Longitudinal trends in use and costs of targeted therapies for common cancers in Taiwan: a retrospective observational study

BMJ Open

Longitudinal trends in use and costs of targeted therapies for common cancers in Taiwan: a retrospective observational study

Jason C Hsu,[1] Christine Y Lu[2]

To cite: Hsu JC, Lu CY. Longitudinal trends in use and costs of targeted therapies for common cancers in Taiwan: a retrospective observational study. *BMJ Open* 2016;**6**: e011322. doi:10.1136/bmjopen-2016-011322

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-011322).

Received 29 January 2016
Revised 28 April 2016
Accepted 18 May 2016

[1]School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan City, Taiwan
[2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts, USA

Correspondence to
Dr Jason C Hsu;
jasonhsuharvard@gmail.com

ABSTRACT

Objectives: Some targeted therapies have improved survival and overall quality of cancer care generally, but these increasingly expensive medicines 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 over time. We also determined which cancer types accounted for the highest use of targeted therapies.

Design: This is a retrospective observational study focusing on the utilisation 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 agent by cancer type. Using a time series design with Autoregressive Integrated Moving Average (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% in that time. Monoclonal antibodies and protein kinase inhibitors contributed the most (respectively, 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: In Taiwan, targeted therapies are increasingly used for different cancers, representing a substantial economic burden. It is important to establish mechanisms to monitor their use and outcomes.

Strengths and limitations of this study

- This is the first study to examine 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 included.
- A time series design with Autoregressive Integrated Moving Average (ARIMA) models was used in this study, to estimate the trends in market shares by prescription volume and costs of targeted therapies.
- Owing to the lack of patient-level data, this study did not investigate the use of combination treatments; these need to be examined in future studies.

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 patients with cancer has been growing.[3] In 2011, ~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, ~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 neutropaenia, anaemia and thrombocytopaenia.[7] In the last decade, however, many new anticancer 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 human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer.[12 13] Dozens of targeted therapies have become available in recent years and many are in the drug development pipeline.[14] While some have demonstrated improvements in progression-free survival, other agents have provided 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 US$4500 to >US$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 10 times during the last 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 3–6 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 with conventional chemotherapy—while the number of eligible patients (due to molecular subtyping) for individual agents is generally small—in aggregate, costs of targeted therapies as a group is an important contributor to growing expenditures for cancer treatments and an important issue of sustainability for all healthcare systems.[25–27]

Owing to limited financial resources, patient access to targeted therapies has been a struggle in many countries.[28] Many countries have different ways to kerb 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/policymakers such as the National Institute for Health and Care Excellence in the UK[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, co-insurance).[34] To deal with high drug costs and imperfect evidence at the time of marketing approval, many countries are increasingly adopting patient access schemes (also known as managed entry agreements or risk-sharing arrangements) to enable patient access to needed medicines, while 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 healthcare budget should be allocated for treatment of cancer, including budget for targeted therapies, and designing and implementing new models for pricing, reimbursement, funding and utilisation decisions for cancer medicines.[37]

In Taiwan, economic evaluation has, since 2007, been part of the health technology assessment to evaluate new drugs, to determine decisions for coverage by the National Health Insurance (NHI).[38 39] In addition, prior authorisation is required for many cancer medicines, especially for targeted therapies with high reimbursement prices. An application for prior authorisation can be made to the NHI system, and the drug will be reimbursed if authorisation 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 were restricted to be used as third-line treatment, that is, patients must first have been treated with platinum and docetaxel or paclitaxel chemotherapy, and must have had locally advanced or metastatic adenocarcinoma of the lung.[41]

Little is known about the utilisation 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 utilisation 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.

METHODS

Data sources

Taiwan's National Health Insurance Research Database provided data for this study. The database contains information from a nationwide, mandatory-enrolment 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 NHI covers a wide range of prescription medicines, as well as 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, Ninth edition (ICD-9) diagnosis codes for cancer (codes 140–239).

Table 1 Prescription volume of antineoplastic agents in Taiwan (2009–2012)

Drug class	Drug name for patients with cancer	Number of prescriptions (market share by prescription volume) 2009 N	2009 Per cent	2010 N	2010 Per cent	2011 N	2011 Per cent	2012 N	2012 Per cent	2009–2012 Growth rate of N (%)	2009–2012 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	2177	0.11	3131	0.15	4521	0.20	8142	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
Sensitisers 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

Drugs of interest

We used the Anatomical Therapeutic Chemical (ATC) classification system developed by the WHO. We identified all antineoplastic agents using ATC codes 'L01'. Antineoplastic agents were grouped into six 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 all 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, sensitisers used in photodynamic/radiation therapy and other antineoplastic agents).

Measurements

To examine trends in use and costs of each class of antineoplastic agent (including targeted therapies), we calculated quarterly and yearly numbers 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 agent.

To understand which cancers accounted for high use of targeted therapies, we first selected the 20 most common types of cancer in Taiwan, based on prevalence (see online supplementary appendix). We used the total prescription volume and total costs for targeted therapies in Taiwan as the denominator and conducted analyses 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, V.9.3 (SAS Institute, Cary, North Carolina, USA).

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% and −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

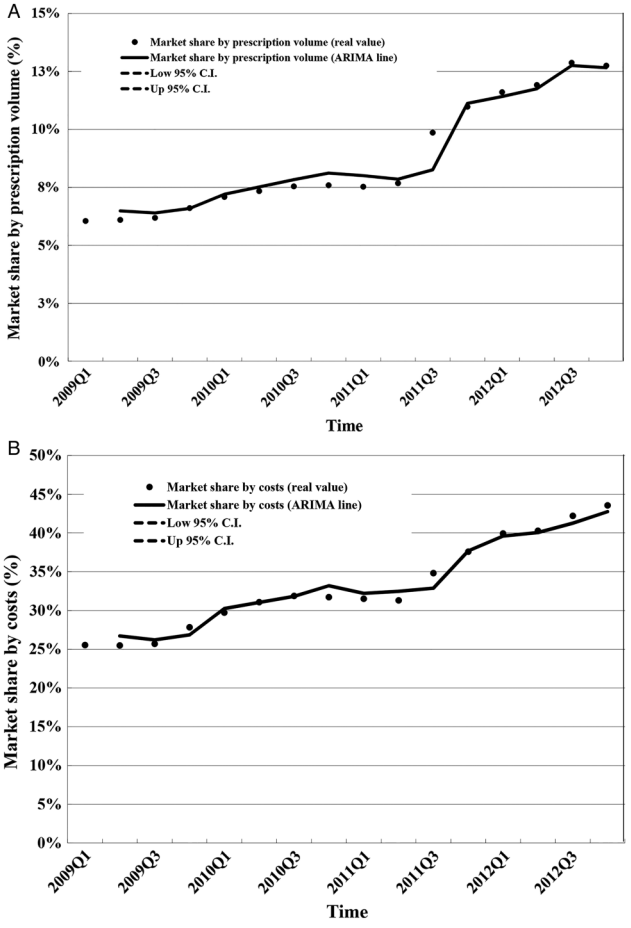

Figure 1 The 2009–2012 trends in market shares by prescription volume (A) and costs (B) for targeted therapies. (A) Market share by prescription volume. (B) Market share by costs. ARIMA, Autoregressive Integrated Moving Average.

Table 2 Costs of antineoplastic agents in Taiwan (2009–2012)

Drug class	Drug name for patients with cancer	Cost (market share by costs) 2009 Cost (US$)	2009 Per cent	2010 Cost (US$)	2010 Per cent	2011 Cost (US$)	2011 Per cent	2012 Cost (US$)	2012 Per cent	2009–2012 Growth rate of N (%)	2009–2012 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

Continued

Table 2 Continued

Drug class	Drug name for patients with cancer	Cost (market share by costs) 2009 Cost (US$)	2009 Per cent	2010 Cost (US$)	2010 Per cent	2011 Cost (US$)	2011 Per cent	2012 Cost (US$)	2012 Per cent	2009–2012 Growth rate of N (%)	2009–2012 Growth rate of market share (%)
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
Sensitisers 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

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 2 presents the costs for all and each type of antineoplastic drug 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% and 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 the ARIMA regression estimated quarterly trend in market share by costs for targeted therapies during the study period.

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$1005), 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.

Figure 2A, B presents the distribution ratios of targeted therapy use for 20 cancers during 2009–2012. Table 4 shows the yearly distribution ratios of targeted

Table 3 Cost per prescription of antineoplastic agents in Taiwan (2009–2012)

Drug class	Drug name for patients with cancer	Cost per prescription (US$)			
		2009	2010	2011	2012
All antineoplastic agents		260	281	287	297
Targeted therapies		1088	1181	1073	1005
Monoclonal antibodies	Rituximab, trastuzumab, cetuximab, bevacizumab	1380	1527	1351	1224
Protein kinase inhibitors	Imatinib, gefitinib, erlotinib, sunitinib, sorafenib, dasatinib, nilotinib, temsirolimus, everolimus, pazopanib	823	858	771	776
Other targeted therapy agents	bortezomib	1847	1739	1631	1461
Alkylating agents		124	132	129	128
Nitrogen mustard analogues	Cyclophosphamide, chlorambucil, melphalan, ifosfamide, bendamustine	40	42	39	33
Alkyl sulfonates	Busulfan	1244	1630	1447	1915
Nitrosoureas	Carmustine	166	199	582	1222
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
Sensitisers used in photodynamic/radiation therapy	Verteporfin	1413	1413	1413	1413
Others	Asparaginase, hydroxycarbamide, estramustine, tretinoin, topotecan, irinotecan, mitotane, arsenic trioxide	750	770	745	710

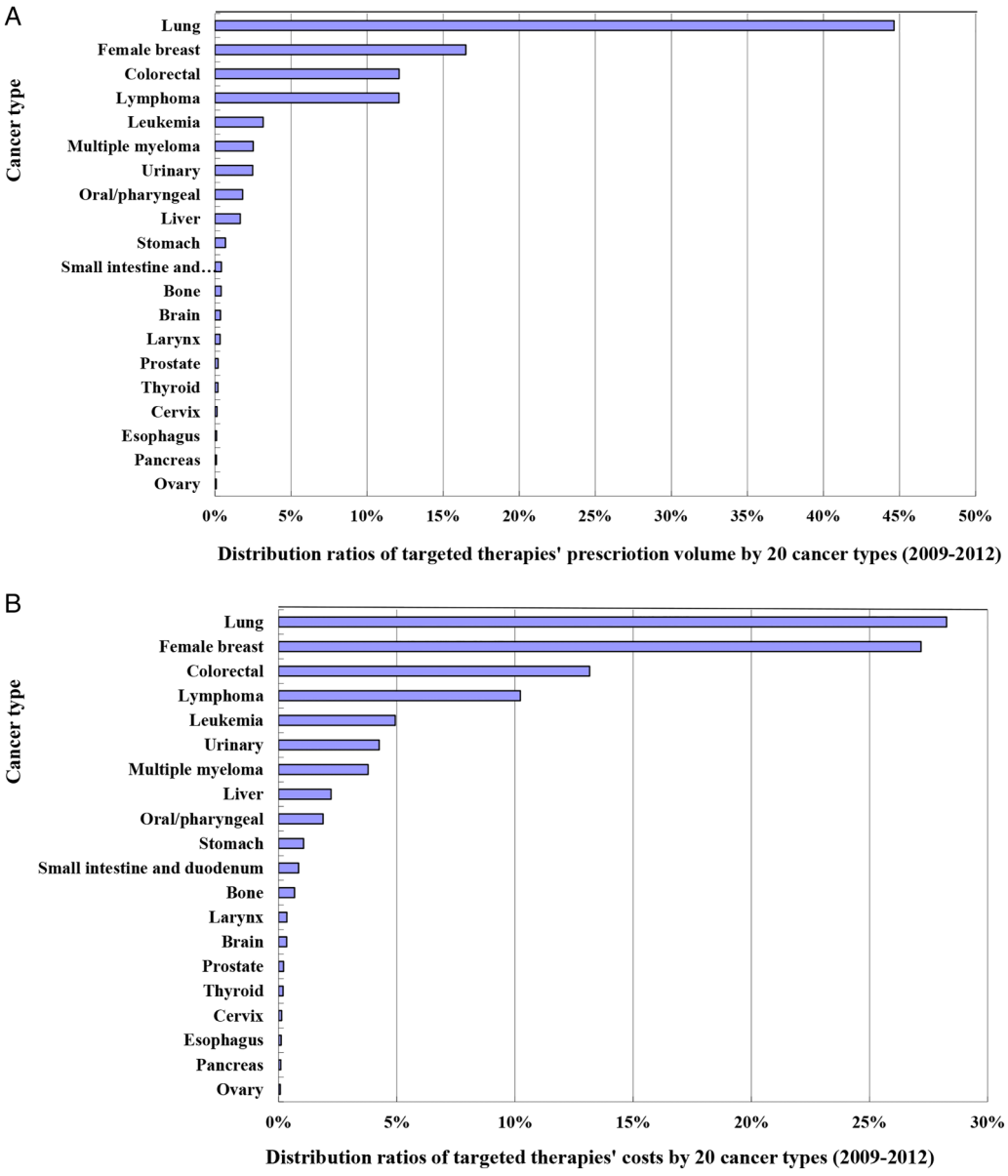

Figure 2 Use (A) and costs (B) of targeted therapies by 20 cancer types (2009–2012). (A) Distribution ratios of prescription volume for targeted therapies by cancer type. (B) Distribution ratios of costs for targeted therapies by cancer type.

therapy 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 the lung and female breast, colorectal cancer, lymphoma and leukaemia, in order of volume. These five cancer types accounted for, respectively, 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.

DISCUSSION

To the best of our knowledge, this is the first study to examine 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 the lung and female breast, and colorectal cancer, accounted for the most used targeted therapies.

Between 2009 and 2012, use and costs of targeted therapies increased almost threefold (tables 1 and 2), with steep growth 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 a 3–10-fold difference in 2012. It is important that policymakers revisit the pricing and reimbursement structures for these

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	Leukaemia	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	Oesophagus	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	

medicines because prices for all targeted therapies are high even for those that offer limited clinical benefits.

Our study adds to the literature stating 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, they accounted for 63% of all cancer drug expenditures in 2011 in the commercially insured US population.[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 healthcare budget, given their clinical benefits. Many experts propose that dialogue involving all parties concerned (eg, policymakers, industry, clinicians, patients and the general public) is needed to address the reasons behind high prices of cancer drugs and to provide 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 resources 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 utilisation 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 analyse patient-level data, to understand the influence of patient characteristics on treatment selection and clinical outcomes of treatments. Additionally, this study did not examine the complex patterns of drug use, such as use of combination treatments, and 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 healthcare system; we did not examine patient contribution to drug costs in Taiwan; this warrants a separate study. Further, we did not characterise changes in the policy environment in Taiwan during the study period. Examples include the launch of new, competing targeted therapies, publication of large randomised clinical trial results, changes in clinical guidelines or reimbursement policies, and patient and provider factors (eg, patient clinical history, physician's knowledge and preference). Future studies are needed to examine the impact of changes in policy and the clinical environment, on use of targeted therapies. Finally, various types of restrictions (eg, prior authorisations) 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 are likely to pose substantial economic burden in the future. Cancers of the lung and female breast, and colorectal cancer, were identified as the main drivers of use and costs of targeted therapies in recent years. Policymakers, industry, clinicians and patients need to communicate and develop strategies to enable access to effective (and cost-effective) targeted therapies without overspending the healthcare budget.

Contributors JCH and CYL conceptualised 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 the authors approved the final version for submission.

Funding JCH was supported by grants from Taiwan Food and Drug Administration (grant ID 104TFDA-JFDA-306) and Taiwan's Ministry of Science and Technology (grant ID MOST 104-2320-B-006-005).

Disclaimer The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests None declared.

Ethics approval National Cheng Kung University Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The authors have obtained nationwide, monthly claims data for cancer-related antineoplastic agents, from 2009 to 2012, from the Taiwan National Health Insurance Research Database (NHIRD). NHIRD does not permit external sharing of any of the data elements.

REFERENCES

1. Dranitsaris G, Truter I, Lubbe MS, *et al*. Advances in cancer therapeutics and patient access to new drugs. *Pharmacoeconomics* 2011;29:213–24.
2. Schoenlein PV, Hou M, Samaddar JS, *et al*. Downregulation of retinoblastoma protein is involved in the enhanced cytotoxicity of 4-hydroxytamoxifen plus mifepristone combination therapy versus antiestrogen monotherapy of human breast cancer. *Int J Oncol* 2007;31:643–55.
3. Taiwan Health Promotion Administration, Ministry of Health and Welfare, 2011 Cancer Registry Annual Report, 2014.

4. Wu CY, Lin JT. The changing epidemiology of Asian digestive cancers: from etiologies and incidences to preventive strategies. *Best Pract Res Clin Gastroenterol* 2015;29:843–53.
5. Biswas M, Ades AE, Hamilton W. Symptom lead times in lung and colorectal cancers: what are the benefits of symptom-based approaches to early diagnosis? *Br J Cancer* 2015;112:271–7.
6. Eeles RA, Morden JP, Gore M, *et al*. Adjuvant hormone therapy may improve survival in epithelial ovarian cancer: results of the AHT randomized trial. *J Clin Oncol* 2015;33:4138–44.
7. Schiller JH, Harrington D, Belani CP, *et al*. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–8.
8. National Cancer Institute, Targeted Cancer Therapies. http://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet (accessed 13 Apr 2016).
9. Kohne CH, Lenz HJ. Chemotherapy with targeted agents for the treatment of metastatic colorectal cancer. *Oncologist* 2009;14:478–88.
10. Mahalingam D, Mita A, Mita MM, *et al*. Targeted therapy for advanced non-small cell lung cancers: historical perspective, current practices, and future development. *Curr Probl Cancer* 2009;33:73–111.
11. Mok TS, Wu YL, Thongprasert S, *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–57.
12. Lu CY, Srasuebkul P, Drew AK, *et al*. Trastuzumab therapy in Australia: which patients with HER2+ metastatic breast cancer are assessed for cardiac function? *Breast* 2013;22:482–7.
13. Lu CY, Srasuebkul P, Drew AK, *et al*. Positive spillover effects of prescribing requirements: increased cardiac testing in patients treated with trastuzumab for HER2+ metastatic breast cancer. *Intern Med J* 2012;42:1229–35.
14. Weingart SN, Brown E, Bach PB, *et al*. NCCN task force report: oral chemotherapy. *J Natl Compr Canc Netw* 2008;6(Suppl 3):S1–14.
15. Kantarjian HM, Fojo T, Mathisen M, *et al*. Cancer drugs in the United States: Justum Pretium—the just price. *J Clin Oncol* 2013;31:3600–4.
16. Lu CY, Cohen JP. Can genomic medicine improve financial sustainability of health systems? *Mol Diagn Ther* 2015;19:71–7.
17. Lu CY, Williams K, Day R, *et al*. Access to high cost drugs in Australia. *BMJ* 2004;329:415–16.
18. Hall WD, Ward R, Liauw WS, *et al*. Tailoring access to high cost, genetically targeted drugs. *Med J Aust* 2005;182:607–8.
19. Mullard A. 2011 FDA drug approvals. *Nat Rev Drug Discov* 2012;11:91–4.
20. Godman B, Malmstrom RE, Diogene E, *et al*. Are new models needed to optimize the utilization of new medicines to sustain healthcare systems? *Expert Rev Clin Pharmacol* 2015;8:77–94.
21. Kelly RJ, Smith TJ. Delivering maximum clinical benefit at an affordable price: engaging stakeholders in cancer care. *Lancet Oncol* 2014;15:e112–18.
22. Howard DH, Bach PB, Berndt ER, *et al*. Pricing in the market for anticancer drugs. *J Econ Perspect* 2015;29:139–62.
23. Ghinea N, Kerridge I, Lipworth W. If we don't talk about value, cancer drugs will become terminal for health systems. The conversation, 2015. https://theconversation.com/if-we-dont-talk-about-value-cancer-drugs-will-become-terminal-for-health-systems-44072
24. Ferguson JS, Summerhayes M, Masters S, *et al*. New treatments for advanced cancer: an approach to prioritization. *Br J Cancer* 2000;83:1268–73.
25. Karaca-Mandic P, McCullough JS, Siddiqui MA, *et al*. Impact of new drugs and biologics on colorectal cancer treatment and costs. *J Oncol Pract* 2011;7(3 Suppl):e30s–7s.
26. Warren JL, Yabroff KR, Meekins A, *et al*. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst* 2008;100:888–97.
27. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood* 2013;121:4439–42.
28. O'Dowd A. Watchdog set to reject four drugs for kidney cancer on the NHS. *BMJ* 2008;337:a1262.
29. Campbell B, Morris R, Mandava L, *et al*. Identifying and selecting new procedures for health technology assessment: a decade of nice experience in the United Kingdom. *Int J Technol Assess Health Care* 2014;30:454–60.
30. Yue J, Tabloski P, Dowal SL, *et al*. NICE to HELP: operationalizing National Institute for Health and Clinical Excellence guidelines to improve clinical practice. *J Am Geriatr Soc* 2014;62:754–61.
31. Streat S, Munn S. Health economics and health technology assessment: perspectives from Australia and New Zealand. *Crit Care Clin* 2012;28:125–33, vii.
32. Chim L, Kelly PJ, Salkeld G, *et al*. Are cancer drugs less likely to be recommended for listing by the Pharmaceutical Benefits Advisory Committee in Australia? *Pharmacoeconomics* 2010;28:463–75.
33. Lu CY, Lupton C, Rakowsky S, *et al*. Patient access schemes in Asia-pacific markets: current experience and future potential. *J Pharm Policy Pract* 2015;8:6.
34. Faden RR, Chalkidou K, Appleby J, *et al*. Expensive cancer drugs: a comparison between the United States and the United Kingdom. *Milbank Q* 2009;87:789–819.
35. Vitry A, Roughead E. Managed entry agreements for pharmaceuticals in Australia. *Health Policy* 2014;117:345–52.
36. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. *Soc Sci Med* 2015;124:39–47.
37. Paris V, Belloni A. Value in Pharmaceutical Pricing. OECD Health Working Papers, No 63: OECD Publishing, 2013.
38. Yang BM. The future of health technology assessment in healthcare decision making in Asia. *Pharmacoeconomics* 2009;27:891–901.
39. Oortwijn W, Mathijssen J, Banta D. The role of health technology assessment on pharmaceutical reimbursement in selected middle-income countries. *Health Policy* 2010;95:174–84.
40. Hsu JC, Lu CY. The evolution of Taiwan's National Health Insurance drug reimbursement scheme. *Daru* 2015;23:15.
41. National Health Insurance Administration, Directions of Drug Restricted Benefit for National Health Insurance. 2013. http://www.nhi.gov.tw/webdata/webdata.aspx?menu=21&menu_id=713&webdata_id=2919
42. Insurance BoNH. National Health Insurance Annual Statistical Report. October 2004. http://www.nhi.gov.tw/Resource/ webdata/Attach_8661_1_s92.pdf (accessed 8 Jun 2011).
43. Liu SZ, Romeis JC. Assessing the effect of Taiwan's outpatient prescription drug copayment policy in the elderly. *Med Care* 2003;41:1331–42.
44. Mills TC. Time series techniques for economists. Cambridge University Press, 1990.
45. Asteriou DH, Stephen G. *ARIMA Models and the Box–Jenkins Methodology, Applied Econometrics.* 2nd edn. Palgrave MacMillan, 2011:265–86.
46. Shih YCT, Smieliauskas F, Geynisman DM, *et al*. Trends in the cost and use of targeted cancer therapies for the privately insured nonelderly: 2001 to 2011. *J Clin Oncol* 2015;33:2190–U232.
47. Jönsson B, Ramsey S, Wilking N. Cost effectiveness in practice and its effect on clinical outcomes. *J Cancer Policy* 2014;2:12–21.
48. Ellis LM, Bernstein DS, Voest EE, *et al*. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol* 2014;32:1277–80.
49. Taiwan National Health Insurance Administration, Schemes for National Health Insurance Drug Reimbursement System, 2014.