P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol Off J Eur Soc Med Oncol*. 1 oct 2019;30(10):1541-57.
11. Pérol D, Robain M, Arveux P, Mathoulin-Pélissier S, Chamorey E, Asselain B, et al. The ongoing French metastatic breast cancer (MBC) cohort: the example-based methodology of the Epidemiological Strategy and Medical Economics (ESME). *BMJ Open*. 21 févr 2019;9(2):e023568.

12. Vaz-Luis I, Cottu P, Mesleard C, Martin AL, Dumas A, Dauchy S, et al. UNICANCER: French prospective cohort study of treatment-related chronic toxicity in women with localised breast cancer (CANTO). *ESMO Open*. 2019;4(5):e000562.
  13. Cardoso F, Costa A, Senkus E, Aapro M, André F, Barrios CH, et al. 3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Ann Oncol*. 5 déc 2016;mdw544.
  14. Bachelot T, Ciruelos E, Schneeweiss A, Puglisi F, Peretz-Yablonski T, Bondarenko I, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent or metastatic breast cancer (PERUSE). *Ann Oncol Off J Eur Soc Med Oncol*. 1 mai 2019;30(5):766-73.
  15. Urruticoechea A, Rizwanullah M, Im S-A, Ruiz ACS, Láng I, Tomasello G, et al. Randomized Phase III Trial of Trastuzumab Plus Capecitabine With or Without Pertuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Who Experienced Disease Progression During or After Trastuzumab-Based Therapy. *J Clin Oncol Off J Am Soc Clin Oncol*. 10 sept 2017;35(26):3030-8.
  16. Perez EA, Barrios C, Eiermann W, Toi M, Im Y-H, Conte P, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab with taxane for human epidermal growth factor receptor 2-positive advanced breast cancer: Final results from MARIANNE. *Cancer*. 15 nov 2019;125(22):3974-84.
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