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An Economic and Regulatory Analysis of Breast Cancer Drugs Approved by the US Food and Drug Administration

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An Economic and Regulatory Analysis of Breast Cancer Drugs Approved by the US Food and Drug Administration

A Thesis by

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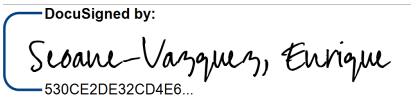

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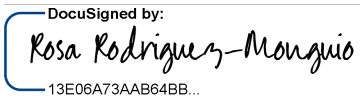

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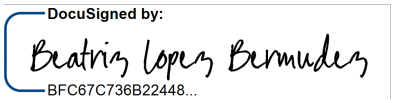

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ABSTRACT

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Introduction

Breast cancer is the most common cancer among women and the leading cause of cancer death among women worldwide. The pharmacological options for breast cancer include chemotherapy, hormone therapy, targeted therapy, and immunotherapy, which are used for the prevention or treatment of breast cancer. This study assessed trends in FDA approvals and prices at the market entry of new drugs indicated for breast cancer in the period 1980-2022. The study also evaluated the factors associated with the price of the new breast cancer drugs at market entry.

Material and Methods

Regulatory data were collected from the FDA website, and the wholesale acquisition cost (WAC) at market entry from the IBM Micromedex Redbook. We estimated the cost per year or per treatment as defined on the FDA-approved drug label. The WAC was adjusted to 2022 dollars using the consumer price index. Descriptive statistics and generalized linear model regression analysis were conducted.

Results

As of December 31, 2022, the FDA approved 30 drugs including 23 new molecular entities and 7 new biologics, with 60 indications for different stages of breast cancer and 71 indications for other diseases. The FDA approved 22 (75.9%) drugs using a priority review designation and 5 (17.2%) were granted orphan designation. The median of the inflation-adjusted WAC treatment cost at market entry was higher for drugs approved for advanced and metastatic stages of breast cancer (n=42, median=$88,019, interquartile range (IQR)=$148,969) than those approved for early stages of breast cancer (n=18, median=$51,150, IQR=$141,203).

The price of breast cancer drugs at market entry was positively associated with the stage of cancer (specifically, stage 4), approval date, priority review designation, and HER2-positive or TNBC breast cancer subtypes.

Conclusions

The FDA approved a large number of drugs indicated for the treatment of different types of breast cancer in the period 1980-2022. The CPI-adjusted WAC treatment cost at market entry significantly increased in the period of analysis. Drugs for advanced cancer states, priority review designation, and for specific cancer subtypes were associated with higher treatment cost.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

Abbreviation	Meaning
AIMA	Antineoplastics and Immunomodulating Agents
AWP	Average Wholesale Price
BLA	Biologic License Applications
CDC	Centers of Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CPI	Consumer Price Index
FDA	Food and Drug Administration
GDP	Gross Domestic Product
GLD	Generlized Linear Model
HER	Human Epidermal Growth Factor Receptor
HR	Hormone Receptor
IQR	Interqurtile Range
NMEs	New Molecular Entities
TNBC	Triple-Negative Breast Cancer
USD	United States Dollars
VIF	Variance Infaltion Factors
WAC	Wholesale Acquisition Cost
WHO	World Health Organization

1. Introduction

1.1 Breast Cancer

Breast cancer is the most common cancer among women and the second leading cause of cancer death among women in the United States [1]. According to the World Health Organization, there were 2.3 million new cases and 700,000 deaths caused by breast cancer in 2020 [2]. From 2015 to 2020, around 7.8 million women have been diagnosed with breast cancer. In the US in 2019, 264,121 new breast cancer cases were reported in females, and 42,280 females died from breast cancer. With an age-adjusted rate per 100,000 standard population of 130 new cases are 19 deaths. From 2015 to 2019, about 2 in 3 breast cancer cases were diagnosed at a localized stage, 1 in 4 at a regional stage, and (the cancer had spread to nearby lymph nodes, tissues, or organs), and 1 in 17 at a distant stage [3].

Breast cancer can be invasive or non-invasive, and there are several types of breast cancer, including ductal, lobular, or inflammatory breast cancer. The inflammatory carcinoma type is considered as the most aggressive. Additionally, there are also three subtypes of breast cancer that can help determine the best treatment plan: Hormone Receptor Positive (HR+), Human Epidermal Growth Factor Receptor 2 Positive (HER-2+), and Triple-Negative Breast Cancer (TNBC). The TNM system is commonly used to determine the stage of breast cancer, with T indicating the size of the tumor, N indicating if the cancer has spread to the lymph nodes, and M indicating the presence of metastasis [4,5].

1.2 FDA Approvals of Breast Cancer Drugs

There are several treatments available for breast cancer including surgery, radiation therapy, and drug therapy [6]. Drug therapy includes chemotherapy, hormone therapy, targeted therapy, and immunotherapy. Drug therapy is used for the prevention and treatment of breast cancer [7].

Breast cancer has received the highest number of FDA approvals among all solid tumors [8]. A recent study evaluated new breast cancer drugs approved in the US from 2010 to 2020 [9]. The study found that the FDA approved 22 (73.3%) new drugs using priority review designation, 7 (23.3%) breakthrough therapy designation and 7 (23.3%) accelerated approval. Other studies assessed FDA approvals of drugs for other cancers [10-12].

However, were could not identify any studies specifically assessing long-term trends in approvals of breast cancer drugs in the US.

1.3 Costs of Breast Cancer Drugs

There is extensive literature assessing the cost of cancer care in the |US [13-15], as well as international comparisons of the cost of cancer care [16]. Previous studies have evaluated the cost of breast cancer in the US. One of those studies found that the cost of breast cancer varied according to the tumor stage and type of services provided, with higher costs for treatment of advanced and metastatic compared to early stages of the disease [17,18]. Additionally, several studies have assessed the cost-effectiveness of drug therapies indicated for breast cancer [19-21]. Another study assessed patient out-of-pocket expenditures for breast cancer treatments [22]. However, studies assessing trends in the prices of new breast cancer drugs in the US are lacking.

2. Objectives and Hypothesis

2.1 Objectives

The aims of this study were:

1. to assess trends in FDA approvals and prices at the market entry of new drugs indicated for breast cancer in the period 1980-2022, and
2. to assess the factors associated with the price of new breast cancer drugs at market entry.

2.2 Hypothesis

We hypothesized that the FDA approvals and market entry prices of breast cancer drugs did not change during the study period.

3. Methods

3.1 Data Sources

Regulatory information for new drugs approved by the FDA for breast cancer from 1980 to 2022 was obtained from the FDA online databases: Approved Drug Products with Therapeutic Equivalence Evaluations, Drugs@FDA, and Purple Book [23-25]. We collected the wholesale acquisition cost (WAC) for the first effective date of each drug from the IBM Micromedex Redbook [26]. The WAC does not account for rebates and discounts provided by pharmaceutical companies to wholesalers, pharmacies, PBMs and other managed care organizations, hospitals, and other providers, third-party payers, and the public sector. However, it is often used as a proxy of the actual acquisition cost to estimate the reimbursement both private and public programs, particularly for new drugs at market entry [27]. The Gross Domestic Product (GDP) was collected from the Bureau of Economic Analysis [28].

We gathered the FDA-recommended dose for adult patients from FDA-approved labels at approval. The duration and number of cycles of the breast cancer treatment were obtained from the FDA-approved label. We estimated the duration of the treatment for drugs used as chronic or in cycles. For drugs for chronic use, we assumed a duration of one year converting the doses expressed in days, weeks, or other periods to the total dose per year. For drugs used in cycles, we multiplied the total dose per cycle by the total number of cycles.

The doses of drugs administered based on weight or body surface area were calculated using a value of 72 kg and an area of 1.9 m^2, respectively [29]. These values are known as the

"average" or "standard" values for weight and body surface area in adults, and they have been derived from population-based studies.

We estimated the cost per year or treatment by multiplying the total number of units per year or per treatment multiplied by the WAC per unit. Prices were converted to 2022 dollars using the not seasonally adjusted, all items in U.S. city average, all urban consumers, consumer price index (CPI) from the U.S. Bureau of Labor Statistics[30].

3.2 Data Analysis

We conducted a descriptive analysis of the variables included in the analysis. Subsequently, we used a generalized linear model (GLM) analysis to evaluate potential factors related to the price at the market entry of new breast cancer drugs. We use the GLM to account for non-constant variances and errors with non-normal distributions. Furthermore, GLM does not require a linear relationship between the dependent and independent variables. These variables examined included the approval date, pharmacological class line of therapy, patients' menopausal status, cancer type and subtype, cancer stage, combination therapy, FDA orphan designation, FDA priority review designation, and country of incorporation of the sponsor company.

In order to assess the robustness of the model, we conducted tests for multicollinearity among the independent variables in the GLM by calculating the variance inflation factor (VIF). Additionally, we assessed the goodness-of-fit of the model by calculating the null deviance and residual deviance values. These values allows us to determine the degree of improvement in model's performance (residual deviance) compared to a model that included only an intercept term (null deviance).

4. Results

4.1 Descriptive Analysis

The FDA approved new 286 antineoplastic and immunomodulating agents (AIMA) from 1980 to 2022, of which 30 (10.5%) were indicated for breast cancer. New breast cancer drug approvals included 23 (76.7%) new molecular entities (NME) and 7 (23.3%) biologic license applications (BLA). These drugs were approved for 60 breast cancer indications and 71 other indications. The percentage of BLA approvals was lower for breast cancer than for other AIMA drugs (Appendix Table 1A). The FDA approved 1 (7.7% of AIMA approvals) breast cancer drug in the 1980s, 10 (19.2%) in the 1990s, 5 (7.8%) in the 2000s, 11 (8.8%) in the 2010s, and 3 (6.7%) in 2020-2022. The FDA approved 22 (75.9%) of breast cancer drugs using priority review designation, and granted orphan designation to 5 (17.2%) breast cancer drugs. No breast cancer drugs were discontinued from the market during the study period.

Goserelin acetate (approved in 1989), the first breast cancer drug approved by FDA in the study period, had a CPI-Adjusted WAC treatment cost of $8,053 per year. Margetuximab-CMKB (approved in 2020), was the last breast cancer drug approved by the FDA during the study period, with a CPI-Adjusted WAC treatment cost of $174,584. The median (interquartile range, IQR) of the CPI-adjusted WAC treatment cost at market entry was $20,727 (IQR=$30,699) for the breast cancer drugs approved in the 1990s, $77,233 (IQR=$51,437) in the 2000s, $158,478 (IQR=$99,733) in the 2010s, and $260,314 (IQR=$74,525) in the period 2020-2022 (Figure 1.).

The highest cost for the adjusted WAC treatment cost at market entry was for pembrolizumab ($375,283), approved by FDA in 2014 for use in the metastatic stage, and the lowest was for raloxifene hydrochloride ($1,109), approved in 1997 for use in an early breast cancer stage. The median of the adjusted WAC treatment cost at the market entry for all breast cancer indications was higher for advanced and metastatic stages ($88,019, n=42, IQR=$148,969) than for drugs approved for early breast cancer stages ($51,150, n=18, IQR=$141,203).

Breast cancer drugs for FDA-approved indications for chronic use (more than one year) has a median CPI-adjusted WAC of $96,801 (n=53, IQR=$142,294). While, breast cancer drugs approved by for use in cycles (less than one year) had a cost of $24,179 (n=7, IQR=$98,966) (**Error! Reference source not found.**.

The median CPI-adjusted WAC at the market entry was higher for breast cancer drugs with injectable forms ($96,801, n=15, IQR=$142,294) than drugs with oral forms ($79,238, n=15, IQR=$150,879). Breast cancer drugs sponsored by US companies had a higher median treatment cost ($135,217, IQR=$134,821) than drugs sponsored by non-US companies ($40,939, IQR=$100,952).

Most drugs were approved for HR-positive cancer, with a median cost of $40,939 (n=33, IQR=120,323). Drugs used for HER2-positive ($154,749, n=17, IQR=79,447) and TNBC ($201,436, IQR=265,549) had higher cost (**Error! Reference source not found.**.

The majority of breast cancer drugs were approved as 1st and 2nd line of therapy with a median-adjusted WAC of 61,380 (n=17, IQR=$145,489) for first-line, $59,048 (n=15, IQR=$151,708) for second-line, 130,773 (n=9, IQR=81,276) for 3rd line, and $29,602 (n=2,

IQR=$21,549) for the drugs used as last line of therapy (Figure 2. Adjusted WAC treatment cost at market entry with Line of Therapy

Table 1. CPI-Adjusted WAC Treatment Cost at Market Entry of Breast Cancer Drugs Approved by the FDA, 1989-2022

Variable		Median treatment cost (2022)	IQR	MIN	MAX
All indications		$88,019	$145,015	$1,109	$375,283
Gene Type	**HR+**	$40,939	$120,323	$1,109	$233,951
	HER-2+	$154,749	$79,447	$56,265	$260,314
	TNBC	$201,436	$265,549	$46,275	$375,283
Used in Combination	**Yes**	$115,684	$136,882	$13,589	$375,283
	No	$40,939	$137,700	$1,109	$323,634
Route of administration	**Oral**	$79,238	$150,879	$1,109	$260,314
	Injectable	$96,801	$142,294	$8.053	$375,283
Orphan designation	**Yes**	$46,275	$236,135	$3,807	$375,283
	No	$96,801	$140,921	$1,109	$323,634
Priority review designation	**Yes**	$98,202	$138,748	$1,109	$375,283
	No	$8,053	$91,513	$3,491	$174,584
Chronic Use	**Yes**	$96,801	$142,294	$1,109	$375,283
	No	$24,179	$98,966	$13,589	$128,546
Country of incorporation (US)	**Yes**	$135,217	$134,821	$1,109	$375,283
	No	$40,939	$100,952	$3,491	$233,951
Application type	**NME**	$41,465	$114,489	$1,109	$260,314
	Biologic	$176,248	$99,678	$96,801	$375,283

IQR:Interquartile Range; HR+: Hormone Receptor Positive; HER-2+: Human Epidermal Growth Factor Receptor 2 Positive; TNBC: Triple-Negative Breast Cancer; NME: New Molecular Entity.

Figure 1. Trends in CPI-Adjusted WAC Treatment Cost at Market Entry of Breast Cancer Drugs Approved by the FDA, 1989-2022.

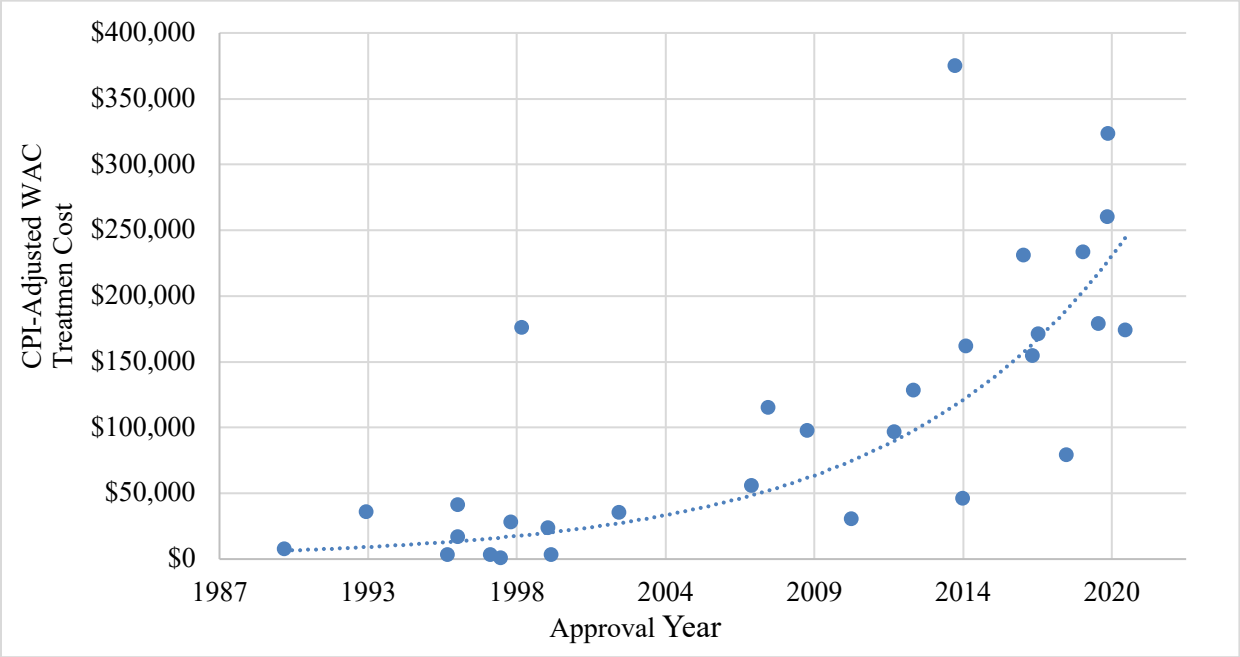
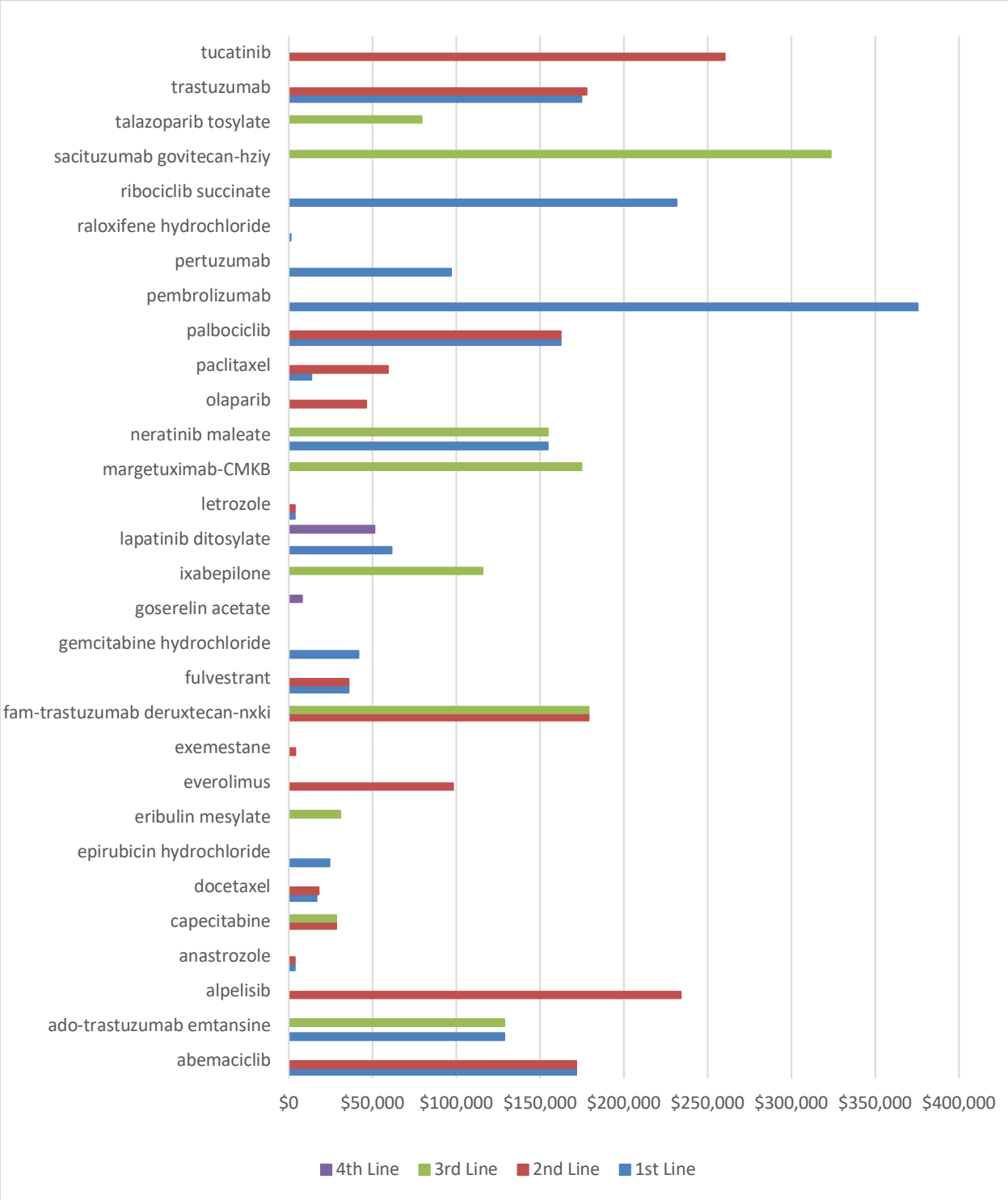


Figure 2. Adjusted WAC treatment cost at market entry with Line of Therapy



4.2 Generalized Linear Model

The generalized linear model included independent variables stage, approval date, use in combination, chronic use, orphan designation, priority review designation, and gene type. Those independent variables were not correlated (VIF<5) (Appendix 3A).

Table 2. Linear Mixed Model Regression Summary of Fixed Effects

Fixed effects		**Coeff**	**Std. Error**	**t value**
Intercept		2.032878**	0.057113	35.594
Stage (Ref =1)	**2**	0.0176	0.061358	0.284
	3	-0.026	0.046881	-0.555
	4	0.100274**	0.034883	2.875
Approval Date		0.006945**	0.00162	4.287
Used in Combination (Ref=No)		0.045635*	0.026633	1.713
Chronic Use (Ref=No)		-0.013259	0.040186	-0.33
Orphan designation (Ref=No)		-0.010513	0.035144	-0.299
Priority review designation (Ref=No)		0.071289**	0.31299	2.278
Gene Type	**HR-positive**	0.057271	0.043185	1.326
	HER2-positive	0.16572**	0.039353	4.211
	HR-positive and HER2-positive	0.043789	0.088836	0.493
	Triple-negative	0.236036**	0.076543	3.084
	HR-positive and triple-negative	0.075452*	0.037751	1.999
Null deviance: 1.39959 on 56 degrees of freedom Residual deviance: 0.29168 on 43 degrees of freedom (3 observations deleted due to missingness) AIC: 160.42; BIC: 191.06 RMSE: 2.37 Pseudo-R^2 0.7915964				

** p<0.05 and *p<0.10

The results of the generalized linear model (GLM) revealed that a drug indication for patients with stage 4 cancer was associated with a 10.0% increase in the treatment cost at market entry using stage 1 cancer as the reference category (

The R-squared value indicates that the independent variables included in the model explain 79.15% of the total variance in the treatment cost at market entry.

). The date of approval was associated with a significant increase in the treatment cost at market entry of 0.6% per year. The FDA priority review designation was significantly associated with a 7.1% increase in the treatment cost at market entry.

Gene HER-2 positive and TNBC drugs were associated with an increased in the treatment cost at the market entry of 16.6% and 23.6%, respectively. Additionally, drugs used in combination with other drugs were associated with a 4.6% increase in treatment cost, while drugs for gene HR-positive and Triple-negative breast cancer were associated with a 7.5% increase in treatment cost at market entry (

The R-squared value indicates that the independent variables included in the model explain 79.15% of the total variance in the treatment cost at market entry.

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5. Discussion

This study found that breast cancer drugs represented one in ten of the new antineoplastic and immunomodulating agents drugs approved by the FDA during 1989-2022. The price of breast cancer treatments increased exponentially during the study period and at a faster pace than the inflation. The prices at the market entry of drugs for breast cancer were positively associated with the disease stage, approval date, priority review designation, and HER-2 and TNBS genes.

Most new breast cancer indications were for advanced and metastatic stages, with approximately 70% of all breast cancer indications receiving such indications. Drugs for advanced and metastatic stages also had higher treatment costs than drugs for other disease stages. These findings confirm the results of a previous study that found that the cost of breast cancer varied according to the tumor stages and type of services providers, with a higher cost found for the treatment of advanced and metastatic stages [17].

Breast cancer drugs approved from 2020-2022 cost 13 times more than those approved in the 1990s. Previous studies have also pointed to the exponential increase in the prices of new drugs for cancer and other conditions [13,16,31].

Our study is the first to evaluate the factors associated with the increase in breast cancer drug prices. The observation that a treatment cost is associated with more advanced disease stages is congruent with the reduced patient population receiving pharmacological interventions for advanced and metastatic cancer, as opposed to treatments prescribed for initial disease stages. HER-2 positive and TNBC breast cancers may also have lower prevalence than other types of breast cancer[9].

Previous studies evaluated the cost of drugs and other healthcare expenditures related to the treatment of breast cancer. Those studies estimated the direct health care costs, with consideration of the sources of payment (private insurance, Medicare, Medicaid, out-of-pocket expenses, and other sources), type of service (ambulatory care, hospital inpatient care, prescription medications, and other services), and patient age group [13,14]. However, this study only considered the drug costs associated with the treatment of breast cancer.

A previous study found that the cost of new cancer drugs at market entry was increasing, despite the increase in the number of new drugs available for the treatment and prevention of breast cancer [31]. Pharmaceutical companies are able to increase drug prices due to monopoly granted by the patent and exclusivity system and the inelastic demand for new drugs. Additionally, the US government does not regulate drug prices, and the Medicare Prescription Drug Improvement and Modernization Act of 2003 specifically prohibits Medicare from directly negotiating prices with drug companies[32,33]. The lack of market competition for breast cancer drugs underscores the need for policies and regulations that promote competition and price control.

6. Limitations

This study assessed the costs of new breast cancer drugs but did not consider the benefits associated with their use. The cost and the effectiveness and safety of drugs must be considered together to appraise the value of new rugs treatments and facilitate the efficient use of available resources. The study only assessed the cost of the drugs and excluded the cost of other healthcare services and products. The study evaluated the prices at market entry and did not consider the increases in prices typically seen in the US healthcare system. The WAC does not account for rebates and discounts provided by pharmaceutical companies to wholesalers, pharmacies, PBMs and other managed care organizations, hospitals, and other providers, third-party payers, and the public sector but is one of the prices used as a proxy of the actual acquisition cost to estimate the reimbursement in private and public programs, particularly for new drugs at market entry.

7. Conclusions

During the period 1980-2022, the FDA approved 30 novel drugs and biologics for the treatment of breast cancer. The cost of treating breast cancer exhibited notable variation based on factors, such as gene type, disease stage, regulatory action by the FDA, route of administration, therapy line, country of incorporation, and date of approval. Moreover, the treatment cost of new drugs at market entry increase significantly over the study period.

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Appendix

Table 1A. Treatment Cost for New Breast Cancer Drugs at Market Entry, 1980-2022.

Drug Name	Approval Date	Breast Cancer Stage	Posology Type	Adjusted WAC Cost Per Year/Treatment at Market Entry
New Molecular Entities				
goserelin acetate	12/29/89	Advanced or Metastatic	Chronic	$8,053
paclitaxel	12/29/92	Early-Stage	Cycles	$13,589
		Advanced or Metastatic	Chronic	$59,048
anastrozole	12/27/95	Both	Chronic	$3,519
docetaxel	05/14/96	Early-Stage	Cycles	$16,718
		Advanced or Metastatic	Chronic	$17,833
gemcitabine HCL	05/15/96	Advanced or Metastatic	Chronic	$41,465
letrozole	07/25/97	Both	Chronic	$3,491
raloxifene HCL	12/9/97	Early-Stage	Chronic	$1,109
capecitabine	04/30/98	Advanced or Metastatic	Chronic	$28,204
epirubicin HCL	9/15/99	Early-Stage	Cycles	$24,179
exemestane	10/21/99	Both	Chronic	$3,807
fulvestrant	04/25/02	Advanced or Metastatic	Chronic	$35,603
lapatinib ditosylate	03/13/07	Advanced or Metastatic	Chronic	$61,380
ixabepilone	10/16/07	Advanced or Metastatic	Cycles	$115,684
everolimus	03/30/09	Advanced or Metastatic	Chronic	$98,202
eribulin mesylate	11/15/10	Advanced or Metastatic	Chronic	$30,641
olaparib	12/19/14	Both	Chronic	$46,275
palbociclib	02/3/15	Advanced or Metastatic	Chronic	$162,208
ribociclib succinate	03/13/17	Advanced or Metastatic	Chronic	$231,476
neratinib maleate	07/17/17	Both	Chronic	$154,749
abemaciclib	09/28/17	Both	Chronic	$171,561
talazoparib tosylate	10/16/18	Advanced or Metastatic	Chronic	$97,238
alpelisib	05/24/19	Advanced or Metastatic	Chronic	$233,951
tucatinib	04/17/20	Advanced or Metastatic	Chronic	$260,314

Table 1A (Continue). Treatment Cost for New Breast Cancer Drugs at Market Entry, 1980-2022

Biologics License Applications				
trastuzumab	09/25/98	Early-Stage	Chronic	$174,605
		Advanced or Metastatic	Chronic	$177,891
pertuzumab	06/8/12	Both	Chronic	$96,801
ado-trastuzumab emtansine	2/22/13	Both	Cycles	$128,546
pembrolizumab	09/4/14	Both	Chronic	$375,283
fam-trastuzumab deruxtecan	12/20/19	Advanced or Metastatic	Chronic	$179,032
sacituzumab govitecan	04/22/20	Advanced or Metastatic	Chronic	$323,634
margetuximab	12/16/20	Advanced or Metastatic	Chronic	$174,584

Table 2A: Correlation Matrix of the Data

	CPI-adjusted	Sage	Approval-date	Cmbination	Duration	Orphan	Priority	Gene
CPI-adjusted	1	0.31	0.73	0.46	0.01	0	0.53	0.27
Stage		1	0.14	0.31	-0.23	-0.2	0.18	0.04
Approval Date			1	0.24	0.16	0.12	0.34	0.39
Combination				1	-0.12	-0.04	0.32	0.21
Duration					1	-0.03	-0.21	0.23
Orphan						1	0.03	0
Priority							1	-0.05
Gene Type								1

Table 3A. Generalized Variance Inflation Factor

Factors	GVIF	Degree of freedom	Increased SE
stage	2.968931	3	1.198855
date	1.879687	1	1.371017
combination	1.507187	1	1.227675
chronic	1.233116	1	1.137152
orphan	1.131189	1	1.063574
priority	1.743141	1	1.32081
gene	3.912869	5	1.146171

Table 4A. Number of Indications for Breast Cancer Drugs Approved from 1980 to 2022

Drug Name	Approval Date	No. of Breast Cancer Indications	No. of Other Indications	Application Type
goserelin aetate	12/29/89	1	4	NDA
paclitaxel	12/29/92	2	4	NDA
anastrozole	12/27/95	3	0	NDA
docetaxel	5/14/96	2	6	NDA
gemcitabine HCL	5/15/96	1	3	NDA
letrozole	7/25/97	4	0	NDA
raloxifene HCL	12/9/97	2	1	NDA
capecitabine	4/30/98	2	2	NDA
trastuzumab	9/25/98	4	1	BLA
epirubicin HCL	9/15/99	1	0	NDA
exemestane	10/21/99	2	0	NDA
fulvestrant	4/25/02	4	0	NDA
lapatinib ditosylate	3/13/07	2	0	NDA
ixabepilone	10/16/07	2	0	NDA
everolimus	3/30/09	1	8	NDA
eribulin mesylate	11/15/10	1	1	NDA
pertuzumab	6/8/12	3	0	BLA
ado-trastuzumab emtansine	2/22/13	2	0	BLA
pembrolizumab	9/4/14	2	18	BLA
olaparib	12/19/14	2	5	NDA
palbociclib	2/3/15	2	0	NDA
ribociclib succinate	3/13/17	2	0	NDA
neratinib maleate	7/17/17	2	0	NDA
abemaciclib	9/28/17	4	0	NDA
talazoparib tosylate	10/16/18	1	0	NDA
alpelisib	5/24/19	1	0	NDA
fam-trastuzumab deruxtecan	12/20/19	2	2	BLA
tucatinib	4/17/20	1	0	NDA
sacituzumab ovitecan	4/22/20	1	1	BLA
margetuximab	12/16/20	1	0	BLA

Table 5A. Breast Cancer FDA Approved Indications from Approved Label, 1980 to 2022

Drug Name	FDA Approved Indications for Breast Cancer
goserelin aetate	For use in the palliative treatment of advanced breast cancer in pre-and perimenopausal women.
paclitaxel	1-Adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.
	2- Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.
anastrozole	1- Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer.
	2-First-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer.
	3- Second-Line Treatment for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.
docetaxel	1- As a single agent, for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy.
	2-In combination with doxorubicin and cyclophosphamide is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.
gemcitabine HCL	In combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.
letrozole	1-Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer.
	2- Extended adjuvant treatment of early breast cancer in postmenopausal women, who have received 5 years of adjuvant tamoxifen therapy.
	3- First-line treatment of postmenopausal women with hormone receptor positive or unknown, locally advanced or metastatic breast cancer.
	4- Treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.
raloxifene HCL	1-Reduction in the Risk of Invasive Breast Cancer in Postmenopausal Women at High Risk of Invasive Breast Cancer.
	2-Reduction in the Risk of Invasive Breast Cancer in Postmenopausal Women with Osteoporosis.
capecitabine	1-Treatment of patients with advanced or metastatic breast cancer as a single agent if an anthracycline- or taxane-containing chemotherapy is not indicated.
	2-Treatment of patients with advanced or metastatic breast cancer in combination with docetaxel after disease progression on prior anthracycline-containing chemotherapy.

Table 5A (Continue). Breast Cancer FDA Approved Indications from Approved Label, 1980 to 2022

trastuzumab	1-Adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel or as part of a treatment regimen with docetaxel and carboplatin.
	2-Adjuvant treatment of HER2 overexpressing node positive or node negative ER/PR negative or with one high risk feature breast cancer as a single agent following multi-modality anthracycline based therapy.
	3-As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.
	4-In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer.
epirubicin HCL	As a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer.
exemestane	1-Adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy.
	2-Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.
fulvestrant	1-Treatment of Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.
	2-Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
	3-Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.
	4-Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib as initial endocrine based therapy or following disease progression on endocrine therapy.

Table 5A (Continue). Breast Cancer FDA Approved Indications from Approved Label 1980 to 2022

lapatinib ditosylate	1-In combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy, including an anthracycline, a taxane, and trastuzumab.
	2-In combination with letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.
ixabepilone	1-As a single agent for the treatment of patients with metastatic or locally advanced breast cancer whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.
	2-In combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.
everolimus	Treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.
eribulin mesylate	Treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease.
pertuzumab	1-In combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.
	2-In combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.
	3-In combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
ado-trastuzumab emtansine	1-Adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.
	2-HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: received prior therapy for metastatic disease, or developed disease recurrence during or within six months of completing adjuvant therapy.
pembrolizumab	1-Triple-negative breast cancer, High-risk early-stage, in combination with chemotherapy as neoadjuvant treatment, then continued as a single agent as adjuvant treatment after surgery.
	2-Triple-negative breast cancer, Locally recurrent unresectable or metastatic disease whose tumors express PD-L1, in combination with chemotherapy

Table 5A (Continue). Breast Cancer FDA Approved Indications from Approved Label 1980 to 2022

olaparib	1-Adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm human epidermal growth factor receptor 2 (HER2)- negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy.
	2-Treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer, who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.
palbociclib	1-Treatment of adult patients with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men.
	2-Treatment of adult patients with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy.
ribociclib succinate	1-Metastatic or advanced, HER-2 negative, HR-positive disease in postmenopausal women or men, in combination with fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy.
	2- Metastatic or advanced, HER-2 negative, hormone receptor-positive, in combination with an aromatase inhibitor as initial endocrine-based treatment.
neratinib maleate	1-As a single agent, for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.
	2-In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens.

Table 5A (Continue). Breast Cancer FDA Approved Indications from Approved Label 1980 to 2022

abemaciclib	1-As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.
	2-In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women, and men, with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
	3-In combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence.
	4-In combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
talazoparib tosylate	Treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.
alpelisib	In combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.
fam-trastuzumab deruxtecan	1-Treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
	2-Treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either: in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
tucatinib	In combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti- HER2-based regimens in the metastatic setting.

Table 5A (Continue). Breast Cancer FDA Approved Indications from Approved Label 1980 to 2022

sacituzumab ovitecan	Treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.
margetuximab	In combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Table 6A. Indications for Breast Cancer Drugs Approved from 1980 to 2022

Drug Name	Approval Date	Route	Country of Incorporation	Application Type	Used in Combination	Line of Therapy	Posology Type	Gene Type	Stage	Adjusted WAC
goserelin aetate	12/29/89	Inj	UK	NDA	No	1st	Chronic	HR+	4	$8053
paclitaxel	12/29/92	Inj	US	NDA	Yes	1st	Cycles	HR+	4	$13,589
					Both	2nd	Chronic	HER2+		$59,048
anastrozole	12/27/95	Oral	UK	NDA	No	1st-2nd	Chronic	HR+	1&3	$3,519
docetaxel	5/14/96	Inj	France	NDA	Yes	1st	Cycles	HR+	4	$16,718
						2nd	Chronic	NA		$17,833
gemcitabine HCL	5/15/96	Inj	US	NDA	Yes	1st	Chronic	NA	4	$41,465
letrozole	7/25/97	Oral	Switzerland	NDA	No	1st-2nd	Chronic	HR+	1&3	$3,491
raloxifene HCL	12/9/97	Oral	US	NDA	No	1st	Chronic	HR+	1	$1,109
capecitabine	4/30/98	Oral	Switzerland	NDA	Both	2nd-3rd	Chronic	NA	4	$28,204
trastuzumab	9/25/98	Inj	US	BLA	Both	1st-2nd	Chronic	HER2+	1	$174,605
									4	$177,891
epirubicin HCL	9/15/99	Inj	US	NDA	Yes	1st	Cycles	NA	2	$24,179
exemestane	10/21/99	Oral	US	NDA	No	2nd	Chronic	HR+	1&4	$3,807
fulvestrant	4/25/02	Inj	UK	NDA	Both	1st-2nd	Chronic	HR+	4	$35,603
lapatinib ditosylate	3/13/07	Oral	UK	NDA	Yes	4th	Chronic	HER2+	4	$51,150
						1st	Chronic	HER2+ & HR+	4	$61,380
ixabepilone	10/16/07	Inj	US	NDA	Both	3rd	Cycles	HR+	4	$115,684
everolimus	3/30/09	Oral	Switzerland	NDA	Yes	2nd	Chronic	HR+	4	$98,202

Table 6A (Continue). Indications for Breast Cancer Drugs Approved from 1980 to 2022

eribulin mesylate	11/15/10	Inj	Japan	NDA	No	3rd	Chronic	NA	4	$30,641
pertuzumab	6/8/12	Inj	US	BLA	Yes	1st	Chronic	HER2+	2&4	$96,801
ado-trastuzumab	2/22/13	Inj	France	BLA	No	1st-3rd	Chronic	HER2+	2&4	$128,546
pembrolizumab	9/4/14	Inj	US	BLA	Yes	1st-3rd	Chronic	TNBC	2&4	$375,283
olaparib	12/19/14	Oral	UK	NDA	No	2nd	Chronic	HR+ & TNBC	1&4	$46,275
palbociclib	2/3/15	Oral	US	NDA	Yes	1st-2nd	Chronic	HR+	4	$162,208
ribociclib	3/13/17	Oral	Switzerland	NDA	Yes	1st	Chronic	HR+	4	$231,476
neratinib maleate	7/17/17	Oral	US	NDA	Both	1st-3rd	Chronic	HER2+	1&4	$154,749
abemaciclib	9/28/17	Oral	US	NDA	Both	1st-2nd	Chronic	HR+	2&4	$171,561
talazoparib	10/16/18	Oral	US	NDA	No	3rd	Chronic	TNBC	4	$97,238
alpelisib	5/24/19	Oral	Switzerland	NDA	Yes	2nd	Chronic	HR+	4	$233,951
fam-trastuzumab	12/20/19	Inj	Japan	BLA	No	2nd-3rd	Chronic	HER2+	4	$179,032
tucatinib	4/17/20	Oral	US	NDA	Yes	2nd	Chronic	HER2+	4	$260,314
sacituzumab	4/22/20	Inj	US	BLA	No	3rd	Chronic	TNBC	4	$323,634
margetuximab	12/16/20	Inj	US	BLA	Yes	3rd	Chronic	HER2+	4	$174,584