Effectiveness of Trastuzumab for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer in a Real-Life Setting: One Decade of Experience Under National Treatment Coverage Regulations

Natalia Camejo, MD; Cecilia Castillo, MD; Rafael Alonso, Eng; Fernando Correa, MD; Emiliano Rivero, MBBS; Camila Mezquita, MBBS; Agustín Rosich, MBBS; Fiamma Dellacasa, MBBS; Luciana Silveira, MBBS; and Lucía Delgado, MD

abstract

PURPOSE Trastuzumab has shown an overall survival (OS) benefit in patients with human epidermal growth factor receptor 2 (HER2)–positive breast cancer (BC), in both the adjuvant and the metastatic setting. We assessed the effectiveness of trastuzumab in patients treated in daily practice according to national treatment coverage protocols and compared our results with those reported by randomized clinical trials. These coverage protocols included patient selection criteria similar to those of those clinical trials and were developed by the Uruguayan National Resource Fund (FNR), the agency that has funded these prescriptions for more than a decade.

PATIENTS AND METHODS We included all patients with HER2-positive BC treated with trastuzumab under FNR coverage approved between January 1, 2006, and December 31, 2016. The source of data was the FNR database, and primary outcome was OS, analyzed through Cox proportional hazards regression analysis.

RESULTS A total of 1,944 women were included: 1,085 women (55.8%) were postmenopausal and 1,240 (63.7%) had HER2 and hormone receptor–positive BC. Trastuzumab was administered as adjuvant therapy to 1,233 patients (63.5%), of whom 154 also received it as a neoadjuvant treatment. Three hundred nineteen patients (16.4%) received trastuzumab for advanced disease. Five-year OS in the adjuvant setting was 86.4% (95% CI, 84.0% to 88.7%). The median survival of patients with advanced BC was 25.1 months (95% CI, 10.1 to 42.5 months).

CONCLUSION Our survival results are not inferior to those reported in clinical trials, in both adjuvant and advanced settings. Importantly, these results support the relevance and the feasibility of treating patients in routine practice, following coverage protocols based on patient selection criteria and methods supported by positive clinical trials. In addition, these results favor quality and appropriate access to BC treatment in our country.

JCO Global Oncol 6:217-223. © 2020 by American Society of Clinical Oncology

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License

INTRODUCTION

In initial clinical trials, trastuzumab in association with paclitaxel as first-line therapy was shown to be beneficial in metastatic human epidermal growth factor receptor 2 (HER2)–positive breast cancer (BC), with a positive impact on patients’ overall survival (OS).1 Subsequent randomized clinical trials also showed its efficacy as adjuvant therapy, improving patients’ disease-free survival and OS.2,4 However, there are doubts as to whether the results from clinical studies can be directly translated to regular clinical practice, not only because there can be differences in patient and health system characteristics but also because global access to cancer care and treatment practices may change.5,6 As a consequence, cost-effectiveness estimations can differ, depending on whether clinical trial or clinical practice data are taken into account. These considerations are particularly important for agencies that finance high-cost drugs when reviewing financial coverage decisions. Therefore, when deciding whether to incorporate high-cost medication into a universal coverage system, payers need well-defined strategies for monitoring indications and evaluating results.

The information available on the use of trastuzumab in routine clinical practice in developed countries indicates that real-life outcomes could resemble those observed in randomized clinical trials, both in adjuvant settings7–9 and in advanced BC.10–13 However, there is
The current study sheds light on the outcomes of Uruguayan patients with HER2-positive BC in real life; therefore, it provides useful information to adjust the coverage protocols of trastuzumab in HER2-positive breast cancer in our country.

CONTEXT

Key Objectives
What are the treatment outcomes of Uruguayan patients with HER2-positive breast cancer treated in daily practice according to national treatment coverage protocols?

Knowledge Generated
Five-year OS in the adjuvant setting was 86.4% (95% CI, 84.0% to 88.7%). The median survival of patients with advanced BC was 25.1 months (95% CI, 10.1 to 42.5 months). Our survival results are not inferior to those reported in clinical trials, in both adjuvant and advanced settings.

Relevance
The current study sheds light on the outcomes of Uruguayan patients with HER2-positive BC in real life; therefore, it provides useful information to adjust the coverage protocols of trastuzumab in HER2-positive breast cancer in our country.

Uruguay has achieved universal health coverage for its entire population, including high-cost drugs, which have been provided by the National Resource Fund (FNR) since 2005 under coverage protocols. The FNR, a nongovernmental public institution created by law in Uruguay in 1979, is part of the National Integrated Health System and provides financial coverage for high-cost procedures and medications. In 2006, trastuzumab was incorporated into the coverage of the FNR for the adjuvant treatment of BC and subsequently, in October 2008, for neoadjuvant therapy and for the treatment of advanced disease. With the aim of obtaining results similar to those reported in the randomized clinical trials that demonstrated clinical benefit, the FNR coverage protocols established selection criteria and methods analogous to those included in the pivotal trials. These protocols are reviewed and updated periodically to reflect the evolution of new scientific evidence and to adapt them to the specific context of the health system in Uruguay. In addition, the FNR has developed an information system to record patients’ clinical and paraclinical data and to monitor therapeutic results. These tools provide decision makers with elements to base their decisions on and offer objective parameters for coverage that remains sustainable over time. Hence, a close relationship is established among quality, equality, and sustainability. Given the key importance of ensuring quality access to high-cost therapies, we considered it of special interest to assess the effectiveness of trastuzumab since its incorporation into the FNR and to compare the results with those obtained in pivotal clinical trials.

PATENTS AND METHODS

Study Goals

Primary goal. To estimate the OS rate of Uruguayan patients with HER2-positive BC treated with trastuzumab provided by the FNR in between 2006 and 2016, globally and according to disease stage and treatment modality (adjuvant, neoadjuvant/adjuvant, and for metastatic disease).

Secondary goal. To analyze the clinical, pathologic, and biologic characteristics at diagnosis of Uruguayan patients with HER2-positive BC, including age, menopausal status, stage, and biologic subtype on the basis of tumor estrogen receptor (ER) and progesterone receptor (PR) expression.

Study Design and Data Collection

We conducted a prospective study of a cohort of patients with HER2-positive BC treated with trastuzumab under FNR coverage approved in the period extending from January 1, 2006, to December 31, 2016. During this period, clinical, paraclinical, and follow-up data were collected by trained data managers from the application forms completed by the patient’s oncologists and from reports of the paraclinical studies, including CBC, liver and renal function tests, assessment of left ventricular ejection function by echocardiography, and systemic imaging studies, (chest computed tomography [CT], abdominal with or without pelvic CT, bone scan, and positron emission tomography /CT) if indicated. Collected data were recorded in the System Information Database of the FNR. After controlling for the validity and quality of the recorded information, the database was anonymized.

The data gathered included age at diagnosis, menopausal status, TNM stage (on the basis of the American Joint Committee on Cancer’s TNM classification, 7th edition, 2010), ER and PR status by immunohistochemistry (IHC; a cutoff point of 1% was used to define ER and/or PR positivity), trastuzumab treatment modality (adjuvant, neoadjuvant, or for metastatic disease), associated systemic therapies (chemotherapy, hormone therapy), and date of death or date of last follow-up.

HER2 testing was performed using the methodology reported in the ASCO/College of American Pathologists HER2 testing guideline. HER2 status was considered positive in IHC 3+ cases or in situ hybridization validated. All patients gave their informed consent to use their information for research.
During the study period, trastuzumab was covered for the adjuvant/neoadjuvant therapy for patients with operable HER2-positive BC with positive regional lymph nodes, or with negative nodes and a primary tumor with an invasive component ≥ 1 cm. Trastuzumab was also covered for patients with HER2-positive, locoregionally advanced, or disseminated tumors.15

All patients received chemotherapy (with or without endocrine therapy, according to ER and/or PR status), with protocols selected from those validated by pivotal clinical trials with trastuzumab. No patient was treated as part of a clinical trial.

**Statistical Analysis**

Two subtypes were defined on the basis of the positive or negative expression of ER and PR in IHC:

1. HER2+, ER+, and/or PR+
2. HER2+, ER−, and PR−

The primary end point was OS, which in patients with nonmetastatic BC (stages I, II, and III) was defined as the interval from the date of BC diagnosis to the date of death or to the date of last follow-up in patients alive at the date of survival analysis. In patients with metastatic BC, OS was defined as the interval between the date of diagnosis of the disseminated disease and the date of death or last follow-up. The patients alive at the date of last follow-up were censored at that date.

The Kaplan-Meier method was used for the statistical analysis, and the difference in survival between groups was evaluated using the log-rank test. Statistical significance was considered when \( P < .05 \). For the comparison between more than 2 groups, analysis of variance was used. The statistics package used was SPSS 22 (Armonk, NY).

**Ethical Aspects**

The current study was performed in compliance with the international ethical standards applied to biomedical research (ie, the MERCOSUR Standards on the Regulation of Clinical Trials and the World Medical Association’s Declaration of Helsinki [including its amendment dated October 2013]). Patient anonymity was maintained in the analysis, and the study had the approval of the research ethics committee of the School of Medicine of the University of the Republic.

**RESULTS**

The analysis included 1,944 patients diagnosed with invasive BC who received trastuzumab funded by the FNR between January 1, 2006, to December 31, 2016. The average time between receipt of the request and authorization for treatment has decreased progressively, and has been 7 days (standard deviation, 26.1 days) since 2016.

The mean age at diagnosis was 52.8 years (standard deviation, 11.0 years), and the peak incidences occurred between the ages of 45 and 60 years. The distribution by age was as follows: ≤ 35 years (n = 120 [6.2%]), 36-45 years (n = 404 [20.8%]), 46-55 years (n = 614 [31.6%]), 56-65 years (n = 514 [26.4%]), and > 65 years (n = 292 [15.1%]). Menopausal status was available for 1,790 patients. Most patients (n = 1,085 [55.8%]) were premenopausal at diagnosis, and 705 patients (36.3%) were premenopausal.

Disease stage was known in 1,874 patients. The distribution by stage was as follows: stage I (n = 294 [15.1%]), stage II (n = 818 [42.1%]), stage III (n = 443 [22.8%]), stage IV (n = 319 [16.4%]), and unknown (n = 70 [3.6%]). The mean age by stage was as follows: stage I, 54.0 years; stage II, 52.3 years; stage III, 52.0 years; and stage IV, 54.6 years.

The majority of patients presented initially with a node-positive axilla (n = 1,053 [54.2%]), of whom 565 (29.1%) had between 1 and 3 positive lymph nodes, 310 (15.9%) had between 4 and 9 positive lymph nodes, and 178 (9.2%) had > 9 positive lymph nodes; 682 patients (35.1%) had a negative axilla. Data on 209 patients (10.7%) are missing.

With regard to biologic characteristics, most patients (n = 1,240 [63.7%]) had HER2-positive, ER and/or PR-positive disease; 628 patients (32.3%) had HER2-positive, ER-negative, and PR-negative disease, and for the remaining patients (n = 76 [3.9%]) ER or PR status was unknown.

Trastuzumab was administered as adjuvant therapy to 1,209 patients (62.1%), as neoadjuvant and adjuvant therapy to 263 patients (13.5%), and for advanced disease to 319 patients (16.4%). Data for the remaining patients (7.8%) were not available.

The baseline characteristics of 1,233 patients with operable BC who received adjuvant trastuzumab (with or without neoadjuvant trastuzumab) are listed in Table 1. The median age was 52 years, 46.6% of the patients had node-negative disease, and 67.5% of the patients had hormone receptor (HR)–positive tumors. One hundred fifty-four patients (12.5%) received neoadjuvant trastuzumab in addition to adjuvant treatment. In all cases, 1 year of adjuvant trastuzumab was completed.

Regarding chemotherapy, in most patients (n = 1,001 [81.2%]), the therapy consisted of regimens containing an anthracycline (doxorubicin, epirubicin) and docetaxel or paclitaxel. The non–anthracycline-containing regimens prescribed were docetaxel and cyclophosphamide (TC-H) and also carboplatin and docetaxel (TCH) followed by trastuzumab until completing a year of adjuvant treatment. No patient received only docetaxel or paclitaxel with trastuzumab or trastuzumab without adjuvant chemotherapy.

Most patients (n = 747 [60.6%]) received trastuzumab concurrently with chemotherapy, and 393 patients (32.1%) received trastuzumab sequentially with chemotherapy. Data on the remaining patients (n = 90 [7.3%]) are missing. All HR-positive patients received adjuvant endocrine therapy.

The characteristics of the 319 women with advanced disease are listed in Table 2. The median age was 54.6
years; most patients (n = 201 [63.0%]) were postmenopausal at diagnosis, 83 patients (26.0%) were premenopausal, and data on the remaining 35 patients (11%) are missing; 58.9% of the patients had HR-positive tumors.

All patients received the first trastuzumab-based therapy together with chemotherapy. Most patients (n = 211 [66.1%]) received paclitaxel or docetaxel. The other chemotherapeutics frequently combined with trastuzumab were vinorelbine, gemcitabine, and capecitabine (Table 2).

At a median follow-up of 44 months, the median OS at 5 years for all patients was 74% (95% CI, 71.8% to 76.7%). The OS at 5 years was 86.2% (95% CI, 83.3% to 88.6%) for patients who received adjuvant treatment and 70% (95% CI, 62.1% to 76.6%) for patients who received neoadjuvant treatment. With regard to patients with advanced BC, median survival was 25.1 months (95% CI, 10.1 to 42.5 months; Fig 1).

The OS at 5 years of patients with operable BC (stages I to IIIA) who received adjuvant (with or without neoadjuvant) trastuzumab (n = 1,233) was 86.4% (95% CI, 84.0% to 88.7%; Fig 2). Figure 3 presents the OS for patients with stages I to III BC according to receptor status (HR− v HR+). The comparison of the OS curves showed statistically significant differences only for patients with stage II (P = .001) and stage III BC (P = .029; log-rank [Mantel-Cox]).

**DISCUSSION**

The allocation of resources for anti-HER2–targeted therapies in BC is a real challenge faced by health policy makers and the agencies that provide the funds for this type of medication.17,18 Because clinical studies are performed with highly selected patients under optimal conditions, their survival and safety outcomes may not be reproduced in routine clinical practice.19-21 Moreover, it is well known that there are social determinants of BC survival, such as access to health services and quality of BC care, which may vary among countries.22,23 Consequently, we can question whether the results obtained from clinical trials will be the same in real life.

Our study included 1,944 women with HER2-positive BC, with a mean age at diagnosis of 52.8 years, and with a peak incidence ranging from 45 to 60 years. This differs from the peak incidence of other biologic subtypes of BC, such as HER2-negative luminal tumors, whose peak incidence is observed in postmenopausal women, and it also differs from that of triple-negative tumors, whose peak is seen in young premenopausal women.24-26 Most patients presented with early-stage tumors (stages I to IIIA, n = 1,233 [63.4%]) and with HR-positive disease (63.7%).

The OS of patients who received adjuvant trastuzumab was comparable to that reported by the pivotal randomized trials of adjuvant trastuzumab.2-4 Indeed, these studies reported a 5-year OS ranging from 87% to 91%, being 86.2% (95% CI, 83.3% to 88.6%) for the 1,366 patients who received adjuvant trastuzumab and 86.4% (95% CI, 84.0% to 88.7%) for the subgroup with operable disease (stages I to IIIA [n = 1,233]). The 5-year OS reported by the HERA trial2 (ClinicalTrials.gov identifier: NCT00045032) was 87%, the same we observed here.

Regarding the selection criteria, we think they are mainly comparable to the HERA trial: (1) similar inclusion criteria for patients with negative axilla, including patients with tumors larger than 1 cm (regardless of HR status), (2) the completion of at least 4 courses of adjuvant chemotherapy, and (3) no requirement for the administration of trastuzumab concurrently with chemotherapy.

With respect to patients characteristics, three differences stand out among our patients who received adjuvant therapy: (1) the mean age at diagnosis (49 years in HERA v

---

**TABLE 1.** Baseline Characteristics of Patients With Operable Breast Cancer (n = 1,233)

| Variable | No. | %  |
|----------|-----|----|
| Age, years |     |    |
| ≤ 35     | 69  | 5.6|
| 36-49    | 453 | 36.7|
| 50-59    | 351 | 28.5|
| ≥ 60     | 360 | 29.2|
| Median   | 52  |    |
| Menopausal status |     |    |
| Premenopausal | 480 | 38.9|
| Postmenopausal | 669 | 54.2|
| Unknown  | 84  | 6.8|
| Nodal status |     |    |
| Not assessed (neoadjuvant chemotherapy) | 46  | 3.8|
| Negative | 575 | 46.6|
| 1-3 positive | 403 | 32.7|
| ≥ 4-9 positive | 191 | 15.5|
| ≥ 10 positive | 18  | 1.5|
| Pathologic tumor size, cm |     |    |
| 0-2 | 535 | 43.4|
| > 2-5 | 557 | 45.2|
| > 5 | 53  | 4.3|
| Unknown | 88  | 7.1|
| Hormone receptor status |     |    |
| ER negative and PR negative | 379 | 30.7|
| ER negative or PR positive | 833 | 67.5|
| Unknown | 21  | 1.7|

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
52 years in our study), (2) the percentage of patients with node-positive axilla (57% in HERA v 49.6% of 1,233 patients with early-stage disease in our study), and (3) the percentage of patients with HR-negative BC (50% in HERA v 30.7% in our study). These differences could have an impact on outcomes because they involve prognostic factors. Regarding this, our study supports the notion that HR expression should still be considered a prognostic factor in HER2-positive BC (Fig 3).

Regarding metastatic BC, the median survival observed in our study was 25.1 months, similar to that reported for stage IV patients treated with trastuzumab in the pivotal study reported by Slamon et al.\(^1\) Comparable results were also reported in previous studies that evaluated the efficacy of trastuzumab in real-life advanced BC.\(^10,11\)

Likewise, our results confirm those reported by the few studies that have addressed the real-life outcome of patients with HER2-positive BC treated with trastuzumab, in both the adjuvant and\(^7,9\) the metastatic setting.\(^10-12\)

This real-life study has undeniable strengths including the high number of patients analyzed, the inclusion of patients in all age groups, and the long follow-up. Furthermore, the data were collected prospectively as the treating physicians requested the medication from the FNR, and the information available provided the main prognostic and predictive factors, such as disease stage, the number of positive lymph nodes, and the status of HRs. A limitation was that, in some cases, the clinical data requested, such as menopausal status, were not complete. Despite the active search to minimize missing data, and regular data monitoring to ensure adequate information, some data could not be retrieved for all patients, which is a limitation of our study.

Importantly, all data were verified by reviewing pathologic reports; HER2, ER and PR reports; and reports corresponding to the imaging studies of disease extension. With regard to the time it takes to authorize or deny trastuzumab applying the current FNR procedures (current median time = 7 days), we consider that it is provided in a timely manner, within an acceptable lapse of time.

---

**TABLE 2.** Baseline Characteristics of Patients With Advanced Breast Cancer (n = 319)

| Variable                                | No. | %   |
|-----------------------------------------|-----|-----|
| Median age, years                       | 54.6|     |
| Menopausal status                       |     |     |
| Premenopausal                           | 83  | 26.0|
| Postmenopausal                          | 201 | 63.0|
| Unknown                                 | 35  | 11  |
| Site of metastatic disease at diagnosis |     |     |
| Bone only                               | 172 | 53.9|
| Visceral                                | 123 | 38.5|
| Liver                                   | 36  | 11.2|
| CNS                                     | 2   | 0.6 |
| Lung/pleura                             | 56  | 17.5|
| Others                                  | 29  | 9.0 |
| Unknown                                 | 24  | 7.5 |
| Trastuzumab combination therapy with chemotherapy |     |     |
| Paclitaxel or docetaxel                 | 211 | 66.1|
| Vinorelbine                             | 41  | 12.8|
| Capecitabine                            | 22  | 6.9 |
| Gemcitabine                             | 29  | 9.0 |
| Others                                  | 2   | 0.6 |
| Unknown                                 | 14  | 4.3 |
| Hormone receptor status                 |     |     |
| ER negative and PR negative             | 90  | 28.2|
| ER negative or PR positive              | 188 | 58.9|
| Unknown                                 | 41  | 12.9|

Abbreviations: ER, estrogen receptor; PR progesterone receptor.
As far as we know, this is the first study in Uruguay and in Latin America to analyze the survival of a significant number of patients with HER2-positive BC treated with trastuzumab in clinical practice and with a long follow-up. The OS results for the Uruguayan patients with HER2-positive BC treated with trastuzumab under the FNR coverage regulations are comparable to those reported by the pivotal randomized clinical studies, in both the adjuvant and metastatic setting. Likewise, our results confirm those reported by the few studies that have addressed the real-life outcome of patients with HER2-positive BC treated with trastuzumab, both in the adjuvant and in the metastatic setting.

In addition, these results confirm the appropriate access to the other components of BC treatment (ie, surgery, radiotherapy, chemotherapy, and hormonotherapy) in our Integrated National Health System. The fact that no serious bureaucratic obstacles were found to be hindering or delaying the appropriate access to trastuzumab led us to conclude that the regulations and administrative procedures currently implemented are reasonable and effective. Importantly, the current study sheds light on the national outcomes of our patients with HER2-positive BC in real life; therefore, it provides useful information to decision makers in charge of deciding policies for the reimbursement of targeted therapies.

**AFFILIATIONS**

1. Department of Clinical Oncology, School of Medicine, University of Uruguay, Montevideo, Uruguay
2. Department of Quantitative Methods, School of Medicine, University of Uruguay, Montevideo, Uruguay
3. Fondo Nacional de Recursos, Montevideo, Uruguay
4. School of Medicine, University of Uruguay, Montevideo, Uruguay

**CORRESPONDING AUTHOR**

Natalia Camejo, MD, Avenida Italia s/n, (5982)4872075; e-mail: ncam3@yahoo.com.

---

**FIG 3.** Overall survival by biologic subtype for (A) stage I, (B) stage III, and (C) stage II disease. ER, estrogen receptor; PR progesterone receptor.
REFERENCES

1. Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783-792, 2001

2. Cameron D, Piccart-Gebhart MJ, Gelber RD, 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 389:1195-1205, 2017

3. Slamon D, Eiermann W, Robert N, et al: Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273-1283, 2011

4. Perez EA, Romond EH, Suman VJ, et al: Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: Joint analysis of data from NCCGT N9831 and NSABP B-31. J Clin Oncol 29:3366-3373, 2011

5. Rothwell PM: External validity of randomised controlled trials: "To whom do the results of this trial apply?". Lancet 365:82-93, 2005

6. Rothwell PM: Factors that can affect the external validity of randomised controlled trials. PLoS Clin Trials 1:e9, 2006

7. Solerina SC, Lobbezoo DJ, de Boer M, et al: Real-life use and effectiveness of adjuvant trastuzumab in early breast cancer patients: A study of the Southeast Netherlands Breast Cancer Consortium. Oncologist 20:856-863, 2015

8. Seal MD, Spears CH, O'Reilly S, et al: Outcomes of women with early-stage breast cancer receiving adjuvant trastuzumab. Curr Oncol 19:197-201, 2012

9. Bonifazi M, Franchi M, Rossi M, et al: Long-term survival of HER2-positive early breast cancer treated with trastuzumab-based adjuvant regimen: A large cohort study from clinical practice. Breast 23:573-578, 2014

10. Jackisch C, Schoenegg W, Reichert D, et al: Trastuzumab in advanced breast cancer—a decade of experience in Germany. BMC Cancer 14:924, 2014

11. Extra JM, Antoine EC, Vincent-Salomon A, et al: Efficacy of trastuzumab in routine clinical practice and after progression for metastatic breast cancer patients: The observational Hermine study. Oncologist 15:799-809, 2010

12. Daniels B, Kiely BE, Lord SJ, et al: Trastuzumab for metastatic breast cancer: Real world outcomes from an Australian whole-of-population cohort (2001-2016). Breast 38:7-13, 2018

13. Rossi M, Cario G, Bonifazi M, et al: Trastuzumab for HER2+ metastatic breast cancer in clinical practice: Cardiotoxicity and overall survival. Eur J Cancer 52:41-49, 2016

14. Uruguayan National Resource Fund. http://www.fnr.gub.uy

15. Uruguayan National Resource Fund. http://www.fnr.gub.uy/sites/default/files/normativas/medicamentos/n_trat_cannama.pdf

16. Wolf AC, Hammond MEH, Allison KH, et al: Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. J Clin Oncol 36:2105-2122, 2018

17. Vitr A, Mintzes B, Lipworth W: Access to new cancer medicines in Australia: Dispelling the myths and informing a public debate. J Pharm Policy Pract 9:13, 2016

18. Karikios DJ, Schofield D, Saikeld G, et al: Rising cost of anticancer drugs in Australia. Intern Med J 44:458-463, 2014

19. Hutchins LF, Unger JM, Crowley JJ, et al: Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 341:2061-2067, 1999

20. Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. Lancet 337:2152-2161, 2008

21. Golds S, Luke YK, Bland M: Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: Methodological overview. PLoS Med 8:e10001026, 2011

22. Coughlin SS: Social determinants of age-incidence curves of female breast cancer by hormone-receptor status. Cancer Causes Control 10:431-437, 1999

23. World Health Organization: World conference on social determinants of health: Case studies on social determinants of health. http://www.who.int/sdhconference/resources/case_studies/en/

24. Anderson WF, Chu KC, Chatterjee N, et al: Tumor variants by hormone receptor expression in white patients with node-negative breast cancer from the surveillance, epidemiology, and end results database. J Clin Oncol 19:18-27, 2001

25. Yasui Y, Potter JD: The shape of age-incidence curves of female breast cancer by hormone-receptor status. Cancer Causes Control 10:431-437, 1999

26. Caddeo KA, Forneris MN, Morris PG: Biological subtypes of breast cancer: Current concepts and implications for recurrence patterns. Q J Nucl Med Mol Imaging 57:312-321, 2013

AUTHOR CONTRIBUTIONS

Conception and design: Natalia Camejo, Cecilia Castillo, Lucia Delgado

Administrative support: Natalia Camejo, Cecilia Castillo, Lucia Delgado

Provision of study material or patients: All authors

Collection and assembly of data: Natalia Camejo, Cecilia Castillo, Agustin Rosich, Fiamma Della Casa, Luciana Silveira, Emiliano Rivero, Fernando Correa, Lucia Delgado

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rcw or ascopubs.org/go/site/misc/authors.html.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

ACKNOWLEDGMENT

We thank the treating oncologists who provided the requested data in the FNR forms and the FNR team for their assistance in preparing the anonymized database of the requested data for this study.