BMJ Open

# Longitudinal Trends in Use and Costs of Targeted Therapies for Common Cancers in Taiwan

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2016-011322 |
| Article Type: | Research |
| Date Submitted by the Author: | 29-Jan-2016 |
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| Primary Subject Heading: | Health services research |
| Secondary Subject Heading: | Oncology, Pharmacology and therapeutics, Health economics, Health policy |
| Keywords: | Cancer, Targeted therapies, Taiwan, Drug costs |
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# Title Page

## Longitudinal Trends in Use and Costs of Targeted Therapies for Common Cancers in Taiwan

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**Abstract**

**Objectives:** Use of targeted therapies has improved survival and quality of cancer care globally, but these innovative and expensive drugs have led to increases in pharmaceutical expenditures. This study examined trends in use and expenditures of antineoplastic agents in Taiwan and estimated market shares by prescription volume and costs of targeted therapies overtime. We also determined which cancer types accounted for the highest use of targeted therapies.

**Design:** Retrospective observational study focusing on the utilization of targeted therapies for treatment of cancer.

**Setting:** The monthly claims data for antineoplastic agents were retrieved from Taiwan's National Health Insurance Research Database (2009-2012).

**Main outcome measures:** We calculated market shares by prescription volume and costs for each class of antineoplastic agents by cancer type. Using a time series design with ARIMA models, we estimated trends in use and costs of targeted therapies.

**Results:** Among all antineoplastic agents, use of targeted therapies grew from 6.24% in 2009 to 12.29% in 2012, but their costs rose from 26.16% to 41.57%. Monoclonal antibodies and protein kinase inhibitors contributed the most (23.84% and 16.12% of costs for antineoplastic agents in 2012). During 2009-2012, lung (44.64% of use; 28.26% of costs), female breast (16.49% of use; 27.18% of costs) and colorectal (12.11% of use; 13.16% of costs) cancers accounted for the highest use of targeted therapies.

**Conclusions:** Targeted therapies are increasingly used for different cancers in Taiwan, representing substantial economic burden. It is important to establish mechanisms to monitor their use and outcomes.

**Keywords:** Cancer, Targeted therapies, Taiwan, Drug costs
**Running title:** Trends of Cancer Targeted Therapies in Taiwan

- **Strengths and limitations of this study**
  - This is the first study that examined the national trend in use and costs of targeted therapies for treatment of cancer in Taiwan.
  - We also determined which cancer types accounted for the highest use of targeted therapies in Taiwan from 2009 to 2012.
  - Data were retrieved from Taiwan's National Health Insurance Research Database with nearly 99% of the Taiwanese population (around 23 million residents) enrolled and 97% of hospitals and clinics throughout the country.
  - A time series design with ARIMA models was used in this study to estimate the trends in market shares by prescription volume and costs of targeted therapies.
  - Due to the lack of patient-level data, this study did not investigate the use of combination treatments which need to be examined in future studies.

| **What is already known on this topic** |
|---|
| ■ Cancer is a major public health issue globally. Approximately 7.4 million people die of cancer each year worldwide, which accounts for 13% of all-cause mortality and this percentage is expected to increase. |
| ■ Previous studies have examined the incidence of cancers, and the trend of incidence over time in Taiwan, little is known about the utilization and economic impacts of targeted cancer therapies in Taiwan. |
| **What this study adds** |
| ■ This study examined the current trends in use and expenditures of antineoplastic agents for treatment of all malignancies in Taiwan from 2009 to 2012. |
| ■ Percent market share of targeted therapies among all cancer medications grew from 6.24% to 12.29% between 2009 and 2012 but they accounted for 41.57% of costs for cancer medications by 2012. |
| ■ Lung cancer, female breast cancer and colorectal cancer accounted for the highest use of targeted therapies in Taiwan. This trend is likely to continue. |

# Manuscript

# Longitudinal Trends in Use and Costs of Targeted Therapies for Common Cancers in Taiwan

## Introduction

Cancer is a major public health issue globally. Approximately 7.4 million people die of cancer each year worldwide, which accounts for 13% of all-cause mortality and this percentage is expected to increase.[1,2] In Taiwan, cancer is a leading cause of mortality and the annual number of cancer patients has been growing.[3] In 2011, approximately 92,682 individuals were diagnosed with cancer (male: 56%, female: 44%). Most common cancers in Taiwan were female breast cancer, colorectal cancer, liver cancer, lung cancer and prostate cancer. In the same year, approximately 42,559 patients died of cancer (male: 64%, female: 36%), accounting for 28% of all deaths. Major cancers causing mortality were lung cancer, liver cancer, colorectal cancer, female breast cancer and oral/pharyngeal cancer.[3]

Cancer care has improved substantially and the average life expectancy has increased in the past two decades due to advances in medical technologies and clinical management. Traditionally, chemotherapies are the main treatments for cancer. But these drugs are not specific to the target, and therefore often cause serious adverse effects including neutropenia, anemia and thrombocytopenia.[4] In the past decade, however, many new anti-cancer drugs, so called targeted therapies, have become available. These drugs target specific vulnerable nodes in molecular pathways; thus, they have demonstrated high treatment response rates,[5,6] including survival gains compared to treatment with chemotherapy alone, but less toxic than traditional chemotherapies.[7] For some cancers, targeted therapies are becoming the main treatments, for example, trastuzumab for early-stage and metastatic (HER2 positive) breast cancer.[8,9] Dozens of targeted therapies have become available in the recent years and many are in drug development pipeline.[10]

Changes in the cancer treatment paradigm are accompanied by significant economic consequences. Targeted therapies are expensive, typically costing over $5000 per patient per treatment month.[11-13] Because of their much higher cost than conventional chemotherapy, while the number of eligible patients (due to molecular sub-typing) is generally small, in aggregate their costs is an important contributor of growing expenditures for cancer treatments.[14,15] Due to limited financial resources, patient access to targeted therapies has been a struggle issue in many countries.[16] Many countries have different ways to curb the growth of pharmaceutical expenditures in general. Examples include formal health technology assessment and pricing tools such as reference pricing,[17] while high patient cost-sharing (co-payments, coinsurance) are commonly applied by most private health insurance plans in the US to reach the similar objective.[18] A major challenge is to determine what proportion of the government's health care budget should be allocated for treatment of cancer, including budget for targeted therapies.

Little is known about the utilization and economic impacts of targeted cancer therapies in Taiwan. Our longitudinal analyses aim to address this gap by examining the recent trend in

utilization and expenditures of cancer treatments, including targeted therapies, in Taiwan from 2009 to 2012. We also identified which types of cancer accounted for the highest use of targeted therapies.

## Method

### *Data sources*

Taiwan's National Health Insurance Research Database provided data for this study. The database contains information from a nationwide, mandatory-enrollment and single-payer healthcare system created in 1995. Nearly 99% of the Taiwanese population (around 23 million residents) is enrolled and this system contracts with 97% of hospitals and clinics throughout the country.[19] The National Health Insurance (NHI) covers a wide range of prescription medicines, and inpatient and outpatient medical services.[20] All monthly claims data, including details of prescription and insurer spending, for antineoplastic agents between 2009 and 2012 were retrieved from Taiwan's National Health Insurance Research Database. The cancer related prescriptions were identified by International Classification of Diseases, 9th edition (ICD-9) diagnosis codes for cancer (codes: 140-239).

### *Drugs of interest*

We used the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization. We identified all antineoplastic agents using ATC codes "L01". Antineoplastic agents were grouped into 6 classes based on the ATC system: (1) targeted therapies, including monoclonal antibodies (rituximab, trastuzumab, cetuximab), protein kinase inhibitors (imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib), and bortezomib; these have been used for the treatment of cancer in Taiwan; (2) alkylating agents (including nitrogen mustard analogues, alkyl sulfonates, nitrosoureas and other alkylating agents); (3) antimetabolites (including folic acid analogues, purine analogues and pyrimidine analogues); (4) plant alkaloids and other natural products (including vinca alkaloids and analogues, podophyllotoxin derivatives and taxanes); (5) cytotoxic antibiotics and related substances (including actinomycines, anthracyclines and related substances and other cytotoxic antibiotics); and (6) other antineoplastic agents (including platinum compounds, sensitizers used in photodynamic/radiation therapy, and other antineoplastic agents).

### *Measurements*

To examine trends in use and costs of each class of antineoplastic agents (including targeted therapies), we calculated quarterly and yearly number of prescriptions and costs from 2009 to 2012. Then, for each class we calculated the proportion of its use and costs among total use and total costs of all antineoplastic agents. For example, market share by prescription volume for targeted therapies was estimated by: number of prescriptions for targeted therapies divided by total number of prescriptions for all antineoplastic agents; and the market share by costs was estimated by: costs of targeted therapies divided by total costs of all antineoplastic agents.

To understand which cancers accounted for high use of targeted therapies, we first selected the most 20 common types of cancer based on their quantitative use of targeted therapies in Taiwan, and we used their total prescription volume and total costs for targeted therapies as the denominator and analyzed the indication of their use by 20 common types of cancer (see appendix).

***Statistical Analysis***

To estimate the trends in market shares by prescription volume and costs of targeted therapies among all antineoplastic agents, we used a time series design with the Autoregressive integrated moving average (ARIMA) model, which was developed by Box and Jenkins.[21] The model is generally referred to as an ARIMA(p,d,q) model where parameters p, d, and q are non-negative integers that refer to the order of the autoregressive, integrated, and moving average parts of the model respectively. These models are fitted to time series data either to better understand the data or to determine points in the series.[22] All analyses were carried out with SAS software, Version 9.3 (SAS Institute, Cary, NC).

## Results

Between 2009 and 2012, prescriptions for antineoplastic agents grew 31.51% (an average rate of 10.5% increase per year) (Table 1). By class, prescriptions for alkylating agents, antimetabolites, plant alkaloids and cytotoxic antibiotics increased in number during this period, but their market shares decreased slightly: -0.67%, -2.22%, -1.43%, -1.51% respectively. However, the market share of targeted therapies grew from 6.24% in 2009 to 12.29% in 2012. Specifically, market shares of monoclonal antibodies and protein kinase inhibitors doubled, from 2.75% to 5.79% and from 3.38% to 6.18%, respectively.

[Table 1]

Table 2 presents the market share by costs for all and each type of antineoplastic drugs between 2009 and 2012. There was a large growth in total costs of antineoplastic agents from 2009 to 2012 (an overall increase of 50.67%, an average rate of 16.89% increase per year). By class, the yearly market share by costs for alkylating agents, antimetabolites, plant alkaloids and cytotoxic antibiotics reduced by 0.60%, 1.93%, 4.49%, 1.81% from 2009 to 2012. However, annual costs of targeted therapies grew from US$129 million (26.16% of all costs for antineoplastic agents) in 2009 to US$308 million (41.57%) in 2012. Specifically, the market share by costs for monoclonal antibodies and protein kinase inhibitors increased from 14.63% to 23.84% and from 10.71% to 16.12%, respectively.

[Table 2]

The quarterly market share by prescription volume of targeted therapies rose from 6.05% in the first quarter of 2009 to 12.74% in the fourth quarter of 2012 (Table 3). Figure 1A shows the trend in market share by prescription volume for targeted therapies during the study period. On the other hand, the quarterly market share by costs for targeted therapies grew from 25.53% in the first quarter of 2009 to 43.56% in the fourth quarter of 2012. Figure 1B shows the trend in market share by costs for targeted therapies during the study period.

[Table 3] [Figure 1]

Figure 2 presents the distribution ratios of targeted therapies use for 20 cancers during 2009-2012. Table 4 shows the yearly distribution ratios of targeted therapies use by cancer type over time. Our results showed that the number of prescriptions and costs for targeted therapies differed substantially between different types of cancer. During 2009-2012, targeted therapies were mostly used for cancers of lung, female breast, colorectal, lymphoma and leukemia in order of volume. These 5 cancer types accounted for 44.64%, 16.49%, 12.11%, 12.09% and 3.17% of prescriptions for targeted therapies (together 88.5%); and 28.26%, 27.18%, 13.16%, 10.23% and 4.94% of costs for targeted therapies (together 83.77%) among these 20 common cancer types.

[Figure 2] [Table 4]

## Discussion

This is the first study that examined the national trend in use and costs of targeted therapies for treatment of cancer in Taiwan. Our findings indicated that, compared with other classes of antineoplastic drugs, use of targeted therapies, novel agents for cancer treatment, increased substantially and is causing great economic burden in Taiwan. Between 2009 and 2012, use and costs of targeted therapies increased almost 3-folds (Tables 1 and 2). In 2012, targeted therapies accounted for only 12.29% of the antineoplastic agents market, but they accounted for 42% of costs. Monoclonal antibodies and protein kinase inhibitors contributed the most (23.84% and 16.12% of costs for antineoplastic agents). This trend is likely to continue in the future. In terms of types of cancer, the top three types – cancers of lung, female breast and colorectal – accounted for the most use of targeted therapies.

The availability and increasing use of innovative but expensive targeted therapies are major drivers of increases in pharmaceutical expenditures.[14,15] Targeted therapies also dominate cancer drug expenditures in other countries, for example, 63% of all cancer drug expenditures in 2011 in the commercially insured population in the US.[23] In response to high prices and rising pharmaceutical expenditures of cancer drugs and prescription drugs in general, many countries have implemented various policies. For instance, economic evaluation of new drugs is required by many payers/policy makers such as the National Institute for Health Care Excellence in the United Kingdom,[24,25] Pharmaceutical Benefits Advisory Committee in Australia[26,27] and others in Europe[28] to select drugs for coverage.

The high cost of targeted therapies is a barrier to access targeted therapies for treatment of cancer.[16] It is important to ensure patient access to effective targeted therapies without overspending the health care budget given their clinical benefits. Use of targeted therapies or combination therapy involving targeted therapies (e.g., targeted therapies together with chemotherapy agents, radiation and/or surgery) have been confirmed to have improved effectiveness of cancer treatment, quality of cancer care[1], less toxicity and adverse effects,[7] and survival, compared with only using traditional chemotherapy agents. However, at the time of product launch, many cancer drugs lack acceptable cost-effectiveness evidence. To deal with their high costs and imperfect evidence at the time of marketing approval, many countries increasingly adopt patient access schemes (also known as managed entry

agreements or risk-sharing arrangements) to enable patient access to needed medicines but ensuring that financing systems are sustainable; the performance of managed entry agreements, however, is largely unknown because most have not been evaluated.[17] In Taiwan, economic evaluation is also part of health technology assessment to evaluate new drugs to determine decisions for coverage by the National Health Insurance since 2007.[29,30] In addition, various types of restrictions (eg. prior authorizations) have been applied for many high-cost targeted therapies for cancer.[31] How these restrictions impact cancer care and outcomes should be studied. A major challenge for the future might be to determine the proportion of health care budget should be allocated to treatment of cancer, as well as the proportion of the budget for targeted therapies. This requires open, ongoing dialogue between policy makers, industry, clinicians, patients, and the general public.

There are some limitations to this study. First, this study aimed to examine recent trends in drug utilization and expenditures for cancer treatment and to estimate the market shares by prescription volume and costs for targeted therapies in Taiwan. We used aggregate data and did not analyze patient-level data to understand the influence of patient characteristics on treatment selection and clinical outcomes of treatments. This study also did not examine the complex patterns of drug use, such as use of combination treatments, targeted therapy adherence and persistence, again because of the lack of patient-level data. This study examined economic burden of targeted therapies from the perspective of the health care system; we did not examine patient contribution to drug costs in Taiwan, which warrants a separate study. Further, we did not characterize changes in the policy environment in Taiwan during the study period and how they might have influenced use of targeted therapies over time. Examples include the launch of new, competing targeted therapies, publication of large randomized clinical trials results, changes in clinical guidelines or reimbursement policies, and patient and provider factors (e.g. patient clinical history, physician's knowledge and preference); these need to be examined in future studies.

## Conclusion

Targeted therapies have played an increasing and more important role in treatment of all malignancies in Taiwan, and they are likely to pose substantial economic burden in the future. Cancers of lung, female breast and colorectal were identified as main drivers of use and costs of targeted therapies in recent years. Policy makers, industry, clinicians and patients need to communicate and develop strategies to enable access to effective (and cost-effective) targeted therapies without overspending the health care budget.

## Author Contributions

JCH designed the study, collected data, performed analysis, and drafted the manuscript. CYL reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

## Competing Interests

The authors have no competing interests.

## Funding

This study received no sponsorship for this work.

## Data Sharing Statement

We obtained nationwide, monthly claims data for cancer related antineoplastic agents between 2009 and 2012 from the Taiwan National Health Insurance Research database. Use of the NHIRD for research purpose is exempt from IRB review in Taiwan. The authors have no additional data to share.

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**Tables**



**Figures**

## Table 1. Prescription volume of antineoplastic agents in Taiwan (2009-2012)

| Drug Class | Drug name for patients with cancer | Number of Prescription (market share by prescription volume) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2009 | | 2010 | | 2011 | | 2012 | | 2009-2012 | |
| | | N | (%) | N | (%) | N | (%) | N | (%) | growth rate of N (%) | growth rate of market share (%) |
| **All Antineoplastic Agents** | | 1,893,439 | 100 | 2,033,160 | 100 | 2,300,629 | 100 | 2,489,973 | 100 | 31.51 | |
| **Targeted Therapies** | | 118,186 | 6.24 | 150,401 | 7.40 | 209,030 | 9.09 | 306,140 | 12.29 | 159.03 | 6.05 |
| Monoclonal antibodies | rituximab, trastuzumab, cetuximab, bevacizumab | 52,073 | 2.75 | 68,595 | 3.37 | 102,074 | 4.44 | 144,234 | 5.79 | 176.98 | 3.04 |
| Protein kinase inhibitors | imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib | 63,936 | 3.38 | 78,675 | 3.87 | 102,435 | 4.45 | 153,764 | 6.18 | 140.50 | 2.80 |
| Other targeted therapy agents | bortezomib | 2,177 | 0.11 | 3,131 | 0.15 | 4,521 | 0.20 | 8,142 | 0.33 | 274.00 | 0.21 |
| **Alkylating Agents** | | 125,811 | 6.64 | 132,109 | 6.50 | 147,076 | 6.39 | 148,654 | 5.97 | 18.16 | -0.67 |
| Nitrogen mustard analogues | cyclophosphamide, chlorambucil, melphalan, ifosfamide, bendamustine | 112,602 | 5.95 | 117,101 | 5.76 | 125,769 | 5.47 | 130,042 | 5.22 | 15.49 | -0.72 |
| Alkyl sulfonates | busulfan | 301 | 0.02 | 279 | 0.01 | 318 | 0.01 | 255 | 0.01 | -15.28 | -0.01 |
| Nitrosoureas | carmustine | 250 | 0.01 | 218 | 0.01 | 263 | 0.01 | 321 | 0.01 | 28.40 | 0.00 |
| Other alkylating agents | temozolomide, dacarbazine | 12,658 | 0.67 | 14,511 | 0.71 | 20,726 | 0.90 | 18,036 | 0.72 | 42.49 | 0.06 |
| **Antimetabolites** | | 911,611 | 48.15 | 965,096 | 47.47 | 1,076,871 | 46.81 | 1,143,596 | 45.93 | 25.45 | -2.22 |
| Folic acid analogues | methotrexate, pemetrexed | 316,174 | 16.70 | 349,463 | 17.19 | 386,008 | 16.78 | 426,480 | 17.13 | 34.89 | 0.43 |
| Purine analogues | mercaptopurine, cladribine, fludarabine | 12,550 | 0.66 | 12,094 | 0.59 | 12,277 | 0.53 | 12,891 | 0.52 | 2.72 | -0.15 |
| Pyrimidine analogues | cytarabine, fluorouracil, tegafur, gemcitabine, capecitabine, tegafur combinations | 582,887 | 30.78 | 603,539 | 29.68 | 678,586 | 29.50 | 704,225 | 28.28 | 20.82 | -2.50 |
| **Plant Alkaloids and other Natural Products** | | 217,347 | 11.48 | 222,304 | 10.93 | 250,312 | 10.88 | 250,273 | 10.05 | 15.15 | -1.43 |
| Vinca alkaloids and analogues | vinblastine, vincristine, vinorelbine | 84,009 | 4.44 | 85,659 | 4.21 | 88,135 | 3.83 | 88,377 | 3.55 | 5.20 | -0.89 |
| Podophyllotoxin derivatives | etoposide | 28,864 | 1.52 | 30,188 | 1.48 | 32,990 | 1.43 | 34,587 | 1.39 | 19.83 | -0.14 |
| Taxanes | paclitaxel, docetaxel | 104,474 | 5.52 | 106,457 | 5.24 | 129,187 | 5.62 | 127,309 | 5.11 | 21.86 | -0.40 |
| **Cytotoxic Antibiotics and Related Substances** | | 140,168 | 7.40 | 140,697 | 6.92 | 145,663 | 6.33 | 146,796 | 5.90 | 4.73 | -1.51 |
| Actinomycines | dactinomycin | 616 | 0.03 | 698 | 0.03 | 667 | 0.03 | 761 | 0.03 | 23.54 | 0.00 |
| Anthracyclines and related substances | doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone | 99,422 | 5.25 | 101,826 | 5.01 | 107,177 | 4.66 | 106,499 | 4.28 | 7.12 | -0.97 |
| Other cytotoxic antibiotics | bleomycin, mitomycin | 40,130 | 2.12 | 38,173 | 1.88 | 37,819 | 1.64 | 39,536 | 1.59 | -1.48 | -0.53 |
| **Other non-Targeted Therapies** | | 380,316 | 20.09 | 422,553 | 20.78 | 471,677 | 20.50 | 494,514 | 19.86 | 30.03 | -0.23 |
| Platinum compounds | cisplatin, carboplatin, oxaliplatin | 254,636 | 13.45 | 286,260 | 14.08 | 304,437 | 13.23 | 306,659 | 12.32 | 20.43 | -1.13 |
| Sensitizers used in photodynamic / radiation therapy | verteporfin | 120 | 0.01 | 88 | 0.00 | 88 | 0.00 | 95 | 0.00 | -20.83 | 0.00 |
| Others | asparaginase, hydroxycarbamide, estramustine, tretinoin, topotecan, irinotecan, mitotane, arsenic trioxide | 125,560 | 6.63 | 136,205 | 6.70 | 167,152 | 7.27 | 187,760 | 7.54 | 49.54 | 0.91 |

## Table 2. Costs of antineoplastic agents in Taiwan (2009-2012)

| Drug Class | Drug name for patients with cancer | Cost (market share by costs) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2009 | | 2010 | | 2011 | | 2012 | | 2009-2012 | |
| | | Cost (US$) | (%) | Cost (US$) | (%) | Cost (US$) | (%) | Cost (US$) | (%) | growth rate of N | growth rate of market share |
| **All Antineoplastic Agents** | | 491,387,822 | 100 | 570,369,759 | 100 | 660,138,086 | 100 | 740,386,783 | 100 | 50.67 | |
| **Targeted Therapies** | | 128,541,502 | 26.16 | 177,668,722 | 31.15 | 224,327,855 | 33.98 | 307,754,974 | 41.57 | 139.42 | 15.41 |
| Monoclonal antibodies | rituximab, trastuzumab, cetuximab, bevacizumab | 71,869,602 | 14.63 | 104,739,673 | 18.36 | 137,951,386 | 20.90 | 176,477,405 | 23.84 | 145.55 | 9.21 |
| Protein kinase inhibitors | imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib | 52,651,186 | 10.71 | 67,484,747 | 11.83 | 79,001,874 | 11.97 | 119,383,796 | 16.12 | 126.74 | 5.41 |
| Other targeted therapy agents | bortezomib | 4,020,714 | 0.82 | 5,444,303 | 0.95 | 7,374,595 | 1.12 | 11,893,774 | 1.61 | 195.81 | 0.79 |
| **Alkylating Agents** | | 15,551,932 | 3.16 | 17,481,103 | 3.06 | 18,968,906 | 2.87 | 18,999,092 | 2.57 | 22.17 | -0.60 |
| Nitrogen mustard analogues | cyclophosphamide, chlorambucil, melphalan, ifosfamide, bendamustine | 4,495,217 | 0.91 | 4,897,936 | 0.86 | 4,878,608 | 0.74 | 4,261,046 | 0.58 | -5.21 | -0.34 |
| Alkyl sulfonates | busulfan | 374,465 | 0.08 | 454,805 | 0.08 | 460,163 | 0.07 | 488,410 | 0.07 | 30.43 | -0.01 |
| Nitrosoureas | carmustine | 41,620 | 0.01 | 43,440 | 0.01 | 153,101 | 0.02 | 392,128 | 0.05 | 842.16 | 0.04 |
| Other alkylating agents | temozolomide, dacarbazine | 10,640,629 | 2.17 | 12,084,922 | 2.12 | 13,477,034 | 2.04 | 13,857,508 | 1.87 | 30.23 | -0.29 |
| **Antimetabolites** | | 96,951,076 | 19.73 | 117,122,829 | 20.53 | 128,199,087 | 19.42 | 131,805,930 | 17.80 | 35.95 | -1.93 |
| Folic acid analogues | methotrexate, pemetrexed | 31,305,924 | 6.37 | 50,705,521 | 8.89 | 61,101,669 | 9.26 | 66,069,402 | 8.92 | 111.04 | 2.55 |
| Purine analogues | mercaptopurine, cladribine, fludarabine | 304,010 | 0.06 | 265,754 | 0.05 | 365,404 | 0.06 | 311,619 | 0.04 | 2.50 | -0.02 |
| Pyrimidine analogues | cytarabine, fluorouracil, tegafur, gemcitabine, capecitabine, tegafur_combinations | 65,341,142 | 13.30 | 66,151,554 | 11.60 | 66,732,014 | 10.11 | 65,424,909 | 8.84 | 0.13 | -4.46 |
| **Plant Alkaloids and other Natural Products** | | 79,509,189 | 16.18 | 72,920,907 | 12.78 | 84,694,476 | 12.83 | 86,583,703 | 11.69 | 8.90 | -4.49 |
| Vinca alkaloids and analogues | vinblastine, vincristine, vinorelbine | 20,326,687 | 4.14 | 22,006,619 | 3.86 | 23,924,553 | 3.62 | 25,170,345 | 3.40 | 23.83 | -0.74 |
| Podophyllotoxin derivatives | etoposide | 2,164,352 | 0.44 | 1,643,415 | 0.29 | 1,651,811 | 0.25 | 1,579,203 | 0.21 | -27.04 | -0.23 |
| Taxanes | paclitaxel, docetaxel | 57,018,150 | 11.60 | 49,270,873 | 8.64 | 59,118,111 | 8.96 | 59,834,155 | 8.08 | 4.94 | -3.52 |
| **Cytotoxic Antibiotics and Related Substances** | | 26,190,529 | 5.33 | 26,232,768 | 4.60 | 27,270,661 | 4.13 | 26,075,058 | 3.52 | -0.44 | -1.81 |
| Actinomycines | dactinomycin | 16,854 | 0.00 | 18,603 | 0.00 | 18,303 | 0.00 | 19,062 | 0.00 | 13.10 | 0.00 |
| Anthracyclines and related substances | doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone | 24,489,365 | 4.98 | 24,531,634 | 4.30 | 25,576,627 | 3.87 | 24,215,313 | 3.27 | -1.12 | -1.71 |
| Other cytotoxic antibiotics | bleomycin, mitomycin | 1,684,311 | 0.34 | 1,682,531 | 0.29 | 1,675,731 | 0.25 | 1,840,682 | 0.25 | 9.28 | -0.09 |
| **Other non-Targeted Therapies** | | 144,643,593 | 29.44 | 158,943,430 | 27.87 | 176,677,101 | 26.76 | 169,168,026 | 22.85 | 16.96 | -6.59 |
| Platinum compounds | cisplatin, carboplatin, oxaliplatin | 50,363,294 | 10.25 | 53,988,423 | 9.47 | 52,077,277 | 7.89 | 35,697,261 | 4.82 | -29.12 | -5.43 |
| Sensitizers used in photodynamic / radiation therapy | verteporfin | 169,600 | 0.03 | 124,373 | 0.02 | 124,373 | 0.02 | 134,267 | 0.02 | -20.83 | -0.02 |
| Others | asparaginase, hydroxycarbamide, estramustine, tretinoin, topotecan, irinotecan, mitotane, arsenic trioxide | 94,110,699 | 19.15 | 104,830,634 | 18.38 | 124,475,451 | 18.86 | 133,336,498 | 18.01 | 41.68 | -1.14 |

**Table 3. 2009-2012 trend in market shares by prescription volume and costs for targeted therapies in Taiwan**

| | Market share by prescription volume | | Market share by costs | |
|---|---|---|---|---|
| Time | Real value | Trend (ARIMA) | Real value | Trend (ARIMA) |
| 2009Q1 | 6.05% | | 25.53% | |
| 2009Q2 | 6.10% | 6.48% | 25.48% | 26.70% |
| 2009Q3 | 6.19% | 6.40% | 25.70% | 26.21% |
| 2009Q4 | 6.60% | 6.59% | 27.83% | 26.85% |
| 2010Q1 | 7.09% | 7.20% | 29.72% | 30.25% |
| 2010Q2 | 7.34% | 7.52% | 31.06% | 31.04% |
| 2010Q3 | 7.54% | 7.83% | 31.88% | 31.83% |
| 2010Q4 | 7.59% | 8.12% | 31.72% | 33.18% |
| 2011Q1 | 7.53% | 8.01% | 31.51% | 32.21% |
| 2011Q2 | 7.68% | 7.85% | 31.30% | 32.47% |
| 2011Q3 | 9.86% | 8.25% | 34.81% | 32.86% |
| 2011Q4 | 10.98% | 11.12% | 37.58% | 37.68% |
| 2012Q1 | 11.61% | 11.42% | 39.93% | 39.59% |
| 2012Q2 | 11.92% | 11.75% | 40.28% | 40.05% |
| 2012Q3 | 12.87% | 12.75% | 42.21% | 41.26% |
| 2012Q4 | 12.74% | 12.66% | 43.56% | 42.74% |

Notes:

Market share by prescription volume (%) = number of prescriptions for targeted therapies / total number of prescriptions for all antineoplastic agents

Market share by costs (%) = costs of targeted therapies / total costs of all antineoplastic agents

**Table 4. Use and costs of targeted therapies by cancer type over time**

| Cancer type | | Distribution ratio based on prescription volume (%) | | | | | | Distribution ratio of costs (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2009 | 2010 | 2011 | 2012 | 2009-2012 overall | 2009-2012 Growth rate | 2009 | 2010 | 2011 | 2012 | 2009-2012 overall | 2009-2012 Growth rate |
| 01 | Lung | 51.87 | 45.94 | 43.03 | 42.18 | 44.64 | -9.68 | 39.55 | 28.79 | 25.48 | 25.24 | 28.26 | -14.32 |
| 02 | Female breast | 11.71 | 18.62 | 18.47 | 15.95 | 16.49 | 4.24 | 20.91 | 31.45 | 30.60 | 24.78 | 27.18 | 3.87 |
| 03 | Colorectal | 9.52 | 7.01 | 12.32 | 15.62 | 12.11 | 6.10 | 12.12 | 8.65 | 13.13 | 16.29 | 13.16 | 4.16 |
| 04 | Lymphoma | 17.87 | 14.92 | 11.84 | 8.50 | 12.09 | -9.37 | 15.24 | 11.63 | 9.96 | 7.49 | 10.23 | -7.74 |
| 05 | Liver | 0.24 | 0.23 | 0.28 | 3.93 | 1.66 | 3.69 | 0.25 | 0.22 | 0.28 | 5.65 | 2.22 | 5.40 |
| 06 | Leukemia | 1.75 | 2.81 | 3.66 | 3.57 | 3.17 | 1.83 | 2.50 | 4.80 | 5.60 | 5.56 | 4.94 | 3.06 |
| 07 | Urinary | 0.43 | 2.70 | 3.01 | 2.82 | 2.48 | 2.39 | 0.52 | 4.53 | 5.25 | 4.95 | 4.26 | 4.43 |
| 08 | Multiple myeloma | 1.92 | 2.11 | 2.39 | 3.07 | 2.52 | 1.15 | 3.37 | 3.19 | 3.60 | 4.45 | 3.79 | 1.08 |
| 09 | Oral/pharyngeal | 1.58 | 2.40 | 2.01 | 1.48 | 1.82 | -0.10 | 1.59 | 2.43 | 2.03 | 1.57 | 1.88 | -0.03 |
| 10 | Stomach | 0.97 | 0.77 | 0.62 | 0.58 | 0.69 | -0.39 | 1.28 | 1.14 | 1.04 | 0.93 | 1.06 | -0.35 |
| 11 | Brain | 0.34 | 0.24 | 0.27 | 0.48 | 0.36 | 0.14 | 0.27 | 0.18 | 0.17 | 0.60 | 0.34 | 0.33 |
| 12 | Small intestine and duodenum | 0.43 | 0.51 | 0.43 | 0.34 | 0.41 | -0.09 | 0.80 | 0.99 | 0.90 | 0.74 | 0.85 | -0.06 |
| 13 | Bone | 0.45 | 0.48 | 0.44 | 0.33 | 0.41 | -0.12 | 0.65 | 0.74 | 0.80 | 0.57 | 0.68 | -0.08 |
| 14 | Thyroid | 0.15 | 0.13 | 0.22 | 0.22 | 0.19 | 0.07 | 0.20 | 0.14 | 0.20 | 0.20 | 0.19 | 0.00 |
| 15 | Prostate | 0.18 | 0.23 | 0.19 | 0.22 | 0.20 | 0.04 | 0.16 | 0.27 | 0.18 | 0.22 | 0.21 | 0.06 |
| 16 | Larynx | 0.24 | 0.48 | 0.41 | 0.26 | 0.34 | 0.02 | 0.26 | 0.47 | 0.41 | 0.27 | 0.35 | 0.01 |
| 17 | Pancreas | 0.01 | 0.02 | 0.10 | 0.14 | 0.09 | 0.13 | 0.01 | 0.02 | 0.06 | 0.20 | 0.10 | 0.19 |
| 18 | Cervix | 0.16 | 0.20 | 0.14 | 0.11 | 0.14 | -0.05 | 0.16 | 0.17 | 0.13 | 0.10 | 0.13 | -0.05 |
| 19 | Esophagus | 0.09 | 0.12 | 0.13 | 0.09 | 0.11 | 0.01 | 0.07 | 0.12 | 0.13 | 0.10 | 0.11 | 0.03 |
| 20 | Ovary | 0.10 | 0.08 | 0.05 | 0.10 | 0.08 | 0.00 | 0.09 | 0.08 | 0.05 | 0.08 | 0.07 | -0.01 |
| | Total | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | |

**Appendix**

ICD-9-CM diagnosis code identifying patients with various types of cancer:

| | Types of cancer in this study | ICD-9 codes |
|---|---|---|
| 1 | Lung (including trachea. bronchus and lung) | 162 |
| 2 | Female breast | 174 |
| 3 | Colorectal (including colon, rectum, rectosigmoid junction and anus) | 153-154 |
| 4 | Lymphoma (including lymphosarcoma, eticulosarcoma and Hodgkin's disease) | 200-202 |
| 5 | Liver (including liver and intrahepatic bile ducts) | 155 |
| 6 | Leukemia (including lymphoid, myeloid monocytic and other specific leukemia) | 204-208 |
| 7 | Urinary (including bladder, kidney and other and unspecified urinary organs) | 188-189 |
| 8 | Multiple myeloma (including multiple myeloma and immunoproliferative neoplasms) | 203 |
| 9 | Oral/pharyngeal (including lip, tongue, major salivary glands, gum, floor of mouth, other and unspecified parts of mouth, oropharynx, nasopharynx, hypopharynx and others) | 140-149 |
| 10 | Stomach | 151 |
| 11 | Brain | 191 |
| 12 | Small intestine and duodenum | 152 |
| 13 | Bone (including bone, articular cartilage, connective and other soft tissue) | 170-171 |
| 14 | Thyroid | 193 |
| 15 | Prostate | 185 |
| 16 | Larynx | 161 |
| 17 | Pancreas | 157 |
| 18 | Cervix | 180 |
| 19 | Esophagus | 150 |
| 20 | Ovary (including ovary and other uterine adnexa) | 183 |

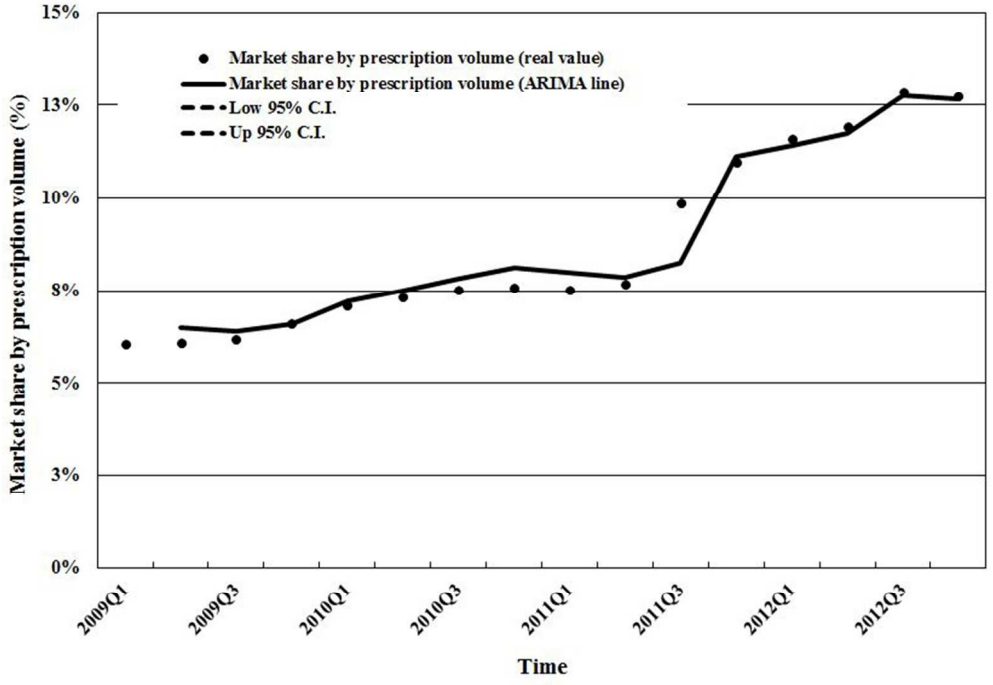



Figure 1. 2009-2012 trends in market shares by prescription volume (A) and costs (B) for targeted therapies
146x102mm (144 x 144 DPI)

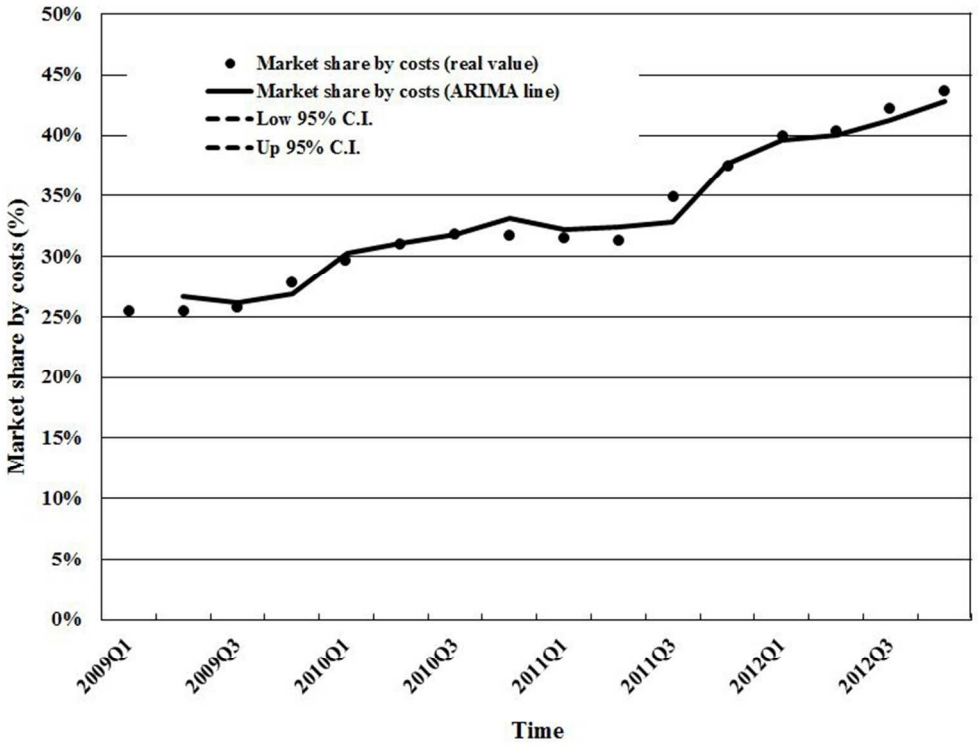



Figure 1. 2009-2012 trends in market shares by prescription volume (A) and costs (B) for targeted therapies
142x108mm (144 x 144 DPI)

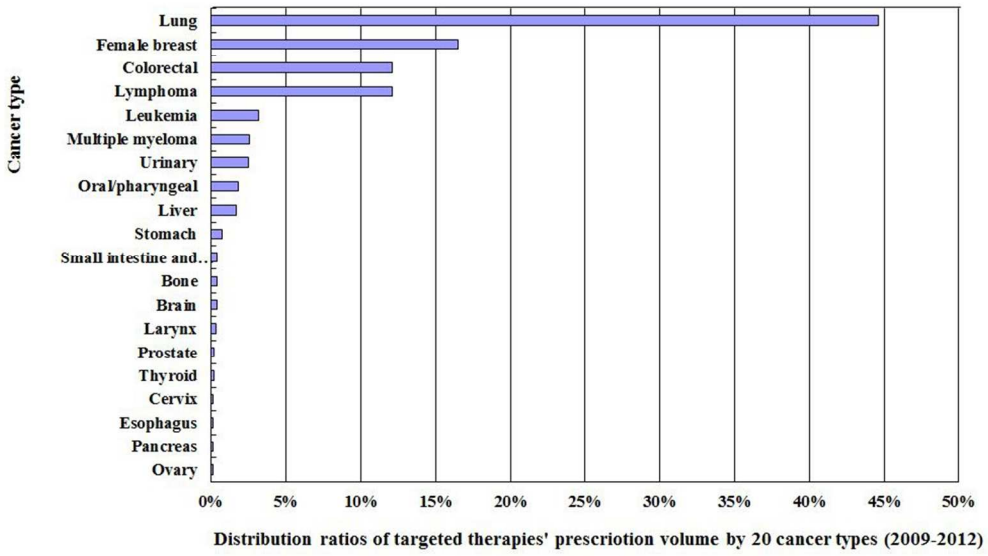



Figure 2. Use (A) and costs (B) of targeted therapies by 20 cancer type (2009-2012)
174x104mm (144 x 144 DPI)

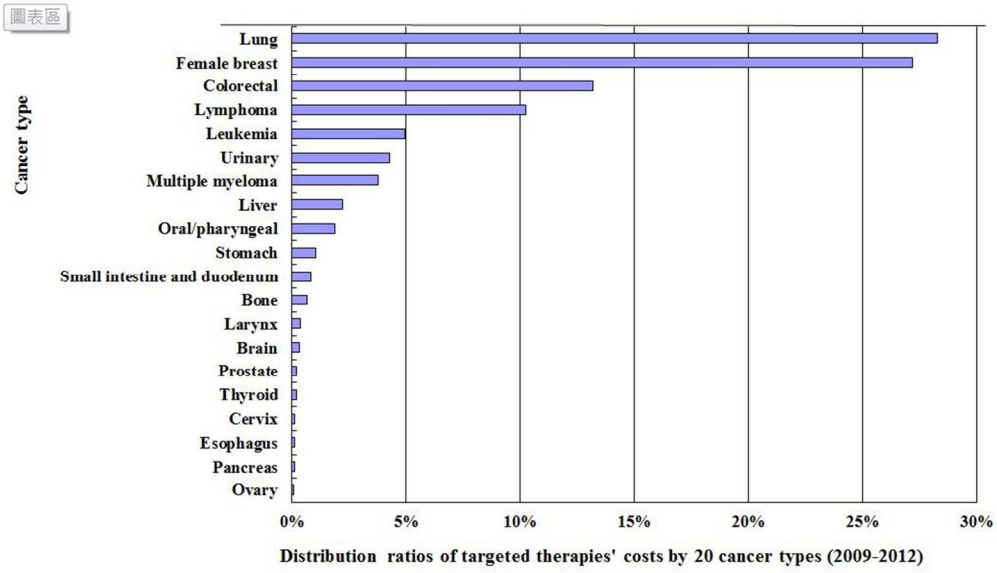
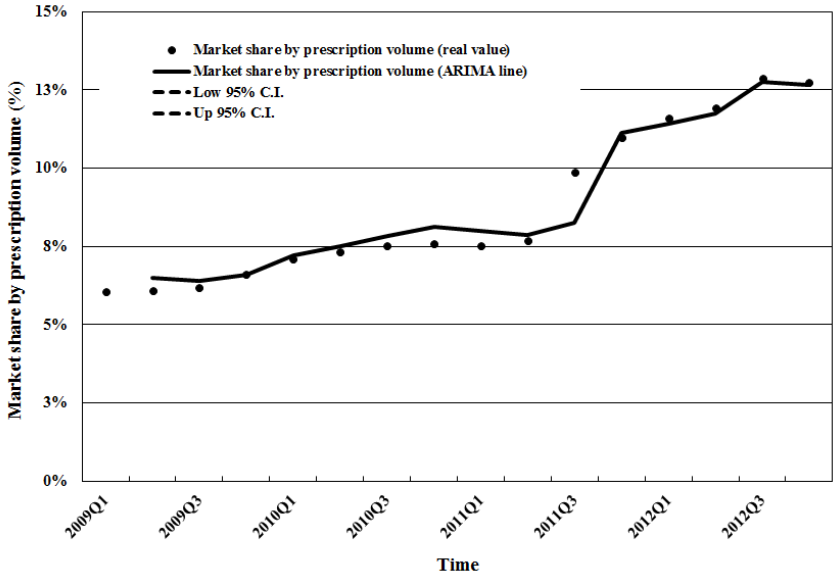



Figure 2. Use (A) and costs (B) of targeted therapies by 20 cancer type (2009-2012)
184x110mm (144 x 144 DPI)

# Figures

## A. Market share by prescription volume




## B. Market share by costs

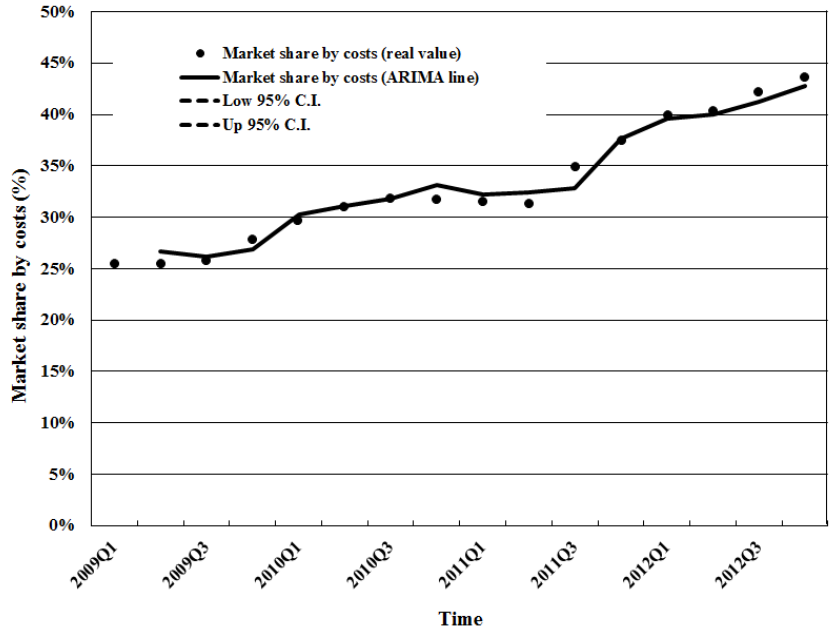
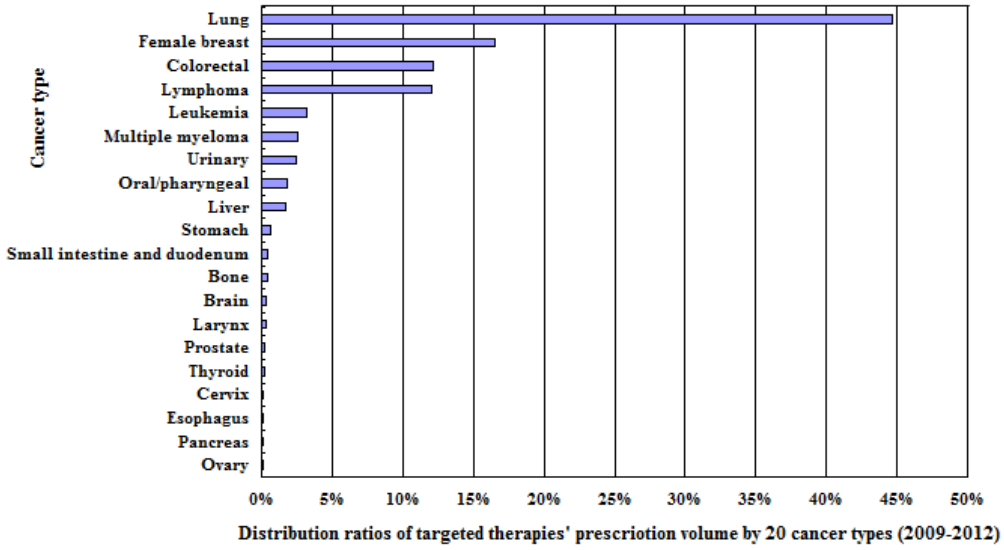



**Figure 1. 2009-2012 trends of market share by prescription volume and costs for targeted therapies**

* Market share by prescription volume (%) = number of prescriptions for targeted therapies / total number of prescriptions for all antineoplastic agents

* Market share by costs (%) = costs of targeted therapies / total costs of all antineoplastic agents

**A. Distribution ratios of prescription volume for targeted therapies by cancer type**




**B. Distribution ratios of costs for targeted therapies by cancer type**

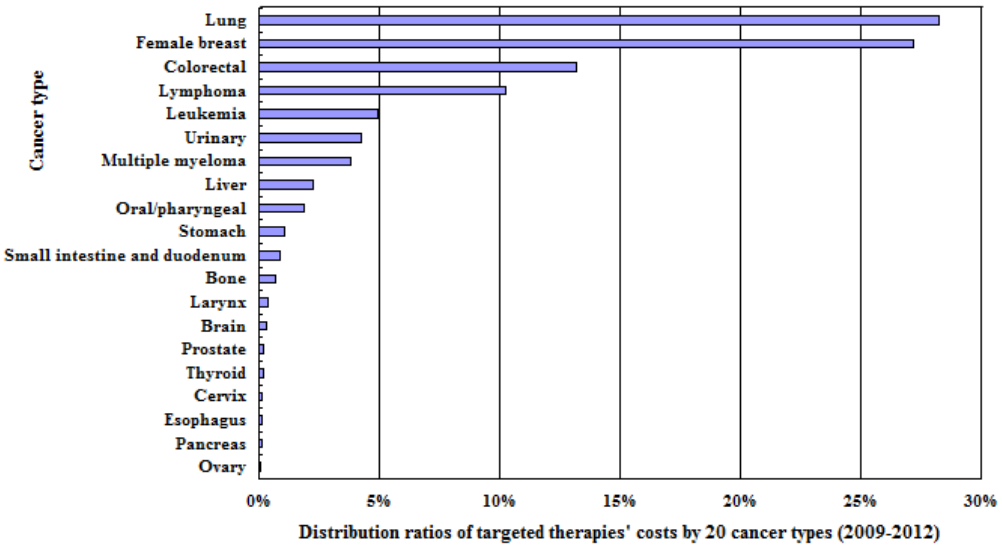



**Figure 2. Use (A) and costs (B) of targeted therapies by 20 cancer type (2009-2012)**

STROBE Statement—checklist of items that should be included in reports of observational studies

| Page | | Item No | Recommendation |
|---|---|---|---|
| 1 | **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| 1-2 | | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| | **Introduction** | | |
| 3 | Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| 3 | Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| | **Methods** | | |
| 4 | Study design | 4 | Present key elements of study design early in the paper |
| 4 | Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| 4 | Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| 4 | | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| 4 | Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| 4 | Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| 4 | Bias | 9 | Describe any efforts to address potential sources of bias |
| 4 | Study size | 10 | Explain how the study size was arrived at |
| 4 | Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| 5 | Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| 4-5 | | | (*b*) Describe any methods used to examine subgroups and interactions |
| NA | | | (*c*) Explain how missing data were addressed |
| NA | | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| NA | | | (*e*) Describe any sensitivity analyses |

Continued on next page

| | | | |
|---|---|---|---|
| Page | **Results** | | |
| NA | Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| NA | | | (b) Give reasons for non-participation at each stage |
| NA | | | (c) Consider use of a flow diagram |
| 11-14 | Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| NA | | | (b) Indicate number of participants with missing data for each variable of interest |
| NA | | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| NA | Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| NA | | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| NA | | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| 5-6; 11-14 | Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| 5-6 | | | (*b*) Report category boundaries when continuous variables were categorized |
| NA | | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| 5-6; 11-14 | Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| | **Discussion** | | |
| 6-7 | Key results | 18 | Summarise key results with reference to study objectives |
| 7 | Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| 6-7 | Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| 6-7 | Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| | **Other information** | | |
| No funding | Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Longitudinal Trends in Use and Costs of Targeted Therapies for Common Cancers in Taiwan: A Retrospective Observational Study



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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2016-011322.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 19-Apr-2016 |
| Complete List of Authors: | Hsu, Jason C.; National Cheng Kung University, School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine<br>Lu, Christine Y.; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine |
| Primary Subject Heading: | Health services research |
| Secondary Subject Heading: | Oncology, Pharmacology and therapeutics, Health economics, Health policy |
| Keywords: | Cancer, Targeted therapies, Taiwan, Drug costs |
| | |

# Title Page

# Longitudinal Trends in Use and Costs of Targeted Therapies for Common Cancers in Taiwan: A Retrospective Observational Study

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## Abstract

**Objectives:** Use of targeted therapies has improved survival and quality of cancer care globally, but these innovative and expensive drugs have led to increases in pharmaceutical expenditures. This study examined trends in use and expenditures of antineoplastic agents in Taiwan and estimated market shares by prescription volume and costs of targeted therapies overtime. We also determined which cancer types accounted for the highest use of targeted therapies.

**Design:** Retrospective observational study focusing on the utilization of targeted therapies for treatment of cancer.

**Setting:** The monthly claims data for antineoplastic agents were retrieved from Taiwan's National Health Insurance Research Database (2009-2012).

**Main outcome measures:** We calculated market shares by prescription volume and costs for each class of antineoplastic agents by cancer type. Using a time series design with ARIMA models, we estimated trends in use and costs of targeted therapies.

**Results:** Among all antineoplastic agents, use of targeted therapies grew from 6.24% in 2009 to 12.29% in 2012, but their costs rose from 26.16% to 41.57%. Monoclonal antibodies and protein kinase inhibitors contributed the most (23.84% and 16.12% of costs for antineoplastic agents in 2012). During 2009-2012, lung (44.64% of use; 28.26% of costs), female breast (16.49% of use; 27.18% of costs) and colorectal (12.11% of use; 13.16% of costs) cancers accounted for the highest use of targeted therapies.

**Conclusions:** Targeted therapies are increasingly used for different cancers in Taiwan, representing substantial economic burden. It is important to establish mechanisms to monitor their use and outcomes.

**Keywords:** Cancer, Targeted therapies, Taiwan, Drug costs
**Running title:** Trends of Cancer Targeted Therapies in Taiwan

## Strengths and limitations of this study

- This is the first study that examined the national trend in use and costs of targeted therapies for treatment of cancer in Taiwan.
- We also determined which cancer types accounted for the highest use of targeted therapies in Taiwan from 2009 to 2012.
- Data were retrieved from Taiwan's National Health Insurance Research Database with nearly 99% of the Taiwanese population (around 23 million residents) enrolled and 97% of hospitals and clinics throughout the country.
- A time series design with ARIMA models was used in this study to estimate the trends in market shares by prescription volume and costs of targeted therapies.
- Due to the lack of patient-level data, this study did not investigate the use of combination treatments which need to be examined in future studies.

**Manuscript**

# Longitudinal Trends in Use and Costs of Targeted Therapies for Common Cancers in Taiwan: A Retrospective Observational Study

## Introduction

Cancer is a major public health issue globally. Approximately 7.4 million people die of cancer each year worldwide, which accounts for 13% of all-cause mortality and this percentage is expected to increase.[1,2] In Taiwan, cancer is a leading cause of mortality and the annual number of cancer patients has been growing.[3] In 2011, approximately 92,682 individuals were diagnosed with cancer (male: 56%, female: 44%). Most common cancers in Taiwan were female breast cancer, colorectal cancer, liver cancer, lung cancer and prostate cancer. In the same year, approximately 42,559 patients died of cancer (male: 64%, female: 36%), accounting for 28% of all deaths. Major cancers causing mortality were lung cancer, liver cancer, colorectal cancer, female breast cancer and oral/pharyngeal cancer.[3]

Cancer care has improved substantially and the average life expectancy has increased in the past two decades due to preventative strategies[4], early diagnosis[5], advances in medical technologies (including surgery and medications)[6] and clinical management. Traditionally, chemotherapies are the main medicines for cancer. But these drugs are not specific to the target, and therefore often cause serious adverse effects including neutropenia, anemia and thrombocytopenia.[7] In the past decade, however, many new anti-cancer drugs, so called targeted therapies[8], have become available. These drugs differ from standard chemotherapy in that they target specific vulnerable nodes in molecular pathways[9,10]; thus, they are generally less toxic than traditional chemotherapies.[11] For some cancers, targeted therapies are becoming the main treatments, for example, trastuzumab for early-stage and metastatic (HER2 positive) breast cancer.[12,13] Dozens of targeted therapies have become available in the recent years and many are in drug development pipeline.[14] While some have demonstrated improvements in progression free survival, some agents have minimal or no gains in overall survival; for instance, sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab, pazopanib, and axitinib for renal cell cancer.[15]

Changes in the cancer treatment paradigm are accompanied by significant economic consequences. Targeted therapies are expensive, typically costing from $4,500 to more than $10,000 per treatment month, even if they demonstrate only improvements in progression free survival without marked gains in overall survival.[15-20] The increasing costs of new targeted cancer therapies have risen ten times during the past decade.[21] Given the number of new cancer medicines in development and likely continual increases in drug prices, pricing of new anticancer drugs is a real concern for accessibility and affordability across all countries.[15,22,23] Some have suggested that a minimum of improvement in median survival of at least 3 to 6 months by new cancer medicines compared with current standards is required for the new agent to be considered as advanced and funded at higher prices.[24] Furthermore, because of the much higher costs of targeted therapies compared to conventional chemotherapy, while the number of eligible patients (due to molecular sub-typing) for individual agents is generally

small, in aggregate costs of targeted therapies as a group is an important contributor of growing expenditures for cancer treatments and an important issue of sustainability for all health care systems.[25-27]

Due to limited financial resources, patient access to targeted therapies has been a struggling issue in many countries.[28] Many countries have different ways to curb the growth of pharmaceutical expenditures in general. Examples include formal health technology assessment (for instance, economic evaluation of new drugs is required by many payers/policy makers such as the National Institute for Health Care Excellence in the United Kingdom,[29,30] and Pharmaceutical Benefits Advisory Committee in Australia[31,32] to select drugs for coverage.), pricing tools such as reference pricing,[33] and high patient cost-sharing (co-payments, coinsurance).[34] To deal with high drug costs and imperfect evidence at the time of marketing approval, many countries increasingly adopt patient access schemes (also known as managed entry agreements or risk-sharing arrangements) to enable patient access to needed medicines but ensuring that financing systems are sustainable[35,36]. The performance of managed entry agreements, however, is largely unknown because most have not been evaluated.[33] Major challenges at present for many health systems include determining what proportion of the health care budget should be allocated for treatment of cancer, including budget for targeted therapies, and designing and implementing new models for pricing, reimbursement, funding and utilization decisions for cancer medicines.[37]

In Taiwan, economic evaluation is part of health technology assessment to evaluate new drugs to determine decisions for coverage by the National Health Insurance since 2007.[38,39] In addition, prior authorization is required for many cancer medicines, especially for targeted therapies with high reimbursement prices. An application for prior authorization can be made to the National Health Insurance, and the drug will be reimbursed if authorization is given.[40] For instance, according to "Directions of Drug Restricted Benefit for National Health Insurance", two targeted therapies, gefitinib and erlotinib, for treatment of lung cancer have been reimbursed since 2004 and 2007, respectively. In the beginning, both of them were restricted to be used as third-line treatment, that is, patients must first be treated by platinum and docetaxel or paclitaxel chemotherapy and must only have locally advanced or metastatic adenocarcinoma of the lung.[41]

Little is known about the utilization and economic impacts of targeted cancer therapies in Taiwan. The aim of our longitudinal analyses was to address this gap by examining the recent trend in utilization and expenditures of cancer treatments, including targeted therapies, in Taiwan. We also identified which types of cancer accounted for the highest use of targeted therapies.

## Method

### *Data sources*

Taiwan's National Health Insurance Research Database provided data for this study. The database contains information from a nationwide, mandatory-enrollment and single-payer healthcare system created in 1995. Nearly 99% of the Taiwanese population (around 23 million residents) is enrolled and this system contracts with 97% of hospitals and clinics

throughout the country.[42] The National Health Insurance (NHI) covers a wide range of prescription medicines, and inpatient and outpatient medical services.[43] All monthly claims data, including details of prescription and insurer spending, for antineoplastic agents between 2009 and 2012 were retrieved from Taiwan's National Health Insurance Research Database. The cancer related prescriptions were identified by International Classification of Diseases, 9th edition (ICD-9) diagnosis codes for cancer (codes: 140-239).

***Drugs of interest***

We used the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization. We identified all antineoplastic agents using ATC codes "L01". Antineoplastic agents were grouped into 6 classes based on the ATC system: (1) targeted therapies, including monoclonal antibodies (rituximab, trastuzumab, cetuximab), protein kinase inhibitors (imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib), and bortezomib; these have been used for the treatment of cancer in Taiwan; (2) alkylating agents (including nitrogen mustard analogues, alkyl sulfonates, nitrosoureas and other alkylating agents); (3) antimetabolites (including folic acid analogues, purine analogues and pyrimidine analogues); (4) plant alkaloids and other natural products (including vinca alkaloids and analogues, podophyllotoxin derivatives and taxanes); (5) cytotoxic antibiotics and related substances (including actinomycines, anthracyclines and related substances and other cytotoxic antibiotics); and (6) other antineoplastic agents (including platinum compounds, sensitizers used in photodynamic/radiation therapy, and other antineoplastic agents).

***Measurements***

To examine trends in use and costs of each class of antineoplastic agents (including targeted therapies), we calculated quarterly and yearly number of prescriptions and costs from 2009 to 2012. Then, for each class we calculated the proportion of its use and costs among total use and total costs of all antineoplastic agents. For example, market share by prescription volume for targeted therapies was estimated by: number of prescriptions for targeted therapies divided by total number of prescriptions for all antineoplastic agents; and the market share by costs was estimated by: costs of targeted therapies divided by total costs of all antineoplastic agents. We also calculated cost per prescription for each class of antineoplastic agents.

To understand which cancers accounted for high use of targeted therapies, we first selected the most 20 common types of cancer in Taiwan based on prevalence (see appendix). We used the total prescription volume and total costs for targeted therapies in Taiwan as the denominator and analyzed using clinical indication of their use by type of cancer.

***Statistical Analysis***

To assess the quarterly trends in market shares by prescription volume and costs of targeted therapies among all antineoplastic agents, we used a time series design with the Autoregressive integrated moving average (ARIMA) model, which was developed by Box

and Jenkins.[44] The model is generally referred to as an ARIMA(p,d,q) model where parameters p, d, and q are non-negative integers that refer to the order of the autoregressive, integrated, and moving average parts of the model respectively. These models are fitted to time series data either to better understand the data or to determine points in the series.[45] We used the estimated rates by ARIMA model for time series graphs. All analyses were carried out with SAS software, Version 9.3 (SAS Institute, Cary, NC).

## Results

Between 2009 and 2012, prescriptions for antineoplastic agents grew 31.51% (an average rate of 10.5% increase per year) (Table 1). By class, prescriptions for alkylating agents, antimetabolites, plant alkaloids and cytotoxic antibiotics increased in number during this period, but their market shares decreased: -0.67%, -2.22%, -1.43%, -1.51% respectively. In contrast, the market share of targeted therapies grew from 6.24% in 2009 to 12.29% in 2012. Specifically, market shares of monoclonal antibodies and protein kinase inhibitors doubled, from 2.75% to 5.79% and from 3.38% to 6.18%, respectively. Figure 1A shows ARIMA regression estimated quarterly trends in market share by prescription volume for targeted therapies during the study period.

[Table 1] [Figure 1A]

Table 2 presents the costs for all and each type of antineoplastic drugs between 2009 and 2012. There was a large growth in total costs of antineoplastic agents from 2009 to 2012 (an overall increase of 50.67%, an average rate of 16.89% increase per year). By class, the yearly market share by costs for alkylating agents, antimetabolites, plant alkaloids and cytotoxic antibiotics reduced by 0.60%, 1.93%, 4.49%, 1.81% from 2009 to 2012. In contrast, annual costs of targeted therapies grew from US$129 million (26.16% of all costs for antineoplastic agents) in 2009 to US$308 million (41.57%) in 2012. Specifically, the market share by costs for monoclonal antibodies and protein kinase inhibitors increased from 14.63% to 23.84% and from 10.71% to 16.12%, respectively. Figure 1B shows ARIMA regression estimated quarterly the trend in market share by costs for targeted therapies during the study period.

[Table 2] [Figure 1B]

Table 3 shows the cost per prescription for each class of antineoplastic agents between 2009 and 2012. We found that, in 2012, targeted therapies had the highest cost per prescription (US$1,005), other antineoplastic agents in descending order by cost per prescription were plant alkaloids and other natural products (US$346), other non-targeted therapies (US$342), cytotoxic antibiotics and related substances (US$178), alkylating agents (US$128) and antimetabolites (US$115). There was about a 3-fold difference in cost per prescription between targeted therapies and plant alkaloids and other natural products, and about a 10-fold difference between targeted therapies and antimetabolites.

[Table 3]

Figure 2A and Figure 2B present the distribution ratios of targeted therapies use for 20 cancers during 2009-2012. Table 4 shows the yearly distribution ratios of targeted therapies use by cancer type over time. Our results showed that use and costs for targeted therapies

differed substantially between different types of cancer. During 2009-2012, targeted therapies were mostly used for cancers of lung, female breast, colorectal, lymphoma and leukemia in order of volume. These 5 cancer types accounted for 44.64%, 16.49%, 12.11%, 12.09% and 3.17% of prescriptions for targeted therapies (together 88.5%); and 28.26%, 27.18%, 13.16%, 10.23% and 4.94% of costs for targeted therapies (together 83.77%) among these 20 common cancer types.

[Figure 2A] [Figure 2B] [Table 4]

## Discussion

To our knowledge this is the first study that examined the national trend in use and costs of targeted therapies for treatment of cancer in Taiwan. Our findings indicated that, compared with other classes of antineoplastic drugs, use of targeted therapies, novel agents for cancer treatment, increased substantially and is causing great economic burden in Taiwan. Cancers of lung, female breast and colorectal accounted for the most use of targeted therapies.

Between 2009 and 2012, use and costs of targeted therapies increased almost 3-folds (Tables 1 and 2) with steep growths since the third quarter of 2011 (Figure 1). This trend is likely to continue in the future. We found that the average cost per prescription of targeted therapies was much higher than that of other classes of antineoplastic agents with 3-10 folds difference in 2012. It is important that policy makers revisit the pricing and reimbursement structures for these medicines because prices for all targeted therapies are high even for those that offer limited clinical benefits.

Our study adds to the literature that the availability and increasing use of innovative but expensive targeted therapies are major drivers of increases in pharmaceutical expenditures.[25,26] We showed that the costs of targeted therapies accounted for almost 42% of expenditures for all antineoplastic agents in Taiwan in 2012. Monoclonal antibodies and protein kinase inhibitors contributed the most (23.84% and 16.12% of costs for antineoplastic agents). Targeted therapies also dominate cancer drug expenditures in other countries, for example, 63% of all cancer drug expenditures in 2011 in the commercially insured population in the US.[46]

The high cost of targeted therapies is a barrier to access targeted therapies for treatment of cancer.[28] It is important to ensure patient access to effective targeted therapies without overspending the health care budget given their clinical benefits. Many experts propose that dialogue involving all parties concerned (eg. policy makers, industry, clinicians, patients, and the general public) is needed to address the reasons behind high prices of cancer drugs and offer solutions to reduce prices. Experts also propose that drug prices should reflect objective measures of benefit, but should not exceed values that could harm patients and societies.[27,47] Overall, strategies for future management of new cancer medicines might include raising the bar for clinical trials by defining clinically meaningful outcomes[48], establishing minimum effectiveness levels for new cancer medicines[15,24], generating a list of essential medicines for patients with cancer, discussing potential future measures to fund new innovative cancer medicines without potentially compromising patients/healthcare systems,[23] and determining the proportion of healthcare spent on cancer medicines based on the consideration of their

balance of costs and outcomes.[47]

There are some limitations to this study. First, this study aimed to examine recent trends in drug utilization and expenditures for cancer treatment and to estimate the market shares by prescription volume and costs for targeted therapies in Taiwan; our analysis only examined data up to 2012 as these were the more recent data available at the time of the analysis. We used aggregate data and did not analyze patient-level data to understand the influence of patient characteristics on treatment selection and clinical outcomes of treatments. This study also did not examine the complex patterns of drug use, such as use of combination treatments, targeted therapy adherence and persistence, again because of the lack of patient-level data. This study examined economic burden of targeted therapies from the perspective of the health care system; we did not examine patient contribution to drug costs in Taiwan, which warrants a separate study. Further, we did not characterize changes in the policy environment in Taiwan during the study period. Examples include the launch of new, competing targeted therapies, publication of large randomized clinical trials results, changes in clinical guidelines or reimbursement policies, and patient and provider factors (e.g. patient clinical history, physician's knowledge and preference). Future studies are needed to examine impact of changes in policy and clinical environment on use of targeted therapies. Finally, various types of restrictions (eg. prior authorizations) have been applied for many high-cost targeted therapies for cancer in Taiwan.[49] How these restrictions impact cancer care and outcomes should be studied.

## Conclusion

Targeted therapies have played an increasing and more important role in treatment of all malignancies in Taiwan, and they are likely to pose substantial economic burden in the future. Cancers of lung, female breast and colorectal were identified as main drivers of use and costs of targeted therapies in recent years. Policy makers, industry, clinicians and patients need to communicate and develop strategies to enable access to effective (and cost-effective) targeted therapies without overspending the health care budget.

## Author Contributions

JCH and CYL conceptualized and designed the study. JCH collected data, performed analysis, and drafted the manuscript. CYL reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

## Competing Interests

The authors have no competing interests.

## Funding

Dr. Hsu was supported by a grant from Taiwan's Ministry of Science and Technology (Grant ID MOST 104-2320-B-006-005). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Dr. Lu received no funding for this study.

## Data Sharing Statement

We obtained nationwide, monthly claims data for cancer related antineoplastic agents between 2009 and 2012 from the Taiwan National Health Insurance Research database (NHIRD). NHIRD does not permit external sharing of any of the data elements.

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**Tables**



**Figures**

## Table 1. Prescription volume of antineoplastic agents in Taiwan (2009-2012)

| Drug Class | Drug name for patients with cancer | Number of Prescription (market share by prescription volume) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2009 | | 2010 | | 2011 | | 2012 | | 2009-2012 | |
| | | N | (%) | N | (%) | N | (%) | N | (%) | growth rate of N (%) | growth rate of market share (%) |
| All Antineoplastic Agents | | 1,893,439 | 100 | 2,033,160 | 100 | 2,300,629 | 100 | 2,489,973 | 100 | 31.51 | |
| Targeted Therapies | | 118,186 | 6.24 | 150,401 | 7.40 | 209,030 | 9.09 | 306,140 | 12.29 | 159.03 | 6.05 |
| Monoclonal antibodies | rituximab, trastuzumab, cetuximab, bevacizumab | 52,073 | 2.75 | 68,595 | 3.37 | 102,074 | 4.44 | 144,234 | 5.79 | 176.98 | 3.04 |
| Protein kinase inhibitors | imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib | 63,936 | 3.38 | 78,675 | 3.87 | 102,435 | 4.45 | 153,764 | 6.18 | 140.50 | 2.80 |
| Other targeted therapy agents | bortezomib | 2,177 | 0.11 | 3,131 | 0.15 | 4,521 | 0.20 | 8,142 | 0.33 | 274.00 | 0.21 |
| Alkylating Agents | | 125,811 | 6.64 | 132,109 | 6.50 | 147,076 | 6.39 | 148,654 | 5.97 | 18.16 | -0.67 |
| Nitrogen mustard analogues | cyclophosphamide, chlorambucil, melphalan, ifosfamide, bendamustine | 112,602 | 5.95 | 117,101 | 5.76 | 125,769 | 5.47 | 130,042 | 5.22 | 15.49 | -0.72 |
| Alkyl sulfonates | busulfan | 301 | 0.02 | 279 | 0.01 | 318 | 0.01 | 255 | 0.01 | -15.28 | -0.01 |
| Nitrosoureas | carmustine | 250 | 0.01 | 218 | 0.01 | 263 | 0.01 | 321 | 0.01 | 28.40 | 0.00 |
| Other alkylating agents | temozolomide, dacarbazine | 12,658 | 0.67 | 14,511 | 0.71 | 20,726 | 0.90 | 18,036 | 0.72 | 42.49 | 0.06 |
| Antimetabolites | | 911,611 | 48.15 | 965,096 | 47.47 | 1,076,871 | 46.81 | 1,143,596 | 45.93 | 25.45 | -2.22 |
| Folic acid analogues | methotrexate, pemetrexed | 316,174 | 16.70 | 349,463 | 17.19 | 386,008 | 16.78 | 426,480 | 17.13 | 34.89 | 0.43 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Purine analogues | mercaptopurine, cladribine, fludarabine | 12,550 | 0.66 | 12,094 | 0.59 | 12,277 | 0.53 | 12,891 | 0.52 | 2.72 | -0.15 |
| | Pyrimidine analogues | cytarabine, fluorouracil, tegafur, gemcitabine, capecitabine, tegafur_combinations | 582,887 | 30.78 | 603,539 | 29.68 | 678,586 | 29.50 | 704,225 | 28.28 | 20.82 | -2.50 |
| Plant Alkaloids and other Natural Products | | | 217,347 | 11.48 | 222,304 | 10.93 | 250,312 | 10.88 | 250,273 | 10.05 | 15.15 | -1.43 |
| | Vinca alkaloids and analogues | vinblastine, vincristine, vinorelbine | 84,009 | 4.44 | 85,659 | 4.21 | 88,135 | 3.83 | 88,377 | 3.55 | 5.20 | -0.89 |
| | Podophyllotoxin derivatives | etoposide | 28,864 | 1.52 | 30,188 | 1.48 | 32,990 | 1.43 | 34,587 | 1.39 | 19.83 | -0.14 |
| | Taxanes | paclitaxel, docetaxel | 104,474 | 5.52 | 106,457 | 5.24 | 129,187 | 5.62 | 127,309 | 5.11 | 21.86 | -0.40 |
| Cytotoxic Antibiotics and Related Substances | | | 140,168 | 7.40 | 140,697 | 6.92 | 145,663 | 6.33 | 146,796 | 5.90 | 4.73 | -1.51 |
| | Actinomycines | dactinomycin | 616 | 0.03 | 698 | 0.03 | 667 | 0.03 | 761 | 0.03 | 23.54 | 0.00 |
| | Anthracyclines and related substances | doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone | 99,422 | 5.25 | 101,826 | 5.01 | 107,177 | 4.66 | 106,499 | 4.28 | 7.12 | -0.97 |
| | Other cytotoxic antibiotics | bleomycin, mitomycin | 40,130 | 2.12 | 38,173 | 1.88 | 37,819 | 1.64 | 39,536 | 1.59 | -1.48 | -0.53 |
| Other non-Targeted Therapies | | | 380,316 | 20.09 | 422,553 | 20.78 | 471,677 | 20.50 | 494,514 | 19.86 | 30.03 | -0.23 |
| | Platinum compounds | cisplatin, carboplatin, oxaliplatin | 254,636 | 13.45 | 286,260 | 14.08 | 304,437 | 13.23 | 306,659 | 12.32 | 20.43 | -1.13 |
| | Sensitizers used in photodynamic / radiation therapy | verteporfin | 120 | 0.01 | 88 | 0.00 | 88 | 0.00 | 95 | 0.00 | -20.83 | 0.00 |
| | Others | asparaginase, hydroxycarbamide, estramustine, tretinoin, | 125,560 | 6.63 | 136,205 | 6.70 | 167,152 | 7.27 | 187,760 | 7.54 | 49.54 | 0.91 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **topotecan, irinotecan, mitotane, arsenic trioxide** | | | | | | | | | | |

**Table 2. Costs of antineoplastic agents in Taiwan (2009-2012)**

| Drug Class | Drug name for patients with cancer | Cost (market share by costs) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2009 | | 2010 | | 2011 | | 2012 | | 2009-2012 | |
| | | Cost (US$) | (%) | Cost (US$) | (%) | Cost (US$) | (%) | Cost (US$) | (%) | growth rate of N (%) | growth rate of market share (%) |
| All Antineoplastic Agents | | 491,387,822 | 100 | 570,369,759 | 100 | 660,138,086 | 100 | 740,386,783 | 100 | 50.67 | |
| Targeted Therapies | | 128,541,502 | 26.16 | 177,668,722 | 31.15 | 224,327,855 | 33.98 | 307,754,974 | 41.57 | 139.42 | 15.41 |
| Monoclonal antibodies | rituximab, trastuzumab, cetuximab, bevacizumab | 71,869,602 | 14.63 | 104,739,673 | 18.36 | 137,951,386 | 20.90 | 176,477,405 | 23.84 | 145.55 | 9.21 |
| Protein kinase inhibitors | imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib | 52,651,186 | 10.71 | 67,484,747 | 11.83 | 79,001,874 | 11.97 | 119,383,796 | 16.12 | 126.74 | 5.41 |
| Other targeted therapy agents | bortezomib | 4,020,714 | 0.82 | 5,444,303 | 0.95 | 7,374,595 | 1.12 | 11,893,774 | 1.61 | 195.81 | 0.79 |
| Alkylating Agents | | 15,551,932 | 3.16 | 17,481,103 | 3.06 | 18,968,906 | 2.87 | 18,999,092 | 2.57 | 22.17 | -0.60 |
| Nitrogen mustard analogues | cyclophosphamide, chlorambucil, melphalan, ifosfamide, bendamustine | 4,495,217 | 0.91 | 4,897,936 | 0.86 | 4,878,608 | 0.74 | 4,261,046 | 0.58 | -5.21 | -0.34 |
| Alkyl sulfonates | busulfan | 374,465 | 0.08 | 454,805 | 0.08 | 460,163 | 0.07 | 488,410 | 0.07 | 30.43 | -0.01 |
| Nitrosoureas | carmustine | 41,620 | 0.01 | 43,440 | 0.01 | 153,101 | 0.02 | 392,128 | 0.05 | 842.16 | 0.04 |
| Other | temozolomide, dacarbazine | 10,640,629 | 2.17 | 12,084,922 | 2.12 | 13,477,034 | 2.04 | 13,857,508 | 1.87 | 30.23 | -0.29 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | alkylating agents | | | | | | | | | | | |
| | Antimetabolites | | 96,951,076 | 19.73 | 117,122,829 | 20.53 | 128,199,087 | 19.42 | 131,805,930 | 17.80 | 35.95 | -1.93 |
| | | Folic acid analogues | methotrexate, pemetrexed | 31,305,924 | 6.37 | 50,705,521 | 8.89 | 61,101,669 | 9.26 | 66,069,402 | 8.92 | 111.04 | 2.55 |
| | | Purine analogues | mercaptopurine, cladribine, fludarabine | 304,010 | 0.06 | 265,754 | 0.05 | 365,404 | 0.06 | 311,619 | 0.04 | 2.50 | -0.02 |
| | | Pyrimidine analogues | cytarabine, fluorouracil, tegafur, gemcitabine, capecitabine, tegafur_combinations | 65,341,142 | 13.30 | 66,151,554 | 11.60 | 66,732,014 | 10.11 | 65,424,909 | 8.84 | 0.13 | -4.46 |
| | Plant Alkaloids and other Natural Products | | | 79,509,189 | 16.18 | 72,920,907 | 12.78 | 84,694,476 | 12.83 | 86,583,703 | 11.69 | 8.90 | -4.49 |
| | | Vinca alkaloids and analogues | vinblastine, vincristine, vinorelbine | 20,326,687 | 4.14 | 22,006,619 | 3.86 | 23,924,553 | 3.62 | 25,170,345 | 3.40 | 23.83 | -0.74 |
| | | Podophyllotoxin derivatives | etoposide | 2,164,352 | 0.44 | 1,643,415 | 0.29 | 1,651,811 | 0.25 | 1,579,203 | 0.21 | -27.04 | -0.23 |
| | | Taxanes | paclitaxel, docetaxel | 57,018,150 | 11.60 | 49,270,873 | 8.64 | 59,118,111 | 8.96 | 59,834,155 | 8.08 | 4.94 | -3.52 |
| | Cytotoxic Antibiotics and Related Substances | | | 26,190,529 | 5.33 | 26,232,768 | 4.60 | 27,270,661 | 4.13 | 26,075,058 | 3.52 | -0.44 | -1.81 |
| | | Actinomycines | dactinomycin | 16,854 | 0.00 | 18,603 | 0.00 | 18,303 | 0.00 | 19,062 | 0.00 | 13.10 | 0.00 |
| | | Anthracyclines and related substances | doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone | 24,489,365 | 4.98 | 24,531,634 | 4.30 | 25,576,627 | 3.87 | 24,215,313 | 3.27 | -1.12 | -1.71 |
| | | Other cytotoxic antibiotics | bleomycin, mitomycin | 1,684,311 | 0.34 | 1,682,531 | 0.29 | 1,675,731 | 0.25 | 1,840,682 | 0.25 | 9.28 | -0.09 |
| | Other non-Targeted Therapies | | | 144,643,593 | 29.44 | 158,943,430 | 27.87 | 176,677,101 | 26.76 | 169,168,026 | 22.85 | 16.96 | -6.59 |
| | | Platinum compounds | cisplatin, carboplatin, oxaliplatin | 50,363,294 | 10.25 | 53,988,423 | 9.47 | 52,077,277 | 7.89 | 35,697,261 | 4.82 | -29.12 | -5.43 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Sensitizers used in photodynamic / radiation therapy** | **verteporfin** | **169,600** | **0.03** | **124,373** | **0.02** | **124,373** | **0.02** | **134,267** | **0.02** | **-20.83** | **-0.02** |
| | | **Others** | **asparaginase, hydroxycarbamide, estramustine, tretinoin, topotecan, irinotecan, mitotane, arsenic trioxide** | **94,110,699** | **19.15** | **104,830,634** | **18.38** | **124,475,451** | **18.86** | **133,336,498** | **18.01** | **41.68** | **-1.14** |

## Table 3. Cost per prescription of antineoplastic agents in Taiwan (2009-2012)

| Drug Class | Drug name for patients with cancer | Cost per Prescription (US$) | | | |
|---|---|---|---|---|---|
| | | 2,009 | 2,010 | 2,011 | 2,012 |
| All Antineoplastic Agents | | 260 | 281 | 287 | 297 |
| Targeted Therapies | | 1,088 | 1,181 | 1,073 | 1,005 |
| Monoclonal antibodies | rituximab, trastuzumab, cetuximab, bevacizumab | 1,380 | 1,527 | 1,351 | 1,224 |
| Protein kinase inhibitors | imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib | 823 | 858 | 771 | 776 |
| Other targeted therapy agents | bortezomib | 1,847 | 1,739 | 1,631 | 1,461 |
| Alkylating Agents | | 124 | 132 | 129 | 128 |
| Nitrogen mustard analogues | cyclophosphamide, chlorambucil, melphalan, ifosfamide, bendamustine | 40 | 42 | 39 | 33 |
| Alkyl sulfonates | busulfan | 1,244 | 1,630 | 1,447 | 1,915 |
| Nitrosoureas | carmustine | 166 | 199 | 582 | 1,222 |
| Other alkylating agents | temozolomide, dacarbazine | 841 | 833 | 650 | 768 |
| Antimetabolites | | 106 | 121 | 119 | 115 |
| Folic acid analogues | methotrexate, pemetrexed | 99 | 145 | 158 | 155 |
| Purine analogues | mercaptopurine, cladribine, fludarabine | 24 | 22 | 30 | 24 |
| Pyrimidine analogues | cytarabine, fluorouracil, tegafur, gemcitabine, capecitabine, tegafur_combinations | 112 | 110 | 98 | 93 |
| Plant Alkaloids and other Natural Products | | 366 | 328 | 338 | 346 |
| Vinca alkaloids and analogues | vinblastine, vincristine, vinorelbine | 242 | 257 | 271 | 285 |
| Podophyllotoxin derivatives | etoposide | 75 | 54 | 50 | 46 |
| Taxanes | paclitaxel, docetaxel | 546 | 463 | 458 | 470 |
| Cytotoxic Antibiotics and Related Substances | | 187 | 186 | 187 | 178 |
| Actinomycines | dactinomycin | 27 | 27 | 27 | 25 |
| Anthracyclines and related substances | doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone | 246 | 241 | 239 | 227 |
| Other cytotoxic antibiotics | bleomycin, mitomycin | 42 | 44 | 44 | 47 |
| Other non-Targeted Therapies | | 380 | 376 | 375 | 342 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **Platinum compounds** | **cisplatin, carboplatin, oxaliplatin** | **198** | **189** | **171** | **116** |
| | | **Sensitizers used in photodynamic / radiation therapy** | **verteporfin** | **1,413** | **1,413** | **1,413** | **1,413** |
| | | **Others** | **asparaginase, hydroxycarbamide, estramustine, tretinoin, topotecan, irinotecan, mitotane, arsenic trioxide** | **750** | **770** | **745** | **710** |

**Table 4. Use and costs of targeted therapies by cancer type over time**

| Cancer type | | Distribution ratio based on prescription volume (%) | | | | | | Distribution ratio of costs (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2009 | 2010 | 2011 | 2012 | 2009-2012 overall | 2009-2012 Growth rate | 2009 | 2010 | 2011 | 2012 | 2009-2012 overall | 2009-2012 Growth rate |
| 01 | Lung | 51.87 | 45.94 | 43.03 | 42.18 | 44.64 | -9.68 | 39.55 | 28.79 | 25.48 | 25.24 | 28.26 | -14.32 |
| 02 | Female breast | 11.71 | 18.62 | 18.47 | 15.95 | 16.49 | 4.24 | 20.91 | 31.45 | 30.60 | 24.78 | 27.18 | 3.87 |
| 03 | Colorectal | 9.52 | 7.01 | 12.32 | 15.62 | 12.11 | 6.10 | 12.12 | 8.65 | 13.13 | 16.29 | 13.16 | 4.16 |
| 04 | Lymphoma | 17.87 | 14.92 | 11.84 | 8.50 | 12.09 | -9.37 | 15.24 | 11.63 | 9.96 | 7.49 | 10.23 | -7.74 |
| 05 | Liver | 0.24 | 0.23 | 0.28 | 3.93 | 1.66 | 3.69 | 0.25 | 0.22 | 0.28 | 5.65 | 2.22 | 5.40 |
| 06 | Leukemia | 1.75 | 2.81 | 3.66 | 3.57 | 3.17 | 1.83 | 2.50 | 4.80 | 5.60 | 5.56 | 4.94 | 3.06 |
| 07 | Urinary | 0.43 | 2.70 | 3.01 | 2.82 | 2.48 | 2.39 | 0.52 | 4.53 | 5.25 | 4.95 | 4.26 | 4.43 |
| 08 | Multiple myeloma | 1.92 | 2.11 | 2.39 | 3.07 | 2.52 | 1.15 | 3.37 | 3.19 | 3.60 | 4.45 | 3.79 | 1.08 |
| 09 | Oral/pharyngeal | 1.58 | 2.40 | 2.01 | 1.48 | 1.82 | -0.10 | 1.59 | 2.43 | 2.03 | 1.57 | 1.88 | -0.03 |
| 10 | Stomach | 0.97 | 0.77 | 0.62 | 0.58 | 0.69 | -0.39 | 1.28 | 1.14 | 1.04 | 0.93 | 1.06 | -0.35 |
| 11 | Brain | 0.34 | 0.24 | 0.27 | 0.48 | 0.36 | 0.14 | 0.27 | 0.18 | 0.17 | 0.60 | 0.34 | 0.33 |
| 12 | Small intestine and duodenum | 0.43 | 0.51 | 0.43 | 0.34 | 0.41 | -0.09 | 0.80 | 0.99 | 0.90 | 0.74 | 0.85 | -0.06 |
| 13 | Bone | 0.45 | 0.48 | 0.44 | 0.33 | 0.41 | -0.12 | 0.65 | 0.74 | 0.80 | 0.57 | 0.68 | -0.08 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **14** | **Thyroid** | **0.15** | **0.13** | **0.22** | **0.22** | **0.19** | **0.07** | **0.20** | **0.14** | **0.20** | **0.20** | **0.19** | **0.00** |
| **15** | **Prostate** | **0.18** | **0.23** | **0.19** | **0.22** | **0.20** | **0.04** | **0.16** | **0.27** | **0.18** | **0.22** | **0.21** | **0.06** |
| **16** | **Larynx** | **0.24** | **0.48** | **0.41** | **0.26** | **0.34** | **0.02** | **0.26** | **0.47** | **0.41** | **0.27** | **0.35** | **0.01** |
| **17** | **Pancreas** | **0.01** | **0.02** | **0.10** | **0.14** | **0.09** | **0.13** | **0.01** | **0.02** | **0.06** | **0.20** | **0.10** | **0.19** |
| **18** | **Cervix** | **0.16** | **0.20** | **0.14** | **0.11** | **0.14** | **-0.05** | **0.16** | **0.17** | **0.13** | **0.10** | **0.13** | **-0.05** |
| **19** | **Esophagus** | **0.09** | **0.12** | **0.13** | **0.09** | **0.11** | **0.01** | **0.07** | **0.12** | **0.13** | **0.10** | **0.11** | **0.03** |
| **20** | **Ovary** | **0.10** | **0.08** | **0.05** | **0.10** | **0.08** | **0.00** | **0.09** | **0.08** | **0.05** | **0.08** | **0.07** | **-0.01** |
| | **Total** | **100.00** | **100.00** | **100.00** | **100.00** | **100.00** | | **100.00** | **100.00** | **100.00** | **100.00** | **100.00** | |

2

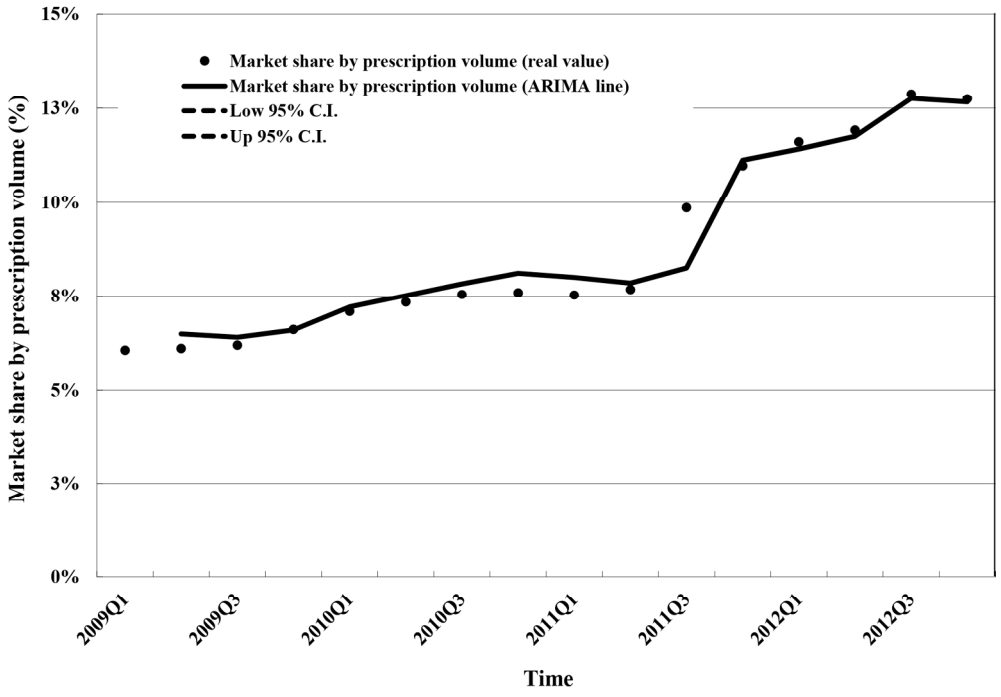


Figure 1A.
173x121mm (300 x 300 DPI)

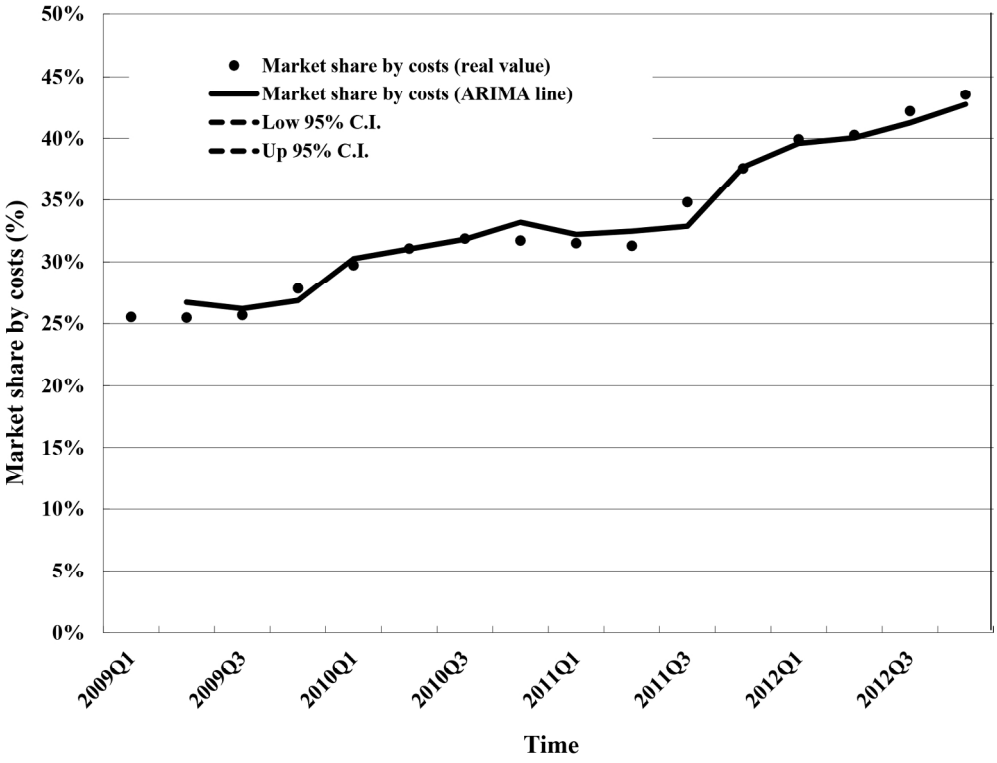


Figure 1B.
173x133mm (300 x 300 DPI)

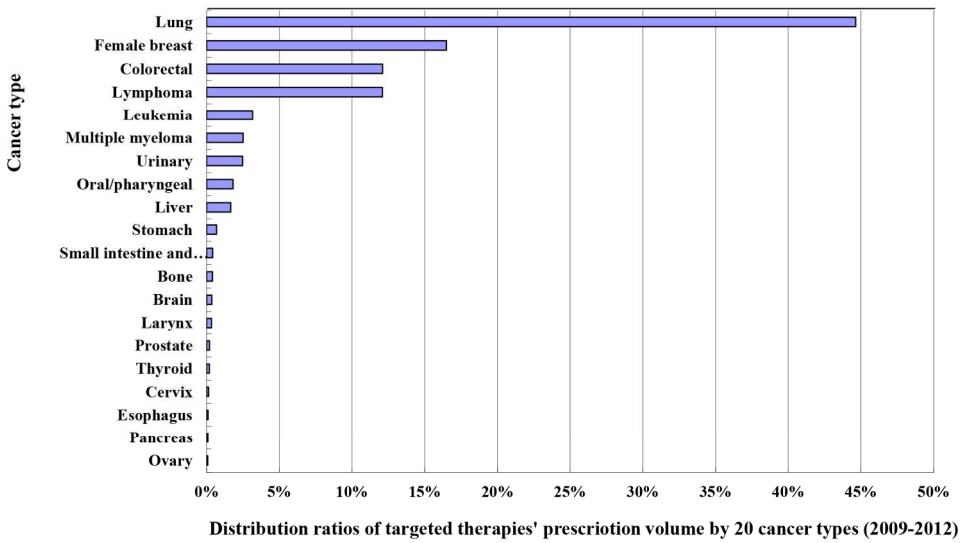


Figure 2A.
173x92mm (300 x 300 DPI)

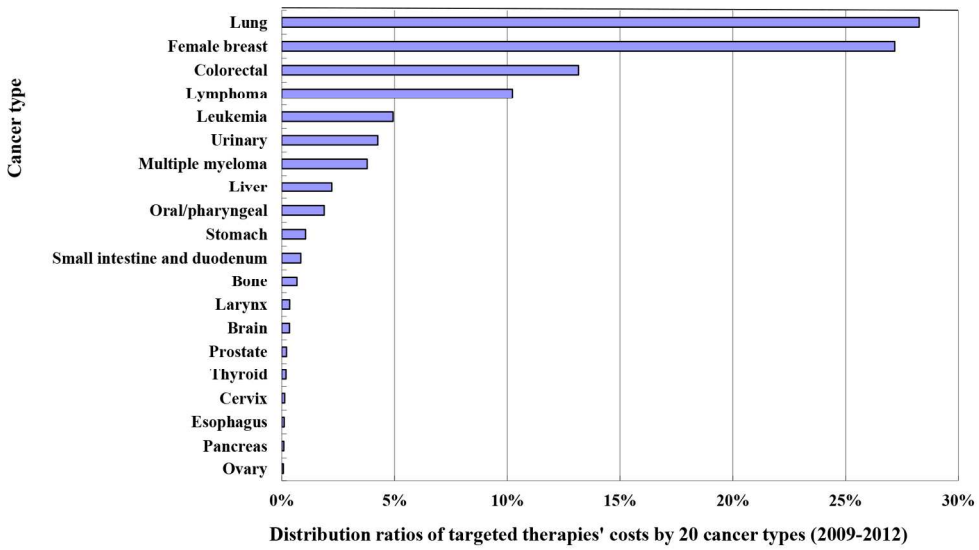


Figure 2B.
173x93mm (300 x 300 DPI)

## Appendix

**ICD-9-CM diagnosis code identifying patients with various types of cancer:**

| | Types of cancer in this study | ICD-9 codes |
|---|---|---|
| 1 | Lung (including trachea. bronchus and lung) | 162 |
| 2 | Female breast | 174 |
| 3 | Colorectal (including colon, rectum, rectosigmoid junction and anus) | 153-154 |
| 4 | Lymphoma (including lymphosarcoma, eticulosarcoma and Hodgkin's disease) | 200-202 |
| 5 | Liver (including liver and intrahepatic bile ducts) | 155 |
| 6 | Leukemia (including lymphoid, myeloid monocytic and other specific leukemia) | 204-208 |
| 7 | Urinary (including bladder, kidney and other and unspecified urinary organs) | 188-189 |
| 8 | Multiple myeloma (including multiple myeloma and immunoproliferative neoplasms) | 203 |
| 9 | Oral/pharyngeal (including lip, tongue, major salivary glands, gum, floor of mouth, other and unspecified parts of mouth, oropharynx, nasopharynx, hypopharynx and others) | 140-149 |
| 10 | Stomach | 151 |
| 11 | Brain | 191 |
| 12 | Small intestine and duodenum | 152 |
| 13 | Bone (including bone, articular cartilage, connective and other soft tissue) | 170-171 |
| 14 | Thyroid | 193 |
| 15 | Prostate | 185 |
| 16 | Larynx | 161 |
| 17 | Pancreas | 157 |
| 18 | Cervix | 180 |
| 19 | Esophagus | 150 |
| 20 | Ovary (including ovary and other uterine adnexa) | 183 |

STROBE Statement—checklist of items that should be included in reports of observational studies

| Page | | Item No | Recommendation |
|---|---|---|---|
| 1 | **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| 1-2 | | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| | **Introduction** | | |
| 3 | Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| 3 | Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| | **Methods** | | |
| 4 | Study design | 4 | Present key elements of study design early in the paper |
| 4 | Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| 4 | Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| 4 | | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| 4 | Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| 4 | Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| 4 | Bias | 9 | Describe any efforts to address potential sources of bias |
| 4 | Study size | 10 | Explain how the study size was arrived at |
| 4 | Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| 5 | Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| 4-5 | | | (*b*) Describe any methods used to examine subgroups and interactions |
| NA | | | (*c*) Explain how missing data were addressed |
| NA | | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| NA | | | (*e*) Describe any sensitivity analyses |

Continued on next page

| | | | |
|---|---|---|---|
| Page | **Results** | | |
| NA | Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| NA | | | (b) Give reasons for non-participation at each stage |
| NA | | | (c) Consider use of a flow diagram |
| 11-14 | Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| NA | | | (b) Indicate number of participants with missing data for each variable of interest |
| NA | | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| NA | Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| NA | | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| NA | | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| 5-6; 11-14 | Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| 5-6 | | | (*b*) Report category boundaries when continuous variables were categorized |
| NA | | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| 5-6; 11-14 | Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| | **Discussion** | | |
| 6-7 | Key results | 18 | Summarise key results with reference to study objectives |
| 7 | Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| 6-7 | Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| 6-7 | Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| | **Other information** | | |
| No funding | Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Longitudinal Trends in Use and Costs of Targeted Therapies for Common Cancers in Taiwan: A Retrospective Observational Study



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2016-011322.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 28-Apr-2016 |
| Complete List of Authors: | Hsu, Jason C.; National Cheng Kung University, School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine<br>Lu, Christine Y.; Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Population Medicine |
| Primary Subject Heading: | Health services research |
| Secondary Subject Heading: | Oncology, Pharmacology and therapeutics, Health economics, Health policy |
| Keywords: | Cancer, Targeted therapies, Taiwan, Drug costs |
| | |

# Title Page

## Longitudinal Trends in Use and Costs of Targeted Therapies for Common Cancers in Taiwan: A Retrospective Observational Study

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**Abstract**

**Objectives:** Some targeted therapies have improved survival and overall quality of cancer care generally, but these increasingly expensive medicine have led to increases in pharmaceutical expenditure. This study examined trends in use and expenditures of antineoplastic agents in Taiwan and estimated market shares by prescription volume and costs of targeted therapies overtime. We also determined which cancer types accounted for the highest use of targeted therapies.

**Design:** Retrospective observational study focusing on the utilization of targeted therapies for treatment of cancer.

**Setting:** The monthly claims data for antineoplastic agents were retrieved from Taiwan's National Health Insurance Research Database (2009-2012).

**Main outcome measures:** We calculated market shares by prescription volume and costs for each class of antineoplastic agents by cancer type. Using a time series design with ARIMA models, we estimated trends in use and costs of targeted therapies.

**Results:** Among all antineoplastic agents, use of targeted therapies grew from 6.24% in 2009 to 12.29% in 2012, but their costs rose from 26.16% to 41.57%. Monoclonal antibodies and protein kinase inhibitors contributed the most (23.84% and 16.12% of costs for antineoplastic agents in 2012). During 2009-2012, lung (44.64% of use; 28.26% of costs), female breast (16.49% of use; 27.18% of costs) and colorectal (12.11% of use; 13.16% of costs) cancers accounted for the highest use of targeted therapies.

**Conclusions:** Targeted therapies are increasingly used for different cancers in Taiwan, representing substantial economic burden. It is important to establish mechanisms to monitor their use and outcomes.

**Keywords:** Cancer, Targeted therapies, Taiwan, Drug costs
**Running title:** Trends of Cancer Targeted Therapies in Taiwan

## Strengths and limitations of this study

- This is the first study that examined the national trend in use and costs of targeted therapies for treatment of cancer in Taiwan.
- We also determined which cancer types accounted for the highest use of targeted therapies in Taiwan from 2009 to 2012.
- Data were retrieved from Taiwan's National Health Insurance Research Database with nearly 99% of the Taiwanese population (around 23 million residents) enrolled and 97% of hospitals and clinics throughout the country.
- A time series design with ARIMA models was used in this study to estimate the trends in market shares by prescription volume and costs of targeted therapies.
- Due to the lack of patient-level data, this study did not investigate the use of combination treatments which need to be examined in future studies.

# Manuscript

# Longitudinal Trends in Use and Costs of Targeted Therapies for Common Cancers in Taiwan: A Retrospective Observational Study

## Introduction

Cancer is a major public health issue globally. Approximately 7.4 million people die of cancer each year worldwide, which accounts for 13% of all-cause mortality and this percentage is expected to increase.[1,2] In Taiwan, cancer is a leading cause of mortality and the annual number of cancer patients has been growing.[3] In 2011, approximately 92,682 individuals were diagnosed with cancer (male: 56%, female: 44%). Most common cancers in Taiwan were female breast cancer, colorectal cancer, liver cancer, lung cancer and prostate cancer. In the same year, approximately 42,559 patients died of cancer (male: 64%, female: 36%), accounting for 28% of all deaths. Major cancers causing mortality were lung cancer, liver cancer, colorectal cancer, female breast cancer and oral/pharyngeal cancer.[3]

Cancer care has improved substantially and the average life expectancy has increased in the past two decades due to preventative strategies[4], early diagnosis[5], advances in medical technologies (including surgery and medications)[6] and clinical management. Traditionally, chemotherapies are the main medicines for cancer. But these drugs are not specific to the target, and therefore often cause serious adverse effects including neutropenia, anemia and thrombocytopenia.[7] In the past decade, however, many new anti-cancer drugs, so called targeted therapies[8], have become available. These drugs differ from standard chemotherapy in that they target specific vulnerable nodes in molecular pathways[9,10]; thus, they are generally less toxic than traditional chemotherapies.[11] For some cancers, targeted therapies are becoming the main treatments, for example, trastuzumab for early-stage and metastatic (HER2 positive) breast cancer.[12,13] Dozens of targeted therapies have become available in the recent years and many are in drug development pipeline.[14] While some have demonstrated improvements in progression free survival, some agents have minimal or no gains in overall survival; for instance, sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab, pazopanib, and axitinib for renal cell cancer.[15]

Changes in the cancer treatment paradigm are accompanied by significant economic consequences. Targeted therapies are expensive, typically costing from $4,500 to more than $10,000 per treatment month, even if they demonstrate only improvements in progression free survival without marked gains in overall survival.[15-20] The increasing costs of new targeted cancer therapies have risen ten times during the past decade.[21] Given the number of new cancer medicines in development and likely continual increases in drug prices, pricing of new anticancer drugs is a real concern for accessibility and affordability across all countries.[15,22,23] Some have suggested that a minimum of improvement in median survival of at least 3 to 6 months by new cancer medicines compared with current standards is required for the new agent to be considered as advanced and funded at higher prices.[24] Furthermore, because of the much higher costs of targeted therapies compared to conventional chemotherapy, while the number of eligible patients (due to molecular sub-typing) for individual agents is generally

small, in aggregate costs of targeted therapies as a group is an important contributor of growing expenditures for cancer treatments and an important issue of sustainability for all health care systems.[25-27]

Due to limited financial resources, patient access to targeted therapies has been a struggling issue in many countries.[28] Many countries have different ways to curb the growth of pharmaceutical expenditures in general. Examples include formal health technology assessment (for instance, economic evaluation of new drugs is required by many payers/policy makers such as the National Institute for Health Care Excellence in the United Kingdom,[29,30] and Pharmaceutical Benefits Advisory Committee in Australia[31,32] to select drugs for coverage.), pricing tools such as reference pricing,[33] and high patient cost-sharing (co-payments, coinsurance).[34] To deal with high drug costs and imperfect evidence at the time of marketing approval, many countries increasingly adopt patient access schemes (also known as managed entry agreements or risk-sharing arrangements) to enable patient access to needed medicines but ensuring that financing systems are sustainable[35,36]. The performance of managed entry agreements, however, is largely unknown because most have not been evaluated.[33] Major challenges at present for many health systems include determining what proportion of the health care budget should be allocated for treatment of cancer, including budget for targeted therapies, and designing and implementing new models for pricing, reimbursement, funding and utilization decisions for cancer medicines.[37]

In Taiwan, economic evaluation is part of health technology assessment to evaluate new drugs to determine decisions for coverage by the National Health Insurance since 2007.[38,39] In addition, prior authorization is required for many cancer medicines, especially for targeted therapies with high reimbursement prices. An application for prior authorization can be made to the National Health Insurance, and the drug will be reimbursed if authorization is given.[40] For instance, according to "Directions of Drug Restricted Benefit for National Health Insurance", two targeted therapies, gefitinib and erlotinib, for treatment of lung cancer have been reimbursed since 2004 and 2007, respectively. In the beginning, both of them were restricted to be used as third-line treatment, that is, patients must first be treated by platinum and docetaxel or paclitaxel chemotherapy and must only have locally advanced or metastatic adenocarcinoma of the lung.[41]

Little is known about the utilization and economic impacts of targeted cancer therapies in Taiwan. The aim of our longitudinal analyses was to address this gap by examining the recent trend in utilization and expenditures of cancer treatments, including targeted therapies, in Taiwan. We also identified which types of cancer accounted for the highest use of targeted therapies.

## Method

### *Data sources*

Taiwan's National Health Insurance Research Database provided data for this study. The database contains information from a nationwide, mandatory-enrollment and single-payer healthcare system created in 1995. Nearly 99% of the Taiwanese population (around 23 million residents) is enrolled and this system contracts with 97% of hospitals and clinics

throughout the country.[42] The National Health Insurance (NHI) covers a wide range of prescription medicines, and inpatient and outpatient medical services.[43] All monthly claims data, including details of prescription and insurer spending, for antineoplastic agents between 2009 and 2012 were retrieved from Taiwan's National Health Insurance Research Database. The cancer related prescriptions were identified by International Classification of Diseases, 9th edition (ICD-9) diagnosis codes for cancer (codes: 140-239).

***Drugs of interest***

We used the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization. We identified all antineoplastic agents using ATC codes "L01". Antineoplastic agents were grouped into 6 classes based on the ATC system: (1) targeted therapies, including monoclonal antibodies (rituximab, trastuzumab, cetuximab), protein kinase inhibitors (imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib), and bortezomib; these have been used for the treatment of cancer in Taiwan; (2) alkylating agents (including nitrogen mustard analogues, alkyl sulfonates, nitrosoureas and other alkylating agents); (3) antimetabolites (including folic acid analogues, purine analogues and pyrimidine analogues); (4) plant alkaloids and other natural products (including vinca alkaloids and analogues, podophyllotoxin derivatives and taxanes); (5) cytotoxic antibiotics and related substances (including actinomycines, anthracyclines and related substances and other cytotoxic antibiotics); and (6) other antineoplastic agents (including platinum compounds, sensitizers used in photodynamic/radiation therapy, and other antineoplastic agents).

***Measurements***

To examine trends in use and costs of each class of antineoplastic agents (including targeted therapies), we calculated quarterly and yearly number of prescriptions and costs from 2009 to 2012. Then, for each class we calculated the proportion of its use and costs among total use and total costs of all antineoplastic agents. For example, market share by prescription volume for targeted therapies was estimated by: number of prescriptions for targeted therapies divided by total number of prescriptions for all antineoplastic agents; and the market share by costs was estimated by: costs of targeted therapies divided by total costs of all antineoplastic agents. We also calculated cost per prescription for each class of antineoplastic agents.

To understand which cancers accounted for high use of targeted therapies, we first selected the most 20 common types of cancer in Taiwan based on prevalence (see appendix). We used the total prescription volume and total costs for targeted therapies in Taiwan as the denominator and analyzed using clinical indication of their use by type of cancer.

***Statistical Analysis***

To assess the quarterly trends in market shares by prescription volume and costs of targeted therapies among all antineoplastic agents, we used a time series design with the Autoregressive integrated moving average (ARIMA) model, which was developed by Box

and Jenkins.[44] The model is generally referred to as an ARIMA(p,d,q) model where parameters p, d, and q are non-negative integers that refer to the order of the autoregressive, integrated, and moving average parts of the model respectively. These models are fitted to time series data either to better understand the data or to determine points in the series.[45] We used the estimated rates by ARIMA model for time series graphs. All analyses were carried out with SAS software, Version 9.3 (SAS Institute, Cary, NC).

## Results

Between 2009 and 2012, prescriptions for antineoplastic agents grew 31.51% (an average rate of 10.5% increase per year) (Table 1). By class, prescriptions for alkylating agents, antimetabolites, plant alkaloids and cytotoxic antibiotics increased in number during this period, but their market shares decreased: -0.67%, -2.22%, -1.43%, -1.51% respectively. In contrast, the market share of targeted therapies grew from 6.24% in 2009 to 12.29% in 2012. Specifically, market shares of monoclonal antibodies and protein kinase inhibitors doubled, from 2.75% to 5.79% and from 3.38% to 6.18%, respectively. Figure 1A shows ARIMA regression estimated quarterly trends in market share by prescription volume for targeted therapies during the study period.

[Table 1] [Figure 1A]

Table 2 presents the costs for all and each type of antineoplastic drugs between 2009 and 2012. There was a large growth in total costs of antineoplastic agents from 2009 to 2012 (an overall increase of 50.67%, an average rate of 16.89% increase per year). By class, the yearly market share by costs for alkylating agents, antimetabolites, plant alkaloids and cytotoxic antibiotics reduced by 0.60%, 1.93%, 4.49%, 1.81% from 2009 to 2012. In contrast, annual costs of targeted therapies grew from US$129 million (26.16% of all costs for antineoplastic agents) in 2009 to US$308 million (41.57%) in 2012. Specifically, the market share by costs for monoclonal antibodies and protein kinase inhibitors increased from 14.63% to 23.84% and from 10.71% to 16.12%, respectively. Figure 1B shows ARIMA regression estimated quarterly the trend in market share by costs for targeted therapies during the study period.

[Table 2] [Figure 1B]

Table 3 shows the cost per prescription for each class of antineoplastic agents between 2009 and 2012. We found that, in 2012, targeted therapies had the highest cost per prescription (US$1,005), other antineoplastic agents in descending order by cost per prescription were plant alkaloids and other natural products (US$346), other non-targeted therapies (US$342), cytotoxic antibiotics and related substances (US$178), alkylating agents (US$128) and antimetabolites (US$115). There was about a 3-fold difference in cost per prescription between targeted therapies and plant alkaloids and other natural products, and about a 10-fold difference between targeted therapies and antimetabolites.

[Table 3]

Figure 2A and Figure 2B present the distribution ratios of targeted therapies use for 20 cancers during 2009-2012. Table 4 shows the yearly distribution ratios of targeted therapies use by cancer type over time. Our results showed that use and costs for targeted therapies

differed substantially between different types of cancer. During 2009-2012, targeted therapies were mostly used for cancers of lung, female breast, colorectal, lymphoma and leukemia in order of volume. These 5 cancer types accounted for 44.64%, 16.49%, 12.11%, 12.09% and 3.17% of prescriptions for targeted therapies (together 88.5%); and 28.26%, 27.18%, 13.16%, 10.23% and 4.94% of costs for targeted therapies (together 83.77%) among these 20 common cancer types.

[Figure 2A] [Figure 2B] [Table 4]

## Discussion

To our knowledge this is the first study that examined the national trend in use and costs of targeted therapies for treatment of cancer in Taiwan. Our findings indicated that, compared with other classes of antineoplastic drugs, use of targeted therapies, novel agents for cancer treatment, increased substantially and is causing great economic burden in Taiwan. Cancers of lung, female breast and colorectal accounted for the most use of targeted therapies.

Between 2009 and 2012, use and costs of targeted therapies increased almost 3-folds (Tables 1 and 2) with steep growths since the third quarter of 2011 (Figure 1). This trend is likely to continue in the future. We found that the average cost per prescription of targeted therapies was much higher than that of other classes of antineoplastic agents with 3-10 folds difference in 2012. It is important that policy makers revisit the pricing and reimbursement structures for these medicines because prices for all targeted therapies are high even for those that offer limited clinical benefits.

Our study adds to the literature that the availability and increasing use of innovative but expensive targeted therapies are major drivers of increases in pharmaceutical expenditures.[25,26] We showed that the costs of targeted therapies accounted for almost 42% of expenditures for all antineoplastic agents in Taiwan in 2012. Monoclonal antibodies and protein kinase inhibitors contributed the most (23.84% and 16.12% of costs for antineoplastic agents). Targeted therapies also dominate cancer drug expenditures in other countries, for example, 63% of all cancer drug expenditures in 2011 in the commercially insured population in the US.[46]

The high cost of targeted therapies is a barrier to access targeted therapies for treatment of cancer.[28] It is important to ensure patient access to effective targeted therapies without overspending the health care budget given their clinical benefits. Many experts propose that dialogue involving all parties concerned (eg. policy makers, industry, clinicians, patients, and the general public) is needed to address the reasons behind high prices of cancer drugs and offer solutions to reduce prices. Experts also propose that drug prices should reflect objective measures of benefit, but should not exceed values that could harm patients and societies.[27,47] Overall, strategies for future management of new cancer medicines might include raising the bar for clinical trials by defining clinically meaningful outcomes[48], establishing minimum effectiveness levels for new cancer medicines[15,24], generating a list of essential medicines for patients with cancer, discussing potential future measures to fund new innovative cancer medicines without potentially compromising patients/healthcare systems,[23] and determining the proportion of healthcare spent on cancer medicines based on the consideration of their

balance of costs and outcomes.[47]

There are some limitations to this study. First, this study aimed to examine recent trends in drug utilization and expenditures for cancer treatment and to estimate the market shares by prescription volume and costs for targeted therapies in Taiwan; our analysis only examined data up to 2012 as these were the more recent data available at the time of the analysis. We used aggregate data and did not analyze patient-level data to understand the influence of patient characteristics on treatment selection and clinical outcomes of treatments. This study also did not examine the complex patterns of drug use, such as use of combination treatments, targeted therapy adherence and persistence, again because of the lack of patient-level data. This study examined economic burden of targeted therapies from the perspective of the health care system; we did not examine patient contribution to drug costs in Taiwan, which warrants a separate study. Further, we did not characterize changes in the policy environment in Taiwan during the study period. Examples include the launch of new, competing targeted therapies, publication of large randomized clinical trials results, changes in clinical guidelines or reimbursement policies, and patient and provider factors (e.g. patient clinical history, physician's knowledge and preference). Future studies are needed to examine impact of changes in policy and clinical environment on use of targeted therapies. Finally, various types of restrictions (eg. prior authorizations) have been applied for many high-cost targeted therapies for cancer in Taiwan.[49] How these restrictions impact cancer care and outcomes should be studied.

## Conclusion

Targeted therapies have played an increasing and more important role in treatment of all malignancies in Taiwan, and they are likely to pose substantial economic burden in the future. Cancers of lung, female breast and colorectal were identified as main drivers of use and costs of targeted therapies in recent years. Policy makers, industry, clinicians and patients need to communicate and develop strategies to enable access to effective (and cost-effective) targeted therapies without overspending the health care budget.

## ■ Author Contributions

JCH and CYL conceptualized and designed the study. JCH collected data, performed analysis, and drafted the manuscript. CYL reviewed all data and revised the manuscript critically for intellectual content. All authors approved the final version for submission.

## ■ Competing Interests

The authors have no competing interests.


## ■ Funding

Dr. Hsu was supported by a grant from Taiwan's Ministry of Science and Technology (Grant ID MOST 104-2320-B-006-005). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Dr. Lu received no funding for this study.


## ■ Data Sharing Statement

We obtained nationwide, monthly claims data for cancer related antineoplastic agents between 2009 and 2012 from the Taiwan National Health Insurance Research database (NHIRD). NHIRD does not permit external sharing of any of the data elements.

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**Tables**



**Figures**

## Table 1. Prescription volume of antineoplastic agents in Taiwan (2009-2012)

| Drug Class | Drug name for patients with cancer | Number of Prescription (market share by prescription volume) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2009 | | 2010 | | 2011 | | 2012 | | 2009-2012 | |
| | | N | (%) | N | (%) | N | (%) | N | (%) | growth rate of N (%) | growth rate of market share (%) |
| All Antineoplastic Agents | | 1,893,439 | 100 | 2,033,160 | 100 | 2,300,629 | 100 | 2,489,973 | 100 | 31.51 | |
| Targeted Therapies | | 118,186 | 6.24 | 150,401 | 7.40 | 209,030 | 9.09 | 306,140 | 12.29 | 159.03 | 6.05 |
| Monoclonal antibodies | rituximab, trastuzumab, cetuximab, bevacizumab | 52,073 | 2.75 | 68,595 | 3.37 | 102,074 | 4.44 | 144,234 | 5.79 | 176.98 | 3.04 |
| Protein kinase inhibitors | imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib | 63,936 | 3.38 | 78,675 | 3.87 | 102,435 | 4.45 | 153,764 | 6.18 | 140.50 | 2.80 |
| Other targeted therapy agents | bortezomib | 2,177 | 0.11 | 3,131 | 0.15 | 4,521 | 0.20 | 8,142 | 0.33 | 274.00 | 0.21 |
| Alkylating Agents | | 125,811 | 6.64 | 132,109 | 6.50 | 147,076 | 6.39 | 148,654 | 5.97 | 18.16 | -0.67 |
| Nitrogen mustard analogues | cyclophosphamide, chlorambucil, melphalan, ifosfamide, bendamustine | 112,602 | 5.95 | 117,101 | 5.76 | 125,769 | 5.47 | 130,042 | 5.22 | 15.49 | -0.72 |
| Alkyl sulfonates | busulfan | 301 | 0.02 | 279 | 0.01 | 318 | 0.01 | 255 | 0.01 | -15.28 | -0.01 |
| Nitrosoureas | carmustine | 250 | 0.01 | 218 | 0.01 | 263 | 0.01 | 321 | 0.01 | 28.40 | 0.00 |
| Other alkylating agents | temozolomide, dacarbazine | 12,658 | 0.67 | 14,511 | 0.71 | 20,726 | 0.90 | 18,036 | 0.72 | 42.49 | 0.06 |
| Antimetabolites | | 911,611 | 48.15 | 965,096 | 47.47 | 1,076,871 | 46.81 | 1,143,596 | 45.93 | 25.45 | -2.22 |
| Folic acid analogues | methotrexate, pemetrexed | 316,174 | 16.70 | 349,463 | 17.19 | 386,008 | 16.78 | 426,480 | 17.13 | 34.89 | 0.43 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Purine analogues | mercaptopurine, cladribine, fludarabine | 12,550 | 0.66 | 12,094 | 0.59 | 12,277 | 0.53 | 12,891 | 0.52 | 2.72 | -0.15 |
| | Pyrimidine analogues | cytarabine, fluorouracil, tegafur, gemcitabine, capecitabine, tegafur_combinations | 582,887 | 30.78 | 603,539 | 29.68 | 678,586 | 29.50 | 704,225 | 28.28 | 20.82 | -2.50 |
| Plant Alkaloids and other Natural Products | | | 217,347 | 11.48 | 222,304 | 10.93 | 250,312 | 10.88 | 250,273 | 10.05 | 15.15 | -1.43 |
| | Vinca alkaloids and analogues | vinblastine, vincristine, vinorelbine | 84,009 | 4.44 | 85,659 | 4.21 | 88,135 | 3.83 | 88,377 | 3.55 | 5.20 | -0.89 |
| | Podophyllotoxin derivatives | etoposide | 28,864 | 1.52 | 30,188 | 1.48 | 32,990 | 1.43 | 34,587 | 1.39 | 19.83 | -0.14 |
| | Taxanes | paclitaxel, docetaxel | 104,474 | 5.52 | 106,457 | 5.24 | 129,187 | 5.62 | 127,309 | 5.11 | 21.86 | -0.40 |
| Cytotoxic Antibiotics and Related Substances | | | 140,168 | 7.40 | 140,697 | 6.92 | 145,663 | 6.33 | 146,796 | 5.90 | 4.73 | -1.51 |
| | Actinomycines | dactinomycin | 616 | 0.03 | 698 | 0.03 | 667 | 0.03 | 761 | 0.03 | 23.54 | 0.00 |
| | Anthracyclines and related substances | doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone | 99,422 | 5.25 | 101,826 | 5.01 | 107,177 | 4.66 | 106,499 | 4.28 | 7.12 | -0.97 |
| | Other cytotoxic antibiotics | bleomycin, mitomycin | 40,130 | 2.12 | 38,173 | 1.88 | 37,819 | 1.64 | 39,536 | 1.59 | -1.48 | -0.53 |
| Other non-Targeted Therapies | | | 380,316 | 20.09 | 422,553 | 20.78 | 471,677 | 20.50 | 494,514 | 19.86 | 30.03 | -0.23 |
| | Platinum compounds | cisplatin, carboplatin, oxaliplatin | 254,636 | 13.45 | 286,260 | 14.08 | 304,437 | 13.23 | 306,659 | 12.32 | 20.43 | -1.13 |
| | Sensitizers used in photodynamic / radiation therapy | verteporfin | 120 | 0.01 | 88 | 0.00 | 88 | 0.00 | 95 | 0.00 | -20.83 | 0.00 |
| | Others | asparaginase, hydroxycarbamide, estramustine, tretinoin, | 125,560 | 6.63 | 136,205 | 6.70 | 167,152 | 7.27 | 187,760 | 7.54 | 49.54 | 0.91 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **topotecan, irinotecan, mitotane, arsenic trioxide** | | | | | | | | | | |

**Table 2. Costs of antineoplastic agents in Taiwan (2009-2012)**

| Drug Class | Drug name for patients with cancer | Cost (market share by costs) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2009 | | 2010 | | 2011 | | 2012 | | 2009-2012 | |
| | | Cost (US$) | (%) | Cost (US$) | (%) | Cost (US$) | (%) | Cost (US$) | (%) | growth rate of N (%) | growth rate of market share (%) |
| All Antineoplastic Agents | | 491,387,822 | 100 | 570,369,759 | 100 | 660,138,086 | 100 | 740,386,783 | 100 | 50.67 | |
| Targeted Therapies | | 128,541,502 | 26.16 | 177,668,722 | 31.15 | 224,327,855 | 33.98 | 307,754,974 | 41.57 | 139.42 | 15.41 |
| Monoclonal antibodies | rituximab, trastuzumab, cetuximab, bevacizumab | 71,869,602 | 14.63 | 104,739,673 | 18.36 | 137,951,386 | 20.90 | 176,477,405 | 23.84 | 145.55 | 9.21 |
| Protein kinase inhibitors | imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib | 52,651,186 | 10.71 | 67,484,747 | 11.83 | 79,001,874 | 11.97 | 119,383,796 | 16.12 | 126.74 | 5.41 |
| Other targeted therapy agents | bortezomib | 4,020,714 | 0.82 | 5,444,303 | 0.95 | 7,374,595 | 1.12 | 11,893,774 | 1.61 | 195.81 | 0.79 |
| Alkylating Agents | | 15,551,932 | 3.16 | 17,481,103 | 3.06 | 18,968,906 | 2.87 | 18,999,092 | 2.57 | 22.17 | -0.60 |
| Nitrogen mustard analogues | cyclophosphamide, chlorambucil, melphalan, ifosfamide, bendamustine | 4,495,217 | 0.91 | 4,897,936 | 0.86 | 4,878,608 | 0.74 | 4,261,046 | 0.58 | -5.21 | -0.34 |
| Alkyl sulfonates | busulfan | 374,465 | 0.08 | 454,805 | 0.08 | 460,163 | 0.07 | 488,410 | 0.07 | 30.43 | -0.01 |
| Nitrosoureas | carmustine | 41,620 | 0.01 | 43,440 | 0.01 | 153,101 | 0.02 | 392,128 | 0.05 | 842.16 | 0.04 |
| Other | temozolomide, dacarbazine | 10,640,629 | 2.17 | 12,084,922 | 2.12 | 13,477,034 | 2.04 | 13,857,508 | 1.87 | 30.23 | -0.29 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | alkylating agents | | | | | | | | | | | |
| Antimetabolites | | | 96,951,076 | 19.73 | 117,122,829 | 20.53 | 128,199,087 | 19.42 | 131,805,930 | 17.80 | 35.95 | -1.93 |
| | Folic acid analogues | methotrexate, pemetrexed | 31,305,924 | 6.37 | 50,705,521 | 8.89 | 61,101,669 | 9.26 | 66,069,402 | 8.92 | 111.04 | 2.55 |
| | Purine analogues | mercaptopurine, cladribine, fludarabine | 304,010 | 0.06 | 265,754 | 0.05 | 365,404 | 0.06 | 311,619 | 0.04 | 2.50 | -0.02 |
| | Pyrimidine analogues | cytarabine, fluorouracil, tegafur, gemcitabine, capecitabine, tegafur_combinations | 65,341,142 | 13.30 | 66,151,554 | 11.60 | 66,732,014 | 10.11 | 65,424,909 | 8.84 | 0.13 | -4.46 |
| Plant Alkaloids and other Natural Products | | | 79,509,189 | 16.18 | 72,920,907 | 12.78 | 84,694,476 | 12.83 | 86,583,703 | 11.69 | 8.90 | -4.49 |
| | Vinca alkaloids and analogues | vinblastine, vincristine, vinorelbine | 20,326,687 | 4.14 | 22,006,619 | 3.86 | 23,924,553 | 3.62 | 25,170,345 | 3.40 | 23.83 | -0.74 |
| | Podophyllotoxin derivatives | etoposide | 2,164,352 | 0.44 | 1,643,415 | 0.29 | 1,651,811 | 0.25 | 1,579,203 | 0.21 | -27.04 | -0.23 |
| | Taxanes | paclitaxel, docetaxel | 57,018,150 | 11.60 | 49,270,873 | 8.64 | 59,118,111 | 8.96 | 59,834,155 | 8.08 | 4.94 | -3.52 |
| Cytotoxic Antibiotics and Related Substances | | | 26,190,529 | 5.33 | 26,232,768 | 4.60 | 27,270,661 | 4.13 | 26,075,058 | 3.52 | -0.44 | -1.81 |
| | Actinomycines | dactinomycin | 16,854 | 0.00 | 18,603 | 0.00 | 18,303 | 0.00 | 19,062 | 0.00 | 13.10 | 0.00 |
| | Anthracyclines and related substances | doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone | 24,489,365 | 4.98 | 24,531,634 | 4.30 | 25,576,627 | 3.87 | 24,215,313 | 3.27 | -1.12 | -1.71 |
| | Other cytotoxic antibiotics | bleomycin, mitomycin | 1,684,311 | 0.34 | 1,682,531 | 0.29 | 1,675,731 | 0.25 | 1,840,682 | 0.25 | 9.28 | -0.09 |
| Other non-Targeted Therapies | | | 144,643,593 | 29.44 | 158,943,430 | 27.87 | 176,677,101 | 26.76 | 169,168,026 | 22.85 | 16.96 | -6.59 |
| | Platinum compounds | cisplatin, carboplatin, oxaliplatin | 50,363,294 | 10.25 | 53,988,423 | 9.47 | 52,077,277 | 7.89 | 35,697,261 | 4.82 | -29.12 | -5.43 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Sensitizers used in photodynamic / radiation therapy** | **verteporfin** | **169,600** | **0.03** | **124,373** | **0.02** | **124,373** | **0.02** | **134,267** | **0.02** | **-20.83** | **-0.02** |
| | | **Others** | **asparaginase, hydroxycarbamide, estramustine, tretinoin, topotecan, irinotecan, mitotane, arsenic trioxide** | **94,110,699** | **19.15** | **104,830,634** | **18.38** | **124,475,451** | **18.86** | **133,336,498** | **18.01** | **41.68** | **-1.14** |

## Table 3. Cost per prescription of antineoplastic agents in Taiwan (2009-2012)

| Drug Class | Drug name for patients with cancer | Cost per Prescription (US$) | | | |
|---|---|---|---|---|---|
| | | 2,009 | 2,010 | 2,011 | 2,012 |
| All Antineoplastic Agents | | 260 | 281 | 287 | 297 |
| Targeted Therapies | | 1,088 | 1,181 | 1,073 | 1,005 |
| Monoclonal antibodies | rituximab, trastuzumab, cetuximab, bevacizumab | 1,380 | 1,527 | 1,351 | 1,224 |
| Protein kinase inhibitors | imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib | 823 | 858 | 771 | 776 |
| Other targeted therapy agents | bortezomib | 1,847 | 1,739 | 1,631 | 1,461 |
| Alkylating Agents | | 124 | 132 | 129 | 128 |
| Nitrogen mustard analogues | cyclophosphamide, chlorambucil, melphalan, ifosfamide, bendamustine | 40 | 42 | 39 | 33 |
| Alkyl sulfonates | busulfan | 1,244 | 1,630 | 1,447 | 1,915 |
| Nitrosoureas | carmustine | 166 | 199 | 582 | 1,222 |
| Other alkylating agents | temozolomide, dacarbazine | 841 | 833 | 650 | 768 |
| Antimetabolites | | 106 | 121 | 119 | 115 |
| Folic acid analogues | methotrexate, pemetrexed | 99 | 145 | 158 | 155 |
| Purine analogues | mercaptopurine, cladribine, fludarabine | 24 | 22 | 30 | 24 |
| Pyrimidine analogues | cytarabine, fluorouracil, tegafur, gemcitabine, capecitabine, tegafur_combinations | 112 | 110 | 98 | 93 |
| Plant Alkaloids and other Natural Products | | 366 | 328 | 338 | 346 |
| Vinca alkaloids and analogues | vinblastine, vincristine, vinorelbine | 242 | 257 | 271 | 285 |
| Podophyllotoxin derivatives | etoposide | 75 | 54 | 50 | 46 |
| Taxanes | paclitaxel, docetaxel | 546 | 463 | 458 | 470 |
| Cytotoxic Antibiotics and Related Substances | | 187 | 186 | 187 | 178 |
| Actinomycines | dactinomycin | 27 | 27 | 27 | 25 |
| Anthracyclines and related substances | doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone | 246 | 241 | 239 | 227 |
| Other cytotoxic antibiotics | bleomycin, mitomycin | 42 | 44 | 44 | 47 |
| Other non-Targeted Therapies | | 380 | 376 | 375 | 342 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Platinum compounds | cisplatin, carboplatin, oxaliplatin | 198 | 189 | 171 | 116 |
| | | Sensitizers used in photodynamic / radiation therapy | verteporfin | 1,413 | 1,413 | 1,413 | 1,413 |
| | | Others | asparaginase, hydroxycarbamide, estramustine, tretinoin, topotecan, irinotecan, mitotane, arsenic trioxide | 750 | 770 | 745 | 710 |

**Table 4. Use and costs of targeted therapies by cancer type over time**

| Cancer type | | Distribution ratio based on prescription volume (%) | | | | | | Distribution ratio of costs (%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2009 | 2010 | 2011 | 2012 | 2009-2012 overall | 2009-2012 Growth rate | 2009 | 2010 | 2011 | 2012 | 2009-2012 overall | 2009-2012 Growth rate |
| 01 | Lung | 51.87 | 45.94 | 43.03 | 42.18 | 44.64 | -9.68 | 39.55 | 28.79 | 25.48 | 25.24 | 28.26 | -14.32 |
| 02 | Female breast | 11.71 | 18.62 | 18.47 | 15.95 | 16.49 | 4.24 | 20.91 | 31.45 | 30.60 | 24.78 | 27.18 | 3.87 |
| 03 | Colorectal | 9.52 | 7.01 | 12.32 | 15.62 | 12.11 | 6.10 | 12.12 | 8.65 | 13.13 | 16.29 | 13.16 | 4.16 |
| 04 | Lymphoma | 17.87 | 14.92 | 11.84 | 8.50 | 12.09 | -9.37 | 15.24 | 11.63 | 9.96 | 7.49 | 10.23 | -7.74 |
| 05 | Liver | 0.24 | 0.23 | 0.28 | 3.93 | 1.66 | 3.69 | 0.25 | 0.22 | 0.28 | 5.65 | 2.22 | 5.40 |
| 06 | Leukemia | 1.75 | 2.81 | 3.66 | 3.57 | 3.17 | 1.83 | 2.50 | 4.80 | 5.60 | 5.56 | 4.94 | 3.06 |
| 07 | Urinary | 0.43 | 2.70 | 3.01 | 2.82 | 2.48 | 2.39 | 0.52 | 4.53 | 5.25 | 4.95 | 4.26 | 4.43 |
| 08 | Multiple myeloma | 1.92 | 2.11 | 2.39 | 3.07 | 2.52 | 1.15 | 3.37 | 3.19 | 3.60 | 4.45 | 3.79 | 1.08 |
| 09 | Oral/pharyngeal | 1.58 | 2.40 | 2.01 | 1.48 | 1.82 | -0.10 | 1.59 | 2.43 | 2.03 | 1.57 | 1.88 | -0.03 |
| 10 | Stomach | 0.97 | 0.77 | 0.62 | 0.58 | 0.69 | -0.39 | 1.28 | 1.14 | 1.04 | 0.93 | 1.06 | -0.35 |
| 11 | Brain | 0.34 | 0.24 | 0.27 | 0.48 | 0.36 | 0.14 | 0.27 | 0.18 | 0.17 | 0.60 | 0.34 | 0.33 |
| 12 | Small intestine and duodenum | 0.43 | 0.51 | 0.43 | 0.34 | 0.41 | -0.09 | 0.80 | 0.99 | 0.90 | 0.74 | 0.85 | -0.06 |
| 13 | Bone | 0.45 | 0.48 | 0.44 | 0.33 | 0.41 | -0.12 | 0.65 | 0.74 | 0.80 | 0.57 | 0.68 | -0.08 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | Thyroid | 0.15 | 0.13 | 0.22 | 0.22 | 0.19 | 0.07 | 0.20 | 0.14 | 0.20 | 0.20 | 0.19 | 0.00 |
| 15 | Prostate | 0.18 | 0.23 | 0.19 | 0.22 | 0.20 | 0.04 | 0.16 | 0.27 | 0.18 | 0.22 | 0.21 | 0.06 |
| 16 | Larynx | 0.24 | 0.48 | 0.41 | 0.26 | 0.34 | 0.02 | 0.26 | 0.47 | 0.41 | 0.27 | 0.35 | 0.01 |
| 17 | Pancreas | 0.01 | 0.02 | 0.10 | 0.14 | 0.09 | 0.13 | 0.01 | 0.02 | 0.06 | 0.20 | 0.10 | 0.19 |
| 18 | Cervix | 0.16 | 0.20 | 0.14 | 0.11 | 0.14 | -0.05 | 0.16 | 0.17 | 0.13 | 0.10 | 0.13 | -0.05 |
| 19 | Esophagus | 0.09 | 0.12 | 0.13 | 0.09 | 0.11 | 0.01 | 0.07 | 0.12 | 0.13 | 0.10 | 0.11 | 0.03 |
| 20 | Ovary | 0.10 | 0.08 | 0.05 | 0.10 | 0.08 | 0.00 | 0.09 | 0.08 | 0.05 | 0.08 | 0.07 | -0.01 |
| | Total | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | | 100.00 | 100.00 | 100.00 | 100.00 | 100.00 | |

2

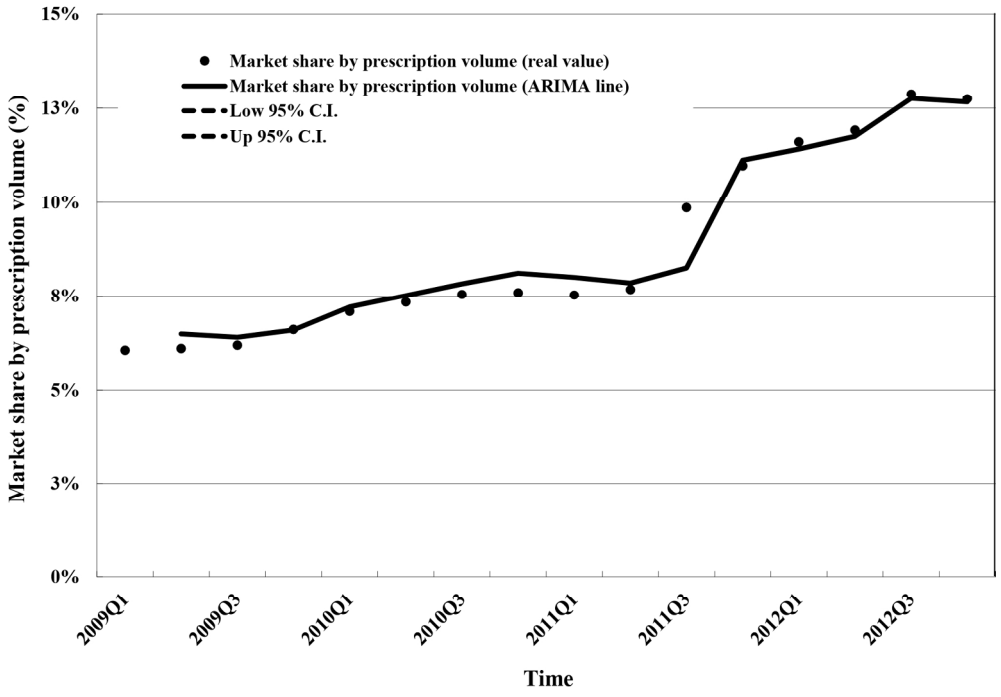


Figure 1A.
173x121mm (300 x 300 DPI)

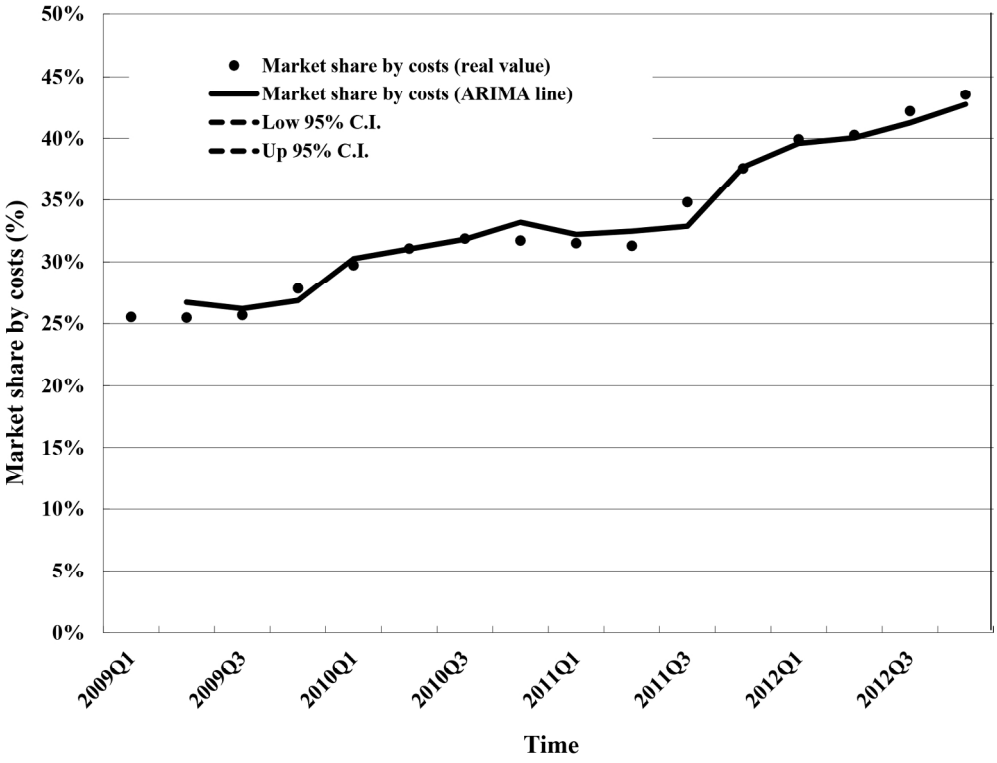


Figure 1B.
173x133mm (300 x 300 DPI)

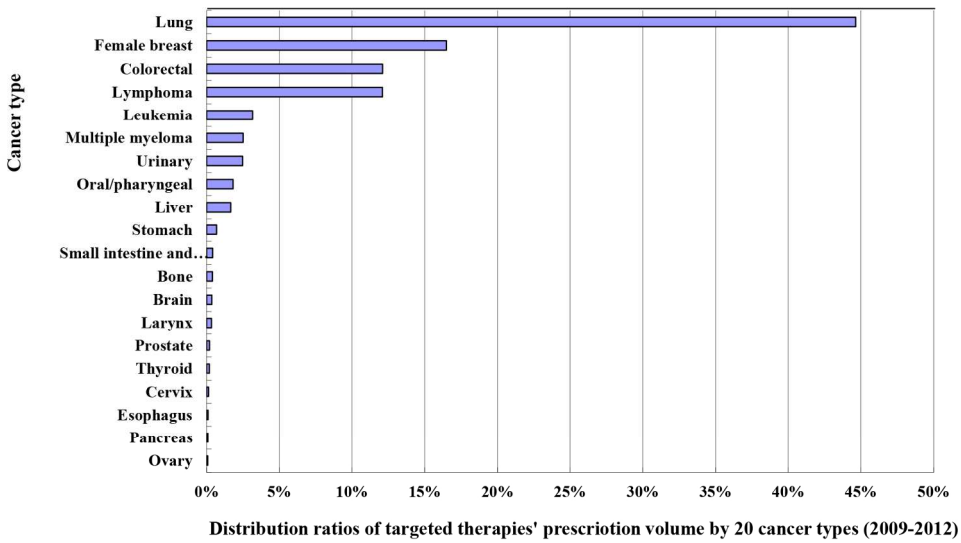


Figure 2A.
173x92mm (300 x 300 DPI)

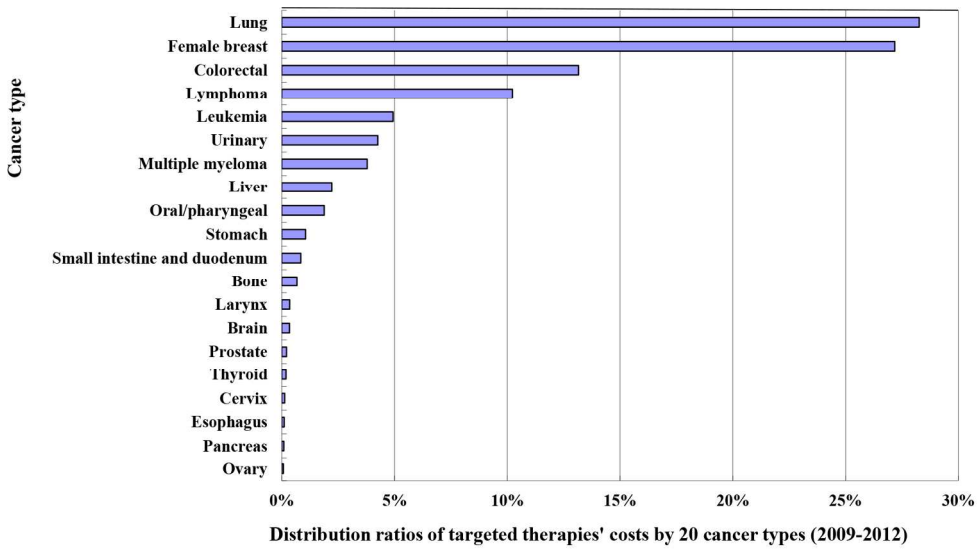


Figure 2B.
173x93mm (300 x 300 DPI)

## Appendix

**ICD-9-CM diagnosis code identifying patients with various types of cancer:**

| | Types of cancer in this study | ICD-9 codes |
|---|---|---|
| 1 | Lung (including trachea. bronchus and lung) | 162 |
| 2 | Female breast | 174 |
| 3 | Colorectal (including colon, rectum, rectosigmoid junction and anus) | 153-154 |
| 4 | Lymphoma (including lymphosarcoma, eticulosarcoma and Hodgkin's disease) | 200-202 |
| 5 | Liver (including liver and intrahepatic bile ducts) | 155 |
| 6 | Leukemia (including lymphoid, myeloid monocytic and other specific leukemia) | 204-208 |
| 7 | Urinary (including bladder, kidney and other and unspecified urinary organs) | 188-189 |
| 8 | Multiple myeloma (including multiple myeloma and immunoproliferative neoplasms) | 203 |
| 9 | Oral/pharyngeal (including lip, tongue, major salivary glands, gum, floor of mouth, other and unspecified parts of mouth, oropharynx, nasopharynx, hypopharynx and others) | 140-149 |
| 10 | Stomach | 151 |
| 11 | Brain | 191 |
| 12 | Small intestine and duodenum | 152 |
| 13 | Bone (including bone, articular cartilage, connective and other soft tissue) | 170-171 |
| 14 | Thyroid | 193 |
| 15 | Prostate | 185 |
| 16 | Larynx | 161 |
| 17 | Pancreas | 157 |
| 18 | Cervix | 180 |
| 19 | Esophagus | 150 |
| 20 | Ovary (including ovary and other uterine adnexa) | 183 |

STROBE Statement—checklist of items that should be included in reports of observational studies

| Page | | Item No | Recommendation |
|---|---|---|---|
| 1 | **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| 1-2 | | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| | **Introduction** | | |
| 3 | Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| 3 | Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| | **Methods** | | |
| 4 | Study design | 4 | Present key elements of study design early in the paper |
| 4 | Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| 4 | Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| 4 | | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| 4 | Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| 4 | Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| 4 | Bias | 9 | Describe any efforts to address potential sources of bias |
| 4 | Study size | 10 | Explain how the study size was arrived at |
| 4 | Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| 5 | Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| 4-5 | | | (*b*) Describe any methods used to examine subgroups and interactions |
| NA | | | (*c*) Explain how missing data were addressed |
| NA | | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| NA | | | (*e*) Describe any sensitivity analyses |

Continued on next page

| | | | |
|---|---|---|---|
| Page | **Results** | | |
| NA | Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| NA | | | (b) Give reasons for non-participation at each stage |
| NA | | | (c) Consider use of a flow diagram |
| 11-14 | Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| NA | | | (b) Indicate number of participants with missing data for each variable of interest |
| NA | | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| NA | Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| NA | | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| NA | | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| 5-6; 11-14 | Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| 5-6 | | | (*b*) Report category boundaries when continuous variables were categorized |
| NA | | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| 5-6; 11-14 | Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| | **Discussion** | | |
| 6-7 | Key results | 18 | Summarise key results with reference to study objectives |
| 7 | Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| 6-7 | Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| 6-7 | Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| | **Other information** | | |
| No funding | Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.