MATCHING MANAGED ENTRY AGREEMENT STRATEGIES WITH HIGH-COST DRUGS TO MAXIMIZE DRUG COST SAVING

BY

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ABSTRACT

Background: The procurement of high-cost drugs presents considerable fiscal challenges to healthcare systems globally. Managed Entry Agreements (MEAs) have emerged as policy instruments designed to facilitate patient access to innovative therapies while maintaining financial sustainability and addressing clinical uncertainty. Nevertheless, empirical evidence regarding the practical implementation and economic implications of MEA strategies within the Thai healthcare context remains scarce. This study sought to develop evidence-based recommendations for policymakers to inform drug procurement decisions through appropriate MEA selection that ensures long-term budgetary sustainability.

Methods: This study utilized an analytic cohort design incorporating real-world data obtained from Thammasat University Hospital (TUH) spanning the period from 2010 to 2025. Six high-cost oncology medications—pertuzumab, osimertinib, afatinib, ceritinib, palbociclib, and ribociclib—were examined under five distinct MEA modalities: price discount, free initiation treatment, conditional treatment continuation, utilization cap, and pay-by-result arrangements. Drug procurement expenditures were calculated from the payer perspective. Each MEA scenario was subsequently compared against a reference case without MEA implementation to determine the most economically advantageous technique.

Results: The findings demonstrate that MEA implementation yielded substantial reductions in drug procurement expenditures. The free initiation treatment modality generated the most pronounced cost savings, achieving total cost reductions ranging from 59.87% to 79.75% relative to conventional procurement without MEA. The conditional treatment continuation technique similarly demonstrated considerable cost containment effects, followed by the price discount strategy, which provided moderate savings while offering enhanced feasibility for implementation. Conversely, utilization cap and pay-by-result modalities resulted in comparatively modest cost reductions.

Conclusions: This investigation establishes that MEA techniques, particularly free initiation treatment and conditional treatment continuation, can effectively mitigate the financial burden associated with high-cost drug procurement. For practical application within the Thai healthcare system, a minimum price discount of 40% is recommended as a sustainable negotiation baseline. Future research should incorporate data from diverse healthcare settings to validate these findings and inform the development of comprehensive national MEA policies.

Keywords: access, budget, cost saving, expenditure, high-cost drug, innovative drug, managed entry agreement, pharmaceutical policy, procurement

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LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
ALK	Anaplastic Lymphoma Kinase
ATC	Anatomical Therapeutic Chemical
AUD	Australian Dollar
CDK4/6	cyclin-dependent kinases 4 and 6
CED	Coverage with evidence development
CGD	Comptroller General's Department
CHE	Current Health Expenditure
CI	Confidence interval
CSMBS	Civil Servant Medical Benefit Scheme
DIT	Department of Internal Trade
DMSIC	Drug and Medical Supply Information Center
EGFR	Epidermal Growth Factor Receptor
EUR	Euros
GBP	British Pound
GDP	Gross Domestic Product
HER2	Human epidermal growth factor receptor 2
HITAP	Health Intervention and Technology Assessment Program
HR	Hazard ratio
HR-positive	hormone receptor positive
HSRI	Health Systems Research Institute
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
MBC	Metastatic Breast Cancer
MEA	Managed Entry Agreement
MOPH	Ministry of Public Health
NHSO	National Health Security Office

NLEM	National List of Essential Medicines
NSCLC	Non-small cell lung cancer
OCPA	Oncology Prior-Authorization System
OECD	Organization for Economic Co-operation and Development
P	p-value
PAPs	Patient Access Programs
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PFS	Progression-free survival
PPRS	Pharmaceutical price regulation scheme
QALY	Quality-adjusted life year
R&D	Research and development
SSO	Social Security Office
SSS	Social Security Scheme
Thai FDA	Thai Food and Drug Administration
TKI	Tyrosine Kinase Inhibitor
TUH	Thammasat University Hospital
UCS	Universal Coverage Scheme
US PPP	United States Purchasing Power Parity
USD	United States Dollar
WHO	World Health Organization

CHAPTER 1
INTRODUCTION

1.1 Background

The World Health Organization (WHO) has promoted equitable access to basic health services through the concepts of primary health care and essential drugs since the 1970s (1). However, countries continue to face a range of obstacles to achieving this goal, including rising prices of new drugs, shortages and stock-outs, overdiagnosis, inappropriate prescribing, and drug use that may result in over-treatment or improper treatment (2). According to the "Thai Drug System 2020" report by the Health Systems Research Institute (HSRI), Thailand's drug system encounters similar challenges, such as limited accessibility to essential drugs, high drug prices, and drug overuse (3).

In 1981, Thailand introduced its first National Drug Policy, which aimed to establish goals and directions for collaboration among all sectors to address these problems. The policy has been continually revised to reflect changing environmental factors and emerging challenges (3). Nevertheless, the Thai drug system continues to struggle with access to novel and high-cost drugs (4). More importantly, high drug costs impose a substantial burden on the national budget in terms of health expenditures (4).

In Thailand, drug expenditure makes up a significant part of health expenditure (5). In 2021, drug expenditure was accounted for 21.7% of Current Health Expenditure (CHE), while CHE represented 5.2% of the gross domestic product (GDP). CHE had been grown from 161,752.4 million Thai Baht in 2001 to 834,259.0 million Thai Baht in 2021. This reflects an increase of 672,506.6 million Thai Baht over twenty years (6). Trends show that both health and drug expenditures in Thailand have been steadily rising. This growth is driven by various factors, including high prices for new drugs, an aging population, changing disease patterns, updates in disease management practices, and the expansion of health insurance coverage (5, 7). Notably, drugs for treating conditions that are increasing among older populations—such as central nervous system drugs, blood and blood-forming organ drugs, cardiovascular drugs, and anticancer drugs—are often more expensive than other drugs. There has been a significant rise in the use of anticancer drugs, which tend to be more costly because of advanced technology in their development and high demand (5).

Currently, Thailand faces a continuous rise in healthcare expenditures, despite its limited financial resources. This challenge is especially evident in countries implementing Universal Health Coverage (UHC), where the primary objective is to ensure equitable access to essential medicines and healthcare services for all citizens. Under these fiscal constraints, prioritization has become an essential strategy for optimizing healthcare resource allocation and maintaining the long-term sustainability of the healthcare system. In this context, the inclusion of high-cost drugs in the National List of Essential Medicines (NLEM) requires a rigorous assessment process that evaluates their clinical effectiveness, safety, cost-effectiveness, and overall value to the healthcare system (8, 9).

One widely recognized policy tool for supporting priority setting is Health Technology Assessment (HTA), especially in processes related to the inclusion of high-cost drugs in the NLEM and the definition of benefit packages under UHC. Full HTA provides comprehensive evaluations of the cost-effectiveness, safety, and social impact of health technologies. However, in practice, the implementation of full HTA in Thailand still faces several limitations, such as delays in data collection, incomplete evidence, and multi-agency review processes that can be time-consuming (10, 11).

Delay in the full HTA process for incorporating new drugs into Thailand's UHC can generate substantial hidden costs across health, economic, and social dimensions. International evidence indicates that delayed access to innovative cancer therapies results in considerable losses in life-year and quality-adjusted life-year (QALY). For instance, a Canadian study reported that delays in access to non-small cell lung cancer (NSCLC) drugs led to a loss of 1,740 person-years and 1,122 QALYs (12), while slower access to similar drugs in Europe compared with the United States caused an estimated 30,000 life-years lost within the first year of registration (13). Global modeling studies further suggest that one life-year is lost for every 12 seconds of delay in access to new oncology drugs (14). Although there are no formal quantitative estimates in Thailand, real-world evidence shows that Thai patients with epidermal growth factor receptor (EGFR) mutation-positive NSCLC treated with osimertinib achieved significantly longer survival (15), implying that delays in HTA approval may translate into measurable health losses. In addition to clinical impact, delayed access increases long-term healthcare costs due to disease progression, hospitalizations, and the need for costly supportive care (16). It also imposes substantial out-of-pocket burdens on patients outside government benefit schemes, resulting in catastrophic health expenditures and inequitable access (17-19). Moreover, prolonged and resource-intensive HTA processes entail opportunity costs for the health system, diverting resources from higher-impact public health initiatives (17, 20), and may force hospitals to use less effective alternatives, leading to poorer outcomes and higher future costs (21).

Given these systemic challenges, Managed Entry Agreements (MEAs) have emerged as an alternative or complementary mechanism to full HTA, particularly for drugs with high prices or uncertain clinical effectiveness. MEAs are structured agreements between payers and pharmaceutical companies that define specific conditions for the introduction and use of new drugs. These agreements aim to facilitate timely patient access while managing both financial and clinical uncertainties (22). The MEA offers several advantages. It can reduce delays in patient access to innovative therapies, provide greater budgetary flexibility, and promote more efficient post-market monitoring of drug utilization and outcomes. In the long term, MEAs can strengthen the effectiveness of HTA by generating real-world evidence that supports ongoing policy decisions. Therefore, MEAs represent a promising mechanism to balance innovation, affordability, and equitable access to high-cost drugs (23). MEA is a common strategy implemented in many countries, such as the United States, the United Kingdom, and European countries (e.g., Belgium, France, the Netherlands, and Italy), because MEA can help with drug expenditure control, especially for new and high-cost drugs.

For example, in the United States, Genentech established MEA in 2006 to cap the annual cost of bevacizumab at 55,000 USD (55,000 United State Dollar; USD) for patients with annual incomes below 75,000 USD. This scheme reduced treatment costs by up to 50% for one year and was particularly relevant for patients with breast cancer and early-stage lung or colon cancer. The company believed this initiative would help address public concern over the rising costs of cancer drugs (24). In the United

Kingdom, a MEA was implemented for lenalidomide in patients with multiple myeloma who had received prior therapy. This scheme was approved to enhance the cost-effectiveness of lenalidomide. Under this agreement, the manufacturer covered the cost of treatment if more than twenty-six cycles were required for any patient (approximately 2,000 patients in the United Kingdom), equating to more than two years of therapy (24). In Italy, the application of a MEA for gefitinib in advanced EGFR mutation-positive NSCLC resulted in an average drug cost saving of 864 EUR (864 euros; EUR) per patient compared to traditional procurement methods (25). In conclusion, MEAs represent an effective strategy for addressing the high cost of innovative drugs. However, further research is needed to determine the most appropriate contexts for their use and to identify which MEA techniques are best suited for different types of drugs.

At present, Thailand lacks clear criteria for selecting MEA techniques in drug price negotiations. Therefore, guidelines are needed to support decision-making by the negotiation working groups when addressing specific high-cost drugs. This study, "Matching Managed Entry Agreement Strategies with High-Cost Drugs to Maximize Drug Cost Saving," was conducted to address this knowledge gap.

1.2 Research questions

1.2.1 How can we choose the right MEA technique for drugs?

1.2.2 How can we know that the proposed MEA technique applies to other drugs in the same uncertainty group?

1.2.3 What should be the drug characteristic that indicates the MEA technique?

1.3 Research objectives

1.3.1 To find out the MEA technique among various groups of drug uncertainty that results in the lowest drug procurement cost.

1.3.2 To summarize the drug characteristics that indicate the appropriate MEA technique.

1.3.3 To propose a guideline for policymakers in purchasing drugs with proper MEA for the sustainable budget of the health care system.

1.4 Expected benefits

1.4.1 The appropriate MEA technique will lead to lower drug procurement costs.

1.4.2 The utilization of cheaper versions of high-cost drugs will reduce the national budget impact.

1.4.3 Patient access to high-cost drugs would be increased under the limited of the national budget.

1.5 Conceptual framework

This study investigated the impact of the MEA technique on drug procurement costs, which varied according to the drug uncertainty characteristics of the high-cost drugs studied. The findings were summarized to guide the policymakers in purchasing drugs with appropriate MEA in order to sustain the healthcare system budget. The conceptual framework of the study was presented in the Figure 1.1.

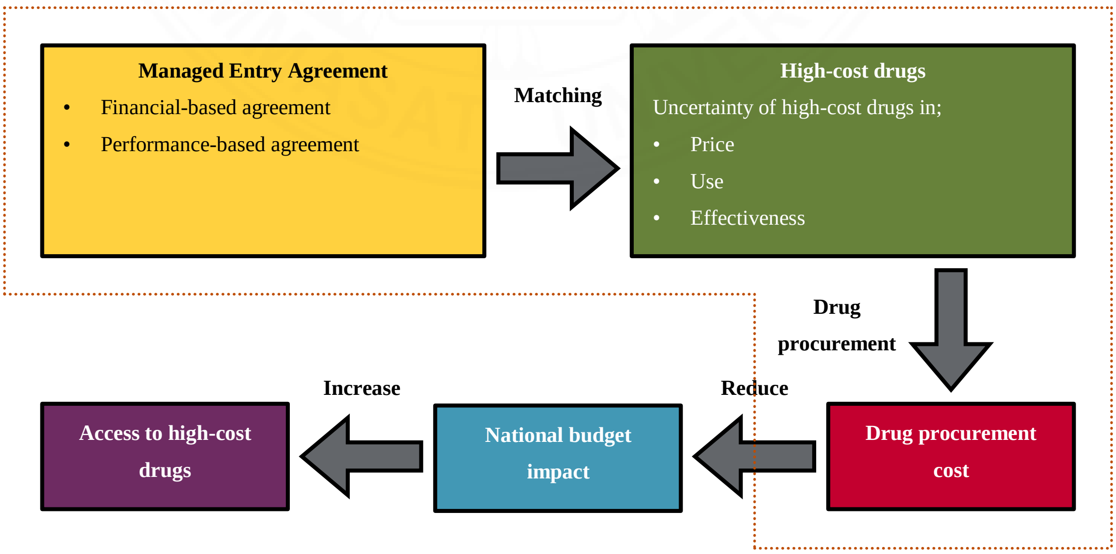


Figure 1.1 Conceptual framework

CHAPTER 2
REVIEW OF LITERATURE

This chapter presents the literature review in four parts. The first part provides an overview of the drug expenditure situation in Thailand, emphasizing the financial challenges posed by high-cost drugs. The second part examines drug pricing strategies, including various control measures and approaches adopted both internationally and within Thailand. The third part reviews the concept, types, and applications of MEAs. The final part discusses high-cost drugs studied on outlining their clinical significance. The findings from these reviews could serve as a guidance for the development of the study's methods.

2.1 Drug expenditure situation

In Thailand, drug expenditure represents a substantial component of health expenditure (5). Over the past two decades, drug expenditure has risen by approximately 7-8% annually (26), a rate exceeding the country's GDP growth (26). This upward trend is driven by multiple factors, including the high cost of new drugs, an aging population, shifting disease patterns, evolving approaches to disease management, and the expansion of health insurance coverage (5, 7, 27).

In 2021, Thailand's drug production was valued at 72,466.8 million Thai Baht (28), with approximately 90% consumed domestically and 10% exported (27). In contrast, imported drugs accounted for 183,220.33 million Thai Baht (28), reflecting a rapid increase in the market share of imported drugs compared to domestically produced ones (28).

In the study of Tunpaiboon N. (2022) (27), it was reported that in 2021, drug consumption in Thailand totaled 193 billion Thai Baht, distributed through public hospitals (60%), private hospitals (20%), and drug stores (20%). Hospitals thus represent the primary distribution channel. Drugs distributed through hospitals can be further categorized into (i) generic drugs, accounting for 61% of the total value, and (ii) original drugs, comprising the remaining 39%. Although the latter group represents a smaller share, the consumption of original drugs is growing at a faster rate than that of generic drugs (27).

A few large pharmaceutical companies monopolize the market for original drugs worldwide. The pharmaceutical industry is the second most profitable sector after the oil industry, with profit margins exceeding 20% of sales. To maximize profits from drug distribution (29), pharmaceutical companies employ a variety of tactics, including:

- Gradual filing of patent applications for a particular drug to extend market exclusivity.
- Expanding new dosage forms that may not improve therapeutic efficacy but stimulate new markets.
- Engaging in legal litigation to prevent patent infringement.
- Using patent linkage to block the registration of generic drugs while original drugs remain under patent protection.
- Producing generic drugs themselves and selling them at lower prices than competitors' generics.
- Offering discounts to maintain market share when competitors enter after patent expiration.
- Protecting against parallel trade and cross-border imports.
- Preventing international price differentials by attempting to enforce uniform pricing within a region and conducting confidential negotiations in price-sensitive countries.

In addition to the tactics mentioned above that influence drug prices, the pharmaceutical industry has increased sales through various promotional strategies targeting healthcare professionals as well as direct-to-consumer advertising. It has been reported that pharmaceutical companies allocate up to 18.2% of their sales revenue to promotional campaigns (30).

Drugs are classified as controlled goods; however, there is no direct legislation regulating prices at the manufacturer level. The Price of Goods and Services Act B.E. 2542 (1999), under the supervision of the Department of Internal Trade (DIT), Ministry of Commerce, requires entrepreneurs to submit information comparing the cost structure at the old price with the proposed new price to the Central Committee on the Price of Goods and Services for consideration prior to any price increase. Nevertheless, command-and-control measures are often ineffective in the pharmaceutical industry, which operates almost entirely within the private sector (with the exception of the Government Pharmaceutical Organization and the Defence Pharmaceutical Factory) (26, 29). In comparison, other regulatory approaches—such as self-regulation, market-based regulation, and incentive-based regulation—are also applied in the non-government healthcare sector (26, 29).

At the healthcare provider level, almost all public hospitals procure drugs independently, with most purchases made directly from manufacturers and distributors. Acquisition costs often vary depending on hospital size, bargaining power, and procurement policies. Large hospitals with higher purchase volumes or experienced procurement officers generally possess stronger bargaining power. Price conditions may also influence whether drugs are included in a hospital's drug formulary. Furthermore, actual purchase price information for individual hospitals is often not publicly available, particularly in cases involving confidential rebates or price–volume agreements (26, 29).

In large hospitals, there is a clear trend toward increased use of new drugs. Manufacturers typically set entry prices for new drugs at the highest possible level—well above the marginal cost in a perfectly competitive market. Considering the market potential protected by patents and the characteristics of the drug, especially when the drug demonstrates superior efficacy over alternatives for acute diseases, launch prices are often very high. New drugs can be up to three times more expensive than existing ones, with price reductions being rare (26, 29, 31). For new drugs targeting chronic diseases, where efficacy is less pronounced, initial prices are usually set lower to gain market share and gradually increase as utilization grows (29). Ultimately, the actual purchase price of a new drug depends heavily on the bargaining ability and negotiating power of each hospital, determined on a case-by-case basis (29).

In the health insurance system, although hospitals have no direct control over drug purchase prices, the purchasing power of the public sector under the Universal Coverage Scheme (UCS) prioritizes access to high-cost essential drugs (category E2). These drugs are defined separately from capitation for outpatients and diagnosis-related groups for inpatients, or through direct compensation with drugs. This structure gives the UCS drug fund substantial leverage to secure demand and negotiate prices with manufacturers, ensuring access to essential medications for patients across the country (29).

In contrast, the Civil Servant Medical Benefit Scheme (CSMBS) creates perverse incentives for healthcare providers to prescribe newly introduced, original drugs that are not listed in the NLEM. Reimbursement price control is limited to the set reimbursement rate, which has contributed to rapid increases in drug expenditures, particularly in outpatient care (29).

For private healthcare providers, including private hospitals, clinics, and pharmacies, drug costs are generally higher than those in public healthcare facilities (32). There is no legislation regulating profit margins from drug sales in the private sector; the only restriction is that drugs must not be sold above the manufacturer-specified price (29). Patients with high purchasing power may appear unaffected by drug prices, but disparities in information regarding drug efficacy and pricing leave room for manufacturers to set unreasonably high prices. Without adequate regulatory controls, patients are at risk of exploitation through excessive drug pricing. Uncontrolled drug prices negatively impact users across all sectors and can contribute to instability in the domestic drug manufacturing industry (33).

The management of drug prices is a national priority, as drug expenditure accounts for 21.7% of CHE (6) and has been continuously increasing over the past several years (5, 7, 26). Originally, monopoly drugs are major contributors to overall health expenditure, particularly within the CSMBS. In addition, pharmaceutical companies employ pricing and promotional strategies to maximize profits over extended periods. Most hospitals have limited bargaining power with these companies, and efforts by the Ministry of Commerce to enforce laws and monitor drug costs have not been fully successful. Collectively, these factors highlight that drug pricing in the country is a critical issue, underscoring the need for the establishment of appropriate, transparent, and effective drug price controls.

2.2 Drug pricing strategy

In Thailand, drugs are classified as controlled goods; however, at the ex-factory price, pharmaceutical companies are able to set drug prices independently (free pricing), particularly for monopoly drugs, which face no market competition to regulate their cost. There are no specific laws or regulatory agencies that effectively control drug pricing, and the system operates in a modular manner, resulting in a lack of coordinated oversight. Consequently, no concrete measures for drug price control have been implemented (29, 33, 34). In contrast, in developed countries—particularly member states of the Organization for Economic Co-operation and Development (OECD) with national health insurance systems—drug price control measures are commonly applied to drugs listed in the pharmaceutical benefit scheme. These measures may include setting reimbursement prices or providing subsidies, and they are typically enforced through structured processes governing drug introduction, price increases, and reimbursement (26, 29, 34).

2.2.1 Drug price control measures

The measures for drug price control in developed countries are as follows:

2.2.1.1 External price benchmarking

External price benchmarking, also known as international reference pricing (35), is a method of drug price control based on international price comparisons with countries of similar economic characteristics or geographic proximity. It applies to drugs that are comparable in terms of active ingredient, dosage form, strength, packaging, and manufacturer (26, 29, 33). This method is the most widely used approach to limiting list or reimbursement prices in many European countries (29, 33, 35). Implementation varies across countries. For example, the Slovak Republic sets its price cap at 10% above the average price in the three lowest-priced countries among its reference group (36). In Japan, drug prices are determined based on the average price in four OECD countries—France, Germany, the United Kingdom, and the United States—for new drugs without therapeutic comparators or for new drugs that demonstrate significant added therapeutic value compared with existing options

(36). The main weakness of this method is that manufacturers may prioritize launching drugs in countries with reimbursement price controls but no strict list-price regulations, such as Germany or the United Kingdom. Moreover, it has been observed that manufacturers often set similar prices across the five major European markets, reducing international price differentials (26, 29).

2.2.1.2 Internal reference pricing

Internal reference pricing involves setting drug prices by comparison with a group of therapeutically equivalent and interchangeable drugs (26, 29, 33, 35, 36). Reference groups are determined based on chemical entities and pharmacological classes according to the Anatomical Therapeutic Chemical (ATC) Classification System or by therapeutic indication (35). This method is widely used by payers and regulators (36) to establish or negotiate drug prices or reimbursement rates within health insurance systems (35, 36). Reference prices are typically calculated using statistical methods such as minimum, mode, or median values. In cases where manufacturers set prices above the reference level, patients may be required to pay the difference (26, 29, 33). Countries that apply internal reference pricing include France, Denmark, Belgium, Spain, Sweden, Australia, Canada, Germany, the Netherlands, and Portugal (26, 29, 33). For new drugs, the reference price is determined by comparing their characteristics with existing drugs in the same class. If a new drug provides no or limited additional therapeutic value, its price is generally restricted to the level of existing alternatives (26).

2.2.1.3 Cost-plus pricing

Cost-plus pricing determines drug prices based on production costs plus a profit margin (26, 29, 33). This basic method is simple to calculate and requires minimal data. The most common approach involves summing direct, indirect, and fixed costs, converting the total into unit prices, and then adding the desired profit margin (26, 29, 33). Despite its simplicity, cost-plus pricing has been criticized for its limited effectiveness in overall cost control, as obtaining accurate production cost data is often challenging. In Spain, for example, the ex-factory price of a listed drug is determined by production costs plus a standard rate of return of 10-12% (36).

2.2.1.4 Profit control

Profit control is an indirect mechanism for regulating drug prices, in which the government limits manufacturers' rates of return to a specified threshold. If profits exceed this threshold, requests for price increases may be denied, or excess profits may be reclaimed (26, 29, 33). However, this method faces challenges due to the complexity of determining actual cost structures, drug prices, and sales data, particularly with respect to research and development (R&D) costs (26, 29, 37).

2.2.1.5 Managed entry agreement (MEA)

Managed entry agreements (MEAs)—also referred to as risk-sharing agreements, special pricing arrangements, or patient access schemes (38)—are contracts between pharmaceutical companies and payers that aim to improve patient access to high-cost, innovative drugs (38-41). MEAs are typically categorized into two types: financial-based agreements and performance-based agreements (39).

Financial-based agreements focus on controlling drug costs to limit budget impact. They are widely adopted because of their relative simplicity and ease of implementation. However, their lack of transparency—owing to confidential contract details—raises concerns about potential conflicts of interest among competing manufacturers (38, 39, 42).

Performance-based agreements link payment to real-world therapeutic outcomes. These agreements aim to maximize the value of new drugs and address uncertainties regarding their effectiveness. Although regarded as good practice, they are complex to implement and involve high administrative costs (39, 42).

Although drug price control measures are effective in reducing drug expenditure, U.S. pharmaceutical companies argue that such measures may negatively affect R&D of new drugs (33). They suggest three potential impacts:

- A reduction in company investment in R&D and other related activities.
- Long-term losses in R&D capacity.
- Negative effects of drug price control on overall economic growth.

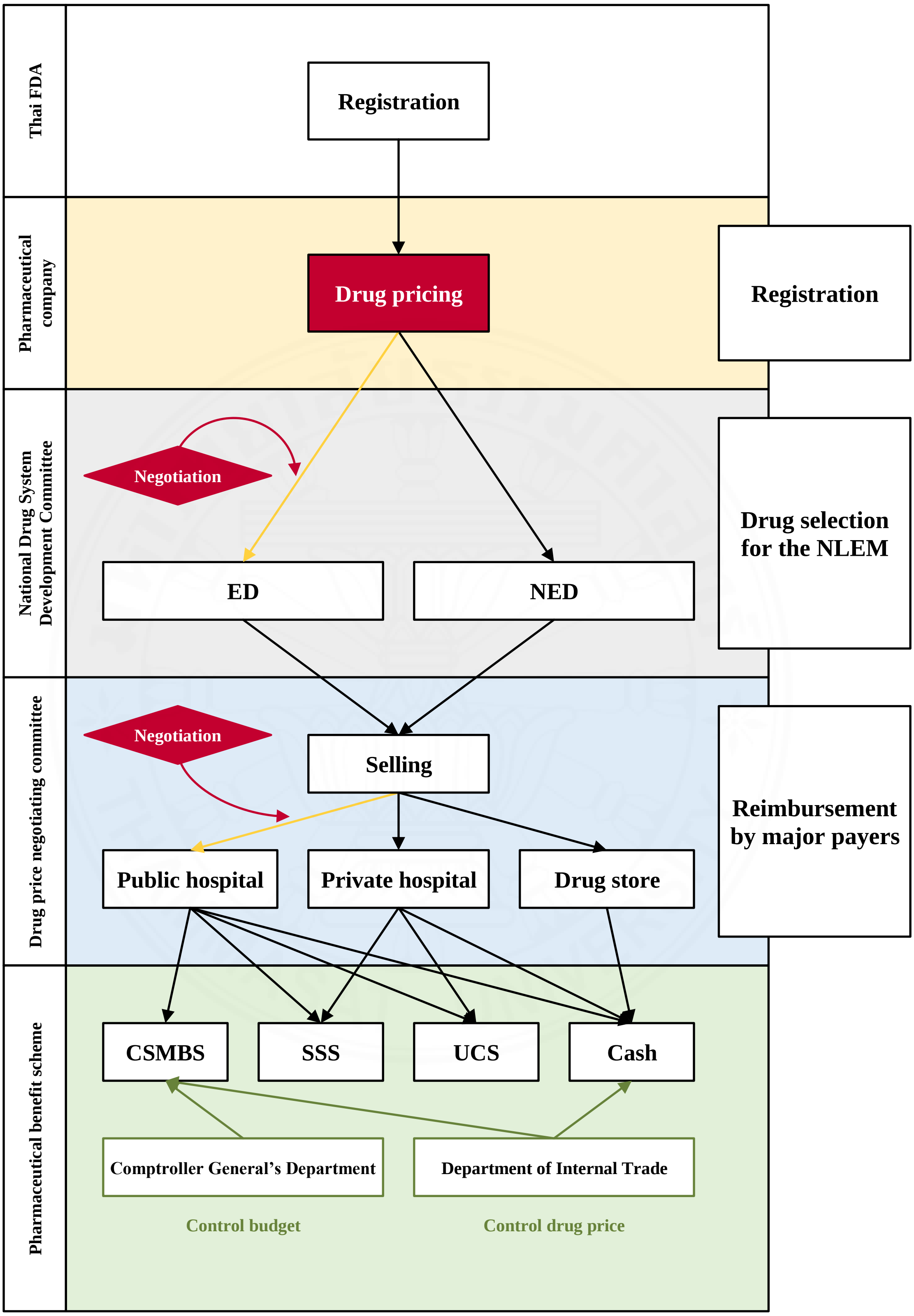
However, evidence from the study of Light et al. (2005) (43) contradicts these claims. Their study found that U.S. R&D expenditure accounted for 21.2% of GDP, which is lower than that of the United Kingdom, Sweden, and Switzerland, at 0.32%, 0.35%, and 0.55%, respectively. Despite lower drug prices in these countries—68.6%, 69.2%, and 63.6% of U.S. drug prices, respectively—their R&D investment was proportionally higher. This suggests that reduced drug prices do not necessarily lead to reduced R&D investment (33, 43).

2.2.2 Drug pricing strategy in Thailand

The aforementioned drug price control measures have not yet been concretely implemented in Thailand, and there are still no specific laws or agencies dedicated to controlling drug pricing. Under the UCS and the Social Security Scheme (SSS), reimbursement for outpatient care is provided through a capitation system (26, 29, 44). This system does not incentivize healthcare providers to prescribe expensive drugs. Consequently, drug expenditure control is limited to drugs listed in the NLEM under the pharmaceutical benefit scheme, except for price negotiations for certain essential drugs, such as those in category E2, which are reimbursed separately by the National Health Security Office (NHSO) (26, 29).

In contrast, the CSMBS reimburses healthcare providers on a fee-for-service basis for outpatient care (29, 44). This reimbursement mechanism is unable to effectively control drug expenditure and does not create incentives for providers to prescribe drugs listed in the NLEM.

In Thailand, government intervention in drug pricing can occur at three levels, as illustrated in Figure 2.1 (33). These include drug registration, inclusion in the NLEM, and reimbursement decisions by major payers. Drug price control measures may be implemented at one or more of these levels, depending on the appropriateness of the context (33).



Source: Data adapted from Reference Numbers (33)

Figure 2.1 Drug pricing throughout the supply chain

2.2.2.1 Drug registration

Once a drug has been registered, it can be launched on the market. At this stage, the government should regulate and set the maximum selling price for drugs available to consumers. Currently, pharmaceutical companies are free to determine their own selling prices, which may result in excessive profits, particularly for monopoly drugs. In addition, companies are permitted to increase drug prices when justified; however, there are no regulations requiring them to reduce prices after patent expiration or when circumstances demand it. To address this, regulations should be amended to grant the government authority to set drug prices. Pharmaceutical companies would be required to submit the prices they intend to charge along with supporting evidence, and the government would determine an appropriate selling price. This pricing policy should apply to all drugs—whether listed or not in the NLEM—and regardless of whether they are dispensed in public hospitals, private hospitals, or private pharmacies (33).

2.2.2.2 Drug selection for the NLEM

The National Drug System Development Committee conducts cost-effectiveness analyses of drugs to select those that are both clinically effective and financially affordable, without placing an undue burden on the national health budget (33, 45). Consequently, drugs seeking inclusion in the NLEM are typically required to undergo price reductions (33). In countries with robust health insurance systems, such as Austria, the Czech Republic, France, Hungary, Italy, Latvia, and Slovakia, the government covers the cost of drugs only for those included in the approved list. As a result, government regulation of drug pricing applies exclusively to drugs it funds. Drugs not included in the list remain outside direct government pricing control (33).

2.2.2.3 Reimbursement by major payers

The major payers in Thailand's health insurance system are the NHSO and the Comptroller General's Department (CGD), Ministry of Finance. These agencies define reimbursement rates for drugs included in the NLEM, thereby exercising indirect control over drug prices (33).

2.3 Managed entry agreement

2.3.1 The concept of the MEA technique

2.3.1.1 Definition of MEA

MEAs are negotiated agreements between drug manufacturers or suppliers and payers or other stakeholders responsible for drug price regulation and decision-making. The primary objective of MEAs is to share the risks associated with the financial burden arising from uncertainties in a drug's therapeutic effectiveness. Various terms are often used interchangeably with MEAs, such as risk-sharing agreements, patient access programs, and special pricing arrangements. The choice of terminology typically reflects either the policy objectives that the agreement seeks to achieve or the specific characteristics of the agreement (38).

The WHO and the OECD have defined the definition of MEA as follows:

"MEA is an arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize their effective use or limit their budget impact (38-40, 46)."

2.3.1.2 Strengths, weaknesses, and challenges of MEA

Most studies provide only general descriptions or limited evidence regarding the actual effects of MEA implementation. The majority highlight common strengths, weaknesses, and challenges rather than presenting robust empirical findings. Overall, MEAs are generally considered a useful tool for the following purposes (42):

- **Improve access to innovative treatments:**
  MEAs can facilitate timely patient access to novel drugs and help manage uncertainty following market launch, thereby reducing the likelihood of coverage rejection solely due to insufficient evidence.

- **Expanding the time horizon for data collection:**
  MEAs enable the collection of real-world evidence on effectiveness, safety, cost-effectiveness, and budget impact beyond the controlled clinical trial setting. This post-market data provides valuable input for both clinical and economic evaluations.
- **Influencing R&D decisions:**
  MEAs may inform manufacturers about therapeutic areas that provide the greatest value from a healthcare system or societal perspective, potentially shaping future R&D strategies. However, there is limited consensus on whether MEAs actively encourage innovation. Some scholars argue that they support innovation by enhancing returns on R&D or by offering financial predictability (e.g., fixed pricing during the MEA period), whereas others remain skeptical.

Despite these strengths, MEAs present challenges that vary across stakeholders:

For manufacturers, challenges include (42):

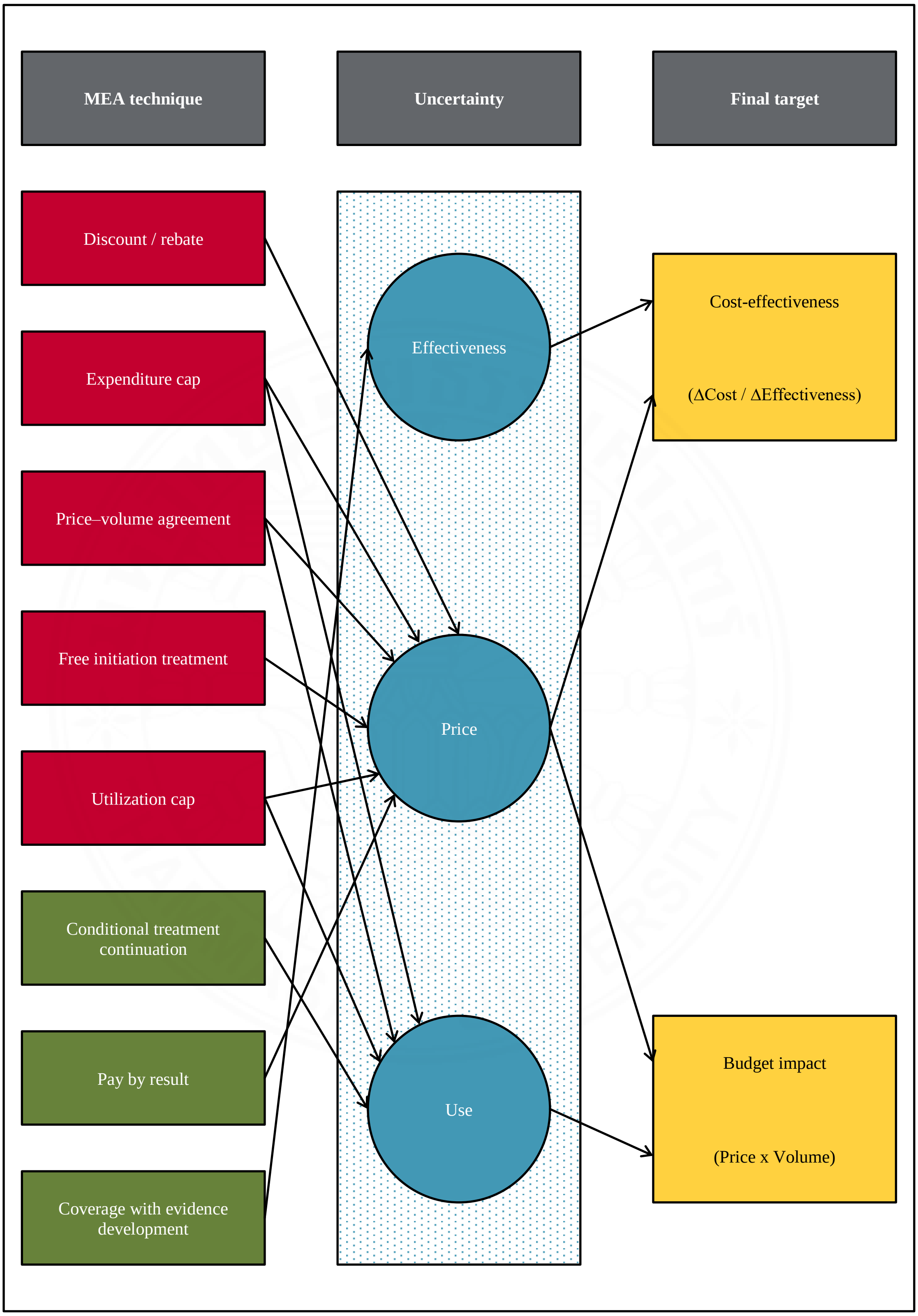
- The risk of free riding, in which competitors indirectly benefit from confidential data or insights generated by other companies engaged in MEAs.
- Uncertainty regarding the returns on investment in additional research, as new evidence may lead to downward price revisions or reduced revenues. This creates limited incentives to generate further data.
- Temporary reimbursement under MEAs may discourage long-term evidence generation.

For regulators and public payers, challenges include (42):

- Difficulties in transferring MEA evidence across countries, due to differences in healthcare practices, costs, resources, and regulatory environments. This is particularly problematic in coverage with evidence development (CED) schemes, which are further complicated by confidentiality restrictions.
- High administrative and transaction costs associated with negotiating, implementing, and monitoring MEAs.
- The risk that manufacturers may withdraw investment in areas with limited patient populations, as MEA conditions might signal low utilization potential.
- The possibility that manufacturers systematically request higher prices when anticipating future MEAs.
- Once a MEA has been established, delisting a drug from reimbursement may be politically or administratively difficult.

2.3.1.3 Framework for MEA

MEAs are implemented in many countries for varying purposes. The primary rationale for adopting MEAs is to enhance patient access to drugs, reduce uncertainty regarding clinical outcomes, lower prices, improve cost-effectiveness, and support personalized treatment strategies. Ultimately, MEAs aim to balance improved drug accessibility with reduced uncertainty and financial burden. Two overarching policy objectives can be identified: improving cost-effectiveness (micro-efficiency) and limiting the budgetary impact (macro-efficiency). To achieve these objectives, countries have adopted various techniques of MEAs. These agreements are designed to influence key target variables—effectiveness, price, and use—that, in turn, affect both cost-effectiveness and overall budget impact, as illustrated in Figure 2.2 (47).



Source: Data adapted from Reference Numbers (47)

Figure 2.2 Framework for MEAs

The framework for MEAs focuses on three key variables—price, effectiveness, and use—with the overarching goal of improving cost-effectiveness and limiting budget impact (47). In the United Kingdom, MEAs are primarily applied in the technique of discounts and free-dose agreements, which directly affect drug pricing to improve access and cost-effectiveness. At the same time, these pricing adjustments help to contain the overall budgetary impact (47). In 2009, the Pharmaceutical Price Regulation Scheme (PPRS) formally established the use of MEAs in the United Kingdom under the designation of "patient access schemes" (48).

In the Netherlands, MEAs are widely implemented in the technique of CED, with the primary objective of improving cost-effectiveness through the generation of real-world evidence on drug effectiveness and utilization. These data are then used to refine cost-effectiveness estimates, which guide final reimbursement decisions at the conclusion of the agreement—even after some agreements have expired. For instance, one drug under such agreements has transitioned to MEA reimbursement through a pay-for-performance technique, while the evaluations of other drugs are ongoing. Dutch health authorities have also highlighted several examples of financial agreements that could potentially reshape the future direction of MEA implementation (42, 47, 48). MEAs in the Netherlands are explicitly integrated into national drug policy, with the objective of improving access to hospital-based treatments and high-cost orphan drugs, particularly those with an annual budget impact exceeding 2.5 million EUR (47, 48).

In Belgium, MEAs are typically structured as finance-based agreements, often combined with performance-based elements, to limit budgetary impact and manage uncertainties associated with clinical and financial outcomes (47, 48).

2.3.1.4 The characteristics of drug uncertainty

MEA focuses on managing the uncertainty of drugs in terms of price, use, and effectiveness. This is to limit the impact on the budget and improve cost-effectiveness. The characteristics of drug uncertainty are summarized in Table 2.1.

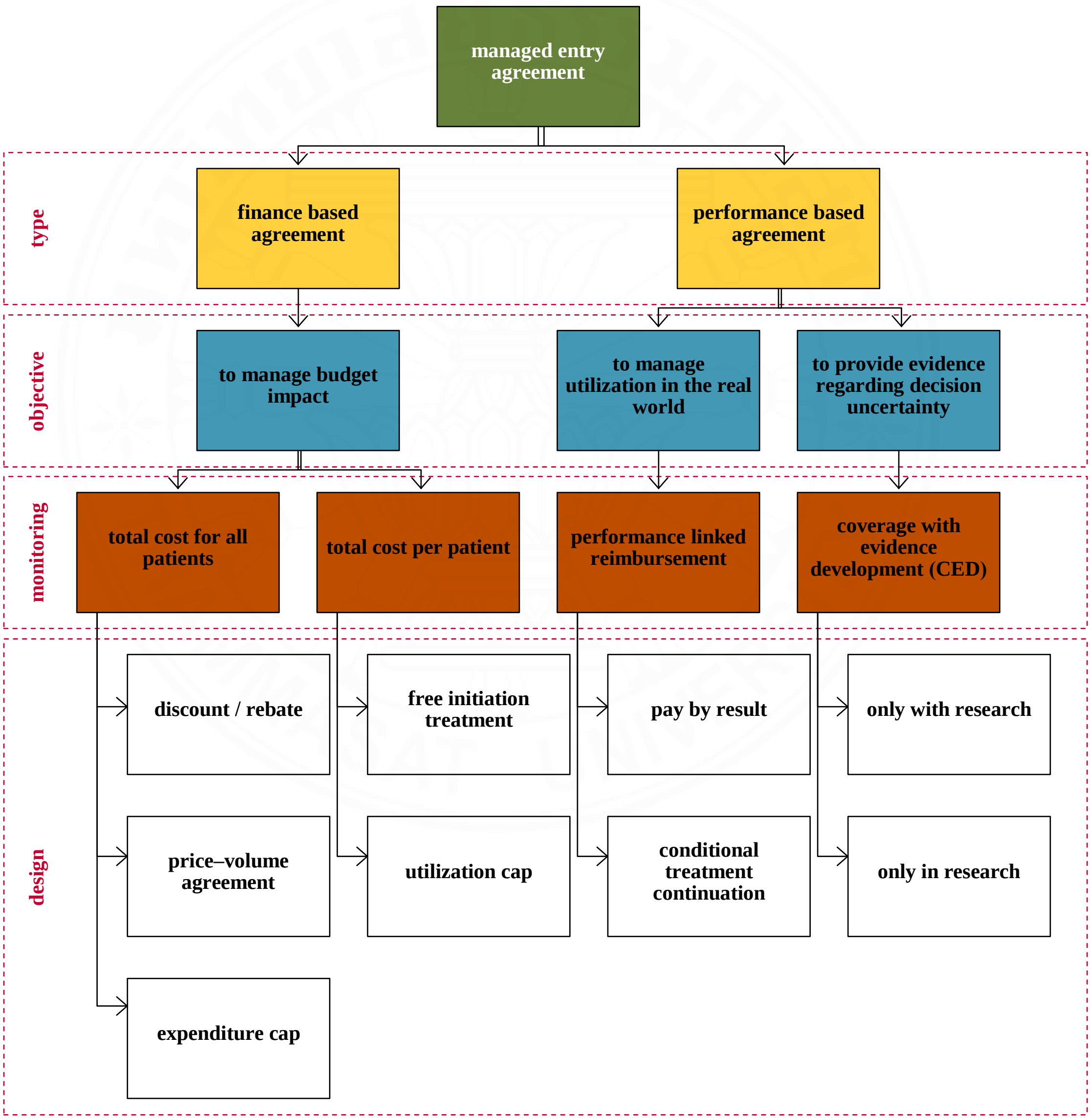
Table 2.1 The characteristics of drug uncertainty leading to MEAs

Uncertainty	Characteristics
Price	• **High-cost drug:** high-priced drugs pose uncertainties for payers, as payers are unable to control drug costs within allocated budgets.
Use	• **Volume:** not clear how many patients will be eligible for the treatment and/or what the market share of the product and risk of excessive budget impact will be if this number is high in practice. • **Treatment duration:** doubts about treatment duration and doses that will be given in practice.
Effectiveness	• **Efficacy:** no robust clinical evidence on the added therapeutic value or no robust clinical evidence on direct comparison with the appropriate alternative. • **Safety:** no robust evidence on safety. • **Long-term data:** no robust clinical evidence on long-term effects. • **Patient adherence and clinical practice:** doubts about the effect in real life because of concerns about wrong use in clinical practice or poor patient adherence. • **Quality of life:** no robust evidence on the quality of life impact. • **Target population:** not clear who is likely to benefit most from the treatment or if there are biomarkers to identify them. • **Optimal treatment schemes:** not clear which duration (e.g., stopping rules), doses, or drug combinations are optimal.

Source: Data adapted from Reference Numbers (49)

2.3.2 Type of MEA technique

The MEA technique is distinctive due to the specific composition and purpose of the agreement between the manufacturer or pharmaceutical company and the payer or provider. MEAs are generally divided into two types: finance-based agreements and performance-based agreements (39), each differing in objectives, follow-up requirements, and contractual forms. They can be implemented at either the population level or the patient level. Further classifications are illustrated in Figure 2.3.



Source: Data adapted from Reference Numbers (38-40, 42, 48, 50)

Figure 2.3 Taxonomy of MEA

2.3.2.1 Financial-based agreement

A financial-based agreement is designed to control costs and facilitate market access for drugs. Such agreements may involve direct financial contributions from the pharmaceutical company. They can also help reduce a drug's incremental cost-effectiveness ratio (ICER), thereby improving its cost-effectiveness, or address ICER uncertainty by increasing the likelihood that the drug will be considered cost-effective (39). Compared to performance-based agreements, financial-based agreements are generally simpler and less administratively complex.

The details of financial-based agreements are often characterized by limited transparency and confidentiality, particularly when MEA is applied as a discount technique. This benefits pharmaceutical companies by allowing them to differentiate prices in an external reference pricing environment. Confidential discounts prevent payers in other countries from accessing the lower MEA-negotiated prices, forcing them to continue paying official retail prices. Furthermore, price confidentiality creates challenges for cost-effectiveness analyses when MEA-covered drugs are used as comparators. Although financial-based agreements are intended to lower treatment costs and limit budget impact, they do not guarantee that patients will benefit directly. Importantly, they do not address uncertainty regarding drug effectiveness—an inherent weakness when such uncertainty exists (42).

Financial-based agreements are primarily used to address concerns about budget impact. Their objective is to ensure affordability within the health insurance system and limit financial pressure on healthcare budgets. By creating greater certainty over drug costs, these agreements contribute to resource allocation strategies that promote equitable or feasible access to care within constrained budgets. Cost reductions achieved through lower prices allow coverage of a larger patient population while providing budgetary certainty (38, 42).

Financial-based agreements can be classified into the following techniques:

(1) Discount/rebate

The discount or rebate technique involves an unconditional price reduction from the retail price, with details typically kept confidential. The agreement may take the form of an upfront discount or a post-sale rebate reimbursed by the pharmaceutical company (38, 42, 51). For example, in the United Kingdom, the pharmaceutical company offered a confidential commercial discount, resulting in an estimated ICER comfortably below 30,000 GBP (30,000 British Pounds; GBP) per QALY gained. Consequently, adjuvant pertuzumab is recommended for patients with human epidermal growth factor receptor 2 (HER2) positive early-stage breast cancer at high risk of recurrence (52). Similarly, a patient access scheme for abiraterone acetate requires the pharmaceutical company to rebate the drug's cost from the eleventh month of treatment onwards for patients who remain on therapy beyond ten months (53).

(2) Expenditure cap

The expenditure cap technique establishes a ceiling on the total treatment cost across all patients or on the number of patients eligible for treatment. Any drug supplied beyond the cap is provided at no additional cost by the pharmaceutical company (38, 42). For example, in Australia, direct-acting antiviral drugs for chronic hepatitis C have been subject to an annual budget cap since 2015, with pharmaceutical companies covering costs beyond this threshold (38).

(3) Price-volume agreement

The price-volume agreement technique links drug price reductions to increased purchasing volumes, applying across all eligible patients (38, 42). For example, in France, nearly all novel drugs entering the market are subject to this MEA technique. The goal is to restrict use to targeted patient populations. Reimbursement structures are determined by sales volume within each drug class. Upon completion of the agreement period, reimbursement terms often convert into discounts. However, the contractual details are typically not publicly disclosed (38).

(4) Free initiation treatment

Under the free initiation treatment technique, the pharmaceutical company provides the initial course of therapy free of charge for each patient, up to an agreed amount, after which the payer purchases subsequent treatments at the negotiated price (38, 42). For example, in the United Kingdom, patients with metastatic renal cell carcinoma can access sunitinib under a scheme where the first treatment cycle is provided at no cost, followed by a 5% discount on subsequent cycles. Enrollment requires patient registration with the company to obtain the free stock (54).

(5) Utilization cap

The utilization cap technique sets a maximum cost threshold per patient, based on treatment duration, quantity, or size. Any treatment beyond this cap is provided free of charge by the pharmaceutical company (38, 42). In the United Kingdom, lenalidomide for multiple myeloma is covered under such an arrangement. To improve its cost-effectiveness, the pharmaceutical company funds treatment beyond twenty-six cycles per patient, equivalent to over two years of therapy (24).

2.3.2.2 Performance-based agreement

A performance-based agreement, also referred to as a health outcome-based agreement, links reimbursement to the actual clinical effectiveness of a drug. It aims to reduce uncertainty regarding real-world clinical outcomes by making pharmaceutical companies accountable for treatment results after market approval (39). Compared with finance-based agreements, its main advantage is that it targets patients most likely to benefit from therapy. In particular, performance-linked reimbursement uses proxy measures of clinical outcomes and relies on existing management systems (e.g., data from patient records). Some experts consider this an "ideal" compromise between simple discount schemes and CED, as it is less costly to implement than CED but still accounts for patient response to treatment—unlike finance-based agreements (42).

Despite these advantages, performance-based agreements also pose challenges. CED techniques, for example, are resource-intensive due to complex requirements for planning, organization, research, and patient registration. Furthermore, clear criteria for determining when CED is necessary are often lacking. When continued, CED may lead to either positive or negative reimbursement decisions depending on new evidence generated. However, the absence of benchmarks for linking decisions to specific additional requirements (e.g., restrictions to certain providers or mandatory registries) complicates implementation. Additional challenges include determining how much evidence is sufficient, when CED should be discontinued, and the appropriate timeframe for decision-making. In practice, the period between evidence generation and final reimbursement decisions varies considerably across MEAs—sometimes being too lengthy, while in other cases insufficient—depending on the indication and outcomes measured (42).

Performance-based agreements can be classified into the following techniques:

(1) Performance-linked reimbursement

This technique aims to address the real-world utilization of novel drugs. It requires clearly defined efficacy indicators with low internal variance, as well as a delivery system that ensures drugs are carefully targeted to eligible patients. Additionally, an information system is necessary to monitor processes, track clinical outcomes, and validate drug efficacy in specific subpopulations. By supporting the appropriate use of novel drugs, such agreements can enhance prescribers' expertise and improve patient safety, thereby sharing risks between physicians and pharmaceutical companies (40).

The techniques included in this group are as follows:

- **Conditional treatment continuation technique**

  Coverage continues only for patients who achieve predefined treatment responses. Pharmaceutical companies must provide drugs free of charge or at reduced prices for patients who do not meet the treatment criteria (38, 55). For example, in Italy, pharmaceutical companies provide Alzheimer's drugs free of charge for the first three months. During this period, the effectiveness of short-term treatment is assessed. If treatment goals are achieved, therapy is extended for up to two years, with costs covered by the National Health Service (38, 55).

- **Pay-by-result technique**

  Payments to pharmaceutical companies are conditional on individual patient outcomes, as agreed in advance. Payers may withhold partial or full reimbursement until treatment success is demonstrated, claim refunds for non-responders, or receive free additional drugs for new patients (38, 55). For example, in the Netherlands, an agreement for erlotinib in NSCLC stipulates that drug costs are fully reimbursed by the pharmaceutical company for patients who show neither partial nor complete response within four cycles (56).

(2) Coverage with evidence development (CED)

CED aims to reduce uncertainty about long-term clinical outcomes and cost-effectiveness. They require measurable data collection in real-world settings under good research governance. If drugs fail to demonstrate clinical benefit or cost-effectiveness, pharmaceutical companies may be required to lower prices, thereby sharing the risk of efficacy (40, 57). CED seeks to balance the needs of patients, pharmaceutical companies, and health system decision-makers. While patients demand early access to promising therapies, health systems must ensure efficient use of limited resources. This technique parallels debates on the rapid approval of new drugs, where timely access must be weighed against patient safety (57). CED is temporary in nature and depends on ongoing evidence generation. They are typically implemented under controlled circumstances, such as randomized controlled trials or registry-based studies (51).

The techniques included in this group are as follows:

- **Only with research:** Evidence is collected from a sample of patients, but all patients remain covered by the agreement.
- **Only in research:** Evidence is collected from all patients, and coverage applies exclusively to those participating in the study.

2.3.3 The selection of the MEA technique

The rationales for selecting each MEA technique are broadly similar in terms of their objectives. Performance-based agreements primarily aim to reduce uncertainty and minimize the payer’s risk of making inappropriate reimbursement decisions. In contrast, financial-based agreements focus on reducing the payer’s risk by improving drug affordability, thereby lowering the cost consequences of a potentially incorrect decision. However, there are slight differences that are observable and summarized in Table 2.2 alongside examples of possible applications (55).

Table 2.2 The rationales for MEA technique selection

MEA technique	Rationale	Possible use
Financial-based agreement		
Discount/rebate	Bring costs down	Treatment is simply too expensive.
Price-volume agreement	Control budget impact	There are economies of scale.
Free initiation treatment	Bring costs down	Treatment is too expensive, and utility gain occurs after a certain period of treatment.
Expenditure cap	Control budget impact	Treatment is prohibitively expensive for the health system.
Utilization cap	Bring costs down and avoid excessive treatment	There is no further benefit after a certain length of treatment or dose.
Cost cap	Bring costs down and enable patients to benefit from treatment after reimbursement has stopped	The length of treatment until a response is achieved is highly uncertain.
Performance-based agreement		
Conditional treatment continuation	Bring costs down and reduce payer risk surrounding the success or failure of treatment	There is a decrement to the likelihood that a treatment results in success after a certain length of time.
Pay-by-result	Bring costs down and reduce payer risk surrounding the success or failure of treatment	Decision uncertainty is mainly associated with treatment success and failure.

Source: Data adapted from Reference Numbers (55)

Although there are rationales for each MEA technique selection, there may be a variety of circumstances that dictate the choice of a different MEA technique. This is because decisions are not based only on the achievement of predetermined conditions. But it also depends on the magnitude of the various factors that may affect the decision. A quantification of risk is therefore inevitable. The issues that must be considered and factors that should be considered in selecting and designing MEA are as follows (55):

1. What are the number and characteristics of treatment options?
2. What is the base case of cost-effectiveness analysis?
3. What is the nature and scale of risk in this appraisal?
    3.1 What is the nature and scale of risk captured by the probabilistic sensitivity analysis?
    3.2 What is the nature of uncertainty not captured by the probabilistic sensitivity analysis?
    3.3 What is the temporal nature of uncertainty, e.g., is there more uncertainty beyond the trial period, or is it resolvable with open-label follow-up?
4. What is the uncertainty caused by individual / groups of parameters?
5. What would be alternative treatment strategies available?
6. What measures of patient-based outcomes are available and measurable?
7. Is price a substantial part of the overall costs associated with treatment?
8. Are there any precedent managed entry agreements in place?
9. Could price agreements be national or local?

MEA can help reduce drug expenditures. But some drugs are not suitable for implementing MEA. Moreover, MEA should not be accepted as a means of transcending poor drug R&D programs or used for price determination or regular reimbursement. MEA should not be used in the following cases (42):

1. When alternatives are proven to be equal or more cost-effective.
2. When the objective of the MEA is unclear.

3. When the variables used in MEA cannot be measured with accurate and reliable methods.
4. When adherence to treatment is generally low.
5. When the cost of implementing the MEA is unacceptable.
6. When the outcome of the MEA will result in payers agreeing to help invest a significant proportion of drug development.
7. When in doubt about transparency and/or MEA compliance.

In the study of Holleman MS. (2019) (56), it was found that various scenarios for MEA techniques were defined to serve as guidelines for calculating drug procurement costs, as shown in Table 2.3.

Table 2.3 The example scenario for the MEA technique

MEA technique	Scenario
Financial-based agreement	
Discount	The discount strategy of 10% on drug cost (58, 59).
Free initiation treatment	The first cycle of the drug was offered for free. Thereafter, the full drug price was paid (60).
Utilization cap	The payer paid for the drug for up to three cycles. The pharmaceutical company subsequently provided free-of-charge drugs for those patients who received more than three cycles (24, 60).
Performance-based agreement	
Conditional treatment continuation	The payer paid for the drug for up to three cycles. Only patients who demonstrated an adequate response (complete or partial) to the therapy continued with treatment. The pharmaceutical company subsequently provided free-of-charge drugs for these patients (56, 61).
Pay by result	Full drug costs were reimbursed by the pharmaceutical company for patients who did not show a partial or complete response within four cycles (62).

Source: Data adapted from Reference Numbers (56)

2.3.4 The monetary benefits of utilizing various MEA techniques

Countries have used the MEA in various techniques with high-cost drugs for managing price, use, and effectiveness to improve the ultimate goal, which includes budget impact and cost-effectiveness (47).

The ten selected studies (25, 52-54, 56, 58, 63-66). Seven studies were studied with a focus on financial-based agreements (52-54, 58, 63-65), and three studies were studied with a focus on performance-based agreements (25, 56, 66). The most commonly chosen financial-based agreement is the discount technique (52, 54, 58, 63, 65), followed by the rebate technique (53, 64). For the performance-based agreement, two techniques were applied: the pay-by-result technique (25, 56) and the cost-sharing technique (66), as follows:

In the study of Júnior et al. (2019) (58), the study focused on the budget impact of erlotinib-based NSCLC treatment from different MEA techniques. It was found that implementing MEA with a 20% discount can reduce the annual budget impact by 24%, from 125.1 million Brazilian reais to 95.1 million Brazilian reais. Comparatively, a pay-by-result technique can reduce the annual budget impact by 19.98%, from 125.1 million Brazilian reais to 100.1 million Brazilian reais. Additionally, a cost-sharing technique can reduce the annual budget impact by 19.90%, from 125.1 million Brazilian reais to 100.2 million Brazilian reais (58). Erlotinib is classified as an anti-epidermal growth factor receptor tyrosine kinase inhibitor. Its high rate of disease control makes a discount technique more effective in reducing budget impact compared to a pay-by-result technique (58). In addition, Brazil does not have any laws or regulatory mechanisms that would allow for the implementation of performance-based MEA (58).

In the study of Navarria et al. (2015) (66), this study focused on the analysis of reimbursement received from the approval of performance-based MEA in Italy. It was found that the use of erlotinib in the treatment of NSCLC under a cost-sharing agreement results in low reimbursement, accounting for only 25,026,477 EUR out of the total 209,003,042 EUR paid for drugs (which is approximately 12% of the total). Most of this amount comes from rebates that are not based on the evaluation of efficacy outcomes (66).

In the study of Holleman et al. (2019) (56), this study focused on evaluating the costs associated with different MEA techniques for NSCLC treatment. It was found that the Netherlands implements MEA in various techniques for the treatment of NSCLC using erlotinib. An agreement in the technique of a price linked to the outcome can reduce costs from 27,463 to 20,837 EUR, representing a decrease of 24.12%. Similarly, an agreement in the technique of a free initiation treatment can reduce costs from 27,463 to 21,869 EUR, representing a decrease of 20.36%. Additionally, an agreement in the technique of utilization caps can reduce costs from 27,463 to 23,071 EUR, representing a decrease of 15.99% (56). An agreement in the technique of a price linked to the outcome resulted in significant cost reductions, particularly for erlotinib (6,626 EUR), due to its high drug cost and relatively large proportion of non-responders (56).

In the study of Clopes et al. (2016) (25), this study focused on evaluating the financial impact of MEA using the pay-by-result technique implemented with gefitinib for NSCLC treatment. It was found that the agreement was signed between the Catalan Institute of Oncology, the Catalan Health Service, and the pharmaceutical company. Under this agreement, the drug cost per patient can be reduced by 4.15%, from 20,811 to 19,947 EUR (25). This agreement mitigates concerns about drug costs and uncertainty about its efficacy, ensuring that the benefits received are appropriate from the perspective of the payer (25).

In the study of Williamson et al. (2010) (54), this study focused on evaluating the financial impact of the MEA implemented with sunitinib for the treatment of metastatic renal cell carcinoma. It was found that the pharmaceutical company has offered the first cycle of treatment for free, followed by a 5% discount on the list price of sunitinib to treat metastatic renal cell carcinoma. To participate in the agreement, patients need to register by submitting a form to the pharmaceutical company to receive the free stock. The results have shown that the implementation of the agreement could save the National Health Service in the United Kingdom 7,224,890 GBP a year. However, only 47% of patients were registered, resulting in a saving of only 3,396,398 GBP (54). The low registration rate may be due to computer systems that do not support “free stock” and prescribing physicians registering fewer patients (54).

In the study of Squires et al. (2019) (52), this study focused on evaluating the ICER of the introduction of a MEA for pertuzumab in the treatment of HER2-positive breast cancer. It was found that the pharmaceutical company has offered a confidential commercial discount on the price of pertuzumab (52). The committee evaluated the pharmaceutical company's data in conjunction with data on the safety and efficacy of pertuzumab. The estimated ICER is comfortably below 30,000 GBP per QALY gained. Therefore, adjuvant pertuzumab is recommended for patients with HER2-positive early-stage breast cancer at high risk of recurrence, particularly those with lymph node-positive disease (52).

In the study of Stevenson et al. (2018) (63), this study focused on evaluating the ICER of the introduction of a MEA for ponatinib in the treatment of acute lymphoblastic leukemia. It was found that the pharmaceutical company has agreed to revise the confidential commercial discount on the price of ponatinib in a MEA. The ICER for ponatinib, compared to best supportive care, can be reduced from 7,892-31,696 GBP to 7,156-29,995 GBP per QALY gained (below 30,000 GBP per QALY gained). The ICER for ponatinib, compared to induction therapy, is likely to be below 5,000 GBP per QALY gained (63). The committee has recommended the use of ponatinib for patients with Philadelphia-chromosome-positive acute lymphoblastic leukemia who are not suitable candidates for allogeneic stem cell transplants (63).

In the study of Ramaekers et al. (2017) (53), this study focused on evaluating the ICER of the introduction of a MEA for abiraterone in the treatment of metastatic castration-resistant prostate cancer. It was found that the base-case ICER ranged between 46,722 and 57,688 GBP per QALY gained. Additionally, after 24 months, approximately 63% of patients in the control group of the trial were still alive, with a median survival of 30.1 months (53). It is unlikely that life expectancy would be less than 24 months; therefore, this treatment did not meet the end-of-life criterion for short life expectancy (53). The pharmaceutical company has agreed to a complex MEA, wherein the company will rebate the cost of the drug abiraterone acetate from the eleventh month until the end of treatment for patients who remain on treatment for more than ten months. The most plausible ICER is likely between 28,600 and 32,800 GBP per QALY gained (53).

In the study of Blommestein et al. (2016) (64), this study focused on evaluating the ICER of the introduction of a MEA for lenalidomide in the treatment of myelodysplastic syndromes. It was the ICER from the pharmaceutical company's revised economic model was 68,125 GBP per QALY gained. The committee did not recommend lenalidomide as a cost-effective treatment (64). Subsequently, the company submitted a MEA that provided lenalidomide free of charge for patients who remained on treatment after twenty-six cycles. This MEA improved the ICER to 25,300 GBP per QALY gained (64). However, the committee considered the proportion of patients who received treatment beyond twenty-six cycles and the resulting ICER to be uncertain. Nevertheless, the committee accepted a commitment from the company to publish data on the proportion of patients eligible for a MEA when available. They believed this provided reassurance that lenalidomide was a cost-effective treatment for patients with low- or intermediate-1-risk myelodysplastic syndrome (64). Based on the proportion of patients on active treatment after twenty-six cycles, lenalidomide remains cost-effective at a threshold of 30,000 GBP per QALY gained when 27% or more patients reach twenty-six cycles of treatment (64).

In the study of Amdahl et al. (2017) (65), this study focused on evaluating the ICER of the introduction of a MEA for pazopanib in the treatment of metastatic renal cell carcinoma. It was found that the pharmaceutical company provides a 12.5% discount on the list price of pazopanib (from 74.73 to 65.38 GBP) (65), resulting in an ICER of 33,000 GBP per QALY gained when compared to best supportive care. However, the committee concluded that pazopanib should be recommended as a first-line treatment option for patients with metastatic renal cell carcinoma at willingness-to-pay thresholds between 35,000 and 50,000 GBP per QALY gained (65). Additionally, at threshold values of cost-effectiveness of 20,000, 30,000, and 50,000 GBP per gained, the net monetary benefit values for pazopanib versus sunitinib were 2,102, 2,696, and 3,886 GBP, respectively. The results of this study suggest that pazopanib is likely to be a cost-effective treatment option when compared with sunitinib as a first-line treatment for metastatic renal cell carcinoma in the United Kingdom (65).

Examples of using MEA in high-cost drugs are shown in Table 2.4.

Table 2.4 Examples of using MEA in high-cost drugs

Drug	Indication	MEA technique	Uncertainty	Country
Financial-based agreement				
Abiraterone	Metastatic castration-resistant prostate cancer	Rebate	Use	UK (53)
Afatinib	Non-small cell lung cancer	Discount	Price	UK (67)
Bevacizumab	Metastatic colorectal cancer	Free initiation treatment	Price	Italy (68)
Bortezomib	Multiple myeloma	Free initiation treatment	Price	Italy (68, 69)
Ceritinib	Non-small cell lung cancer	Discount	Price	UK (70)
Erlotinib	Non-small cell lung cancer	Free initiation treatment	Price	Italy (24, 68), Netherlands (56)
Erlotinib	Non-small cell lung cancer	Utilization cap	Use	Netherlands (56)
Erlotinib	Non-small cell lung cancer	Discount	Price	Brazil (58)
Everolimus	Hormone receptor-positive, HER2-negative metastatic breast cancer	Utilization cap	Use	Thailand (71)
Lenalidomide	Multiple myeloma	Expenditure cap	Price	UK (24)
Osimertinib	Non-small cell lung cancer	Discount	Price	UK (72)
Pazopanib	Renal cell carcinoma	Discount	Price	UK (73)
Pertuzumab	HER2-positive breast cancer	Discount	Price	UK (52)
Ponatinib	Acute lymphoblastic leukemia	Discount	Price	UK (63)
Regorafenib	Hepatocellular carcinoma	Rebate	Price	South Korea (74)
Ribociclib	Hormone receptor-positive, HER2-negative metastatic breast cancer	Discount	Price	UK (75)
Sorafenib	Renal cell carcinoma	Free initiation treatment	Price	Italy (24, 73), UK (24)
Sunitinib	Renal cell carcinoma	Free initiation treatment	Price	Italy (24, 73), UK (24)
Trastuzumab emtansine	HER2-positive breast cancer	Utilization cap	Use	South Korea (74, 76-78)
Performance-based agreement				
Bevacizumab	Metastatic breast cancer	CED	Effectiveness	USA (79)
Bevacizumab	Metastatic colorectal cancer	CED	Effectiveness	USA (80)
Bortezomib	Multiple myeloma	Pay by result	Price	UK (69, 73)
Cetuximab	Metastatic colorectal cancer	CED	Effectiveness	USA (80)
Cetuximab	Renal cell carcinoma	Pay by result	Price	Italy (69)
Clofarabine	Acute lymphoblastic leukemia	CED	Effectiveness	South Korea (74)
Erlotinib	Non-small cell lung cancer	Pay by result	Price	Netherlands (56)
Gefitinib	Non-small cell lung cancer	Pay by result	Price	USA (81)
Irinotecan	Metastatic colorectal cancer	CED	Effectiveness	USA (80)
Lapatinib	HER2-positive breast cancer	Pay by result	Price	Italy (24, 82)
Nilotinib	Chronic myeloid leukemia	Pay by result	Effectiveness	Italy (66)
Oxaliplatin	Metastatic colorectal cancer	CED	Effectiveness	USA (80)
Palbociclib	Hormone receptor-positive, HER2-negative metastatic breast cancer	Pay by result	Price	China (83)
Pazopanib	Renal cell carcinoma	Pay by result	Price	Italy (69)

Source: Data adapted from Reference Numbers (24, 52, 53, 56, 58, 63, 68, 69, 71, 73-84)

2.4 High-cost drugs

WHO states that the concept of expensive or high-cost drugs has not been clearly defined internationally. Price alone may not be the sole criterion; other factors, such as product usage or necessity, must also be considered, as these may lead to higher overall treatment costs for patients (41).

Most high-cost drugs are identified based on their perceived value, as they can substantially increase expenditures for both patients and healthcare systems. One of the greatest challenges for health systems worldwide is ensuring equitable access to high-cost drugs while maintaining the sustainability of already resource-constrained systems. Global healthcare expenditures are expected to rise with the growing use of such high-cost drugs across a widening range of diseases. Many newly developed drugs demonstrate advantages in treating various conditions and have shown effectiveness; however, they remain more expensive for both patients and health systems compared with existing therapies. Patients' access to high-cost drugs is directly related to a country's wealth and the affordability of its healthcare system. Markets in developed countries are generally better resourced than those in developing countries, enabling greater responsiveness to demands for access and use. Nevertheless, all countries face challenges in allocating and prioritizing access to these drugs, particularly where patients must pay a significant share of medical costs (85).

The definition of "high-cost drugs" is central to this work, yet no universal consensus exists. In general, the term may refer to (i) drugs with relatively low unit acquisition costs but high overall usage or (ii) drugs that are expensive even in small quantities, both of which can heavily impact budgets. Definitions may also vary across regions and decision-making bodies. For example, the WHO Regional Office for Europe defines high-cost drugs as therapies costing more than 10,000 EUR per patient per year for reimbursement by a public payer (86).

In Australia, Victorian public hospitals define high-cost drugs as those with an acquisition cost exceeding 1,000 AUD (1,000 Australian Dollar; AUD) per treatment. This includes drugs covered by special programs and those with an acquisition cost above 10,000 AUD per patient per treatment course. Under the Pharmaceutical Benefits Scheme (PBS), the concept extends to drugs with an estimated budget impact above 5 million AUD. Drugs recommended positively by the Pharmaceutical Benefits Advisory Committee require funding approval from the Commonwealth Department of Finance and Administration or from the Cabinet if the anticipated impact exceeds 10 million AUD (87).

The Department of Health, Government of South Australia, further specifies high-cost drugs as those with projected annual expenditure equal to or greater than (88):

- 7,246.71 United States Purchasing Power Parity (US PPP), or approximately 76,031.56 Thai Baht (10.49 Thai Baht per US PPP, at 2024 (89)) per patient per treatment course (88); or
- 72,467.08 US PPP, or approximately 760,315.56 Thai Baht (10.49 Thai Baht per US PPP, at 2024 (89)) per public hospital (88); or
- 217,401.23 US PPP, or approximately 2,280,946.69 Thai Baht (10.49 Thai Baht per US PPP, at 2024 (89)) across the public hospital system (88)

In Thailand, “high-cost drugs” are defined within the NLEM as category E(2), covering drugs for patients with specific needs. These drugs are limited to certain medical indications, carry a high risk of inappropriate use, or require specialized knowledge, disease-specific expertise, or advanced technology. They are often costly and can significantly burden both patients and society. As such, an authorized system for approval and oversight is required, managed by benefits agencies or central authorities, to ensure compliance with prescribing criteria. Healthcare facilities must also implement systems for monitoring, evaluation, and record-keeping, with data subject to review by central mechanisms (45). In practice, the NLEM category E(2) system has improved access to high-cost drugs in Thai hospitals, thereby supporting better health outcomes and potentially reducing medical costs. However, continuous monitoring is necessary to assess its broader impact on care quality and the financial sustainability of the health system (90).

This study focused on three drug uncertainty characteristics, including price, effectiveness, and use. Six high-cost drugs were selected for analysis: pertuzumab, osimertinib, afatinib, ceritinib, palbociclib, and ribociclib.

The classification of each drug under its respective uncertainty type was determined through a comprehensive literature review of both international and national evidence. This process involved examining HTA reports, peer-reviewed publications, real-world utilization data, and previous MEA implementations in other countries. Integrating these multiple sources of evidence ensured that each drug was categorized according to its dominant source of uncertainty, reflecting the key factor influencing its clinical performance, cost-effectiveness, or utilization pattern.

2.4.1 Price uncertainty

2.4.1.1 Pertuzumab

Pertuzumab is a humanized anti-HER2 monoclonal antibody, similar to trastuzumab, and is administered via intravenous infusion (91). Unlike trastuzumab, pertuzumab binds to a distinct epitope on the HER2 receptor, resulting in a more comprehensive blockade of HER2 signaling when the two agents are used in combination (92). In the study of Swain et al. (2015) (92), patients with HER2-positive metastatic breast cancer (MBC) who received pertuzumab in combination with trastuzumab and docetaxel achieved a median progression-free survival (PFS) of 18.7 months, compared with 12.4 months in the control group (placebo plus trastuzumab and docetaxel) (Hazard ratio (HR), 0.68; 95% Confidence interval (CI), 0.58 to 0.80; p-value (P) < 0.001) (92). This corresponds to a median PFS benefit of 6.3 months with the addition of pertuzumab (92).

For first-line therapy of HER2-positive MBC, the recommended dose of pertuzumab is an initial loading dose of 840 mg, followed every three weeks by a maintenance dose of 420 mg, administered in combination with trastuzumab and docetaxel. Treatment with pertuzumab should be continued until disease progression or the occurrence of unacceptable toxicity (91-93).

Although pertuzumab demonstrates high clinical effectiveness in treating HER2-positive MBC, it is associated with considerable price uncertainty due to its substantial procurement cost and the significant budgetary burden it imposes on healthcare systems (49). The price of pertuzumab is 2,068.62 USD per vial (420 mg) (94) (1 USD = 33.6215 Thai Baht (95)), resulting in an estimated annual treatment cost of approximately 37,235.10 USD per patient. This high level of expenditure raises concerns regarding affordability and long-term financial sustainability. Consequently, various MEA techniques have been implemented internationally to mitigate price-related uncertainties.

For example, in the United Kingdom, the pharmaceutical company provides a confidential commercial discount as part of a financial-based MEA. Under this agreement, pertuzumab is recommended for patients with HER2-positive MBC (91), reflecting an effort to manage the drug's price uncertainty through negotiated discounts. Similarly, in Thailand, the MEA has been applied in the form of Patient Access Programs (PAPs). According to this agreement, patients who received pertuzumab for twelve months (seventeen cycles) and continued to demonstrate clinical benefit were eligible to receive the drug free of charge thereafter. Hospitals were required to submit patient outcome data as evidence to obtain the free supply of pertuzumab from the pharmaceutical company (96). This agreement helps balance clinical value and financial sustainability while addressing price uncertainties associated with pertuzumab.

2.4.1.2 Osimertinib

Osimertinib is an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) and is administered orally (97, 98). In the study of Mok Tony et al. (2017) (98), patients with locally advanced or metastatic EGFR mutation-positive NSCLC who received osimertinib achieved a median PFS of 10.1 months, compared with 4.4 months in the control group (platinum therapy plus pemetrexed) (HR, 0.30; 95% CI, 0.23 to 0.41; P<0.001) (98). This figure corresponds to a median PFS benefit of 5.7 months with the addition of osimertinib (98).

The recommended schedule and dose of osimertinib for the treatment of locally advanced or metastatic EGFR-mutation-positive NSCLC is an 80 mg capsule taken orally once daily, every day (thirty days per cycle). Treatment with osimertinib should be continued until disease progression or the occurrence of unacceptable toxicity (97, 98).

Although osimertinib demonstrates high clinical effectiveness in patients with EGFR mutation-positive NSCLC, it is also associated with considerable price uncertainty due to its exceptionally high procurement cost and the resulting financial burden on healthcare budgets (49). The price of osimertinib is 6,168.45 USD per treatment cycle (30 tablets) (94) (1 USD = 33.6215 Thai Baht (95)), corresponding to an estimated annual treatment cost of approximately 74,021.46 USD per patient. Such a high expenditure raises concerns regarding affordability and sustainability. Consequently, MEA techniques have been employed internationally to mitigate price-related uncertainties.

For example, in the United Kingdom, the pharmaceutical company provides a confidential commercial discount as part of a financial-based MEA. Under this agreement, osimertinib is recommended for patients with locally advanced or metastatic EGFR mutation-positive NSCLC (72), reflecting an effort to manage the drug's price uncertainty through negotiated discounts. Similarly, in Thailand, osimertinib is subject to the MEA implemented by the pharmaceutical company, designed to address price uncertainty. According to this agreement, patients who received osimertinib for ten months (ten cycles) and continued to demonstrate clinical benefit and treatment response were eligible to receive the drug free of charge thereafter. Hospitals were required to submit real-world patient data as supporting evidence to obtain the free drug supply (99). This agreement reduces the financial burden on payers while ensuring that continued reimbursement aligns with demonstrated clinical benefit.

2.4.2 Effectiveness uncertainty

2.4.2.1 Afatinib

Afatinib is an EGFR-TKI and is administered orally (100, 101). In the study of Sequist LV et al. (2013) (101), patients with locally advanced or metastatic EGFR mutation-positive NSCLC who received afatinib achieved a median PFS of 11.1 months, compared with 6.9 months in the control group (chemotherapy) (HR, 0.58; 95% CI, 0.43 to 0.78; P=0.001) (101). This figure corresponds to a median PFS benefit of 4.2 months with the addition of afatinib (101).

The recommended schedule and dose of afatinib for the treatment of locally advanced or metastatic EGFR-mutation-positive NSCLC is a 40 mg capsule taken orally once daily, every day (thirty days per cycle). Treatment with afatinib should be continued until disease progression or the occurrence of unacceptable toxicity (100, 101).

The treatment effectiveness of afatinib remains subject to effectiveness uncertainty, as its comparative efficacy against other first-line EGFR-

TKIs, such as gefitinib and erlotinib, is primarily derived from indirect or network meta-analyses rather than head-to-head randomized controlled trials (49). This introduces uncertainty regarding the true magnitude of clinical benefit across diverse patient subgroups (49). The price of afatinib is 1,814.02 USD per cycle (30 tablets) (94) (1 USD = 33.6215 Thai Baht (95)), resulting in an estimated annual treatment cost of approximately 21,768.21 USD. Although the unit cost of afatinib is lower than that of some newer agents, its long-term budget impact remains substantial, particularly when effectiveness in real-world practice may differ from clinical trial outcomes. Therefore, MEA techniques have been adopted to manage effectiveness uncertainties associated with afatinib.

For example, in the United Kingdom, the pharmaceutical company has provided a confidential commercial discount, under which afatinib is recommended for patients with locally advanced or metastatic EGFR mutation-positive NSCLC (67). In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) and the pharmaceutical company established a risk-sharing MEA to address concerns about effectiveness uncertainty and potential overuse specifically. This agreement includes monitoring of treatment patterns in patients with rare EGFR-activating mutations and mandates the generation of additional real-world evidence on clinical outcomes and diagnostic accuracy. The resulting data are expected to be made available to researchers, government bodies, and industry stakeholders (102), thereby facilitating evidence-based reassessment of afatinib's value in routine clinical practice.

2.4.2.2 Ceritinib

Ceritinib is an oral small-molecule tyrosine kinase inhibitor (TKI) of anaplastic lymphoma kinase (ALK) (103, 104). In the study of Soria JC et al. (2017) (104), patients with locally advanced or metastatic ALK-rearranged-positive NSCLC who received ceritinib achieved a median PFS of 16.6 months, compared with 8.1 months in the control group (chemotherapy) (HR, 0.55; 95% CI, 0.42 to 0.73; P<0.00001) (104). This figure corresponds to a median PFS benefit of 8.5 months with the addition of ceritinib (104).

The recommended schedule and dose of ceritinib for the treatment of locally advanced or metastatic ALK-rearranged-positive NSCLC is 450 mg (150 mg per tablet) taken orally once daily, every day (thirty days per cycle).

Treatment with ceritinib should be continued until disease progresses or unacceptable toxicity occurs (103).

Ceritinib presents an effectiveness uncertainty due to its complex safety profile and variability in real-world tolerability. Although the drug demonstrates good clinical activity in patients with ALK-rearranged NSCLC, it is associated with substantial adverse events—including gastrointestinal toxicity (such as diarrhea, nausea, and vomiting), hepatotoxicity, and elevated liver enzymes (104). These toxicities often necessitate dose reduction, treatment interruption, or discontinuation (104), potentially diminishing the drug’s overall therapeutic effectiveness in clinical practice compared to outcomes observed in controlled trials (49). The price of ceritinib is 2,232.47 USD per cycle (90 tablets) (94) (1 USD = 33.6215 Thai Baht (95)), resulting in an estimated annual treatment cost of 26,789.68 USD. This combination of high financial burden and uncertainty in real-world effectiveness has prompted the adoption of MEAs to manage risk and ensure value-based access.

For example, in the United Kingdom, the pharmaceutical company has provided a confidential commercial discount. With this agreement, ceritinib is recommended for patients with locally advanced or metastatic ALK-rearranged-positive NSCLC (70). In Australia, the PBAC accepted that ceritinib was similar or better in efficacy but worse in safety compared with platinum-based chemotherapy followed by pemetrexed maintenance. Given uncertainties regarding treatment duration, overall survival, and tolerability, the PBAC required a risk-sharing MEA to address effectiveness uncertainties. Under this agreement, the pharmaceutical company and the government share financial responsibility if real-world effectiveness or utilization patterns deviate from expectations (105). Such an agreement ensures that reimbursement reflects the drug’s actual clinical value and supports evidence-based reassessment of its long-term role in national formularies.

2.4.3 Use uncertainty

2.4.3.1 Palbociclib

Palbociclib is an oral small-molecule cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor (106, 107). In the study of Mangini NS et al. (2015) (107), patients with postmenopausal, hormone receptor positive (HR-positive), HER2-

negative MBC who received palbociclib in combination with letrozole achieved a median PFS of 20.2 months, compared with 10.2 months in the control group (placebo plus letrozole) (HR, 0.488; 95% CI, 0.319 to 0.748; 1-sided P=0.0004) (107). This figure corresponds to a median PFS benefit of 10 months with the addition of palbociclib (107).

The recommended schedule and dose of palbociclib for the treatment of postmenopausal, HR-positive, HER2-negative MBC is 125 mg (125 mg per tablet) taken orally once daily for 21 consecutive days, followed by 7 days off treatment to comprise a complete cycle of 28 days. Treatment with palbociclib should be continued until the disease progresses or unacceptable toxicity occurs (106, 107).

Palbociclib presents a use uncertainty, primarily due to its real-world variability in treatment adherence and continuation. The drug's substantial hematologic toxicity, particularly severe neutropenia (106, 107), is a well-documented adverse effect (106, 107). Although generally manageable through close monitoring and dose adjustments (106, 107), these toxicities can lead to treatment interruptions, dose delays, or early discontinuation. Consequently, the actual drug usage in clinical practice may differ from that observed in controlled clinical trials, thereby introducing uncertainty in utilization patterns (49). The price of palbociclib is 2,885.72 USD per cycle (21 tablets) (94) (1 USD = 33.6215 Thai Baht (95)), resulting in an estimated annual treatment cost of 34,628.67 USD. This high expenditure, coupled with variability in real-world use, underscores the need for MEAs to manage financial exposure and ensure value-based reimbursement.

For example, in the United Kingdom, the pharmaceutical company has provided a confidential commercial discount. Under this agreement, palbociclib with an aromatase inhibitor is recommended for patients with postmenopausal, HR-positive, HER2-negative MBC (108). In Australia, reimbursement under the PBS has been made possible through risk-sharing agreements and special pricing agreements. Following the March 2018 PBAC recommendation, palbociclib was listed with financial risk-sharing mechanisms, including annual subsidization caps, to address uncertainties in utilization volume and cost-effectiveness. The March 2022 PBAC deliberations subsequently confirmed that palbociclib, when used in combination with fulvestrant, would be incorporated into existing class-based

MEAs shared with ribociclib and abemaciclib. These agreements were designed to stabilize utilization patterns, limit budgetary risks arising from unpredictable treatment duration, and ensure equitable patient access. Collectively, they exemplify how MEA mechanisms can effectively manage use uncertainty in high-cost anticancer drugs (109).

2.4.3.2 Ribociclib

Ribociclib is an oral small-molecule CDK4/6 inhibitor (110, 111). In the study of Hortobagyi GN et al. (2018) (111), patients with postmenopausal, hormone receptor (HR)-positive, HER2-negative MBC who received ribociclib in combination with letrozole achieved a median PFS of 25.3 months, compared with 16.0 months in the control group (placebo plus letrozole) (HR, 0.568; 95% CI, 0.457 to 0.704; log-rank $P=9.63\times10^{-8}$) (111). This figure corresponds to a median PFS benefit of 9.3 months with the addition of ribociclib (111).

The recommended schedule and dose of ribociclib for the treatment of postmenopausal, HR-positive, HER2-negative MBC is 600 mg (200 mg per tablet) taken orally once daily for 21 consecutive days, followed by 7 days off treatment to comprise a complete cycle of 28 days. Treatment with ribociclib should be continued until the disease progresses or unacceptable toxicity occurs (110, 111).

Ribociclib is characterized by use uncertainty, primarily driven by variability in treatment duration, adherence, and discontinuation in real-world settings. The drug's substantial adverse effects—particularly severe neutropenia, QT interval prolongation, and hepatotoxicity (110, 111)—necessitate close monitoring and may require dose adjustments or temporary treatment discontinuation (110, 111), directly influencing the consistency of drug utilization across patients. Consequently, the real-world use of ribociclib often deviates from clinical trial protocols, introducing uncertainty regarding its utilization volume. The price of ribociclib is 1,515.76 USD per cycle (200 mg, 63 tablets) (94) (1 USD = 33.6215 Thai Baht (95)), resulting in an estimated annual treatment cost of 18,189.06 USD. This combination of high expenditure and unpredictable utilization underscores the need for MEAs to mitigate financial risk and manage variability in real-world drug use.

For example, in the United Kingdom, the pharmaceutical company has provided a confidential commercial discount. With this agreement, ribociclib with an aromatase inhibitor is recommended for patients with postmenopausal, HR-positive, HER2-negative MBC (75). In Australia, the PBAC addressed use uncertainty and budgetary risk related to ribociclib (used with fulvestrant for HR-positive, HER2-negative MBC) through a risk-sharing MEA. The PBAC identified significant uncertainties in the cost-effectiveness model—particularly those arising from indirect comparisons, extrapolated survival assumptions, and variable treatment durations—and required financial safeguards, including annual expenditure caps, to contain fiscal exposure. These MEAs were structured to ensure that government spending remained aligned with real-world utilization and that reimbursement reflected the drug's demonstrated value under routine practice conditions. Accordingly, ribociclib's MEA serves as a policy example of how use-uncertainty can be effectively managed through adaptive, outcome-linked reimbursement mechanisms that balance utilization variability, clinical benefit, and fiscal sustainability (112).

CHAPTER 3
RESEARCH METHODOLOGY

This chapter describes the research methodology, including the overall methods used, research design, study population and sample, inclusion and exclusion criteria, data sources and collection methods, and procedures for data analysis.

3.1 Methods

The methods of this study comprised two analytical parts designed to find out the most appropriate MEA techniques for reducing drug procurement costs, thereby optimizing budget utilization and improving patient access to high-cost drugs.

The first analytical part involved calculating drug procurement costs under various MEA techniques to determine which technique resulted in the lowest costs, considering three key domains of drug uncertainty characteristics: price, effectiveness, and use.

The second analytical part compared the findings from the first analysis to summarize the relationship between drug uncertainty characteristics and the MEA techniques that were most appropriate for addressing each type of uncertainty.

3.2 Research design

This study's research design employed an analytic cohort study incorporating quantitative analysis.

3.3 Population and sample

The unit of analysis in this study consisted of two levels: the drug level and the patient level.

3.3.1 Drug-level analysis

At the drug level, the study population comprised high-cost anticancer drugs available at Thammasat University Hospital (TUH).

A purposive sampling approach was used to select six high-cost anticancer drugs that represented different drug uncertainty characteristics, namely price, effectiveness, and use uncertainty.

3.3.1.1 Inclusion criteria

The inclusion criteria required that drugs meet at least one of these uncertainty characteristics, as defined below:

(1) Price uncertainty (88, 89)

Price uncertainty refers to drugs with high procurement costs that pose a potential budgetary burden on the healthcare system (88, 89).

In this study, price uncertainty was defined as drugs with a predicted annual expenditure equal to or greater than 7,246.71 USD per patient per treatment course (88, 89).

The drugs meeting this criterion were:

- Pertuzumab, indicated for patients with HER2-positive MBC.
- Osimertinib, indicated for patients with locally advanced or metastatic EGFR mutation-positive NSCLC.

Both drugs had an annual expenditure equal to or greater than 7,246.71 USD per patient per treatment course, which introduces significant price uncertainty and justifies the use of MEA techniques for financial risk management (94, 95).

(2) Effectiveness uncertainty (49)

Effectiveness uncertainty applies to drugs for which there is limited or inconclusive evidence regarding comparative efficacy, long-term outcomes, or real-world treatment effectiveness (49).

The following characteristics were used to identify effectiveness uncertainty (49):

- Limited evidence on therapeutic value or comparison with alternatives.

- Lack of long-term or safety data.
- Doubts about real-world effectiveness due to adherence or clinical practice issues.
- Uncertainty regarding optimal dose, duration, or patient subgroup.

The drugs meeting this criterion were:

- Afatinib, for patients with locally advanced or metastatic EGFR mutation-positive NSCLC. Its comparative efficacy versus gefitinib or erlotinib is derived from indirect comparisons, raising uncertainty about its relative effectiveness (102).
- Ceritinib, for patients with locally advanced or metastatic ALK-rearranged NSCLC. The drug's adverse effects—including gastrointestinal toxicity and hepatotoxicity—can lead to dose reduction or treatment discontinuation, thereby compromising real-world effectiveness (104).

(3) Use uncertainty (49)

Use uncertainty refers to ambiguity regarding the number of eligible patients, treatment duration, or utilization patterns in real-world settings (49).

The drug with use uncertainty included:

- Palbociclib, indicated for postmenopausal patients with HR-positive, HER2-negative MBC.
- Ribociclib, indicated for postmenopausal patients with HR-positive, HER2-negative MBC.

Both drugs are associated with hematologic toxicity (notably severe neutropenia), which often necessitates dose adjustment or temporary discontinuation (107, 111). These factors contribute to substantial variability in treatment duration and overall drug utilization, reflecting real-world use uncertainty.

3.3.2 Patient-level analysis

At the patient level, the study population included all patients who received any of the six selected high-cost anticancer drugs at TUH between 2010 and 2025.

The study employed an analytic cohort design, following patients from the initiation of therapy until treatment discontinuation.

3.3.2.1 Exclusion criteria

Patients who were still undergoing treatment and had completed fewer than the median PFS cycles for their respective drug were excluded. This ensured adequate treatment duration for assessing drug utilization and cost outcomes. The exclusion criteria were as follows:

Table 3.1 Exclusion criteria based on the number of treatment cycles for each drug

Drug	Exclusion criterion (fewer than.....treatment cycles)
Pertuzumab	Seventeen
Osimertinib	Ten
Afatinib	Eleven
Ceritinib	Sixteen
Palbociclib	Ten
Ribociclib	Ten

3.4 Data source and collection method

3.4.1 Data source

The data sources include secondary data from the hospital database of TUH from January 1, 2010, to April 30, 2025, and the website of the Drug and Medical Supply Information Center (DMSIC).

In this study, the variable collected from the website of DMSIC is the median price for each drug. The variables collected from the hospital database at TUH are as follows (113):

- The number of patients using the drug
- The number of doses each patient used
- The response from the patients treated
    - Progressive disease by response evaluation criteria in solid tumors (RECIST) guideline (114)

- Serious adverse events (grade 3 or higher) (115)

Table 3.2 RECIST guideline

Overall response	Definition
Complete response (CR)	• Disappearance of all lesions and pathologic lymph nodes • No new lesions
Partial response (PR)	• ≥ 30% decrease in the sum of the longest diameters of the target lesions • No new lesions • No progression of non-target lesions
Stable disease (SD)	• No partial response or progressive disease
Progressive disease (PD)	• ≥ 20% increase in the sum of longest diameters of the target lesions compared to the smallest sum of longest diameters of the target lesions in the study; or • New lesions; or • Progression of non-target lesions

Source: Data adapted from Reference Numbers (114)

Table 3.3 The severity of the adverse event

Severity	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to an adverse event.

Source: Data adapted from Reference Numbers (115)

3.4.2 Data collection method

The data for the first analytical part were collected using a data collection form. The data for the second analytical part were extracted from the first and subsequently compared to summarize the drug uncertainty characteristics, which indicated the most appropriate MEA technique.

3.4.3 Data collection form

The data collection form was developed by the authors of this study for use in data collection. This data collection form was reviewed and approved by three experts through an evaluation of the index of item congruence (IOC). In this study, the data collection form was designed to capture variables as outlined in Table 3.4.

Table 3.4 The variables in the data collection form

Variable name	Definition
Research the patient's code	The research patient's code is used instead of the patient's name and hospital number
Gender	Patient's gender
Age (year)	Patient's age
Health insurance schemes	Health insurance schemes that covered patients during treatment
Diagnosis	Diseases that the patient was treated for...
Drug name	A drug that patients received to treat their disease
Visit date	The date that the patient came to see the doctor at the outpatient department of the hospital
Admission date	The date that the patient was admitted to the hospital.
Discharge date	The date that the patient was discharged from the hospital
Discharge status	Patient's status after discharge from the hospital
Date of receiving the drug	The date that the patient received the drug
Drug quantity	The number of drugs that the patient received
Drug median price	The median price for each drug
Patient response	Progressive disease according to the RECIST guideline
Adverse events	The severity of the adverse event

Table 3.5 Dictionary of variables

Variable	Variable name	Value label	Measure
id	Research the patient's code	001, 002, 003, 004, ...	Nominal scale
sex	Gender	0 = Male, 1 = Female	Nominal scale
age	Age (year)		Ratio scale
cov	Health insurance schemes	0 = UCS, 1 = SSS, 2 = CSMBS, 3 = Others	Nominal scale
dx	Diagnosis	0 = HER2-positive MBC 1 = locally advanced or metastatic EGFR mutation-positive NSCLC 2 = locally advanced or metastatic ALK-rearranged-positive NSCLC 3 = postmenopausal, HR-positive, HER2-negative MBC	Nominal scale
med1	Drug name	0 = Pertuzumab 1 = Osimertinib 2 = Afatinib 3 = Ceritinib 4 = Palbociclib 5 = Ribociclib	Nominal scale
med2	Patient response	0 = Complete response 1 = Partial response 2 = Stable disease 3 = Progressive disease	Nominal scale
med3	Adverse event	0 = grade 1 or 2 1 = grade 3 or higher	Nominal scale
opd1	Visit date		Ratio scale
ipd2	Admission date		Ratio scale
ipd3	Discharge date		Ratio scale
dis	Discharge status	0 = Death 1 = Survived	Nominal scale
med4	Date of receiving the drug		Ratio scale
med5	Drug quantity		Ratio scale
med6	Drug median price		Ratio scale

3.5 Data analysis

This study aimed to find out the MEA technique that resulted in the lowest drug procurement cost. A statistical program was utilized to calculate the drug procurement cost for each drug based on its uncertainty characteristics. Various scenarios were designed according to the MEA taxonomy, and the changes in drug procurement costs under each scenario were examined to determine which MEA techniques resulted in the lowest drug procurement costs.

3.5.1 The method for calculating the change in drug procurement cost

The calculation of changes in drug procurement cost was conducted to find out the MEA techniques that resulted in the lowest drug procurement costs for each drug. Patient profiles were retrieved from the TUH database and analyzed to assess drug utilization patterns and treatment outcomes.

For each of the six selected drugs, procurement costs were calculated under multiple MEA scenarios, as outlined in Tables 3.6 through 3.11. All analyses were performed from the payer's perspective using the median drug price. The results were reported as (1) total drug procurement cost, (2) drug procurement cost per patient, and (3) total cost savings over a twenty-four-month period.

Although all five MEA techniques were applied uniformly across the six selected drugs, classifying each drug according to its dominant uncertainty characteristic—whether related to price, effectiveness, or use—was an essential methodological step. This classification ensured a clear understanding of the mechanism by which each MEA technique addresses drug uncertainty, as well as the contextual interpretation and policy relevance of the results, by aligning each drug with the type of uncertainty most influencing its treatment outcomes and cost-saving potential.

Table 3.6 Scenarios for drug procurement cost calculation of pertuzumab

Scenario	MEA technique	Definition	Method
Reference case	No MEA technique	No MEA technique was applied.	• C = (P × Q)
One	Discount	A 30% discount on the price of pertuzumab was provided by the pharmaceutical company.	• C = (P – 30%) × Q
Two	Free initiation treatment	Pertuzumab was provided free of charge by the pharmaceutical company for the first seventeen treatment cycles. Thereafter, the full cost of pertuzumab was covered by the payer until treatment discontinuation.	• If a patient received pertuzumab for no more than seventeen treatment cycles, the drug procurement cost was zero (C = 0). • If a patient received pertuzumab for more than seventeen treatment cycles, the drug procurement cost was calculated as C = (P × Q) – (P × 18).
Three	Utilization cap	The cost of pertuzumab was covered by the payer for up to seventeen treatment cycles. Thereafter, pertuzumab was provided free of charge by the pharmaceutical company for patients who received more than seventeen cycles.	• If a patient received pertuzumab for no more than seventeen treatment cycles, the drug procurement cost was calculated as C = (P × Q) • If a patient received pertuzumab for more than seventeen treatment cycles, the drug procurement cost was 37,235.10 USD (C = 37,235.10).
Four	Conditional treatment continuation	The cost of pertuzumab was covered by the payer for up to seventeen treatment cycles. Only patients who demonstrated stable disease, partial response, or complete response within seventeen treatment cycles were permitted to continue treatment. Thereafter, pertuzumab was provided free of charge by the pharmaceutical company for patients who received more than seventeen cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within seventeen treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within seventeen treatment cycles and continued receiving pertuzumab beyond seventeen cycles, the drug procurement cost was 37,235.10 USD (C = 37,235.10).
Five	Pay-by-result	The full cost of pertuzumab was reimbursed by the pharmaceutical company for patients who did not demonstrate stable disease, partial response, or complete response within seventeen treatment cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within seventeen treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within seventeen treatment cycles and continued receiving pertuzumab beyond seventeen cycles, the drug procurement cost was calculated as C = (P × Q).

C: drug procurement cost per patient; P: median price of pertuzumab (2,068.62 USD per vial (420 mg)); Q: number of treatment cycles per patient

Note: Each treatment cycle required 420 mg of pertuzumab (1 vial), except for the first cycle, which required 840 mg (2 vials)

Table 3.7 Scenarios for drug procurement cost calculation of osimertinib

Scenario	MEA technique	Definition	Method
Reference case	No MEA technique	No MEA technique was applied.	• C = (P × Q)
One	Discount	A 50% discount on the price of osimertinib was provided by the pharmaceutical company.	• C = (P – 50%) × Q
Two	Free initiation treatment	Osimertinib was provided free of charge by the pharmaceutical company for the first ten treatment cycles. Thereafter, the full cost of osimertinib was covered by the payer until treatment discontinuation.	• If a patient received osimertinib for no more than ten treatment cycles, the drug procurement cost was zero (C = 0). • If a patient received osimertinib for more than ten treatment cycles, the drug procurement cost was calculated as C = (P × Q) – (P × 10).
Three	Utilization cap	The cost of osimertinib was covered by the payer for up to ten treatment cycles. Thereafter, osimertinib was provided free of charge by the pharmaceutical company for patients who received more than ten cycles.	• If a patient received osimertinib for no more than ten treatment cycles, the drug procurement cost was calculated as C = (P × Q) • If a patient received osimertinib for more than ten treatment cycles, the drug procurement cost was 61,684.55 USD (C = 61,684.55).
Four	Conditional treatment continuation	The cost of osimertinib was covered by the payer for up to ten treatment cycles. Only patients who demonstrated stable disease, partial response, or complete response within ten treatment cycles were permitted to continue treatment. Thereafter, osimertinib was provided free of charge by the pharmaceutical company for patients who received more than ten cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within ten treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within ten treatment cycles and continued receiving osimertinib beyond ten cycles, the drug procurement cost was 61,684.55 USD (C = 61,684.55).
Five	Pay-by-result	The full cost of osimertinib was reimbursed by the pharmaceutical company for patients who did not demonstrate stable disease, partial response, or complete response within ten treatment cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within ten treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within ten treatment cycles and continued receiving osimertinib beyond ten cycles, the drug procurement cost was calculated as C = (P × Q).

C: drug procurement cost per patient; P: median price of osimertinib (6,168.45 USD per cycle, 30 tablets); Q: number of treatment cycles per patient

Note: Each treatment cycle required 30 tablets of osimertinib (80 mg)

Table 3.8 Scenarios for drug procurement cost calculation of afatinib

Scenario	MEA technique	Definition	Method
Reference case	No MEA technique	No MEA technique was applied.	• C = (P × Q)
One	Discount	A 50% discount on the price of afatinib was provided by the pharmaceutical company.	• C = (P – 50%) × Q
Two	Free initiation treatment	Afatinib was provided free of charge by the pharmaceutical company for the first eleven treatment cycles. Thereafter, the full cost of afatinib was covered by the payer until treatment discontinuation.	• If a patient received afatinib for no more than eleven treatment cycles, the drug procurement cost was zero (C = 0). • If a patient received afatinib for more than eleven treatment cycles, the drug procurement cost was calculated as C = (P × Q) – (P × 11).
Three	Utilization cap	The cost of afatinib was covered by the payer for up to eleven treatment cycles. Thereafter, afatinib was provided free of charge by the pharmaceutical company for patients who received more than eleven cycles.	• If a patient received afatinib for no more than eleven treatment cycles, the drug procurement cost was calculated as C = (P × Q) • If a patient received afatinib for more than eleven treatment cycles, the drug procurement cost was 19,954.20 USD (C = 19,954.20).
Four	Conditional treatment continuation	The cost of afatinib was covered by the payer for up to eleven treatment cycles. Only patients who demonstrated stable disease, partial response, or complete response within eleven treatment cycles were permitted to continue treatment. Thereafter, afatinib was provided free of charge by the pharmaceutical company for patients who received more than eleven cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within eleven treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within eleven treatment cycles and continued receiving afatinib beyond eleven cycles, the drug procurement cost was 19,954.20 USD (C = 19,954.20).
Five	Pay-by-result	The full cost of afatinib was reimbursed by the pharmaceutical company for patients who did not demonstrate stable disease, partial response, or complete response within eleven treatment cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within eleven treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within eleven treatment cycles and continued receiving afatinib beyond eleven cycles, the drug procurement cost was calculated as C = (P × Q).

C: drug procurement cost per patient; P: median price of afatinib (1,814.02 USD per cycle, 30 tablets); Q: number of treatment cycles per patient

Note: Each treatment cycle required 30 tablets of afatinib (40 mg)

Table 3.9 Scenarios for drug procurement cost calculation of ceritinib

Scenario	MEA technique	Definition	Method
Reference case	No MEA technique	No MEA technique was applied.	• $C = (P \times Q)$
One	Discount	A 30% discount on the price of ceritinib was provided by the pharmaceutical company.	• $C = (P – 30\%) \times Q$
Two	Free initiation treatment	Ceritinib was provided free of charge by the pharmaceutical company for the first sixteen treatment cycles. Thereafter, the full cost of ceritinib was covered by the payer until treatment discontinuation.	• If a patient received ceritinib for no more than sixteen treatment cycles, the drug procurement cost was zero ($C = 0$). • If a patient received ceritinib for more than sixteen treatment cycles, the drug procurement cost was calculated as $C = (P \times Q) – (P \times 16)$.
Three	Utilization cap	The cost of ceritinib was covered by the payer for up to sixteen treatment cycles. Thereafter, ceritinib was provided free of charge by the pharmaceutical company for patients who received more than sixteen cycles.	• If a patient received ceritinib for no more than sixteen treatment cycles, the drug procurement cost was calculated as $C = (P \times Q)$ • If a patient received ceritinib for more than sixteen treatment cycles, the drug procurement cost was 35,719.57 USD ($C = 35,719.57$).
Four	Conditional treatment continuation	The cost of ceritinib was covered by the payer for up to sixteen treatment cycles. Only patients who demonstrated stable disease, partial response, or complete response within sixteen treatment cycles were permitted to continue treatment. Thereafter, ceritinib was provided free of charge by the pharmaceutical company for patients who received more than sixteen cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within sixteen treatment cycles, the drug procurement cost was zero ($C = 0$). • If a patient demonstrated stable disease, partial response, or complete response within sixteen treatment cycles and continued receiving ceritinib beyond sixteen cycles, the drug procurement cost was 35,719.57 USD ($C = 35,719.57$).
Five	Pay-by-result	The full cost of ceritinib was reimbursed by the pharmaceutical company for patients who did not demonstrate stable disease, partial response, or complete response within sixteen treatment cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within sixteen treatment cycles, the drug procurement cost was zero ($C = 0$). • If a patient demonstrated stable disease, partial response, or complete response within sixteen treatment cycles and continued receiving ceritinib beyond sixteen cycles, the drug procurement cost was calculated as $C = (P \times Q)$.

C: drug procurement cost per patient; P: median price of ceritinib (2,232.47 USD per cycle, 90 tablets); Q: number of treatment cycles per patient

Note: Each treatment cycle required 90 tablets of ceritinib (150 mg)

Table 3.10 Scenarios for drug procurement cost calculation of palbociclib

Scenario	MEA technique	Definition	Method
Reference case	No MEA technique	No MEA technique was applied.	• C = (P × Q)
One	Discount	A 50% discount on the price of palbociclib was provided by the pharmaceutical company.	• C = (P – 50%) × Q
Two	Free initiation treatment	Palbociclib was provided free of charge by the pharmaceutical company for the first ten treatment cycles. Thereafter, the full cost of palbociclib was covered by the payer until treatment discontinuation.	• If a patient received palbociclib for no more than ten treatment cycles, the drug procurement cost was zero (C = 0). • If a patient received palbociclib for more than ten treatment cycles, the drug procurement cost was calculated as C = (P × Q) – (P × 10).
Three	Utilization cap	The cost of palbociclib was covered by the payer for up to ten treatment cycles. Thereafter, palbociclib was provided free of charge by the pharmaceutical company for patients who received more than ten cycles.	• If a patient received palbociclib for no more than ten treatment cycles, the drug procurement cost was calculated as C = (P × Q) • If a patient received palbociclib for more than ten treatment cycles, the drug procurement cost was 28,857.22 USD (C = 28,857.22).
Four	Conditional treatment continuation	The cost of palbociclib was covered by the payer for up to ten treatment cycles. Only patients who demonstrated stable disease, partial response, or complete response within ten treatment cycles were permitted to continue treatment. Thereafter, palbociclib was provided free of charge by the pharmaceutical company for patients who received more than ten cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within ten treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within ten treatment cycles and continued receiving palbociclib beyond ten cycles, the drug procurement cost was 28,857.22 USD (C = 28,857.22).
Five	Pay-by-result	The full cost of palbociclib was reimbursed by the pharmaceutical company for patients who did not demonstrate stable disease, partial response, or complete response within ten treatment cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within ten treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within ten treatment cycles and continued receiving palbociclib beyond ten cycles, the drug procurement cost was calculated as C = (P × Q).

C: drug procurement cost per patient; P: median price of palbociclib (2,885.72 USD per cycle, 21 tablets); Q: number of treatment cycles per patient

Note: Each treatment cycle required 21 tablets of palbociclib (125 mg)

Table 3.11 Scenarios for drug procurement cost calculation of ribociclib

Scenario	MEA technique	Definition	Method
Reference case	No MEA technique	No MEA technique was applied.	• C = (P × Q)
One	Discount	A 50% discount on the price of ribociclib was provided by the pharmaceutical company.	• C = (P – 50%) × Q
Two	Free initiation treatment	Ribociclib was provided free of charge by the pharmaceutical company for the first ten treatment cycles. Thereafter, the full cost of ribociclib was covered by the payer until treatment discontinuation.	• If a patient received ribociclib for no more than ten treatment cycles, the drug procurement cost was zero (C = 0). • If a patient received ribociclib for more than ten treatment cycles, the drug procurement cost was calculated as C = (P × Q) – (P × 10).
Three	Utilization cap	The cost of ribociclib was covered by the payer for up to ten treatment cycles. Thereafter, ribociclib was provided free of charge by the pharmaceutical company for patients who received more than ten cycles.	• If a patient received ribociclib for no more than ten treatment cycles, the drug procurement cost was calculated as C = (P × Q) • If a patient received ribociclib for more than ten treatment cycles, the drug procurement cost was 15,157.55 USD (C = 15,157.55).
Four	Conditional treatment continuation	The cost of ribociclib was covered by the payer for up to ten treatment cycles. Only patients who demonstrated stable disease, partial response, or complete response within ten treatment cycles were permitted to continue treatment. Thereafter, ribociclib was provided free of charge by the pharmaceutical company for patients who received more than ten cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within ten treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within ten treatment cycles and continued receiving ribociclib beyond ten cycles, the drug procurement cost was 15,157.55 USD (C = 15,157.55).
Five	Pay-by-result	The full cost of ribociclib was reimbursed by the pharmaceutical company for patients who did not demonstrate stable disease, partial response, or complete response within ten treatment cycles.	• If a patient did not demonstrate stable disease, partial response, or complete response within ten treatment cycles, the drug procurement cost was zero (C = 0). • If a patient demonstrated stable disease, partial response, or complete response within ten treatment cycles and continued receiving ribociclib beyond ten cycles, the drug procurement cost was calculated as C = (P × Q).

C: drug procurement cost per patient; P: median price of ribociclib (1,515.76 USD per cycle, 63 tablets); Q: number of treatment cycles per patient

Note: Each treatment cycle required 63 tablets of ribociclib (200 mg)

3.5.2 Criteria to summarize the drug uncertainty characteristics that indicate the appropriate MEA technique

The drug procurement costs obtained from the first analytical part were compared with those of other drugs that have similar drug uncertainty characteristics. This analysis was conducted to summarize the uncertainty characteristics and improve confidence in the accuracy and suitability of the MEA technique obtained.

CHAPTER 4
RESULTS AND DISCUSSION

This chapter presents the outcomes of the study conducted across two analytical parts.

The first analytical part consists of the demographic characteristics of patients for each studied high-cost drug, the patterns of drug response, and drug procurement costs for each MEA technique.

The second analytical part identifies the most appropriate MEA technique for each drug uncertainty characteristic by comparing drug procurement costs obtained from the first analytical part.

4.1 Drug procurement costs varied by MEA techniques

This study focused on three drug uncertainty characteristics, including price, effectiveness, and use. There were 161 patients who received six studied high-cost drugs. For price uncertainty, there were 13 patients who received pertuzumab and 66 patients who received osimertinib. For effectiveness uncertainty, there were 9 patients who received afatinib and 11 patients who received ceritinib. For use uncertainty, there were 23 patients who received palbociclib and 39 patients who received ribociclib.

4.1.1 Price uncertainty

4.1.1.1 Pertuzumab

(1) Demographic characteristics

Table 4.1 reports the demographic characteristics of patients with HER2-positive MBC. There were thirteen patients, the mean age was 59.23 years (SD = 8.82), and all patients were female (100%). The majority were patients under the CSMBS (69.23%), followed by the UCS (23.08%) and other schemes (7.69%). Notably, no patients under the SSS were enrolled in this study. Most patients (76.92%) exhibited strong HER2-positivity (3+). Intermediate HER2-positivity (2+) was found in only 23.08%. All patients (100%) were diagnosed with clinical stage IV disease according to the prescribing criteria of pertuzumab.

Table 4.1 Demographic characteristics of patients who received pertuzumab

Parameters	**n (%)**
Age, years	
Mean (SD)	59.23 (8.82)
Gender, n (%)	
Female	13 (100.00)
Male	0 (0.00)
Health insurance schemes, n (%)	
Civil Servant Medical Benefit Scheme (CSMBS)	9 (69.23)
Social Security Scheme (SSS)	0 (0.00)
Universal Coverage Scheme (UCS)	3 (23.08)
Others	1 (7.69)
HER2 expression status, n (%)	
2+	3 (23.08)
3+	10 (76.92)
Clinical stage, n (%)	
Stage I	0 (0.00)
Stage II	0 (0.00)
Stage III	0 (0.00)
Stage IV	13 (100.00)

(2) The patterns of drug response

Figure 4.1 shows the patterns of drug response. The drug use profiles are derived from real-world data of patients with HER2-positive MBC.

At the Cycle Ninth, approximately six months after treatment initiation, the majority of patients demonstrated favorable disease control. The disease control consists of 61.55% of patients showing stable disease and 23.07% of patients showing partial response. Progressive disease was observed in 15.38% of the cohort.

Neither a complete response nor death was reported at this time point. These findings suggest that pertuzumab can provide good disease control within the first six months of the treatment.

By the Cycle Seventeenth, approximately twelve months after treatment initiation, most patients continued to demonstrate either stable disease (46.17%) or partial response (7.69%). These findings indicate that pertuzumab therapy could sustain disease control in the real-world treatment of HER2-positive MBC.

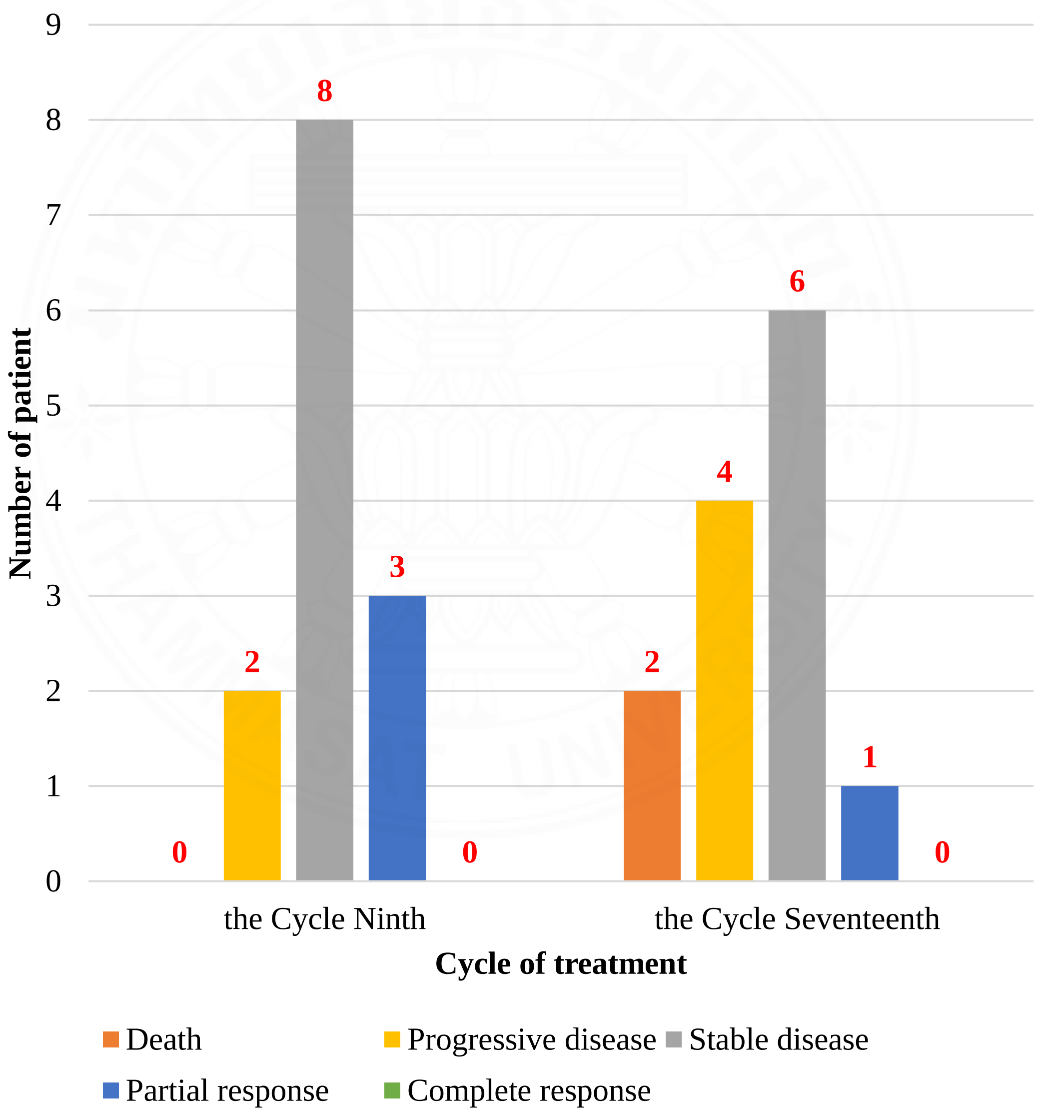


Figure 4.1 The patterns of drug response for pertuzumab

(3) Drug procurement costs for each MEA technique

Table 4.3 reports the total drug procurement cost for thirteen patients receiving pertuzumab over a 24-month period. MEA techniques were applied to analyze real-world data under each scenario, as demonstrated in Table 4.2. Without any MEA technique application (reference case), the total drug procurement cost was 562,663.77 USD (1 USD = 33.6215 Thai Baht) (94, 95).

Table 4.2 Definition of the analyzed scenarios of pertuzumab

Scenario	MEA technique	Definition
1	Discount	The discount strategy of 30% on drug price.
2	Free initiation treatment	The first seventeen cycles of the drug are offered free of charge; thereafter, the full price is paid.
3	Utilization cap	The payer covers the cost for the first seventeen cycles, and the pharmaceutical company subsequently provides the remaining treatment cycle free of charge.
4	Conditional treatment continuation	The payer funds up to seventeen cycles of treatment. Only patients who demonstrate stable disease, partial response, or complete response within seventeen cycles continue therapy, after which the pharmaceutical company provides the drug free of charge.
5	Pay-by-result	The pharmaceutical company reimburses the full drug cost for patients who do not achieve stable disease, partial response, or complete response within seventeen cycles.

Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing the total cost by 407,517.51 USD (72.43%), compared to the reference case. The conditional treatment continuation technique also demonstrated substantial savings, with a cost reduction of 302,018.05 USD (53.68%). Similarly, the discount technique led to a 30.00% cost reduction.

Other MEA techniques, such as the utilization cap and pay-by-result, were associated with more modest savings of 27.57% and 26.10%, respectively. Despite providing some degree of cost control, these techniques offered comparatively lower economic benefits.

The results indicate that the choice of MEA technique has a significant impact on the budgetary implications of pertuzumab procurement. In this analysis of real-world data, the free initiation treatment technique was identified as the most cost-effective MEA technique.

However, in real-world practice, when pertuzumab was first introduced to the market, the pharmaceutical company initially implemented the utilization cap technique. Under this agreement, the payer covered the cost of the drug for up to seventeen cycles. Thereafter, the pharmaceutical company provided the drug free of charge for patients continuing beyond that point (96). Based on the findings of this study, the utilization cap technique resulted in minimal cost savings.

This study found that among the various MEA techniques analyzed, the free initiation treatment technique resulted in the greatest cost savings, reducing the total drug procurement cost by 72.43% compared to procurement without MEA implementation.

Figure 4.2 demonstrates the individual-level treatment durations of thirteen patients with HER2-positive MBC who receive pertuzumab. Among these patients, six discontinue treatment before the Cycle Seventeenth, meaning the entire course is provided free of charge by the pharmaceutical company under the free initiation treatment technique. This highlights a key advantage of the technique: payers incur no cost if patients discontinue treatment early. Furthermore, in this cohort, seven receive seventeen or more treatment cycles. Under this technique, the first seventeen cycles are provided free of charge, with costs incurred only from the eighteenth cycle onward. Consequently, for patients requiring prolonged treatment, this MEA technique still results in substantial cost savings (47, 56).

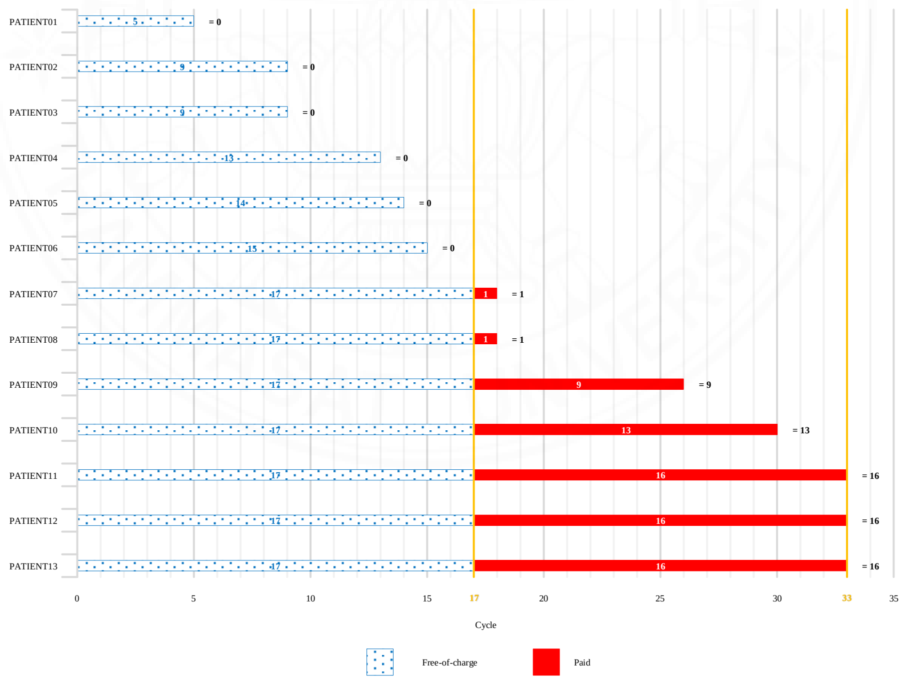


Figure 4.2 The payment patterns associated with the free initiation treatment technique of pertuzumab

These findings are particularly noteworthy, as they demonstrate that the free initiation treatment technique aligns well with both clinical outcomes and economic objectives. Specifically, it provides financial protection in cases of early discontinuation while also offering budgetary efficiency for longer treatment durations. The alignment between clinical response and treatment duration reinforces the economic viability of this technique—particularly for drugs like pertuzumab, which confer prolonged benefit in a subset of patients (47, 56).

Under the utilization cap technique (Figure 4.3), six patients in this cohort discontinue treatment before reaching the Cycle Seventeenth. In this technique, payers incur costs for all treatment cycles up to cycle seventeen, regardless of early discontinuation. In contrast, the free initiation treatment technique provides full coverage for the initial seventeen cycles, resulting in zero cost for patients who discontinue early and incurring costs only for those who continue treatment beyond the Cycle Seventeenth. Consequently, the free initiation treatment technique results in greater cost savings compared to the utilization cap technique (47, 56).

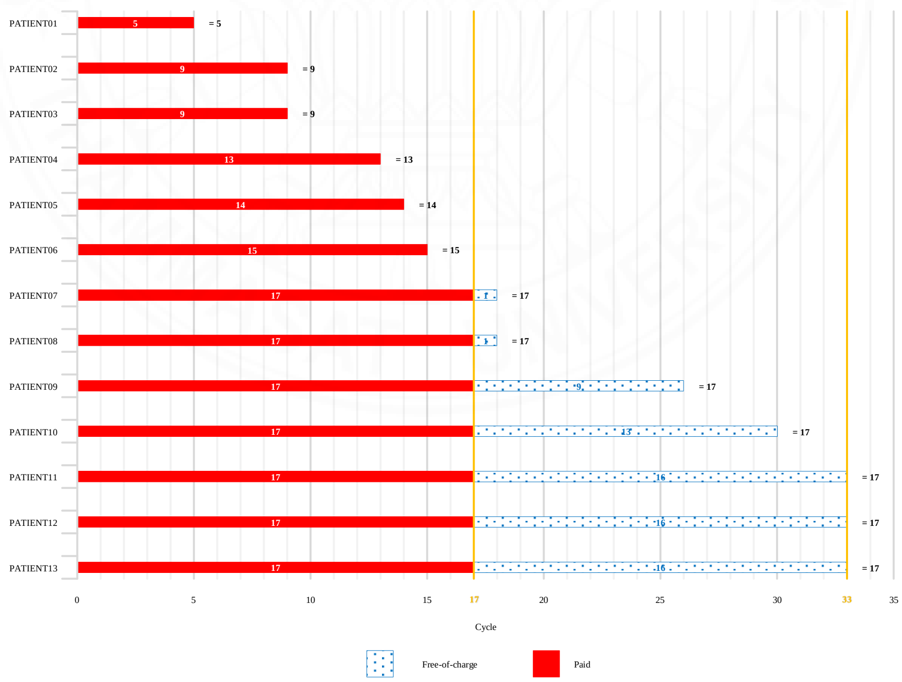


Figure 4.3 The payment patterns associated with the utilization cap technique of pertuzumab

Under the conditional treatment continuation technique (Figure 4.4), six patients discontinue treatment before the Cycle Seventeenth, meaning no drug costs are incurred for these patients, as the pharmaceutical company fully absorbs the cost. However, for the remaining seven patients who receive more than seventeen cycles, the payer is responsible for covering the cost of the first seventeen cycles, with the pharmaceutical company covering only the subsequent cycles. In contrast, under the free initiation treatment technique, all patients—regardless of treatment duration—receive the first seventeen cycles free of charge, with costs incurred only if treatment continues beyond that point. As a result, since seven patients in this cohort receive seventeen or more cycles, the free initiation treatment technique results in greater overall cost savings (47, 56).

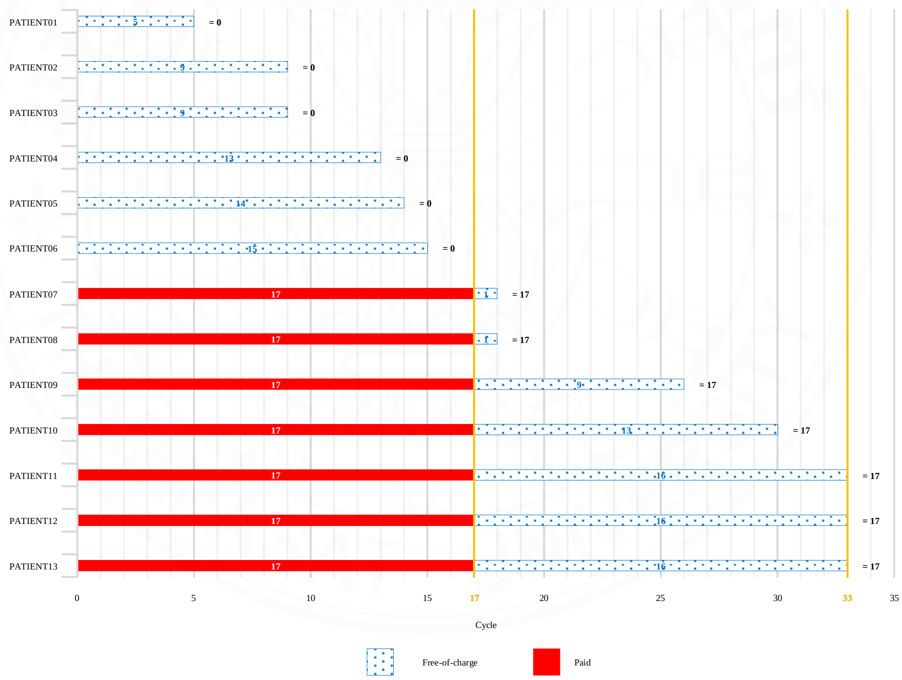


Figure 4.4 The payment patterns associated with the conditional treatment continuation technique of pertuzumab

Under the pay-by-result technique (Figure 4.5), six patients discontinue treatment before the Cycle Seventeenth, and their lack of favorable response during this period renders them eligible for full cost reimbursement by the pharmaceutical company. Consequently, no drug procurement costs are incurred by the payer for these patients. In contrast, the remaining seven patients, who demonstrate clinical benefit and continue treatment beyond the Cycle Seventeenth, incur full treatment costs borne by the payer for both the initial and subsequent cycles. While this technique provides financial protection for non-responders, the overall cost savings in this cohort are lower than those achieved with the free initiation treatment technique. This is primarily because the majority of patients (53.87%) experience prolonged clinical benefit, thereby shifting a greater financial burden to the payer under the pay-by-result technique (47, 56).

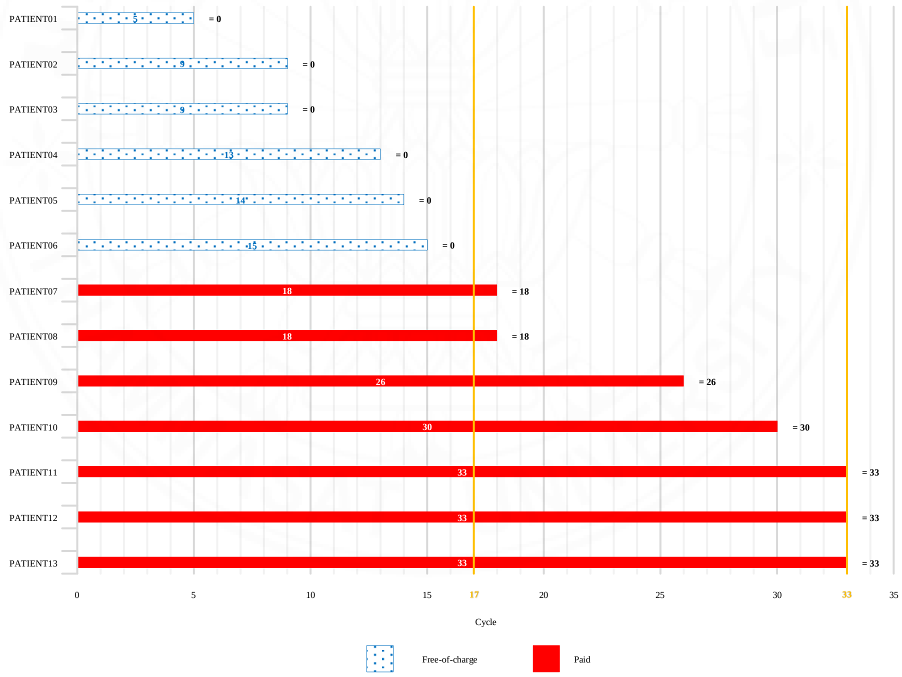


Figure 4.5 The payment patterns associated with the pay-by-result technique of pertuzumab

Under the discount technique (Figure 4.6), the pharmaceutical company applies a 30% reduction to the listed drug price across all treatment cycles. This technique offers a straightforward and predictable method of cost containment, as the discount is uniformly applied regardless of treatment duration or clinical response. However, in this cohort, where seven patients receive seventeen or more treatment cycles, the discount technique results in less cost savings compared to performance-based techniques such as conditional treatment continuation. This technique does not distinguish between responders and non-responders and does not provide additional financial protection for early treatment discontinuation. As a result, while the discount technique offers moderate cost relief, its economic efficiency is relatively limited in settings involving high-cost, long-duration therapies such as pertuzumab (47, 56).

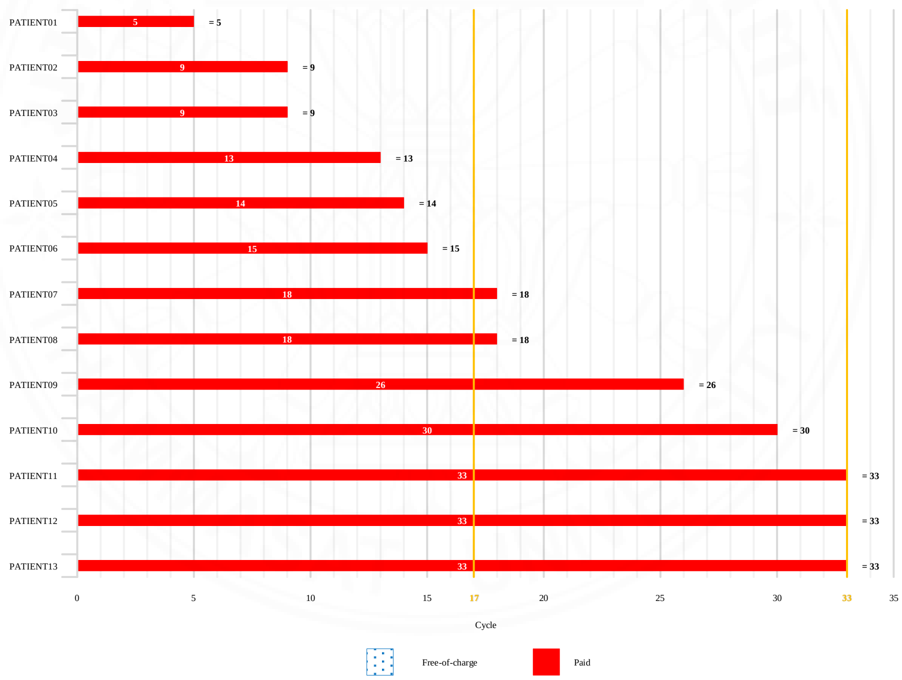


Figure 4.6 The payment patterns associated with the discount technique of pertuzumab

Table 4.3 The drug procurement costs for pertuzumab

Scenario	MEA technique	Drug procurement cost per patient (USD)			Total drug procurement cost (USD)			Total cost saving (USD)[a]			Cost saving (%)		
		PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]
Reference case	No MEA	43,281.83	43,281.83	43,281.83	562,663.77	562,663.77	562,663.77						
1	Discount	30,297.28	30,297.28	30,297.28	393,864.64	393,864.64	393,864.64	168,799.13	168,799.13	168,799.13	30.00	30.00	30.00
2	Free initiation technique	14,162.07	11,934.33	10,024.84	184,106.90	155,146.26	130,322.86	378,556.88	407,517.51	432,340.91	67.28	72.43	76.84
3	Utilization cap	29,119.76	31,347.50	33,256.99	378,556.88	407,517.51	432,340.91	184,106.90	155,146.26	130,322.86	32.72	27.57	23.16
4	Conditional treatment continuation	20,367.92	20,049.67	15,912.44	264,782.95	260,645.72	206,861.68	297,880.82	302,018.05	355,802.09	52.94	53.68	63.24
5	Pay-by-result	34,529.99	31,984.00	25,937.27	448,889.85	415,791.98	337,184.54	113,773.92	146,871.79	225,479.23	20.22	26.10	40.07

[a] Difference in drug procurement cost between the reference case and after applying the MEA technique.

[b] The median PFS was decreased by 10%.

[c] Base line PFS.

[d] The median PFS was increased by 10%.

4.1.1.2 Osimertinib

(1) Demographic characteristics

Table 4.4 reports the demographic characteristics of patients with metastatic EGFR mutation-positive NSCLC. There were sixty-six patients, the mean age was 70.67 years (SD = 12.02), and 54.55% of the patients were female. The majority were patients under the CSMBS (81.82%), followed by the UCS (15.15%) and other schemes (3.03%). Notably, no patients under the SSS were enrolled in this study. Most patients (68.18%) had no history of smoking. All patients (100%) were diagnosed with clinical stage IV disease and EGFR mutation-positive NSCLC according to the prescribing criteria of osimertinib.

Table 4.4 Demographic characteristics of patients who received osimertinib

Parameters	n (%)
Age, years	
Mean (SD)	70.67 (12.02)
Gender, n (%)	
Female	36 (54.55)
Male	30 (45.45)
Health benefit schemes, n (%)	
Civil Servant Medical Benefit Scheme (CSMBS)	54 (81.82)
Social Security Scheme (SSS)	0 (0.00)
Universal Coverage Scheme (UCS)	10 (15.15)
Others	2 (3.03)
History of smoking, n (%)	
No	45 (68.18)
Yes	21 (31.82)

Table 4.4 Demographic characteristics of patients who received osimertinib (Cont.)

Parameters	**n (%)**
Type of EGFR mutation, n (%)	
Exon 20 T790M	57 (86.36)
Exon 19 deletion	33 (50.00)
Exon 21 L858R	30 (45.45)
Exon 18 G719X	2 (3.03)
Exon 19 L747V1	1 (1.51)
Clinical stage, n (%)	
Stage I	0 (0.00)
Stage II	0 (0.00)
Stage III	0 (0.00)
Stage IV	66 (100.00)

(2) The patterns of drug response

Figure 4.7 shows the patterns of drug response. The drug use profiles are derived from real-world data of patients with metastatic EGFR mutation-positive NSCLC.

At the Cycle Fifth, approximately five months after treatment initiation, the majority of patients demonstrated favorable disease control. The disease control consists of 56.06% of patients showing stable disease and 16.67% of patients showing partial response. There were few patients who demonstrated either progressive disease (21.21%) or death (6.06%). These findings suggest that osimertinib can provide good disease control within the first five months of the treatment.

By the Cycle Tenth, approximately ten months after treatment initiation, most patients continued to demonstrate either stable disease (50.01%) or partial response (4.54%). These findings indicate that osimertinib therapy could sustain disease control in the real-world treatment of metastatic EGFR mutation-positive NSCLC.

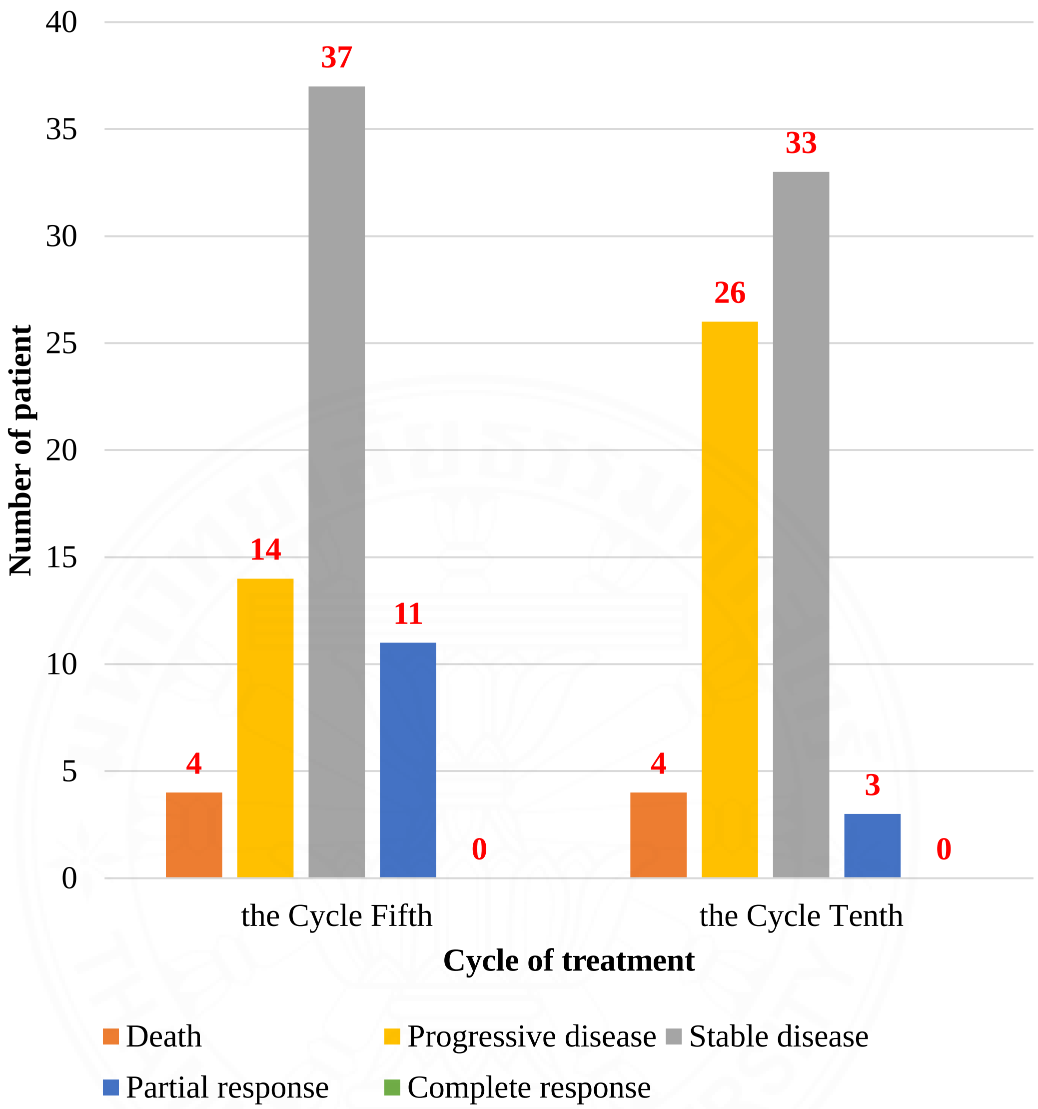


Figure 4.7 The patterns of drug response for osimertinib

(3) Drug procurement costs for each MEA technique

Table 4.6 reports the total drug procurement cost for sixty-six patients receiving osimertinib over a 24-month period. MEA techniques were applied to analyze real-world data under each scenario, as demonstrated in Table 4.5. Without any MEA technique application (reference case), the total drug procurement cost was 5,107,480.50 USD (1 USD = 33.6215 Thai Baht) (94, 95).

Table 4.5 Definition of the analyzed scenarios of osimertinib

Scenario	**MEA technique**	**Definition**
1	Discount	The discount strategy of 50% on drug price.
2	Free initiation treatment	The first ten cycles of the drug are offered free of charge; thereafter, the full price is paid.
3	Utilization cap	The payer covers the cost for the first ten cycles, and the pharmaceutical company subsequently provides the remaining treatment free of charge.
4	Conditional treatment continuation	The payer funds up to ten cycles of treatment. Only patients who demonstrate stable disease, partial response, or complete response within ten cycles continue therapy, after which the pharmaceutical company provides the drug free of charge.
5	Pay-by-result	The pharmaceutical company reimburses the full drug cost for patients who do not achieve stable disease, partial response, or complete response within ten cycles.

Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing the total cost by 3,207,596.45 USD (62.80%), compared to the reference case. The conditional treatment continuation technique also demonstrated substantial savings, with a cost reduction of 2,701,783.16 USD (52.90%). Similarly, the discount technique led to a 50.00% cost reduction.

Other techniques, such as the utilization cap and pay-by-result, were associated with more modest savings of 37.20% and 15.70%, respectively. Despite providing some degree of cost control, these techniques offered comparatively lower economic benefits.

The results indicate that the choice of MEA technique has a significant impact on the budgetary implications of osimertinib procurement. In this analysis of real-world data, free initiation treatment has been identified as the most effective MEA technique.

However, in real-world practice, when osimertinib was first introduced to the market, the pharmaceutical company initially implemented the utilization cap technique. Under this agreement, the payer covered the cost of the drug for up to ten treatment cycles. Thereafter, the pharmaceutical company provided the medication free of charge for patients who continued treatment beyond that point (99). Over time, this agreement was replaced by the discount technique, which involved a 50% reduction in the drug price. This discount technique was adopted to align the price of osimertinib with the specified median drug price threshold.

This study found that among the various MEA techniques analyzed, the free initiation treatment technique resulted in the greatest cost savings—reducing total drug procurement costs by 62.80% compared to procurement without MEA implementation. This financial benefit is strongly linked to the clinical profile of osimertinib, particularly its median PFS of approximately ten months, a figure supported by both clinical trial data and real-world evidence (116).

In this cohort, thirty patients discontinue treatment within the first ten cycles, indicating that their entire course of therapy is provided free of charge under the free initiation treatment technique. This highlights a key advantage of the technique: no cost is incurred by the payer for patients who discontinue treatment early.

Additionally, the majority of patients (54.54%) receive eleven or more treatment cycles. For these patients, the first ten cycles are covered by the pharmaceutical company, with the payer incurring costs only from the Cycle Eleventh onward. Even in extended treatment scenarios, the free initiation technique provides meaningful cost savings compared to alternative MEA techniques or procurement without MEA implementation.

Under this technique, osimertinib is provided free of charge for the first ten treatment cycles (Figure 4.8), a duration that aligns closely with the median PFS. This alignment between the cost coverage period and the expected clinical benefit enhances the economic efficiency of the MEA. By covering costs during the period when most patients are likely to respond to treatment, the free initiation technique significantly reduces the financial burden without compromising clinical outcomes (47, 56).

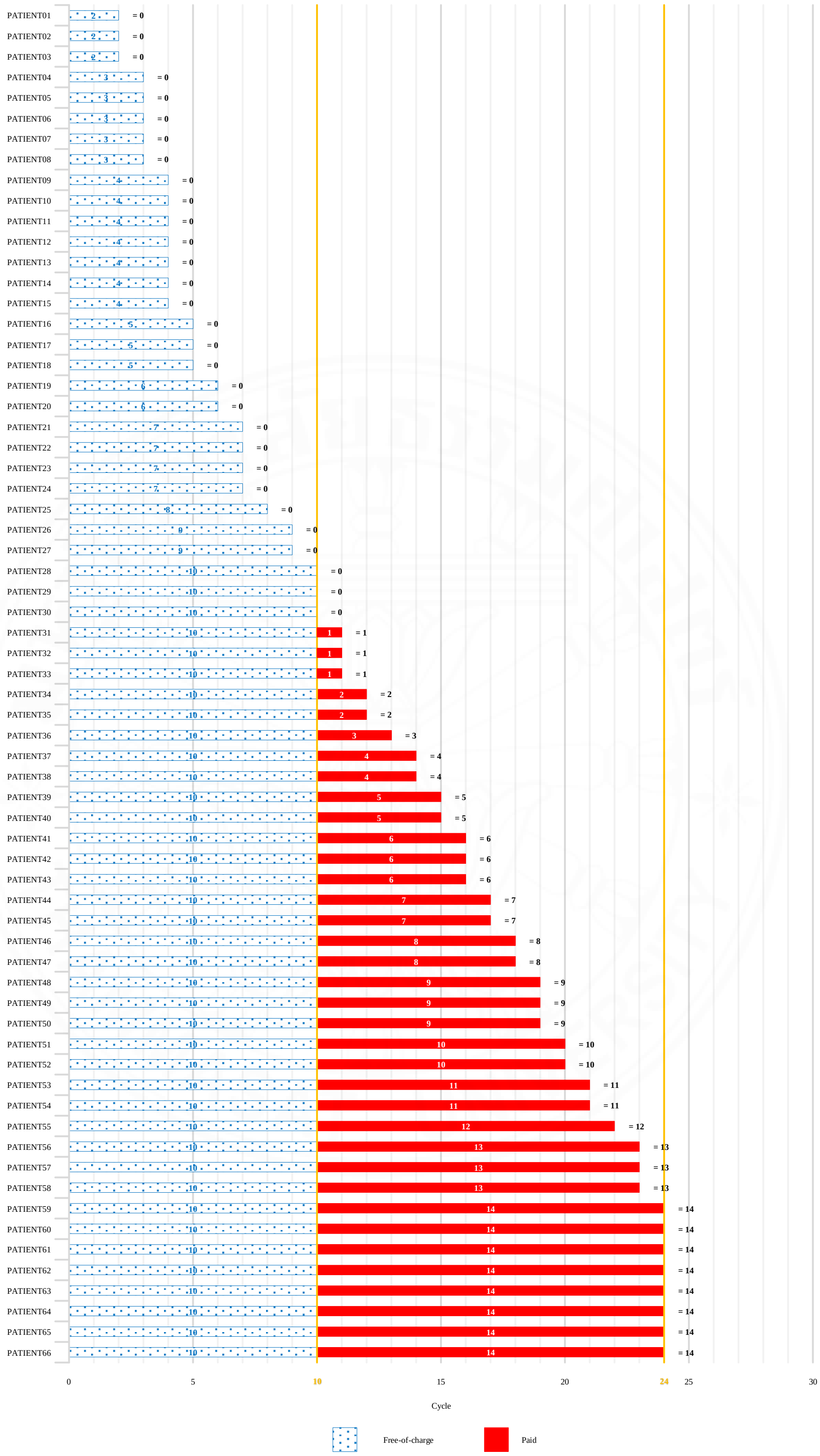


Figure 4.8 The payment patterns associated with the free initiation treatment technique of osimertinib

Under the utilization cap technique (Figure 4.9), payers are obligated to cover the full cost of treatment for all patients during the first ten cycles, regardless of whether patients continue or discontinue therapy within this period. This means that even patients who discontinue treatment early—within the first ten cycles—generate drug costs that the payer fully bears. In this cohort, thirty patients discontinue treatment during this initial phase. Therefore, the payer incurs costs for their entire treatment period up to the Cycle Tenth, despite the absence of continued clinical benefit, resulting in a substantial financial burden.

In contrast, the free initiation treatment technique allocates the cost burden for cycles one through ten entirely to the pharmaceutical company. All patients receive the first ten cycles free of charge, regardless of whether they discontinue early or continue treatment beyond this period. Consequently, payers do not incur any drug-related costs during this initial phase, effectively eliminating financial risk associated with early treatment discontinuation.

During the post–Cycle Tenth phase, cost responsibilities diverge further between the two MEA techniques. Among the thirty-six patients who continue treatment beyond the Cycle Tenth, the utilization cap technique stipulates that payers are no longer responsible for treatment costs beyond this point. In contrast, under the free initiation treatment technique, payers begin to incur drug costs only after patients progress beyond the Cycle Tenth. Since the pharmaceutical company covers all costs for the initial ten cycles, the payer's financial responsibility is limited to the continuation of treatment thereafter. Although long-term responders may eventually incur higher cumulative drug costs under this technique, the overall cost remains lower compared to the utilization cap technique, which requires partial payments from the outset of treatment—even for patients who do not complete ten cycles.

The utilization cap technique exposes payers to significant costs during cycles one to ten, which is particularly problematic when a substantial proportion of patients discontinue early. In such cases, payers bear financial burdens disproportionate to the clinical value gained. In contrast, the free initiation treatment technique reduces payer expenditure by transferring initial treatment costs to the pharmaceutical company and more effectively aligns financial responsibility with actual treatment duration and benefit (47, 56).

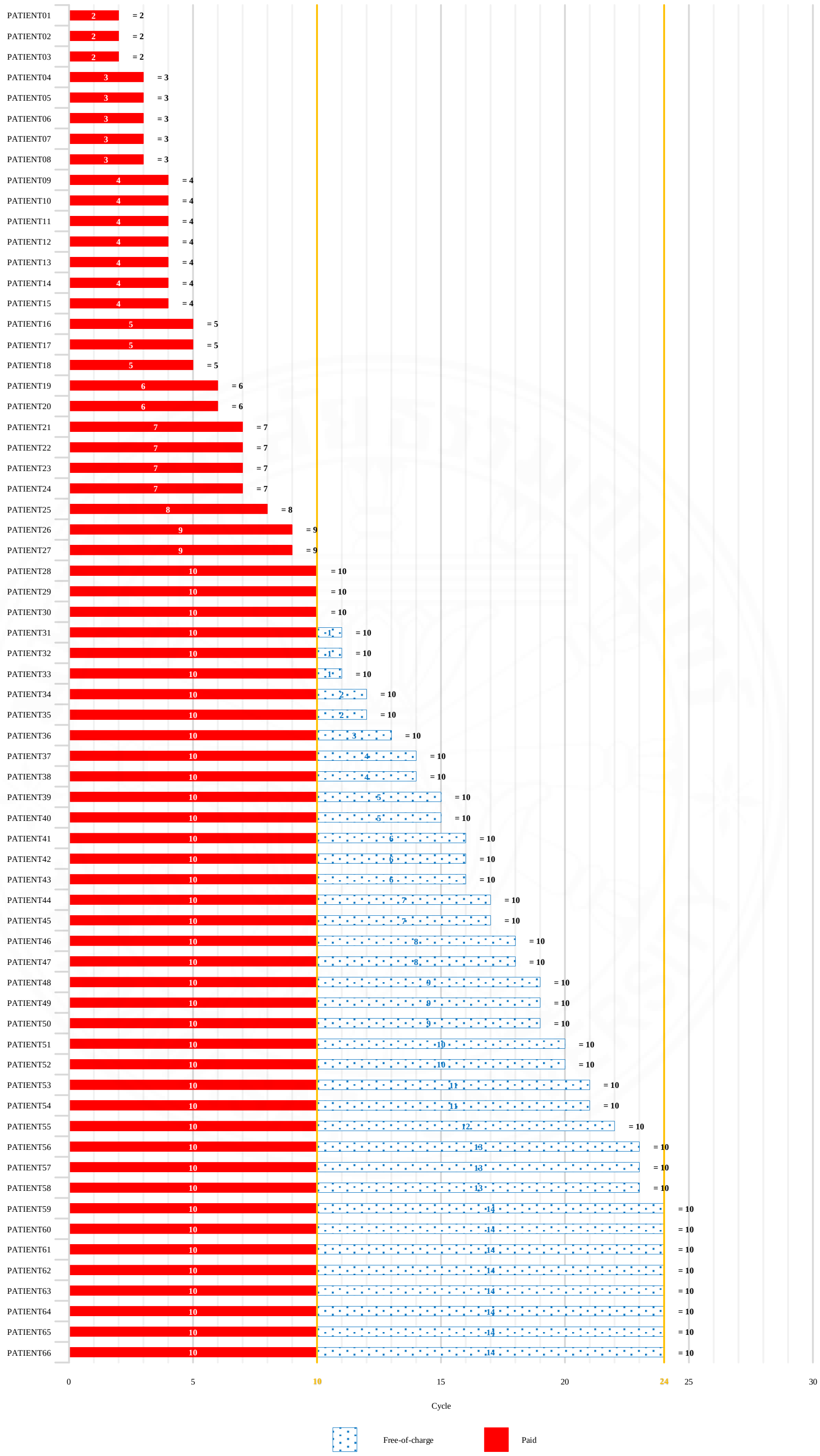


Figure 4.9 The payment patterns associated with the utilization cap technique of osimertinib

Under the conditional treatment continuation technique (Figure 4.10), thirty patients in this cohort discontinue treatment by the Cycle Tenth or earlier. As a result, no drug costs are incurred for these patients, since the pharmaceutical company fully absorbs the cost associated with their early treatment discontinuation. For the remaining thirty-six patients who receive more than ten treatment cycles, the payer is responsible for covering the cost of the initial ten cycles, while subsequent cycles are provided free of charge by the pharmaceutical company (47, 56).

In contrast, the free initiation treatment technique offers the first ten treatment cycles free of charge to all patients, regardless of total treatment duration. Under this technique, the payer incurs drug costs only if treatment continues beyond the Cycle Tenth. This technique shifts the financial burden of the initial treatment phase entirely to the pharmaceutical company, thereby significantly reducing upfront costs for payers.

Given that thirty-six patients in this cohort receive ten or more treatment cycles, the free initiation treatment technique results in greater overall cost savings compared to the conditional treatment continuation technique. This difference arises because, under the conditional treatment continuation technique, payers must fund the first ten cycles for all patients who continue treatment, whereas under the free initiation treatment technique, these cycles are universally provided free of charge—offering more effective cost mitigation for the payer.

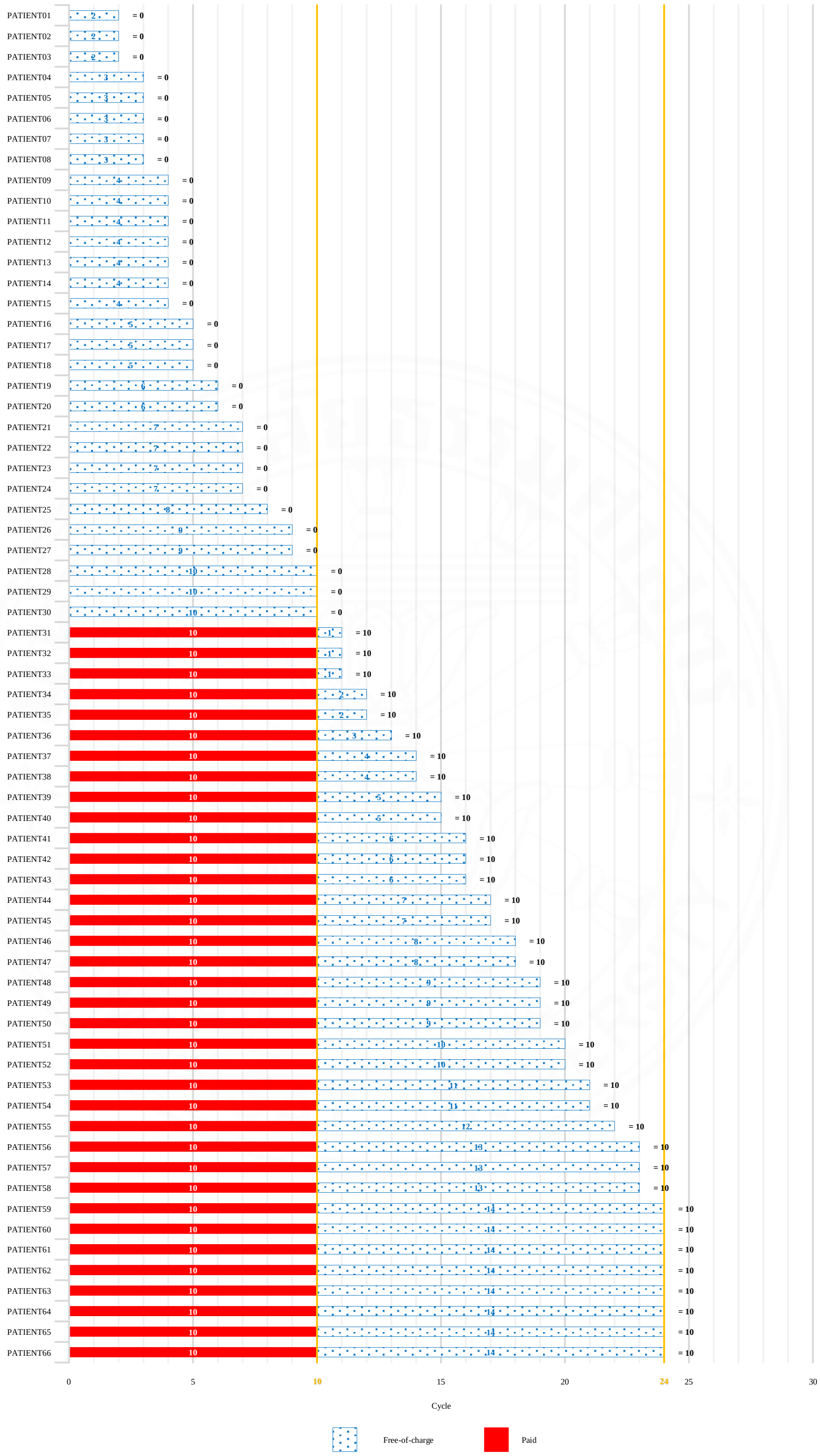


Figure 4.10 The payment patterns associated with the conditional treatment continuation technique of osimertinib

Under the pay-by-result technique (Figure 4.11), thirty patients in this cohort discontinue treatment within the early phase due to a lack of clinical benefit, thereby incurring no net cost to the payer. However, for the remaining thirty-six patients who demonstrate clinical benefit and continue beyond the Cycle Tenth, the payer is responsible for the full cost of both the initial ten cycles and all subsequent treatment. Thus, while the pay-by-result technique provides cost protection for non-responders, it imposes a considerable financial burden on the payer for patients who experience prolonged therapeutic benefit (47, 56).

In contrast, the free initiation treatment technique provides the first ten cycles of osimertinib free of charge to all patients, irrespective of treatment response or duration. Under this technique, the payer incurs zero cost during the first ten cycles across the entire cohort. For patients who continue beyond ten cycles—comprising the same thirty-six individuals—the payer assumes cost responsibility only from the Cycle Eleventh onward. Consequently, while both MEA techniques eliminate early-phase costs for non-responders, the free initiation treatment technique delivers additional cost savings for long-term responders by shifting the financial responsibility for the high-cost early phase entirely to the pharmaceutical company.

In this cohort, the free initiation treatment technique ultimately results in greater overall cost savings compared to the pay-by-result technique. This difference arises from the high proportion of patients (54.54%) who continue treatment beyond ten cycles, for whom the payer bears full treatment costs under the pay-by-result technique. These findings underscore the importance of aligning MEA design with both the clinical efficacy profile of the drug and real-world treatment patterns to optimize budget impact and ensure sustainable access to innovative drugs.

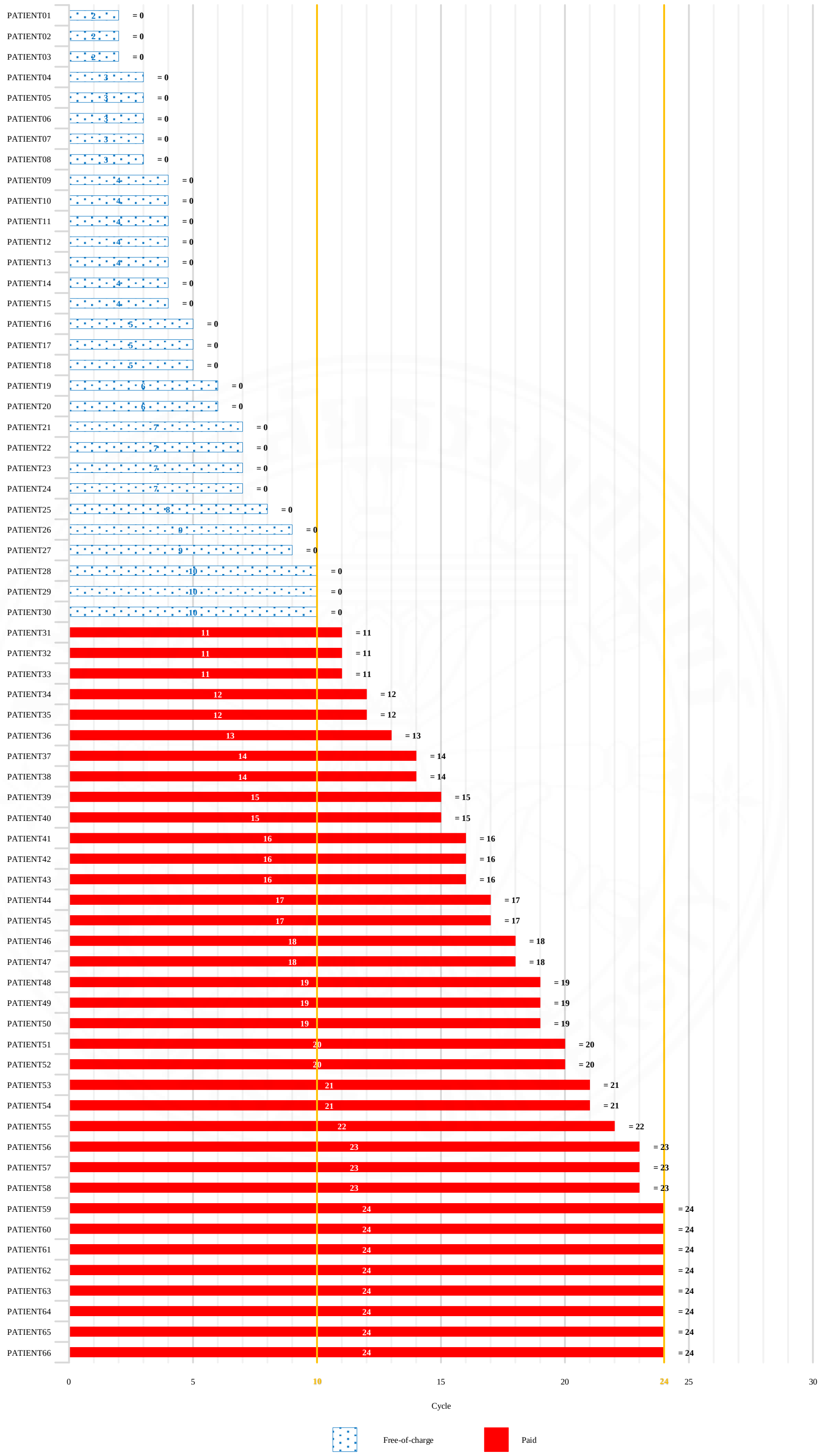


Figure 4.11 The payment patterns associated with the pay-by-result technique of osimertinib

Under the discount technique (Figure 4.12), during cycles one to ten, the payer incurs 50% of the drug cost for all patients. As a result, the payer bears a significant financial burden regardless of whether patients respond to therapy or discontinue early due to disease progression. In this cohort, thirty patients (45.45%) discontinue treatment within the first ten cycles. Therefore, despite not deriving long-term clinical benefit from osimertinib, drug costs—albeit at a discounted rate—are still incurred by the payer for the entirety of these patients' treatment duration (47, 56).

In contrast, under the free initiation treatment technique, the payer incurs no drug costs during cycles one to ten, as the pharmaceutical company provides the medication free of charge throughout this period. For the thirty patients who discontinue treatment early, the total drug procurement cost is therefore effectively zero, leading to immediate and substantial cost savings. This technique significantly reduces the budget impact, particularly for patients who do not respond to therapy or discontinue early due to disease progression.

During the post–Cycle Tenth phase, cost responsibilities diverge between the two MEA techniques. Among the thirty-six patients (54.55%) who continue treatment beyond the Cycle Tenth, the discount technique requires the payer to continue covering 50% of the drug cost for all subsequent cycles, resulting in a fixed but ongoing financial obligation. In contrast, under the free initiation treatment technique, the payer begins to incur costs only from the Cycle Eleventh onward. Although long-term responders eventually generate drug costs under this technique, the total cumulative expenditure remains lower compared to the discount technique, which involves partial payments from the outset of treatment.

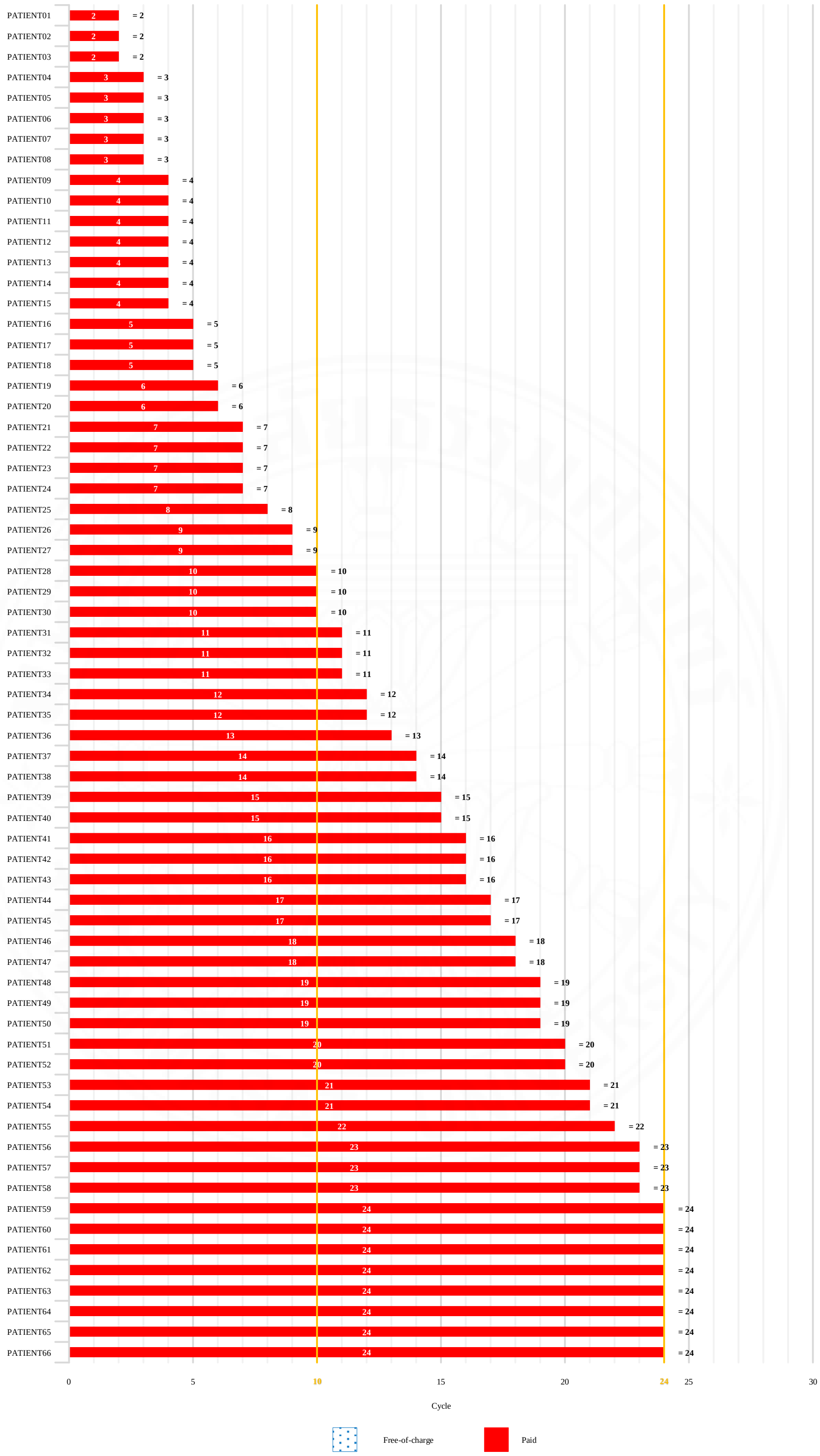


Figure 4.12 The payment patterns associated with the discount technique of osimertinib

Table 4.6 The drug procurement costs for osimertinib

Scenario	MEA technique	Drug procurement cost per patient (USD)			Total drug procurement cost (USD)			Total cost saving (USD)[a]			Cost saving (%)		
		PFS -10%[b]	**PFS[c]**	**PFS +10%[d]**	**PFS -10%[b]**	**PFS[c]**	**PFS +10%[d]**	**PFS -10%[b]**	**PFS[c]**	**PFS +10%[d]**	**PFS -10%[b]**	**PFS[c]**	**PFS +10%[d]**
Reference case	No MEA	77,386.07	77,386.07	77,386.07	5,107,480.50	5,107,480.50	5,107,480.50						
1	Discount	38,693.03	38,693.03	38,693.03	2,553,740.25	2,553,740.25	2,553,740.25	2,553,740.25	2,553,740.25	2,553,740.25	50.00	50.00	50.00
2	Free initiation technique	32,431.12	28,786.12	25,421.51	2,140,453.78	1,899,884.05	1,677,819.68	2,967,026.72	3,207,596.45	3,429,660.82	58.09	62.80	67.15
3	Utilization cap	44,954.95	48,599.95	51,964.56	2,967,026.72	3,207,596.45	3,429,660.82	2,140,453.78	1,899,884.05	1,677,819.68	41.91	37.20	32.85
4	Conditional treatment continuation	34,487.27	36,449.96	37,010.73	2,276,159.79	2,405,697.34	2,442,708.06	2,831,320.71	2,701,783.16	2,664,772.43	55.43	52.90	52.17
5	Pay-by-result	66,918.39	65,236.08	62,432.24	4,416,613.57	4,305,581.39	4,120,527.75	690,866.93	801,899.11	986,952.75	13.53	15.70	19.32

[a] Difference in drug procurement cost between the reference case and after applying the MEA technique.

[b] The median PFS was decreased by 10%.

[c] Base line PFS.

[d] The median PFS was increased by 10%.

4.1.2 Effectiveness uncertainty

4.1.2.1 Afatinib

(1) Demographic characteristics

Table 4.7 reports the demographic characteristics of patients with metastatic EGFR mutation-positive NSCLC. There were nine patients, the mean age was 71.56 years (SD = 11.95), and 55.56% of patients were female. The majority were patients under the CSMBS (55.56%), followed by the UCS (33.33%) and other schemes (11.11%). Notably, no patients under the SSS were enrolled in this study. Most patients (55.56%) had no history of smoking. All patients (100%) were diagnosed with clinical stage IV disease and EGFR mutation-positive NSCLC according to the prescribing criteria of afatinib.

Table 4.7 Demographic characteristics of patients who received afatinib

Parameters	n (%)
Age, years	
Mean (SD)	71.56 (11.95)
Gender, n (%)	
Female	5 (55.56)
Male	4 (44.44)
Health benefit schemes, n (%)	
Civil Servant Medical Benefit Scheme (CSMBS)	5 (55.56)
Social Security Scheme (SSS)	0 (0.00)
Universal Coverage Scheme (UCS)	3 (33.33)
Others	1 (11.11)
History of smoking, n (%)	
No	5 (55.56)
Yes	4 (44.44)

Table 4.7 Demographic characteristics of patients who received afatinib (Cont.)

Parameters	n (%)
Type of EGFR mutation, n (%)	
Exon 21 L858R	3 (33.33)
Exon 21 L861Q	2 (22.22)
Exon 21 L861R	1 (11.11)
Exon 20 S768L	1 (11.11)
Exon 20 insertion	1 (11.11)
Exon 19 deletion	1 (11.11)
Clinical stage, n (%)	
Stage I	0 (0.00)
Stage II	0 (0.00)
Stage III	0 (0.00)
Stage IV	9 (100.00)

(2) The patterns of drug response

Figure 4.13 shows the patterns of drug response. The drug use profiles are derived from real-world data of patients with metastatic EGFR mutation-positive NSCLC.

At the Cycle Fifth, approximately five months after treatment initiation, the majority of patients demonstrated favorable disease control. The disease control consists of 33.33% showing stable disease and 22.22% showing partial response. Progressive disease and death were observed in 33.33% and 11.11%, respectively. These findings suggest that afatinib could provide disease control within the first five months of the treatment.

By the Cycle Eleventh, approximately eleven months after treatment initiation, the clinical response profile had shifted. A total of 22.22% of patients had died, reflecting a cumulative increase in mortality from earlier cycles. Among the remaining patients, 44.44% showed progressive disease, 22.22% showed stable disease, and only 11.11% maintained partial response. These findings indicate that afatinib therapy could decline in treatment efficacy over time among patients with metastatic EGFR mutation-positive NSCLC.

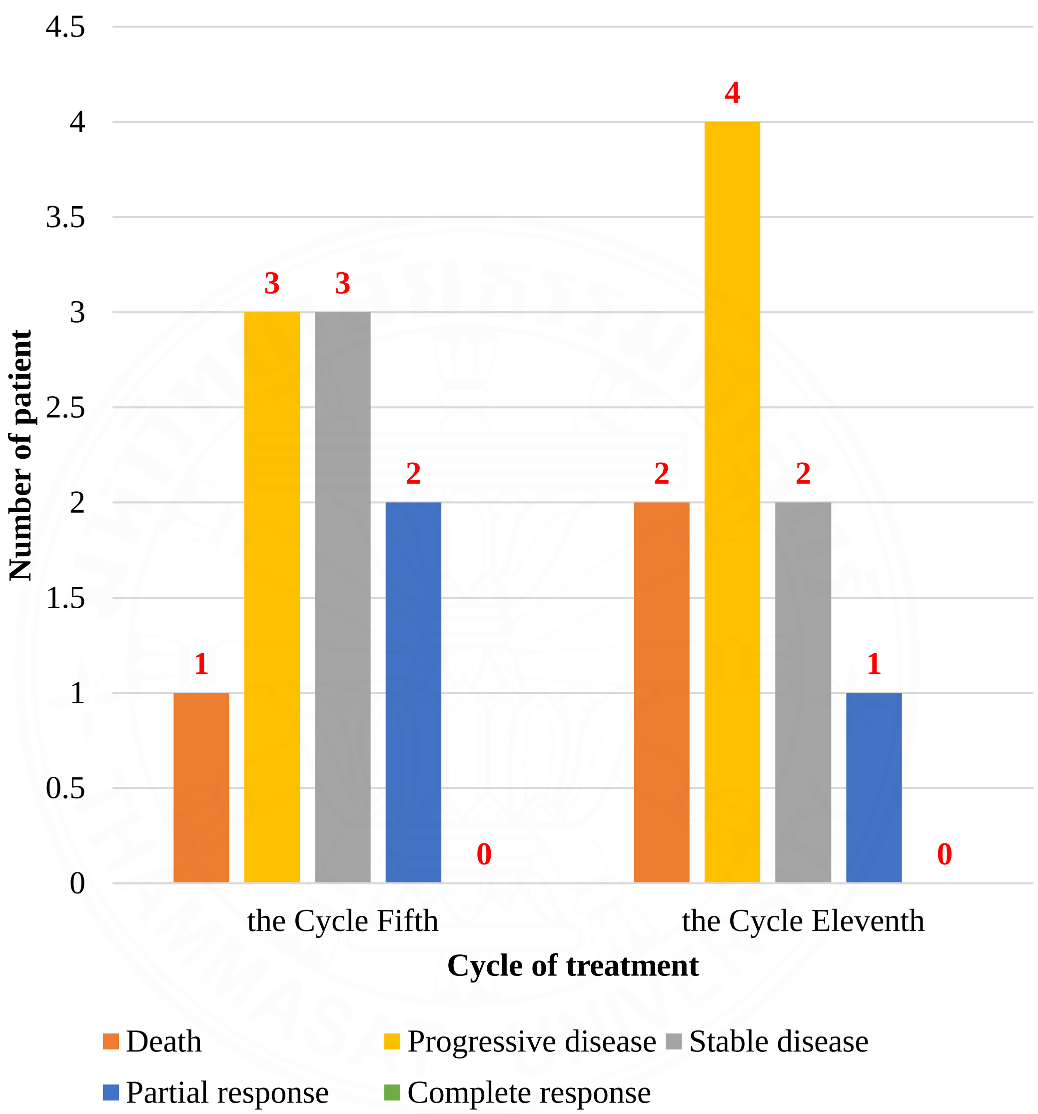


Figure 4.13 The patterns of drug response for afatinib

(3) Drug procurement costs for each MEA technique

Table 4.9 reports the total drug procurement cost for nine patients receiving afatinib over a 24-month period. MEA techniques were applied to analyze real-world data under each scenario, as demonstrated in Table 4.8. Without any MEA technique application (reference case), the total drug procurement cost was 143,307.41 USD (1 USD = 33.6215 Thai Baht) (94, 95).

Table 4.8 Definition of the analyzed scenarios of afatinib

Scenario	MEA technique	Definition
1	Discount	The discount strategy of 50% on drug price.
2	Free initiation treatment	The first eleven cycles of the drug are offered free of charge; thereafter, the full price is paid.
3	Utilization cap	The payer covers the cost for the first eleven cycles, and the pharmaceutical company subsequently provides the remaining treatment free of charge.
4	Conditional treatment continuation	The payer funds up to eleven cycles of treatment. Only patients who demonstrate stable disease, partial response, or complete response within eleven cycles continue therapy, after which the pharmaceutical company provides the drug free of charge.
5	Pay-by-result	The pharmaceutical company reimburses the full drug cost for patients who do not achieve stable disease, partial response, or complete response within eleven cycles.

Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing the total cost by 114,283.12 USD (79.75%), compared to the reference case. The conditional treatment continuation technique also demonstrated substantial savings, with a cost reduction of

83,444.82 USD (58.23%). Similarly, the discount technique led to a 50.00% cost reduction.

Other techniques, such as the pay-by-result and utilization cap, were associated with more modest savings of 37.97% and 20.25%, respectively. Despite providing some degree of cost control, these techniques offered comparatively lower economic benefits.

The results indicate that the choice of MEA technique has a significant impact on the budgetary implications of afatinib procurement. In this analysis of real-world data, free initiation treatment has been identified as the most effective MEA technique.

However, in real-world practice, afatinib—classified as a second-generation TKIs—is used in the treatment of metastatic NSCLC with EGFR mutations. Following the market introduction of third-generation TKIs such as osimertinib, pharmaceutical companies adopted the discount technique for afatinib to sustain its market competitiveness and improve accessibility.

This study found that among the various MEA techniques analyzed, the free initiation treatment technique resulted in the greatest cost savings, reducing the total drug procurement cost by 79.75% compared to procurement without MEA implementation.

Figure 4.14 demonstrates the individual-level treatment durations of nine patients with metastatic NSCLC with EGFR mutations who received afatinib. Among these patients, six discontinue treatment before the Cycle Eleventh, meaning the entire course is provided free of charge by the pharmaceutical company under the free initiation treatment technique. In such cases, the payer incurs no cost when patients discontinue treatment early. Only a minority of patients (33.33%) continue for eleven or more treatment cycles. Under this technique, the first eleven cycles are provided free of charge, with costs incurred only from the Cycle Twelfth onward. Consequently, for patients requiring prolonged treatment, this MEA technique still results in substantial cost savings (47, 56).

These findings highlight that the free initiation treatment technique aligns with both clinical response and cost savings, offering financial protection in early discontinuation and budget efficiency for longer treatments. This makes it particularly viable for therapies such as afatinib, which provide prolonged benefit in a subset of patients.

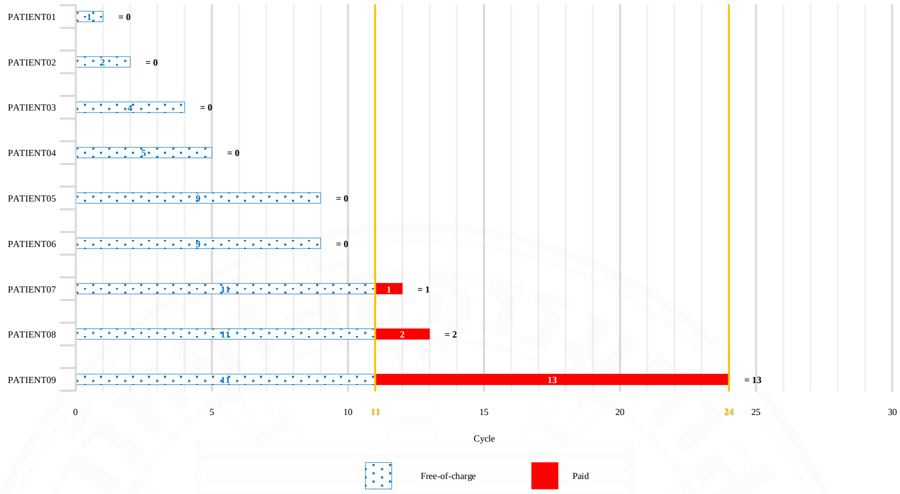


Figure 4.14 The payment patterns associated with the free initiation treatment technique of afatinib

Under the utilization cap technique (Figure 4.15), payers are required to cover the full cost of treatment for all patients during the first eleven cycles, irrespective of whether patients continue or discontinue therapy within this period. As a result, even patients who discontinue treatment early—within the first eleven cycles—generate drug costs that are fully borne by the payer. In this cohort, six patients discontinue treatment during this initial phase, leading to a situation in which the payer absorbs the entire treatment cost up to the Cycle Eleventh, despite the absence of sustained clinical benefit. This technique imposes a considerable financial burden, particularly in populations with high rates of early treatment discontinuation.

In contrast, the free initiation treatment technique transfers the financial responsibility for cycles one through eleven entirely to the pharmaceutical company. Under this technique, all patients receive the first eleven cycles of treatment free of charge, regardless of whether they continue or discontinue therapy during this period. Consequently, payers incur no drug-related costs in the initial phase, thereby eliminating financial risk associated with early treatment discontinuation and optimizing cost containment during the period of highest attrition.

During the post–Cycle Eleventh phase, three patients (33.33%) continue treatment beyond the Cycle Eleventh. Under the utilization cap technique, the pharmaceutical company assumes full cost responsibility beyond this point, relieving the payer of any further expenditure. In contrast, the free initiation treatment technique requires the payer to begin covering treatment costs starting from the Cycle Twelfth. However, because the pharmaceutical company subsidizes the entire cost of the first eleven cycles, the payer's cumulative financial responsibility remains lower compared to the utilization cap technique, which obligates payment for all patients from the outset—even for those who do not complete eleven cycles.

The utilization cap technique exposes payers to upfront costs that may not correlate with clinical outcomes, especially when treatment discontinuation occurs early. In such scenarios, the financial burden incurred may exceed the therapeutic value obtained. Conversely, the free initiation treatment technique provides a more financially efficient structure by aligning cost responsibility with treatment duration and clinical response. By shifting early-phase costs to the pharmaceutical company, this technique safeguards payer budgets more effectively while maintaining access to potentially beneficial therapies (47, 56).

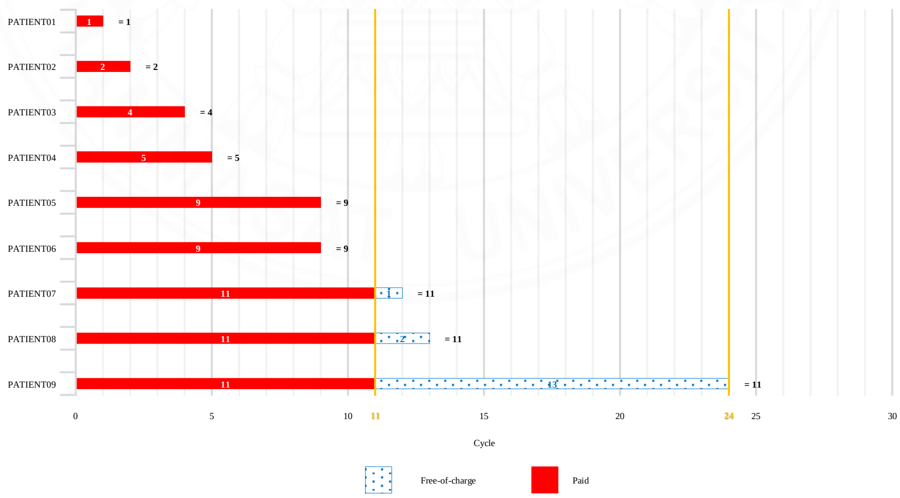


Figure 4.15 The payment patterns associated with the utilization cap technique of afatinib

Under the conditional treatment continuation technique (Figure 4.16), six patients in this cohort discontinue treatment on or before the Cycle Eleventh. As a result, no drug costs are incurred for these patients, since the pharmaceutical company fully absorbs the expenses associated with their early discontinuation. For the remaining three patients who receive more than eleven treatment cycles, the payer is responsible for covering the cost of the first eleven cycles, while the pharmaceutical company provides all subsequent cycles free of charge.

In contrast, the free initiation treatment technique offers the first eleven treatment cycles at no cost to all patients, regardless of total treatment duration. Under this technique, the payer incurs drug costs only if a patient continues therapy beyond the Cycle Eleventh. This technique shifts the financial burden of the initial treatment phase entirely to the pharmaceutical company, thereby significantly reducing upfront expenditures for the payer.

Given that three patients in this cohort continue treatment beyond the Cycle Eleventh, the free initiation treatment technique results in greater cost savings compared to the conditional treatment continuation technique. This difference arises because, under the free initiation technique, the first eleven cycles are fully subsidized for all patients, offering more effective cost mitigation—particularly for therapies like afatinib (47, 56).

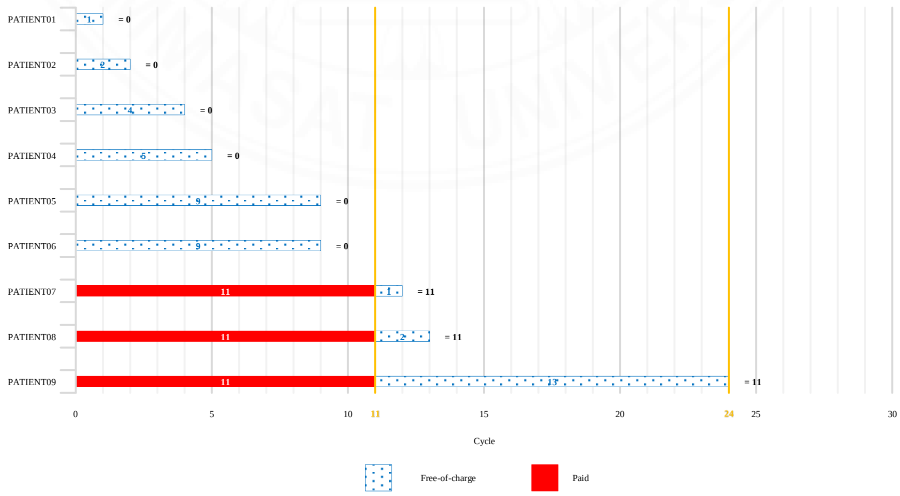


Figure 4.16 The payment patterns associated with the conditional treatment continuation technique of afatinib

Under the pay-by-result technique (Figure 4.17), six patients in this cohort discontinue treatment within the first eleven cycles due to a lack of clinical benefit, thereby incurring no cost to the payer. However, for the remaining three patients who demonstrate clinical benefit and continue treatment beyond the Cycle Eleventh, the payer is responsible for the full cost of both the initial eleven cycles and all subsequent treatment. While the pay-by-result technique provides financial protection for non-responders, it imposes a substantial cost burden on the payer for patients deriving prolonged therapeutic benefit.

In contrast, the free initiation treatment technique offers the first eleven cycles of afatinib free of charge to all patients, regardless of treatment response or duration. This results in zero cost for the payer during the initial eleven-cycle period. For the same three patients who continue beyond this point, the payer assumes cost responsibility only from the Cycle Twelfth onward. Therefore, although both MEA techniques protect payers from early-phase costs for non-responders, the free initiation treatment technique delivers additional cost savings for long-term responders by shifting the financial responsibility for the high-cost initial phase entirely to the pharmaceutical company. This outcome is driven by the subset of patients requiring extended treatment, for whom full costs would otherwise be incurred under the pay-by-result technique (47, 56).

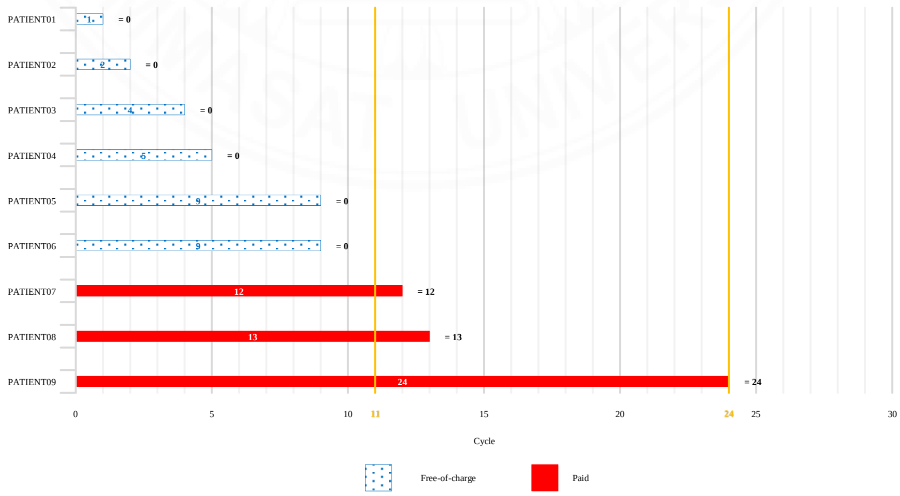


Figure 4.17 The payment patterns associated with the pay-by-result technique of afatinib

Under the discount technique (Figure 4.18), during cycles one to eleven, the payer is responsible for 50% of the drug cost for all patients, regardless of treatment response or duration. Consequently, this technique imposes a significant financial burden on the payer, even in cases where patients discontinue early due to disease progression. In this cohort, six patients (66.67%) discontinue treatment within the first eleven cycles. Despite deriving limited or no long-term clinical benefit from afatinib, drug costs—albeit at a discounted rate—are still incurred by the payer for the full duration of their treatment.

In contrast, the free initiation treatment technique offers a more favorable cost structure during the initial treatment phase. Under this technique, no drug costs are incurred by the payer during cycles one to eleven, as the pharmaceutical company provides the drug free of charge throughout this period. As a result, for the six patients who discontinue treatment early, the total drug procurement cost is effectively zero. This leads to immediate and substantial cost savings while reducing the financial risk associated with early discontinuation (47, 56).

During the post–Cycle Eleventh treatment phase, drug cost responsibilities between the two techniques diverge further. Among the three patients (33.33%) who continue treatment beyond the Cycle Eleventh, the discount technique requires the payer to continue covering 50% of the drug cost for all subsequent cycles, resulting in a fixed, ongoing financial obligation. In contrast, under the free initiation treatment technique, the payer begins to incur costs only from the Cycle Twelfth onward. Although long-term responders eventually generate drug costs under this technique, the total cumulative expenditure remains lower compared to the discount technique, which imposes partial payment obligations from the outset of therapy (47, 56).

In summary, the free initiation treatment technique demonstrates superior cost efficiency in this real-world cohort, particularly due to its ability to eliminate early-phase costs while limiting later costs to only those patients who derive sustained clinical benefit. This makes it a more economically viable MEA strategy for therapies such as afatinib, especially in populations with high early discontinuation rates.

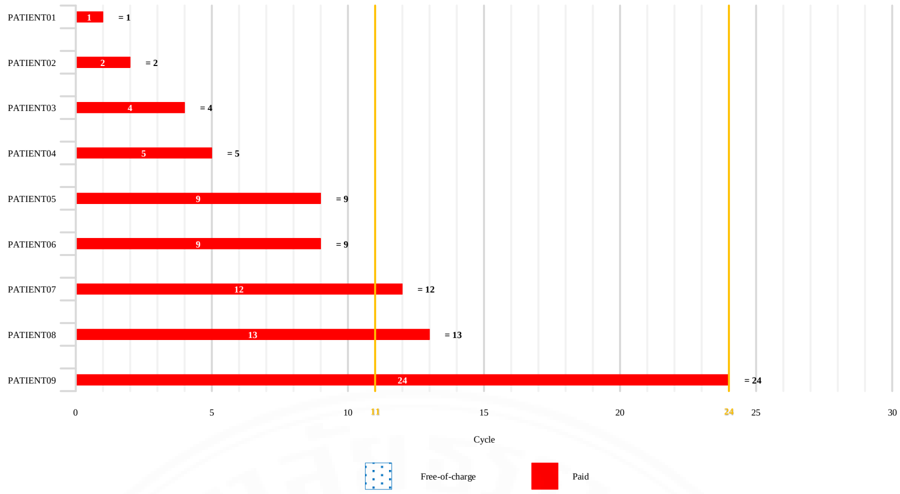


Figure 4.18 The payment patterns associated with the discount technique of afatinib

Table 4.9 The drug procurement costs for afatinib

Scenario	MEA technique	Drug procurement cost per patient (USD)			Total drug procurement cost (USD)			Total cost saving (USD)[a]			Cost saving (%)		
		PFS -10%[b]	**PFS[c]**	**PFS +10%[d]**	**PFS -10%[b]**	**PFS[c]**	**PFS +10%[d]**	**PFS -10%[b]**	**PFS[c]**	**PFS +10%[d]**	**PFS -10%[b]**	**PFS[c]**	**PFS +10%[d]**
Reference case	No MEA	15,923.05	15,923.05	15,923.05	143,307.41	143,307.41	143,307.41						
1	Discount	7,961.52	7,961.52	7,961.52	71,653.70	71,653.70	71,653.70	71,653.70	71,653.70	71,653.70	50.00	50.00	50.00
2	Free initiation technique	3,829.59	3,224.92	2,620.25	34,466.34	29,024.29	23,582.23	108,841.07	114,283.12	119,725.18	75.95	79.75	83.54
3	Utilization cap	12,093.45	12,698.12	13,302.80	108,841.07	114,283.12	119,725.18	34,466.34	29,024.29	23,582.23	24.05	20.25	16.46
4	Conditional treatment continuation	6,046.73	6,651.40	7,256.07	54,420.53	59,862.59	65,304.64	88,886.87	83,444.82	78,002.77	62.03	58.23	54.43
5	Pay-by-result	9,876.32	9,876.32	9,876.32	88,886.87	88,886.87	88,886.87	54,420.53	54,420.53	54,420.53	37.97	37.97	37.97

[a] Difference in drug procurement cost between the reference case and after applying the MEA technique.

[b] The median PFS was decreased by 10%.

[c] Base line PFS.

[d] The median PFS was increased by 10%.

4.1.2.2 Ceritinib

(1) Demographic characteristics

Table 4.10 reports the demographic characteristics of patients with ALK-positive metastatic NSCLC. There were eleven patients, the mean age was 61.27 years (SD = 8.06), and 72.73% of patients were female. The majority were patients under the CSMBS (72.73%), followed by the UCS (18.18%) and the SSS (9.09%). Notably, no patients under other schemes were enrolled in this study. Most patients (72.73%) had no history of smoking. All patients (100%) tested positive for ALK expression and were diagnosed with clinical stage IV disease according to the prescribing criteria of ceritinib.

Table 4.10 Demographic characteristics of patients who received ceritinib

Parameters	n (%)
Age, years	
Mean (SD)	61.27 (8.06)
Gender, n (%)	
Female	8 (72.73)
Male	3 (27.27)
Health benefit schemes, n (%)	
Civil Servant Medical Benefit Scheme (CSMBS)	8 (72.73)
Social Security Scheme (SSS)	1 (9.09)
Universal Coverage Scheme (UCS)	2 (18.18)
Others	0 (0.00)
History of smoking, n (%)	
No	8 (72.73)
Yes	3 (27.27)

Table 4.10 Demographic characteristics of patients who received ceritinib (Cont.)

Parameters	n (%)
ALK expression status, n (%)	
Positive	11 (100.00)
Negative	0 (0.00)
Clinical stage, n (%)	
Stage I	0 (0.00)
Stage II	0 (0.00)
Stage III	0 (0.00)
Stage IV	11 (100.00)

(2) The patterns of drug response

Figure 4.19 shows the patterns of drug response. The drug use profiles are derived from real-world data of patients with ALK-positive metastatic NSCLC.

At the Cycle Eighth, approximately eight months after treatment initiation, patients showed either stable disease (54.54%) or progressive disease (45.45%). Neither complete response nor partial response nor death was reported at this time point. These findings suggest that ceritinib could provide limited disease control within the first eight months of the treatment.

By the Cycle Sixteenth, approximately sixteen months after treatment initiation, the clinical response profile had shifted. The patients with progressive disease increased to 54.54%, and stable disease declined to 45.45%. These findings indicate that ceritinib therapy could decline in treatment efficacy over time among patients with ALK-positive metastatic NSCLC.

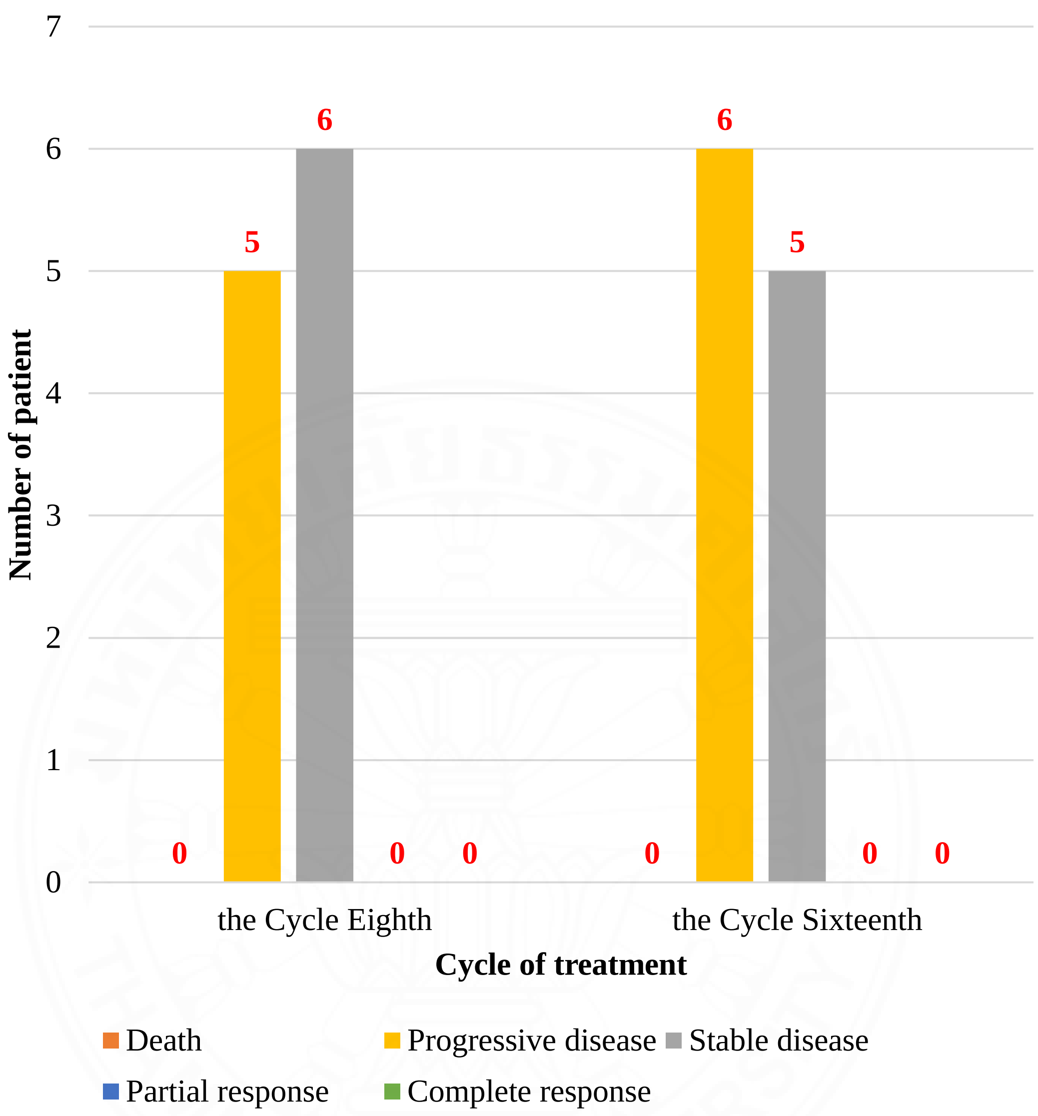


Figure 4.19 The patterns of drug response for ceritinib

(3) Drug procurement costs for each MEA technique

Table 4.12 reports the total drug procurement cost for eleven patients receiving ceritinib over a 24-month period. MEA techniques were applied to analyze real-world data under each scenario, as demonstrated in Table 4.11. Without any MEA technique application (reference case), the total drug procurement cost was 312,546.26 USD (1 USD = 33.6215 Thai Baht) (94, 95).

Table 4.11 Definition of the analyzed scenarios of ceritinib

Scenario	MEA technique	Definition
1	Discount	The discount strategy of 30% on drug price.
2	Free initiation treatment	The first sixteen cycles of the drug are offered free of charge; thereafter, the full price is paid.
3	Utilization cap	The payer covers the cost for the first sixteen cycles, and the pharmaceutical company subsequently provides the remaining treatment free of charge.
4	Conditional treatment continuation	The payer funds up to sixteen cycles of treatment. Only patients who demonstrate stable disease, partial response, or complete response within sixteen cycles continue therapy, after which the pharmaceutical company provides the drug free of charge.
5	Pay-by-result	The pharmaceutical company reimburses the full drug cost for patients who do not achieve stable disease, partial response, or complete response within sixteen cycles.

Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing the total cost by 247,804.53 USD (79.29%), compared to the reference case. The conditional treatment continuation technique also demonstrated substantial savings, with a cost reduction of 133,948.40 USD (42.86%). Similarly, the discount technique led to a 30.00% cost reduction.

Other techniques, such as the pay-by-result and utilization cap, were associated with more modest savings of 22.14% and 20.71%, respectively. Despite providing some degree of cost control, these techniques offered comparatively lower economic benefits.

The results indicate that the choice of MEA technique has a significant impact on the budgetary implications of ceritinib procurement. In this analysis of real-world data, the free initiation treatment technique was identified as the most cost-effective MEA technique. However, in real-world practice, ceritinib—classified as a selective oral ALK inhibitor used in the treatment of ALK-positive metastatic NSCLC—after ceritinib had been on the market for some time, pharmaceutical companies adopted the discount technique, which involved a 30% reduction in the drug price.

This study found that among the various MEA techniques analyzed, the free initiation treatment technique resulted in the greatest cost savings, reducing the total drug procurement cost by 79.29% compared to procurement without MEA implementation.

Figure 4.20 demonstrates the individual-level treatment durations of eleven patients with advanced ALK-rearranged NSCLC who received ceritinib. Among these, six patients discontinue treatment before the Cycle Sixteenth, meaning that, under the free initiation treatment technique, the entire course is provided free of charge by the pharmaceutical company. This outcome highlights a key advantage of the technique: payers incur no cost for patients who discontinue early, thereby minimizing financial risk in cases where limited clinical benefit is observed (47, 56).

In addition, only five patients receive sixteen or more treatment cycles. Under this technique, the first sixteen cycles are provided free of charge, and costs are incurred only from the Cycle Seventeenth onward. As such, even in cases requiring extended treatment, the free initiation treatment technique still offers substantial cost savings compared to other MEA techniques or procurement without MEA implementation.

These findings highlight that the free initiation treatment technique aligns with both clinical response and cost savings, offering financial protection in early discontinuation and budget efficiency for longer treatments. This makes it particularly viable for therapies such as afatinib, which provide prolonged benefit in some patients.

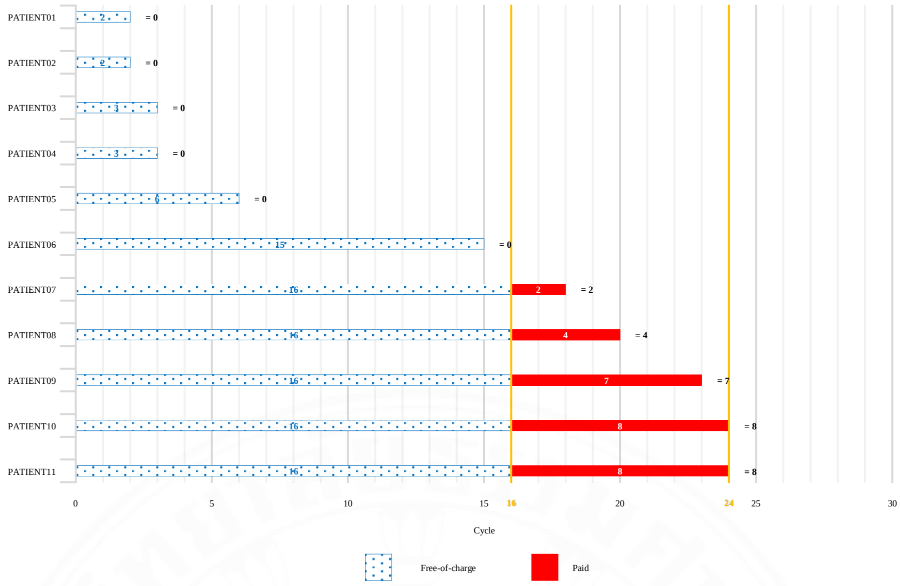


Figure 4.20 The payment patterns associated with the free initiation treatment technique of ceritinib

Under the utilization cap technique (Figure 4.21), payers cover the full cost of treatment for all patients during the first sixteen cycles, regardless of whether patients continue or discontinue therapy within this period. As a result, even patients who discontinue treatment early—within the first sixteen cycles—generate drug costs fully borne by the payer. In this cohort, six patients (54.54%) discontinue treatment during this early phase, creating a scenario in which the payer absorbs the entire cost of treatment up to the Cycle Sixteenth despite the absence of sustained clinical benefit. This technique imposes a considerable financial burden, particularly in populations with high early discontinuation rates.

In contrast, the free initiation treatment technique transfers financial responsibility for cycles one through sixteen entirely to the pharmaceutical company. All patients receive the first sixteen treatment cycles free of charge, regardless of treatment continuation or discontinuation. Consequently, payers incur no drug-related costs during this initial period, effectively eliminating financial risk associated with early discontinuation.

In the post-Cycle Sixteenth period, five patients (45.45%) continue treatment beyond the Cycle Sixteenth. Under the utilization cap technique, the pharmaceutical company assumes full cost responsibility beyond this point, relieving the payer of any further expenditure. Conversely, the free initiation treatment technique shifts the cost burden to the payer starting from the Cycle Seventeenth. However, because the pharmaceutical company subsidizes the entire cost of the initial sixteen cycles, the cumulative financial responsibility for the payer remains lower under this technique compared to the utilization cap technique, which requires payment for all patients from the outset—even for those who do not complete sixteen cycles.

Overall, this technique exposes payers to substantial upfront costs that may not correspond to clinical outcomes, particularly when early discontinuation is common. In such scenarios, the financial burden may outweigh the therapeutic value obtained. Conversely, the free initiation treatment technique provides a more economically efficient structure by aligning cost responsibility with treatment duration and demonstrated clinical benefit. By shifting early-phase costs to the pharmaceutical company, this technique enhances budget protection for payers while maintaining access to potentially beneficial therapies (47, 56).

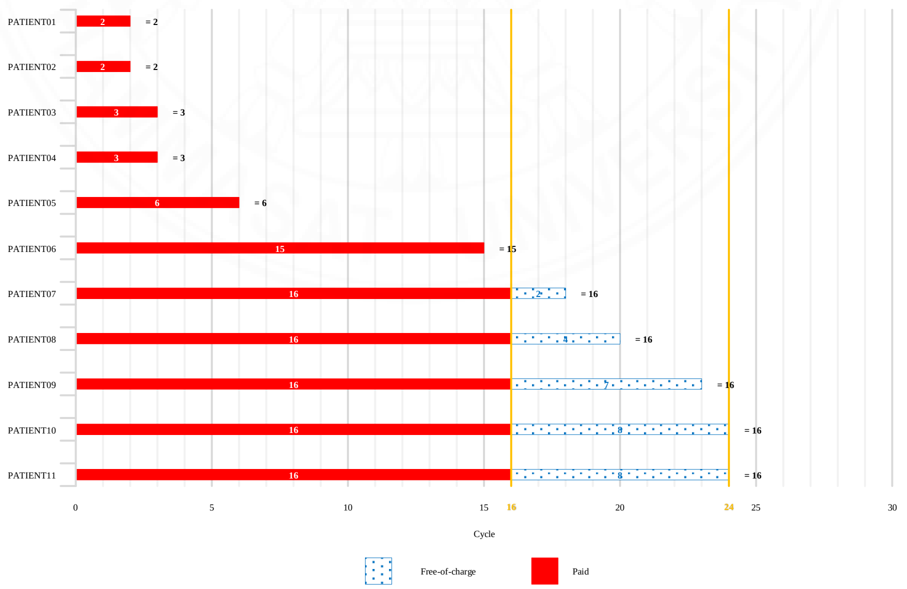


Figure 4.21 The payment patterns associated with the utilization cap technique of ceritinib

Under the conditional treatment continuation technique (Figure 4.22), six patients in this cohort discontinue treatment before the Cycle Sixteenth. Consequently, no drug costs are incurred for these patients, as the company fully absorbs the costs associated with their early discontinuation. For the remaining five patients who receive more than sixteen treatment cycles, the payer covers the cost of the first sixteen cycles, while the company provides subsequent cycles free of charge.

In contrast, the free initiation treatment technique provides the first sixteen treatment cycles at no cost to all patients, regardless of total treatment duration. Under this technique, the payer incurs drug costs only if the patient continues therapy beyond the Cycle Sixteenth. This technique shifts the financial burden of the initial treatment phase entirely to the pharmaceutical company, thereby significantly reducing upfront costs for the payer.

Given that five patients in this cohort continue treatment beyond the Cycle Sixteenth, the free initiation treatment technique generates greater overall cost savings than this technique. Unlike the latter, the first sixteen cycles are fully subsidized for all patients, offering more effective cost mitigation—particularly for drugs like ceritinib (47, 56).

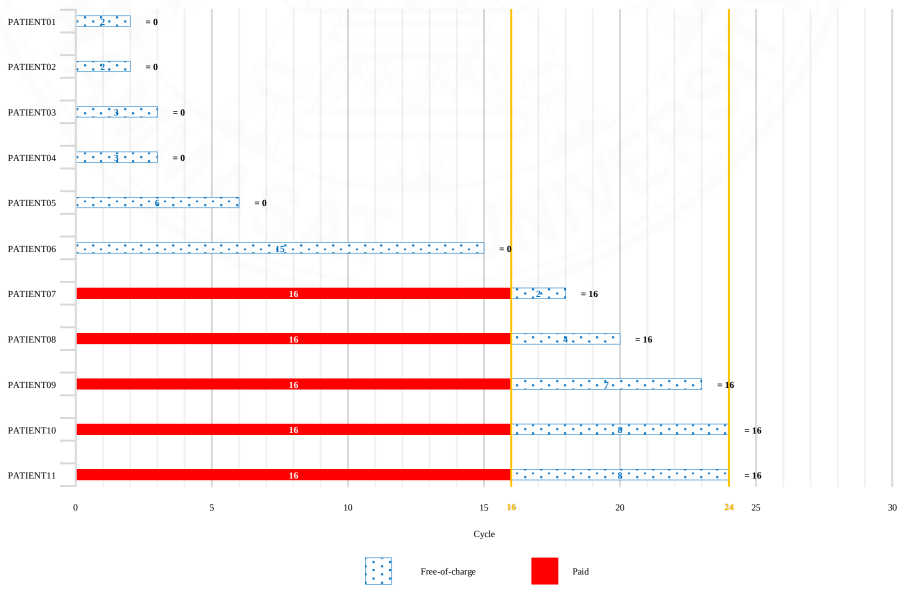


Figure 4.22 The payment patterns associated with the conditional treatment continuation technique of ceritinib

Under the pay-by-result technique (Figure 4.23), six patients in this cohort discontinue treatment within the first sixteen cycles due to a lack of clinical benefit, thereby incurring no cost to the payer. However, for the remaining five patients who demonstrate clinical benefit and continue treatment beyond the Cycle Sixteenth, the payer covers the full cost of both the initial sixteen cycles and all subsequent treatment. While this technique provides financial protection for non-responders, it places a considerable cost burden on the payer for patients deriving prolonged therapeutic benefit.

In contrast, the free initiation treatment technique provides the first sixteen cycles of ceritinib free of charge to all patients, regardless of treatment response or duration. Consequently, the payer incurs no cost during the first sixteen-cycle period. For the same five patients who continue beyond this point, the payer assumes cost responsibility only from the Cycle Seventeenth onward. Thus, although both MEA techniques offer financial protection for non-responders, the free initiation treatment technique generates greater overall cost savings by shifting financial responsibility for the high-cost early phase entirely to the pharmaceutical company (47, 56).

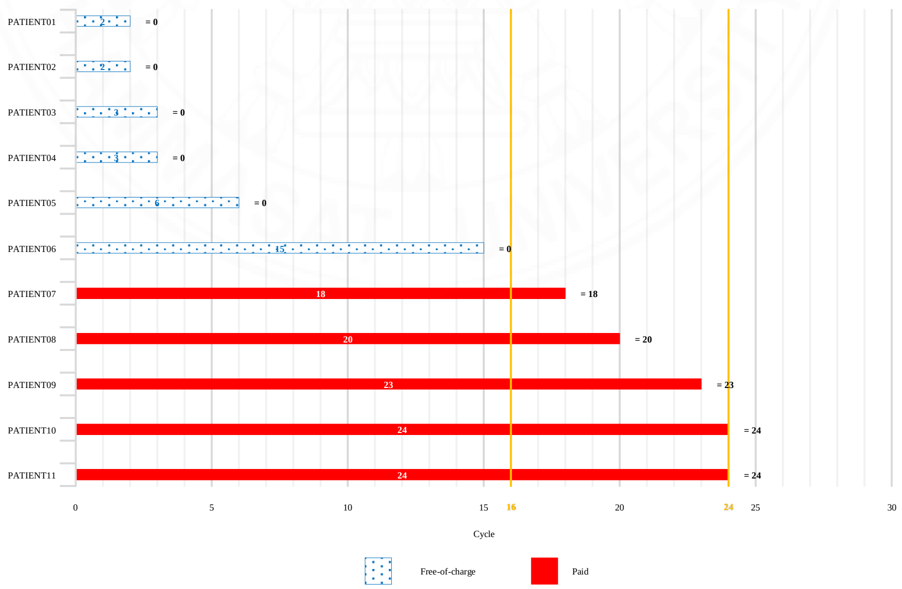


Figure 4.23 The payment patterns associated with the pay-by-result technique of ceritinib

Under the discount technique (Figure 4.24), during cycles one through sixteen, the payer covers 70% of the drug cost for all patients, regardless of treatment response or duration. Consequently, this technique imposes a considerable financial burden on the payer, even when patients discontinue treatment early due to disease progression. In this cohort, six patients (54.55%) discontinue treatment within the first sixteen cycles. Despite deriving limited clinical benefit from ceritinib, drug costs—albeit at a discounted rate—are still incurred by the payer for the entirety of their treatment duration.

In contrast, the free initiation treatment technique provides a more favorable cost structure during the initial treatment phase. Under this technique, the payer incurs no drug costs during cycles one through sixteen, as the pharmaceutical company supplies the medication free of charge throughout this period. As a result, for the six patients who discontinue treatment early, the total drug procurement cost is effectively zero. This generates immediate and substantial cost savings while mitigating financial risk associated with early discontinuation (47, 56).

During the post–Cycle Sixteenth phase, the cost responsibilities of the two techniques further diverge. Among the five patients (45.45%) who continue treatment beyond the Cycle Sixteenth, the discount technique requires the payer to continue covering 70% of the drug cost for all subsequent cycles, resulting in a fixed, ongoing financial obligation. In contrast, under the free initiation treatment technique, the payer begins to incur costs only from the Cycle Seventeenth onward. Although long-term responders eventually generate drug costs under this technique, the total cumulative cost remains lower compared to the discount technique, which imposes payment obligations from the outset of therapy (47, 56).

In summary, the free initiation treatment technique demonstrates superior cost efficiency in this real-world cohort, primarily due to its ability to eliminate early-phase costs and restrict later-phase expenditures to patients who derive sustained clinical benefit. This makes it a more economically favorable MEA technique for therapies such as ceritinib, particularly in populations characterized by high early discontinuation rates.

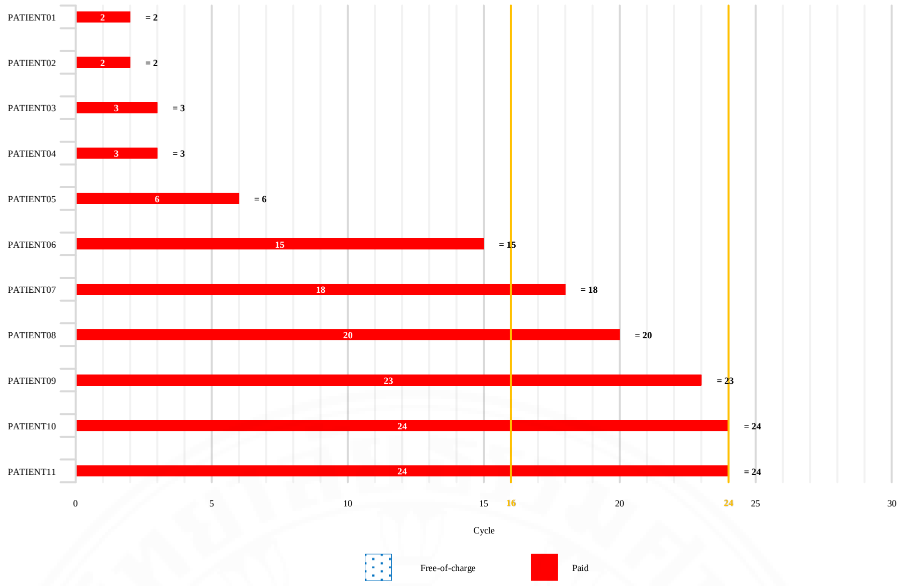


Figure 4.24 The payment patterns associated with the discount technique of ceritinib

Table 4.12 The drug procurement costs for ceritinib

Scenario	MEA technique	Drug procurement cost per patient (USD)			Total drug procurement cost (USD)			Total cost saving (USD)[a]			Cost saving (%)		
		PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]
Reference case	No MEA	28,413.30	28,413.30	28,413.30	312,546.26	312,546.26	312,546.26						
1	Discount	19,889.31	19,889.31	19,889.31	218,782.38	218,782.38	218,782.38	93,763.88	93,763.88	93,763.88	30.00	30.00	30.00
2	Free initiation technique	8,118.08	5,885.61	3,856.09	89,298.93	64,741.72	42,416.99	223,247.33	247,804.53	270,129.27	71.43	79.29	86.43
3	Utilization cap	20,295.21	22,527.68	24,557.21	223,247.33	247,804.53	270,129.27	89,298.93	64,741.72	42,416.99	28.57	20.71	13.57
4	Conditional treatment continuation	17,047.98	16,236.17	14,612.55	187,527.75	178,597.86	160,738.08	125,018.50	133,948.40	151,808.18	40.00	42.86	48.57
5	Pay-by-result	25,166.06	22,121.78	18,468.64	276,826.69	243,339.59	203,155.07	35,719.57	69,206.67	109,391.19	11.43	22.14	35.00

[a] Difference in drug procurement cost between the reference case and after applying the MEA technique.

[b] The median PFS was decreased by 10%.

[c] Base line PFS.

[d] The median PFS was increased by 10%.

4.1.3 Use uncertainty

4.1.3.1 Palbociclib

(1) Demographic characteristics

Table 4.13 reports the demographic characteristics of patients with HER2-negative MBC. There were twenty-three patients, the mean age was 65.04 years (SD = 11.57), and all patients were female (100%). The majority were patients under the CSMBS (52.18%), followed by the UCS (26.09%), other schemes (13.04%), and the SSS (8.69%). All patients (100%) tested negative for HER2 and were diagnosed with clinical stage IV disease according to the prescribing criteria of palbociclib.

Table 4.13 Demographic characteristics of patients who received palbociclib

Parameters	n (%)
Age, years	
Mean (SD)	65.04 (11.57)
Gender, n (%)	
Female	23 (100.00)
Male	0 (0.00)
Health benefit schemes, n (%)	
Civil Servant Medical Benefit Scheme (CSMBS)	12 (52.18)
Social Security Scheme (SSS)	2 (8.69)
Universal Coverage Scheme (UCS)	6 (26.09)
Others	3 (13.04)
HER2 expression status, n (%)	
Negative	23 (100.00)
Positive	0 (0.00)

Table 4.13 Demographic characteristics of patients who received palbociclib (Cont.)

Parameters	n (%)
Clinical stage, n (%)	
Stage I	0 (0.00)
Stage II	0 (0.00)
Stage III	0 (0.00)
Stage IV	23 (100.00)

(2) The patterns of drug response

Figure 4.25 shows the patterns of drug response. The drug use profiles are derived from real-world data of patients with HER2-negative MBC.

At the Cycle Fifth, approximately five months after treatment initiation, the majority of patients demonstrated favorable disease control. The disease control consists of 47.82% of patients showing stable disease and 26.09% of patients showing partial response. Progressive disease was observed in 26.09% of the cohort. Neither complete response nor death was reported at this time point. These findings suggest that palbociclib can provide good disease control within the first five months of the treatment.

By the Cycle Tenth, approximately ten months after treatment initiation, most patients continued to demonstrate either stable disease (43.47%) or partial response (21.74%). Although patients with progressive disease increased to 34.79%, more than half of patients showed disease control. These findings indicate that palbociclib therapy could sustain disease control in the real-world treatment of HER2-negative MBC.

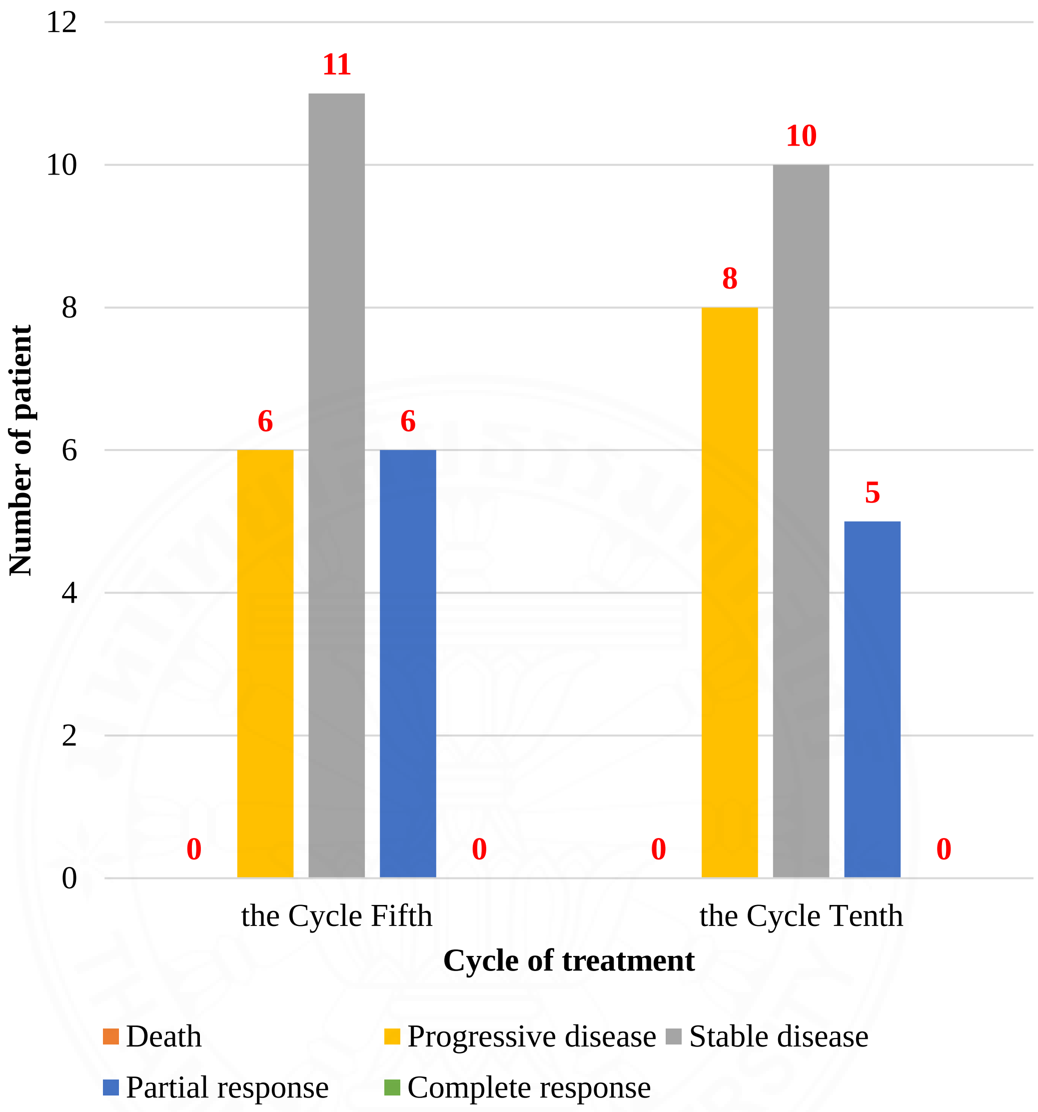


Figure 4.25 The patterns of drug response for palbociclib

(3) Drug procurement costs for each MEA technique

Table 4.15 reports the total drug procurement cost for twenty-three patients receiving palbociclib over a 24-month period. MEA techniques were applied to analyze real-world data under each scenario, as demonstrated in Table 4.14. Without any MEA technique application (reference case), the total drug procurement cost was 906,116.78 USD (1 USD = 33.6215 Thai Baht) (94, 95).

Table 4.14 Definition of the analyzed scenarios of palbociclib

Scenario	MEA technique	Definition
1	Discount	The discount strategy of 50% on drug price.
2	Free initiation treatment	The first ten cycles of the drug are offered free of charge; thereafter, the full price is paid.
3	Utilization cap	The payer covers the cost for the first ten cycles, and the pharmaceutical company subsequently provides the remaining treatment free of charge.
4	Conditional treatment continuation	The payer funds up to ten cycles of treatment. Only patients who demonstrate stable disease, partial response, or complete response within ten cycles continue therapy, after which the pharmaceutical company provides the drug free of charge.
5	Pay-by-result	The pharmaceutical company reimburses the full drug cost for patients who do not achieve stable disease, partial response, or complete response within ten cycles.

Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing the total cost by 542,515.78 USD (59.87%), compared to the reference case. The conditional treatment continuation technique also demonstrated substantial savings, with a cost reduction of 473,258.45 USD (52.23%). Similarly, the discount technique led to a 50.00% cost reduction.

Other techniques, such as the utilization cap and pay-by-result, were associated with more modest savings of 40.13% and 12.10%, respectively. Despite providing some degree of cost control, these techniques offered comparatively lower economic benefits.

The results indicate that the choice of MEA technique has a significant impact on the budgetary implications of palbociclib procurement. In this analysis of real-world data, free initiation treatment has been identified as the most effective MEA technique. Palbociclib—classified as a selective inhibitor of CDK4 and CDK6—is used in the treatment of hormone-receptor-positive, HER2-negative MBC.

However, in real-world practice, when palbociclib was first introduced to the market, the pharmaceutical company initially implemented the utilization cap technique. Under this agreement, the payer covered the cost of the drug for up to ten treatment cycles, after which the pharmaceutical company provided the medication free of charge for patients who continued treatment beyond that point. Based on the findings of this study, the utilization cap technique resulted in minimal cost savings.

This study found that among the various MEA techniques analyzed, the free initiation treatment technique resulted in the greatest cost savings, reducing the total drug procurement cost by 59.87% compared to procurement without MEA implementation.

Figure 4.26 demonstrates the individual-level treatment durations of twenty-three patients with HER2-negative MBC who receive palbociclib. Eight patients discontinue treatment before the Cycle Tenth. Under this technique, their treatment is entirely free of charge. This outcome highlights a key advantage of the technique: payers incur no cost for patients who discontinue early, thereby minimizing financial risk when limited clinical benefit is observed.

In addition, the remaining fifteen patients receive ten or more treatment cycles. Under this technique, the first ten cycles are provided free of charge, and costs are incurred only from the Cycle Eleventh onward. Therefore, even for patients requiring extended treatment, this technique continues to offer substantial cost savings compared to other MEA techniques.

These findings highlight that the free initiation treatment technique aligns both with clinical response and cost savings, offering financial protection in early discontinuation and budget efficiency for longer treatments. This makes it particularly suitable for therapies such as palbociclib, which provide prolonged benefit for some patients (47, 56).

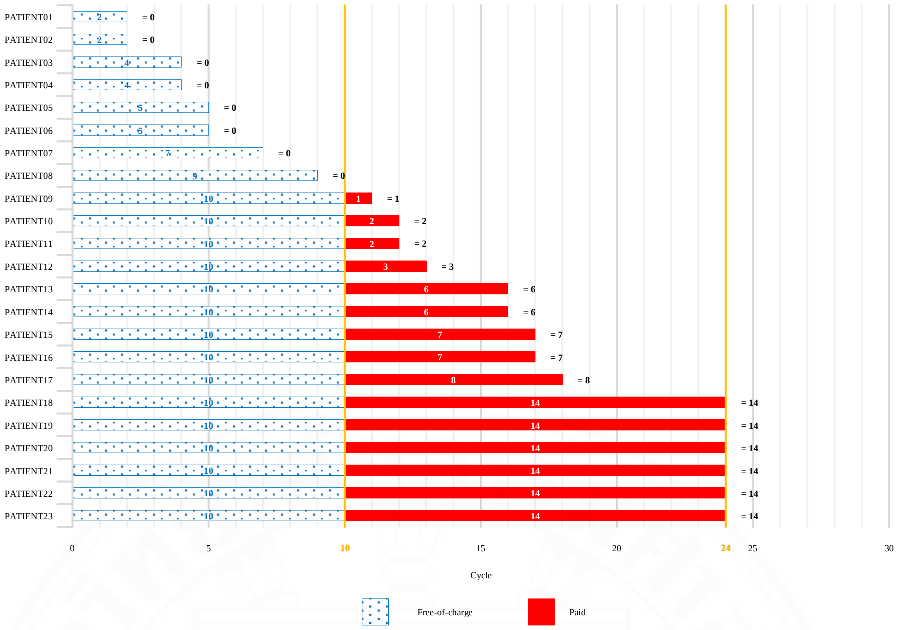


Figure 4.26 The payment patterns associated with the free initiation treatment technique of palbociclib

Under the utilization cap technique (Figure 4.27), payers cover the full cost of treatment for all patients during the first ten cycles, regardless of whether patients continue or discontinue therapy within this period. As a result, even patients who discontinue treatment early—within the initial ten cycles—generate drug costs fully borne by the payer. In this cohort, eight patients (34.79%) discontinue treatment during this early phase, creating a situation in which the payer absorbs the entire cost of treatment up to the Cycle Tenth, despite limited or no sustained clinical benefit. This technique imposes a considerable financial burden, particularly in populations with low to moderate early discontinuation rates.

In contrast, the free initiation treatment technique transfers financial responsibility for cycles one through ten entirely to the pharmaceutical company. All patients receive the first ten treatment cycles free of charge, regardless of whether they continue or discontinue therapy. Consequently, payers incur no drug-related costs during this initial period, effectively eliminating financial risk associated with early discontinuation.

In the post-Cycle Tenth period, fifteen patients (65.21%) continue treatment beyond the Cycle Tenth. Under this technique, the pharmaceutical company assumes full cost responsibility from the Cycle Eleventh onward, relieving the payer of any further expenditure. Conversely, the free initiation treatment technique shifts the cost burden to the payer starting from the Cycle Eleventh. However, because the pharmaceutical company subsidizes the entire cost of the initial ten cycles, the cumulative financial responsibility for the payer remains lower under this technique compared to the utilization cap technique, which requires payment for all patients from the outset—even for those who do not derive long-term clinical benefit.

Overall, the utilization cap technique exposes payers to substantial upfront costs that may not align with clinical outcomes, especially in cohorts with frequent early discontinuation. In such scenarios, the financial burden may exceed the therapeutic value achieved. By contrast, the free initiation treatment technique provides a more economically efficient technique by aligning cost responsibility with treatment duration and observed clinical benefit. By shifting early-phase costs to the pharmaceutical company (47, 56).

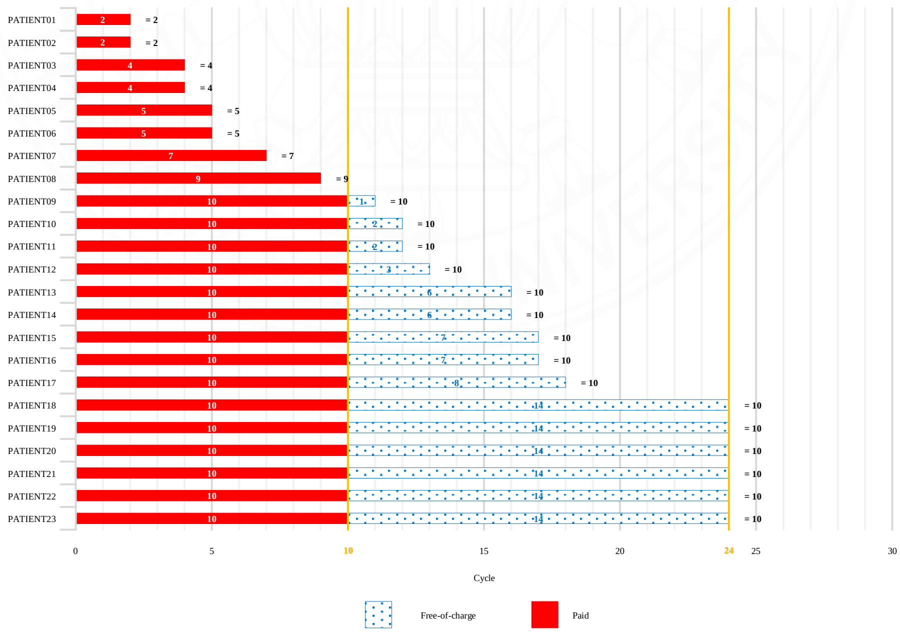


Figure 4.27 The payment patterns associated with the utilization cap technique of palbociclib

Under the conditional treatment continuation technique (Figure 4.28), eight patients in this cohort discontinue treatment before the Cycle Tenth. Consequently, no drug costs are incurred for these patients, as the company fully absorbs the costs associated with their early discontinuation. For the remaining fifteen patients who receive more than ten treatment cycles, the payer covers the cost of the initial ten cycles, while the company provides all subsequent cycles free of charge.

In contrast, the free initiation treatment technique provides the first ten treatment cycles at no cost to all patients, regardless of treatment duration or response. Under this technique, the payer incurs drug costs only if the patient continues therapy beyond the Cycle Tenth. This technique shifts the financial burden of the initial treatment phase entirely to the company, thereby significantly reducing upfront costs for the payer. Given that fifteen patients in this cohort continue treatment beyond the Cycle Tenth, this technique generates greater overall cost savings than the conditional treatment continuation technique. This advantage arises from the full subsidy of the first ten cycles for all patients, providing more effective cost mitigation—particularly for drugs like palbociclib, where early discontinuation is common (47, 56).

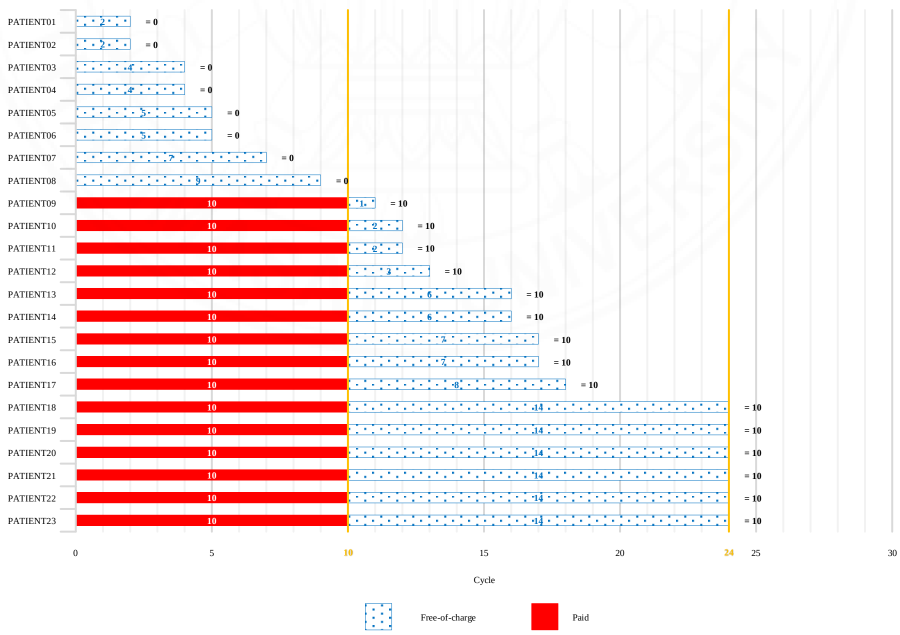


Figure 4.28 The payment patterns associated with the conditional treatment continuation technique of palbociclib

Under the pay-by-result technique (Figure 4.29), eight patients in this cohort discontinue treatment within the first ten cycles due to a lack of clinical benefit, thereby incurring no cost to the payer. However, for the remaining fifteen patients who demonstrate clinical benefit and continue treatment beyond the Cycle Tenth, the payer covers the full cost of both the initial ten cycles and all subsequent treatment. Although this technique provides financial protection for non-responders, it imposes a considerable cost burden on the payer for patients who derive prolonged therapeutic benefit.

In contrast, the free initiation treatment technique provides the first ten cycles of palbociclib free of charge to all patients, regardless of treatment response or duration. Consequently, the payer incurs no costs during the first ten-cycle period. For the same fifteen patients who continue beyond this point, the payer assumes financial responsibility only from the Cycle Eleventh onward. Thus, although both MEA techniques offer cost protection for non-responders, the free initiation treatment technique generates greater overall cost savings by shifting financial responsibility for the high-cost early phase entirely to the pharmaceutical company (47, 56).

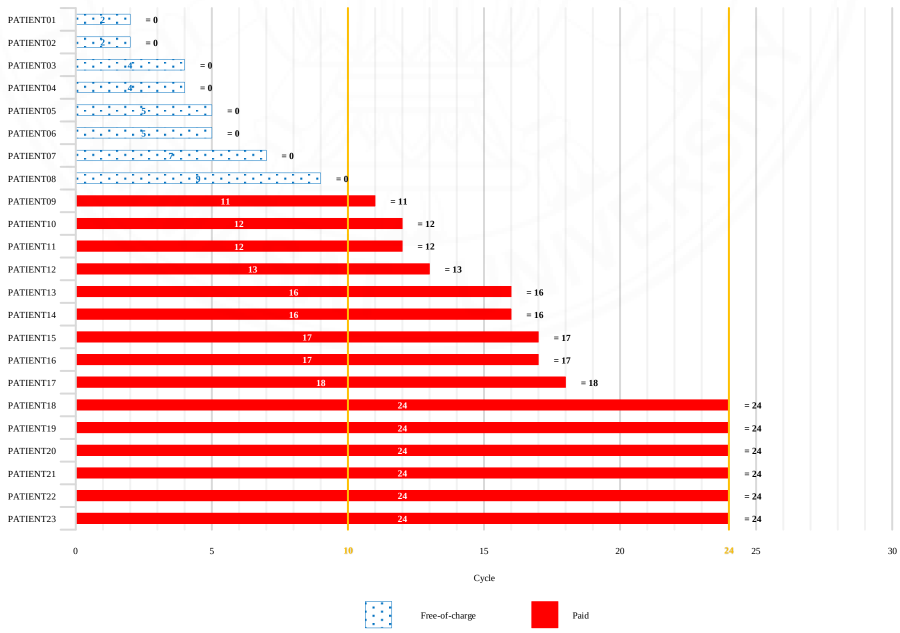


Figure 4.29 The payment patterns associated with the pay-by-result technique of palbociclib

Under the discount technique (Figure 4.30), the payer covers 50% of the drug cost during cycles one through ten for all patients, regardless of treatment response or duration. Although this technique offers immediate cost reductions compared to full-price procurement, it does not account for clinical outcomes or early treatment discontinuation. In this cohort, eight patients (34.79%) discontinue treatment within the first ten cycles, largely due to disease progression or lack of clinical benefit. Despite the limited therapeutic value obtained in these cases, drug costs—albeit at a reduced rate—are still incurred by the payer throughout the early treatment phase. This underscores a key limitation of the discount technique: it distributes financial burden uniformly, irrespective of real-world treatment effectiveness.

In contrast, the free initiation treatment technique provides a more outcome-aligned cost structure during the initial treatment period. Under this technique, the pharmaceutical company fully subsidizes the cost of palbociclib during cycles one through ten for all patients. Consequently, for patients who discontinue treatment early, such as the eight in this cohort, no drug-related expenditure is incurred by the payer. This effectively eliminates financial risk associated with early discontinuation and generates substantial upfront cost savings.

In the post-Cycle Tenth period, further divergence in financial impact between the two techniques becomes evident. Among the fifteen patients (65.21%) who continue treatment beyond the Cycle Tenth, the discount technique requires the payer to maintain payment of 50% of the drug cost for all subsequent cycles, creating a consistent and ongoing financial obligation. In contrast, under the free initiation treatment technique, the payer incurs costs only from the Cycle Eleventh onward. Although drug costs arise in long-term responders under this technique, the total cumulative cost to the payer remains lower than that of the discount technique, which requires co-payment from the outset regardless of clinical benefit (47, 56).

In summary, the free initiation treatment technique demonstrates superior economic efficiency in this real-world cohort. By eliminating drug costs in the early phase—when discontinuation is more likely—and confining expenditure to patients with sustained clinical benefit, this technique provides a more rational and targeted allocation of limited healthcare resources. For drugs such as palbociclib, where early treatment discontinuation is common, this MEA technique offers a more sustainable reimbursement model compared to traditional discount mechanisms.

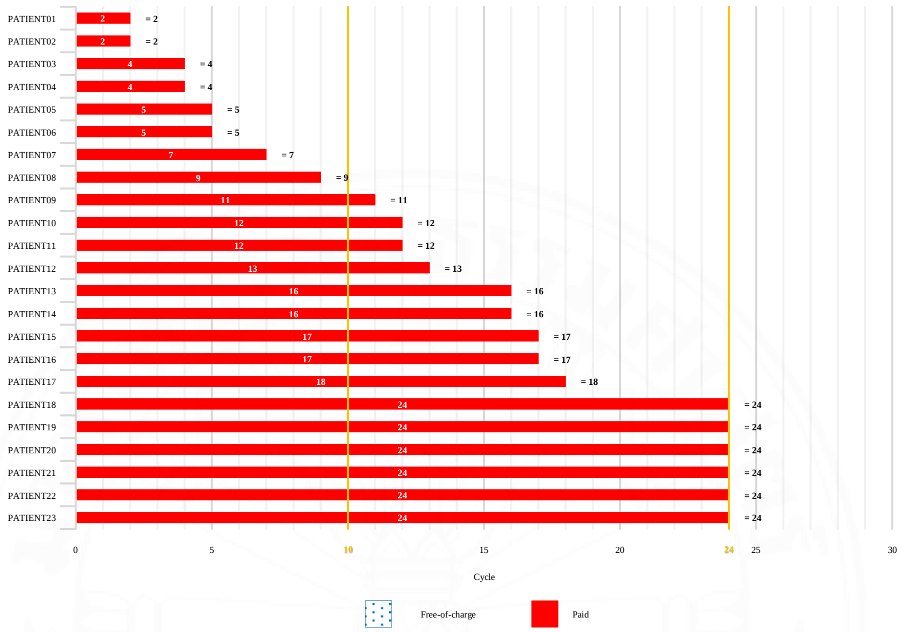


Figure 4.30 The payment patterns associated with the discount technique of palbociclib

Table 4.15 The drug procurement costs for palbociclib

Scenario	MEA technique	Drug procurement cost per patient (USD)			Total drug procurement cost (USD)			Total cost saving (USD)[a]			Cost saving (%)		
		PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]
Reference case	No MEA	39,396.38	39,396.38	39,396.38	906,116.78	906,116.78	906,116.78						
1	Discount	19,698.19	19,698.19	19,698.19	453,058.39	453,058.39	453,058.39	453,058.39	453,058.39	453,058.39	50.00	50.00	50.00
2	Free initiation technique	17,690.73	15,808.74	13,926.75	406,886.83	363,601.00	320,315.17	499,229.95	542,515.78	585,801.61	55.10	59.87	64.65
3	Utilization cap	21,705.65	23,587.64	25,469.64	499,229.95	542,515.78	585,801.61	406,886.83	363,601.00	320,315.17	44.90	40.13	35.35
4	Conditional treatment continuation	18,067.13	18,819.93	19,321.79	415,544.00	432,858.33	444,401.22	490,572.78	473,258.45	461,715.56	54.14	52.23	50.96
5	Pay-by-result	35,757.86	34,628.67	33,248.54	822,430.84	796,459.34	764,716.39	83,685.94	109,657.44	141,400.39	9.24	12.10	15.61

[a] Difference in drug procurement cost between the reference case and after applying the MEA technique.

[b] The median PFS was decreased by 10%.

[c] Base line PFS.

[d] The median PFS was increased by 10%.

4.1.3.2 Ribociclib

(1) Demographic characteristics

Table 4.16 reports the demographic characteristics of patients with HER2-negative MBC. There were thirty-nine patients, the mean age was 62.56 years (SD = 10.46), and all patients were female (100%). The majority were patients under the CSMBS (61.53%), followed by the UCS (33.33%), other schemes (2.57%), and the SSS (2.57%). All patients (100%) tested negative for HER2 and were diagnosed with clinical stage IV disease according to the prescribing criteria of ribociclib.

Table 4.16 Demographic characteristics of patients who received ribociclib

Parameters	n (%)
Age, years	
Mean (SD)	62.56 (10.46)
Gender, n (%)	
Female	39 (100.00)
Male	0 (0.00)
Health benefit schemes, n (%)	
Civil Servant Medical Benefit Scheme (CSMBS)	24 (61.53)
Social Security Scheme (SSS)	1 (2.57)
Universal Coverage Scheme (UCS)	13 (33.33)
Others	1 (2.57)
HER2 expression status, n (%)	
Negative	39 (100.00)
Positive	0 (0.00)
Clinical stage, n (%)	
Stage I	0 (0.00)
Stage II	0 (0.00)
Stage III	0 (0.00)
Stage IV	39 (100.00)

(2) The patterns of drug response

Figure 4.31 shows the patterns of drug response. The drug use profiles are derived from real-world data of patients with HER2-negative MBC.

At the Cycle Fifth, approximately five months after treatment initiation, the majority of patients demonstrated favorable disease control. The disease control consists of 61.54% of patients showing stable disease and 7.69% of patients showing partial response. Progressive disease was observed in 30.77% of the cohort. Neither complete response nor death was reported at this time point. These findings suggest that ribociclib can provide good disease control within the first five months of the treatment.

By the Cycle Tenth, approximately ten months after treatment initiation, most patients continued to demonstrate either stable disease (46.15%) or partial response (5.12%). Although patients with progressive disease increased to 48.73%, more than half of patients showed disease control. These findings indicate that ribociclib therapy could sustain disease control in the real-world treatment of HER2-negative MBC.

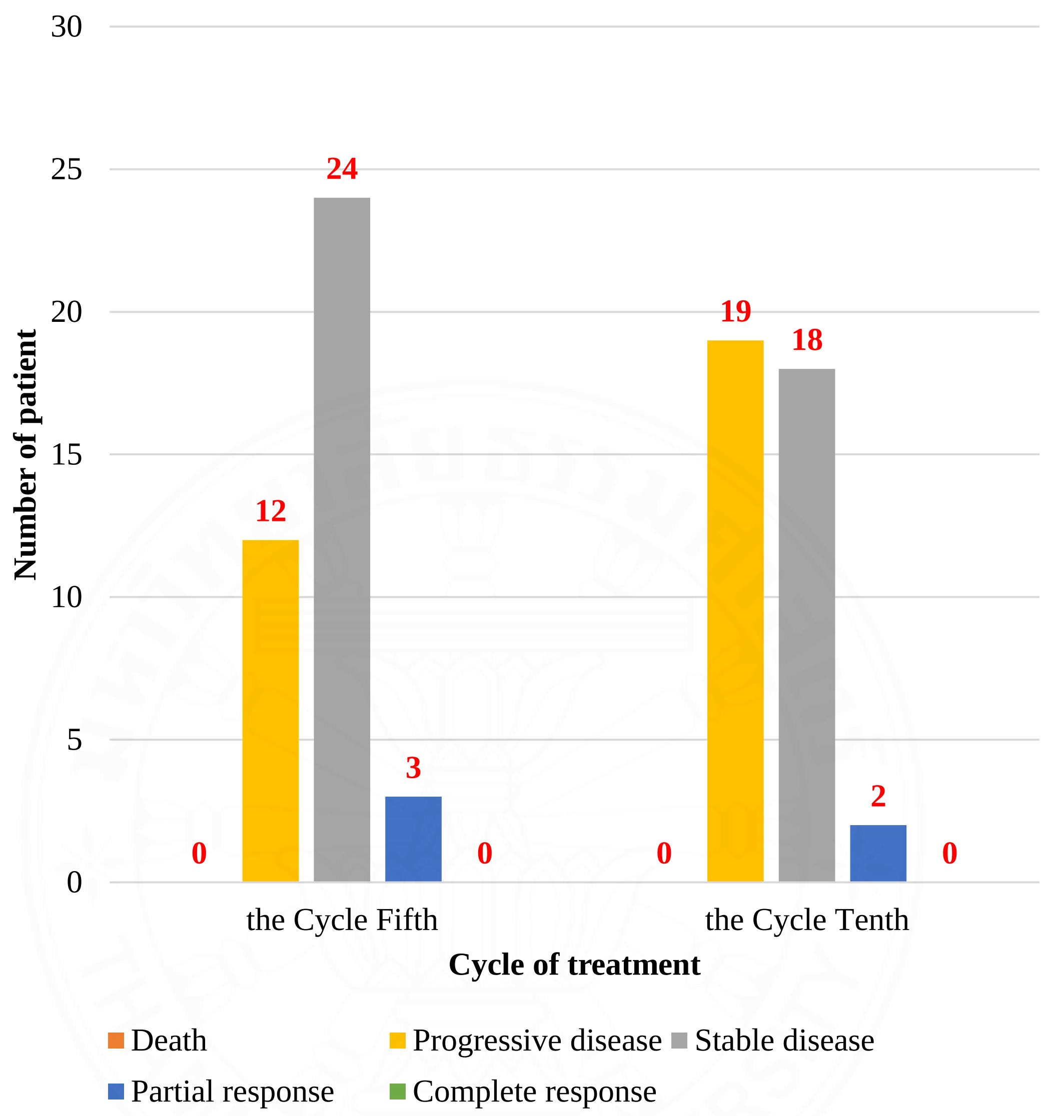


Figure 4.31 The patterns of drug response for ribociclib

(3) Drug procurement costs for each MEA technique

Table 4.18 reports the total drug procurement cost for thirty-nine patients receiving ribociclib over a 24-month period. MEA techniques were applied to analyze real-world data under each scenario, as demonstrated in Table 4.17. Without any MEA technique application (reference case), the total drug procurement cost was 741,204.24 USD (1 USD = 33.6215 Thai Baht) (94, 95).

Table 4.17 Definition of the analyzed scenarios of ribociclib

Scenario	MEA technique	Definition
1	Discount	The discount strategy of 50% on drug price.
2	Free initiation treatment	The first ten cycles of the drug are offered free of charge; thereafter, the full price is paid.
3	Utilization cap	The payer covers the cost for the first ten cycles, and the pharmaceutical company subsequently provides the remaining treatment free of charge.
4	Conditional treatment continuation	The payer funds up to ten cycles of treatment. Only patients who demonstrate stable disease, partial response, or complete response within ten cycles continue therapy, after which the pharmaceutical company provides the drug free of charge.
5	Pay-by-result	The pharmaceutical company reimburses the full drug cost for patients who do not achieve stable disease, partial response, or complete response within ten cycles.

Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing the total cost by 454,726.53 USD (61.35%), compared to the reference case. The conditional treatment continuation technique also demonstrated substantial savings, with a cost reduction of 453,210.77 USD (61.15%). Similarly, the discount technique led to a 50.00% cost reduction.

Other techniques, such as the utilization cap and pay-by-result, were associated with more modest savings of 38.65% and 22.49%, respectively. Despite providing some degree of cost control, these techniques offered comparatively lower economic benefits.

The results indicate that the choice of MEA technique has a significant impact on the budgetary implications of ribociclib procurement. In this analysis of real-world data, free initiation treatment has been identified as the most effective MEA technique.

Ribociclib, a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6), is indicated for the treatment of hormone receptor–positive, HER2-negative MBC. In real-world practice, when ribociclib was first introduced to the market, the pharmaceutical company initially implemented the utilization cap technique. Under this agreement, the payer covered the cost of the drug for up to ten treatment cycles. For patients who continued therapy beyond this point, the pharmaceutical company provided the drug free of charge. Based on the findings of this study, the utilization cap technique resulted in minimal cost savings.

This study found that among the various MEA techniques analyzed, the free initiation treatment technique resulted in the greatest cost savings, reducing the total drug procurement cost by 61.35% compared to procurement without MEA implementation.

Figure 4.32 demonstrates the individual-level treatment durations of thirty-nine patients with hormone receptor–positive, HER2-negative MBC who receive ribociclib. Among these, nineteen patients discontinue treatment before the Cycle Tenth. Under the free initiation treatment technique, the entire treatment course for these patients is provided free of charge by the pharmaceutical company. This outcome highlights a key advantage of the technique: payers incur no costs for patients who discontinue early, thereby minimizing financial risk in cases with limited clinical benefit.

In addition, the remaining twenty patients receive ten or more treatment cycles. Under the free initiation treatment technique, the first ten cycles are provided at no cost, and costs are incurred only from the Cycle Eleventh onward. Therefore, even for patients requiring extended treatment, this technique continues to deliver substantial cost savings compared to other MEA techniques or procurement without MEA implementation.

These findings are particularly noteworthy as they demonstrate that the free initiation treatment technique aligns closely with both clinical outcomes and economic efficiency. Specifically, it offers financial protection in cases of early discontinuation while maintaining cost-effectiveness for patients who derive sustained clinical benefit. The observed correlation between treatment duration and clinical response further supports the economic viability of this technique in real-world settings—particularly for targeted therapies such as ribociclib, which may offer prolonged benefit to a select subgroup of patients (47, 56).

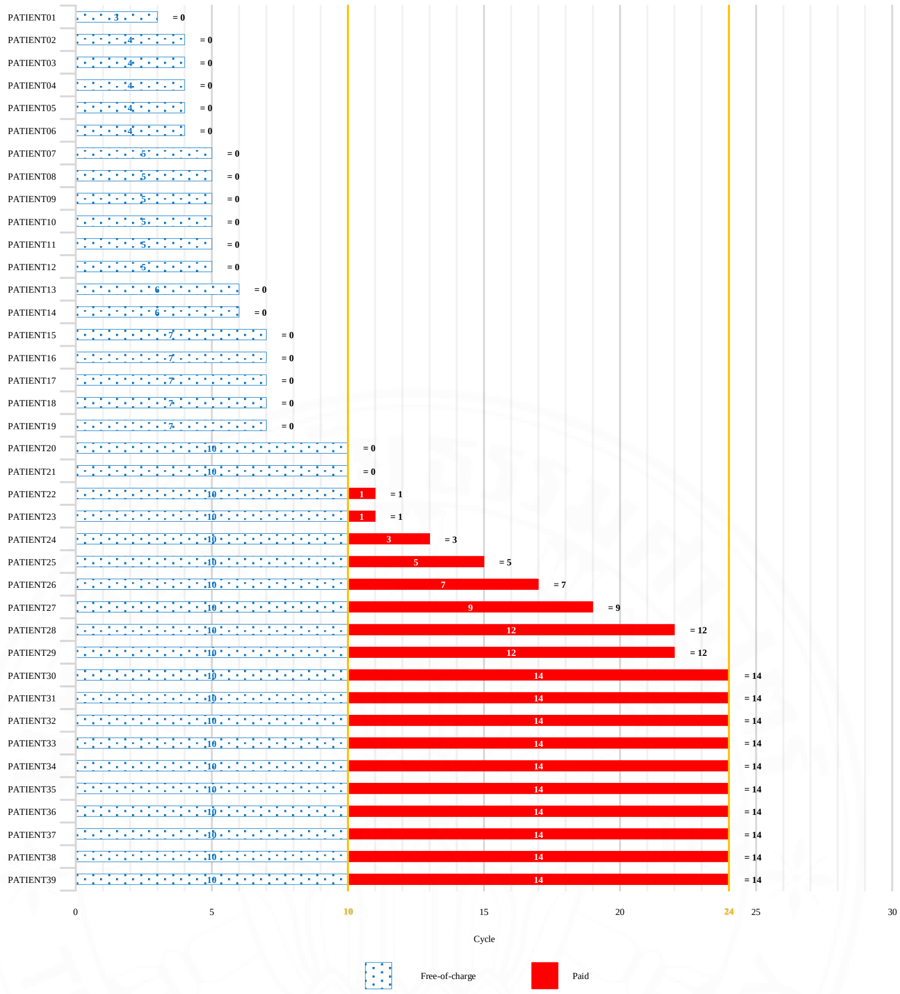


Figure 4.32 The payment patterns associated with the free initiation treatment technique of ribociclib

Under the utilization cap technique (Figure 4.33), payers cover the full cost of treatment for all patients during the first ten cycles, regardless of whether patients continue or discontinue therapy within this period. As a result, even patients who discontinue treatment early—within the initial ten cycles—incur drug costs entirely borne by the payer. In this cohort, nineteen patients (48.72%) discontinue treatment during this early phase, creating a situation in which the payer absorbs the full cost of treatment up to the Cycle Tenth, despite limited or no sustained clinical benefit. This technique imposes a considerable financial burden, particularly in populations with early discontinuation rates, as observed in this study.

In contrast, the free initiation treatment technique transfers financial responsibility for cycles one through ten entirely to the pharmaceutical company. All patients receive the first ten treatment cycles free of charge, regardless of whether they continue or discontinue therapy. Consequently, payers incur no drug-related costs during this initial period, effectively eliminating financial risk associated with early discontinuation.

During the post-Cycle Tenth period, twenty patients (51.28%) continue treatment beyond the Cycle Tenth. Under the utilization cap technique, the pharmaceutical company covers costs from the Cycle Eleventh onward, relieving the payer of any further expenditure. Conversely, the free initiation treatment technique shifts the cost burden to the payer starting from the Cycle Eleventh. However, because the pharmaceutical company subsidizes the entire cost of the first ten cycles, the cumulative costs for the payer remain lower under this technique compared to the utilization cap technique, which requires upfront payments for all patients—even those who do not achieve long-term clinical benefit.

Overall, the utilization cap technique exposes payers to substantial upfront costs that may not align with clinical outcomes, particularly in cohorts with frequent early discontinuation. In such cases, the financial burden may exceed the therapeutic value gained. By contrast, the free initiation treatment technique provides a more economically efficient technique by aligning cost responsibility with treatment duration and observed clinical benefit. By shifting early-phase costs to the pharmaceutical company, this technique enhances budgetary protection for payers while maintaining patient access to potentially effective therapies (47, 56).

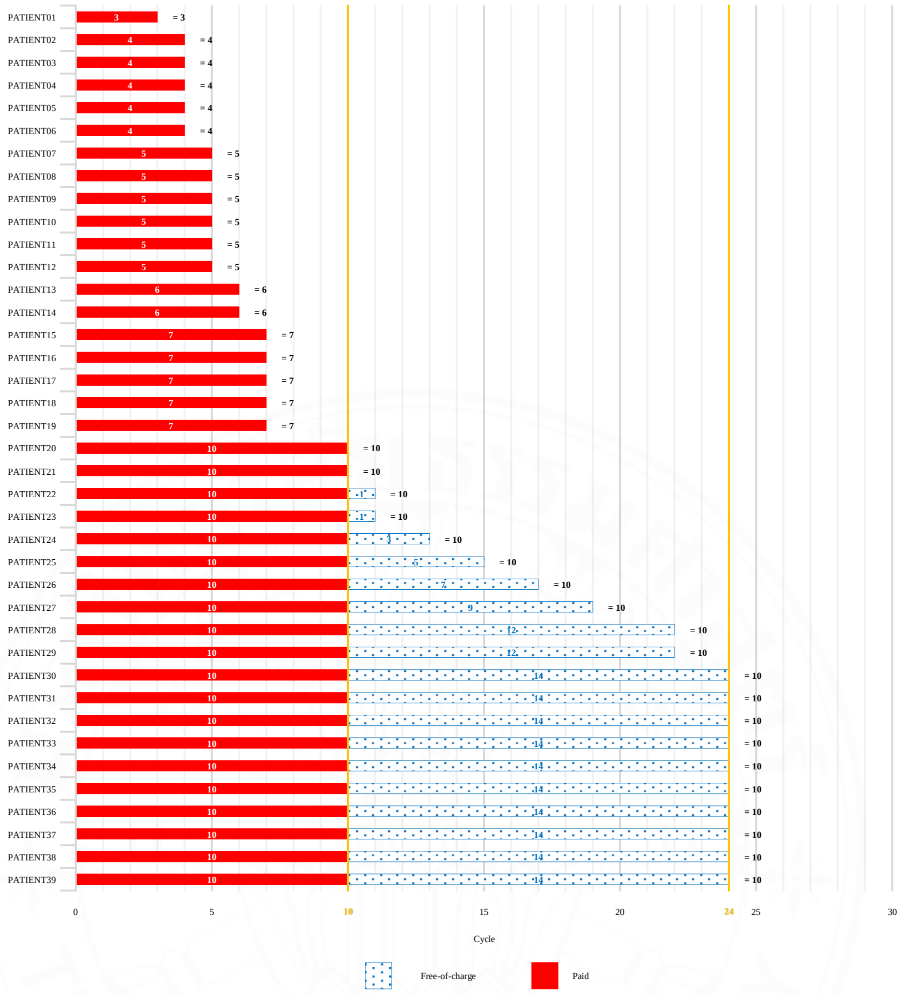


Figure 4.33 The payment patterns associated with the utilization cap technique of ribociclib

Under the conditional treatment continuation technique (Figure 4.34), nineteen patients in this cohort discontinue treatment before the Cycle Tenth. Consequently, no drug costs are incurred for these patients, as the pharmaceutical company fully absorbs the costs associated with early discontinuation. For the remaining twenty patients who receive more than ten treatment cycles, the payer covers the cost of the first ten cycles, while the pharmaceutical company provides all subsequent cycles free of charge.

In contrast, the free initiation treatment technique provides the first ten treatment cycles at no cost to all patients, regardless of treatment duration or clinical response. Under this technique, the payer incurs drug costs only if the patient continues therapy beyond the Cycle Tenth. This technique shifts the financial burden of the initial treatment phase entirely to the pharmaceutical company, thereby substantially reducing upfront costs for the payer.

Given that twenty patients in this cohort continue treatment beyond the Cycle Tenth, the free initiation treatment technique generates greater overall cost savings than the conditional treatment continuation technique. This advantage stems from the full subsidy of the first ten cycles for all patients, providing more effective cost mitigation—particularly for high-cost therapies like ribociclib, where early treatment discontinuation is relatively common (47, 56).

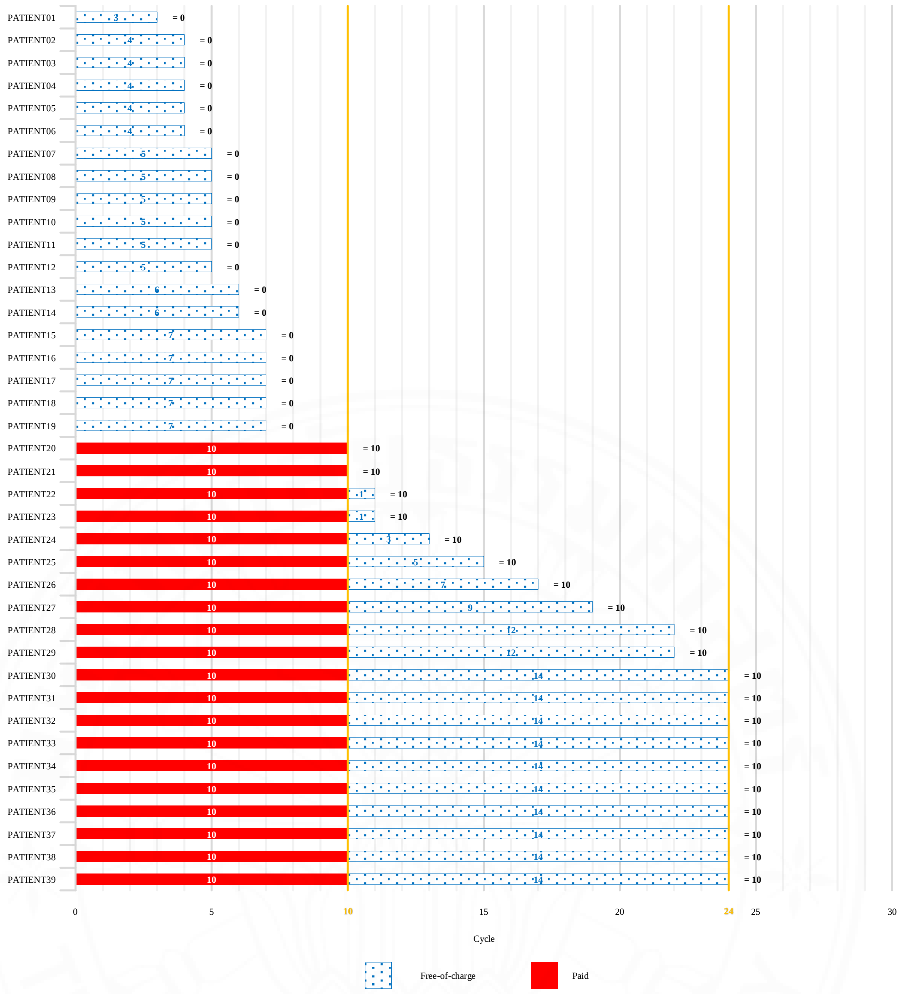


Figure 4.34 The payment patterns associated with the conditional treatment continuation technique of ribociclib

Under the pay-by-result technique (Figure 4.35), nineteen patients (48.73%) in this cohort discontinue treatment within the first ten cycles due to a lack of clinical benefit, thereby incurring no cost to the payer. However, for the remaining twenty patients who demonstrate clinical benefit and continue treatment beyond the Cycle Tenth, the payer covers the full cost of both the initial ten cycles and all subsequent treatment. Although this technique provides financial protection for non-responders, it imposes a considerable cost burden on the payer for patients who derive prolonged therapeutic benefit.

In contrast, the free initiation treatment technique provides the first ten cycles of ribociclib free of charge to all patients, regardless of treatment response or duration. Consequently, the payer incurs no costs during the first ten-cycle period. For the same twenty patients who continue beyond this point, the payer assumes financial responsibility only from the Cycle Eleventh onward. Thus, although both MEA techniques offer cost protection for non-responders, the free initiation treatment technique generates greater overall cost savings by shifting financial responsibility for the high-cost early phase entirely to the pharmaceutical company. This advantage is particularly evident among long-term responders, for whom the full cost would otherwise be borne by the payer under the pay-by-result technique (47, 56).

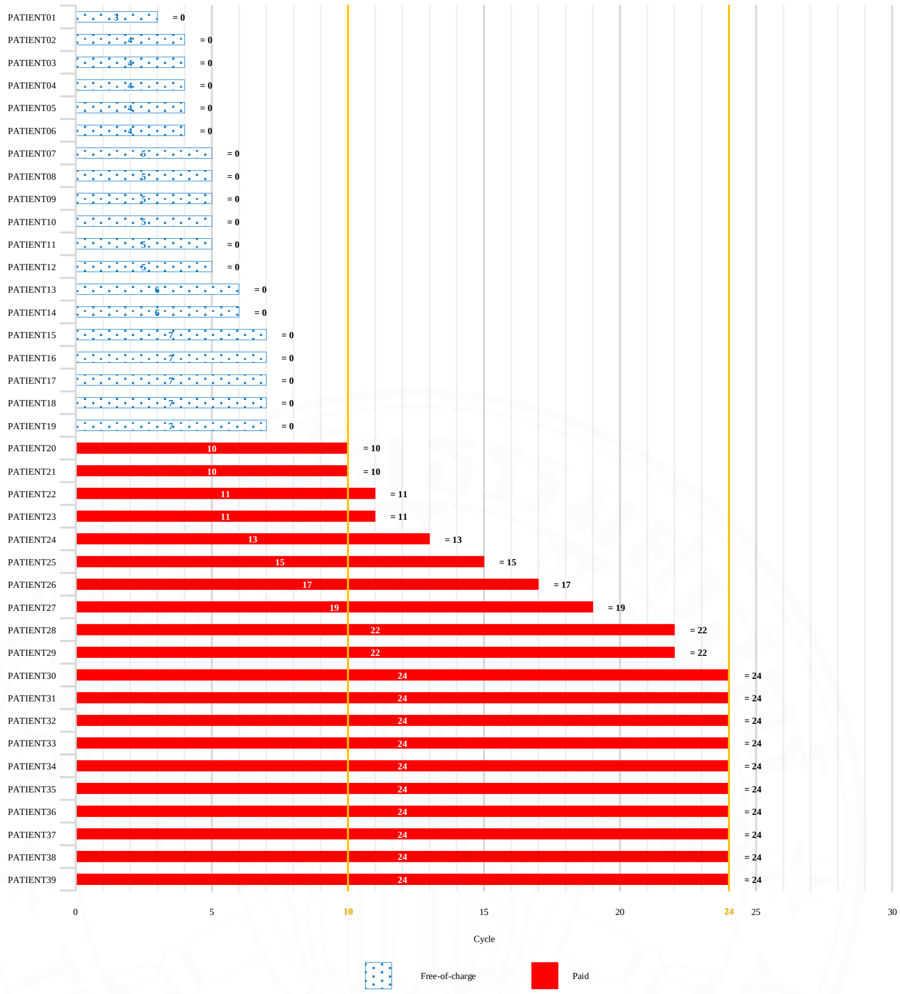


Figure 4.35 The payment patterns associated with the pay-by-result technique of ribociclib

Under the discount technique (Figure 4.36), the payer covers 50% of the drug cost during cycles one through ten for all patients, regardless of treatment response or duration. Although this technique offers immediate cost reductions compared to full-price procurement, it does not account for clinical outcomes or early treatment discontinuation. In this cohort, nineteen patients (48.73%) discontinue treatment within the first ten cycles, largely due to disease progression or lack of clinical benefit. Despite the limited therapeutic value obtained in these cases, drug costs—albeit at a reduced rate—are still incurred by the payer throughout the early treatment phase. This underscores a key limitation of the discount technique: it distributes financial burden uniformly, irrespective of real-world treatment effectiveness.

In contrast, the free initiation treatment technique provides a more outcome-aligned cost structure during the initial treatment period. Under this technique, the pharmaceutical company fully subsidizes the cost of ribociclib during cycles one through ten for all patients. Consequently, for patients who discontinue treatment early, such as the nineteen in this cohort, no drug-related expenditure is incurred by the payer. This effectively eliminates financial risk associated with early discontinuation and generates substantial upfront cost savings.

In the post-Cycle Tenth period, further divergence in financial impact between the two techniques becomes evident. Among the twenty patients (51.28%) who continue treatment beyond the Cycle Tenth, the discount technique requires the payer to maintain payment of 50% of the drug cost for all subsequent cycles, creating a consistent and ongoing financial obligation. In contrast, under the free initiation treatment technique, the payer incurs costs only from the Cycle Eleventh onward. Although drug costs arise in long-term responders under this technique, the total cumulative cost to the payer remains lower than that of the discount technique, which demands co-payment from the outset regardless of clinical benefit (47, 56).

In summary, the free initiation treatment technique demonstrates superior economic efficiency in this real-world cohort. By eliminating drug costs in the early phase—when discontinuation is more likely—and confining expenditure to patients with sustained clinical benefit, this technique provides a more rational and targeted allocation of limited healthcare resources. For drugs such as ribociclib, where early treatment discontinuation is common, this MEA technique offers a more sustainable reimbursement model compared to traditional discount mechanisms.

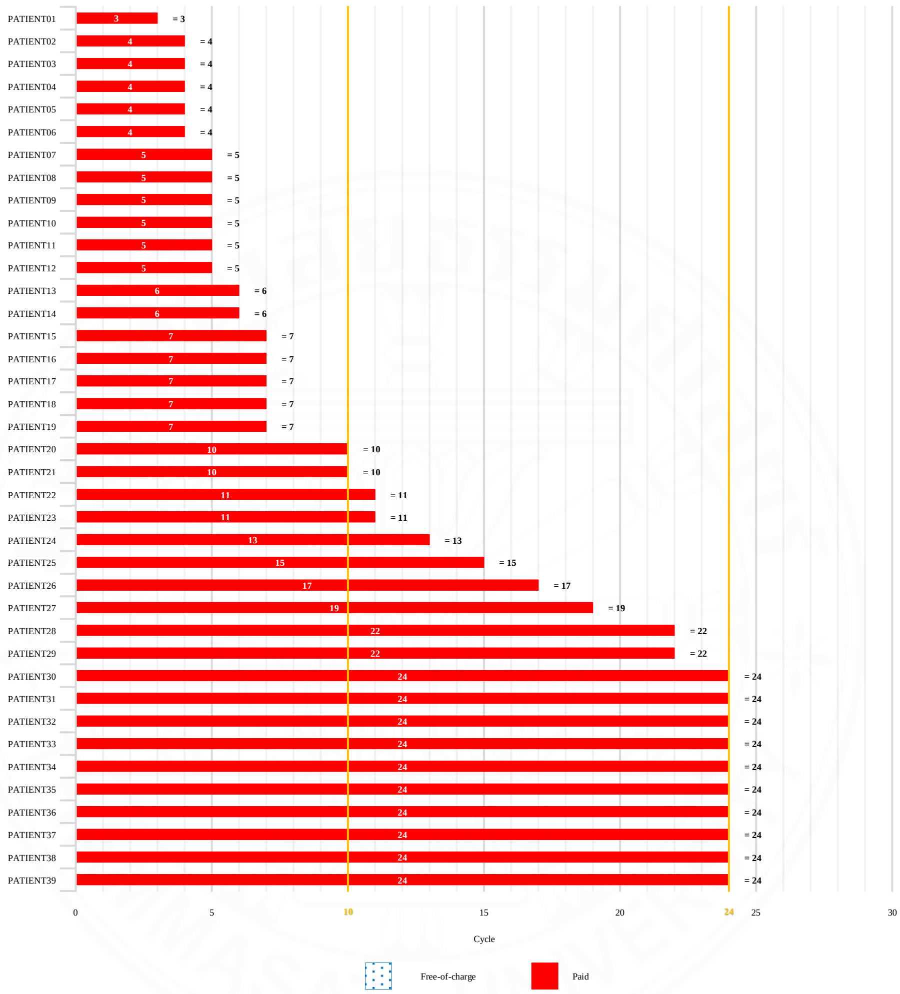


Figure 4.36 The payment patterns associated with the discount technique of ribociclib

Table 4.18 The drug procurement costs for ribociclib

Scenario	MEA technique	Drug procurement cost per patient (USD)			Total drug procurement cost (USD)			Total cost saving (USD)[a]			Cost saving (%)		
		PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]	PFS -10%[b]	PFS[c]	PFS +10%[d]
Reference case	No MEA	19,005.24	19,005.24	19,005.24	741,204.24	741,204.24	741,204.24						
1	Discount	9,502.62	9,502.62	9,502.62	370,602.12	370,602.12	370,602.12	370,602.12	370,602.12	370,602.12	50.00	50.00	50.00
2	Free initiation technique	8,122.89	7,345.58	6,646.00	316,792.82	286,477.71	259,194.12	424,411.43	454,726.53	482,010.12	57.26	61.35	65.03
3	Utilization cap	10,882.34	11,659.65	12,359.23	424,411.43	454,726.53	482,010.12	316,792.82	286,477.71	259,194.12	42.74	38.65	34.97
4	Conditional treatment continuation	6,995.79	7,384.45	7,695.37	272,835.92	287,993.47	300,119.51	468,368.33	453,210.77	441,084.73	63.19	61.15	59.51
5	Pay-by-result	15,118.69	14,730.03	14,341.38	589,628.73	574,471.18	559,313.63	151,575.51	166,733.06	181,890.61	20.45	22.49	24.54

[a] Difference in drug procurement cost between the reference case and after applying the MEA technique.

[b] The median PFS was decreased by 10%.

[c] Base line PFS.

[d] The median PFS was increased by 10%.

4.2 The appropriate MEA technique for each drug uncertainty characteristic

This study focused on three drug uncertainty characteristics, including price, effectiveness, and use. Table 4.19 presents the drug procurement cost savings obtained from applying MEA techniques for each drug uncertainty characteristic. Based on these results, we identified the most appropriate MEA technique for each drug uncertainty characteristic, as follows:

4.2.1 Price uncertainty

Based on the findings of this study, the appropriate MEA technique for addressing price uncertainty is the free initiation treatment technique. This technique resulted in the highest percentage of drug procurement cost savings across all drugs in this uncertainty (Figure 4.37).

4.2.1.1 Pertuzumab

For pertuzumab, which is used in the treatment of HER2-positive MBC, price uncertainty remains a significant concern due to the substantial annual treatment cost. Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing drug procurement costs by 72.43%, and ranked first among the five techniques evaluated. This technique was followed by the conditional treatment continuation technique, which achieved a cost saving of 53.68% and ranked second. The discount technique provided a 30% cost saving and ranked third, while the utilization cap and pay-by-result techniques resulted in the lowest savings at 27.57% and 26.10%, respectively.

In this analysis, nearly half of patients discontinued treatment during early cycles; MEA techniques such as discount and utilization cap exposed payers to substantial early-phase costs without corresponding clinical benefit. Conversely, conditional treatment continuation and pay-by-result provided partial financial protection but were outperformed by free initiation treatment, which transferred the entire cost burden of the early treatment phase to the pharmaceutical company, providing protection against price uncertainty.

4.2.1.2 Osimertinib

For osimertinib, which is used in the treatment of EGFR mutation-positive metastatic NSCLC, price uncertainty remains a significant concern due to the substantial annual treatment cost. Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing drug procurement costs by 62.80%, and ranked first among the five techniques evaluated. This technique was followed by the conditional treatment continuation technique, which achieved a cost saving of 52.90% and ranked second. The discount technique provided a 50% cost saving and ranked third, while the utilization cap and pay-by-result techniques resulted in the lowest savings at 37.20% and 15.70%, respectively.

As with pertuzumab, a significant proportion of patients discontinued osimertinib early in treatment. This pattern reinforces that the free initiation treatment technique is particularly effective for drugs with high upfront costs and uncertain long-term duration, as it mitigates financial risk from early discontinuation while preserving patient access.

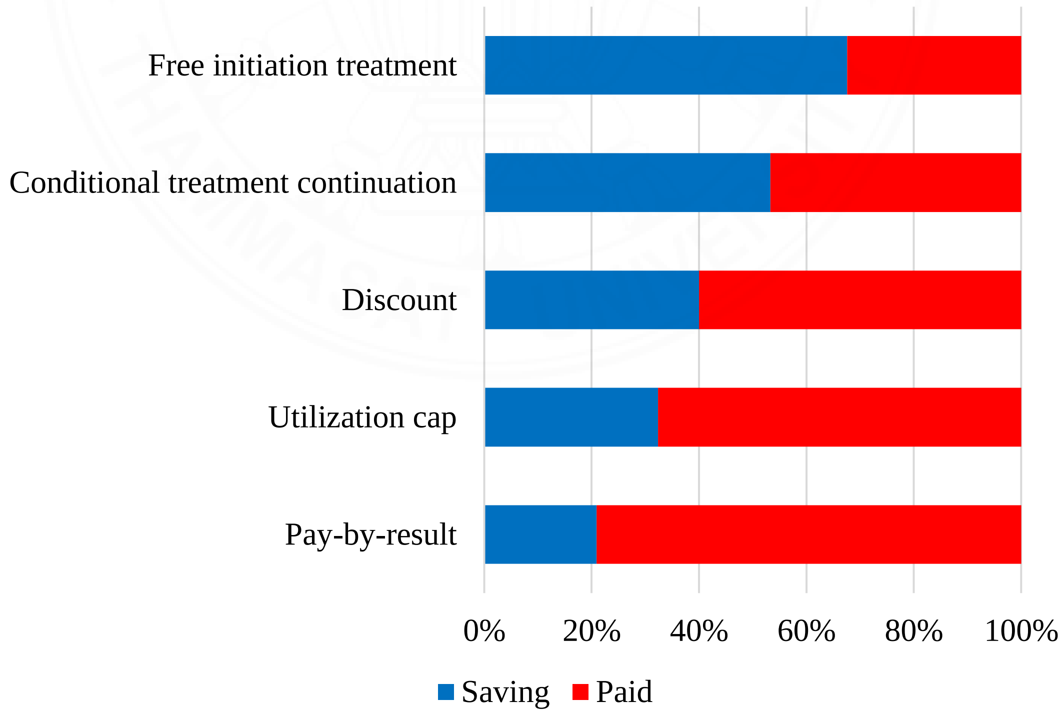


Figure 4.37 Cost savings from MEA techniques under price uncertainty

4.2.2 Effectiveness uncertainty

The findings indicate that for effectiveness uncertainty, the free initiation treatment technique again achieved the highest cost savings (Figure 4.38). However, the conditional treatment continuation technique also performed strongly, highlighting its relevance where real-world treatment outcomes are uncertain.

4.2.2.1 Afatinib

For afatinib, which is used in the treatment of EGFR mutation-positive metastatic NSCLC, effectiveness uncertainty arises from indirect comparative evidence with gefitinib and erlotinib. Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing drug procurement costs by 79.75%, and ranked first among the five techniques evaluated. This technique was followed by the conditional treatment continuation technique, which achieved a cost saving of 58.23% and ranked second. The discount technique provided a 50% cost saving and ranked third, while the pay-by-result and utilization cap techniques resulted in the lowest savings at 37.97% and 20.25%, respectively.

In this analysis, high rates of early treatment discontinuation were observed, leading to higher early-phase costs under MEA techniques like discount and utilization cap. The conditional treatment continuation technique offered partial risk control by linking payment to real-world outcomes, but the free initiation treatment technique performed best due to its ability to eliminate costs during uncertain early response periods.

4.2.2.2 Ceritinib

For ceritinib, which is used in the treatment of ALK-positive metastatic NSCLC, effectiveness uncertainty is heightened by safety concerns such as hepatotoxicity and gastrointestinal toxicity, which often necessitate dose reduction or discontinuation. Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing drug procurement costs by 79.29%, and ranked first among the five techniques evaluated. This technique was followed by the conditional treatment continuation technique, which achieved a cost saving of 42.86% and ranked second. The discount technique provided a 30% cost saving and ranked third, while the pay-by-result and utilization cap techniques resulted in the lowest savings at 22.14% and 20.71%, respectively.

Similar to afatinib, early discontinuation reduced payer efficiency under discount and utilization cap techniques. The conditional treatment continuation technique addressed this uncertainty by linking payment to patient benefit, but the free initiation treatment technique offered the most robust mitigation of financial risk during the uncertain early-response phase.

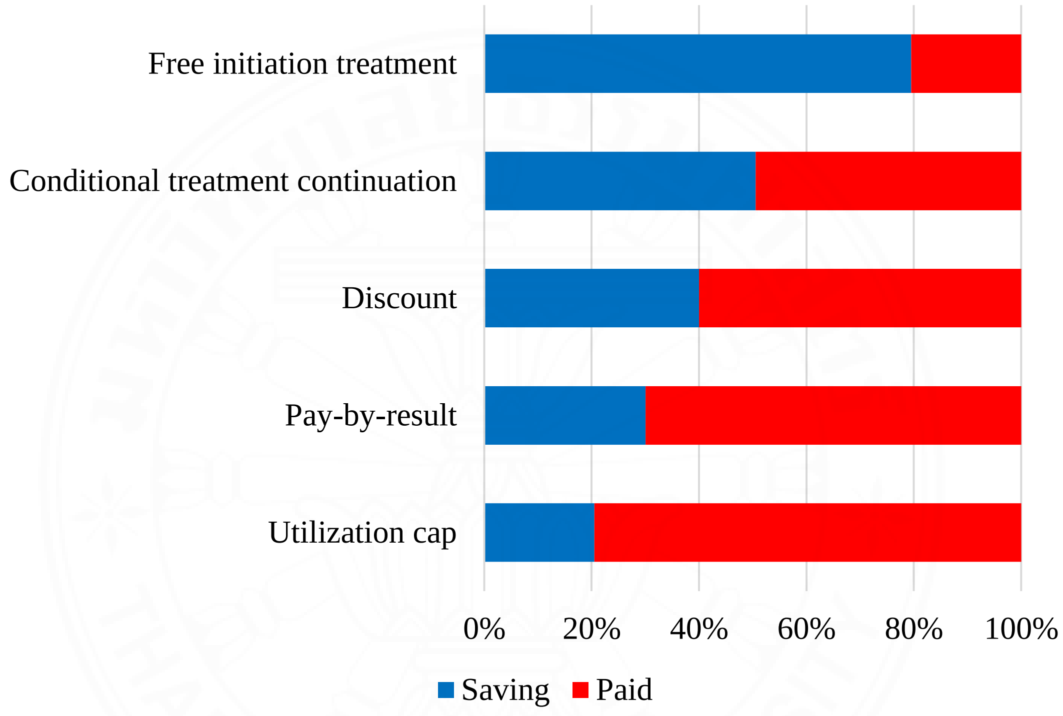


Figure 4.38 Cost savings from MEA techniques under effectiveness uncertainty

4.2.3 Use uncertainty

For use uncertainty, the free initiation treatment technique also provided the highest cost savings (Figure 4.39). However, conditional treatment continuation and utilization cap techniques demonstrated strong applicability where patient adherence and treatment duration are variable.

4.2.3.1 Palbociclib

For palbociclib, which is used in the treatment of postmenopausal, HR-positive, HER2-negative MBC, real-world treatment interruptions due to hematologic toxicity contribute to significant use uncertainty.

Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing drug procurement costs by 59.87%, and ranked first among the five techniques evaluated. This technique was followed by the conditional treatment continuation technique, which achieved a cost saving of 52.23% and ranked second. The discount technique provided a 50% cost saving and ranked third, while the utilization cap and pay-by-result techniques resulted in the lowest savings at 40.13% and 12.10%, respectively.

In this analysis, while the discount and utilization cap techniques require payers to cover costs regardless of early discontinuation, the conditional treatment continuation technique provided protection but required complex treatment outcome monitoring. The free initiation treatment technique was the most cost-saving, as it aligns with early dropout patterns and shifts financial responsibility for initial cycles entirely to the pharmaceutical company.

4.2.3.2 Ribociclib

For ribociclib, which is used in the treatment of postmenopausal, HR-positive, HER2-negative MBC, use uncertainty arises from dose adjustments and variable adherence due to neutropenia, QT prolongation, and hepatotoxicity. Among the MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings, reducing drug procurement costs by 61.35%, and ranked first among the five techniques evaluated. This technique was followed by the conditional treatment continuation technique, which achieved a cost saving of 61.15% and ranked second. The discount technique provided a 50% cost saving and ranked third, while the utilization cap and pay-by-result techniques resulted in the lowest savings at 38.65% and 22.49%, respectively.

As with palbociclib, the free initiation treatment technique effectively mitigates cost exposure in early discontinuation scenarios. However, its implementation in real-world negotiations may be limited, as pharmaceutical companies may resist offering extensive free treatment cycles.

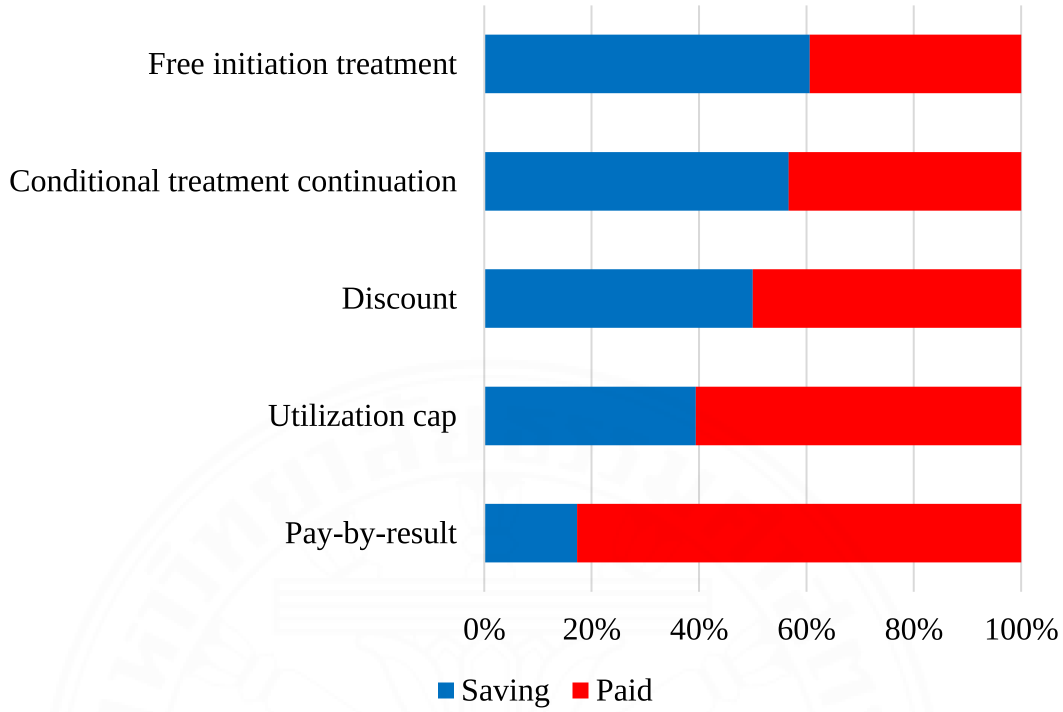


Figure 4.39 Cost savings from MEA techniques under use uncertainty

Table 4.19 Drug procurement cost savings and rankings across MEA techniques for the studied high-cost drugs

Scenario	MEA technique	Uncertainty: price				Uncertainty: effectiveness				Uncertainty: use			
		Pertuzumab		Osimertinib		Afatinib		Ceritinib		Palbociclib		Ribociclib	
		Cost saving (%)	Ranking	Cost saving (%)	Ranking	Cost saving (%)	Ranking	Cost saving (%)	Ranking	Cost saving (%)	Ranking	Cost saving (%)	Ranking
1	Discount	30.00	3	50.00	3	50.00	3	30.00	3	50.00	3	50.00	3
2	Free initiation treatment	72.43	1	62.80	1	79.75	1	79.29	1	59.87	1	61.35	1
3	Utilization cap	27.57	4	37.20	4	20.25	5	20.71	5	40.13	4	38.65	4
4	Conditional Treatment continuation	53.68	2	59.20	2	58.23	2	42.86	2	52.23	2	61.15	2
5	Pay-by-result	26.10	5	15.70	5	37.97	4	22.14	4	12.10	5	22.49	5

4.2.4 Impact from the change of median PFS

Sensitivity analyses demonstrated that variations in the median PFS, either an increase or a decrease of 10%, influenced the magnitude of cost savings across all MEA techniques. These results highlight the critical role of treatment duration in determining the financial outcomes of different MEA techniques.

When the median PFS increased by 10%, cost savings under the free initiation treatment technique improved because the extended treatment duration allowed a greater number of treatment cycles to be provided free of charge by the pharmaceutical company. Conversely, when the median PFS decreased by 10%, cost savings declined due to the reduced number of free treatment cycles utilized. Nevertheless, regardless of whether the PFS increased or decreased, the free initiation treatment technique consistently remained the most effective in achieving cost savings, ranking first among all MEA techniques.

For the conditional treatment continuation technique, an increase in median PFS resulted in reduced cost savings, as the payer was required to fund additional treatment cycles before discontinuation criteria were met. Conversely, a 10% decrease in PFS enhanced cost savings by requiring fewer payer-funded cycles. However, this technique consistently ranked second in terms of cost-saving efficiency, indicating its robustness despite changes in treatment duration.

Similarly, the utilization cap technique demonstrated sensitivity to changes in median PFS. When PFS increased, cost savings decreased because the payer had to finance more treatment cycles before reaching the cap threshold. Conversely, a shorter PFS improved cost savings by reducing the total number of cycles paid by the payer.

Under the pay-by-result technique, changes in PFS had a limited influence on overall cost savings. However, if the number of non-responding patients increased, reimbursements from the pharmaceutical company would rise, resulting in higher cost savings for the payer.

By contrast, the discount technique remained largely unaffected by changes in PFS, as its savings are determined by a fixed percentage reduction per cycle rather than by treatment duration.

Overall, the findings indicate that MEA techniques involving conditional or time-dependent components—particularly the free initiation treatment and utilization cap techniques—are most sensitive to variations in median PFS. These results emphasize the importance of incorporating real-world median PFS data into MEA design and negotiation processes to ensure optimal cost-effectiveness and financial sustainability.

4.2.5 Potential of cost savings from each MEA technique

This study demonstrated that different MEA techniques result in varying levels of cost savings depending on the type of drug-related uncertainty (Table 4.20). The magnitude of cost savings observed across the five MEA techniques reflects the structural design of each technique and its capacity to align payment with real-world treatment duration and treatment outcomes.

4.2.5.1 Free initiation treatment technique

The free initiation treatment technique consistently achieved the highest cost savings across all drug uncertainty characteristics. It was particularly effective in addressing effectiveness uncertainty (79.29-79.75%) and price uncertainty (62.80-72.43%). This technique transfers the initial treatment cost burden to the pharmaceutical company during the early treatment phase—when the probability of treatment discontinuation is high—thereby minimizing financial exposure for payers.

By subsidizing early treatment cycles, this MEA technique aligns reimbursement duration with the median PFS, optimizing cost efficiency. Furthermore, it provides significant protection against premature discontinuation and real-world variability in treatment response. However, despite its superior cost-saving potential, implementation challenges remain, as pharmaceutical companies may be reluctant to offer full-cycle subsidies.

4.2.5.2 Conditional treatment continuation technique

The conditional treatment continuation technique was identified as the second most effective technique, generating substantial cost savings under use uncertainty (52.23-61.15%) and effectiveness uncertainty (42.86-58.23%). This technique links reimbursement to clinical response, ensuring that continued payment is made only for patients demonstrating meaningful treatment benefit.

Its performance reflects a balanced technique between financial risk-sharing and clinical accountability. The technique not only improves payer protection but also reinforces post-marketing data collection to assess real-world effectiveness. However, operational challenges—such as the requirement for systematic data capture, monitoring, and reporting—can limit its feasibility, particularly in healthcare systems with limited digital infrastructure.

4.2.5.3 Utilization cap technique

The utilization cap technique demonstrated moderate cost-saving potential, particularly in addressing use uncertainty (38.65-40.13%) and price uncertainty (27.57-37.20%). By setting an upper limit on reimbursable treatment cycles, this technique effectively prevents uncontrolled budget escalation while ensuring predictable expenditure.

In the Thai context, this technique has been implemented through PAPs, allowing patients who continue to respond beyond the cap threshold to receive a free drug supply from pharmaceutical companies. However, despite its advantages in cost predictability and administrative workload, the need for detailed utilization tracking may impose significant operational burdens on healthcare providers.

4.2.5.4 Pay-by-resulted technique

The pay-by-result technique provided few cost savings, with a range of 22.14-37.97% under effectiveness uncertainty and 15.70-26.10% under price uncertainty. This technique offers refunds only for non-responding cases, promoting accountability and aligning cost with treatment outcomes.

However, its savings potential is limited when most patients respond favorably, as fewer reimbursement claims occur. Moreover, extensive outcome monitoring and verification are required, posing data collection and administrative challenges that may offset its financial benefits.

4.2.5.5 Discount technique

The discount technique resulted in consistent but relatively moderate cost savings across all drug uncertainty characteristics. Despite its limited financial impact, this technique remains widely adopted due to its simplicity, transparency, and ease of negotiation. By offering upfront price reductions, the technique reduces the unit cost of high-cost drugs without imposing additional reporting requirements.

Although it lacks adaptive mechanisms to manage clinical or utilization uncertainty, its straightforward implementation and predictable budgetary impact make it a pragmatic option for initial MEA negotiation or as a complementary mechanism alongside other performance-based agreements.

4.2.5.6 Real-world feasibility of the free initiation treatment technique compared with the utilization cap technique: a case of osimertinib

In the case of osimertinib, the free initiation treatment technique demonstrated the highest potential for cost savings, as it allows the pharmaceutical company to bear the cost of the initial treatment cycles. Under this agreement, the first ten treatment cycles of osimertinib are provided free of charge by the pharmaceutical company, after which the payer pays the full cost. This technique effectively shifts early-phase financial risk away from the payer, particularly during the period of highest treatment discontinuation.

However, the implementation of this technique remains challenging in practice. Pharmaceutical companies are often reluctant to provide full subsidies for ten treatment cycles, as this represents a substantial financial commitment. In real-world negotiations, pharmaceutical companies may seek to reduce the number of cycles they are required to subsidize, thereby diminishing the overall cost-saving potential for payers.

According to the findings of this study, the utilization cap technique—commonly implemented in Thailand through PAPs—resulted in approximately 37.20% savings on drug procurement costs for osimertinib. Under this agreement, payers cover drug costs only up to ten treatment cycles, after which the pharmaceutical company provides the drug free of charge for patients who continue to benefit.

To compare the cost-saving outcomes between these two techniques, cost-saving scenarios were calculated assuming different levels of pharmaceutical company-subsidized treatment cycles (ranging from one to ten free cycles). As presented in Table 4.20, if the pharmaceutical company provides fewer than six free treatment cycles of osimertinib, the resulting cost savings would be lower than those achieved under the utilization cap technique implemented through PAPs.

This finding suggests that, while the free initiation treatment technique offers the greatest theoretical cost-saving potential, its practical benefit depends heavily on the extent of pharmaceutical company participation. Negotiation outcomes that significantly reduce the number of free treatment cycles can decrease payer savings and make the utilization cap technique more favorable and sustainable in real-world settings.

Table 4.20 Incremental cost savings of osimertinib based on the number of free treatment cycles under MEA Implementation

MEA technique	Number of cycles	Paid condition	Drug cost per patient (USD)	Total drug cost (USD)	Total cost saving (USD)	Cost saving (%)
Free initiation treatment technique	1	Free-01	71,217.61	4,700,362.49	407,118.01	7.97
	2	Free-02	65,049.16	4,293,244.48	814,236.02	15.94
	3	Free-03	59,161.09	3,904,631.83	1,202,848.67	23.55
	4	Free-04	53,740.33	3,546,861.46	1,560,619.04	30.56
	5	Free-05	48,973.79	3,232,270.27	1,875,210.23	36.71
	6	**Free-06**	**44,487.64**	**2,936,184.44**	**2,171,296.06**	**42.51**
	7	Free-07	40,188.42	2,652,435.52	2,455,044.97	48.07
	8	Free-08	36,263.04	2,393,360.43	2,714,120.07	53.14
	9	Free-09	32,431.12	2,140,453.78	2,967,026.72	58.09
	10	Free-10	28,786.12	1,899,884.05	3,207,596.45	62.80
Utilization cap technique	1	Paid-01	6,168.45	407,118.01	4,700,362.49	92.03
	2	Paid-02	12,336.91	814,236.02	4,293,244.48	84.06
	3	Paid-03	18,224.98	1,202,848.67	3,904,631.83	76.45
	4	Paid-04	23,645.74	1,560,619.04	3,546,861.46	69.44
	5	Paid-05	28,412.28	1,875,210.23	3,232,270.27	63.29
	6	Paid-06	32,898.43	2,171,296.06	2,936,184.44	57.49
	7	Paid-07	37,197.65	2,455,044.97	2,652,435.52	51.93
	8	Paid-08	41,123.03	2,714,120.07	2,393,360.43	46.86
	9	Paid-09	44,954.95	2,967,026.72	2,140,453.78	41.91
	10	**Paid-10**	**48,599.95**	**3,207,596.45**	**1,899,884.05**	**37.20**

Table 4.21 Cost savings of MEA techniques according to the drug uncertainty characteristic

Scenario	MEA technique	Uncertainty: price		Uncertainty: effectiveness		Uncertainty: use	
		Cost saving (%)	Ranking[a]	Cost saving (%)	Ranking[a]	Cost saving (%)	Ranking[a]
1	Discount	30.00-50.00		30.00-50.00		50.00	
2	Free initiation treatment	62.80-72.43	2	**79.29-79.75**	**1**	59.87-61.35	3
3	Utilization cap	27.57-37.20	2	20.25-20.71	3	**38.65-40.13**	**1**
4	Conditional treatment continuation	52.90-53.68	3	42.86-58.23	2	**52.23-61.15**	**1**
5	Pay-by-result	15.70-26.10	2	**22.14-37.97**	**1**	12.10-22.49	3

[a] The ranking of cost-saving potential for each drug uncertainty characteristic by the MEA technique.

4.3 Limitations

This study has several limitations that should be acknowledged.

First, the analysis was based on data obtained from a single hospital setting, which may limit the representativeness of the findings to other healthcare settings. Differences in patient demographics, disease severity, and treatment patterns could affect both the treatment outcomes and the magnitude of drug procurement cost savings observed. Consequently, the external validity of these results may be limited, and caution should be exercised when extrapolating the findings to a broader national context. In addition, the relatively small sample size may influence the robustness of the cost-saving analysis. Including larger and more diverse patient populations from multiple hospitals would improve the reliability and accuracy of future estimations.

Second, this study evaluated only a limited number of MEA techniques, focusing specifically on five commonly implemented techniques. More complex techniques—such as hybrid MEAs or portfolio-based MEAs—were not analyzed. The omission of these techniques may lead to an underestimation of the potential cost-saving outcomes that could be achieved through more advanced or flexible contractual mechanisms. Consequently, the policy implications derived from this study may not fully capture the range of strategies available for national-level implementation.

4.4 Recommendations for policymakers

Findings from this study provide several implications for policymakers seeking to improve patient access to high-cost drugs while maintaining financial sustainability. Although the free initiation treatment technique resulted in the greatest cost-saving potential across most drug uncertainty characteristics—including price, effectiveness, and use—it is also among the most challenging to implement in practice. Pharmaceutical companies are often reluctant to adopt this technique beyond pilot or promotional programs, as it requires them to bear the full cost of early treatment cycles. In real-world settings, such agreements are typically limited to providing only the first dose or cycle free of charge (38, 54).

In contrast, the conditional treatment continuation technique demonstrated substantial cost-saving potential while maintaining a clear linkage between reimbursement and treatment outcomes. However, its implementation requires robust data infrastructure and consistent reporting by healthcare providers. The feasibility of routine data collection and monitoring must therefore be a key consideration in future MEA adoption (38, 51).

The discount technique, while producing only moderate cost savings, remains highly practical and widely applicable. It offers simplicity and administrative ease (42, 58)—attributes that make it particularly suitable for broad negotiation with pharmaceutical companies (38, 42). Similarly, the utilization cap technique, commonly used in Thailand through PAPs, provides predictable budget control but entails a considerable administrative burden for healthcare professionals due to the need for detailed utilization tracking and reporting (38, 42, 51).

Lastly, the pay-by-result technique, although conceptually attractive for linking payment to treatment outcomes, resulted in the lowest cost-saving potential in this study. This is primarily because the number of non-responders—who trigger reimbursement—tends to be small. Moreover, the extensive data monitoring required imposes significant operational challenges similar to those seen with the conditional treatment continuation techniques (38, 42, 51).

To translate the findings of this study into actionable recommendations for policymakers, several key implementation dimensions are proposed for Thailand's three main health insurance schemes: the CSMBS, the SSS, and the UCS.

4.4.1 Establishing a coordinated MEA governance mechanism

MEA implementation should be coordinated through a joint governance body comprising representatives from the NHSO, the CGD, and the Social Security Office (SSO), in collaboration with technical experts from the Health Intervention and Technology Assessment Program (HITAP) and the MOPH. This multi-stakeholder committee would be responsible for (a) selecting candidate drugs suitable for MEA, (b) negotiating with pharmaceutical companies, and (c) ensuring transparency and equity across health benefit schemes. Centralized negotiation through a shared mechanism would strengthen the government's bargaining power and prevent duplication of efforts (38).

4.4.2 Integrating MEA into the drug assessment timeline

MEA should be introduced before or during the HTA process—particularly for high-cost drugs with substantial uncertainty, such as anticancer drugs, biological products, or targeted therapies. Applying MEA in the pre-HTA or interim phase allows early patient access to drugs under controlled conditions (e.g., MEA in the technique of coverage with evidence development), while real-world data are continuously collected to support later full HTA appraisal (42).

4.4.3 Determining the appropriate MEA duration and renewal

The optimal duration of an MEA contract should be three to five years, or until sufficient real-world evidence is obtained to confirm clinical and economic value (48). Contract renewal should depend on updated outcome data and cost-effectiveness reassessments. This time-limited structure ensures accountability and enables adaptive decision-making based on evolving evidence (48).

4.4.4 Monitoring and evaluation framework

Policymakers should develop a national MEA monitoring framework integrated with hospital information systems. The framework should track (55):

- Clinical outcomes (treatment response, median PFS, adverse events)
- Utilization metrics (patient numbers, treatment cycles, discontinuation rates)
- Economic impact (drug expenditure, budget deviation, cost-sharing balance)
- Equity indicators (access gaps between schemes)

Periodic evaluations should be reported to a national MEA registry to promote transparency and knowledge sharing among all health benefit schemes.

4.4.5 Expected policy impact

If effectively implemented, MEAs can accelerate patient access to innovative therapies while limiting budgetary risks and enhancing value-based drug purchasing. Furthermore, integrating MEA outcomes into HTA decision-making could shorten the time lag between marketing authorization and public reimbursement. Ultimately, the alignment of MEA strategies across all three health benefit schemes would support system-wide equity, financial sustainability, and evidence-based policymaking in Thailand's pharmaceutical reimbursement framework.

CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

This study evaluated the financial implications of applying different MEA techniques to high-cost drugs in Thailand, specifically focusing on drug procurement cost savings. Six anticancer drugs—pertuzumab, osimertinib, afatinib, ceritinib, palbociclib, and ribociclib—were analyzed using real-world data to determine the cost-saving potential of five MEA techniques: free initiation treatment, conditional treatment continuation, discount, utilization cap, and pay-by-result.

The findings illustrate that the choice of the MEA technique has a significant impact on drug procurement cost savings. Among all MEA techniques analyzed, the free initiation treatment technique resulted in the highest cost savings across all drugs, with reductions ranging from 59.87% to 79.75%. This technique was particularly effective in scenarios with a high rate of early treatment discontinuation, as it shifted the cost burden of the initial treatment cycles to the pharmaceutical company, thereby reducing the financial risk for payers.

The conditional treatment continuation technique also showed strong performance in terms of drug procurement cost savings, ranking second across all drugs. This technique offered financial protection by linking payment to clinical outcomes; however, it required robust data collection systems and imposed administrative burdens on healthcare professionals.

The discount technique, while resulting in slightly lower drug procurement cost savings—ranking third across all drugs—proved to be the most practical and widely applicable in real-world settings. It was easy to apply, required minimal monitoring, and still achieved cost savings of 30 to 50%, making it particularly appropriate for national-level price negotiations and use within the public sector.

Conversely, the utilization cap and pay-by-result techniques generally resulted in lower drug procurement cost savings and imposed administrative burdens. Both required intensive tracking of patient-level drug utilization data. Despite their theoretical advantages in aligning payment with treatment outcomes, the real-world complexity limited the cost-saving potential of these techniques.

In conclusion, the findings from this study not only identify the appropriate MEA technique for each drug uncertainty characteristic but also highlight a 40% discount as a key figure for drug price negotiations.

5.2 Recommendations

5.2.1 Recommendations for policy implication

This study emphasizes the possible use of MEAs as a strategic policy mechanism to address delays in the inclusion of high-cost drugs in Thailand's NLEM. MEAs can balance early patient access with financial sustainability, particularly in the context of drugs with high clinical value but uncertainty in real-world effectiveness. To ensure coordinated and transparent implementation, a joint governance mechanism involving the NHSO, the SSO, and the CGD, with technical support from HITAP and the MOPH, should oversee MEA negotiations and evaluations.

MEAs should be integrated before or during the full HTA process, allowing conditional access while collecting real-world data to inform future reimbursement decisions. MEA should generally last three to five years, with renewal contingent upon updated clinical and economic outcomes. The national monitoring framework should also be established to track treatment outcomes, utilization patterns, and financial impact across the three health benefit schemes (CSMBS, SSS, and UCS).

In practice, the discount technique could serve as a baseline approach due to its simplicity and feasibility, while the free initiation treatment technique is suitable for drugs with high early discontinuation rates but requires robust monitoring systems. The utilization cap technique may offer limited cost-saving potential and should be reassessed for administrative efficiency.

In summary, this study provides an evidence-based framework for selecting MEA techniques that balance cost savings, feasibility, and administrative burden. Implementing these recommendations can enhance equitable access, improve negotiation efficiency, and strengthen value-based purchasing across Thailand's health benefit schemes, thereby promoting a more sustainable and evidence-informed pharmaceutical reimbursement system.

5.2.2 Recommendations for further studies

Regarding the limitations identified in this study, several directions for further studies are recommended.

First, further studies should aim to validate these findings using larger datasets derived from multiple hospitals across Thailand, which would enhance the representativeness and generalizability of results. Such multicenter analyses would allow for a more accurate estimation of cost-saving potential and improve the external validity of MEA evaluations.

Second, further studies should investigate additional MEA techniques, particularly hybrid and portfolio-based MEAs, to better capture the complexity of modern pricing negotiations for high-cost drugs. Hybrid MEAs combine elements of both financial-based agreements and performance-based agreements, allowing for flexible, stepwise agreements that address multiple aspects of drug uncertainty. For example, in the case of palbociclib, a hybrid MEA was implemented in which the first treatment cycle was provided free of charge, the second to tenth cycles followed a “buy two, get one free” program, and subsequent cycles were supplied entirely free. Such blended mechanisms may offer enhanced potential for cost containment while maintaining drug access.

Portfolio MEAs, on the other hand, involve agreements that span multiple drugs or indications within a company’s portfolio rather than focusing on a single drug. A notable example is ribociclib, where the pharmaceutical company offered a 50% discount on another drug, nilotinib, and the resulting savings were redirected to purchase ribociclib, also at a 50% discounted price. This technique enables more complex, high-level negotiations and may optimize overall resource allocation.

Comparative analyses of hybrid and portfolio MEAs in future research could provide valuable insights into their effectiveness in reducing costs, their administrative feasibility, and their acceptability among stakeholders, ultimately informing policy decisions and pricing strategies for high-cost innovative drugs.

Third, further studies should incorporate a detailed assessment of administrative and operational costs associated with implementing and monitoring different MEA techniques. Quantifying these transaction costs would allow policymakers to evaluate the net economic benefit of each technique and identify the most feasible technique for large-scale adoption within Thailand's healthcare system.

Finally, further studies should focus on the long-term impact of MEA implementation on patient outcomes, healthcare budgets, and system sustainability. Establishing real-world evidence networks and national MEA registries could enable continuous learning, policy refinement, and adaptive contracting based on accumulated experience.

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Publications

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