Cost-utility analysis of Immuno-Oncotherapy in chemotherapy-pretreated, recurrent, non-small cell lung cancer in Thailand.

Sarayut Lucien Geater

A Thesis Submitted in Fulfillment of the Requirements for the
Degree of Doctor of Philosophy in Health Sciences
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I hereby certify that this work has not been accepted in substance for any degree, and is not being currently submitted in candidature for any degree.

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ชื่อวิทยานิพนธ์ การศึกษาต้นทุนอรรถประโยชน์ ยาภูมิคุ้มกันมะเร็งในผู้ป่วยมะเร็งปอดชนิดเซลล์

ไม่เล็กที่กลับเป็นซ้ำหลังจากได้รับการรักษาด้วยยาเคมีบำบัดในประเทศไทย

ผู้เขียน นาย ศรายุทธ ลูเซียน กีเตอร์

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บทคัดย่อ

บทนำ

มะเร็งปอด เป็นมะเร็งที่พบบ่อยอันดับหนึ่งในชาย และ อันดับสี่ในหญิง แม้ว่าจะมีการรักษาใหม่ที่มีประสิทธิภาพสูงออกสู่ท้องตลอด แต่ผู้ป่วยส่วนใหญ่ไม่สามารถเข้าถึงการรักษาดังกล่าวได้ อุปสรรคที่สำคัญที่สุดของการเข้าถึงยาคือราคาค่ารักษา ซึ่งค่ารักษาดังกล่าวสามารถทำให้เกิดปัญหาทางการเงินได้ ไม่เฉพาะกับผู้ป่วยแต่รวมถึงครอบครัว และแม้กระทั่งระบบของสาธารณสุขของประเทศซึ่งอยู่ในระดับรายได้ต่ำถึงปานกลาง ก็สามารถจะได้รับผลกระทบจากราคานี้เช่นกัน การศึกษานี้มีเป้าประสงค์ 1- ศึกษาความคุ้มค่าของการรักษาด้วยยากลุ่มปรับภูมิคุ้มกันมะเร็งในผู้ป่วยมะเร็งปอด ชนิดเซลล์ไม่เล็กในประเทศไทย และ 2- ประเมินผลกระทบทางการเงินของผู้ป่วยมะเร็งปอด ในประเทศไทย

วิธีการศึกษา

การประเมินความคุ้มค่าทางเศรษฐศาสตร์ อาศัยข้อมูลทางคลินิก จากผลการศึกษาที่ได้รับการเผยแพร่แล้ว และข้อมูลด้านต้นทุน และอรรถประโยชน์จากการสัมภาษณ์แบบสอบถามแบบ ตัวต่อตัว การคำนวณความคุ้มค่า ของต้นทุนอรรถประโยชน์สำหรับยากลุ่มปรับภูมิคุ้มกันมะเร็ง เทียบกับยา โดซิเทคเซล ใช้อัตราการรอดชีพแบบแบ่งส่วน และ ตัวแบบมาร์คอฟ ผลกระทบทางการเงินประเมินจากข้อมูลที่ได้จากการแบบสอบถาม แบบการศึกษาแบบตัดขวาง

ผลการศึกษา

การรักษาด้วย ยากลุ่มปรับภูมิคุ้มกันมะเร็ง ช่วยเพิ่มอัตราการรอดชีวิต 0.55 ถึง 0.81 ปีชีวิต ค่าใช้จ่ายที่เพิ่มขึ้นของการรักษาด้วย ยากลุ่มปรับภูมิคุ้มกันมะเร็ง อยู่ที่ 18683 ดอลลาร์สหรัฐฯ สำหรับ อธิโซลิซูแมบ ถึง 69723 ดอลลาร์สหรัฐฯ สำหรับ เพมโบรลิซูแมบ การรักษายากลุ่มปรับภูมิคุ้มกันมะเร็ง เพิ่ม ปีสุขภาวะ ประมาณ 0.43-0.62   ต้นทุนอรรถประโยชน์ต่อปีสุขภาวะสำหรับ นิโวลูแมบ เพมโบรลิซูแมบ และ อธิโซลิซูแมบ เท่ากับ 84957 ดอลลาร์สหรัฐฯ 115365 ดอลลาร์สหรัฐฯ และ 30003 ดอลลาร์สหรัฐฯ ตามลำดับ ประมาณร้อยละ 66 ของผู้ป่วยที่เป็นมะเร็งปอดประสบปัญหาค่าใช้จ่ายด้านสุขภาพ และ ร้อยละ 29 ของผู้ป่วยมีความยากจนทางการแพทย์

สรุปผลการศึกษา

        การรักษาด้วย ยากลุ่มปรับภูมิคุ้มกันมะเร็ง ช่วยให้รอดชีวิตได้ดีขึ้นและ ปีสุขภาวะ แต่มีค่าใช้จ่ายสูงกว่า อธิโซลิซูแมบ เป็นสูตรที่ได้รับความคุ้มค่ามากที่สุดเมื่อเทียบกับ ยากลุ่มปรับภูมิคุ้มกันมะเร็ง อีกสองตัว อย่างไรก็ตาม ต้นทุนอรรถประโยชน์ต่อปีสุขภาวะสำหรับ อธิโซลิซูแมบ นั้นสูงกว่าเกณฑ์การยอมรับความคุ้มค่าด้านต้นทุนของประเทศไทยที่ 5208 ดอลลาร์สหรัฐฯ ผู้ป่วยมะเร็งปอดในประเทศไทยสัดส่วนที่มีนัยสำคัญประสบภาวะพิษทางการเงิน

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ABSTRACT

Introduction

Lung cancer is the most common cancer in males and the fourth most common in females. Although there are many novel effective treatments available on the market, patients are mainly unable to access them. The biggest barrier factor is the cost of treatment which may cause financial toxicity to the patients, family, or even to the healthcare system, especially in low or middle-income countries. This study aims to (1) evaluate the cost-effectiveness of applying immune checkpoint inhibitors (ICI) in second-line non-small cell lung cancer in Thailand., and (2) evaluate the financial toxicity among lung cancer patients in Thailand.

Materials and Methods

Economics evaluation using clinical input from published clinical trials data together with the cost and utility information from face-to-face questionnaire interviews. The incremental cost-effectiveness of ICI compared with docetaxel was computed using partition survival and the Markov model. Financial toxicity evaluation using data from the questionnaires in the cross-sectional design.

Results

The ICI treatment improved survival by 0.55 to 0.81 life years. The incremental cost of ICI treatment ranged from USD 18,683 for atezolizumab to USD 69,723 for pembrolizumab. The ICI treatment improves QALY of about 0.43-0.62. The ICER for nivolumab, pembrolizumab, and atezolizumab were USD 84,957, USD 115,365, and USD 30,003, respectively. About 66% of the patients with lung cancer experience catastrophic health expenditure (CHE) and 29% of the patients develop medical impoverishment.

Conclusion

The ICI treatment provided better survival and QALY but was more costly. Atezolizumab was the most favored regimen compared with the other two ICI. However, the ICER for atezolizumab was higher than Thailand's cost-effectiveness acceptability threshold of USD 5,208. A significant proportion of lung cancer patients in Thailand experienced financial toxicity.

ACKNOWLEDGEMENT

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LIST OF ABBREVIATIONS

cAnemia – cost of treatment for ≥ Gr 3 anemia

cBasiclab – cost of safety lab

cPneumonia – cost of treatment for ≥ Gr 3 pneumonia

cFN – cost of treatment for ≥ Gr 3 febrile neutropenia

cNausea – cost of treatment for ≥ Gr 3 nausea

cInfect – cost of treatment for ≥ Gr3 infection

cHypoNa – cost of treatment for ≥ Gr3 hyponatremia

cDoc – cost for docetaxel

cNivo – cost for nivolumab

cPembro – cost for pembrolizumab

cAtezeo – cost for atezolizumab

cAddlab_io – additional safety lab for ICI

c_PD_doc – cost of docetaxel treatment beyond disease progression

c_PD_gem – cost of gemcitabine treatment beyond disease progression

doc_os_con – _cons parameter for docetaxel OS

doc_os_shape – shape parameter for docetaxel OS

doc_pfs_con – _cons parameter for docetaxel PFS

doc_pfs_shape – shape parameter for docetaxel PFS

atezo_os_con – _cons parameter for atezolizumab OS

atezo_os_shape – shape parameter for atezolizumab OS

atezo_pfs_con – _cons parameter for atezolizumab PFS

atezo_pfs_shape – shape parameter for atezolizumab PFS

nivo_os_con – _cons parameter for nivolumab OS

nivo_os_shape – shape parameter for nivolumab OS

nivo_pfs_con – _cons parameter for nivolumab PFS

nivo_pfs_shape – shape parameter for nivolumab PFS

pembro_os_con – _cons parameter for pembrolizumab OS

pembro_os_shape – _cons parameter for pembrolizumab OS

pembro_pfs_con – _cons parameter for pembrolizumab PFS

pembro_pfs_shape – _cons parameter for pembrolizumab PFS

uPFS – utility of PFS stage

uPD – utility of PD stage

wt – weight

QALY – quality-adjusted life year

OS – overall survival

PFS – progression-free survival

AIC – Akaike information criterion

BIC – Bayesian information criterion

LL – log logistic

LN – log normal

PH2 – flexible parametric survival with proportional hazard with 2 degrees of freedom

PH3 – flexible parametric survival with proportional hazard with 3 degrees of freedom

PH4 – flexible parametric survival with proportional hazard with 4 degrees of freedom

PO2 – flexible parametric survival with proportional odd with 2 degrees of freedom

PO3 – flexible parametric survival with proportional odd with 3 degrees of freedom

PO4 – flexible parametric survival with proportional odd with 4 degrees of freedom

Probit2 – flexible parametric survival with probit with 2 degrees of freedom

Probit3 – flexible parametric survival with probit with 3 degrees of freedom

Probit4 – flexible parametric survival with probit with 4 degrees of freedom

MOPH – Ministry of Public Health

UCS – Universal Coverage scheme

CSMBS – Civil Servant Medical Benefit Scheme

SSS- Social Security Scheme

CHE – Catastrophic Health Expenditure

WHO – World Health Organization

OOP – out of pocket

DMSIC – Drug and Medical Supply Information Center

FES_h – food expenditure share for household

FE_h – food expenditure of household

TE_h – total expenditure of household

HES – household equivalent size

HS – household size

EFE_h – equivalent food expenditure of household

PL – poverty line

SE_h – Subsistence expenditure of household

$ctpay_h$ – household's capacity to pay

Chapter 1

Introduction

Background and Rationale

In Thailand, lung cancer is the most common type of cancer that results in mortality. The age-standardized incidence rates are 22.7 per 100,000 for males and 10.1 per 100,000 for females yearly.[1,2] Numerous pathological subtypes of lung cancer can be roughly classified as either small-cell lung cancer or non-small cell lung cancer (NSCLC). Patients with NSCLC typically present with advanced disease at the time of diagnosis (i.e., distant spread, malignant effusion, or bilateral lung disease). Chemotherapy was a standard treatment option for advanced NSCLC in the past. Identifying driver mutations in tumors have led to modifications in the treatment of certain advanced NSCLCs over the past few years. Patients who have mutations in the epidermal growth factor receptor (EGFR) kinase area and anaplastic lymphoma kinase (ALK) are now generally given tyrosine kinase inhibitors (TKIs) as first-line therapy. This is the standard of care. More recently, an immunotherapy that focuses on modifying checkpoint inhibition using the programmed death 1 (PD-1) receptor or its ligand (PD-L1) has shown to be beneficial in at least some patients with non-small cell lung cancer (NSCLC).

Although chemotherapy can extend survival in people with advanced NSCLC, it is not curative in individuals with advanced illness, and many patients may not be able to tolerate the side effects of the most effective regimens. These intense chemotherapy regimens are often chemotherapy doublets based on platinum (cisplatin and paclitaxel, carboplatin and gemcitabine, etc.), and they are still indicated as first-line therapy for patients with advanced NSCLC who do not have a driver mutation. Major guidelines, such as those from the National Comprehensive Cancer Network (NCCN), list tyrosine kinase inhibitors (also known as TKIs) as first-line therapy for non-small cell lung cancer

(NSCLC) patients who have driven mutations (also known as EGFR+ NSCLC or ALK+ NSCLC).[3]

The production of chemicals by tumor cells that change the immune response to the tumor, such as by changing a regulatory "checkpoint" or brake on the T-cell response to the tumor, enables cancer to circumvent the body's natural defenses and spread. Immunotherapy that targets the PD-1 receptor or its ligand, PD-L1, and attempts to suppress such a checkpoint has been shown to be beneficial in at least some patients with non-small cell lung cancer (NSCLC).[4] Atezolizumab is an antibody that targets PD-L1, and nivolumab and pembrolizumab are antibodies that target PD-1. Nivolumab and pembrolizumab are also focusing on this pathway as potential cancer treatments. In this particular investigation, the terms "PD-1 Checkpoint inhibitor" and "antibody" were used interchangeably to refer to both groups.

In Thailand, patients who the government employed were the only ones eligible for reimbursement of the cost of immune checkpoint inhibitors (ICI) when they were used in a second-line scenario (Civil Servant Medical Benefit Scheme). However, there are still many unanswered questions concerning the most appropriate way to adapt treatment with these more recent drugs, the function of particular tests in informing decisions regarding treatment, and the management of the expenses associated with these therapies. In addition, there are limitations in evidence of the financial burden for the patients with lung cancer treatment in Thailand.

Review of literature

Immunotherapy in non-small cell lung cancer

In normal circumstances, the immune checkpoint is responsible for regulating the excessive inflammatory response; nevertheless, in some cases, cancer depends on such mechanisms in order to evade the immune cells of the body. Preventing the body from being able to eliminate cancer cells from its system. Mechanisms for immune checkpoints that already have clinical data include anticytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1). PD-1 is an inhibitory receptor in T cells that can be matched with PD-L1 or PD-L2, where the results of these pairings inhibit T cell activity. CTLA-4 is an antigen that blocks the activity of cytotoxic T-lymphocytes, and PD-1 is a protein that blocks the activity. Numerous kinds of cancer, including lung cancer, have been shown to have detectable levels of the protein PD-1.

Early-phase clinical trials

Nivolumab, a completely human immunoglobulin G4 monoclonal antibody, is the subject of the research being conducted as part of the CheckMate 003 trial.[5] Nivolumab was administered at a dose ranging from 1 to 10 mg/kg every two weeks to a total of 296 volunteers, including 122 patients with non-small cell lung cancer. The study lasted for a total of 12 cycles. The symptoms of weariness (24 percent), diarrhea (11 percent), and rash (12 percent) were found to be the most common, although only 14 percent of patients experienced grades 3 to 4 adverse reactions. Some of the adverse effects of immunity, known as immune-related toxicity, include pneumonia (which affects 3 percent of patients), hypothyroidism (which affects 2 percent), and infusion-related allergies (3 percent). The objective response rate was 17 percent. The vast majority of them exhibited a prolonged response period. Most patients in the non-small cell lung cancer subgroups had previously been treated with at least three different regimens before receiving nivolumab every two weeks for a maximum of 96 weeks. Patients who were given an intravenous infusion of nivolumab at a dose of 3 mg/kg experienced a response that lasted for a median

of 17 months. Fatigue, pneumonitis, and diarrhea were the most often experienced adverse effects.[6]

KEYNOTE 001 This is a study of pembrolizumab, which is a humanized immunoglobulin G4 monoclonal antibody that has efficacy against the PD-1 receptor in non-small cell lung cancer patients. KEYNOTE 001 was conducted on 495 patients with non-small cell lung cancer. Pembrolizumab was administered at a dosage of 2 or 10 mg/kg once every three weeks or at a dosage of 10 mg/kg once every two weeks. Fatigue (19%), itching (11%), and anorexia are among the most often experienced adverse effects (11 percent). Ten percent of the study's patients reported experiencing side effects in grades 3–4. Some of the adverse consequences of immunity include pneumonia (four percent), hypothyroidism (seven percent), and infusion allergy (one percent) (3 percent). Nineteen percent of people responded to the survey objectively. At the end of the year, 84% of the respondents were still active.[7]

Atezolizumab is a humanized monoclonal antibody that contains anti-PD-L1 receptor activity. It is an immunoglobulin G4 monoclonal antibody. In the phase I research, which included 88 participants, the most prevalent adverse effects were described as fatigue (21%), nausea (15%), and anorexia (13%). (14 percent). The rate of response is determined by the expression of PD-L1 in cancer cells as well as in immune cells.[8] Atezolizumab demonstrated a response rate of 17 percent in the phase II BIRCH research, which was conducted on patients with pretreated non-small cell lung cancer who also expressed the PD-L1 protein.[9,10]

The comparative of ICI in second-line NSCLC, phase 3 studies show in Table 1.

Table 1. Phase 3 studies of ICI in second-line treatment of NSCLC.

Factor	Drug		Pembrolizumab[13]	Atezolizumab[14]
	Nivolumab[11,12]			
Mechanism of action	IgG fully human antibody		IgG humanized antibody	IgG humanized antibody
Target	PD-1		PD-1	PD-L1
Phase 3 study	CheckMate 017	CheckMate 057	KEYNOTE 010	OAK
Histology	Squamous	Non-squamous	NSCLC	NSCLC
PD-L1 testing	Retrospective	Retrospective	PD-L1 $\geq$ 1%	Need to have the (any) result of PD-L1 testing before randomization
Control arm	Docetaxel	Docetaxel	Docetaxel	Docetaxel

Nivolumab is a humanized IgG4 monoclonal antibody against PD-1. It is a medicine that has been approved for use in non-small cell lung cancer patients who have already been treated with platinum chemotherapy. Patients who have squamous non-small cell lung cancer are participating in the CheckMate 017 research, which compares the effects of receiving intravenous nivolumab 3 mg/kg every two weeks to receiving docetaxel 75 mg/m^2 intravenous every three weeks. The group that received nivolumab had a median survival time of 9.2 months, while the group that received docetaxel only had 6.0 months (HR 0.59, 95% CI 0.44-0.79). In the nivolumab treatment arm, the median progression-free survival was 3.5 months, whereas, in the docetaxel treatment arm, it was 2.8 months (HR 0.62, 95% CI 0.47-0.81). The objective response rate was significantly higher in the group that was given nivolumab, which was 20%, than in the group that was given docetaxel, which was only 9% (p = 0.008). In this particular investigation, the level of PD-L1 expression did not have any bearing on the prognostic or predictive outcomes.

It was shown that Nivolumab was related to a variety of frequently occurring side effects, the most common of which were fatigue (16%), anorexia (11%), and asthenia (10%). There were no adverse effects that were either more severe than or on par with those that were recorded in grade 3.[11] In addition to that, the nivolumab package also includes

data from the CheckMate 057 study. In this trial, patients with non-squamous, non-small cell lung cancer were given either intravenous nivolumab 3 mg/kg every two weeks or docetaxel 75 mg/m^2 intravenous every three weeks. Both treatments were given through the same vein. It has been discovered that treatment with platinum chemotherapy can increase median survival. The duration of the dose was 12.2 months in the group that was given nivolumab, while it was only 9.4 months in the group that was given docetaxel (HR 0.73, 95 percent CI 0.59-0.89). In contrast to progression-free survival, there is a trend that the group receiving docetaxel (4.2 months) will have longer progression-free survival than those who got nivolumab (2.3 months), but this difference is not statistically significant (p = 0.39). Even though the group that received nivolumab had a higher survival rate than the group that received docetaxel, regardless of the level of PD-L1 expression (greater than or equal to 1 percent, greater than or equal to 5 percent, or greater than or equal to 10 percent), the benefits of nivolumab increased as the expression of PD-L1 increased. The proportion of patients who experienced the adverse effect was 69 in the nivolumab arm and 88 in the docetaxel arm, respectively. Those who take nivolumab often have a variety of unpleasant side effects, including fatigue (16 percent), nausea (12 percent), and anorexia (10 percent).[12]

Pembrolizumab 2 mg/kg (Pem2) or 10 mg/kg (Pem10) intravenous treatment for non-small cell lung cancer patients with PD-L1 expression in at least 1 percent of their cancer is being evaluated in the KEYNOTE 010 study. This treatment will be compared to docetaxel 75 mg/m^2 (Doc) intravenous treatment given every three weeks. Patients in the study will have received at least one prior treatment and will In the group that was given the medication, the median lengths of survival were 10.4, 12.7, and 8.5 months. (HR 0.71, 95% CI 0.58-0.88 in pembrolizumab group 2 mg/kg, 10 mg/kg compared with docetaxel and HR 0.61, 95% CI 0.49-0.75 in the pembrolizumab group 10 mg/kg vs. Docetaxel) On the other hand, there was no discernible difference in progression-free survival between the pembrolizumab and docetaxel treatments administered to the groups. Pembrolizumab 2 mg/kg and pembrolizumab 10 mg/kg gave better progression-free survival compared to

docetaxel (HR 0.54, 95% CI 0.38-0.77 and HR 0.50, 95% CI 0.36-0.70, respectively), and in the analysis of such subgroups, it was found that the median progression-free survivals were 5.0, 5.2, and 4.1 months in the pembrolizumab 2 mg/kg, 10 mg/kg and docetaxel, respectively.[13]

Patients with non-small cell lung cancer who have been treated with platinum chemotherapy and were randomly assigned intravenous atezolizumab 1200 mg every three weeks compared to docetaxel 75 mg/m^2 every three weeks are the subjects of the OAK study, which is a Phase 3 clinical research investigation. In the group that received atezolizumab, the median survival was 13.3 months, while in the group that received docetaxel, the median survival was 9.8 months (HR 0.80, 95% CI 0.70-0.92). However, there was no difference in terms of progression-free survival between the two groups (HR 0.96, 95% CI 0.85-1.08). When PD-L1 expression was factored into the studies, it was found that the disparity in benefits between progression-free survival and overall survival grew as the level of PD-L1 expression rose.[14]

As indicated in Table 2, treatment with immune checkpoint inhibitors improved overall survival, progression-free survival, and safety profiles in both squamous cell carcinoma and non-squamous cell carcinoma. Although the level of PD-L1 correlates with the likelihood of therapeutic response, the clinical utility of PD-L1 is unclear in selecting an immune checkpoint group for second-line cancer therapy.

Table 2. The percentage of side effects of an immune checkpoint inhibitor in second-line NSCLC.

Side effect	Percent								
	Nivolumab[11,12]				Pembrolizumab[13]			Arezolizumab[14]	
	CheckMate 017		CheckMate 057		KEYNOTE 010			OAK	
	Nivo	Doc	Nivo	Doc	Pembro 2	Pembro 10	Doc	Atezo	Doc
All grade	58	86	69	88	63	66	81	64	86
≥ grade 3	7	57	10	54	13	16	35	15	43
Leading to drop out	3	10	5	15	4	5	10	8	19
Pneumonitis	5		3		5	4		1	
Hepatitis	2		<1		<1	1		0.3	
Colitis	1		1		1	<1		0.3	

In each of the studies, a unique approach was taken to analyze the PD-L1 expression. In the investigation of pembrolizumab, nivolumab, and avelumab, respectively, antibody detection kits 22C3, 28-8, and 7810 were obtained, and these kits are included in the test kit manufactured by Dako Corporation (Dako Corporation, Glostrup, Denmark). Antibody SP142 and SP263 kits were used in the research on atezolizumab and durvalumab, respectively, as part of the PD-L1 test that is offered by Ventana (Ventana Medical System).

Several experiments demonstrated that the outcomes were comparable when using techniques 28-8, 22C3, and SP263. However, SP142 produced significantly less expression than the other approaches. Alternately, one may say that SP142 has a lesser sensitivity to identify PD-L1 but a greater specificity when compared to other testing methods.[15] Nivolumab, atezolizumab, and pembrolizumab are the three immune checkpoint inhibitors (ICI) that have been approved for the treatment of non-small cell lung cancer (NSCLC). Only pembrolizumab was approved for patients who have PD-L1 expression of more than or equal to 1%.

A minority of patients respond to ICI, but the majority of those who do tend to have sustained responses and increased survival. Expression of PD-L1 on tumors appears to be useful in choosing patients for PD-1-based therapy; nevertheless, there are questions about the comparability of different methodologies used to quantify expression levels. Pembrolizumab is indicated by the FDA for patients whose tumors express PD-L1. While nivolumab does not have this restriction, response rates are higher in tumors expressing PD-L1 when nivolumab is administered.[4,16] Nonetheless, some cancers that do not express PD-L1 can be treated with PD-1 immunotherapy. Consequently, a significant question is whether solely treating patients based on PD-L1 expression might result in a percentage of patients missing an opportunity for therapy. In addition, a subset of patients has tissue that cannot be evaluated for PD-L1 using the currently available tests.[11–13]

Pembrolizumab is taken every three weeks, while atezolizumab may be approved with a dosing schedule every three weeks; nivolumab is administered every two weeks. As mentioned in Table 3, all drugs are administered intravenously until the disease progresses. In addition to fatigue, these agents have been associated with more severe immune-mediated conditions, such as pneumonitis and encephalitis. These immunological responses are infrequent, and overall, PD-1 immunotherapy is associated with significantly fewer major adverse events than docetaxel.

Table 3. ICI administration details.

Drug	Administration	Dose	Rx Duration
Nivolumab	IV infusion	3 mg/kg over 60 minutes q 2 weeks	Until progressive disease or intolerant toxicity
Pembrolizumab	IV infusion	200 mg over 30 minutes q 3 weeks	Until progressive disease or intolerant toxicity
Atezolizumab	IV infusion	1200 mg over 30 minutes q 3 weeks	Until progressive disease or intolerant toxicity

In the early stages of ICI development, the majority of patients evaluated in ICI trials have received prior treatment with a chemotherapeutic doublet, regardless of whether they were EGFR+ and/or had received prior TKI therapy.[12–14] The majority of health authorities recommend utilizing ICI solely in EGFR-negative and ALK-negative patients nowadays. In this situation, a single-agent chemotherapy regimen with a drug that was not included in the initial doublet, such as docetaxel, would be the alternate treatment.

Definitions

In order to assist with the interpretation of the study results that are presented throughout this thesis, the researcher has provided the following definitions.

Response Criteria

It is important to note that response assessment criteria in solid tumors (RECIST) version 1.0 criteria were commonly utilized in clinical trials before 2009[17], and RECIST version 1.1 criteria were typically used in clinical trials after 2009.[18] The criteria that follow mirror version 1.1; in the vast majority of patients with advanced NSCLC, there is a high degree of concordance between the two versions in determining how well response measures are assessed.[19]

- *Progressive disease:* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on the study (this includes the baseline sum if that is the smallest on the study); in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm or unequivocal progression of existing non-target lesions or the appearance of one or more new lesions.
- *Stable disease:* Between progressive disease and partial response.
- *Partial response:* At least a 30% decrease in the sum of the diameters of target lesions and not meeting criteria for progressive disease or complete response.

- *Complete response:* Disappearance of all target and non-target lesions and normalization of tumor marker levels. Any pathologic lymph nodes (whether target or non-target) must have a reduction in the short axis to <10 mm.

Eastern Cooperative Oncology Group (ECOG) performance status

A 6-point scale that measures functional status and the ability to perform activities of daily living:

0- Fully active

1- Restricted only in strenuous activity

2- Ambulatory and capable of self-care but unable to work

3- Capable of limited self-care, confined to bed or chair >50% of waking hours

4- Totally disabled

5- Dead

Advanced disease

Advanced disease: lung cancer in stages IIIB, IIIC, or IV according to the American Joint Committee on Cancer Staging TNM staging system (editions 7 or 8).[20,21]

Stage IIIB: Cancer is present in the lung and lymph nodes (on the opposite side of the chest from the affected lung or near the collarbone or supraclavicular area), in different lobes of the same lung, or in structures surrounding the lung (i.e., the mediastinum, heart, aorta, trachea, esophagus, backbone, or carina combine with at least mediastinal node involvement).

Stage IIIC: Cancer is present on the opposite side of the primary tumor, or the longest diameter is greater than 5 centimeters, in conjunction with contralateral mediastinal lymph node or supraclavicular node involvement.

Stage IV: Cancer has spread to both lungs, to the fluid surrounding the lungs or heart, or to another organ, such as the brain, bones, liver, or adrenal glands.

Problems Arise from the Clinical Practice

Patients may not receive the same level of care in rural or low-income community clinics as they would in major medical centers. Some patients do not receive molecular testing (or are not informed of the results of such testing) and are administered chemotherapy without regard to their individual disease's clinical characteristics. Those who live far from major treatment centers and lack the financial means to travel are unable to access innovative and emerging therapies. These patients may be less likely to receive adequate support, participate in clinical trials in which new treatments may be available, or receive education regarding their diagnosis, prognosis, and treatment options.

Multiple patients have brought up the issue of the "financial toxicity" of lung cancer treatment. This refers to the fact that patients and their families run a high risk of experiencing severe financial hardship or even filing for bankruptcy if they or their families require treatment that is in excess of the basic treatment package provided by the Universal Coverage Scheme (UCS). The financial toxicity of cancer includes the cost of medications, their administration, travel to receive treatments and other care, missed work, and even the need to purchase new clothing due to weight loss. All of these costs add up. Treatment costs are expected to rise over time because patients are living longer. Lung cancer now disproportionately affects patients who have fewer resources to combat the illness as a result of the declining prevalence of smoking among patients with higher socioeconomic status. Some of these patients have reached the point where they have accepted their impending demise and have stopped seeking treatment.

It is possible that patients participating in clinical trials, which in most cases are given significant resources by the trial and are not required to pay for their medications, do not exhibit distress levels comparable to those of patients treated outside of clinical trials.

Not only for the patient's own clinical benefit but also to minimize the patient's financial burden, the NCCN guideline[3] suggested participating in clinical trials whenever possible. This was not only for the patient's clinical benefit. It is possible that patients

taking part in clinical trials, which in most scenarios are given significant resources by the trial and are not required to pay for their medications, do not exhibit distress levels comparable to those of patients treated outside of clinical trials. This is because patients taking part in clinical trials are given significant resources by the trial.

Summary of Health Coverage Policies and Local Treatment Guidelines

Since 2002, the country of Thailand has been governed by the Universal Coverage Scheme (UCS) Act, which mandates that all Thai nationals who do not receive coverage from another source must enroll in the UCS. The purpose of this initiative is to improve the standard of living, health security, equity, and access to medical treatment for all individuals.[22]

Nevertheless, Thailand makes use of three basic payment systems. To begin, the Civil Servant Medical Benefit Scheme (CSMBS) is responsible for paying healthcare facilities on a fee-for-service basis for the treatment of government officers and the officers' dependents. The Universal Coverage Scheme provides protection for the vast majority of the people living in Thailand (UCS). Workers in the private sector who are of working age are eligible for coverage under the Social Security Scheme (SSS). The broader health insurance system can be broken down into these component parts.

Patients in Thailand can be grouped into three distinct categories according to the country's various payment systems. Patients in the CSMBS group, which consists of government employees and their parents and numbers between 4.4 and 4.5 million, have access to the new standard treatments thanks to the well-established Oncology Prior Authorization Program (OCPA), even though the regimens are not on the Thai National Drug list. Patients in the CSMBS group have access to the new standard treatments. The CSMBS payment system that are used for outpatient charges includes fee-for-service and diagnostic-related groups, each of which can have various cost bands. Patients who fall within the UCS group, which is the largest group and comprises between 48 and 60 million people, are only qualified for reimbursement for the regimens and treatments that are

included on the National Drug List. In the event that this is not the case, they are accountable for payment (out-of-pocket, OOP). Patients in the UCS receive reimbursement for outpatient costs and diagnostic-related groups (DRG) based on a capitation system together with the global budget caption, as well as a flexible timetable for some high-cost treatments for inpatient expenditures. Patients who fall into the SSS group are on average younger than patients who fall into the CSMBS and UCS groups. Patients in the SSS group work mainly for private companies and number between 8.2 and 10.6 million. Patients who fall under this category have access to very similar therapy options as patients who fall into the UCS category. The SSS group uses capitation as a method for determining the amount of money that will be reimbursed to in-patients and diagnostic-related groups (DRG). Out-patients, on the other hand, are subject to a global budget.[22,23]

Thai-FDA has approved docetaxel, pemetrexed, nivolumab, pembrolizumab, and atezolizumab for second-line lung cancer treatment regimens, but only docetaxel can be reimbursed in all reimbursed schemes (UCS, CSMBS, and SSS). Pemetrexed can only be reimbursed for CSMBS in the case of docetaxel intolerance. Atezolizumab is the only ICI that is reimbursable for CSMBS under the OCPA pre-authorization program. Both nivolumab and pembrolizumab are not reimbursable for every Thai patient.

Narrative Review

To inform this analysis of the comparative clinical effectiveness of ICI treatment, nivolumab, pembrolizumab, and atezolizumab, in the treatment of advanced, second-line NSCLC, we extracted data from published, unpublished, and abstract clinical studies of these agents. Comparators of interest included ICI and chemotherapy, as described in the Background section, for the second-line treatment of NSCLC. The focus of the review was on clinical benefits (i.e., overall and progression-free survival, biochemical response, and health-related quality of life) and potential harms (drug-related adverse events). We focused on both descriptive and quantitative analyses of these outcomes, including both direct and indirect comparisons between the newer regimens.

Study selection

To inform this analysis of the comparative clinical effectiveness of ICI treatment in the treatment of advanced, second-line NSCLC, we extracted data from published, unpublished, and abstract clinical studies of these agents. Comparators of interest included chemotherapy, docetaxel, for the second-line treatment of NSCLC. The review included evidence from randomized controlled trials (RCTs), comparative observational studies, and high-quality systematic reviews were available and excluded single-arm studies, studies without an active control arm, studies with combined ICI and chemotherapy, and studies from the earliest phases of clinical development (i.e., phase I). The focus of the review was on clinical benefits (i.e., overall and progression-free survival, biochemical response, and health-related quality of life) and potential harms (treatment-related adverse events, TRAE). The researchers focused on both descriptive and quantitative analyses of these outcomes, including both direct and indirect comparisons between the newer regimens.

Our search was limited to PubMed articles published between January 1996 and December 13, 2022. We restricted each search to studies of human subjects and excluded guidelines, letters, editorials, narrative reviews, case reports, and news articles.

Our search identified about 3,000 potentially relevant references of which 44 met our inclusion criteria; these citations pertained to 17 individual studies and seven systematic reviews. Use of an FDA-unapproved combination regimen, comparison to a treatment that does not reflect current best practice (e.g., single-agent docetaxel in treatment-naive EGFR+ patients), study population outside of our scope, and non-comparative study design were the primary reasons for study exclusion. We discovered 36 references that met the inclusion/exclusion criteria. The included studies are described in detail study-inclusion flow diagram below (Figure 1).

```
┌─────────────────────────────┐
│  3000 -relevant articles    │
└─────────────────────────────┘
              │
              ▼
┌─────────────────────────────────────┐
│  36 -articles met the study criteria │
│  for second-line treatment           │
└─────────────────────────────────────┘
              │
              ▼
┌──────────────────────────────────────────────────┐
│  11 -articles met the specific drug of interest   │
│  in this study                                     │
└──────────────────────────────────────────────────┘
              │
              ▼
┌─────────────────────────────────────┐
│  8 -articles met the study criteria  │
│  3 / 8 were the same subjects        │
└─────────────────────────────────────┘
              │
              ▼
┌──────────────────────────────────────────────────────────────────────┐
│  5 -studies were included in the data extracted process for           │
│  economic evaluation                                                   │
└──────────────────────────────────────────────────────────────────────┘
```
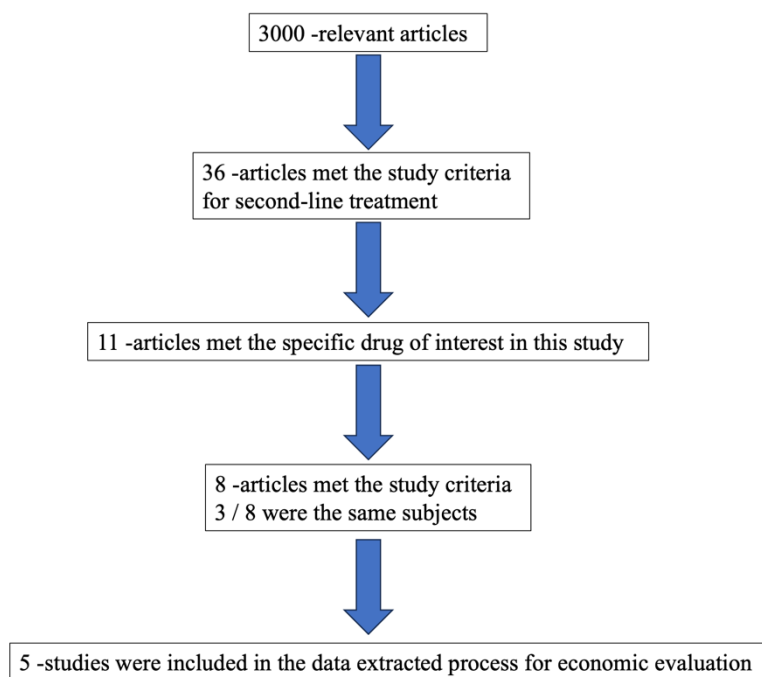
Figure 1. Study-selection flow diagram.

Eleven references met our criteria for atezolizumab, nivolumab, or pembrolizumab; these citations pertained to four systematic reviews and eight individual studies, all of which were of high quality and compared PD-1 immunotherapy to docetaxel alone. Three out of eight studies were from the same population. We identified one phase IIb randomized controlled trial of atezolizumab, three phase III randomized controlled trials of nivolumab, and one phase II/III trial of pembrolizumab. In addition, three conference abstracts pertaining to the two nivolumab studies were included in our research sample. All four trials provided evidence that informed our evaluation of the use of PD-1 immunotherapy in the second-line setting of NSCLC patients, as shown in Table 4.

All five studies corresponded to our target population (second-line treatment of NSCLC). These studies did not only include patients with tumors absent a driver mutation. Researchers present these results, as well as results from the overall populations of the remaining two studies, as they are likely representative of the therapeutic efficacy in patients with EGFR-wt tumors. One of the remaining studies (Checkmate 017 trial of

nivolumab) was composed entirely of patients with squamous-cell NSCLC, who were unlikely to have an EGFR-mt tumor, whereas 89 percent of patients in the POPLAR study and 74 percent of patients in the OAK study had an EGFR-wt tumor. Although the KEYNOTE 010 trial evaluated relevant outcomes at two doses of pembrolizumab (2 mg/kg and 10 mg/kg), we only report results from the 2 mg/kg group because this dose was consistent with the FDA-approved indication for pembrolizumab in the time this report was published. CheckMate 017, CheckMate 057 and OAK studies published the primary results and the extended results which were published 1-3 years after the primary result published. Most of the clinical outcomes in this thesis used the data from the primary results except for OS which was usually more mature in longer follow up.

The inclusion criteria for the trials were nearly equivalent, and the trial populations were comparable in terms of age and ECOG performance status. In all trials, the proportion of never-smokers was approximately 20%, with the exception of the CheckMate 017 trial of nivolumab (6%), in which all patients had squamous NSCLC and were thus more likely to have a smoking history. In these trials, the percentages of EGFR-mt patients were generally low, ranging from 8% to 14% when reported. EGFR mutations are uncommon in squamous NSCLC, and CheckMate 017 did not report their frequency.

All patients are required to submit tumor samples for PD-L1 testing. However, PD-L1 expression levels were not comparable across trials due to different test methods and cutoff values. Subgroup analyses stratified by PD-L1 expression level were not comparable across drugs, even at the same cut point, for the same reason. In addition, the KEYNOTE 010 trial was limited to patients with at least 1% PD-L1 expression in tumor cells and provided no information regarding the efficacy of pembrolizumab in PD-L1-negative patients.

In summary, trials of ICI utilized different assays to measure PD-L1 levels and different PD-L1 cut-points as entry criteria and for subgroup analyses. Due to the

difficulties in comparing results across trials and patient populations, we found insufficient evidence to differentiate ICI on any outcome. ICI improve survival compared with docetaxel in patients with advanced NSCLC without a driver mutation who have progressed following treatment with a platinum doublet. Patients whose tumors express high levels of PD-L1 are more likely to respond to immunotherapies targeting PD-1. Nevertheless, only a minority of patients respond to these agents, even among those with elevated PD-L1 levels as measured by assays. In contrast, some patients respond to PD-1 immunotherapy even when their PD-L1 levels are negative. Among the minority of patients who respond to PD-L1 immunotherapy, substantial survival enhancements can be observed. Due to the limited follow-up in existing studies, we are unsure of the exact magnitude of this benefit. Fatigue, nausea, and appetite loss are the most frequent adverse effects observed with ICI. With these agents, immune-related severe adverse events, such as pneumonitis and encephalitis, can occur; these adverse events are uncommon with chemotherapy. In general, PD-1 immunotherapy is more tolerable than docetaxel. Insufficient evidence exists to evaluate the quality of life benefits of ICI, as show in Table 4.

Table 4. Summary ICI trials.

Study (Drug)	Patient	Treatment	Control	AE for treatment arm
CheckMate 017[11,24] (Nivolumab)	Mean age: 63	Nivolumab (135)	Docetaxel (137)	AE result in death: 0
	PS 1: 76%	mOS 9.2 mo	mOS 6.0 mo	AE ≥ Gr 3: 7%
	Never smoke: 6%	mPFS 3.5 mo	mPFS 2.8 mo	Withdraw due to AE:
	One prior Rx: 100%	OS HR 0.62 (0.48-0.79)		3%
	Non-sq NSCLC: 0%	PFS HR 0.62 (0.47-0.81)		
		EGFR mt: NR		
	EGFR mt: NR	EGFR wt: NR		
	EGFR wt: NR			
CheckMate 057[12,24] (Nivolumab)	Mean age: 62	Nivolumab (292)	Docetaxel (290)	AE result in death: 1
	PS 1: 69%	mOS 12.2 mo	mOS 9.5 mo	AE ≥ Gr 3: 3.46%
	Never smoke: 20%	mPFS 2.3 mo	mPFS 4.2 mo	Withdraw due to AE:
	One prior Rx: 88%	OS HR 0.70 (0.58-0.83)		5%

Study (Drug)	Patient	Treatment	Control	AE for treatment arm
	Non-sq NSCLC: 100%	PFS HR 0.91 (0.76-2.37)		
	EGFR mt: 14%	EGFR mt:		
	EGFR wt: 58%	OS HR 1.18 (0.69-2.00)		
		PFS HR 1.46 (0.90-2.37)		
		EGFR wt:		
		OS HR 0.66 (0.51-0.86)		
		PFS HR 0.83 (0.65-1.06)		
KEYNOTE 010[13] (Pembrolizumab)	Mean age: 63	Pembrolizumab (344)	Docetaxel (343)	AE result in death: 3
	PS 1: 66%			AE ≥ Gr 3: 13%
	Never smoke: 19%	mOS 10.4 mo	mOS 8.5 mo	Withdraw due to AE:
	One prior Rx: 70%	mPFS 3.9 mo	mPFS 4.0 mo	10%
	Non-sq NSCLC: 70%	OS HR[#] 0.71 (0.58-0.88)		
		PFS HR 0.88 (0.74-1.05)		
	EGFR mt: 8%	EGFR mt:		
	EGFR wt: 85%	OS HR 0.88 (0.45-1.70)		
		PFS HR 1.79 (0.94-3.42)		
		EGFR wt:		
		OS HR 0.66 (0.55-0.80)		
		PFS HR 0.83 (0.71-0.98)		
POPLAR[25] (Atezolizumab)	Mean age: 62	Atezolizumab (144)	Docetaxel (143)	AE result in death: NR
	PS 1: 68%	mOS 12.6 mo	mOS 9.7 mo	
	Never smoke: 20%	mPFS 2.7 mo	mPFS 3.0 mo	AE ≥ Gr 3: 40%
	One prior Rx: 66%	OS HR 0.73 (0.53-0.99)		Withdraw due to AE:
	Non-sq NSCLC: 66%	PFS HR 0.94 (0.72-1.23)		8%
		EGFR mt: NR		
	EGFR mt: 11%	EGFR wt: NR		
	EGFR wt: 89%			
OAK[14,25] (Atezolizumab)	Mean age: 63	Atezolizumab (613)	Docetaxel (612)	AE result in death: 0
	PS 1: 64%	mOS 13.3 mo	mOS 9.8 mo	AE ≥ Gr 3: 15%
	Never smoke: 18%	mPFS 2.7 mo	mPFS 3.8 mo	Withdraw due to AE:
	One prior Rx: 76%	OS HR 0.80 (0.70-0.92)		8%
	Non-sq NSCLC: 64%	PFS HR 0.96 (0.85-1.08)		
		EGFR mt: NR		
	EGFR mt: 10%	EGFR wt: NR		
	EGFR wt: 74%			

[#]KEYNOTE 010 included two dosing groups, but we only report results from the 2 mg/kg group because this dose is consistent with the FDA prescribing information for pembrolizumab

Clinical Efficacy

Overall Survival

Immune checkpoint inhibitors are superior to docetaxel in terms of overall survival. This improvement reflects prolonged benefits in a minority of patients and no benefit in the majority of patients, rendering standard descriptive statistics of survival benefit (median survival and hazard ratios) potentially misleading when attempting to comprehend the overall effects of these therapies. In addition, trials were not long enough to fully assess the survival benefit of PD-1 immunotherapy in patients who respond. Higher levels of PD-L1 correlate with greater sensitivity to ICI. Due to the incompatibility of the study populations, it is impossible to determine if there are clinically significant differences in OS between the ICI.

Only two of the five major studies of ICI stratified results by the presence or absence of EGFR mutations. In patients without an EGFR-mt tumor, ICI provided a survival advantage over docetaxel, as indicated by statistically significant risk reductions. In the KEYNOTE 010 trial, pembrolizumab (2mg/kg and 10mg/kg groups combined) showed improved survival relative to single-agent docetaxel (HR 0.66, 95% CI 0.55-0.80). EGFR-wt patients treated with nivolumab in the CheckMate 057 trial saw a similar benefit (HR 0.66, 95% CI 0.51-0.86). Although the key trials of atezolizumab and nivolumab in squamous-cell carcinoma only reported OS in the overall populations, risk reductions were similar to those seen in EGFR-wt patients in the KEYNOTE 010 and CheckMate 057 trials: overall survival favored both atezolizumab (POPLAR: HR 0.73, 95% CI 0.53-0.99; p=0.040 OAK: HR 0.80, 95% CI 0.70-0.92) and nivolumab in squamous-cell carcinoma (HR 0.62, 95% CI 0.48-0.79) relative to single-agent docetaxel. During the time of the primary analysis, absolute gains in median OS were 2 to 3 months. CheckMate 057[24] extended follow-ups demonstrated a 16-month improvement in overall survival for non-squamous histology patients treated with nivolumab. These outcomes are shown in Table 5

Table 5. Overall survival: ICI vs. docetaxel.

	CheckMate 017[11,24]		CheckMate 057[12,24]		KEYNOTE 010[13]		POPLAR[25]		OAK[14,26]	
	Nivo	**Doc**	**Nivo**	**Doc**	**Pemb**	**Doc**	**Atez**	**Doc**	**Atez**	**Doc**
Overall population										
mOS (95% CI) in month	9.2 (7.3-13.3)	6.0 (5.1-7.3)	12.2 (9.7-15.0)	9.5 (8.1-10.7)	10.4 (9.4-11.9)	8.5 (7.5-9.8)	12.6 (9.7-16.4)	9.7 (8.6-12.0)	13.3 (11.3-14.9)	9.8 (8.89-11.3)
HR (95%CI)	0.62 (0.48-0.79)		0.70 (0.58-0.83)		0.71 (0.58-0.88)		0.73 (0.53-0.99)		0.80 (0.70-0.92)	
EGFR-wt population										
HR (95%CI)	NR		0.66 (0.51-0.86)		0.66 (0.55-0.80)		NR		0.69 (0.57-0.83)	

Despite statistical risk reductions and clinically significant absolute survival gains, we have substantial uncertainty regarding the true survival benefits of ICI over time, which may have a higher death rate in the first 5 to 6 months compared to docetaxel but a lower death rate after that. It is likely that the survival curves do not exhibit proportional hazards, which is the assumption underlying one of the most prevalent methods for modeling and reporting relative benefits in survival analysis. The HR from subgroup analyses by the level of PD-L1 expression are shown in Table 6

This is evidenced by the crossing of OS curves at 6 months in the CheckMate 057 trial of nivolumab and the general observation that OS curves flattened out between 15 and 18 months in the PD-1 immunotherapy arms of all the major trials. To address this issue, the researcher extracts individual data from the published Kaplan-Meier curves, combines them, and computes the best-fitting curve using parametric survival analysis with time-varying covariate before calculating the point estimate of the difference in hazard between ICI and docetaxel.

We also looked into whether PD-1 immunotherapies have differential efficacy according to histology. In the POPLAR and KEYNOTE 010 trials of atezolizumab and pembrolizumab, respectively, hazard ratios for OS with ICI compared with docetaxel were slightly *lower* in patients with non-squamous NSCLC, atezolizumab HR 0.69 (95% CI 0.47-1.01), pembrolizumab HR 0.63 (95% CI 0.50-0.79) than in patients with squamous NSCLC, atezolizumab HR 0.80 (95% CI 0.49-1.30), pembrolizumab HR 0.74 (95% CI 0.50-1.09). In contrast, in the two CheckMate studies that assessed nivolumab in squamous and non-squamous cell histologies, patients with non-squamous NSCLC had a higher hazard ratio; HR 0.72 (95 percent CI HR 0.60-0.88) vs. HR 0.59. (95 percent CI 0.44-0.79). However, OAK extended study reported nearly the same HR for atezolizumab vs. docetaxel, HR 0.79 (95% CI 0.68-0.93) and HR 0.79 (95% CI 0.62-1.01) in non-squamous and squamous NSCLC, respectively.

When we looked at the squamous and non-squamous subgroups of the three ICI, we observed no consistent direction of differences, and expert opinion suggested that there is no persuasive evidence of a differential effect across subgroups. As a result, we decided to report combined data for ICI across different histologic subtypes. Patients with higher levels of PD-L1 expression responded better to all three treatments. However, the randomized trials used different cutpoints and assays for each medication. As a result, determining whether the effect of PD-L1 expression is the same for the three medications is difficult. The lack of correlation between PD-L1 levels and response to nivolumab in patients with squamous histology in CheckMate 017 raises the question of whether histology is an impact modifier. We do not have data on whether PD-L1 levels predict treatment response in patients with squamous histology in POPLAR, OAK or KEYNOTE 010, but given the lack of an overall subgroup effect discussed above, we present combined data for both histologies when looking at responses at different levels of PD-L1 expression.

Table 6. OS HR according to PD-L1 expression level vs docetaxel.

Study (Drug)	PD-L1 expression	HR (95% CI)	PD-L1 expression	HR (95% CI)
CheckMate 017[11] (Nivolumab)	<10%	0.70 (0.48-1.01)	≥10%	0.50 (0.28-0.89)
	<1%	0.58 (0.37-0.92)	≥1%	0.69 (0.45-1.05)
CheckMate 057[12] (Nivolumab)	<10%	1.00 (0.76-1.31)	≥10%	0.40 (0.26-0.59)
	<1%	0.90 (0.66-1.24)	≥1%	0.59 (0.43-0.82)
KEYNOTE 010[13] (Pembrolizumab)	1-49%	0.76 (0.60-0.96)	≥50%	0.53 (0.40-0.70)
POPLAR[25] (Atezolizumab)	< median expression	1.1 (0.63-1.93)	≥ median expression	0.49 (0.22-1.07)
	TC0 and IC0	1.04 (0.62-1.75)	TC3 or IC3TC1/2/3 or IC1/2/3	0.59 (0.40-0.85)
OAK[14] (Atezolizumab)	TC1/2/3 or IC 1/2/3	0.74 (0.59-0.93)	TC3 or IC3	0.40 (0.27-0.61)
	TC0 and IC0	0.77 (0.61-0.97)	TC2/3 or IC2/3	0.66 (0.50-0.89)

Progression-free Survival

Compared to docetaxel, ICI has modest and variable effects on PFS. As with OS, this may represent the effects of a mixed population of responders and non-responders; patients whose tumors express high levels of PD-L1 are more likely to experience PFS improvements with ICI. All five major studies evaluated PFS and found small and inconsistent results regarding benefits and the predictive value of PD-L1 expression level in determining the magnitude of the benefit. The outcomes are shown in Table 7.

Table 7. PFS hazard ratio and 95%CI.

Study (Drug)	PD-L1 expression	HR (95%CI)
CheckMate 017[11]	≥10%	0.58 (0.33-1.00)
(Nivolumab)	≥5	0.54 (0.32-0.90)
	≥1%	0.67 (0.44-1.00)
	<1%	0.66 (0.43-1.00)
CheckMate 057[12]	≥10%	0.52 (0.37-0.75)
(Nivolumab)	≥5	0.54 (0.37-0.75)
	≥1%	0.54 (0.39-0.76)
	<1%	0.70 (0.53-0.94)
KEYNOTE 010[13]	≥50%	0.59 (0.45-0.78)
(Pembrolizumab)	≥1%	0.88 (0.74-1.05)
POPLAR[25]	TC3 or IC3	0.60 (0.31-1.16)
(Atezolizumab)	TC2/3 or IC2/3	0.72 (0.47-1.10)
	TC1/2/3 or IC1/2/3	0.85 (0.63-1.16)
	TC0 and IC0	1.12 (0.72-1.77)
OAK[14]	TC3 or IC3	0.59 (0.41-0.84)
(Atezolizumab)	TC2/3 or IC2/3	0.73 (0.57-0.92)
	TC1/2/3 or IC1/2/3	0.87 (0.73-1.02)
	TC0 and IC0	1.11 (0.93-1.34)

In the CheckMate 017 and CheckMate 057 trials, patients with squamous and non-squamous NSCLC were compared to docetaxel with nivolumab. In CheckMate 017, nivolumab improved median progression-free survival (PFS) from 3.5 months to 2.8

months (HR 0.62, 95% CI 0.47 to 0.81). Among the 225 (83%) patients with quantifiable PD-L1 expression at baseline, there was no correlation between PD-L1 expression level and PFS. CheckMate 057, in contrast, found no difference in PFS overall; however, among 455 (78%) patients with quantifiable PD-L1 expression, higher PD-L1 expression was associated with an improvement in PFS with nivolumab at all three pre-specified levels (HR 0.70 for 1 percent vs. 0.54 for 5 percent vs. 0.52 for 10 percent).

In KEYNOTE 010, EGFR-wt patients treated with pembrolizumab (2mg/kg and 10mg/kg groups combined) had a modest improvement in progression-free survival (HR 0.83, 95% CI 0.71 to 0.98). In the total study population (EGFR-mt and EGFR-wt patients), PFS was improved with pembrolizumab 2 mg/kg compared to docetaxel in patients with tumors expressing PD-L1 at 50% (median PFS, 5.0 months vs. 4.1 months; HR, 0.59; 95% CI, 0.44-0.80). In patients with low PD-L1 expression, PFS was unaffected by treatment.

In the POPLAR study, there was no statistically significant difference in the median progression-free survival (PFS) between arms, neither in the total population nor in subgroups with different PD-L1 expression levels. In contrast to POPLAR, OAK demonstrates PFS benefits in subgroups TC3/IC3 and TC2/3 or IC2/3.

Objective Response Rate

Given the difficulty in interpreting median survival and hazard ratios for OS, objective response rates (ORRs) and duration of response provide an additional method for assessing the benefits of ICI. The ORRs of patients with tumors expressing high levels of PD-L1 were significantly higher with ICI than with docetaxel, and the duration of response was significantly longer with ICI. In some trials, among patients who had responded to ICI, the duration of response at the end of the trial could not be reported as a median value because the duration had not reached its midpoint. Each of the key ICI studies evaluated treatment response, however no stratification response endpoints by EGFR mutation status. However, the majority of patients who participated in the trials of interest did not have a

driver mutation (EGFR-wt and ALK-ve in the majority of trials), so results from the ITT population may be indicative of the response in patients without an EGFR-wt tumor.

Table 8 provides response data from the most important studies. Using RECIST v1.1 criteria, objective response rate (ORR) was universally defined as a partial or complete response. Patients treated with nivolumab and pembrolizumab had significantly higher response rates than those treated with docetaxel (18- 20% vs. 9-12%). In addition, the responses were long-lasting and ongoing at the time of analysis. While atezolizumab and docetaxel produced nearly identical results in the POPLAR study (15% ORRs) and slightly better results in the OAK study (13.7% and 11.8% ORRs for atezolizumab and docetaxel, respectively), the median duration of response was approximately 7 to 31 months longer with atezolizumab.

Table 8. Objective response rate and time-to-response.

	CheckMate 017[11]		CheckMate 057[12]		KEYNOTE 010[13]		POPLAR[25]		OAK[14,26]	
	Nivo	**Doc**	**Nivo**	**Doc**	**Pemb**	**Doc**	**Atez**	**Doc**	**Atez**	**Doc**
ORR %	20.0	8.8	19.2	12.4	18.0	9.3	14.6	14.7	13.7	11.8
(95% CI)	(14-28)	(5-15)	(15-24)	(9-17)	(14-23)	(7-13)	(NR)	(NR)	(11-17)	(9-15)
mTTR	2.2	2.1	2.1	2.6	2.1	2.1	NR	NR	NR	NR
(range)	(1.6-11.8)	(1.8-9.5)	(1.2-8.6)	(1.4-6.3)	(2.1-4.1)	(2.1-4.1)				
PD: n (%)	56 (41)	48 (35)	129 (44)	85 (29)	124 (37)	89 (29)	NR	NR	187 (44)	117 (28)

Intriguingly, while nivolumab and pembrolizumab were associated with higher objective response rates compared to docetaxel, patients treated with these agents demonstrated more disease progression. This phenomenon may suggest that ICIs are best suited for patients with specific clinical characteristics, such as a higher level of PD-L1 expression, as depicted in Table 9. As with overall survival, objective response rates were higher in subgroups with higher PD-L1 expression levels among those treated with PD-1 immunotherapy. The CheckMate 017 trial, which evaluated nivolumab in patients with advanced squamous NSCLC, was the only major trial in which a correlation between PD-L1 expression and response was not observed.

Table 9. ORR of ICI and docetaxel by PD-L1 expression.

Study	PD-L1 expression	ICI ORR (%)	Docetaxel ORR (%)
CheckMate 017[11] (Nivolumab)	Total population	20.0	8.8
	≥10 %	19	9
	≥5 %	21	8
	≥1 %	17	11
	<1 %	17	10
CheckMate 057[12] (Nivolumab)	Total population	19.2	12.4
	≥10 %	37	13
	≥5 %	36	13
	≥1 %	31	12
	<1 %	9	15
KEYNOTE 010[13] (Pembrolizumab)	Total population	18	9
	≥50 %	30	8
POPLAR[25] (Atezolizumab)	Total population	15	15
	TC3 or IC3	38	13
	TC0 and IC0	8	10
OAK[14] (Atezolizumab)	Total population	14	13
	TC3 or IC3	30.6	10.8
	TC2/3 or IC2/3	22.5	12.5
	TC1/2/3 or IC1/2/3	17.8	16.2
	TC0 and IC0	8	10.6

Quality of Life

Out of the five clinical trials of interest, four publications report patient-reported outcomes. CheckMate 017[27] and CheckMate 057[28] evaluated patient-reported health status utilizing the EQ-5D preference-based health state utility measure (EQ-5D utility index; scaled from 0 to 1) and the visual analog scale (EQ-VAS, scaled from 0-100). The minimum clinically-important difference (MID) is defined as 0.08 for the EQ-5D index and 7 for the EQ-VAS. In CheckMate 017[27], both EQ-5D and EQ-VAS were statistically significantly higher during a 48-week and 54-week follow-up than at baseline in the nivolumab arm (p 0.05), whereas they were not different from baseline in the docetaxel arm at week 18, after which the sample size dropped below ten, and no analysis was performed. At the first follow-up after treatment discontinuation in the docetaxel arm, the EQ-VAS showed statistically and clinically significant deterioration, whereas no deterioration was observed in the nivolumab arm. Not reported were statistical tests comparing the nivolumab and docetaxel arms. KEYNOTE 010[29] is the first study to examine the effect of pembrolizumab on HRQoL in advanced NSCLC patients receiving second-line therapy. Pembrolizumab treatment was associated with a numerically smaller decrease in the EORTC QLQ-C30 GHS/QoL score from baseline to week 12. (the estimated time at which more than half of patients in the docetaxel arm would have experienced disease progression) Although the difference between treatment groups was not statistically significant, this finding suggests that patients with previously treated PD-L1-expressing NSCLC experienced less decline in HRQoL with pembrolizumab than with docetaxel. EQ-5D and EQ-VAS analyses yielded comparable results. Pembrolizumab (2 mg/kg) was associated with a higher proportion of improved EORTC QLQ- C30 GHS/QoL scores and functioning and symptom domains and a lower proportion of deteriorated scores compared to docetaxel. Numerous symptom domains exhibited nominally significant improvement with pembrolizumab, whereas they exhibited nominally significant deterioration with docetaxel. Overall, the QoL analysis supports the objective response rate

and progression-free survival results without revealing any unanticipated adverse effects regarding pembrolizumab's known safety profile. From the OAK study, compared to chemotherapy, atezolizumab resulted in an overall benefit over risk for patients, with a longer TTD in patient-reported functioning (physical function and role function). Atezolizumab also resulted in a statistically significant improvement in HRQoL from baseline compared to docetaxel, as well as a longer TTD for chest pain. In contrast, there was no difference between the two arms for other lung cancer symptoms. Patients receiving atezolizumab did not experience any clinically significant worsening of treatment-related symptoms.

Adverse Event

The most common side effects of PD-1 immunotherapies include fatigue, nausea, and loss of appetite. Various organs, including the lungs, brain, liver, and skin, can be affected by immune-related adverse effects. Some of these incidents may be serious. Docetaxel is associated with a higher incidence of serious adverse events, particularly hematologic adverse events, than PD-1 immunotherapy. In Table 10, the frequencies and rates of Grade 3-4 (severe and life-threatening) treatment-emergent adverse events (TEAE) are reported per regimen. In the primary studies, the PD-1 immunotherapies were well tolerated, with safety profiles usually superior to docetaxel. Compared to patients treated with docetaxel, individuals treated with nivolumab, pembrolizumab, or atezolizumab had lower rates of discontinuation owing to TEAEs, fewer grade 3-4 TEAEs, and fewer treatment-related fatalities. The increased incidence of grade 3-4 TEAEs observed with docetaxel was mostly due to hematologic toxicity.

Table 10.Serious adverse events.

	CheckMate 017[11]		CheckMate 057[12]		KEYNOTE 010[13]		POPLAR[25]		OAK[26]	
	Nivo	Doc	Nivo	Doc	Pem b	Doc	Ate z	Doc	Ate z	Do c
≥ gr3 TEAE (%)	7	55	10	54	13	35	11	39	15	43
Discont due to TEAE (%)	3	10	5	15	4	10	1	18	8	19
Gr 5 TEAE %	0	2	0.3	0.3	0.9	2	0.7	2	1	<1
Gr 3-4 TEAE (%) in AE that occurred more than 10%										
Alopecia	0	1	0	0	0	1	0	1	0	0.2
Anemia	0	3	<1	3	1	2	NR	NR	2.3	5.7
Asthenia	0	4	<1	2	<1	2	1	3	1.3	2.2
Decrease appetite	1	1	0	1	1	1	2	0	0.3	1.6
Diarrhea	0	2	1	1	1	2	1	4	0.7	1.9
Dyspnea	NR	NR	<1	0	0.6	1.3	7	2	2.5	2.4
Fatigue	1	8	1	5	1	4	NR	NR	2.8	4.0
Hypothyroidism	0	0	0	0	0	0	1	0	NA	NA
Musculoskeletal pain	0	0	NR	NR	0	0	2	2	0.7	0.2
Myalgia	0	0	<1	0	0	0	1	3	0.2	0.7
Nausea	0	2	1	1	<1	<1	1	0	0.7	0.3
Leukopenia	1	4	0	8	0	2.6	NR	NR	NA	NA
Neutropenia	0	30	<1	27	0	12	0	12	0.5	13.0
Febrile neutropenia	0	10	0	10	0	4.9	0	8	0.2	10.7
Peripheral neuropathy	0	2	0	1	0	0.3	0	1	0	1.2
Pneumonia	0	0	0	2	0.9	1.3	6	2	NR	NR
Pneumonitis	0	0	1	<1	1.8	0.3	NR	NR	NR	NR
Rash	0	2	<1	0	<1	0	NR	NR	NR	NR

Immune-related adverse events (irAEs) have been linked to ICI, which include dermatologic toxicity (e.g., rash, pruritus), diarrhea or colitis, hepatotoxicity, elevations in serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), pulmonary inflammatory complications (e.g., pneumonitis, pneumonia), and endocrinopathies (e.g., hypothyroidism). The most prevalent side effects associated with ICI include fatigue, nausea, and loss of appetite. Table 11 lists the most frequently reported treatment-related adverse events of any severity level, as well as AEs with a suspected immunological cause. Immune-mediated TEAEs occurred more frequently with PD-1 immunotherapies than with docetaxel.

Table 11. Common treatment-related AE with ICI and TEAE of immune etiology.

	CheckMate 017[11]		CheckMate 057[12]		KEYNOTE 010[13]		POPLAR[25]		OAK[26]	
	Nivo	Doc	Nivo	Doc	Pemb	Doc	Atez	Doc	Atez	Doc
Asthenia	10	14	10	18	6	11	6	13	19.0	19.7
Decrease appetite	11	19	10	16	14	16	18	16	23.5	23.5
Diarrhea	8	20	2	23	7	18	7	22	15.4	24.4
Fatigue	16	33	16	29	14	25	20	35	26.8	35.5
Nausea	9	23	12	26	11	15	12	27	17.7	22.7
Gr 3-4 TEAE (%) in AE that occurred more than 10%										
Alopecia	0	1	0	0	0	1	0	1	0	0.2
Anemia	0	3	<1	3	1	2	NR	NR	2.3	5.7
Asthenia	0	4	<1	2	<1	2	1	3	1.3	2.2
Decrease appetite	1	1	0	1	1	1	2	0	0.3	1.6
Diarrhea	0	2	1	1	1	2	1	4	0.7	1.9
Dyspnea	NR	NR	<1	0	0.6	1.3	7	2	2.5	2.4
Fatigue	1	8	1	5	1	4	NR	NR	2.8	4.0
Hypothyroidism	0	0	0	0	0	0	1	0	NA	NA
Musculoskeletal pain	0	0	NR	NR	0	0	2	2	0.7	0.2
Myalgia	0	0	<1	0	0	0	1	3	0.2	0.7
Nausea	0	2	1	1	<1	<1	1	0	0.7	0.3
Leukopenia	1	4	0	8	0	2.6	NR	NR	NA	NA
Neutropenia	0	30	<1	27	0	12	0	12	0.5	13.0
Febrile neutropenia	0	10	0	10	0	4.9	0	8	0.2	10.7
Peripheral neuropathy	0	2	0	1	0	0.3	0	1	0	1.2

Pneumonia	0	0	0	2	0.9	1.3	6	2	NR	NR
Pneumonitis	0	0	1	<1	1.8	0.3	NR	NR	NR	NR
Rash	0	2	<1	0	<1	0	NR	NR	NR	NR

Prior Economic Evaluation

We compared the outcomes, expenses, and cost-effectiveness of second-line ICI with docetaxel in patients with advanced NSCLC who had progressed on first-line doublet chemotherapy. A simulation model based on partition survival curves was used to conduct the analyses. Drug cost estimations were based on Thai government-announced median costs and estimates of adverse events and other clinical factors derived from relevant clinical trial data.

A search of the literature for past economic models turned up numerous published cost-effectiveness models comparing treatment regimens among ICI classes in second-line lung cancer.

There are eight publications on cost-effectiveness studies conducted by ICI. Four were supported by manufacturers, while the remaining four were not as shown in Table 12.

All four trials supported by non-manufacturers found no cost-effectiveness between ICIs and docetaxel when comparing the two treatments. In comparison to four other studies with manufacturing funding. Goeree et al. revealed the findings of a cost-effectiveness analysis comparing pembrolizumab to docetaxel, which was funded by Bristol-Myers Squibb. Depending on the type of model, this study showed an incremental cost-effectiveness ratio ranging from USD 151,560 to USD 153,229. However, the willingness to pay was not reported in this study, and the author did not infer whether or not nivolumab was cost-effective.[30] Huang et al., a study supported by Merck & Co. Inc. that compared pembrolizumab to docetaxel, found an additional cost-effectiveness ratio of USD 168,691. At the same time, the willingness to pay was USD 171,60, which was somewhat higher than the ICER finding. Pembrolizumab was more cost-effective than docetaxel, according

to the authors.[31] Ondhia et al. and Marine et al. completed in Canada and France, respectively, two more investigations sponsored by Hoffmann-La Roche Limited. Ondhia et al. reached the conclusion that atezolizumab is more economical than docetaxel. Atezolizumab is more effective and more expensive than docetaxel, according to Marine et al.[32,33]

Testing for PD-L1 provides a significant influence in the improvement of ICER for ICI in comparison to docetaxel. The British National Institute for Health and Care Excellence (NICE) concluded in December 2015 that nivolumab was not cost-effective as a second-line treatment for squamous NSCLC. They calculated ICERs between GBP 109,000 and GBP 129,000 (USD 133,895 and USD 154,465) in the absence of biomarker selection, although the institute's approved limit is typically under GBP 30,000 (USD 36,852).[34] The US data also confirmed that the PD-L1 test plays a significant role in the cost-effectiveness of ICI compared to docetaxel in second-line NSCLC setting, with ICERs of USD 155,605, USD 187,685, and USD 215,802 in patients without PD-L1 testing in squamous cell, non-squamous cell, and all histology, respectively. In contrast to the ICER of USD 98,421 for PD-L1 $\geq$ 1% across all histologies.[35]

Table 12. Published cost-effectiveness analysis.

Author (year), funding	Costs	QALYs	ICER	WTP threshold	Conclusions
Non-manufactural funded					
Matter-Walstra et al. (2016)[36], Swiss Group for Clinical Cancer Research and the Cantonal Hospital Lucerne	nivo: USD 68,419 doc: USD 38,874 nivo with dose reduction: USD 48,993 nivo with duration reduction: USD 57,244	nivo: 0.69 doc: 0.53 nivo with dose reduction: 0.69 nivo with duration reduction: 0.69	nivo vs doc: USD 183,406 nivo (PD-L1≥1%) vs doc: USD 137,718 nivo (PD-L1≥1%) vs nivo: USD 67,971 nivo (PD-L1≥10%) vs doc: USD 129,062 nivo (PD-L1≥10%) vs nivo: USD 39,125 nivo with dose reduction vs doc: USD 62,817 nivo with reduced duration vs doc: USD 114,035	USD 103,340	Comparing Nivo to docetaxel for non-squamous NSCLC from the perspective of the Swiss health care system, Nivo is not cost-effective. Nivo is, nevertheless, cost-effective due to dose reduction and an elevated PD-L1 threshold.
Aguiar et al. (2017)[35], None declared	Sq (PD-L1 unselected): nivo: USD 104,453 doc: USD 39,516 non-Sq (PD-L1 unselected): nivo: USD 100,791 doc: USD 46,856	Sq (PD-L1 unselected): nivo: 0.82 doc: 0.40 Non-Sq (PD-L1 unselected): nivo: 0.87 doc: 0.59 All histology (PD-L1≥1%):	nivo vs doc (Sq, PD-L1 unselected): USD 155,605 nivo vs doc (non-Sq, PD-L1 unselected): USD 187,685 pembro vs doc (all histology, PD-L1≥1%): USD 98,421	USD 100,000	Atezo is not cost-effective; pembro is; and while not being cost-effective at baseline, nivo is cost-effective when the PD-L1 threshold is raised. The use of PD-L1 expression as a biomarker boosts the cost-effectiveness of immunotherapy, as

	All histology (PD-L1≥1%): pembro: USD 82,201 doc: USD 48,182 All histology (PD-L1 unselected): atezo: USD 122,155 doc: USD 45,864	pembro:0.92; doc: 0.57 All histology (PD-L1 unselected): atezo: 0.90; doc: 0.54	atezo vs doc (all histology, PD-L1≥1%): USD 215,802		measured by the Medicare system in the United States.
Gao et al. (2019)[37], Alfred Deakin Postdoctoral Research Fellowship funded by Deakin University	Markov model: nivo: USD 70,316 doc: USD 15,808 PS model: nivo: USD 96,763 doc: USD 13,509	Markov model: nivo: 1.03 doc: 0.68 PS model: nivo: 1.06 doc: 0.46	Nivo vs doc: Markov model: USD 154,179 PS model: USD 139,347	USD 35,036	In the Australian healthcare system, Nivo is not cost-effective for patients with previously treated advanced or metastatic squamous NSCLC.
Liu et al. (2019)[38], Provincial Natural Science Foundation	nivo: USD 40,599 doc: USD 18,338	Nivo: 0.55 Doc: 0.31	nivo vs doc: USD 93,307	USD 28,899 for general regions; USD 63,564 for affluent regions	In the Chinese healthcare system, Nivo is not cost-effective compared to doc for patients with previously treated advanced NSCLC.

Manufactural funded

Goeree et al. (2016)[30], Bristol-Myers Squibb Canada.	Markov model: nivo: USD 139,016 doc: USD 38,812 erlo: USD 39,920 PS model:	Markov model: nivo: 1.23 doc: 0.58 erlo: 0.54 PS model: nivo: 1.24 doc: 0.59	Markov model: nivo vs doc: USD 152,229 novo vs erlo: USD 141,838 PS model	NR	Using a PS or Markov model gave estimates of projected cost, outcomes, and incremental cost-utility that were nearly identical from the standpoint of the

Study	Cost	QALY	ICER	WTP	Conclusion
	nivo: USD 141,973 doc: USD 38,029 erlo: USD 40,329	erlo: 0.55	nivo vs doc: USD 151,560 nivo vs erlo: USD 140,601		publicly financed Canadian healthcare system. Compared with doc or erlo, nivo may or may not cost-effective depending on WTP threshold.
Huang et al. (2017)[31], Merck & Co. Inc.	Pembro: USD 297,443 Doc: USD 136,921	pembro: 1.71 doc: 0.76	pembro vs doc: USD 168,619	USD 171,660	In pre-treated advanced NSCLC patients with PD-L1 ≥ 50%, Pembro is more cost-effective than docetaxel from the perspective of US third-party payers.
Ondhia et al. (2019)[32], Hoffmann-La Roche Limited	atezo: USD 100,541 doc: USD 35,030 nivo: USD 103,834	atezo: 1.31 doc: 0.71 nivo: 1.28	atezo vs doc: USD 109,406 Nivo vs doc: USD 122,343	USD 125,000	Atezo is more cost-effective than doc, and from the perspective of the publicly-funded healthcare system in Canada, atezo dominated nivo.
Marine et al. (2020)[33], Hoffmann-La Roche Limited	atezo: EUR 65,753 doc: EUR 16,324 nivo: EUR 71,837	atezo: 1.27 doc: 0.80 nivo: NR	atezo vs doc: EUR 104,835	NR	Atezolizumab is more effective and more expensive than docetaxel in France for stage IIIB or IV NSCLC second-line treatment, consistent with prior French evaluations of immunotherapies in similar indication. Last, atezolizumab is a cheaper option to nivolumab based on list pricing.

In the scenario of economic evaluation of ICI without docetaxel, the most recent publication on real-world data on cost-effectiveness analysis from Italy indicates that atezolizumab is the ICI with the best favorable cost-effectiveness characteristics relative to nivolumab and pembrolizumab.[39]

Research Questions

What are the cost-effectiveness of ICI treatments?

Are there any financial toxicities in patients with non-small cell lung cancer?

Objectives

Economic Evaluation of ICI

To assess the cost-effectiveness of PD-1 checkpoint inhibitor treatment with docetaxel for patients in Thailand who have previously been treated for non-small cell lung cancer with chemotherapy from a government perspective, patient perspective, and societal perspective.

Financial toxicity in lung cancer patients

To determine the extent of the patient's financial burden caused by having cell lung cancer.

To determine the disparity between reimbursed schemes.

Chapter 2

Research Methodology

The primary objective of this study was to compare the cost-effectiveness of second-line therapies for NSCLC patients who have progressed following first-line chemotherapy. In clinical studies, each PD-1 immunotherapy was compared to docetaxel in populations that varied slightly. The efficacy of docetaxel was believed to be independent of PD-L1 levels and was therefore aggregated across all trials.

Conceptual framework

Conceptual Framework for Economic Evaluation of Applying ICI
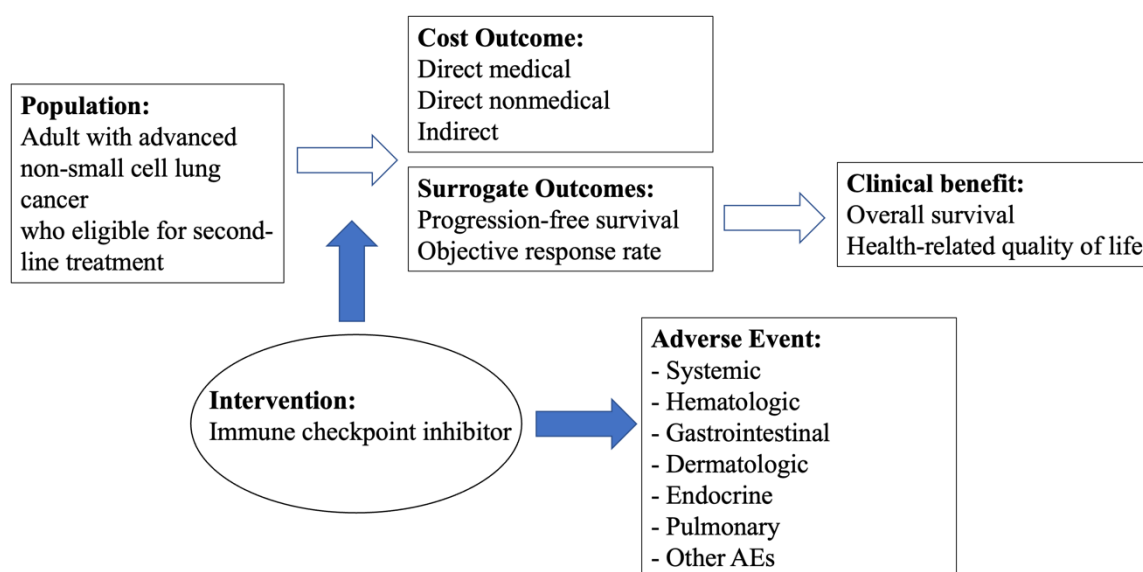
Figure 2. Conceptual framework of economic evaluation of applying ICI in the second-line setting of lung cancer.

The population group in the framework mentioned above referred to lung cancer patients who visited the chest clinic at Songklanagarind Hospital, Prince of Songkla University and consented to join a questionnaire interview. Data on surrogate outcomes,

PFS and ORR, were collected and extracted from the publication of the relevant clinical trials. The overall survival was also collected. And extract form the clinical trials but the utility, health-related quality of life, was collected from the questionnaire. The cost parameters except for drug cost, AE cost and post-progressive disease cost were collected from face-to-face interviews. Drug costs were collected from drug price given by MOPH database. AE costs and port-progressive disease costs using the actual costs in the real-world database.

Conceptual Framework for Evaluation of Financial Burden
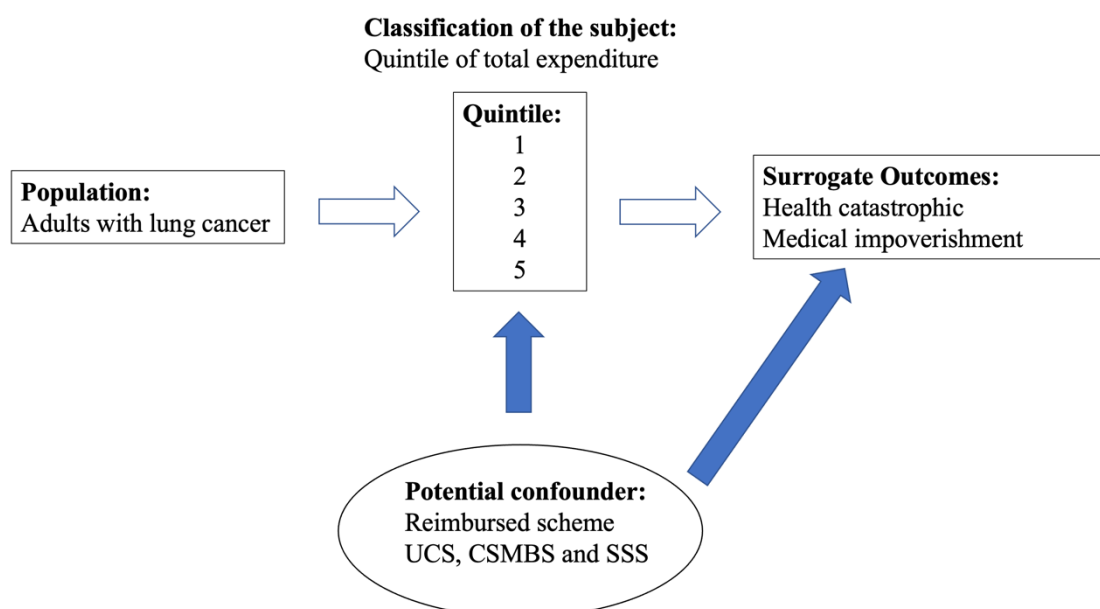
Figure 3. Conceptual framework of financial burden in lung cancer.

The population for the financial burden section referred to all lung cancer patients who attended the chest clinic during the study period. The quintiles of the subject were created based on the rank of total expenditures, a surrogate for wealth, within each payment scheme. Catastrophic health expenditure and medical impoverishment were computed from the total expenditure and the capacity-to-pay of the patients.

Scope of the Assessment for Economic Evaluation of Applying ICI

Several programmed death 1 (PD-1) medications are used in the treatment of second-line setting of non-small cell lung cancer. This analysis aims to analyze these medicines' health economic results (NSCLC). The effects of various treatments are studied in non-small cell lung cancer with no driver mutation (EGFR-, ALK-). The PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework that be used to explain the scope of the economic evaluation part of the study in conceptual framework paragraphs (Figure 2).

Populations

The populations of interest were adults with advanced EGFR-negative, ALK-negative, non-small cell lung cancer who had failed treatment with first-line therapy. Treatment with immune checkpoint inhibitors (ICIs) interventions following administration of platinum-based chemotherapeutic doublets at the time of progression

Comparators

Monotherapy or chemotherapy using only one drug (e.g., docetaxel).

Outcomes

In this analysis, major clinical outcomes that occur in patients treated for advanced NSCLC were investigated, along with surrogate outcomes typically used in cancer trials. The following are examples of interesting outcomes:

Overall survival

Progression-free survival

Objective response rate

Treatment-related adverse events

Timing

Evidence on the efficiency of interventions, as well as the risks associated with them, was collected from trials of every period.

Settings

The inpatient, clinic, and office settings were all considered; these are the important settings.

Scope of the Assessment for Evaluation of Financial Burden for Lung Cancer in Thailand

Cancers are substantial contributors to health burdens, and lung cancer is one of the leading causes of death in males. Patients and their families, as well as the healthcare system and society as a whole, are put under a significant financial burden as a result of lung cancer-related deaths, which account for one-fifth of all deaths caused by cancer. These financial toxicity effects come from the direct expenses of treatment and non-medication and the costs of other things.[40] Patients with lower incomes are more likely to experience this type of financial toxicity, also known as catastrophic health expenditure (CHE).[41,42]

Method for Economic Evaluation for Applying ICI

Material and equipment

Key assumptions

Lists a number of essential model-building assumptions are shown in Table 13. The body weight, BSA, and age of diagnosis were collected from real-world information in Songklanagarind Hospital, Prince of Songkla University.

Table 13. Modeling assumptions.

Assumption	Rationale
Docetaxel survival curves pooled across all ICI trails	Docetaxel efficacy is not expected to vary across the trials
No vial sharing allowed	According to the drug labelling, vial sharing is not allowed
Weight (Kg) mean ± SE	54.95 ± 1.01 based on PSU data
Height (cm) mean ± SE	159.04 ± 0.79 based on PSU data
Age (year) mean ± SE	65.84 ± 0.80 based on PSU data
BSA (m^2) mean ± SE	1.57 ± 0.01 based on PSU data

Model structure

The framework of the model is represented in Figure 4. As depicted in Figure 5, outcomes were modeled using a partition survival strategy and three health states: progression-free (PF), progressing disease (PD), and death. Partition survival models are advantageous because they require less data than other, more complex modeling approaches, and they can utilize data widely disclosed in clinical trial journals. For each treatment regimen, a hypothetical patient population will spend time in the PF and PD health states. To assess life expectancy, quality-adjusted life expectancy, and total expenses, the meantime, quality-adjusted time and costs spent in each health condition are added together. We utilized a one-week cycle length to represent the dosing timings for the included medication regimens. We utilized both the health system perspective (i.e., solely direct medical care costs), the patient perspective (including direct nonmedical

expenditures), and the societal perspective (including direct nonmedical and indirect expenditures) with a lifetime horizon to model patients from treatment beginning to death. Costs and health outcomes were discounted at a rate of 3 percent each year, as specified by the US Guidelines for the Economic Evaluation of Health Technologies.[43] The model was created by Microsoft Excel (Redmond, WA). In this second-line context, the baseline comparison was monotherapy with docetaxel. The extracted individual time-to-event analysis from the published KM curve using the Guyot method was utilized to construct a pooled dataset for predicting the time-to-event for docetaxel and ICIs.[44–46]
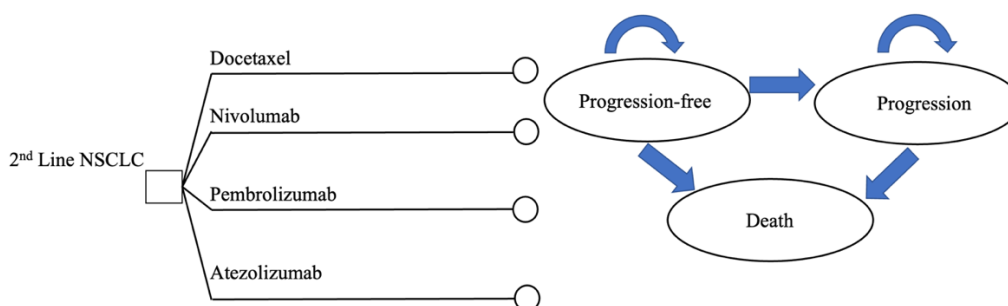
Figure 4. Model structure.

Options of treatment for second-line lung cancer in real-world and in this study were docetaxel which was aa current practice standard, nivolumab, pembrolizumab and atezolizumab. The Markov node comprise progression-free, progress, and death.
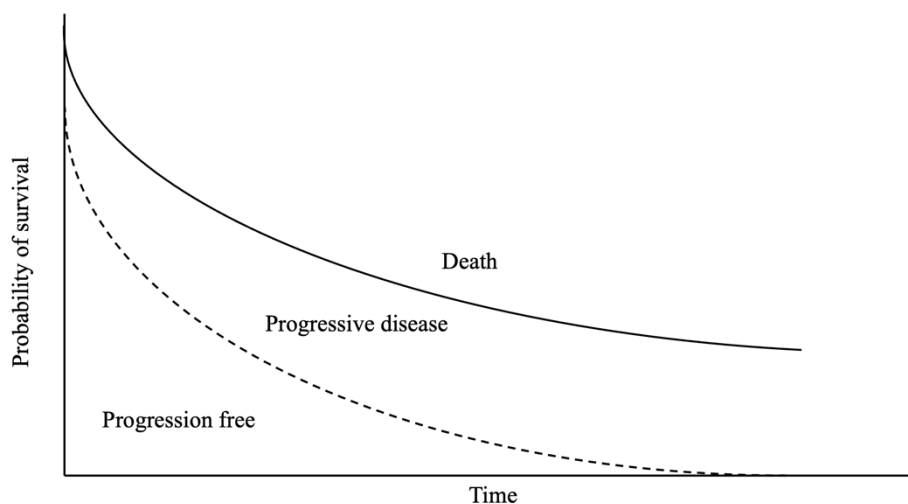
Figure 5. Partition survival model.

Model Input: Clinical benefit

Although our initial intention was to also fit parametric survival curves to progression-free survival (PFS) Kaplan-Meier data for the docetaxel comparator for ICIs in the second-line context, using the method outlined by Hoyle and Henley[47], the Guyot method[44–46] was chosen after extensive review.[48] First, we retrieved data points from digital copies of available survival curves, then we utilized the recovered values, the number of surviving patients at each time interval, and the maximum likelihood function to estimate the individual patient data.

As the example of KM curve crosses between the ICI and docetaxel groups in Figure 6 (and others in Appendix D), the proportional hazard assumption may be violated. Consequently, the use of hazard ratios or the combination of hazard ratios may mislead the ICI results. There are numerous ways to fix this problem, including time-varying hazard approaches, separating the data into two (or more) periods, and calculating the hazard rate

for each line of the KM curve without using the hazard ratio from the publication. This study utilized the individual level.

As per the Guyot approach, the individual level of time-to-event can be retrieved from the published KM curve whose curve patterns, patient at-risk, and censored duration appear virtually identical to the original. Figure 6 and Figure 7 illustrate examples of extracted KM curves and published KM versions, respectively. In accordance with the Guyot method, the individual level of time-to-event can be extracted from a published KM curve whose curve patterns, patient at-risk, and censored duration are nearly equal to the original.
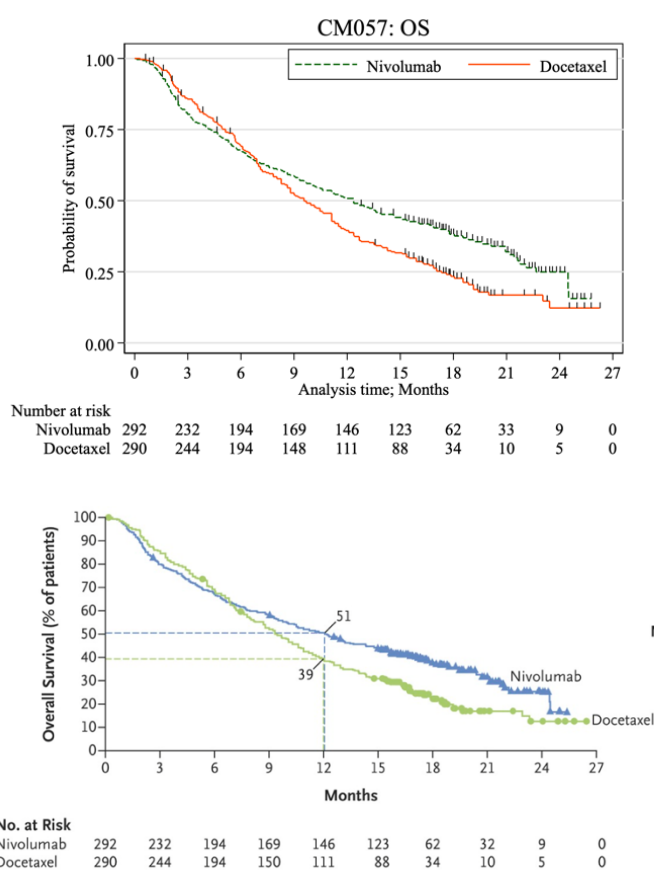
Figure 6. KM curve of OS for nivolumab and docetaxel from CheckMate057 (lower) and extracted from CheckMate057 (upper).
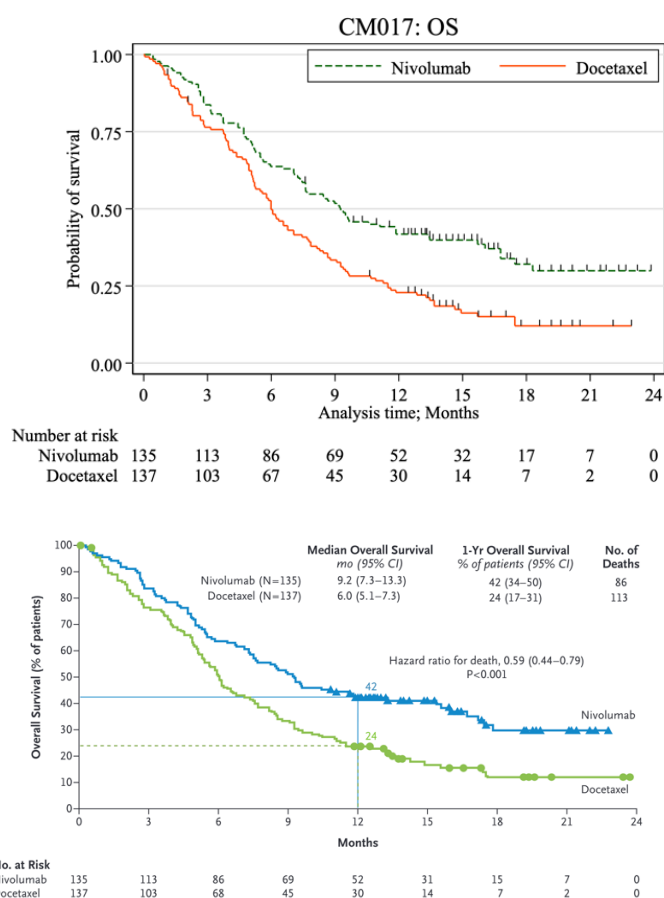
Figure 7. KM curve of OS for nivolumab and docetaxel from CheckMate017 (left) and extracted from CheckMate017 (right).

Using data extracted from the publication, all time-to-event data pertaining to the same drug would be aggregated. For instance, the time-to-event data for docetaxel from CM017, CM057, KN010, OAK, and POPLAR should be concatenated to a single dataset. Weibull, exponential, log-logistic, log-normal, and two/three/four degree-of-freedom of flexible parametric (fp) with proportional hazard-fp, proportional odds-fp, and probit-fp were employed to estimate the hazard parameters. The model's selected techniques for the parametric survival model consisted of the information criterion, a virtual graphic, a plausible explanation, and an accepted logic. Although the flexible parametric models

looked more accurate to the Kaplan-Meier curve, the flexible parametric models were used for the data visualization and to identify the potential bias of using parametric models. (Appendix D)

A survival and rate function of log-logistic distribution are shown below.

$$S(t) = \frac{1}{(1 + (\alpha t)^{\gamma})}$$

Equation 1. Log-logistic survival function.

$$r(t) = \frac{ba^b t^{b-t}}{1 + (at)^b}$$

Equation 2. Log-logistic rate function.

$$a = \exp{(-\alpha_0)}$$

Equation 3. a parameter for Equation 2.

$$b = \exp{(-\beta_0)}$$

Equation 4. b parameter for Equation 2.

In response to Stata output, the parameter α_0 is called _cons, and β_0 is called /ln_gam.

A survival function of log-normal distribution is shown below.

$$S(t) = 1 - \Phi\left(\frac{ln(t) - \mu}{\sigma}\right)$$

Equation 5. Survival function of log-normal distribution.

Where as Φ is the cumulative distribution function of the standard normal random variable and μ is an intercept (_cons) value.

Model input: Adverse events

The model incorporated adverse events of Grade 3/4 that occurred in at least 5% of patients for either of the treatment comparators and was gathered from key clinical trials and/or the prescribing information for each medicine.

Model inputs: Drug Utilization and Costs

The estimation of medication utilization (Appendix E) was obtained from a number of variables, including the dosing schedule, in which the dose may be defined by weight or body surface area (BSA; see Key Assumptions). If a regimen was based on treat-to-progression, treatment utilization, and expense would be applied to all patients who remained in the progression-free health status throughout time. Patients could remain in the progression-free state without active treatment if a limited number of cycles were administered, as with docetaxel. No sharing of vials was believed to occur. Utilization estimates were multiplied by drug unit costs to calculate the overall expected drug treatment costs. The drug cost parameters are shown in Table 14. All costs were converted to the first trimester of 2023 at a rate of THB 30.72 for one USD.

Table 14. Drug unit cost.

Drug	Detail	Mean	SE	n	Ref.
Doc	Per mg	.61652019	.10573234	34	Calculated
	80 mg vial	49.321615	8.4585872	34	DMSIC
	20 mg vial	17.521484	3.4362457	26	DMSIC
	Administration	39.0625			PSU data
Nivo	Per mg	15.325521	8.8481937	3	Calculated
	100 mg vial	1532.5521	884.81937	3	DMSIC
	40 mg vial	766.27604		2	DMSIC
	Administration	13.020833			PSU data
Pembro	100 mg vial	3239.2578	1322.4215	6	DMSIC
	Administration	13.020833			PSU data
Atezo	1200 mg vial	2124.6745	867.39473	6	DMSIC
	Administration	13.020833			PSU data

We utilized the median pricing supplied by the Drug and Medical Supply Information Center (DMSIC) , Ministry of Public Health, for each drug and recorded the formulations that were accessible. Based on the regimen-specific dosage stated above, the model selected the combination of vials with the lowest cost for each regimen.

The costs per adverse event were taken from the Thai DRG seeker database provided by the Thai CaseMix Center and the actual price charged to lung cancer patients who were hospitalized due to adverse events during 2019-2022. Because the cost from the actual subjects is significantly greater than the cost in Thai DRG seeker, the author designed to utilize the cost from the actual one as shown in the Appendix E.

To estimate costs throughout the progressive health stage, second-line ICI patients were administered docetaxel, and second-line docetaxel patients were administered gemcitabine monotherapy. During each weekly model cycle, the cost of each successive regimen was multiplied by the cumulative proportion of individuals whose disease had progressed. The subsequent regimen costs were determined by calculating the average weekly cost of docetaxel and gemcitabine regimens which were collected from real-world data from lung cancer who were treated at Prince of Songkla University; the treatment duration was used to calculate the average weekly cost of post-progression therapy was the average number of months spent in the progressed state for each drug class. Based on the modeled regimens, this corresponded to 7.5 months of (post-ICI) docetaxel therapy and 7.1 months of (post-docetaxel) gemcitabine therapy. More details about the post-treatment cost are shown Appendix E. Direct nonmedical costs also had been collected via face-to-face interviews as the results, to be used in the economic model.

The indirect cost inputs were gathered from face-to-face questionnaires of lung cancer patients, including the frequency and time spent each month for OPD in IPD for patients and caregivers. In this study, the Human-capital technique was employed to determine the productivity loss from a societal perspective, which was computed by

multiplying the number of days lost by the mean minimum wage in Thailand (mean 10.977, SE 0.226 USD/month).[49]

Model Inputs: Health State Utilities

The EQ5D5L Thai version was collected from the questionnaires of lung cancer patients who were in the second-line setting without progression, in the second-line setting with progression, and in more than the second-line setting for progression-free and progressive stages, respectively. In the case of multiple questionnaires collected on the same subject, for utility calculation purposes, we used only the last questionnaire which was correlated to the more advanced treatment stage.

Health state utilities were collected and calculated from the EQ5D5L Thai version (Appendix E). We assumed that the health state utility values did not differ amongst the treatments examined by the model.

The overall percentage of patients who encountered any grade 3/4 adverse event for each regimen was multiplied by the adverse event disutility and removed from the first month of PFS for each treatment. We assumed that patients having any grade 3/4 adverse event would have a total of 4 weeks with a grade 3/4 adverse event. The disutility to be used in the models are shown in Table 15.

Table 15. Disutility parameters (mean SE).

Parameter	Disutility	SE	Source
Neutropenia	-0.08973	0.01543	Nafees et al.[50]
Febrile neutropenia	-0.09002	0.01633	Nafees et al.
Nausea	-0.0468	0.01618	Nafees et al.
Infection	-0.09002	0.01633	Assume to be equal to FN
Hyponatremia	-0.0468	0.01618	Assume to be equal to nausea
Pneumonia	-0.09002	0.01633	Assume to be equal to FN
Anemia	-0.0073	0.018	Westwood et al[51]

Model Outcomes

The model evaluated the average time progression-free and progression-free patients spent. The summation of unadjusted and utility-adjusted time spent in each health state yielded estimates of life expectancy and quality-adjusted life year (QALY).

Model outcomes of interest for each intervention included quality-adjusted life years (discounted), life years (discounted), mean time in progression-free and post-progression health states (discounted), pre-progression, post-progression, and total costs (discounted), and incremental cost-effectiveness ratios for each intervention relative to the standard comparator, docetaxel, in pairwise comparison. The 3% discount value was used indeterministic model and zero to six percent discounting were used in probabilistic models.

Sensitivity Analysis

The sensitivity analyses were calculated only for the main (base-case) analysis, the governmental perspective, and in the case without a patient access program (PAP).

The programming of the model enables adaptable and intensive sensitivity studies. Where applicable, one-way sensitivity analyses utilized 95% confidence intervals from clinical data as ranges. In the absence of 95% confidence intervals, uncertainty intervals were derived from plausible values from the published literature and real-world data from Prince of Songkla University. In addition, we conducted a probabilistic sensitivity analysis (PSA) by jointly altering all model parameters across 1,000 simulations and then obtaining reasonable range estimates for each model outcome with a credibility level of 95%.

The one-way sensitivity analyses were shown only for the government perspective without the PAP scenario. The uncertainties of PAP were shown from all perspectives.

Method for Economic Evaluation of Financial Burden in Lung Cancer

Data source

Data were extracted from the Hospital Information System (HIS) of Songklanagarind Hospital and face-to-face questionnaires based on an interview of all pathologically-proved lung cancer patients who visited the clinic between November 9, 2020, and March 24, 2023. The clinical information, height, weight, performance status, therapy alternatives, histology, treatment regimen, and clinical response are all included in the data that come from the HIS. The following topics were addressed in the questionnaires: demographics, health state, and functionality, healthcare scheme, income and consumption, and working loss among the patient and their relatives. The statistics collectively give information on patient tertiary healthcare facility utilization, which includes the demographic, clinical, social, and economic status of persons with lung cancer, in addition to information on the cost of healthcare services and the cost of healthcare overall. For the duplicated questionnaire in the same subject which was collected from different stage of the disease, Only the first one was used in this part of analysis.

Indicators

During the interviews, information on medical expenses was gathered. This included the total spending, reimbursement, and out-of-pocket expenses for the outpatient visit in the previous month as well as the inpatient visit in the previous year. The yearly household consumption expenditure was employed as a proxy for household economic status in the examination of the economic-related disparities. This spending included everything from food and entertainment to education and traveling.

We used the catastrophic health expenditure (CHE), which is defined as annual household health payments that are higher than 40 percent of capacity-to-pay (CTP), which is defined as non-food household costs, to measure the degree of financial risk. We also

used the medical impoverishment, which is defined as total spending that is lower than the computed subsistence expenditure plus total out-of-pocket health payments and does not meet the criteria for being poor.

Previous research indicates that there are two distinct approaches to the measuring of CHE. Payments made out of pocket (OOP) that exceed more than 10 percent of overall household expenditures or more than 40 percent of the household's capacity to pay. For the purposes of this investigation, the OOP/capacity to pay technique was utilized to define CHE.[52] Alongside this, the capacity of the household to pay (denominator) was defined as the household's expenditure on non-food consumption, and the out-of-pocket expenditure (numerator) was defined as the sum of the respondent's and their spouse's out-of-pocket medical expenses for out-patient and in-patient care in the previous year. Both of these definitions were used. If the proportion was higher than 40 percent, CHE was coded as "yes," and if it wasn't, it was "no." As variables, these parameters, which include age, gender, healthcare plan, current stage and original stage of lung cancer, type of treatment being received, and quintile of economic position, were taken into consideration.

Calculate CHE using the capacity to pay (ctpay) method.[53]

CHE = OOP/ctpay

capacity to pay = X- S_{exp}

X = total household consumption expenditure

S_{exp} = subsistence expenditure

The threshold of household expenditure required to calculate CHE varied between studies. CHE is considered by the World Health Organization when the out-of-pocket cost of health care equals or exceeds 40 percent of a household's non-subsistence income or capacity to pay. In light of this, we set the CHE cutoff at 40 percent for the purposes of this study.

This method employs a poverty level based on food shares to estimate subsistence expenditures. Food expenditures at the 50th (45th-55th) percentile of total household food expenditures represent the poverty line.

Variables:

    FES_h =Food expenditure share for household

    FE_h = food expenditure of household

    TE_h = total expenditure of household

    HES = household equivalent size

    Coefficient β = household scale multiplier.

It is used to alter a household's subsistence expenditures to account for economies of scale as its size increases. The value 0.56 is derived using the following regression equation based on 59 countries[54]:

    $\ln(FE_h) = \ln(k) + \beta \ln(HS) + \Sigma \gamma_i country$

    HS = household size

    EFE_h = equivalent food expenditure of household

    PL = poverty line

    SE_h = Subsistence expenditure of household

    $ctpay_h$ = household's capacity to pay

    CHE = catastrophic health expenditure

Step 1 Calculate food expenditure share (FES_h) for each household

    FES_h = food expenditure of household/total household expenditure

    $FES_h = FE_h/TE_h$

Step 2 Generate the equivalent household size (HES) for each household

HES = HS (household size)$^{\beta}$, $\beta = 0.56$

Step 3: Determine the equivalent food expenditure (EFEh) by dividing each household's food expenditure (FEh) by its equivalent household size (HES)

EFE$_h$ = household food expenditure/equivalent household size

EFEh = FE$_h$/HES

Step 4 computes the poverty line by identifying the food expenditure shares of total household expenditure at the 45th and 55th percentiles across the entire sample (FES$_h$45 and FES$_h$55) and then calculating the average of the food expenditure of the households in the 45th to 55th percentile range to obtain the subsistence expenditure per capita.

Poverty line (PL) = average of EFE$_h$, where FES$_h$45 < EFE$_h$ < FES$_h$55

Step 5 Calculate the subsistence expenditure for each household (SE$_h$)

SE$_h$ =PL*HES

Step 6 Calculate the household's ctpay$_h$

ctpay$_h$ = non-subsistence effective expenditures of the household

ctpay$_h$ =TE$_h$ –SE$_h$ if SE$_h$ < FE$_h$

ctpay$_h$ =TE$_h$ –FE$_h$ if FE$_h$ < SE$_h$

Step 7 calculates the ratio of OOP payments to the household's capacity to pay (OOPr).

$$\text{OOPr} = \text{OOP spending}/\text{ctpay}_h$$

Step 8 Catastrophic health expenditure (CHE)

CHE occurs when a household's out-of-pocket spending on health care services equals or exceeds their non-subsistence spending or a certain percentage of its capacity to pay. The threshold changes based on the findings of various researchers. We utilized a cutoff of forty percent. CHE is 1 if the OOP ratio above the threshold and 0 otherwise.

$$\text{CHE} = 1 \text{ if OOP ratio} \geq \text{threshold } (0.4)$$
$$0 \text{ if OOP ratio} < \text{threshold}$$

Step 9 Poverty or a poor household is incurred when overall household expenditures exceed subsistence expenditures.

$$\text{Poor}_h = 1 \text{ if TE}_h > \text{SE}_h$$

Step 10 Medical impoverished refers to a household that did not fulfill the requirements for poverty (step 9) prior to accounting for health expenditures but does so after accounting for health expenditures.

Statistical Analysis

Categorical data are displayed in numbers (percent). All cost statistics discounted by the inflation adjustment factor (IAF) to be valued in 2023 are shown as geometric means (SD) due to the right skewness property (arithmetic means and SD to be shown in the appendix). Using ranking within each payment system, quintiles of the overall cost were constructed. The socio-demographic disparities in lung cancer individuals' treatment type, health service utilization, CHE, and medical impoverishment were analyzed using Chi-square testing. Concentration curves (CC) and concentration index (CI) were employed to

examine economic-related discrepancies among reimbursed health schemes. The further the CC is from the equality line (45-degree line), the greater the level of disparities in healthcare and expenditures. Extension of the concentration index reduced to the Erreygers index, which was employed as a measure of the degree of discrepancy.[55,56]

The influence of the quintile of total expenditure (QTE) on the outcomes, including CHE and medical impoverishment, was evaluated using a variety of logistic regression models. First, the QTE and payment systems that determine interest were incorporated into the model. The interface between QTE and payment systems was then introduced. Lastly, additional factors potentially linked with the outcomes were added and deleted using a backward, step-by-step process. In the final two models, the quadratic effect of QTE was introduced only for the medical deprivation outcome. AIC, BIC, and AUC of logistic-ROC were utilized as performance indicators.

After controlling for potential predictors of the outcomes, multivariable logistic regression models were used to estimate the effects of cancer treatment on CHE and medical impoverishment among quintiles of total expenditure in each of the three major reimbursement schemes. Using the Delta-Margins approach from modified logistic regression, the probability of outcomes is displayed visually. All statistical analyses were performed using STATA 18.0, and p-values less than 0.05 were regarded as statistically significant.

Chapter 3

Results

Source data for economic modeling

Time-to-event parameters

Time-to-event, PFS and OS, pseudo individual patient data were extracted from the published data. Multiple parametric survival models were applied to those. The log-logistic and log-normal distributions were chosen for the best-fit shape parameter for all treatment groups (docetaxel, nivolumab, pembrolizumab and atezolizumab) The AIC, BIC and regression modeling are shown in the appendix. These parameters from the models would be used in the transitional probability in the Markov models.

Table 16. Survival parameters for OS and PFS.

Outcome	Regimen	Distribution	Intercept (_cons)	Gamma	Sigma
OS	Doc	Log-logistic	3.64	0.62	NA
	Nivo	Log-normal	3.85	NA	1.32
	Pembro	Log-logistic	3.98	0.76	NA
	Atezo	Log-logistic	4.03	0.74	NA
PFS	Doc	Log-normal	2.76	NA	0.88
	Nivo	Log-normal	2.78	NA	1.15
	Pembro	Log-normal	2.90	NA	1.11
	Atezo	Log-normal	2.72	NA	1.13

Adverse event parameters

The percentage of grade 3 or more adverse event from the publication are shown in table below. Docetaxel regimen shows the highest rate of anemia, febrile neutropenia, infection, leukopenia, nausea, neuromotor, neutropenia and pneumonia (Table17).

Table 17. Adverse events of each regimen (%).

Gr 3/4 AE	Doc[57]	Nivo[58]	Pembro[59]	Atezo[60]
Anemia	9		3.8	3
Febrile neutropenia	6			
Hyponatremia		7	8	7
Infection	10			
Leukopenia	49			
Nausea	5		1.3	
Neuromotor	5			
Neutropenia	65			
Pneumonia	21			

Post-treatment cost parameters

The costs of treatment information for patient who progress after docetaxel assumed to be treated with gemcitabine monotherapy. The data from real-world setting in Songklanagarind Hospital revealed that the cost was 127 (SE 10.6) USD/week. The patients who were progressed after ICI treatments would be received treatment with docetaxel which was 92 (SE 14.7) USD / week (Table 18)

Table 18. Post-treatment cost parameters

Treatment regimen	Subsequent treatment	Cost / week in USD
Doc	Gem	127.274 ± 10.570
Nivo	Doc	91.716 ± 14.790
Pembro	Doc	91.716 ± 14.790
Atezo	Doc	91.716 ± 14.790

Direct non-medical costs

As a result of the face-to-face interviews, direct nonmedical expenditures were also collected to be utilized in the economic model. The majority of the direct nonmedical expenditure was spent on travel for both IPD and OPD. The equipment expenditures were likewise significant, but only 16 to 24 percent of patients needed to pay for it (Table 19).

Table 19. Direct nonmedical costs for second-line NSCLC (Mean ± SE).

Domain	2L, non-PD (N=73)	2L-PD and > 2L (N=50)	Total (N=123)
Outpatient frequency	1.107 ± 0.064	1.043 ± 0.067	1.081 ± 0.046
Travel cost for OPD visit	31.850 ± 2.978	40.939 ± 5.292	35.545 ± 2.800
Extra cost for meal per OPD visit	16.244 ± 2.648	18.859 ± 3.404	17.307 ± 2.089
OPD-Accommodation cost	14.214 ± 2.468	12.220 ± 2.579	13.496 ± 1.809
IPD travel cost	32.455 ± 6.899	28.097 ± 5.531	30.683 ± 4.659
Number of admission/year	1.043 ± 0.043	1.000 ± 0.000	1.027 ± 0.027
Proportion needed to buy equipment	0.164 ± 0.044	0.240 ± 0.061	0.195 ± 0.036
if yes equipment cost	53.059 ± 28.695	64.541 ± 25.467	57.726 ± 19.864

Indirect cost parameters

The time spend parameters for the patients and caregiver(s) were collected as shown in table 20.

Table 20. Indirect cost parameters (Mean ± SE)

Domain	2L, non-PD (N=74)	2L-PD and > 2L (N=50)	Total (N=124)
income/month	448.393 ± 81.643	364.647 ± 73.470	414.624 ± 56.936
main income/month	608.598 ± 108.200	727.534 ± 90.818	656.556 ± 74.156
number of caregiver	1.297 ± 0.069	1.380 ± 0.090	1.331 ± 0.055
Pr.(OPD-caregiver number 1)	0.959 ± 0.023	0.960 ± 0.028	0.960 ± 0.018
Pr.(OPD-caregiver number 2)	0.284 ± 0.053	0.340 ± 0.068	0.306 ± 0.042
Pr.(OPD-caregiver number 3)	0.041 ± 0.023	0.060 ± 0.034	0.048 ± 0.019
Outpatient frequency c1	1.105 ± 0.063	1.043 ± 0.067	1.080 ± 0.046
Outpatient frequency c2	1.198 ± 0.141	1.108 ± 0.113	1.158 ± 0.092
Outpatient frequency c3	1.000 ± 0.000	1.667 ± 0.333	1.333 ± 0.211
Outpatient duration (hr) each day c1	5.718 ± 0.210	5.896 ± 0.258	5.790 ± 0.162
Outpatient duration (hr) each day c2	5.095 ± 0.425	5.824 ± 0.274	5.421 ± 0.268
Outpatient duration (hr) each day c3	4.667 ± 0.882	6.333 ± 0.882	5.500 ± 0.671
Outpatient money loss for job c1	21.132 ± 4.536	17.063 ± 3.613	19.633 ± 3.142
Outpatient money loss for job c2	23.364 ± 5.722	15.988 ± 3.435	20.782 ± 3.924
Outpatient money loss for job c3	16.510 ± NA	26.378 ± 8.649	23.088 ± 5.979
IPD number of caregiver	1.340 ± 0.093	1.138 ± 0.065	1.263 ± 0.063
Pr.(IPD-caregiver number 1)	0.635 ± 0.056	0.580 ± 0.071	0.613 ± 0.044
Pr.(IPD-caregiver number 2)	0.176 ± 0.045	0.080 ± 0.039	0.137 ± 0.031
Pr.(IPD-caregiver number 3)	0.054 ± 0.026	0.000 ± 0.000	0.032 ± 0.016
Inpatient frequency c1	3.511 ± 0.640	1.655 ± 0.458	2.803 ± 0.443
Inpatient frequency c2	2.308 ± 0.548	1.750 ± 0.750	2.176 ± 0.448
Inpatient frequency c3	2.750 ± 1.750	NA	2.750 ± 1.750
Inpatient duration (day) c1	8.149 ± 0.441	9.345 ± 0.581	8.605 ± 0.355
Inpatient duration (day) c2	8.231 ± 1.051	7.000 ± 1.683	7.941 ± 0.881
Inpatient duration (day) c3	10.250 ± 1.750	NA	10.250 ± 1.750
Inpatient money loss for job c1	22.934 ± 8.161	19.116 ± 5.811	21.326 ± 5.210
Inpatient money loss for job c2	27.419 ± 7.607	10.508 ± NA	21.782 ± 7.146

Utility parameters

The utility values to be used in the economic model are shown in Table 21 (more details are shown in Appendix E).

Table 21. Mean ± SE of utility.

Variable	2L, non-PD	2L-PD and > 2L	Total
	(N=74)	(N=50)	(N=124)
Utility from EQ5D5L	0.822 ± 0.028	0.748 ± 0.042	0.792 ± 0.024

Economic evaluation results

Government perspective without PAP

Deterministic Analyses: Governmental perspective without PAP

Based on the deterministic model, from the government perspective without PAP, each of the second-line ICI regimens improved survival compared to docetaxel (range: 0.55 to 0.81 incremental life-years for nivolumab and atezolizumab, respectively). QALYs gained relative to docetaxel varied from 0.43 for nivolumab to 0.62 for atezolizumab. Atezolizumab's incremental expenses relative to docetaxel varied from a low of USD 18,683 to a high of USD 69,728 for pembrolizumab. Cost-effectiveness estimates for atezolizumab ranged from USD 30,003 per QALY gained over docetaxel to USD 115,365 per QALY for pembrolizumab (Table 22 and Table 23). Again, it is essential to emphasize that this study was based on experience with each drug within the trial.

Table 22. Economic evaluation: Governmental perspective, deterministic, without PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Life year	PFS	0.46	0.61	0.66	0.56
	PD	0.93	1.41	1.66	1.78
	Total	1.29	1.84	2.07	2.11
Cost	Drug	349.96	39183.15	71423.24	20216.50
	Administrative	262.45	171.65	122.02	105.31
	CT scan	627.22	623.02	885.72	764.45
	Safety lab	76.57	838.70	596.18	514.55
	Post PD	5582.82	5932.30	6860.13	7432.59
	AE	11662.47	8048.10	8403.04	8211.25
	DNM	NA	NA	NA	NA
	Indirect	NA	NA	NA	NA
	Total	18561.48	54796.9	88290.33	37244.65
QALY		0.99	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.78	0.81
	Cost	-	36235.43	69728.85	18683.17
	QALY	-	0.43	0.60	0.62
ICER		-	84956.55	115364.78	30003.28

The results of the probabilistic model closely mirror those of the deterministic model as shown in Table 23.

Table 23. Economic evaluation: Governmental perspective, probabilistic, without PAP scenario.

		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Total	Life year	1.29	1.85	2.08	2.11
	Cost	18538.81	55022.41	87188.16	37263.61
	QALY	0.99	1.43	1.60	1.62
Incremental	Life year	-	0.55	0.23	0.03
	Cost	-	36406.84	68649.36	18724.80
	QALY	-	0.43	0.61	0.62
ICER		-	84923.01	112685.26	29986.47

Sensitivity Analyses: Governmental perspective without PAP

The results of sensitivity analysis by varying each input parameter between mean ± 1.96 * SE are shown in Figures 8 9 and 10 for nivolumab, pembrolizumab and atezolizumab, respectively. The ICER for each drug is most sensitive to the cost of the drug covering a range of 158% difference for nivolumab to 173 for atezolizumab. The ICER was also sensitive to the parameters of the survival profiles, namely the _cons and shape parameters, but considerably less than the sensitivity to drug cost. It is notable that the ICER for atezolizumab was more sensitive to the values of cost of the adverse events, than that on the other two drugs. More details about these three tornado plot are shown in Tables 24, 25 and 26 for nivolumab, pembrolizumab and atezolizumab, respectively.
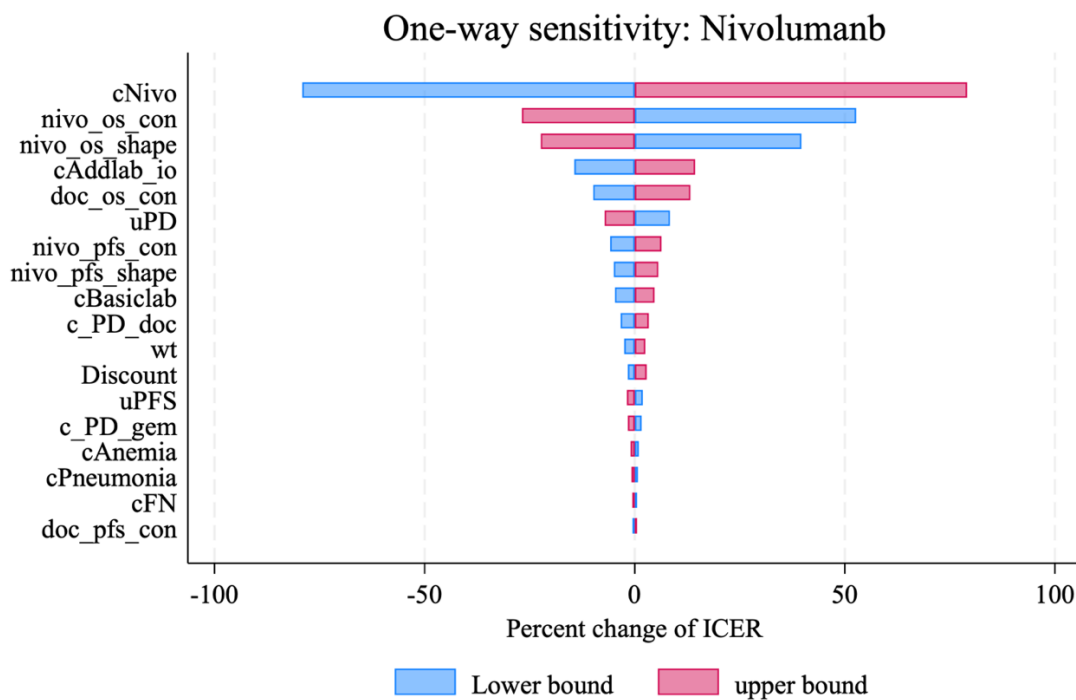
Figure 8. One-way sensitivity analysis results: Tornado diagrams for Nivolumab

cNivo – cost for nivolumab, nivo_os_con – _cons parameter for nivolumab OS, nivo_os_shape – shape parameter for nivolumab OS, cAddlab_io – additional safety lab for ICI, doc_os_con – _cons parameter for docetaxel OS, uPD – utility of PD stage, nivo_pfs_con – _cons parameter for nivolumab PFS, nivo_pfs_shape – shape parameter for nivolumab PFS, cBasiclab – cost of safety lab, c_PD_doc – cost of docetaxel treatment beyond disease progression, wt – weight, uPFS – utility of PFS stage, c_PD_gem – cost of gemcitabine treatment beyond disease progression, cAnemia – cost of treatment for ≥ Gr 3 anemia, cPneumonia – cost of treatment for ≥ Gr 3 pneumonia, cFN – cost of treatment for ≥ Gr 3 febrile neutropenia, doc_pfs_con – _cons parameter for docetaxel PFS

Table 24.One-way sensitivity analysis results: Nivolumab

Domain	mean	SE	Distribution	Lower CI	Upper CI	Lower ICER	Upper ICER	Percent diff
cNivo	15	9	gamma	-2	33	27437	235353	158
nivo_os_con	4	0	normal	4	4	200632	96128	80
nivo_os_shape	1	0	gamma	1	1	183502	102015	62
cAddlab_io	40	11	gamma	19	61	112519	150271	29
doc_os_con	4	0	normal	4	4	118420	148811	23
uPD	1	0	beta	1	1	142397	121971	16
nivo_pfs_con	3	0	normal	3	3	123720	139745	12
nivo_pfs_shape	1	0	gamma	1	1	124852	138789	11
cBasiclab	14	4	gamma	7	21	125218	137572	9
c_PD_doc	92	15	gamma	63	121	126999	135791	7
wt	55	1	normal	53	57	128085	134705	5
Discount				0	0	129256	135108	4
uPFS	1	0	beta	1	1	133913	128970	4
c_PD_gem	127	11	gamma	107	148	133526	129264	3
cAnemia	5438	3088	gamma	-614	11491	132672	130118	2
cPneumonia	7540	1053	gamma	5476	9604	132411	130379	2
cFN	9905	2721	gamma	4571	15238	132145	130645	1
doc_pfs_con	3	0	normal	3	3	130704	132128	1

cNivo – cost for nivolumab, nivo_os_con – _cons parameter for nivolumab OS, nivo_os_shape – shape parameter for nivolumabOS, cAddlab_io – additional safety lab for ICI, doc_os_con – _cons parameter for docetaxel OS, uPD – utility of PD stage, nivo_pfs_con – _cons parameter for nivolumab PFS, nivo_pfs_shape – shape parameter for nivolumab PFS, cBasiclab – cost of safety lab, c_PD_doc – cost of docetaxel treatment beyond disease progression, wt – weight, uPFS – utility of PFS stage, c_PD_gem – cost of gemcitabine treatment beyond disease progression, cAnemia – cost of treatment for ≥ Gr 3 anemia, cPneumonia – cost of treatment for ≥ Gr 3 pneumonia, cFN – cost of treatment for ≥ Gr 3 febrile neutropenia, doc_pfs_con – _cons parameter for docetaxel PFS

Figure 9. One-way sensitivity analysis results: Tornado diagrams for pembrolizumab.

cPembro – cost for pembrolizumab, pembro_os_con – _cons parameter for pembrolizumab OS, pembro_os_shape – _cons parameter for pembrolizumab OS, uPD – utility of PD stage, doc_os_con – _cons parameter for docetaxel OS, pembro_pfs_con – _cons parameter for pembrolizumab PFS, pembro_pfs_shape – _cons parameter for pembrolizumab PFS, c_PD_doc – cost of docetaxel treatment beyond disease progression, uPFS – utility of PFS stage, c_PD_gem – cost of gemcitabine treatment beyond disease progression, cPneumonia – cost of treatment for ≥ Gr 3 pneumonia

Table 25. One-way sensitivity analysis results: Pembrolizumab.

Domain	mean	SE	Distribution	Lower CI	Upper CI	Lower ICER	Upper ICER	Percent diff
cPembro	3239.26	1322.42	gamma	647.31	5831.20	20811	209919	163.92
pembro_os_con	3.98	0.06	normal	3.87	4.10	146543	94250	45.33
pembro_os_shape	-0.27	0.05	normal	-0.37	-0.18	142744	95478	40.97
Discount	0.03	NA	NA	0.00	0.06	101052	129582	24.73
uPD	0.75	0.04	beta	0.67	0.83	125535	106719	16.31
doc_os_con	3.64	0.03	normal	3.58	3.70	107151	125618	16.01
pembro_pfs_con	2.90	0.04	normal	2.81	2.98	106812	124522	15.35
pembro_pfs_shape	1.11	0.04	gamma	1.04	1.18	108282	123178	12.91
c_PD_doc	91.72	14.79	gamma	62.73	120.70	111777	118952	6.22
uPFS	0.82	0.03	beta	0.77	0.88	117343	113453	3.37
c_PD_gem	127.27	10.57	gamma	106.56	147.99	116868	113861	2.61
cPneumonia	7539.70	1053.10	gamma	5475.62	9603.78	116082	114648	1.24

cPembro – cost for pembrolizumab, pembro_os_con – _cons parameter for pembrolizumab OS, pembro_os_shape – _cons parameter for pembrolizumab OS, uPD – utility of PD stage, doc_os_con – _cons parameter for docetaxel OS, pembro_pfs_con – _cons parameter for pembrolizumab PFS, pembro_pfs_shape – _cons parameter for pembrolizumab PFS, c_PD_doc – cost of docetaxel treatment beyond disease progression, uPFS – utility of PFS stage, c_PD_gem – cost of gemcitabine treatment beyond disease progression, cPneumonia – cost of treatment for ≥ Gr 3 pneumonia
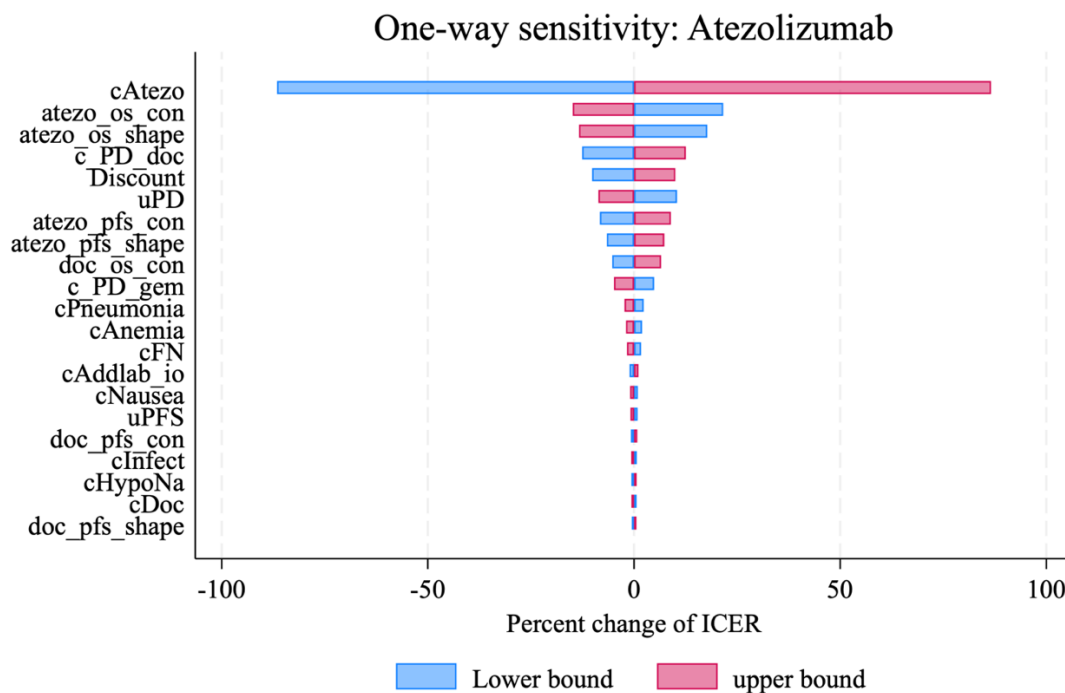
Figure 10. One-way sensitivity analysis results: Tornado diagrams for Atezolizumab.

cAtezeo – cost for atezolizumab, atezo_os_con – _cons parameter for atezolizumab OS, atezo_os_shape – shape parameter for atezolizumab OS, c_PD_doc – cost of docetaxel treatment beyond disease progression, uPD – utility of PD stage, atezo_pfs_con – _cons parameter for atezolizumab PFS, atezo_pfs_shape – shape parameter for atezolizumab PFS, doc_os_con – _cons parameter for docetaxel OS, c_PD_gem – cost of gemcitabine treatment beyond disease progression, cPneumonia – cost of treatment for ≥ Gr 3 pneumonia, cAnemia – cost of treatment for ≥ Gr 3 anemia, cFN – cost of treatment for ≥ Gr 3 febrile neutropenia, cAddlab_io – additional safety lab for ICI, cNausea – cost of treatment for ≥ Gr 3 nausea, uPFS – utility of PFS stage, doc_pfs_con – _cons parameter for docetaxel PFS, cInfect – cost of treatment for ≥ Gr3 infection, cHypoNa – cost of treatment for ≥ Gr3 hyponatremia, cDoc – cost for docetaxel, doc_pfs_shape – shape parameter for docetaxel PFS

Table 26.One-way sensitivity analysis results: Atezolizumab.

Domain	mean	SE	Distribution	Lower CI	Upper CI	Lower ICER	Upper ICER	Percent diff
cAtezo	2124.67	867.39	gamma	424.58	3824.77	4025	55981	173.17
atezo_os_con	4.03	0.06	normal	3.92	4.15	36494	25546	36.49
atezo_os_shape	-0.30	0.05	normal	-0.39	-0.21	35336	25998	31.12
c_PD_doc	91.72	14.79	gamma	62.73	120.70	26231	33776	25.15
Discount	0.03	NA	NA	0.00	0.06	26952	33011	20.19
uPD	0.75	0.04	beta	0.67	0.83	33135	27413	19.07
atezo_pfs_con	2.72	0.05	normal	2.62	2.81	27522	32684	17.21
atezo_pfs_shape	1.13	0.04	gamma	1.06	1.21	28025	32201	13.92
doc_os_con	3.64	0.03	normal	3.58	3.70	28416	31974	11.86
c_PD_gem	127.27	10.57	gamma	106.56	147.99	31463	28544	9.73
cPneumonia	7539.70	1053.10	gamma	5475.62	9603.78	30699	29307	4.64
cAnemia	5438.30	3088.00	gamma	-614.18	11490.78	30586	29420	3.89
cFN	9904.60	2721.10	gamma	4571.24	15237.96	30517	29489	3.43
cAddlab_io	40.28	10.76	gamma	19.20	61.37	29681	30326	2.15
cNausea	7757.20	1795.60	gamma	4237.82	11276.58	30286	29721	1.88
uPFS	0.82	0.03	beta	0.77	0.88	30266	29745	1.74
doc_pfs_con	2.76	0.03	normal	2.71	2.81	29779	30241	1.54
cInfect	8909.00	652.40	gamma	7630.30	10187.70	30209	29798	1.37
cHypoNa	4744.30	873.70	gamma	3031.85	6456.75	29811	30196	1.28
cDoc	0.62	0.11	gamma	0.41	0.82	30192	29814	1.26
doc_pfs_shape	0.88	0.02	gamma	0.85	0.92	29844	30174	1.10

cAtezeo – cost for atezolizumab, atezo_os_con – _cons parameter for atezolizumab OS, atezo_os_shape – shape parameter for atezolizumab OS, c_PD_doc – cost of docetaxel treatment beyond disease progression, uPD – utility of PD stage, atezo_pfs_con – _cons parameter for atezolizumab PFS, atezo_pfs_shape – shape parameter for atezolizumab PFS, doc_os_con – _cons parameter for docetaxel OS, c_PD_gem – cost of gemcitabine treatment beyond disease progression, cPneumonia – cost of treatment for ≥ Gr 3 pneumonia, cAnemia – cost of treatment for ≥ Gr 3 anemia, cFN – cost of treatment for ≥ Gr 3 febrile neutropenia, cAddlab_io – additional safety lab for ICI, cNausea – cost of treatment for ≥ Gr 3 nausea, uPFS – utility of PFS stage, doc_pfs_con – _cons parameter for docetaxel PFS, cInfect – cost of treatment for ≥ Gr3 infection, cHypoNa – cost of treatment for ≥ Gr3 hyponatremia, cDoc – cost for docetaxel, doc_pfs_shape – shape parameter for docetaxel PFS

Probabilistic sensitivity analysis of all ICI using 1000 simulations shows that nearly all possible ICERs lie above the cost-effectiveness threshold for Thailand (USD 5208 or THB 160000 per QALY) (Figures 11 and 12).
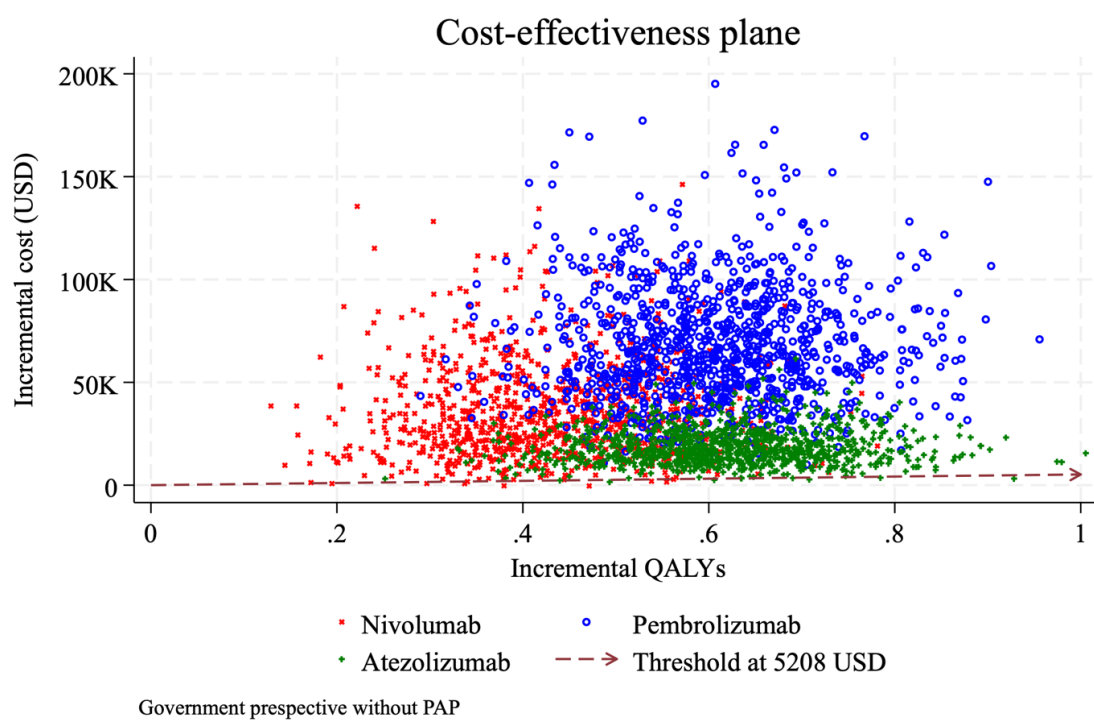
Figure 11.Cost-effectiveness plane for all drugs from a government perspective without PAP.
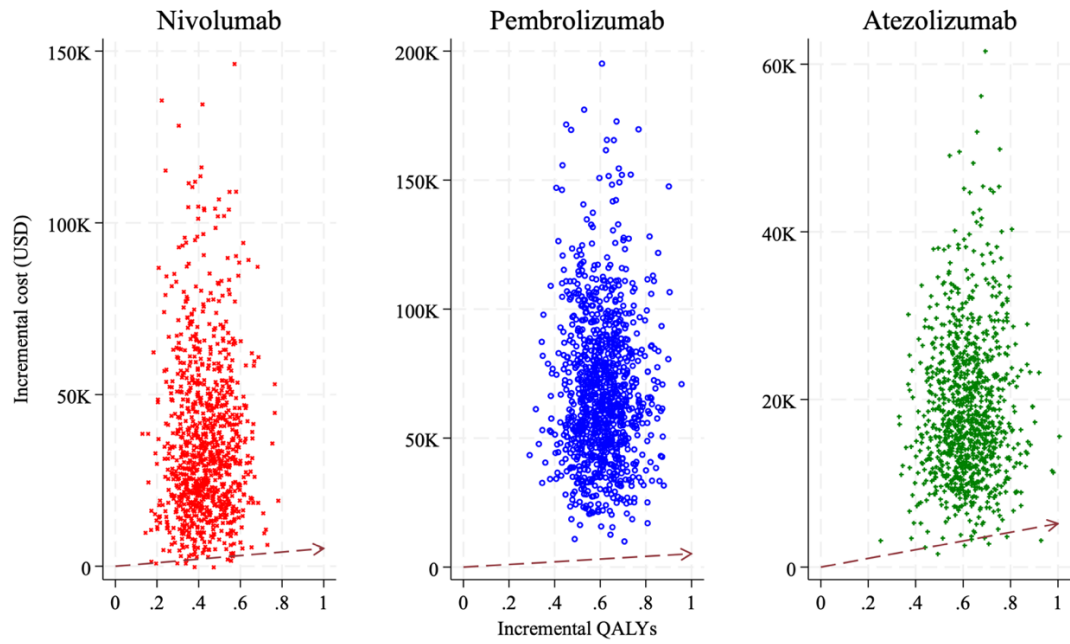
Figure 12.Cost-effectiveness planes separated by drug

With the cost-effectiveness threshold for Thailand of USD 5208, there is minimal probability of favoring any of the newer drugs (Figure 13)., Only atezolizumab has a significant increase in the probability of acceptance if the threshold increase above approximately USD 30000.
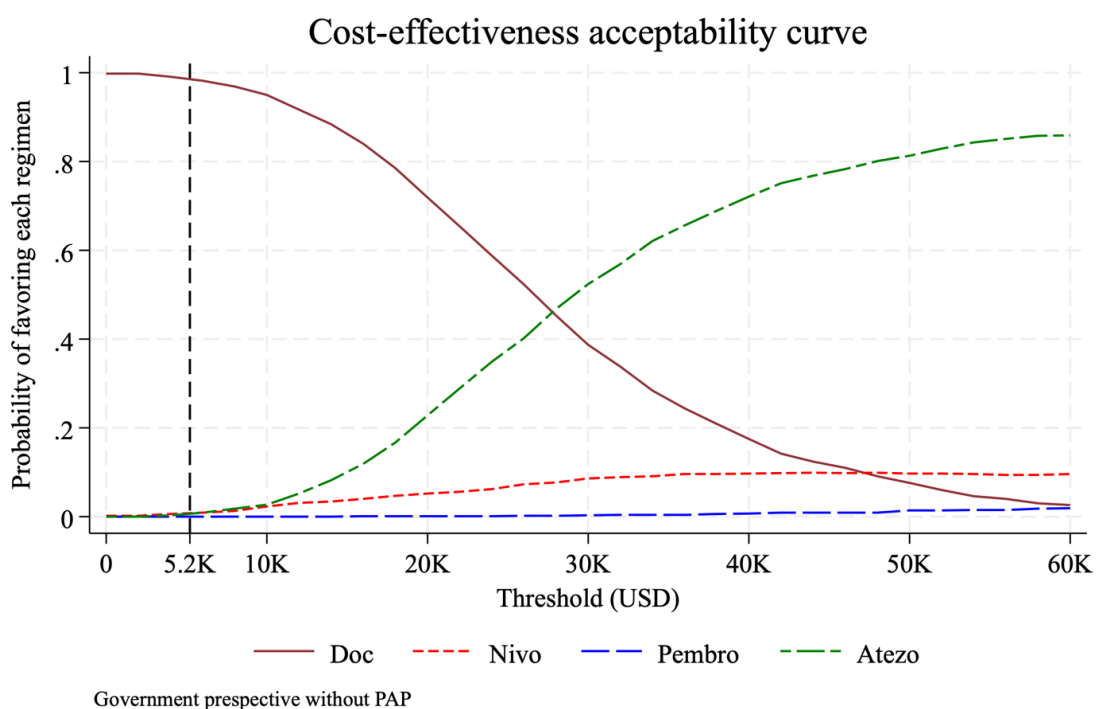
Figure 13. Cost-effectiveness acceptability curve in government perspective without PAP.

Government perspective with PAP

Deterministic Analyses: Government perspective with PAP

According to the government's deterministic model, each of the second-line ICI regimens enhanced survival relative to docetaxel in PAP patients (range: 0.55 to 0.81 incremental life-years for nivolumab and atezolizumab, respectively). QALYs gained relative to docetaxel ranged between 0.43 and 0.62 for nivolumab and atezolizumab, respectively. The increased costs of nivolumab relative to docetaxel were between USD 16,644 and USD 34,017 for pembrolizumab. Cost-effectiveness estimates ranged from USD 30,003 per QALY gained over docetaxel for atezolizumab to USD 56,280 per QALY for pembrolizumab (Table 27 and Table 28).

Table 27.Economic evaluation: Government perspective, deterministic, with PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Life year	PFS	0.46	0.61	0.66	0.56
	PD	0.93	1.41	1.66	1.78
	Total	1.29	1.84	2.07	2.11
Cost	Drug	349.96	19591.57	35711.62	20216.50
	Administrative	262.45	171.65	122.02	105.31
	CT scan	627.22	623.02	885.72	764.45
	Safety lab	76.57	838.70	596.18	514.55
	Post PD	5582.82	5932.30	6860.13	7432.59
	AE	11662.47	8048.10	8403.04	8211.25
	DNM	NA	NA	NA	NA
	Indirect	NA	NA	NA	NA
	Total	18561.48	35205.35	52578.71	37244.65
QALY		0.99	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.78	0.81
	Cost	-	16643.86	34017.23	18683.17
	QALY	-	0.43	0.60	0.62
ICER		-	39022.71	56280.72	30003.28

Table 28. Economic evaluation: Government perspective, probabilistic, with PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Total	Life year	1.30	1.84	2.08	2.11
	Cost	18529.77	36118.20	52891.88	37084.00
	QALY	1.00	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.23	0.03
	Cost	-	17588.43	34362.12	18554.24
	QALY	-	0.43	0.60	0.62
ICER		-	41067.28	56801.16	29823.34

Sensitivity Analyses: Government perspective with PAP

A probabilistic sensitivity analysis of every ICI utilizing 1000 simulations reveals that nearly all potential ICERs exceed Thailand's cost-effectiveness threshold although the analysis accounts for PAP (Figure 14).
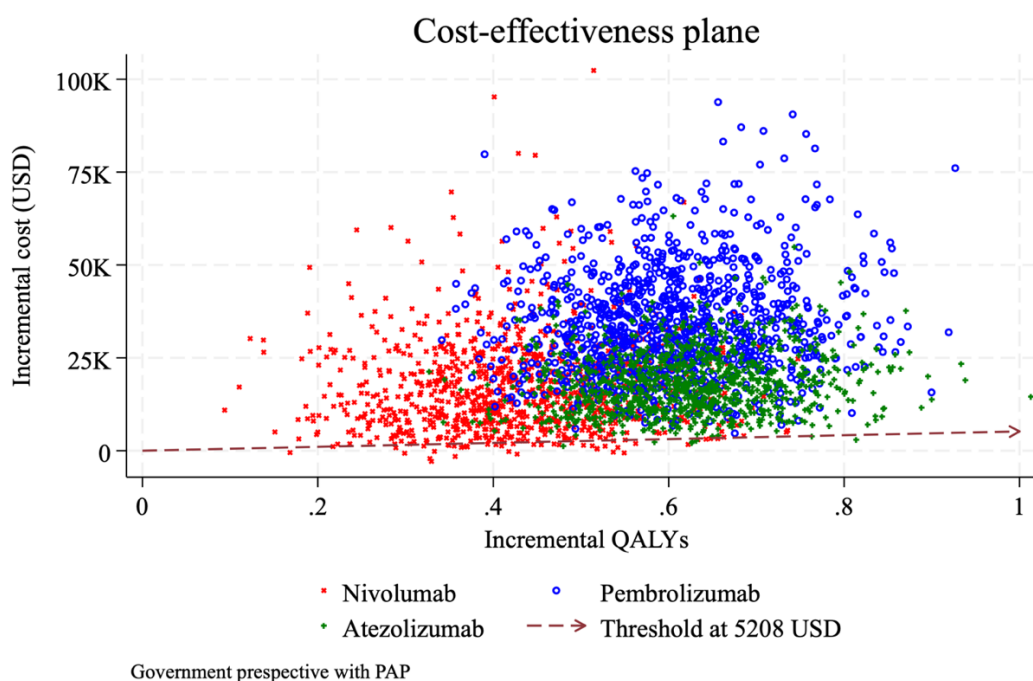
Figure 14. Cost-effectiveness plane for all drugs in government perspective with PAP.

Even though there is a low probability of favoring ICI in the PAP (Figure 15) especially with the current threshold, only atezolizumab has a significant increase in acceptance probability if the threshold is raised above approximately USD 30000, and approximately one-fifth of payers may favor nivolumab if the acceptability threshold is raised to USD 20000.
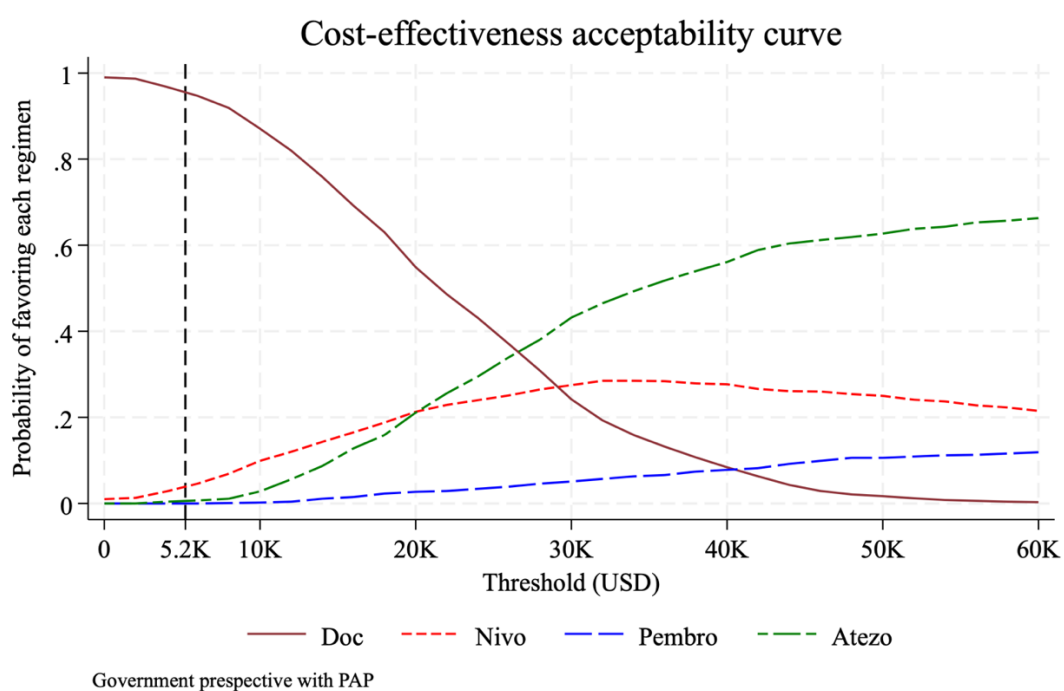
Figure 15. Cost-effectiveness acceptability curve in government perspective with PAP.

Patient perspective without PAP

Deterministic Analyses: Patient perspective without PAP

Based on the deterministic model, each of the second-line ICI regimens enhanced survival relative to docetaxel from the patient perspective without PAP (range: 0.55 to 0.81 incremental life-years for nivolumab and atezolizumab, respectively). QALYs gained relative to docetaxel ranged between 0.43 and 0.62 for nivolumab and atezolizumab, respectively. The increased cost of atezolizumab relative to docetaxel ranged from USD 19,285 to USD 70,307 for pembrolizumab. Cost-effectiveness estimates varied from USD 30,970 per QALY gained over docetaxel to USD 116,321 per QALY for atezolizumab and pembrolizumab, respectively (Table 29 and Table 30).

Table 29. Economic evaluation: Patient perspective, deterministic, without PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Life year	PFS	0.46	0.61	0.66	0.56
	PD	0.93	1.41	1.66	1.78
	Total	1.29	1.84	2.07	2.11
Cost	Drug	349.96	39183.15	71423.24	20216.50
	Administrative	262.45	171.65	122.02	105.31
	CT scan	627.22	623.02	885.72	764.45
	Safety lab	76.57	838.70	596.18	514.55
	Post PD	5582.82	5932.30	6860.13	7432.59
	AE	11662.47	8048.10	8403.04	8211.25
	DNM	958.06	1362.65	1535.95	1560.34
	Indirect	NA	NA	NA	NA
	Total	19530.82	56170.76	89837.48	38816.19
QALY		0.99	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.78	0.81
	Cost	-	36639.94	70306.66	19285.37
	QALY	-	0.43	0.60	0.62
ICER		-	85904.95	116320.76	30970.36

Table 30. Economic evaluation: Patient perspective, probabilistic, without PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Total	Life year	1.29	1.84	2.08	2.11
	Cost	19467.91	54697.87	90166.60	39436.60
	QALY	0.99	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.24	0.03
	Cost	-	35229.96	70698.69	19968.69
	QALY	-	0.43	0.61	0.63
ICER		-	82226.23	115746.54	31900.98

Sensitivity Analyses: Patient perspective without PAP

A probabilistic sensitivity analysis of each ICI employing 1000 simulations for patient perspective without PAP finds that virtually all potential ICERs exceed Thailand's cost-effectiveness threshold. (Figure 16).
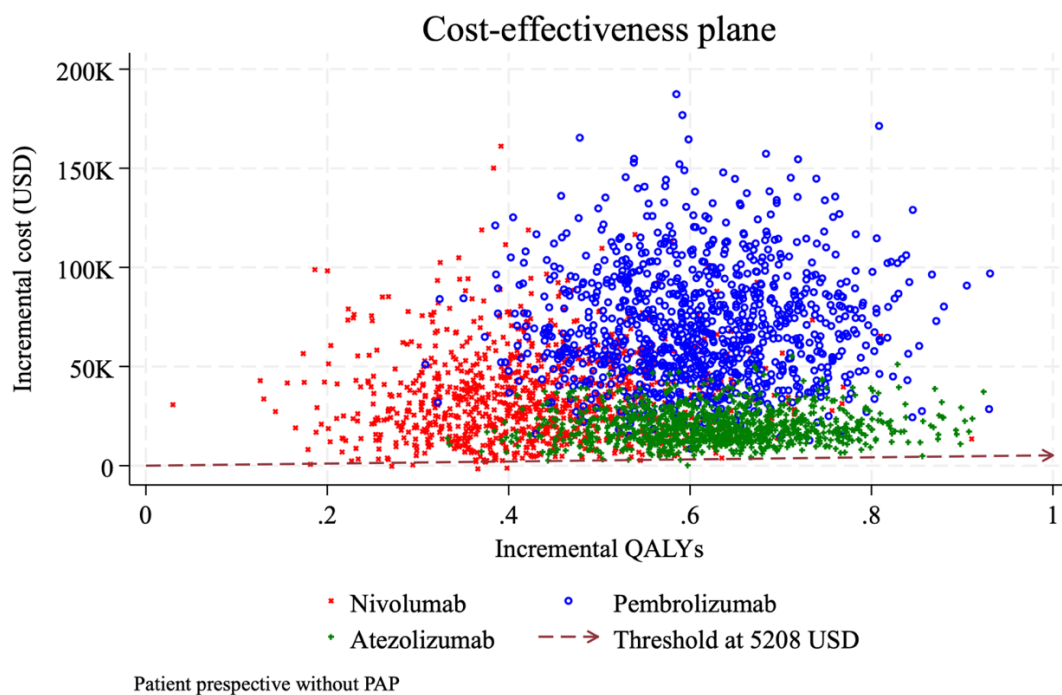
Figure 16. Cost-effectiveness plane for all drugs in patient perspective without PAP.

Even though there is a limited probability of favoring ICI in this setting (Figure 17), especially with the current threshold. Only atezolizumab shows a considerable increase in probability of acceptance if the threshold is raised over about USD 30,000, however there is no indication that the other two ICIs are acceptable from the patient perspective without PAP.
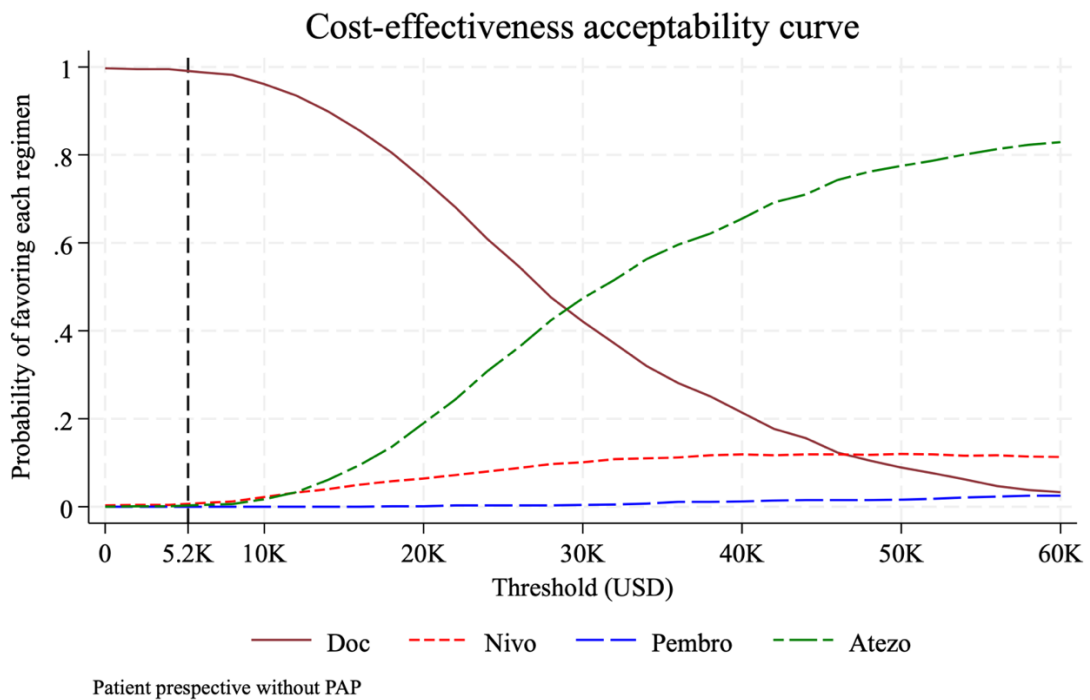
Figure 17. Cost-effectiveness acceptability curve in patient perspective without PAP.

Patient perspective with PAP

Deterministic Analyses: Patient perspective with PAP

Based on the deterministic model, each of the second-line ICI regimens improved patient survival relative to docetaxel with PAP (range: 0.55 to 0.81 incremental life-years for nivolumab and atezolizumab, respectively). The range of QALYs gained relative to docetaxel for nivolumab and atezolizumab was between 0.43 and 0.62. The price difference between nivolumab and docetaxel varied from USD 17,048 to USD 34,595 for pembrolizumab. Cost-effectiveness estimates for atezolizumab and pembrolizumab ranged from USD 30,970 per QALY gained over docetaxel to USD 57,237 per QALY, respectively (Table 31 and Table 32).

Table 31. Economic evaluation: Patient perspective, deterministic, with PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Life year	PFS	0.46	0.61	0.66	0.56
	PD	0.93	1.41	1.66	1.78
	Total	1.29	1.84	2.07	2.11
Cost	Drug	349.96	19591.57	35711.62	20216.50
	Administrative	262.45	171.65	122.02	105.31
	CT scan	627.22	623.02	885.72	764.45
	Safety lab	76.57	838.70	596.18	514.55
	Post PD	5582.82	5932.30	6860.13	7432.59
	AE	11662.47	8048.10	8403.04	8211.25
	DNM	958.06	1362.65	1535.95	1560.34
	Indirect	NA	NA	NA	NA
	Total	19530.82	36579.19	54125.86	38816.19
QALY		0.99	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.78	0.81
	Cost	-	17048.37	34595.04	19285.37
	QALY	-	0.43	0.60	0.62
ICER		-	39971.11	57236.70	30970.36

Table 32. Economic evaluation: Patient perspective, probabilistic, with PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Total	Life year	1.30	1.84	2.08	2.11
	Cost	19639.54	36990.41	54935.35	39128.14
	QALY	1.00	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.24	0.03
	Cost	-	17350.87	35295.81	19488.60
	QALY	-	0.43	0.60	0.62
ICER		-	40730.46	58348.28	31399.69

Sensitivity Analyses: Patient perspective with PAP

A probabilistic sensitivity analysis of each ICI employing 1000 simulations for patient perspective with PAP finds that virtually all potential ICERs exceed Thailand's cost-effectiveness threshold despite the inclusion of PAP in the analysis (Figure 18)
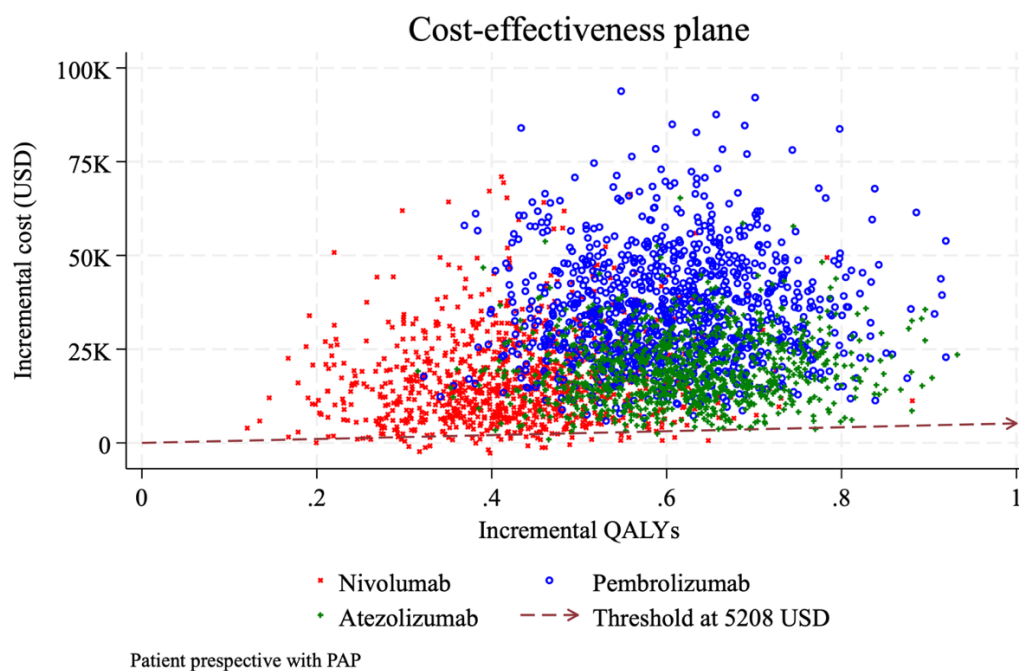
Figure 18. Cost-effectiveness plane for all drugs in patient perspective with PAP.

Even while there is a little likelihood of favoring ICI in the PAP (Figure 19), especially with the current threshold, there is a small probability of favoring ICI. Only atezolizumab exhibits a significant increase in likelihood of acceptance if the threshold is raised over around USD 30,000, but less than one-fourth of patients may accept nivolumab if the threshold is raised to USD 20,000 or more.
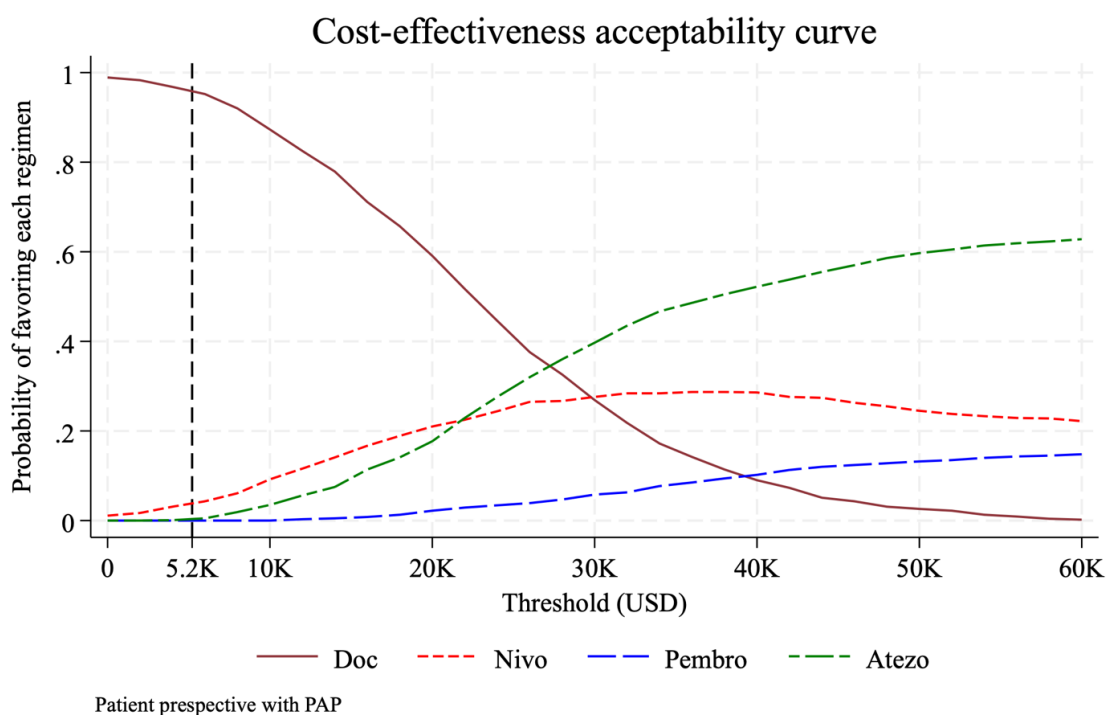
Figure 19. Cost-effectiveness acceptability curve in patient perspective with PAP.

Societal perspective without PAP

Deterministic Analyses: Societal perspective without PAP

Based on the deterministic model, each of the second-line ICI regimens enhanced survival relative to docetaxel from the societal perspective without PAP (range: 0.55 to 0.81 incremental life-years for nivolumab and atezolizumab, respectively). QALYs gained relative to docetaxel ranged between 0.43 and 0.62 for nivolumab and atezolizumab, respectively. The increased cost of atezolizumab relative to docetaxel ranged from USD 19,288 to USD 70,309 for pembrolizumab. Cost-effectiveness estimates varied from USD 30,974 per QALY gained over docetaxel to USD 116,325 per QALY for atezolizumab and pembrolizumab, respectively (Table 33 and Table 34).

Table 33. Economic evaluation: Societal perspective, deterministic, without PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Life year	PFS	0.46	0.61	0.66	0.56
	PD	0.93	1.41	1.66	1.78
	Total	1.29	1.84	2.07	2.11
Cost	Drug	349.96	39183.15	71423.24	20216.50
	Administrative	262.45	171.65	122.02	105.31
	CT scan	627.22	623.02	885.72	764.45
	Safety lab	76.57	838.70	596.18	514.55
	Post PD	5582.82	5932.30	6860.13	7432.59
	AE	11662.47	8048.10	8403.04	8211.25
	DNM	958.06	1362.65	1535.95	1560.34
	Indirect	4.12	5.94	6.72	6.66
	Total	19534.94	56176.70	89844.20	38822.84
QALY		0.99	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.78	0.81
	Cost	-	36641.76	70309.26	19287.90
	QALY	-	0.43	0.60	0.62
ICER		-	85909.20	116325.06	30974.43

Table 34. Economic evaluation: Societal perspective, probabilistic, without PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Total	Life year	1.29	1.85	2.08	2.11
	Cost	19595.39	57593.20	88361.37	38870.38
	QALY	0.99	1.43	1.60	1.62
Incremental	Life year	-	0.56	0.23	0.03
	Cost	-	37997.81	68765.98	19274.99
	QALY	-	0.43	0.61	0.63
ICER		-	87596.10	112827.64	30768.67

Sensitivity Analyses: Societal perspective without PAP

Almost all potential ICERs exceed Thailand's cost-effectiveness barrier, as determined by a probabilistic sensitivity analysis of each ICI employing 1,000 simulations for societal perspective without PAP. (Figure 20).
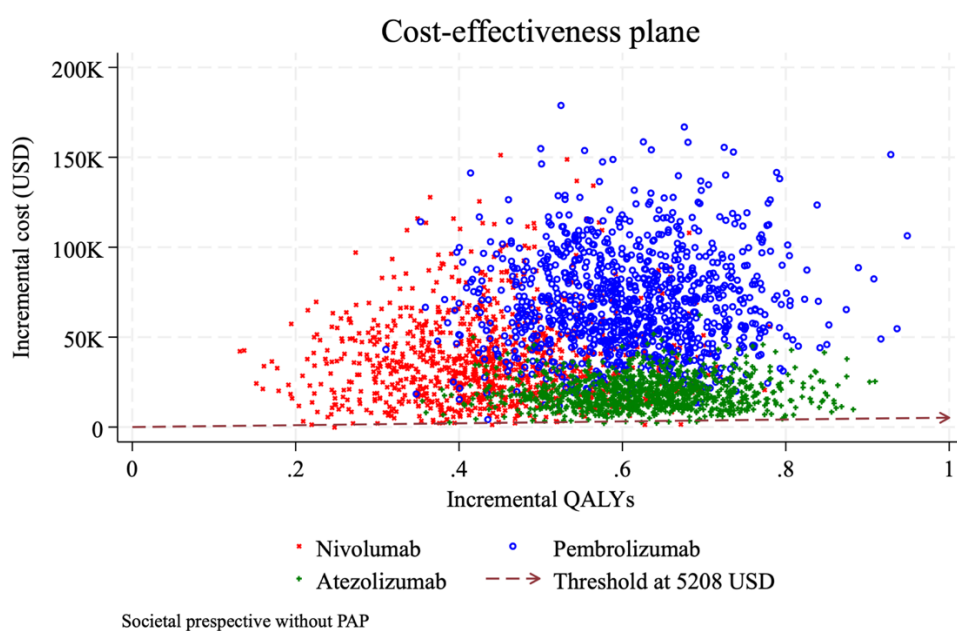
Figure 20. Cost-effectiveness plane for all drugs in societal perspective without PAP.

Even while there is a small chance of favoring ICI from a societal standpoint without PAP (Figure 21), especially with the current threshold, the possibility is still small. Only atezolizumab exhibits a significant increase in chance of acceptance if the threshold is raised over around USD 30,000, however there is no evidence that the other two ICIs are socially acceptable without PAP.
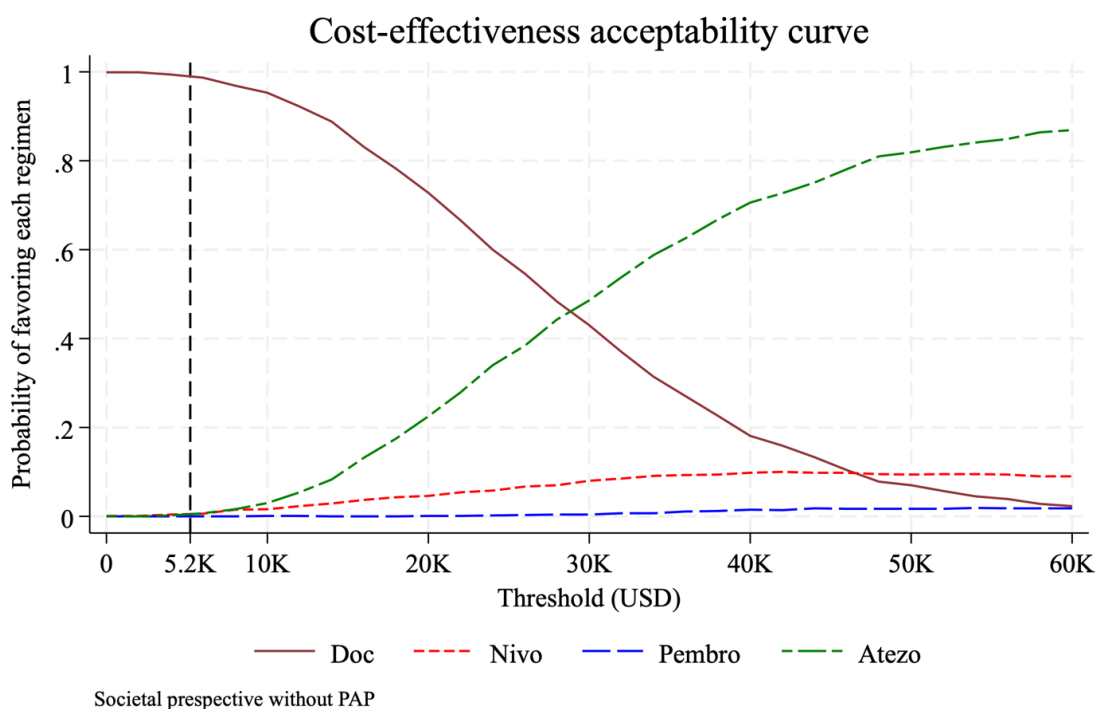
Figure 21. Cost-effectiveness acceptability curve in societal perspective without PAP.

Societal perspective with PAP

Deterministic Analyses: Societal perspective with PAP

Based on the deterministic model, with a societal perspective with PAP, each of the second-line ICI regimens improved patient survival relative to docetaxel with PAP (range: 0.55 to 0.81 incremental life-years for nivolumab and atezolizumab, respectively). The range of QALYs gained relative to docetaxel for nivolumab and atezolizumab was between 0.43 and 0.62. The price difference between atezolizumab and docetaxel varied from USD 19,287 to USD 34,598 for pembrolizumab. Cost-effectiveness estimates for atezolizumab and pembrolizumab ranged from USD 30,974 per QALY gained over docetaxel to USD 57,241 per QALY, respectively (Table 35 and Table 36).

Table 35. Economic evaluation: Societal perspective, deterministic, with PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Life year	PFS	0.46	0.61	0.66	0.56
	PD	0.93	1.41	1.66	1.78
	Total	1.29	1.84	2.07	2.11
Cost	Drug	349.96	19591.57	35711.62	20216.50
	Administrative	262.45	171.65	122.02	105.31
	CT scan	627.22	623.02	885.72	764.45
	Safety lab	76.57	838.70	596.18	514.55
	Post PD	5582.82	5932.30	6860.13	7432.59
	AE	11662.47	8048.10	8403.04	8211.25
	DNM	958.06	1362.65	1535.95	1560.34
	Indirect	4.12	5.94	6.72	6.66
	Total	19534.94	36585.12	54132.58	38822.84
QALY		0.99	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.78	0.81
	Cost	-	17050.18	34597.64	19287.90
	QALY	-	0.43	0.60	0.62
ICER		-	39975.37	57241.00	30974.43

Table 36. Economic evaluation: Societal perspective, probabilistic, with PAP scenario.

Domain		Docetaxel	Nivolumab	Pembrolizumab	Atezolizumab
Total	Life year	1.30	1.84	2.08	2.11
	Cost	19542.24	36226.16	54219.58	38747.59
	QALY	1.00	1.42	1.60	1.62
Incremental	Life year	-	0.55	0.24	0.03
	Cost	-	16683.92	34677.34	19205.35
	QALY	-	0.43	0.61	0.62
ICER		-	39094.08	57048.50	30800.15

Sensitivity Analyses: Societal perspective with PAP

Despite the addition of PAP, practically all potential ICERs exceed Thailand's cost-effectiveness threshold according to a probabilistic sensitivity analysis of each ICI employing 1000 simulations for societal perspective with PAP (Figure 22)
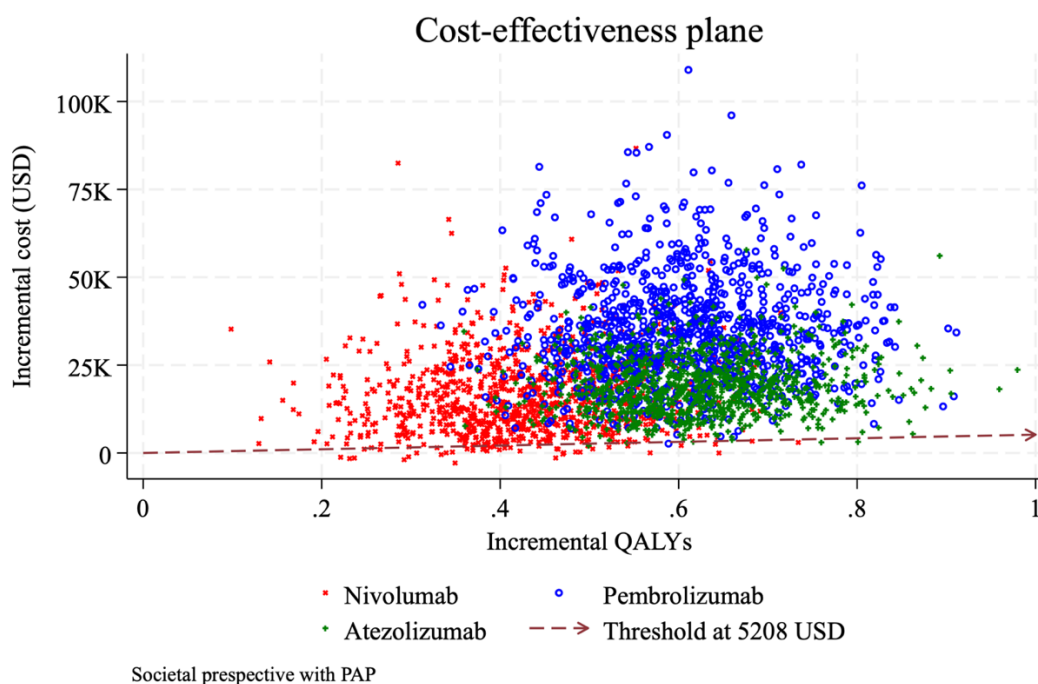
Figure 22. Cost-effectiveness plane for all drugs in societal perspective with PAP.

Even if there is a little chance of favoring ICI in this environment (Figure 23), especially with the present threshold, there is still a small chance of benefiting ICI. Only atezolizumab exhibits a significant increase in acceptance likelihood when the threshold is raised above around USD 30,000 followed by nivolumab and pembrolizumab.
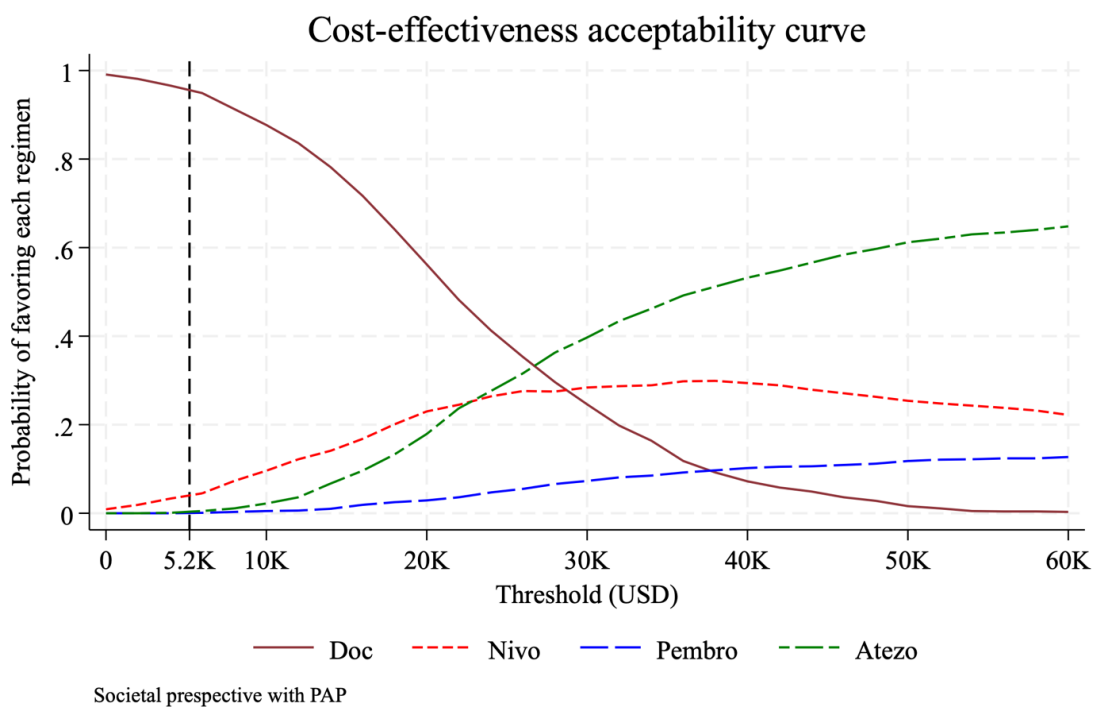
Figure 23. Cost-effectiveness acceptability curve in societal perspective with PAP.

Threshold analysis

Based on the USD 5,208 in the government model, the acceptable nivolumab (100 mg) cost should be reduced from USD 1,533 to USD 202 and USD 404 in the absence and presence of PAP (buy-one-get-one-free). Pembrolizumab (100 mg) should cost USD 220 (or USD 439 with PAP) rather than USD 3,239. Finally, the price of 1200 mg atezolizumab should be reduced to USD 502 rather than USD 2,125.

Table 37. Threshold analysis for drug cost.

Drug	Cost		
	Base	Accepted condition	
Nivo 100 mg	1532.55	without PAP	202.17
		with PAP	404.35
Pembro 100 mg	3239.26	without PAP	219.61
		with PAP	439.22
Atezo 1200 mg	2124.67		501.98

Financial Burden in Lung Cancer Results

Sample characteristics

A total of 437 lung cancer patients were enrolled in the study. Table 38 depicts demographic characteristics. In total, 51% of patients were male, with a median age of 66, and 58% were receiving active treatment. The current treatment regimens consisted of 45% chemotherapy and 32% targeted/immune-oncotherapy (TKI/IO). The others received no medical treatment. Fifty-seven percent of the cases began as stage IV lung cancer. Adenocarcinoma, squamous cell carcinoma, and small cell carcinoma were the most common histological subtypes, accounting for 87%, 8%, and 3% of all cases, respectively. Fifty-five percent of the patients had no/unknown driver mutation, while 38 percent had EGFR mutation. Paclitaxel-carboplatin (Pac/Cb) was the most widely given first-line treatment, accounting for 39% of all prescriptions, followed by erlotinib (19%) and gefitinib (15%). In the second-line setting, 40% of patients were treated with paclitaxel-carboplatin, while 31% were treated with docetaxel.

Table 38. Demographic data.

Variable	UCS (N=197)	CSMBS (N=217)	SSS (N=23)	Total (N=437)	Test
Stage of treatment					
Locally adv	65 (33.0%)	68 (31.3%)	8 (34.8%)	141 (32.3%)	0.201
First-line	98 (49.7%)	91 (41.9%)	11 (47.8%)	200 (45.8%)	
Second-line or more	34 (17.3%)	58 (26.7%)	4 (17.4%)	96 (22.0%)	
current status					
active Rx	116 (58.9%)	126 (58.1%)	13 (56.5%)	255 (58.4%)	0.969
complete Rx	81 (41.1%)	91 (41.9%)	10 (43.5%)	182 (41.6%)	
Current Rx type					
No active Rx	43 (21.8%)	52 (24.0%)	7 (30.4%)	102 (23.3%)	0.293
CMT	99 (50.3%)	89 (41.0%)	8 (34.8%)	196 (44.9%)	
Tki/IO	55 (27.9%)	76 (35.0%)	8 (34.8%)	139 (31.8%)	
age	64.5 ± 10.5	67.5 ± 9.9	55.4 ± 9.2	65.5 ± 10.5	<0.001
sex					
male	94 (47.7%)	119 (54.8%)	10 (43.5%)	223 (51.0%)	0.266
female	103 (52.3%)	98 (45.2%)	13 (56.5%)	214 (49.0%)	
Initial stage					
1A	29 (14.7%)	36 (16.6%)	5 (21.7%)	70 (16.0%)	0.746
1B	7 (3.6%)	18 (8.3%)	3 (13.0%)	28 (6.4%)	
2A	3 (1.5%)	6 (2.8%)	1 (4.3%)	10 (2.3%)	
2B	10 (5.1%)	6 (2.8%)	1 (4.3%)	17 (3.9%)	
3A	14 (7.1%)	15 (6.9%)	2 (8.7%)	31 (7.1%)	
3B	12 (6.1%)	14 (6.5%)	0 (0.0%)	26 (5.9%)	
3C	3 (1.5%)	2 (0.9%)	0 (0.0%)	5 (1.1%)	
4A	65 (33.0%)	64 (29.5%)	7 (30.4%)	136 (31.1%)	
4B	54 (27.4%)	56 (25.8%)	4 (17.4%)	114 (26.1%)	
T stage					
1a	7 (3.6%)	4 (1.8%)	0 (0.0%)	11 (2.5%)	0.285
1b	15 (7.6%)	25 (11.5%)	1 (4.3%)	41 (9.4%)	
1c	33 (16.8%)	40 (18.4%)	8 (34.8%)	81 (18.5%)	
2a	31 (15.7%)	35 (16.1%)	7 (30.4%)	73 (16.7%)	
2b	21 (10.7%)	27 (12.4%)	1 (4.3%)	49 (11.2%)	
3	36 (18.3%)	33 (15.2%)	2 (8.7%)	71 (16.2%)	
4	54 (27.4%)	53 (24.4%)	4 (17.4%)	111 (25.4%)	
N stage					
0	83 (42.1%)	100 (46.1%)	11 (47.8%)	194 (44.4%)	0.343

Variable	UCS (N=197)	CSMBS (N=217)	SSS (N=23)	Total (N=437)	Test
1	17 (8.6%)	18 (8.3%)	1 (4.3%)	36 (8.2%)	
2	38 (19.3%)	53 (24.4%)	3 (13.0%)	94 (21.5%)	
3	59 (29.9%)	46 (21.2%)	8 (34.8%)	113 (25.9%)	
M stage					
0	83 (42.1%)	99 (45.6%)	12 (52.2%)	194 (44.4%)	0.576
1	114 (57.9%)	118 (54.4%)	11 (47.8%)	243 (55.6%)	
Pathology					
Adeno	163 (82.7%)	193 (88.9%)	23 (100.0%)	379 (86.7%)	0.293
Sq	19 (9.6%)	17 (7.8%)	0 (0.0%)	36 (8.2%)	
SCLC	7 (3.6%)	6 (2.8%)	0 (0.0%)	13 (3.0%)	
NSCLC-NOS	3 (1.5%)	0 (0.0%)	0 (0.0%)	3 (0.7%)	
Adeno-Sq	3 (1.5%)	1 (0.5%)	0 (0.0%)	4 (0.9%)	
LCNET	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	
Biomarker					
NOS/unknown	119 (60.4%)	107 (49.3%)	14 (60.9%)	240 (54.9%)	0.463
EGFR	68 (34.5%)	91 (41.9%)	7 (30.4%)	166 (38.0%)	
ALK	10 (5.1%)	17 (7.8%)	2 (8.7%)	29 (6.6%)	
MET 14	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)	
ROS1	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)	
definite surgery					
no	144 (73.1%)	140 (64.5%)	11 (47.8%)	295 (67.5%)	0.021
yes	53 (26.9%)	77 (35.5%)	12 (52.2%)	142 (32.5%)	
curative XRT					
no	190 (96.4%)	211 (97.2%)	23 (100.0%)	424 (97.0%)	0.617
yes	7 (3.6%)	6 (2.8%)	0 (0.0%)	13 (3.0%)	
adjuvant CMT					
no	175 (88.8%)	197 (90.8%)	19 (82.6%)	391 (89.5%)	0.442
yes	22 (11.2%)	20 (9.2%)	4 (17.4%)	46 (10.5%)	
CCRT					
no	176 (89.3%)	200 (92.2%)	23 (100.0%)	399 (91.3%)	0.187
yes	21 (10.7%)	17 (7.8%)	0 (0.0%)	38 (8.7%)	
First-line					
Afatinib	13 (9.9%)	6 (4.1%)	2 (13.3%)	21 (7.2%)	0.072
Alectinib	0 (0.0%)	2 (1.4%)	1 (6.7%)	3 (1.0%)	
Atezo Tirago	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.3%)	
Atezolizumab	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.3%)	
Brigatinib	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.3%)	

Variable	UCS (N=197)	CSMBS (N=217)	SSS (N=23)	Total (N=437)	Test
CAV	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Ceritinib	5 (3.8%)	8 (5.5%)	1 (6.7%)	14 (4.8%)	
Crizotinib	1 (0.8%)	3 (2.1%)	0 (0.0%)	4 (1.4%)	
Docetaxel	2 (1.5%)	1 (0.7%)	0 (0.0%)	3 (1.0%)	
Durvalumab	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Erlotinib	32 (24.4%)	20 (13.7%)	4 (26.7%)	56 (19.2%)	
Eto Cb	1 (0.8%)	2 (1.4%)	0 (0.0%)	3 (1.0%)	
Eto Cis	3 (2.3%)	2 (1.4%)	0 (0.0%)	5 (1.7%)	
Gefitinib	4 (3.1%)	41 (28.1%)	0 (0.0%)	45 (15.4%)	
Gem Cb	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Gemcitabine	2 (1.5%)	1 (0.7%)	0 (0.0%)	3 (1.0%)	
Medi5752	1 (0.8%)	1 (0.7%)	0 (0.0%)	2 (0.7%)	
Osimertinib	2 (1.5%)	3 (2.1%)	0 (0.0%)	5 (1.7%)	
Pac Cb	55 (42.0%)	51 (34.9%)	7 (46.7%)	113 (38.7%)	
Pac Cb Beva	2 (1.5%)	1 (0.7%)	0 (0.0%)	3 (1.0%)	
Pac Cb Pemb	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Pem Cb	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.3%)	
Pem Cb Osimer	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Pem Cb Pemb ACZ	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Peme C6 Pem	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Peme Cb Pemb Cana	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
Second-line					
Afatinib	3 (9.4%)	0 (0.0%)	0 (0.0%)	3 (3.2%)	0.058
Ceritinib	0 (0.0%)	2 (3.4%)	0 (0.0%)	2 (2.1%)	
Crizotinib	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (1.1%)	
Docetaxel	14 (43.8%)	14 (24.1%)	1 (25.0%)	29 (30.9%)	
Erlotinib	1 (3.1%)	1 (1.7%)	0 (0.0%)	2 (2.1%)	
Gefitinib	0 (0.0%)	5 (8.6%)	2 (50.0%)	7 (7.4%)	
Osimertinib	1 (3.1%)	10 (17.2%)	0 (0.0%)	11 (11.7%)	
Pac Cb	13 (40.6%)	23 (39.7%)	1 (25.0%)	37 (39.4%)	
Pem Cb	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (1.1%)	
Pem Cis	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (1.1%)	
Third-line					
Afatinib	1 (25.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	0.121
Atezolizumab	1 (25.0%)	1 (4.8%)	1 (33.3%)	3 (10.7%)	
Docetaxel	1 (25.0%)	11 (52.4%)	1 (33.3%)	13 (46.4%)	
Erlotinib	1 (25.0%)	1 (4.8%)	0 (0.0%)	2 (7.1%)	

Variable	UCS (N=197)	CSMBS (N=217)	SSS (N=23)	Total (N=437)	Test
Gefitinib	0 (0.0%)	3 (14.3%)	0 (0.0%)	3 (10.7%)	
Gemcitabine	0 (0.0%)	0 (0.0%)	1 (33.3%)	1 (3.6%)	
Osimertinib	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (3.6%)	
Pac Cb	0 (0.0%)	1 (4.8%)	0 (0.0%)	1 (3.6%)	
Premetrexed	0 (0.0%)	3 (14.3%)	0 (0.0%)	3 (10.7%)	
Fourth-line					
Atezolizumab	0 (.%)	1 (16.7%)	0 (0.0%)	1 (14.3%)	0.221
Ceritinib	0 (.%)	1 (16.7%)	0 (0.0%)	1 (14.3%)	
Docetaxel	0 (.%)	0 (0.0%)	1 (100.0%)	1 (14.3%)	
Gemcitabine	0 (.%)	1 (16.7%)	0 (0.0%)	1 (14.3%)	
Osimertinib	0 (.%)	2 (33.3%)	0 (0.0%)	2 (28.6%)	
Premetrexed	0 (.%)	1 (16.7%)	0 (0.0%)	1 (14.3%)	
Fifth-line					
Erlotinib	0 (.%)	1 (25.0%)	0 (.%)	1 (25.0%)	.
Gem	0 (.%)	1 (25.0%)	0 (.%)	1 (25.0%)	
Pac Cb	0 (.%)	1 (25.0%)	0 (.%)	1 (25.0%)	
Premetrexed	0 (.%)	1 (25.0%)	0 (.%)	1 (25.0%)	

Expenditure data

As indicated in Table 39, the total yearly out-of-pocket (OOP) payment included unreimbursed prescription costs, non-medical charges, food costs, supplemental costs, accommodation costs, transportation costs, in-patient costs, housing improvement/facility costs, and caretaker costs. In UCS, CSMBS, and SSS, the geometric means (geometric standard deviation, GSD) of total yearly expenses were 1665 (4.2), 1733 (3.0), and 1329 (6.8), respectively. Except for supplemental and extra-medical costs for hospitalized patients, which were highest in the CSMBS group, other costs were not statistically different among payment schemes. The figure of the total expenditure and annual health care cost is shown in the appendix E.

Table 39. Demographic cost data (geometric mean) in USD.

Variable	UCS (n=197)	CSMBS (n=217)	SSS (n=23)	Total (N=437)	*p-value*
Annual extra-medical cost for OPD, n=437	1369.2 (20.5)	136.6 (29.6)	1252.8 (40.5)	540.8 (29.4)	0.203
Annual extra-medical cost OPD visit other hospital, n=437	1277.2 (6.3)	481.2 (4.7)	746.3 (1.8)	852.9 (5.4)	0.865
Annual drug cost outside hospital, n=437	52.3 (3.5)	60.7 (3.4)	66.6 (1.8)	58.0 (3.3)	0.240
Annual herb cost, n=437	372.3 (2.7)	245.4 (3.7)	336.4 (5.1)	275.7 (3.4)	0.477
Annual supplement cost, n=437	493.6 (2.2)	610.4 (2.7)	466.7 (2.9)	550.1 (2.5)	0.004
Annual extra-medical cost IPD, n=273	104.4 (6.1)	220.5 (4.0)	66.0 (9.3)	155.8 (5.2)	<0.001
Annual OOP for medical cost, n=437	739.1 (6.7)	841.8 (4.1)	723.7 (10.6)	788.3 (5.5)	0.095
Annual non-medical cost of OPD visit at study hospital, n=437	417.7 (3.5)	323.5 (3.5)	423.0 (5.7)	366.6 (3.6)	0.570
Annual food cost OPD visit at study hospital, n=417	102.2 (3.6)	87.6 (3.2)	122.0 (3.7)	95.1 (3.4)	0.532
Annual stay cost OPD visit at study hospital, n=417	320.9 (8.8)	689.0 (4.3)	1192.5 (2.8)	479.2 (6.6)	0.209
Annual non-medical cost of OPD visit at study hospital, n=437	417.7 (3.5)	323.5 (3.5)	423.0 (5.7)	366.6 (3.6)	0.570
Annual IPD cost, n=437	47.5 (2.2)	39.6 (2.4)	28.9 (2.3)	42.1 (2.3)	0.279
Annual house improvement and facility cost, n=437	375.2 (4.6)	487.9 (4.5)	320.4 (3.8)	429.5 (4.5)	0.783
Annual cost of formal caregiver, n=437	1049.0 (5.1)	2484.9 (3.0)	840.6 (NA)	1599.7 (4.0)	0.994
Annual OOP for non-medical, n=437	534.1 (3.8)	498.7 (3.8)	358.3 (5.7)	505.4 (3.9)	0.489
Total annual OOP, n=437	1665.3 (4.2)	1733.3 (3.0)	1328.5 (6.8)	1678.7 (3.7)	0.566

CHE and medical impoverishment

Sixty-six percent of all subjects reported having CHE. In UCS, CSMBS, and SSS, 69 percent, 64 percent, and 57 percent, respectively, reported CHE. Among UCS patients, 36% were already impoverished, and another 30% became impoverished as a result of medical-related expenses. The equivalent figures for CSMBS patients were 20% and 27%, respectively, and for SSS patients, 26% and 30% as shown in Table 40.

Table 40. Prevalence of CHE and medical impoverishment.

Columns by: payment scheme	UCS (n=197)	CSMBS (n=217)	SSS (n=23)	Total (N=437)	*p-value*
Pre-OOP impoverishment, n=437	70 (35.5)	41 (18.9)	6 (26.1)	117 (26.8)	<0.001
Medical impoverishment, n=437	59 (29.9)	59 (27.2)	7 (30.4)	125 (28.6)	0.809
CHE, n=437	136 (69.0)	138 (63.6)	13 (56.5)	287 (65.7)	0.323

A quarter of the patients, or 27 percent, fulfilled the criterion for poor before meeting the costs of healthcare, and nearly ninety percent of the patients in the quintiles with the lowest incomes were also in the poor group.

In the lowest income quintile, 8.9 percent of patients suffered medical impoverishment. In the group with the second-lowest earnings, this rate jumped dramatically to 47.3%. After that, the percentage of patients living in medical poverty decreased gradually to 40.5 percent, 32.6% in the third and fourth quintiles, and swiftly to 13.1% in the fifth quintile (Table 41).

Table 41. CHE and medical impoverishment by QTE: n (col%).

Columns by: QTE	Q 1 (n=90)	Q 2 (n=93)	Q 3 (n=84)	Q 4 (n=86)	Q 5 (n=84)	Total (N=437)	*p-value*
Pre-OOP impoverishment, n=437	80 (88.9)	27 (29.0)	10 (11.9)	0 (0.0)	0 (0.0)	117 (26.8)	<0.001
Medical impoverishment, n=437	8 (8.9)	44 (47.3)	34 (40.5)	28 (32.6)	11 (13.1)	125 (28.6)	<0.001
CHE, n=437	87 (96.7)	68 (73.1)	58 (69.0)	43 (50.0)	31 (36.9)	287 (65.7)	<0.001

Concentration curve and concentration index

Both the inequality of CHE (Figure 24A) and the impoverishment of medical care (Figure 24B) are portrayed as concentration curves. The upper-left shift of concentration curves relative to the line of equity (diagonal line) in all payment systems suggested that CHE occurred more frequently in patients with less wealth. This was the case regardless of the payment scheme.
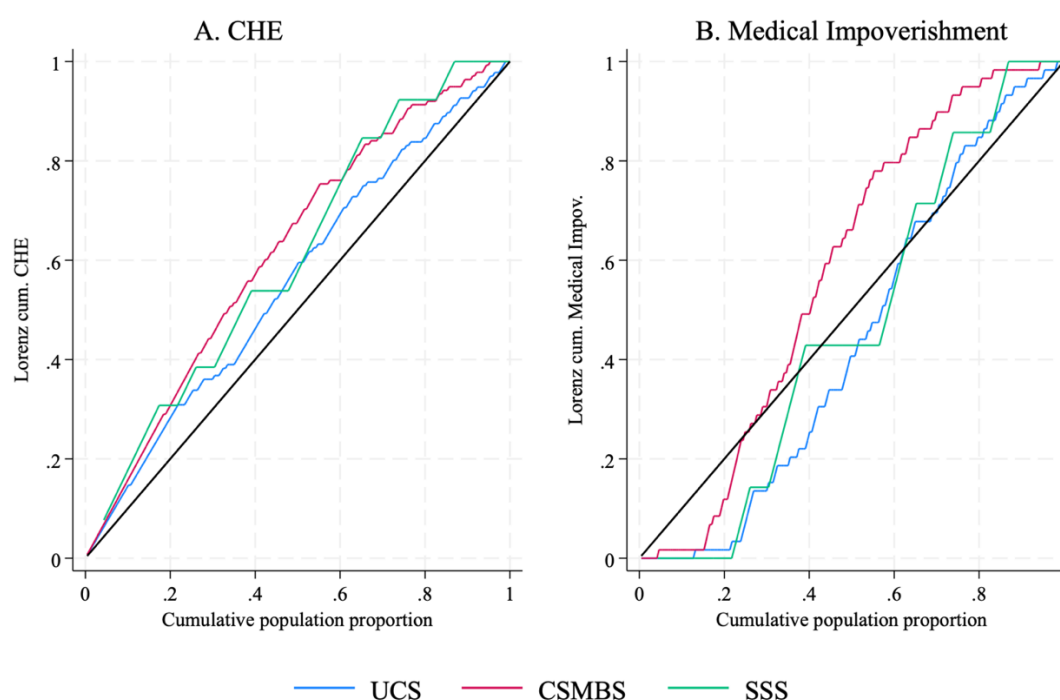
Figure 24. Concentration curves for payment schemes and cumulative proportion of CHE (A) and Medical impoverishment (B).

It can be seen from the data that the concentration curve for CHE in the CSMBS group was very distant from the line of equality that there was a greater degree of inequality in the CSMBS group. The concentration indices, expressed as standard errors, were as follows: -0.35 (0.07) in UCS, -0.62 (0.06) in CSMBS, and -0.47 (0.23) in SSS. Only

between the UCS and CSMBS groups was the difference in the CI among payments statistically significant (diff = -0.27, p-value = 0.006).

The concentration curves for medical impoverishment began below the diagonal line. After then, it moved closer to the line of equity in just UCS and SSS, whereas the CI line clearly passed above the line of equity in CSMBS. The concentration index (SE) for medical impoverishment was 0.15 (0.07) in UCS, -0.17 (0.07) in CSMBS, and 0.05 (0.23) in SSS. Each of these three systems had a different value. Only the CI for CSMBS showed a statistically significant difference from that of UCS (the difference was -0.32 and the p-value was 0.001).

Logistic regression modeling

Table 42 illustrates the logistic regression models for medical impoverishment. For the QTE model, the multivariable-adjusted interaction with a quadratic term provides the best fit and the greatest discriminatory power (AUC = 0.79).

Table 42. Odds ratio and 95% CI for medical impoverishment from various logistic models.

Variable	Naive	Int_L_qTE_noAdj	Int_Q_qTE_Adj
Quintile of TE for each payment scheme	0.975	1.238	64.079
	(0.842 1.129)	(0.993 1.542)	(12.579 326.414)
CSMBS	0.873	3.696	14.133
	(0.570 1.339)	(1.349 10.131)	(0.724 276.029)
SSS	1.023	1.340	6.449
	(0.400 2.617)	(0.148 12.169)	(0.007 5618.965)
		0.610	0.323
		(0.447 0.833)	(0.038 2.746)
SSS x Quintile of TE for each payment scheme		0.917	0.281
		(0.479 1.756)	(0.003 29.986)
Quintile of TE for each payment scheme x Quintile of TE for each payment scheme			0.535
			(0.416 0.688)
CSMBS x Quintile of TE for each payment scheme x Quintile of TE for each payment scheme			1.038
			(0.727 1.482)
SSS x Quintile of TE for each payment scheme x Quintile of TE for each payment scheme			1.197
			(0.578 2.480)
EGFR			1.019
			(0.586 1.770)
ALK			3.750
			(1.366 10.298)
MET 14			1.000
complete Rx			0.386

Variable	Naive	Int_L_qTE_noAdj	Int_Q_qTE_Adj
			(0.217 0.688)
progression			4.817
			(1.457 15.923)
weight :			0.982
			(0.961 1.003)
Equivalence house hold size			0.625
			(0.369 1.059)
Intercept	0.461	0.223	0.011
	(0.272 0.782)	(0.105 0.475)	(0.001 0.148)
AIC	531	524	446
BIC	547	549	507
LROC_AUC	0.521	0.588	0.792

Naïve – the logistic model with QTE and payment schemes as determinators for medical impoverishment, Int_L_qTE_noAdj – the logistic model with QTE interaction with payment schemes as determinators for medical impoverishment, Int_Q_qTE_Adj – the logistic model with quadratic-QTE interaction with payment schemes as determinators for medical impoverishment with adjusted potential covariates

The outcomes of the logistic regression models for CHE. Based on AIC/BIC, the multivariable-adjusted interaction model exhibited the best fit and also the highest discriminating power (AUC = 0.84) (Table 43).

Table 43. Odds ratio and 95% CI for CHE from various logistic models.

Variable	Naive	IntAct	IntAct_Adj
Quintile of TE for each payment scheme	0.485	0.596	0.539
	(0.408 0.575)	(0.470 0.757)	(0.411 0.708)
CSMBS	0.737	3.269	3.068
	(0.468 1.160)	(0.893 11.971)	(0.744 12.658)
SSS	0.513	0.671	1.143
	(0.191 1.379)	(0.064 7.060)	(0.089 14.682)
CSMBS x Quintile of TE for each payment scheme		0.642	0.627
		(0.447 0.922)	(0.422 0.929)
SSS x Quintile of TE for each payment scheme		0.935	0.807
		(0.470 1.863)	(0.373 1.743)
less than 6 mo			2.249
			(0.928 5.447)
complete Rx			0.269
			(0.145 0.499)
1B			2.321
			(0.790 6.821)
2A			1.581
			(0.292 8.558)
2B			3.122
			(0.680 14.329)
3A			2.567
			(0.878 7.511)
3B			0.859
			(0.282 2.622)
3C			0.684
			(0.072 6.447)
4A			1.270
			(0.570 2.827)
4B			2.567
			(1.057 6.230)

Variable	Naive	IntAct	IntAct_Adj
progression			4.878
			(1.128 21.097)
age			1.027
			(1.002 1.053)
Intercept	23.012	11.368	2.923
	(11.659 45.422)	(4.825 26.784)	(0.421 20.277)
AIC	484	482	441
BIC	500	506	514
LROC_AUC	0.760	0.770	0.836

Naïve – the logistic model with QTE and payment schemes as determinators for CHE, IntAct – the logistic model with QTE interaction with payment schemes as determinators for CHE, IntAct_Adj – the logistic model with QTE interaction with payment schemes as determinators for CHE and backward stepwise removal of other covariates

Figure 25A depicts the medical impoverishment probability derived from the QTE model's multivariable-adjusted interaction with a quadratic term. The odds of medical impoverishment in the bottom quintile were low for all payment schemes: 0.05 [0 – 0.11] for UCS, 0.19 [0.08 – 0.30] for CSMBS, and 0.10 [-0.15 – 0.35] for SSS. In the third quintile, they reached their maximum levels for each payment scheme: 0.53 [0.42 – 0.64] for UCS, 0.44 [0.35 – 0.54] for CSMBS, and 0.46 [0.14 – 0.78] for SSS.

Figure 25B depicts the probabilities of CHE derived from the final adjusted logistic model with the interaction of QTE and payment schemes with the previously indicated adjusted covariates. In the lowest quintile, CSMBS had the highest chance of CHE (0.93 [0.88 – 0.98]), followed by UCS (0.88 [0.81 – 0.95] and SSS (0.87 [0.69 – 0.98]). As the quintile of TE increased, the probability of CHE decreased. In the highest quintiles, the likelihood of CHE was greatest in UCS (0.47 [0.35-0.59]), but about one-fifth in CSMBS and SSS.
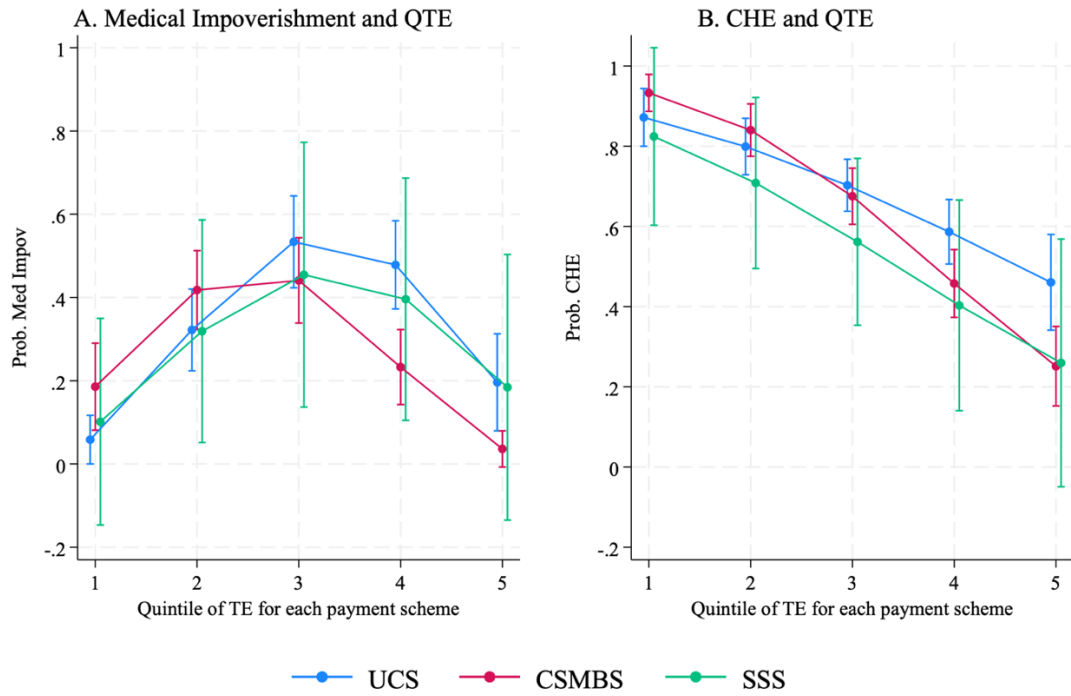
Figure 25. Medical impoverishment, CHE, and QTA from multivariable logistic models.

Chapter 4

Discussion

Economic Evaluation for Applying ICIs

From a government perspective, the ICER of ICIs for second-line NSCLC treatment ranged from USD 30,003 to USD 115,365. Atezolizumab had the lowest value, and pembrolizumab had the highest value. All of those ICER values, however, are far greater than the Thai cost-effectiveness threshold.

The ICER values of nivolumab and pembrolizumab (USD 84,957 and USD 115,365, respectively) in the present study were similar to other reports, which ranged from USD 93,307 to USD 183,406 for nivolumab and from USD 98,421 to USD 168,619 for pembrolizumab. However, the ICER for atezolizumab in this study was lower than that for others.[30–33,35–38] One probable explanation why atezolizumab had a lower ICER than others is that the selling price of atezolizumab is much lower than that of others, making atezolizumab the only ICI that can be paid by the government for patients who meet the requirements for Civil Servant Medical Benefit schemes (CSMBS). While the current price of atezolizumab is less than half of what it was when it was initially introduced in Thailand, the prices of nivolumab and pembrolizumab remain the same. The prices of nivolumab and atezolizumab remain costly; however, they also have a patient access program (PAP) with a "buy-one-get-one-free" offer that reduces the price by half.

Because the PAP is an uncertainty parameter, it was included in the sensitivity analysis. From the government, patient, and societal perspectives, the PAP package reduces the ICER for nivolumab from USD 84,957 to USD 39,023, USD 85,905 to USD 39,971, and USD 85,909 to USD 39,975, respectively. PAP reduces ICER in pembrolizumab from

USD 115,365 to USD 56,281, 116,321 to USD 57,237, and 116325 to USD 57,241 in the government, patient, and societal perspectives, respectively.

Unsurprisingly, drug costs are the most crucial factor in the one-way sensitivity analysis. Despite the fact that atezolizumab has the lowest cost, changes in drug cost still create a significant difference in ICER results, with a 173 percent change from lower bound to upper bound.

The OS parameters, which include _cons and shape parameters, were the second and third elements that may influence ICER outcomes in the range of 60-80 percent for nivolumab, 40-45 percent for pembrolizumab, and 30-40 percent for atezolizumab. The PFS parameters, on the other hand, influence only about 18% or less of the ICER outcomes.

However, as a result of vast confidence bands around key parameters such as PFS and OS parameters, outcomes for all analyses differed substantially in both deterministic and probabilistic sensitivity analyses. As a result, these findings should be regarded with caution.

Because the indirect cost was computed using the minimum wage, the results from the patient and societal perspectives are fairly close. It may not reflect the medium to upper-income groups.

Based on the Thai acceptability threshold of USD 5,208, it is quite difficult to compare our final conclusion, no any ICI is good value, to other studies using their threshold range from USD 28,899 to USD 171,660. Aguiar et al. (2017) concluded that atezolizumab was not cost-effective but pembrolizumab was.[35] This conclusion is quite different from ours, which is more favoring for atezolizumab than pembrolizumab. Two possible explanation is that 1- we conduct studies in different periods(2017 vs 2023). In this 6-year period, the price of atezolizumab had been reduced by more than half of the

initial price in Thailand, 2- the threshold using Aguiar's study was USD 100,000, more than 10 times higher than ours, whereas its ICER for pembrolizumab was USD 98,421.

The final conclusion of the present study that nivolumab is not cost-effective aligns with those from Matter-Walstra et al. (2016)[36], Gao et al.(2019)[37] and Liu et al.(2019)[38]although the threshold used in those studies were much higher than ours.

The study in US by Huang et al.(2017)[31] reported ICER for pembrolizumab of USD 168,619 but they concluded that pembrolizumab is more cost-effective than docetaxel. Even the ICER number was higher than the present study, the threshold, USD 171,660, was for more higher than ours.

Atezolizumab which was more cost-effective and docetaxel at ICER of USD 109,406 and threshold of 125,000 was reported by Ondhia et al.(2019)[32]. This result is quite similar to the present study.

An important strength of this study is the inclusion of post-PD expenses. These were obtained from real-world data in the Songklanagarind Hospital database.

Another strength is the use of individual time-to-event data extracted from the published literature. This provides more reliable estimates of the model input to create transitional stage probabilities closely similar to those actually occurring in the respective clinical trials. It has been frequently suggested that summary hazard ratios can be used as inputs to the Markov models but such hazard ratios may mask the true time-to-event profiles, as may be obvious from the examination of the profiles, which may have different shape and even cross.

Several limitations of our analysis are noted. The expenses of the pharmaceuticals themselves were the major cost drivers in our model, and all patients were considered to

have identical disease severity. In the absence of published and reputable data on the incidence of this practice in NSCLC, we also hypothesized that no infused medication vials would be shared. If vial sharing occurs in actual practice for some patients, our research would, to an unknown extent, exaggerate drug prices for the impacted regimens. Furthermore, our assumptions about treatment after progression being limited to gemcitabine or docetaxel (in the ICI treated group) may not reflect all real-world possibilities. Some patients, for example, may be given pemetrexed or recruited in clinical studies. The median price lists in our study comprised price from local-made docetaxel; in contrast, the original price lists were obtained from novel ICI regimens.

Further limitations are that death costs were not included in the analysis and the disutility for some adverse events that were not available from the literature were assumed to be equal to those reported for similar or related events.

Financial Burden in Lung Cancer Results

In descending order, UCS, SSS, and CSMBS had the highest, second-highest, and third-highest rates of poverty, respectively, although there was no significant difference in the proportion falling into poverty due to medical expenses, which was almost 30 percent in each case. Socioeconomic disparities based on CHE and medical poverty were observed in each payment scheme, but the gradient of CHE likelihood was most pronounced among CSMBS patients. If not already impoverished, the chance of medical poverty peaked in the middle quintile of all payment schemes and thereafter fell.

Unanticipated was the bigger socioeconomic discrepancy between CSMBS and UCS in terms of CHE and medical poverty. CSMBS patients may include the parents of government employees, and the definition of CHE is based on the ratio of total OOP cost to total significant non-food spending, which is typically low among older individuals living alone. Another probable explanation is that CSMBS patients, even those in the

lowest quintile, prefer premium services or are more ready to pay for comfort and convenience, which incurs additional supplementary and extra medical costs, as indicated by Table 39.

As expected, CHE was more prevalent among the lowest quintile groups in this study. This result is consistent with a Chinese study. Leng et al. [38] investigated the likelihood of CHE in terminal cancer patients. Even though that study was limited to the end-of-life period, CHE was observed in 100 percent of the lowest three quintiles, which was significantly higher than the current study. The extreme wealth disparities in China, with the wealthiest 1 percent holding more than 33 percent of the total national household wealth and the poorest 25 percent having less than 2 percent, maybe a plausible explanation.

Fu et al.[61] reported 47 percent, 15 percent, 9 percent, 5 percent, and 3 percent, respectively, post-treatment poverty among Chinese cancer patients in quintiles one through five. These proportions fall within a range comparable to that of the proportion of medical poverty in the current study, but follow a distinct trend. In the Chinese study, the proportion decreased as the quintiles increased, whereas in the current study, the proportions peaked in the second quintile for raw data and in the middle quintiles for the adjusted probability, which was the opposite of what was predicted by a multivariable logistic regression model. This is because the Chinese study included participants who were already poor prior to incurring medical expenses. In contrast, medical poverty patients in the present study did not include patients who were already poor.

There are two main methodological concerns. First, the current study used total expenditure as a proxy for standard of living/wealth. It is still debated whether expenditures should replace income. Both income and expenditure data are challenging to collect precisely. However, there are a number of individuals who do not have formal employment or a salary, particularly in developing nations, and many individuals may be reluctant to

reveal their actual income. On the other hand, it is more convenient to respond to the expenditures questionnaire by referencing specific purchases of goods or services. Second, to define the quintile of total expenditure, the author ranked the quintiles inside each payment scheme as an independent variable, which is not directly translatable into real-world meaning, as opposed to the ranking by the total number of participants. However, regardless of the chosen method of ranking, there will always be limitations.

Chapter 5

Conclusion

In conclusion, second-line treatment in NSCLC appears to provide therapeutic benefits in terms of increased progression-free and overall survival, as well as enhanced quality of life. Although the predicted cost-effectiveness of ICI exceeds these criteria at current wholesale procurement costs, there is greater uncertainty in these findings due to variations in estimates of overall and progression-free survival. The drug cost should be reduced by three-fourth to be met the Thailand cost-effectiveness threshold of USD 5,208 (THB 160,000). When patients with lung cancer are in the high health-care accessibility group, such as CSMBS, the therapy can be financially hazardous. Based on these findings, we propose that cost discussions between payers and firms, as well as the continuation and expansion of the PAP program, are critical problems for removing the barrier to medicine access. Financial support for patients and families is one of the most difficult difficulties for the healthcare system because it is not just the prescription costs that are financially toxic, but also the total expenditures, which comprise direct, nonmedical, and indirect costs.

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Appendices

A. Case record form

B. Ethics Committee approval

C. Information sheet and informed consent form

D. Time-to-event parameters to be used in economic evaluation models

E. Cost and utility parameters to be used in economic evaluation models

F. Publication

Appendix A

Case record form

mvsta	Markov state	_1=progression-free, 2-progression
sn	Subject number	_ _ _ _
ini	Initial	_ _ _
datcol	Date collect	_ _ / _ _ _ / 2 0 _ _
dob	Date of Birth	_ _ / _ _ _ / _ _ _ _
sex	Sex	_ _1=male, 2=female
datdx	Diagnosis Lung cancer	_ _ / _ _ _ / 2 0 _ _
datpatho	Date of first patho report	_ _ / _ _ _ / 2 0 _ _
datinista	Date of complete initial staging	_ _ / _ _ _ / 2 0 _ _
inista	Stage at diagnosis	_ _ TNM 8th edition
tsta	T	_ _
nsta	N	_ _
msta	M	_ _
datadv	Date of advanced NSCLC	_ _ / _ _ _ / 2 0 _ _
sx	Definite surgery	_ 0=no, 1=yes
datsx	Date of surgery	_ _ / _ _ _ / 2 0 _ _
cuxrt	Curative XRT	_ 0=no, 1=yes
datxrt	Date of XRT	_ _ / _ _ _ / 2 0 _ _
adjcmt	Adjuvant CMT	_ 0=no, 1=yes
datstaadj	Date of adj CMT start	_ _ / _ _ _ / 2 0 _ _
datstoadj	Date of last dose of adj CMT	_ _ / _ _ _ / 2 0 _ _
cmt	Palliative CMT	_ 0=no, 1=yes
reg1	Regimen 1	………………………………..
datreg1sta	Regiment 1 start	_ _ / _ _ _ / 2 0 _ _
datreg1sto	Regiment 1 last dose	_ _ / _ _ _ / 2 0 _ _
reg1cy	Number of cycles	_ _
reg1rs	Best response	_1 = CR, 2 = PR, 3 = SD, 4 = PD, 9 = unknown

reg1pd	Date of imaging (or clinical) PD	_ _ / _ _ _ / 2 0 _ _
reg2	Regimen 2	……………………………..
datreg2sta	Regiment 2 start	_ _ / _ _ _ / 2 0 _ _
datreg2sto	Regiment 2 last dose	_ _ / _ _ _ / 2 0 _ _
reg2cy	Number of cycles	_ _
reg2rs	Best response _1 = CR, 2 = PR, 3 = SD, 4 = PD, 9 = unknown	
reg2pd	Date of imaging (or clinical) PD	_ _ / _ _ _ / 2 0 _ _
reg3	Regimen 3	……………………………..
datreg3sta	Regiment 3 start	_ _ / _ _ _ / 2 0 _ _
datreg3sto	Regiment 3 last dose	_ _ / _ _ _ / 2 0 _ _
reg3cy	Number of cycles	_ _
reg3rs	Best response _1 = CR, 2 = PR, 3 = SD, 4 = PD, 9 = unknown	
reg3pd	Date of imaging (or clinical) PD	_ _ / _ _ _ / 2 0 _ _
reg4	Regimen 4	……………………………..
datreg4sta	Regiment 4 start	_ _ / _ _ _ / 2 0 _ _
datreg4sto	Regiment 4 last dose	_ _ / _ _ _ / 2 0 _ _
reg4cy	Number of cycles	_ _
reg4rs	Best response _1 = CR, 2 = PR, 3 = SD, 4 = PD, 9 = unknown	
reg4pd	Date of imaging (or clinical) PD	_ _ / _ _ _ / 2 0 _ _
reg5	Regimen 5	……………………………..
datreg5sta	Regiment 5 start	_ _ / _ _ _ / 2 0 _ _
datreg5sto	Regiment 5 last dose	_ _ / _ _ _ / 2 0 _ _
reg5cy	Number of cycles	_ _
reg5rs	Best response _1 = CR, 2 = PR, 3 = SD, 4 = PD, 9 = unknown	
reg5pd	Date of imaging (or clinical) PD	_ _ / _ _ _ / 2 0 _ _

reg6	Regimen 6	…………………………………..
datreg6sta	Regiment 6 start	_ _ / _ _ _ / 2 0 _ _
datreg6sto	Regiment 6 last dose	_ _ / _ _ _ / 2 0 _ _
reg6cy	Number of cycles	_ _
reg6rs	Best response	_1 = CR, 2 = PR, 3 = SD, 4 = PD, 9 = unknown
reg6pd	Date of imaging (or clinical) PD	_ _ / _ _ _ / 2 0 _ _

reg7	Regimen 7	…………………………………..
datreg7sta	Regiment 7 start	_ _ / _ _ _ / 2 0 _ _
datreg7sto	Regiment 7 last dose	_ _ / _ _ _ / 2 0 _ _
reg7cy	Number of cycles	_ _
reg7rs	Best response	_1 = CR, 2 = PR, 3 = SD, 4 = PD, 9 = unknown
reg7pd	Date of imaging (or clinical) PD	_ _ / _ _ _ / 2 0 _ _

datls	Date of last seen to be alive	_ _ / _ _ _ / 2 0 _ _
dstatus	Death status	_0=alive, 1 death, 2 loss to F/U
datd	Date death	_ _ / _ _ _ / 2 0 _ _

EQ5D5L scale 1-5 1-ไม่มีปัญหา, 2-มีปัญหาเล็กน้อย, 3-มีปัญหาปานกลาง, 4-มีปัญหามาก, 5-มีปัญหามาก
ที่สุด

mov	การเคลื่อนไหว	_
self	การดูแลตนเอง	_
act	กิจกรรมที่ทำเป็นประจำ	_
pain	อาการเจ็บปวด/อาการไม่สบายตัว	_
anxie	ความวิตกกังวล/ความซึมเศร้า	_

paysch	Payment scheme_ 1=UCS, 2=CSMBS, 3=SSS, 4=private ins, 5=OOP
moinccat	Income/month _
	1= <10000, 2=10001-20000, 3=30001-40000, 4=40001, 5= >50000
moinc	income/month _ _ _ _ _ _ THB
dayinc	Income/day _ _ _ _ _ _ THB
daywomo	Days work / month _ _

te	total household expenditure/month _ _ _ _ _ _ THB
hs	household size _ _
fe	food household expenditure/month _ _ _ _ _ _ THB
inc	total household income/month _ _ _ _ _ _ THB
he	health expenditure/month _ _ _ _ _ _ THB

maincare	Main caregiver ……………………………………
main_paysch	Payment scheme_ 1=UCS, 2=CSMBS, 3=SSS, 4=private ins, 5=OOP
main_moincat	Income/month _
	1= <10000, 2=10001-20000, 3=30001-40000, 4=40001, 5= >50000 THB
main_moinc	income/month _ _ _ _ _ _ THB
main_dayinc	Income/day _ _ _ _ _ _ THB
main_daywomo	Days work/month _ _

oop_lm	Average total OOP / month for the treatment in last month. _ _ _ _ _ _ THB
dc_lm	Drug cost in last month _ _ _ _ _ _ THB
rc_eachv	Residential cost each visit _ _ _ _ _ _ THB
tc_eachv	Travel cost each visit _ _ _ _ _ _ THB
mc_eachv	Meal cost each visit _ _ _ _ _ _ THB (extra from daily meal)

num_mainc	Number of caregiver (each visit) _ _

Other Cost			Caregiver		
Variable	**unit**		**Main**	**2nd caregiver**	**3rd caregiver**
1. Age of caregiver	Year				
2. Relative to patient (เช่น พ่อ แม่ ตา ยาย)	-				
3. frequency	Day/week				
4. duration each day	Hr/day				
5. cost of resident	THB/day				
6. duration of resident	day				
7. travel cost (ที่พักชั่วคราว-รพ.)*	THB/day				
8. number of travel (ที่พักชั่วคราว-รพ.)*	number				
9. travel cost (รพ. - บ้าน)*	THB/day				
10. number of travel (รพ. - บ้าน)*	number				
11. extra for meal	THB/day				
12. Money loss for job	THB/day				
13. Other					

Inpatient cost

i_adm_date   Previous IPD date   _ _ / _ _ _ / 20 _ _

i_dc_date   to date   _ _ / _ _ _ / 20 _ _

ioop   OOP for IPD   _ _ _ _ _ _ THB

ctv_ipd   Travel cost   _ _ _ _ _ _ THB

no_c_ipd   Number of caregiver   _ _

Other Cost			Caregiver		
Variable	**unit**		**Main**	**2nd caregiver**	**3rd caregiver**
14. Age of caregiver	Year				
15. Relative to patient (เช่น พ่อ แม่ ตา ยาย)	-				
16. frequency	Day/week				
17. duration each day	Hr/day				
18. cost of resident	THB/day				

19.	duration of resident	day			
20.	travel cost (ที่พักชั่วคราว-รพ.)*	THB/day			
21.	number of travel (ที่พักชั่วคราว-รพ.)*	number			
22.	travel cost (รพ. - บ้าน)*	THB/day			
23.	number of travel (รพ. - บ้าน)*	number			
24.	extra for meal	THB/day			
25.	Money loss for job	THB/day			
26.	Other				

<u>Indirect cost</u>

idc_c_lt_job	Need caregiver absent the job for looked after	_	0=no, 1=yes
no_c	How many caregiver	_ _	
mo_loss	Money loss for look after	_ _ _	THB/time/person
c_in_h	Caregiver live in the same house	_	0=no, 1=yes
tv_c_c	If no, travel cost	_ _ _ _ _	THB/time
pay_4_c	Need to pay for caregiver	_	0=no, 1=yes
pay_4_c_am	If yes, cost	_ _ _ _ _	THB/time
equip	Need to buy equipment for lung cancer pt	_	0=no, 1=yes
equip_cost	If yes, cost	_ _ _ _ _	THB
suppot	Other supportive at different hospital	_	0=no, 1=yes
support_cost	If yes, cost	_ _ _ _ _	THB/6month
medica	Other medication from other pharmacy	_	0=no, 1=yes
med_cost	If yes, cost	_ _ _ _ _	THB/6month
tred	Other traditional medicine cost	_	0=no, 1=yes
tred_cost	If yes, cost	_ _ _ _ _	THB/6month
diet	Other diet supplement	_	0=no, 1=yes
diet_cost	If yes, cost	_ _ _ _ _	THB/6month
other	Other	_	0=no, 1=yes
other_cost	If yes, cost	_ _ _ _ _	THB/6month

การเคลื่อนไหว

ข้าพเจ้าไม่มีปัญหาในการเดิน ❑

ข้าพเจ้ามีปัญหาในการเดินเล็กน้อย ❑

ข้าพเจ้ามีปัญหาในการเดินปานกลาง ❑

ข้าพเจ้ามีปัญหาในการเดินอย่างมาก ❑

ข้าพเจ้าไม่สามารถไปไหนได้ และจำเป็นต้องอยู่บนเตียง ❑

การดูแลตนเอง

ข้าพเจ้าไม่มีปัญหาในการอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเอง ❑

ข้าพเจ้ามีปัญหาในการอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเองเล็กน้อย ❑

ข้าพเจ้ามีปัญหาในการอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเองปานกลาง ❑

ข้าพเจ้ามีปัญหาในการอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเองอย่างมาก ❑

ข้าพเจ้าอาบน้ำ หรือใส่เสื้อผ้าด้วยตนเองไม่ได้ ❑

กิจกรรมที่ทำเป็นประจำ *(เช่น การทำงาน, การเรียนหนังสือ, การทำงานบ้าน, การทำกิจกรรมใน*

ครอบครัว หรือการทำกิจกรรมยามว่าง)

ข้าพเจ้าไม่มีปัญหาในการทำกิจกรรมที่ทำเป็นประจำ ❑

ข้าพเจ้ามีปัญหาในการทำกิจกรรมที่ทำเป็นประจำเล็กน้อย ❑

ข้าพเจ้ามีปัญหาในการทำกิจกรรมที่ทำเป็นประจำปานกลาง ❑

ข้าพเจ้ามีปัญหาในการทำกิจกรรมที่ทำเป็นประจำอย่างมาก ❑

ข้าพเจ้าทำกิจกรรมที่ทำเป็นประจำไม่ได้ ❏

อาการเจ็บปวด / อาการไม่สบายตัว

ข้าพเจ้าไม่มีอาการเจ็บปวดหรืออาการไม่สบายตัว ❏

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สบายตัวเล็กน้อย ❏

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สบายตัวปานกลาง ❏

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สบายตัวอย่างมาก ❏

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สบายตัวอย่างมากที่สุด ❏

ความวิตกกังวล / ความซึมเศร้า

ข้าพเจ้าไม่รู้สึกวิตกกังวลหรือซึมเศร้า ❏

ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าเล็กน้อย ❏

ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าปานกลาง ❏

ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าอย่างมาก ❏

ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าอย่างมากที่สุด ❏

The best health

เพื่อช่วยในการประเมินภาวะสุขภาพของท่าน ทางเราได้

จัดทำสเกลวัดระดับสุขภาพขึ้น เริ่มตั้งแต่ระดับ 0 ถึง 100

โดยที่ 100 หมายถึงภาวะสุขภาพที่ดีที่สุด และ 0 หมายถึง

ภาวะสุขภาพที่แย่ที่สุด ตามความคิดของท่าน

กรุณาประเมินภาวะสุขภาพของท่านในวันนี้ว่าดีหรือไม่ดี

เพียงไร โดยการลากเส้น จากช่องสี่เหลี่ยมข้างล่างนี้ไปยัง

จุดบนสเกลวัดระดับสุขภาพที่ตรงกับภาวะสุขภาพของท่าน

ในวันนี้

**ภาวะสุขภาพของท่าน
ในวันนี้**
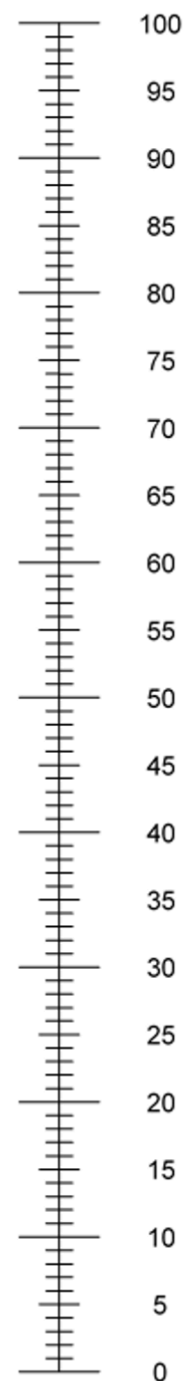
The worse health

Appendix B

Ethics Committee approval

คณะกรรมการจริยธรรมการวิจัยในมนุษย์
คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

หนังสือรับรองฉบับนี้ให้ไว้เพื่อแสดงว่า

รหัสโครงการ :	REC.62-268-14-1
ชื่อโครงการ :	การศึกษาต้นทุนอรรถประโยชน์ในการรักษามะเร็งปอดชนิดเซลล์ไม่เล็กซึ่งไม่มีการกลายพันธุ์ อีจีเอฟอาร์ และ เอเอลเค ด้วยยากลุ่มภูมิคุ้มกันใน ประเทศไทย (Cost-utility analysis of Immuno-Oncotherapy in chemotherapy-pretreated, recurrent, EGFR -wt, ALK -ve, non-small cell lung cancer in Thailand.)
ผู้วิจัยหลัก :	ศรายุทธ ลูเซียน กีเตอร์ ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์
ผู้ร่วมวิจัย :	ปารมี ทองสุกใส ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

เอกสารที่รับรอง :

1. โครงการวิจัยฉบับสมบูรณ์ เวอร์ชั่น 2.0 ฉบับวันที่ 20 ตุลาคม 2563
2. เอกสารชี้แจงอาสาสมัคร เวอร์ชั่น 2.0 ฉบับวันที่ 27 ตุลาคม 2563
3. เอกสารแสดงเจตนายินยอมของอาสาสมัคร เวอร์ชั่น 2.0 ฉบับวันที่ 27 ตุลาคม 2563
4. ประวัติผู้วิจัยและหลักฐานการอบรมจริยธรรมการวิจัย

ได้ผ่านการพิจารณาและรับรองจากคณะกรรมการจริยธรรมการวิจัยในมนุษย์คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์ โดยยึดหลักจริยธรรมของประกาศเฮลซิงกิ (Declaration of Helsinki) และแนวทางการปฏิบัติการวิจัยทางคลินิกที่ดี (The International Conference on Harmonization in Good Clinical Practice) โดยบรรจุ วาระในการประชุมคณะกรรมการจริยธรรมการวิจัยในมนุษย์ ครั้งที่ 31/2563 วาระที่ 3.4

ขอให้นักวิจัยรายงานความก้าวหน้าโครงการวิจัย ทุก 12 เดือน และยื่นต่ออายุก่อนถึงวันหมดอายุอย่างน้อย 30 วัน

ลงชื่อ

(รศ.นพ.บุญสิน ตั้งตระกูลวนิช)
ประธานคณะกรรมการจริยธรรมการวิจัยในมนุษย์
คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

วันที่รับรอง : 30 ตุลาคม พ.ศ. 2563
หมดอายุ : 29 ตุลาคม พ.ศ. 2564

Appendix C

Information sheet and informed consent form

Participant information sheet

ชื่อโครงการ การวิเคราะห์ต้นทุนอรรถประโยชน์ ของการใช้ยากลุ่มภูมิคุ้มกันในผู้ป่วยซึ่งไม่พบการกลายพันธุ์ อีจีเอฟอาร์ และไม่พบการกลายพันธุ์ เอเอลเค ในผู้ป่วยมะเร็งปอดชนิดเซลล์ไม่เล็กซึ่งผ่านได้รับการรักษาด้วยเคมีบำบัด

ชื่อผู้วิจัย นายแพทย์ศรายุทธ ลูเซียน กีเตอร์

สถานที่วิจัย คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

ผู้ให้ทุน คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์

ก่อนที่ท่านจะลงนามในหนังสือแสดงเจตนายินยอมร่วมวิจัยท่านควรได้รับทราบว่า

- โครงการนี้เป็นโครงการวิจัย ไม่ใช่ การรักษาตามปกติ

- ท่าน ไม่จำเป็นจะต้องเข้าร่วมในโครงการวิจัยนี้ และสามารถถอนตัวออกจากโครงการได้ทุกเมื่อ โดยจะไม่มีผลกระทบต่อคุณภาพการบริการหรือการรักษาพยาบาลที่ท่านพึงได้รับตามสิทธิ

- ในเอกสารนี้อาจมีข้อความที่ท่านอ่านแล้วยังไม่เข้าใจ โปรดสอบถามหัวหน้าโครงการวิจัยหรือผู้แทนให้ช่วยอธิบายจนกว่าจะเข้าใจดี

- นักวิจัยผู้ขอความยินยอมต้องให้ ข้อมูลและเวลาที่เพียงพอ ในการตัดสินใจอย่างอิสระ ก่อนที่ท่านจะเข้าร่วมโครงการวิจัย ท่านอาจจะขอเอกสารนี้กลับไปอ่านที่บ้านเพื่อปรึกษาหารือกับญาติพี่น้อง เพื่อนสนิท แพทย์ประจำตัวของท่าน หรือแพทย์ท่านอื่น เพื่อช่วยในการตัดสินใจเข้าร่วมการวิจัย

โครงการนี้เป็นโครงการเพื่อประเมินประสิทธิผลด้านต้นทุนในการใช้ยากลุ่มภูมิคุ้มกันในผู้ป่วยซึ่ง
ไม่พบการกลายพันธุ์ อีจีเอฟอาร์ และไม่พบการกลายพันธุ์ เอเอลเค ในผู้ป่วยมะเร็งปอดชนิดเซลล์ไม่
เล็กซึ่งผ่านได้รับการรักษาด้วยเคมีบำบัด เพื่อเป็นแนวทางในการช่วยเลือกทางเลือกในการรักษาแต่
ผู้ป่วยในอนาคต

การที่ท่านได้รับเชิญชวนให้ร่วมโครงการเนื่องจากท่านเป็นผู้ป่วยรายหนึ่งซึ่งได้รับผลกระทบ
ไม่ทางตรงก็ทางอ้อมจากการรักษาโรคซึ่งมีค่าใช้จ่ายสูง การได้รับข้อมูลซึ่งถูกต้องจากผู้ป่วยจำนวนมาก
ทำให้สามารถคาดคะเนผลกระทบทางเศรษฐศาสตร์ ได้อย่างแม่นยำขึ้น

ข้อมูลที่ได้จากการวิจัยจะใช้ประกอบการเลือกใช้ยาโดยพิจารณาด้านผลการทบทุกด้านไม่ว่าจะ
เป็นประสิทธิภาพ ประสิทธิผล ผลข้างเคียงและผลกระทบทางเศรษฐศาสตร์สาธารณสุข โดยจะไม่มี
การเปิดเผยข้อมูลรายบุคคล

หากท่านสนใจเข้าร่วมโครงการและลงนามในเอกสารยินยอมแล้ว ผู้วิจัย (หรือผู้ช่วย) จะ
สัมภาษณ์ ท่าน โดยที่ไม่ได้มีการทำหัตถการอื่น ๆ แต่อย่างใด โครงการนี้ถือเป็นโครงการความเสี่ยง
น้อย (ไม่มากกว่าความเสี่ยงที่ผู้ป่วยทั่วไปได้รับจากการรักษาตามปกติ)

การศึกษานี้ไม่มีค่าตอบแทนท่าน (อาสาสมัคร)

การศึกษานี้ได้รับการสนับสนุนเงินทุนวิจัยจากคณะแพทยศาสตร์มหาวิทยาลัยสงขลานครินทร์

ความเจ็บปวดของท่านยังคงได้รับการดูแลตามระบบการรักษาปกติไม่เปลี่ยนแปลงแต่อย่างใด

ท่านมีสิทธิ์ถอนตัวจากโครงการได้ ด้วยการแจ้งทีมผู้วิจัยได้ตลอดเวลา

โครงการนี้ไม่มีค่าใช้จ่ายแต่อย่างใด

หากท่านมีข้อข้องใจเกี่ยวกับขั้นตอนของการวิจัยหรือได้รับผลข้างเคียงที่ไม่พึงประสงค์จากการวิจัย

ท่านสามารถติดต่อกับ นพ.ศรายุทธ ลูเซียน กีเตอร์ ได้ที่ ภาคอายุรศาสตร์ คณะแพทยศาสตร์

มหาวิทยาลัยสงขลานครินทร์ โทรศัพท์ 074-451-474 (เบอร์โทรติดต่อ 086-9633-222) ได้ตลอด

24 ชั่วโมง

หากท่านได้รับการปฏิบัติไม่ตรงตามที่ระบุไว้ในเอกสารชี้แจงผู้เข้าร่วมการวิจัย สามารถขอรับ

คำปรึกษา/แจ้งเรื่อง/ร้องเรียน ได้ที่สำนักงานคณะกรรมการจริยธรรมการวิจัย คณะแพทยศาสตร์

มหาวิทยาลัยสงขลานครินทร์ โทรศัพท์ 0-7445-1157 หรือจดหมายอิเล็กทรอนิกส์

medpsu.ec@gmail.com

อาสาสมัคร โปรดให้ความสำคัญ

ท่านจะได้รับเอกสารชี้แจงและหนังสือแสดงเจตนายินยอมที่มีข้อความเดียวกันกับที่นักวิจัยเก็บไว้ 1

ชุด ท่านควรเก็บไว้กับตัวเพื่อเป็นหลักฐานและอ่านเมื่อมีข้อสงสัย

ส่วนท้ายหนังสือแสดงเจตนายินยอมเข้าร่วมโครงการ จะต้องมี 1) ลายมือชื่อของท่าน 2) ลายมือชื่อ

นักวิจัยที่ให้คำอธิบายเกี่ยวกับโครงการ และ 3) วันที่ที่ลงนาม ซึ่งท่านต้องเป็นผู้ลงวันที่ด้วยตนเอง

Informed consent form

หนังสือแสดงเจตนายินยอมเข้าร่วมการวิจัย

วันที่.................เดือน...................พ.ศ. ....

ข้าพเจ้า (นาย /นาง /นางสาว).......................

นามสกุล...อายุ.....................…....ปี

อยู่บ้านเลขที่................หมู่...............ตำบล.............................อำเภอ

.........................จังหวัด.................................ขอแสดงเจตนายินยอมเข้า

ร่วมการวิจัย ในโครงการวิจัย

เรื่อง...

......

   ขอแสดงเจตนายินยอมเข้าร่วมการวิจัย ในโครงการวิจัยเรื่องการวิเคราะห์ต้นทุน

อรรถประโยชน์ ของการใช้ยากลุ่มภูมิคุ้มกันในผู้ป่วยซึ่งไม่พบการกลายพันธุ์ อีจีเอฟอาร์ และ ไม่พบ

การกลายพันธุ์ เอเอลเค ในผู้ป่วยมะเร็งปอดชนิดเซลล์ไม่เล็กซึ่งผ่านได้รับการรักษาด้วยเคมีบำบัด

   โดยข้าพเจ้าได้อ่านเอกสารคำอธิบายโครงการวิจัยและ /หรือได้รับฟังคำอธิบายจาก นพ. ศรา

ยุทธ ลูเซียน กีเตอร์ และได้รับทราบถึงรายละเอียดของโครงการวิจัยเกี่ยวกับ วัตถุประสงค์และ

ระยะเวลาที่ทำการวิจัย ขั้นตอนและวิธีการปฏิบัติตัวที่ข้าพเจ้า ต้องปฏิบัติ ผลประโยชน์ที่ข้าพเจ้าจะ

ได้รับ ผลข้างเคียงหรืออันตรายที่อาจเกิดขึ้นจากการเข้าร่วมโครงการ ตลอดจนค่าตอบแทนที่จะได้รับ และค่าใช้จ่ายที่ข้าพเจ้าจะต้องรับผิดชอบจ่ายเอง และข้าพเจ้ายินยอมให้ผู้วิจัยใช้ข้อมูลส่วนตัวของข้าพเจ้าที่ได้รับจากการวิจัย โดยให้นำเสนอเป็นข้อมูลโดยรวมจากการวิจัยนั้นแต่จะไม่เผยแพร่ ต่อสาธารณะเป็นรายบุคคล ทั้งนี้ข้าพเจ้า สามารถถอนตัวหรืองดเข้าร่วมการวิจัยได้ทุกเมื่อ โดยจะไม่มีผลกระทบและไม่เสียสิทธิ์ใด ๆ ในการรับการบริการและการรักษาพยาบาลที่ข้าพเจ้าได้รับต่อไปในอนาคต

หากข้าพเจ้ามี ข้อข้องใจเกี่ยวกับขั้นตอนของการวิจัยหรือเกิดผลข้างเคียงที่ไม่พึงประสงค์จากการวิจัยกับตัวข้าพเจ้า ข้าพเจ้าสามารถติดต่อกับ น.พ. ศรายุทธ ลูเซียน กีเตอร์ ได้ที่ ภาคอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์ โทรศัพท์ 074-451-474 (ในเวลาราชการ) และ มือถือ 086-9633-222 ได้ตลอด 24 ชั่วโมง

หากได้รับการปฏิบัติไม่ตรงตามที่ระบุไว้ในเอกสารชี้แจงผู้เข้าร่วมการวิจัย ข้าพเจ้าสามารถขอรับคำปรึกษา/แจ้งเรื่อง/ร้องเรียน ได้ที่สำนักงานคณะกรรมการจริยธรรมการวิจัย คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์ โทรศัพท์ 0-7445-1157 หรือทางจดหมายอิเล็กทรอนิกส์ medpsu.ec@gmail.com

ข้าพเจ้า เข้าใจข้อความในเอกสารชี้แจงผู้เข้าร่วมการวิจัย และหนังสือแสดงเจตนายินยอมนี้โดยตลอดแล้ว จึงได้ลงนามยินยอเข้าร่วมโครงการ

ลายมือชื่อผู้เข้าร่วมโครงการวิจัย

………………………………………………

(………………………………………..………………)

วันที่……………เดือน…………………พ.ศ……..……

ลายมือชื่อผู้ขอความยินยอม

………………………………………………

(………………………………………..………………)

วันที่……………เดือน…………………พ.ศ……..……

Appendix D

Time-to-event parameters to be used in economic evaluation model
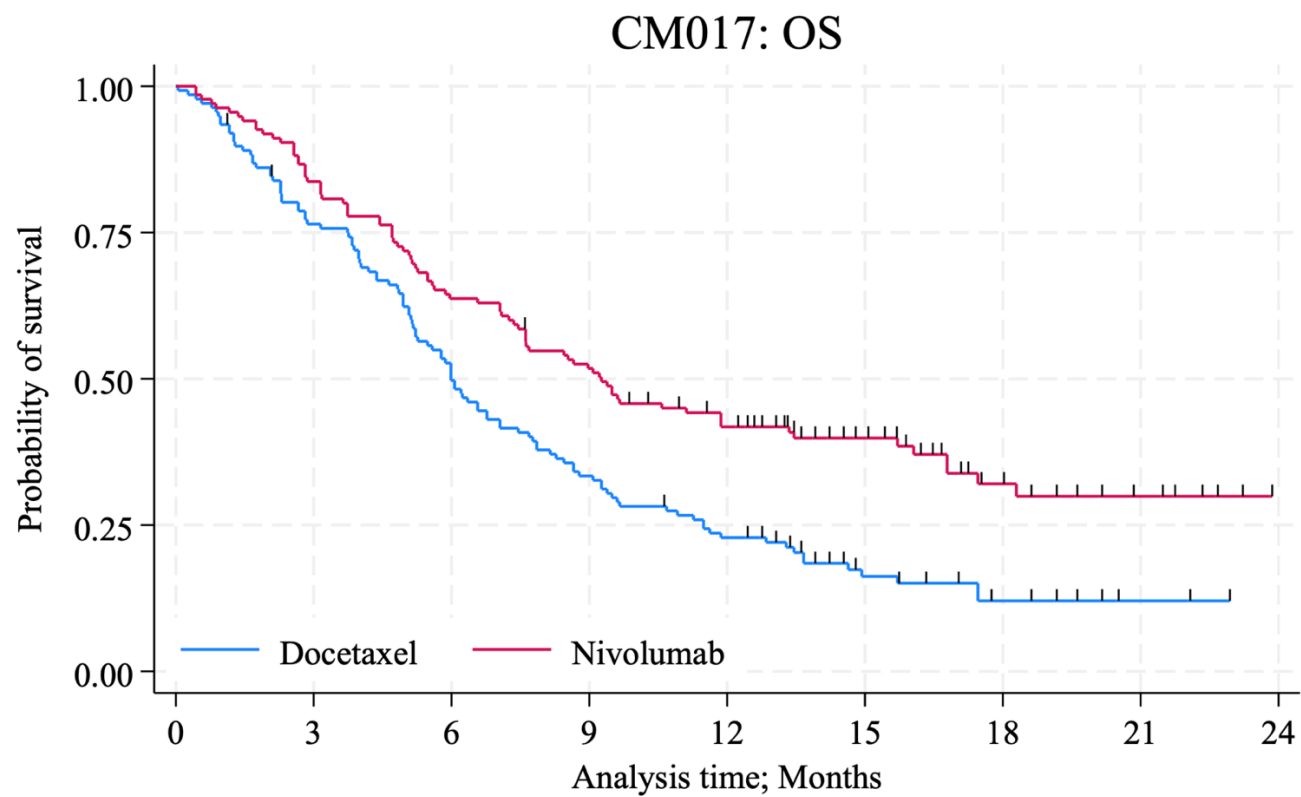
Figure 26. Reconstructed KM curve for OS from CM017 study.
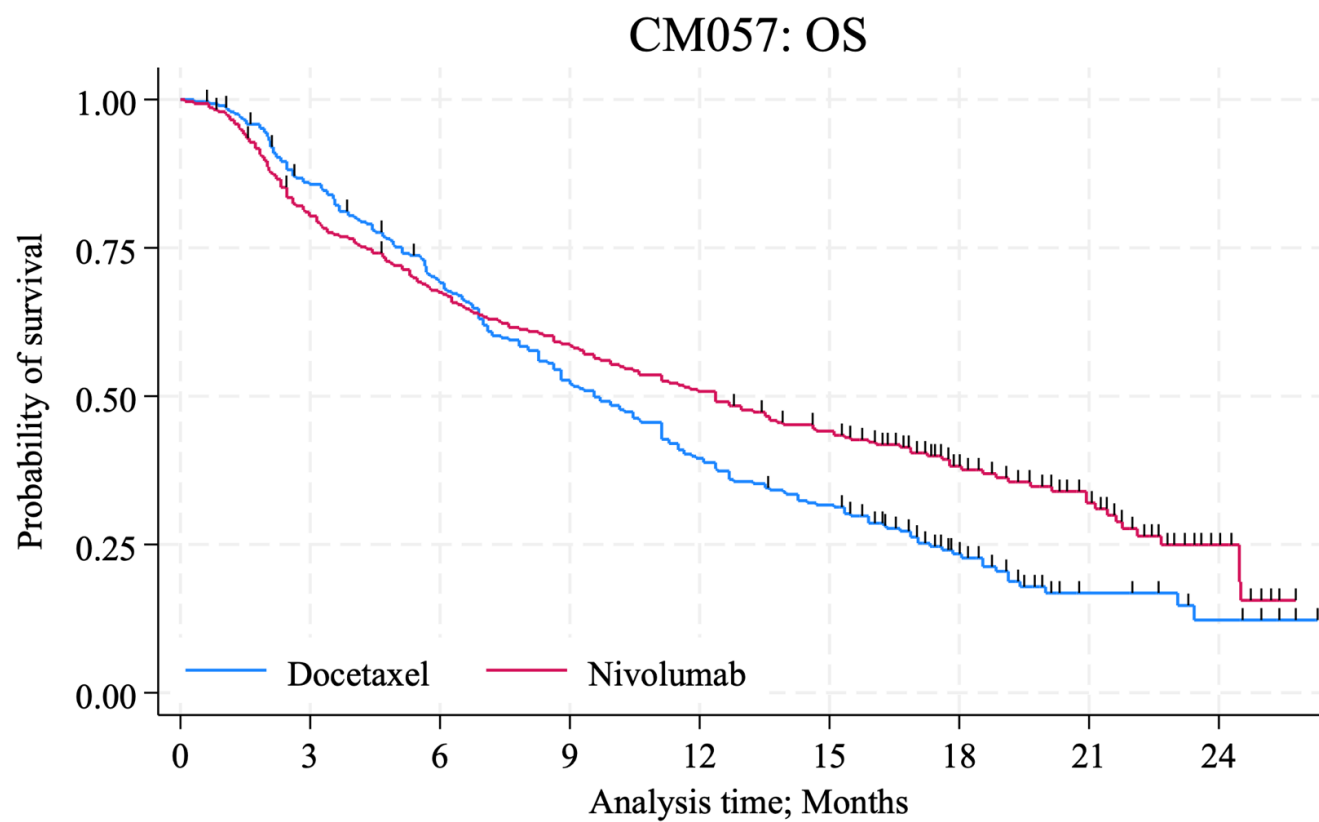
Figure 27. Reconstructed KM curve for OS from CM057 study.
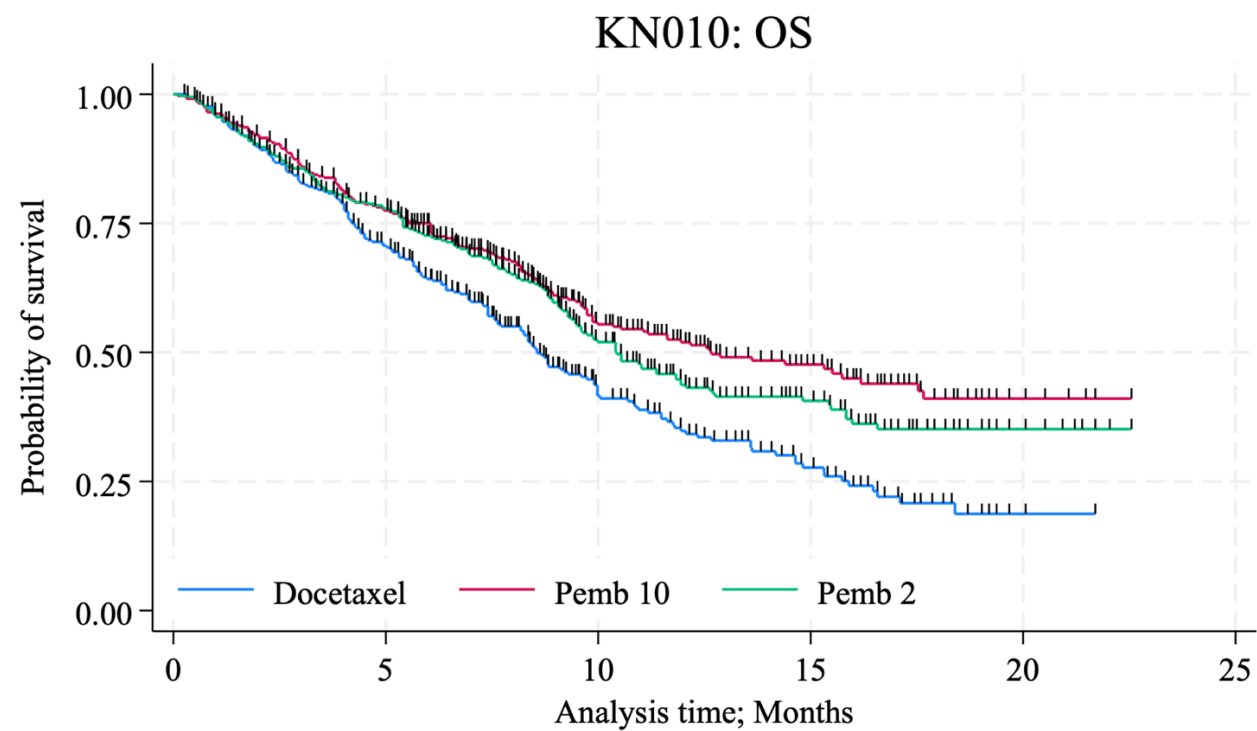
Figure 28. Reconstructed KM curve for OS from HN010 study.
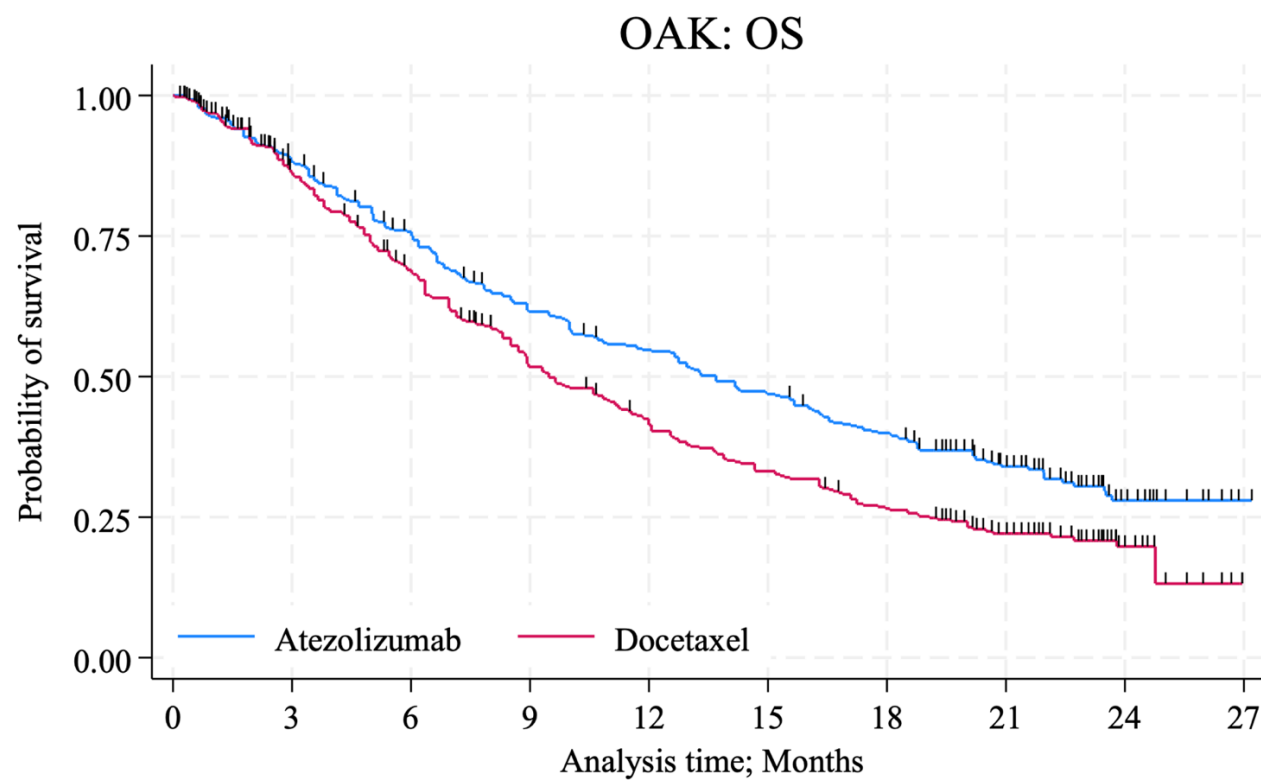
Figure 29. Reconstructed KM curve for OS from OAK study.
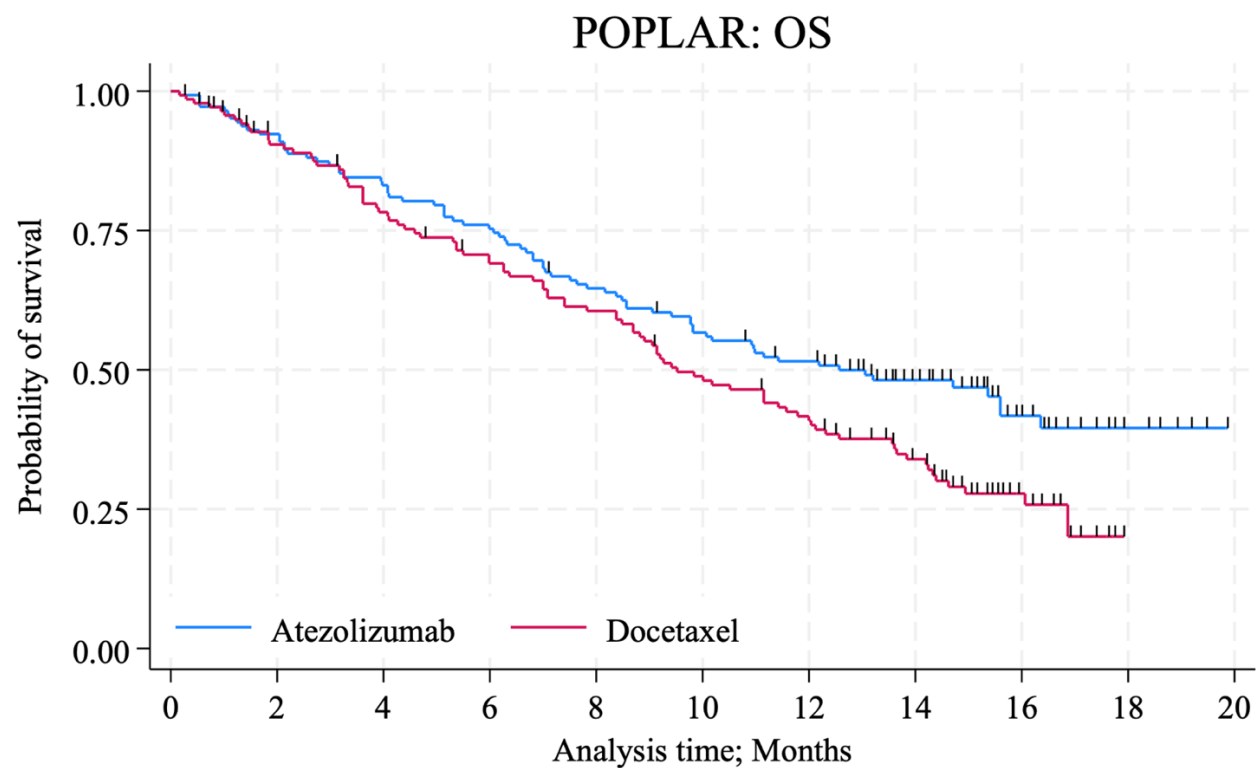
Figure 30. Reconstructed KM curve for OS from POPLAR study.
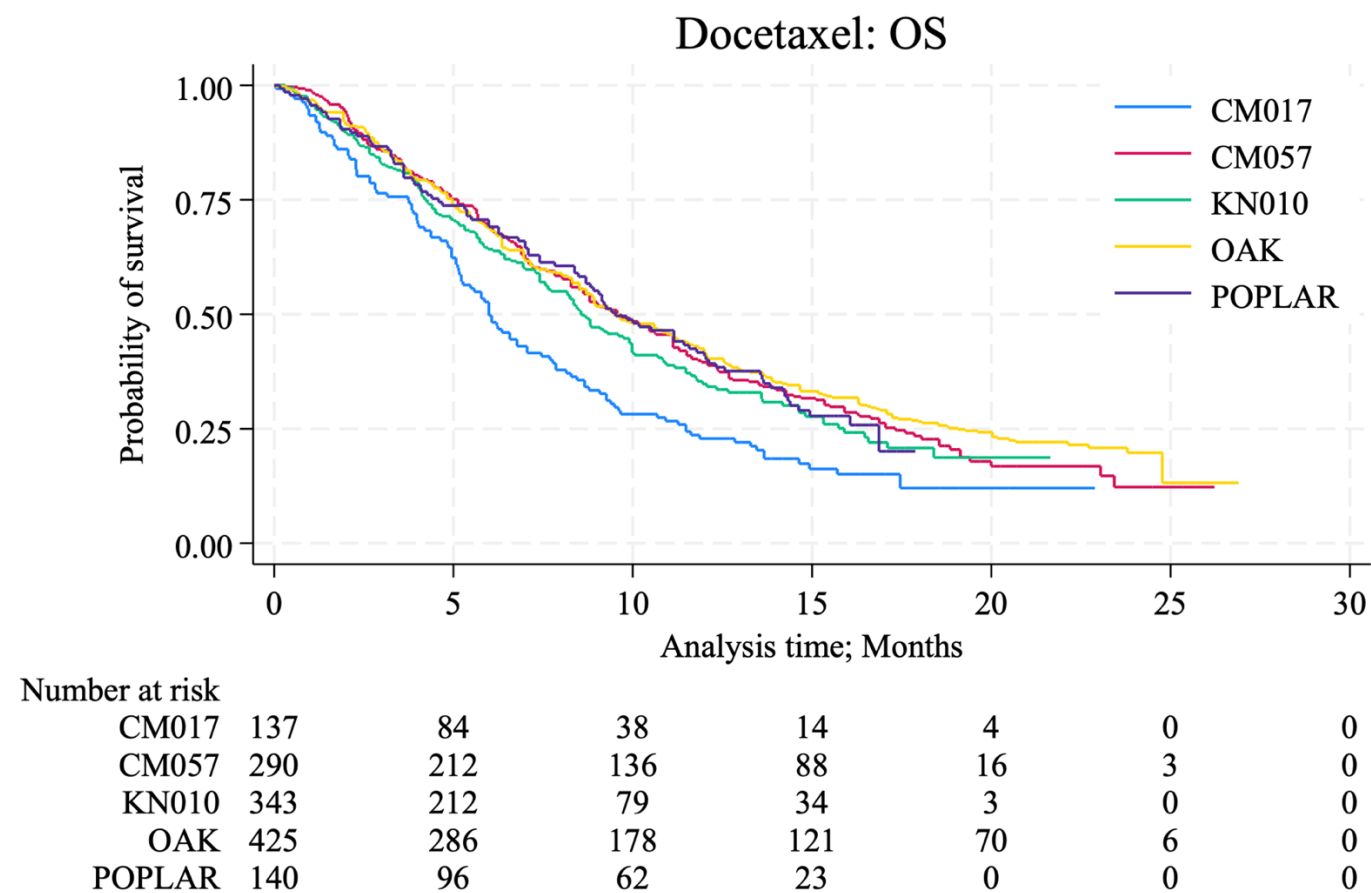
Figure 31. OS KM curves for docetaxel from 5 studies.
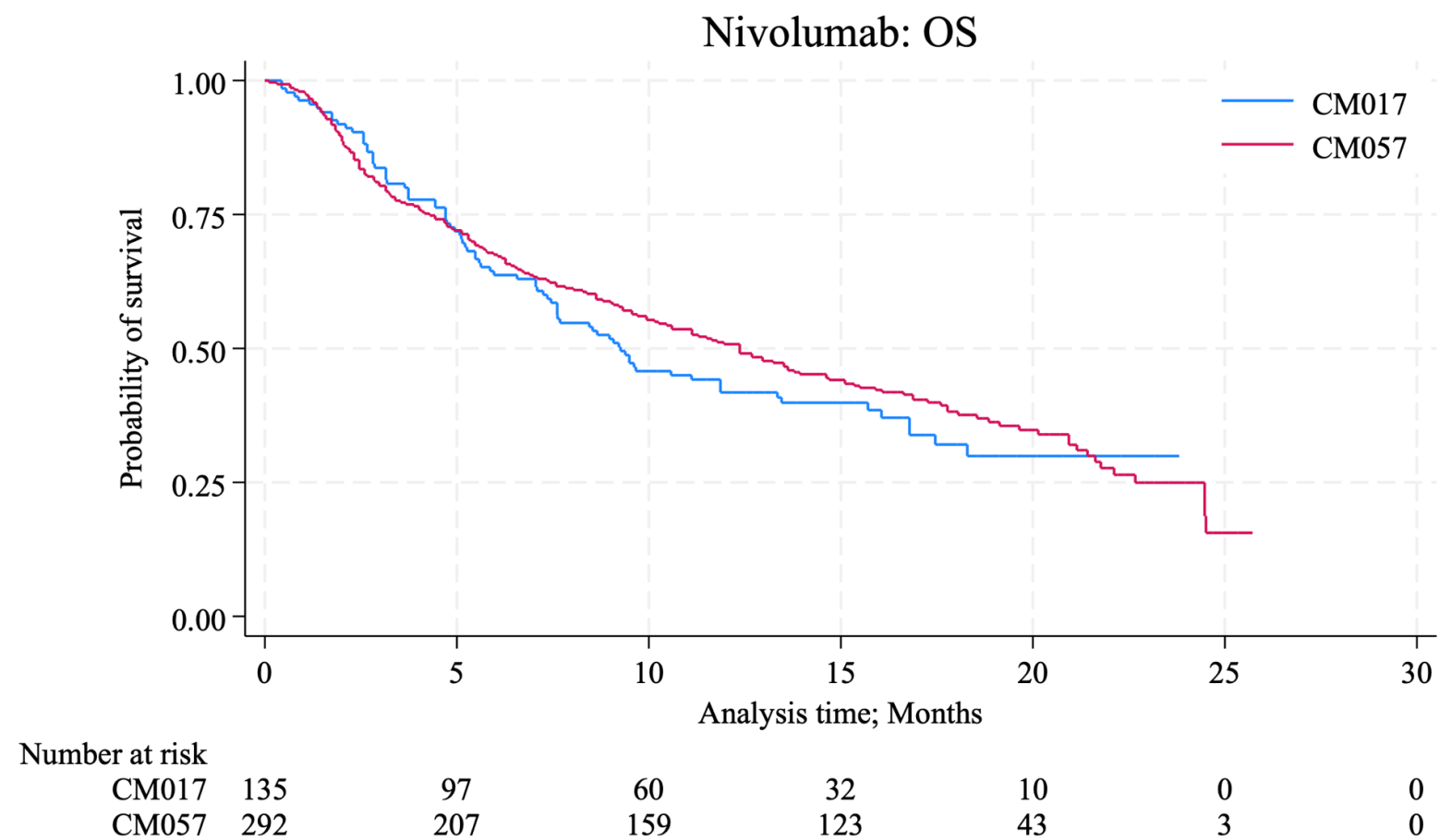
Figure 32. OS KM curves for nivolumab from 2 studies.

Figure 33. OS KM curves for pembrolizumab.

Figure 34. OS KM curves for nivolumab from 2 studies.
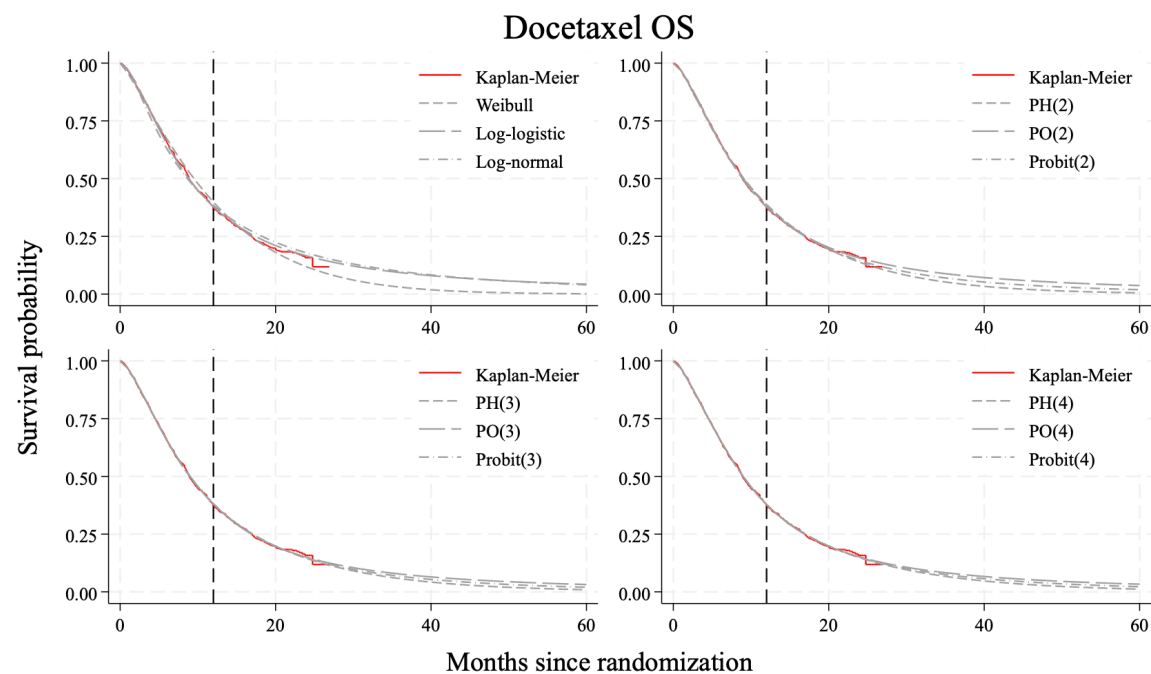
Figure 35. Projected survival probability from pool data of docetaxel-treated patients.

Table 44. Model fit for OS of docetaxel-pool data.

	Weibull	Expnential	**LL**	LN	PH2	PH3	PH4	PO2	PO3	PO4	Probit2	Probit3	Probit4
N	1335	1335	**1335**	1335	1335	1335	1335	1335	1335	1335	1335	1335	1335
AIC	3390.1	3435.6	**3373.8**	3406.7	3374.6	3374.0	3375.3	3373.0	3373.7	3375.3	3371.6	3373.6	3375.2
BIC	3400.5	3440.8	**3384.1**	3417.1	3390.1	3394.8	3401.3	3388.6	3394.5	3401.3	3387.2	3394.4	3401.2

Figure 36. Projected survival probability from pool data of nivolumab-treated patients.

Table 45. Model fit for OS of nivolumab-pool data.

	Weibull	Exponential	LL	**LN**	PH2	PH3	PH4	PO2	PO3	PO4	Probit2	Probit3	Probit4
N	427	427	427	**427**	427	427	427	427	427	427	427	427	427
AIC	1203.7	1201.9	1194.2	**1187.8**	1188.5	1186.8	1188.5	1191.7	1188.8	1190.3	1189.8	1190.9	1191.0
BIC	1211.8	1206.0	1202.3	**1195.9**	1200.7	1203.0	1208.8	1203.9	1205.1	1210.6	1202.0	1207.1	1211.3

Figure 37. *Projected survival probability from data of pembrolizumab-treated patients.*

Table 46. *Model fit for OS of pembrolizumab data*

	Weibull	Exponential	**LL**	LN	PH2	PH3	PH4	PO2	PO3	PO4	Probit2	Probit3	Probit4
N	690	690	**690**	690	690	690	690	690	690	690	690	690	690
AIC	1604.7	1605.9	**1595.5**	1598.5	1599.7	1601.4	1595.6	1597.3	1597.8	1595.7	1596.5	1597.9	1597.0
BIC	1613.7	1610.4	**1604.6**	1607.6	1613.4	1619.5	1618.3	1611.0	1616.0	1618.3	1610.1	1616.1	1619.7

Figure 38. Projected survival probability from pool data of atezolizumab-treated patients.

Table 47. Model fit for OS of atezolizumab-pool data.

	Weibull	Exponential	**LL**	LN	PH2	PH3	PH4	PO2	PO3	PO4	Probit2	Probit3	Probit4
N	569	569	**569**	569	569	569	569	569	569	569	569	569	569
AIC	1506.8	1507.9	**1501.4**	1505.2	1502.1	1504.1	1505.9	1503.4	1505.1	1506.5	1501.8	1503.8	1505.5
BIC	1515.5	1512.2	**1510.1**	1513.9	1515.2	1521.5	1527.7	1516.5	1522.5	1528.2	1514.8	1521.1	1527.2
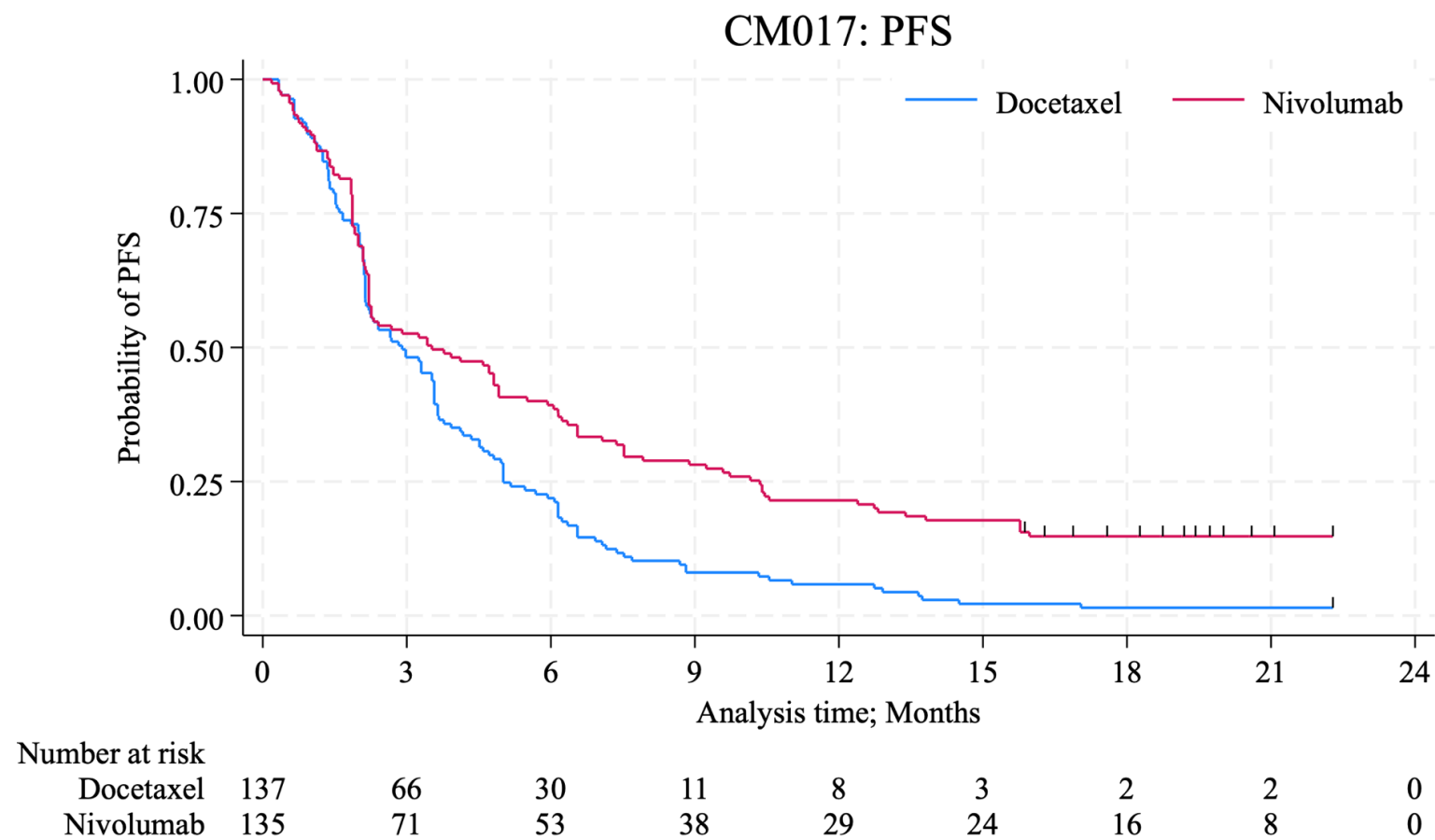
Figure 39. Reconstructed KM curve for OS from CM017 study.
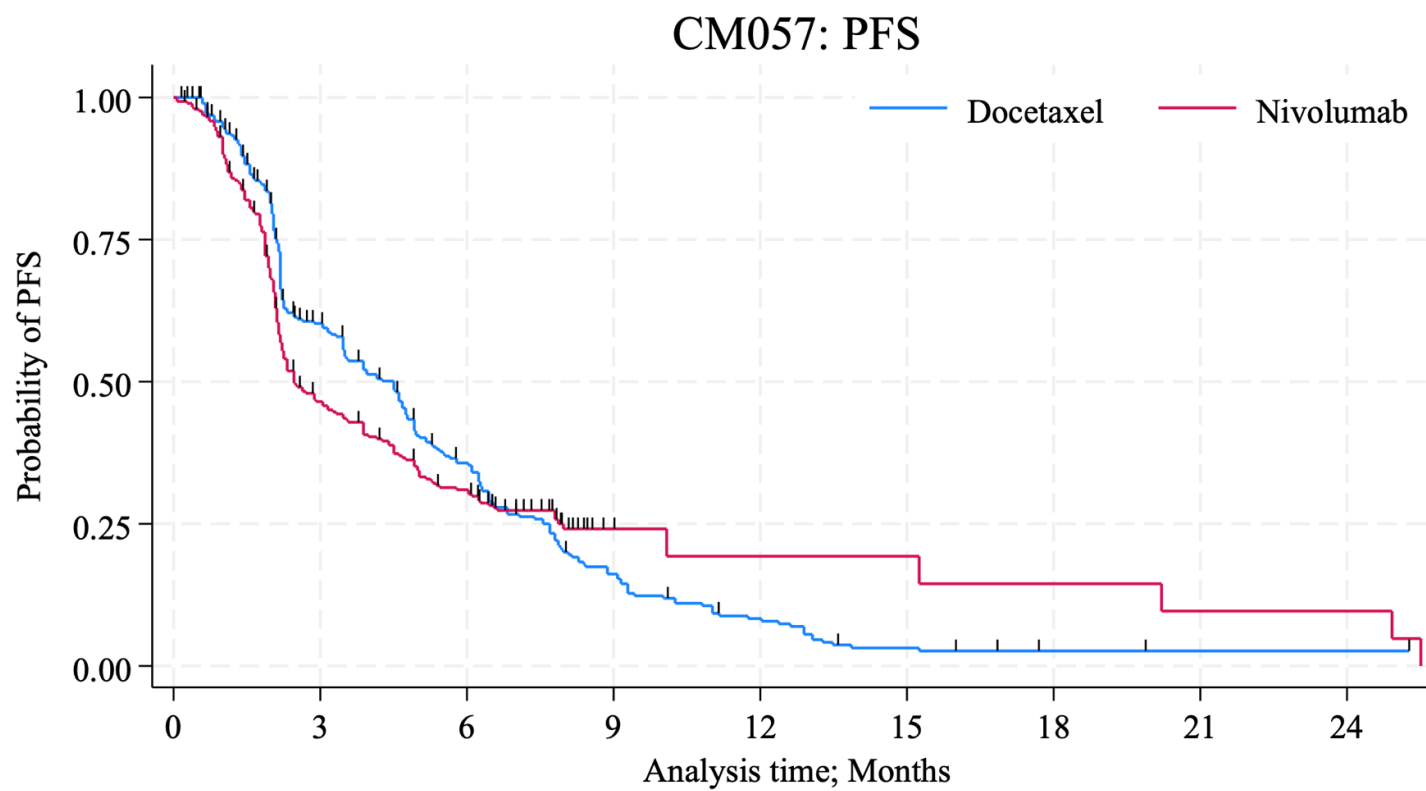
Figure 40. Reconstructed KM curve for PFS from CM057 study.
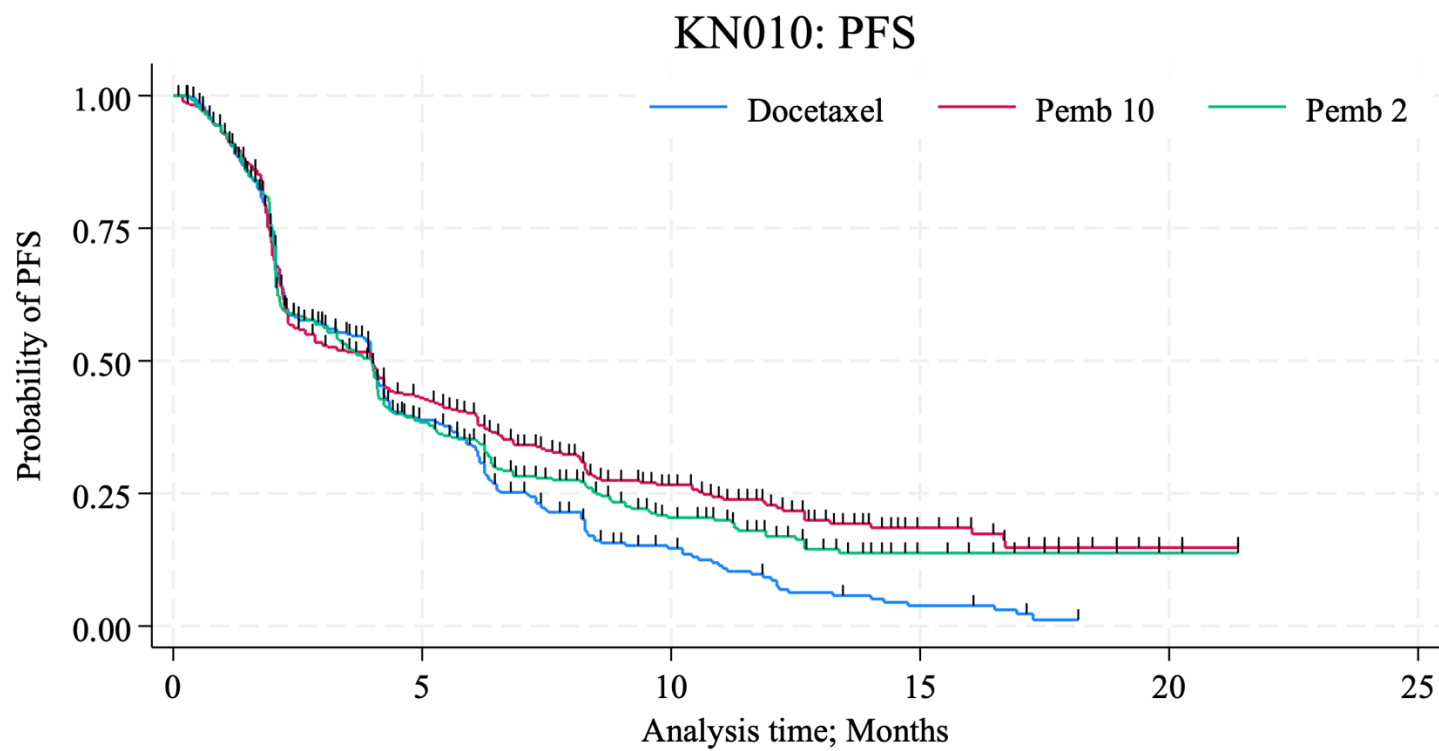
Figure 41. Reconstructed KM curve for PFS from HN010 study.
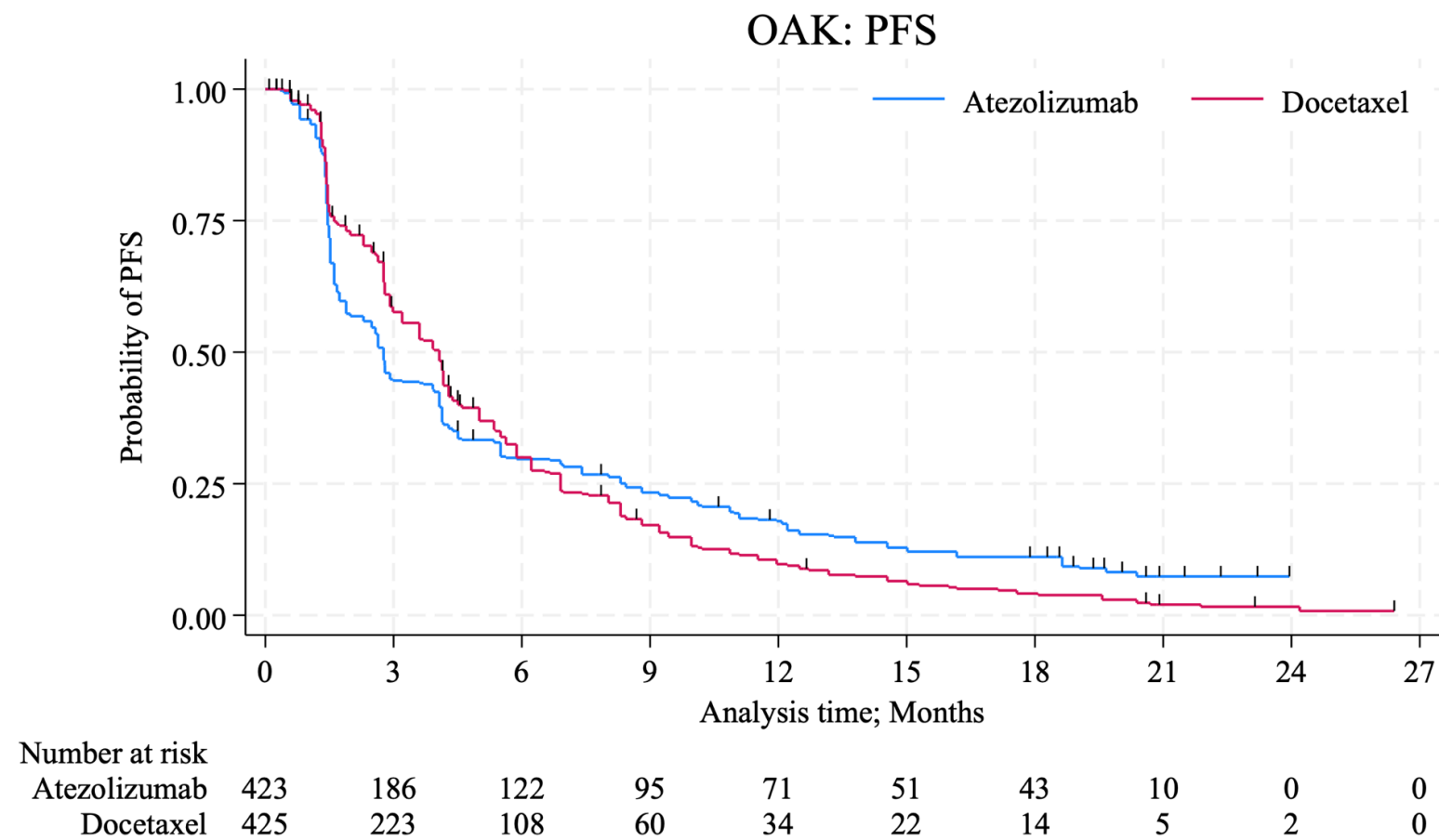
Figure 42. Reconstructed KM curve for PFS from OAK study.
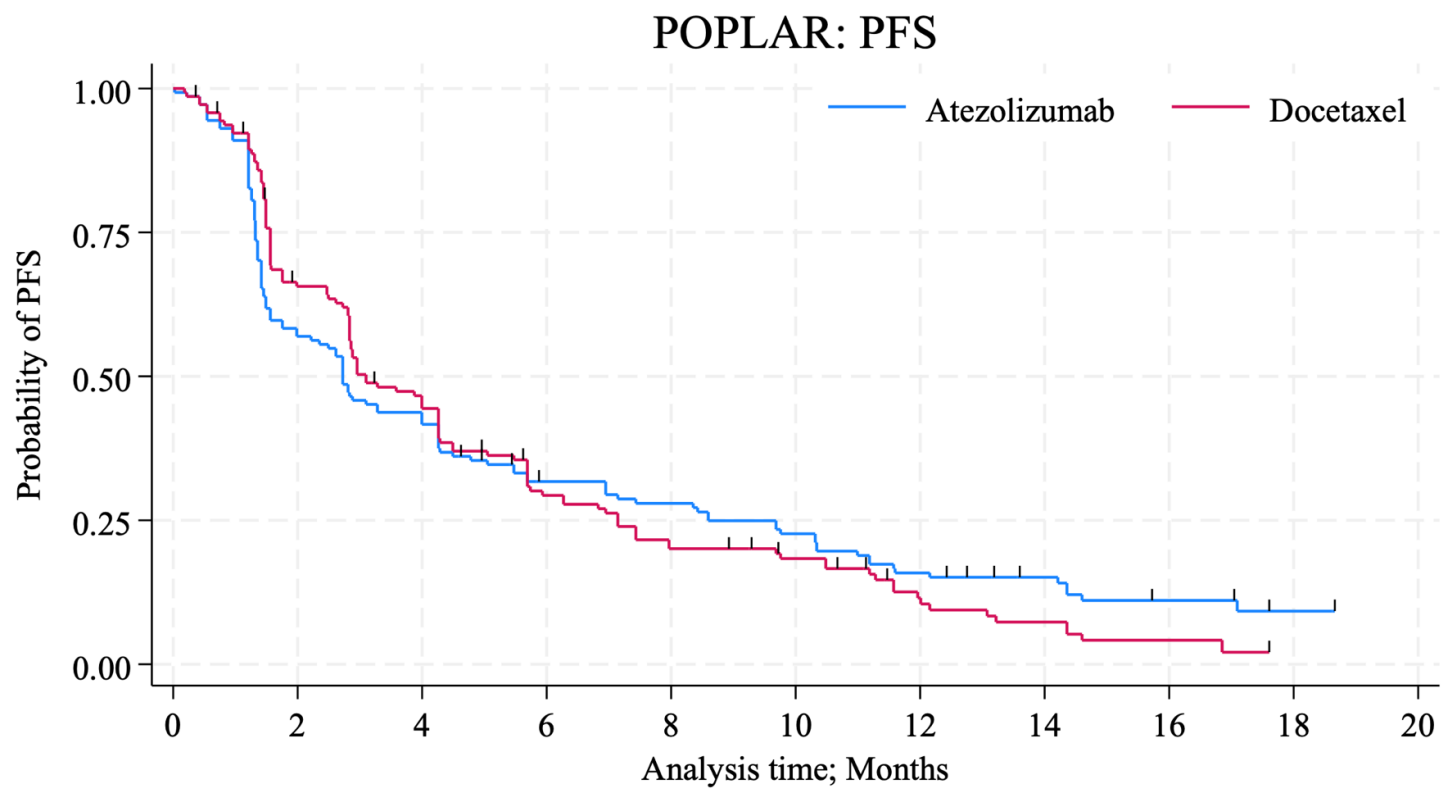
Figure 43. Reconstructed KM curve for PFS from POPLAR study.
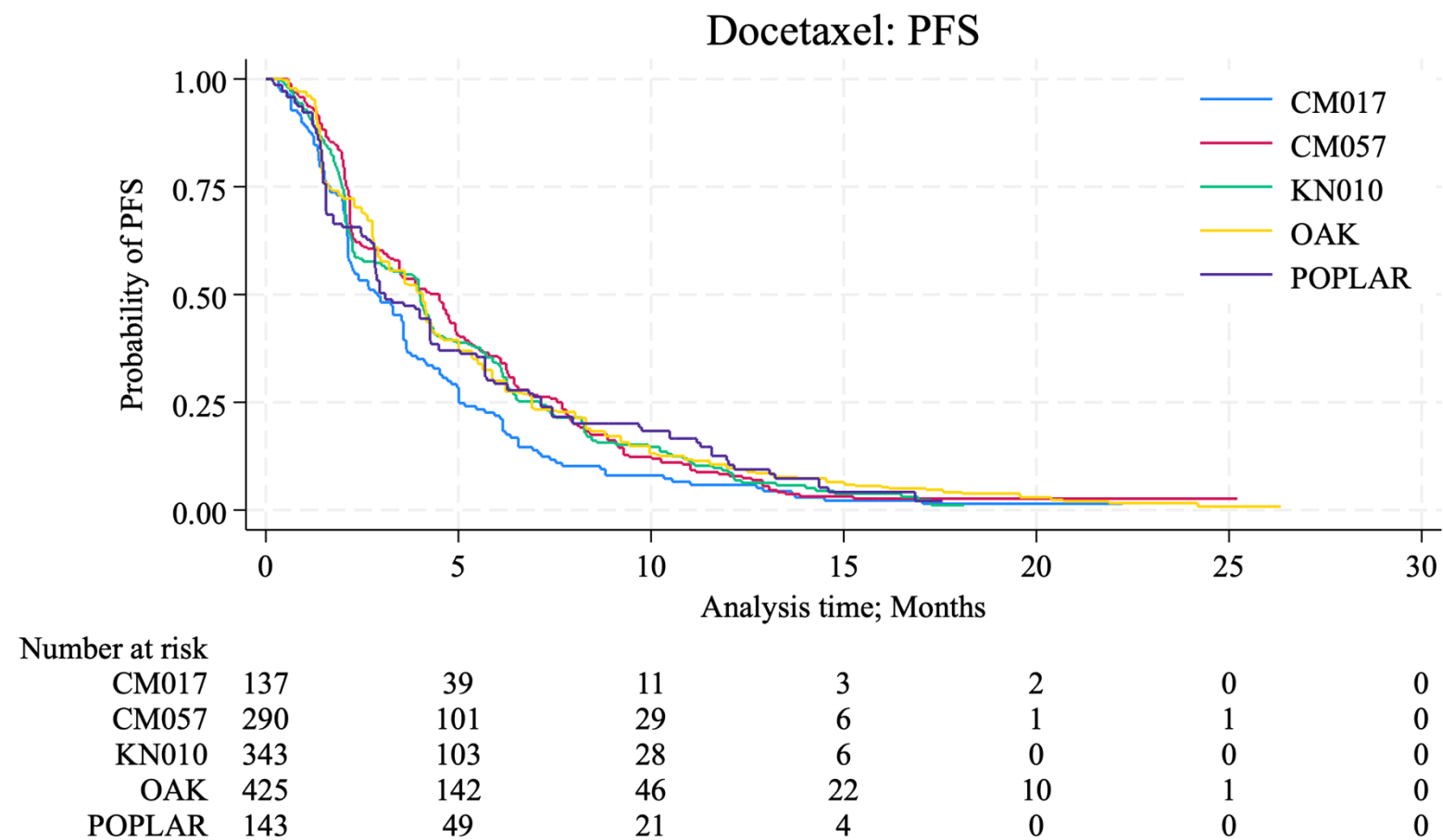
Figure 44. PFS KM curves for docetaxel from 5 studies.
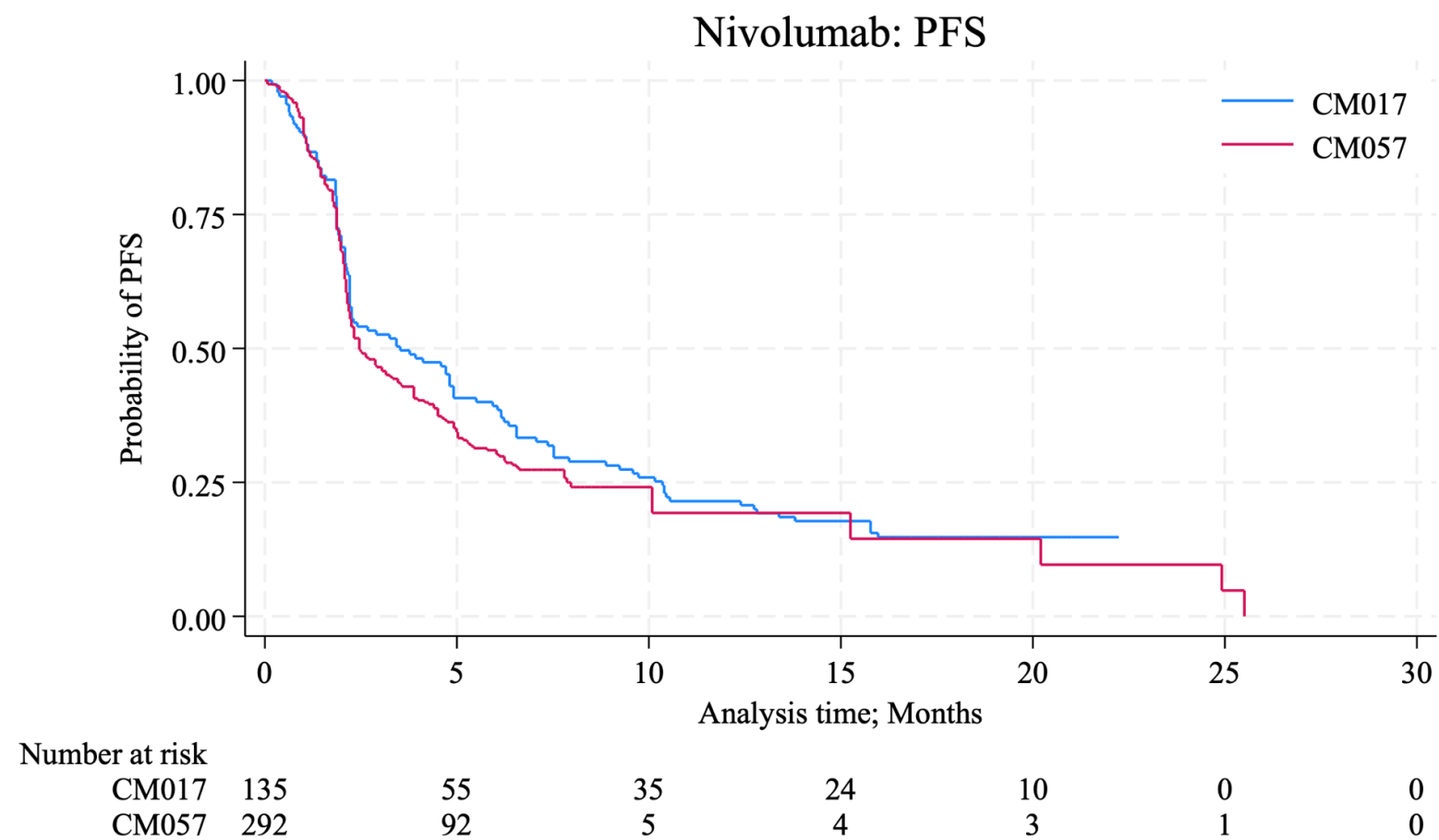
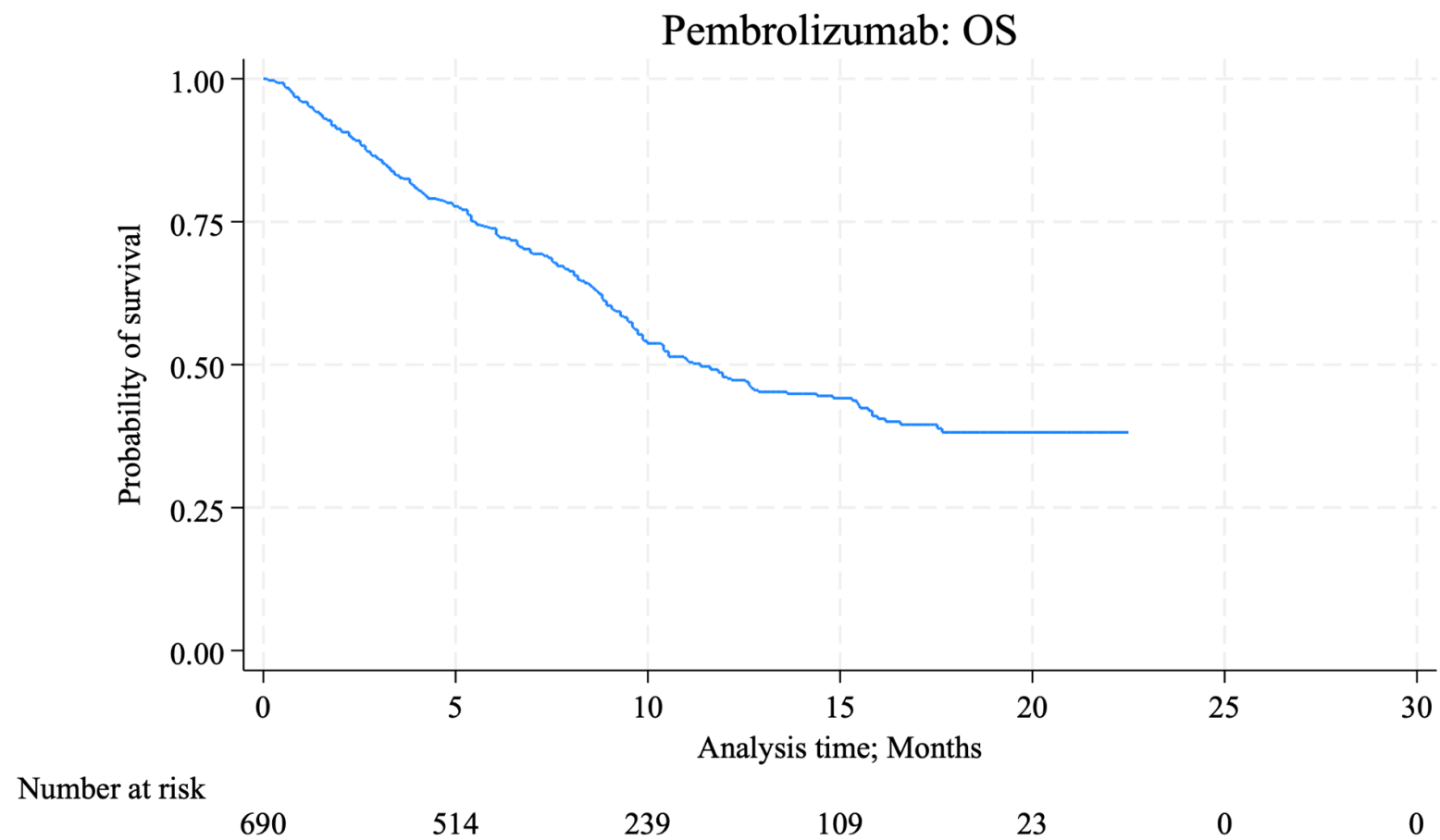*Figure 45. PFS KM curves for nivolumab from 2 studies.*
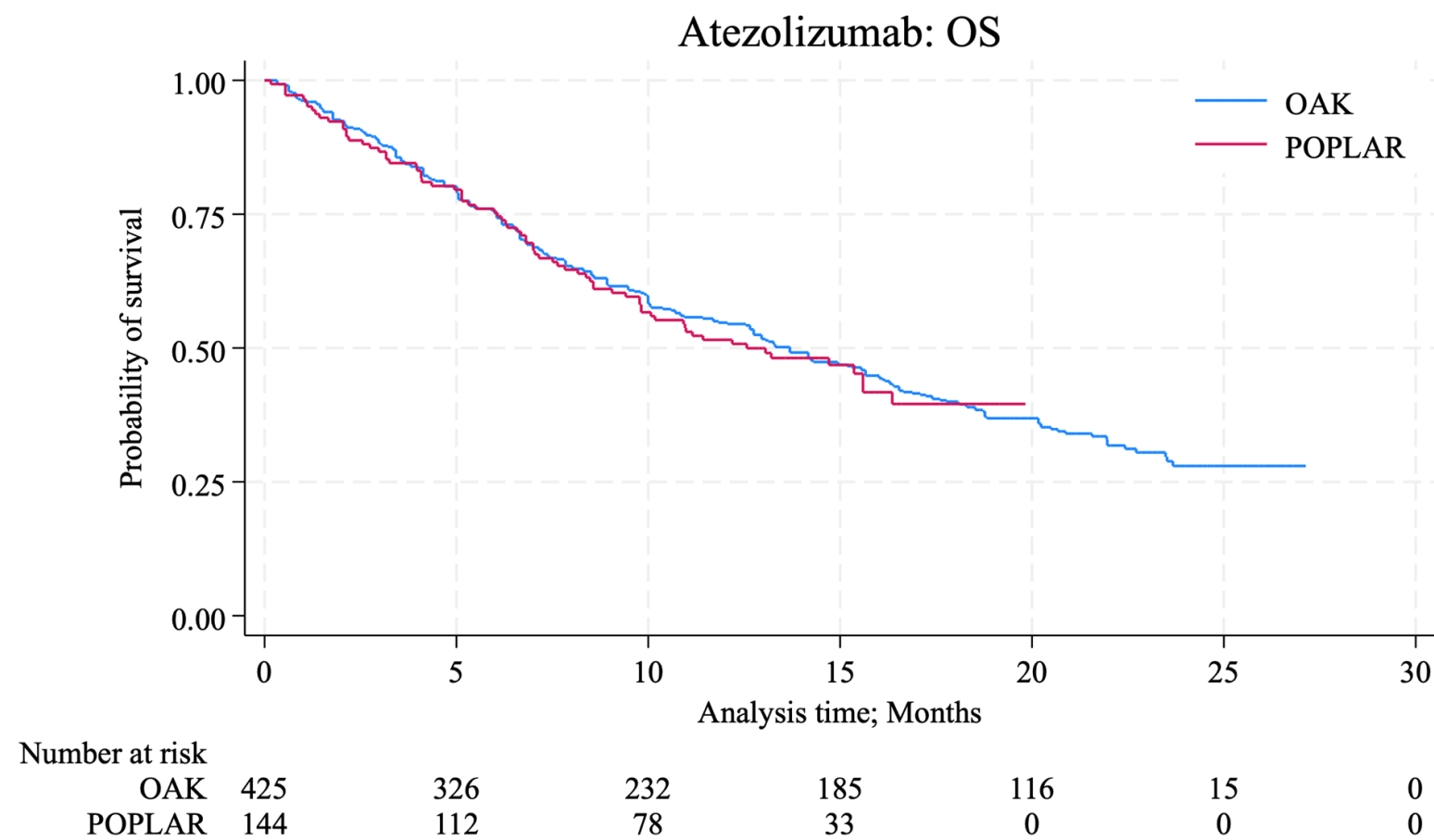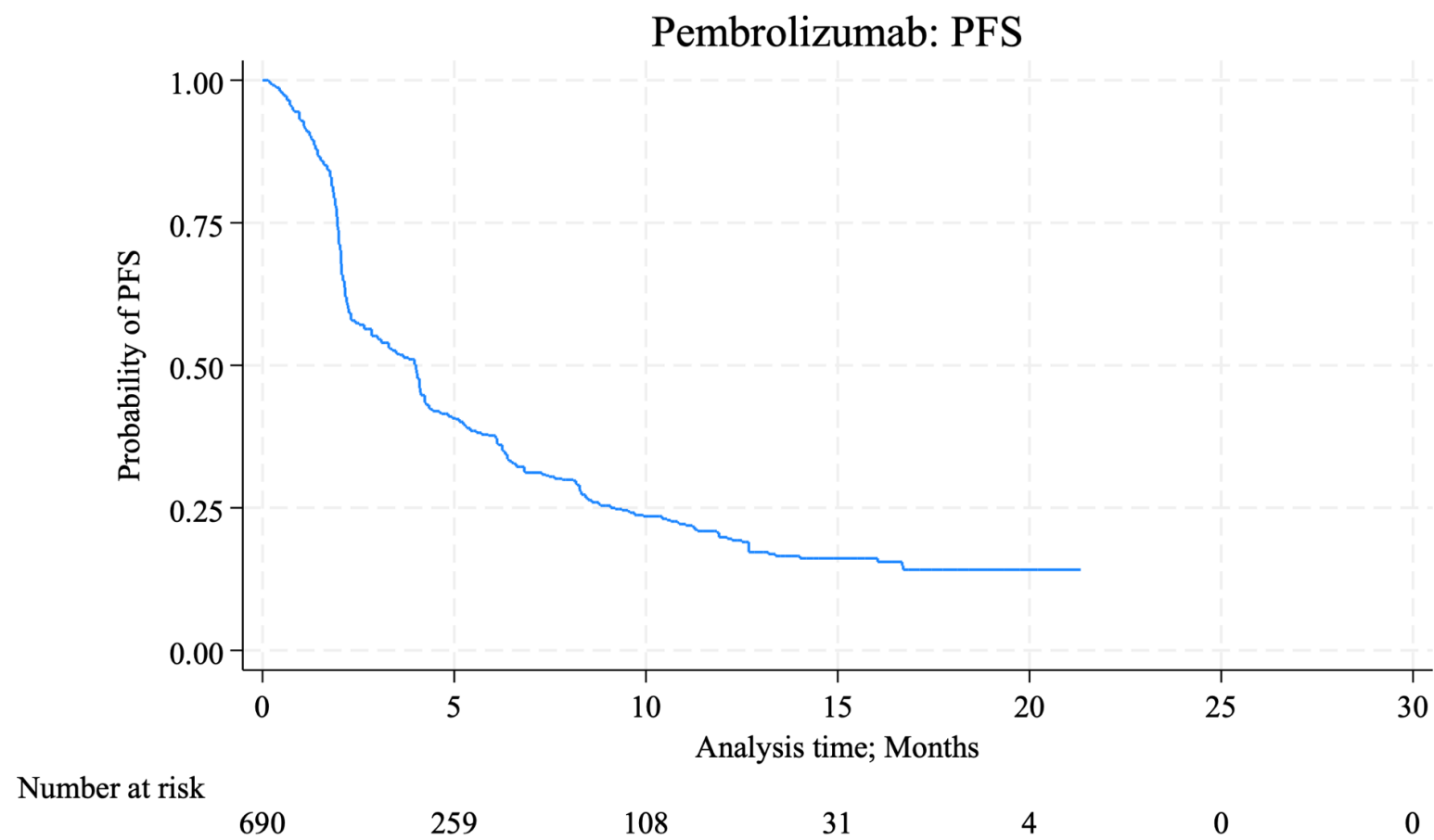
Figure 46. PFS KM curves for pembrolizumab.

Atezolizumab: PFS
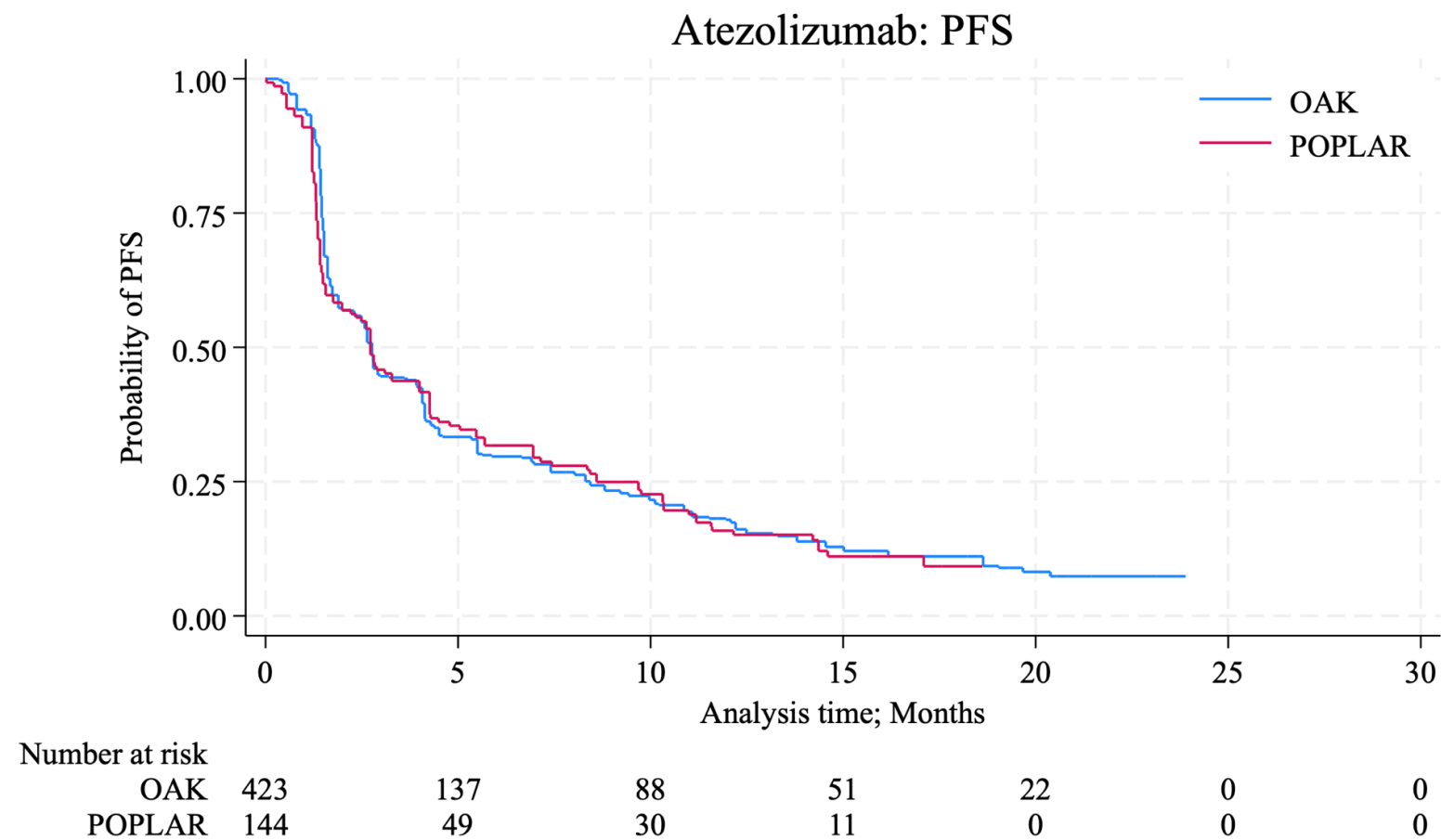
Figure 47. PFS KM curves for nivolumab from 2 studies.
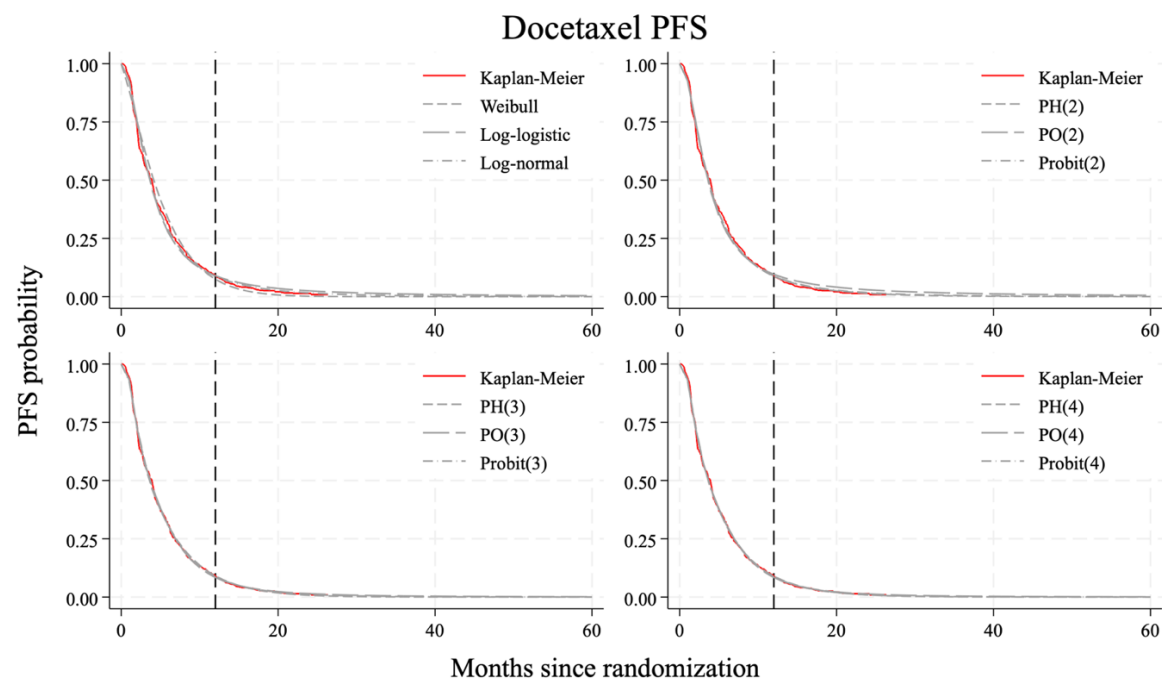
Figure 48. Projected PFS probability from pool data of docetaxel-treated patients.

Table 48. Model fit for PFS of docetaxel-pool data.

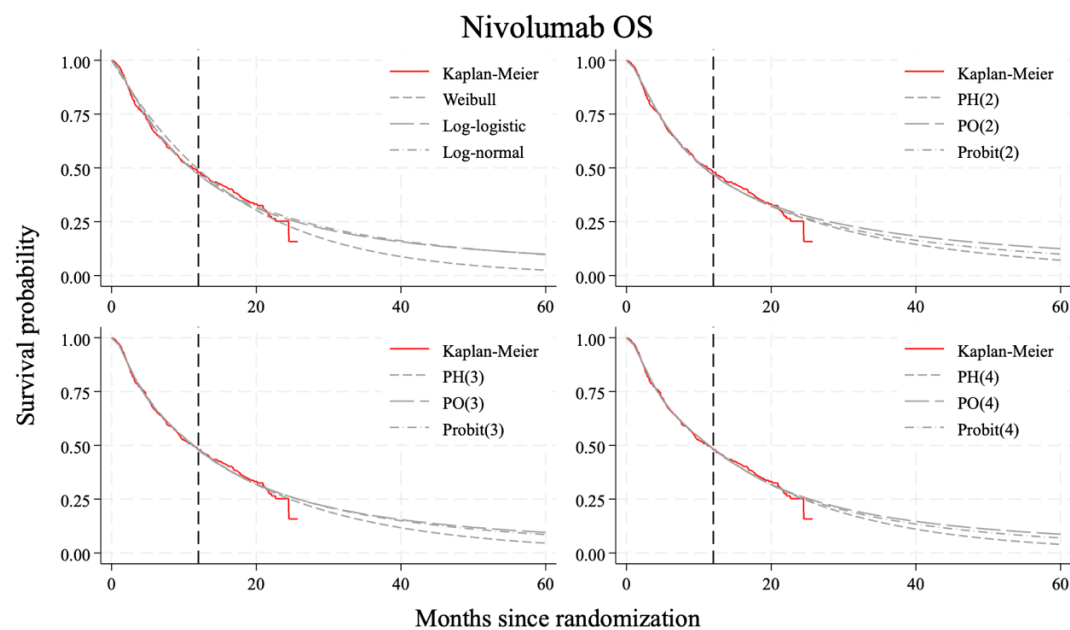|	Weibull	Exponential	LL	**LN**	PH2	PH3	PH4	PO2	PO3	PO4	Probit2	Probit3	Probit4
N	1338	1338	1338	**1338**	1338	1338	1338	1338	1338	1338	1338	1338	1338
AIC	3351.5	3435.2	3251.0	**3211.0**	3225.3	3192.0	3193.2	3249.8	3188.2	3193.2	3212.8	3201.3	3202.4
BIC	3361.9	3440.4	3261.4	**3221.4**	3240.9	3212.8	3219.2	3265.4	3209.0	3219.2	3228.3	3222.1	3228.4
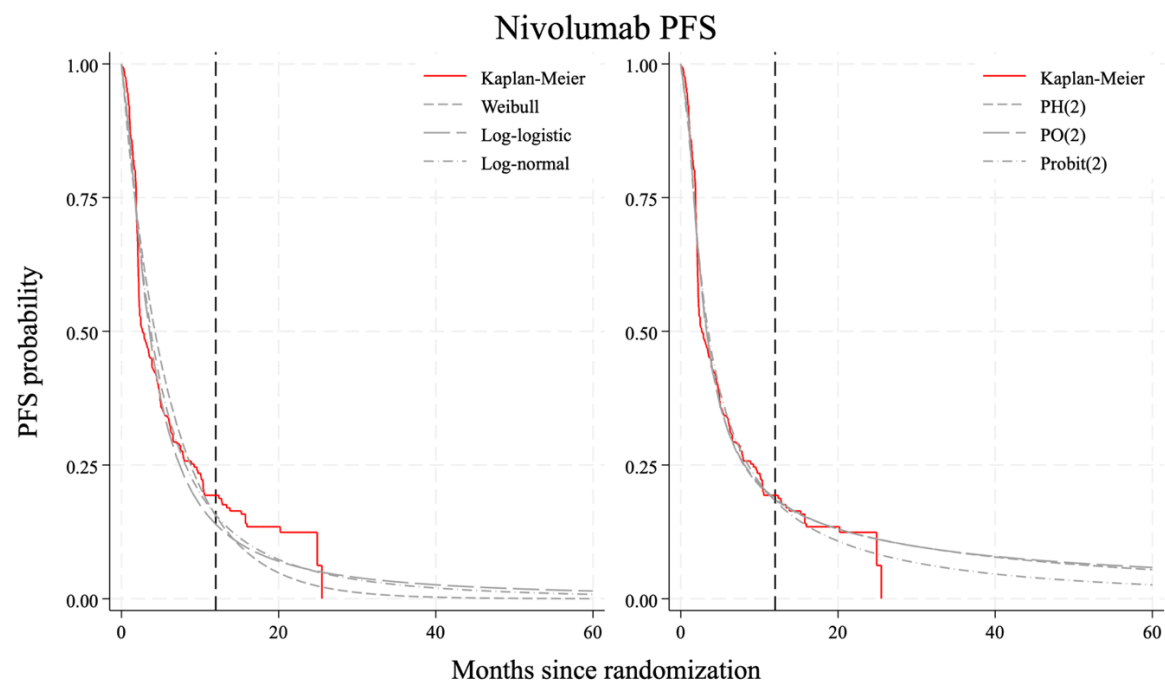
Figure 49. Projected survival probability from pool data of nivolumab-treated patients.

Table 49. Model fit for PFS of nivolumab-pool data.

	Weibull	Exponential	LL	**LN**	PH2	PO2	Probit2
N	427	427	427	**427**	427	427	427
AIC	1281.2	1280.6	1209.9	**1209.2**	1180.9	1178.8	1199.2
BIC	1289.3	1284.7	1218.0	**1217.3**	1193.0	1190.9	1211.3
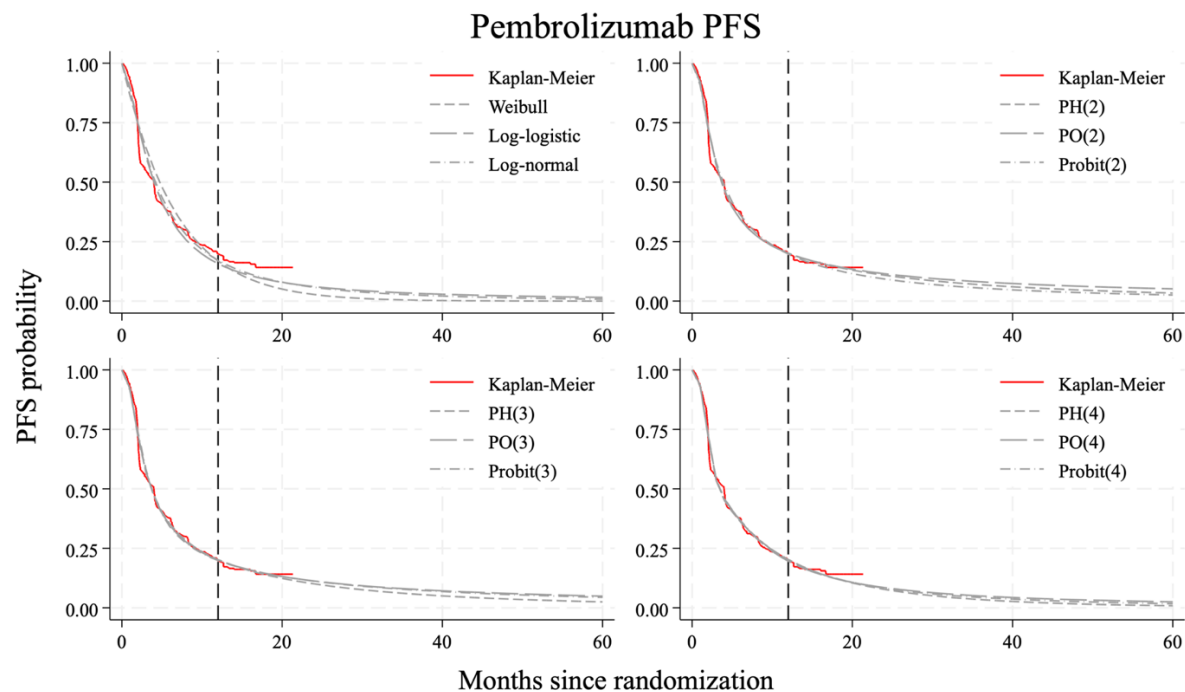
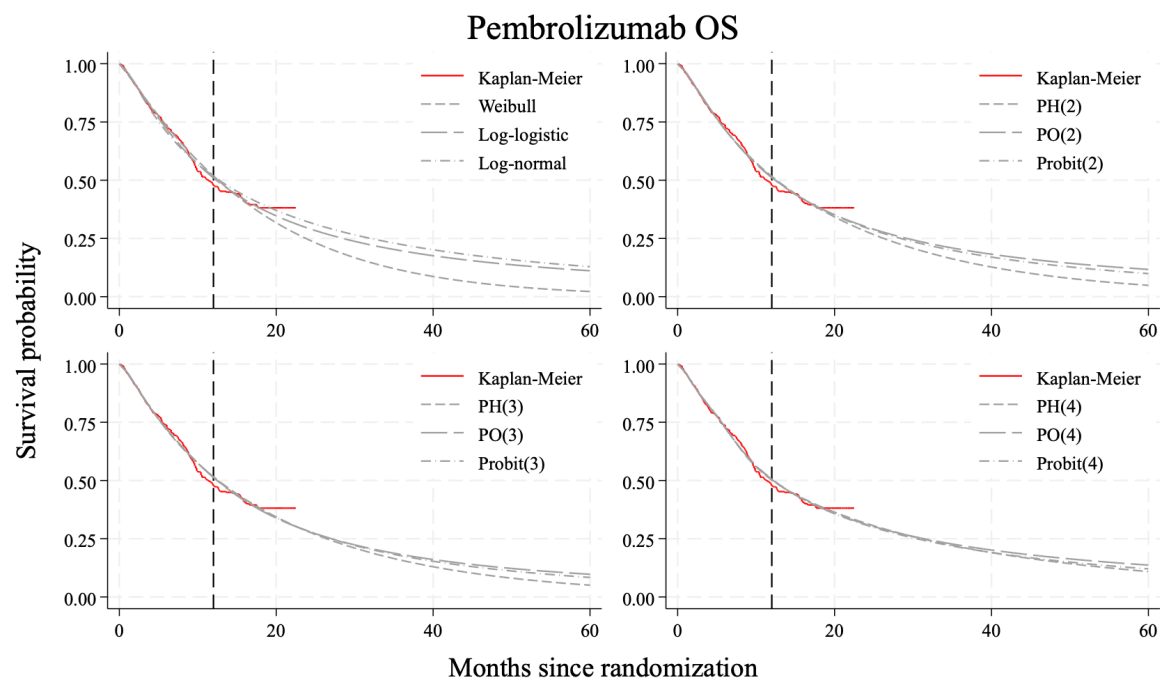*Figure 50. Projected PFS probability from data of pembrolizumab-treated patients.*

Table 50. Model fit for PFS of pembrolizumab data

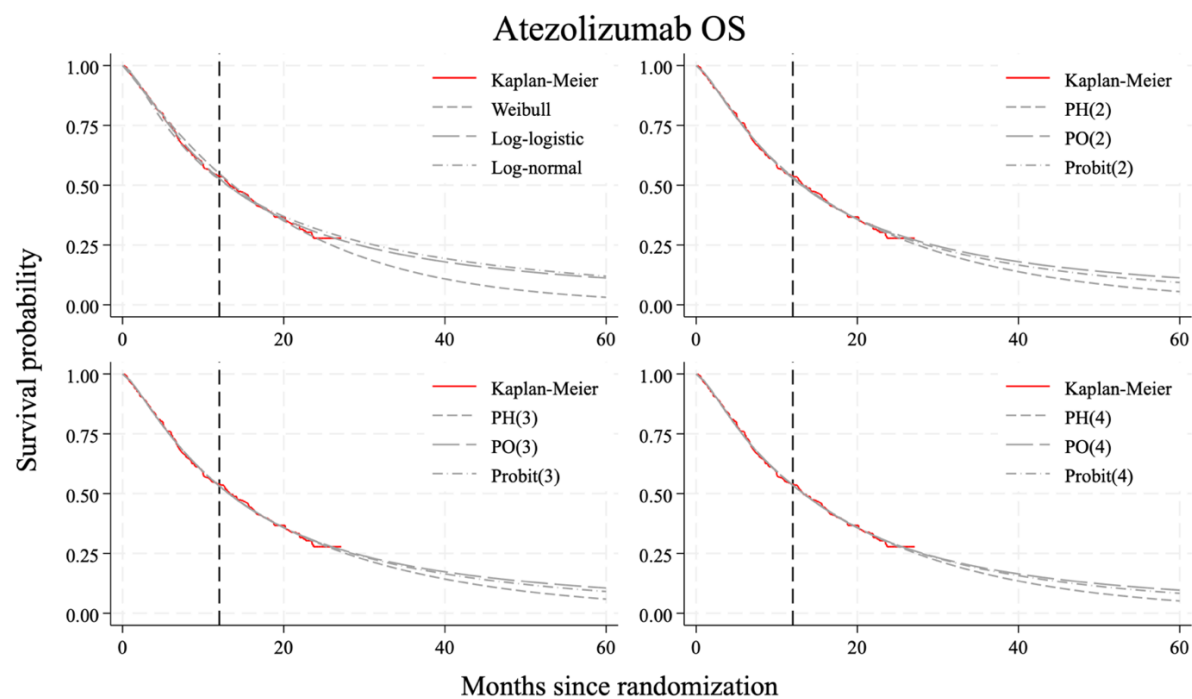|	Weibull	Exponential	LL	**LN**	PH2	PH3	PH4	PO2	PO3	PO4	Probit2	Probit3	Probit4
N	690	690	690	**690**	690	690	690	690	690	690	690	690	690
AIC	2015.3	2013.4	1917.4	**1907.7**	1868.9	1870.4	1825.0	1867.7	1870.9	1815.0	1887.0	1879.3	1817.3
BIC	2024.4	2017.9	1926.5	**1916.8**	1882.5	1888.6	1847.7	1881.3	1889.0	1837.7	1900.6	1897.5	1840.0
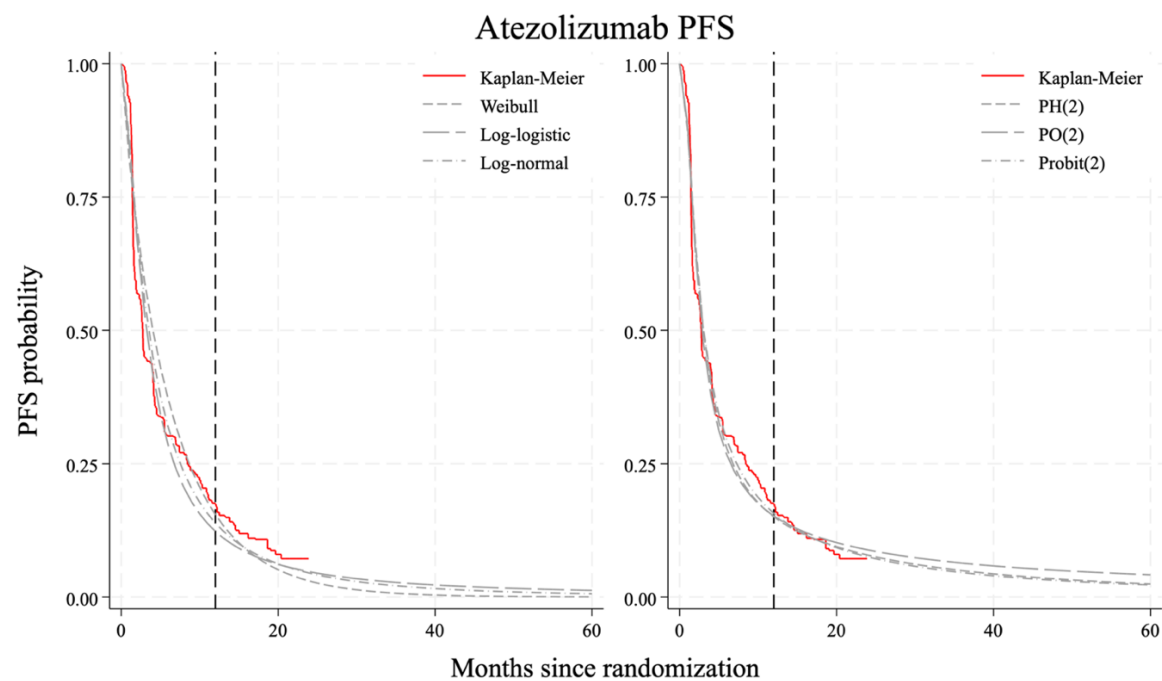
Figure 51. Projected PFS probability from pool data of atezolizumab-treated patients.

Table 51. Model fit for PFS of atezolizumab-pool data.

	Weibull	Exponential	LL	**LN**	PH2	PO2	Probit2
N	567	567	567	**567**	567	567	567
AIC	1821.0	1826.9	1708.6	**1698.5**	1654.5	1643.8	1660.0
BIC	1829.7	1831.2	1717.3	**1707.2**	1667.6	1656.9	1673.1

Table 52. Parameters to be used in the transitional stage from the best-fit models for all outcomes.

Docetaxel OS — Log-logistic

_t	Coefficient	Std. err.	z	P>|z|	[95% conf. interval]	
_cons	3.643551	0.0307682	1.18E+02	0	3.583246	3.703855
/lngamma	-0.480551	0.0274087	-1.75E+01	0	-0.5342712	-0.4268309
gamma	0.6184425	0.0169507			0.5860963	0.6525739

Nivolumab OS — Log-normal

_t	Coefficient	Std. err.	z	P>|z|	[95% conf. interval]	
_cons	3.853784	0.0698283	5.52E+01	0	3.716923	3.990645
/lnsigma	0.2741999	0.0456442	6.01	0	0.184739	0.3636608
sigma	1.315478	0.0600439			1.202904	1.438586

Pembrolizumab OS — Log-logistic

_t	Coefficient	Std. err.	z	P>|z|	[95% conf. interval]	
_cons	3.981171	0.0585699	6.80E+01	0	3.866377	4.095966
/lngamma	-0.2743739	0.0473622	-5.79E+00	0	-0.3672021	-0.1815456
gamma	0.7600479	0.0359975			0.6926696	0.8339802

Atezolizumab — Log-logistic

_t	Coefficient	Std. err.	z	P>|z|	[95% conf. interval]	
_cons	4.033677	0.0569132	7.09E+01	0	3.922129	4.145225
/lngamma	-0.3036841	0.0455201	-6.67E+00	0	-0.3929018	-0.2144663
gamma	0.738094	0.0335981			0.675095	0.806972

Docetaxel   PFS   Log-normal

_t	Coefficient	Std. err.	z	P>|z|	[95% conf. interval]	
_cons	2.757932	0.0250048	1.10E+02	0	2.708923	2.80694
/lnsigma	-0.1264179	0.0208879	-6.05E+00	0	-0.1673574	-0.0854784
sigma	0.8812465	0.0184074			0.8458973	0.918073

Nivolumab   PFS   Log-normal

_t	Coefficient	Std. err.	z	P>|z|	[95% conf. interval]	
_cons	2.784726	0.0584481	4.76E+01	0	2.67017	2.899282
/lnsigma	0.14387	0.0409253	3.52	0	0.0636579	0.224082
sigma	1.154734	0.0472578			1.065728	1.251174

Pembrolizumab   PFS   Log-normal

_t	Coefficient	Std. err.	z	P>|z|	[95% conf. interval]	
_cons	2.897293	0.0443358	6.53E+01	0	2.810397	2.98419
/lnsigma	0.1061587	0.0322873	3.29	0.001	0.0428768	0.1694406
sigma	1.111998	0.0359034			1.043809	1.184642

Atezolizumab   PFS   Log-normal

_t	Coefficient	Std. err.	z	P>|z|	[95% conf. interval]	
_cons	2.719468	0.0483402	5.63E+01	0	2.624723	2.814213
/lnsigma	0.1259843	0.0323122	3.9	0	0.0626536	0.189315
sigma	1.134264	0.0366506			1.064658	1.208422

Appendix E

Cost and utility parameters to be used in economic evaluation models

Table 53. Details of the drug cost.

Drug	Detail	Lowest	Mode	Median	Mean	SE	n	Distribution to be used in sensitivity analysis	Distribution from sources	Ref.
Doc	Per mg				0.62	0.10	34	Normal	Normal/Gamma	Calculated
	80 mg vial	16.62	20.07	20.07	49.32	8.45	34	Normal	Normal/Gamma	DMSIC
	20 mg vial	6.32		15.49	17.52	3.44	26	Normal	Normal/Gamma	DMSIC
	Administration				39.06			Normal	Normal	PSU data
Nivo	Per mg				15.32	8.85	3	Normal	Normal	Calculated
	100 mg vial	766.27*		1915.69	1532.55	884.81	3	Normal	Normal	DMSIC
	40 mg vial	766.27		766.27	766.27		2	Normal	Constant	DMSIC
	Administration				13.02					PSU data
Pembro	100 mg vial	3239.25	3239.25	3239.25	3239.25	1322.42	6	Normal	Constant	DMSIC
	Administration				13.02					PSU data
Atezo	1200 mg vial	2124.67	2124.67	2124.67	2124.6	867.39	6	Normal	Constant	DMSIC
	Administration				13.020833					PSU data

* Possible error from the DMSC.

Table 54. Direct non-medial cost parameters.

Domain	Locally adv (N=134)	FL (N=176)	2L, non-PD (N=73)	2L-PD and > 2L (N=50)	Total (N=433)	Test
Outpatient frequency	0.421 ± 0.066	1.135 ± 0.044	1.107 ± 0.064	1.043 ± 0.067	0.904 ± 0.034	<0.001
Travel cost for OPD visit	31.066 ± 2.033	39.478 ± 2.381	31.791 ± 2.982	40.939 ± 5.292	35.748 ± 1.409	0.027
Extra cost for meal per OPD visit	13.424 ± 1.091	20.174 ± 1.931	16.225 ± 2.649	18.859 ± 3.404	17.268 ± 1.047	0.051
OPD-Accommodation cost	14.613 ± 1.882	17.661 ± 2.133	14.214 ± 2.468	12.220 ± 2.579	15.422 ± 1.164	0.434
IPD travel cost	38.021 ± 2.929	41.622 ± 6.482	32.427 ± 6.899	28.097 ± 5.531	37.396 ± 3.086	0.522
Number of admission/year	1.136 ± 0.042	1.034 ± 0.019	1.043 ± 0.043	1.000 ± 0.000	1.073 ± 0.020	0.059
Proportion needed to buy equipment	0.149 ± 0.031	0.193 ± 0.030	0.178 ± 0.045	0.240 ± 0.061	0.182 ± 0.019	0.525
if yes equipment cost	55.440 ± 22.306	68.671 ± 17.883	53.285 ± 28.690	64.541 ± 25.467	61.506 ± 11.480	0.953

Table 55. Indirect cost parameters in mean ± SE.

Domain	Locally adv (N=135)	FL (N=174)	2L, non-PD (N=74)	2L-PD and > 2L (N=50)	Total (N=433)	Test
income/month	360.675 ± 46.722	354.208 ± 69.343	448.393 ± 81.643	364.647 ± 73.470	373.526 ± 35.367	0.818
main income/month	704.857 ± 84.440	623.296 ± 67.014	608.598 ± 108.200	727.534 ± 90.818	658.250 ± 43.166	0.766
number of caregiver	1.258 ± 0.051	1.433 ± 0.050	1.297 ± 0.069	1.380 ± 0.090	1.349 ± 0.030	0.086
Pr.(OPD-caregiver number 1)	0.933 ± 0.022	0.971 ± 0.013	0.959 ± 0.023	0.960 ± 0.028	0.956 ± 0.010	0.449
Pr.(OPD-caregiver number 2)	0.252 ± 0.037	0.351 ± 0.036	0.284 ± 0.053	0.340 ± 0.068	0.307 ± 0.022	0.271
Pr.(OPD-caregiver number 3)	0.037 ± 0.016	0.075 ± 0.020	0.041 ± 0.023	0.060 ± 0.034	0.055 ± 0.011	0.488
Outpatient frequency c1	0.434 ± 0.067	1.132 ± 0.044	1.105 ± 0.063	1.043 ± 0.067	0.905 ± 0.034	<0.001
Outpatient frequency c2	0.615 ± 0.231	1.142 ± 0.082	1.198 ± 0.141	1.108 ± 0.113	1.012 ± 0.077	0.024
Outpatient frequency c3	0.314 ± 0.016	1.308 ± 0.175	1.000 ± 0.000	1.667 ± 0.333	1.107 ± 0.135	0.006
Outpatient duration (hr) each day c1	5.000 ± 0.142	5.994 ± 0.137	5.718 ± 0.210	5.896 ± 0.258	5.633 ± 0.087	<0.001
Outpatient duration (hr) each day c2	4.471 ± 0.302	6.443 ± 0.256	5.095 ± 0.425	5.824 ± 0.274	5.647 ± 0.174	<0.001
Outpatient duration (hr) each day c3	4.200 ± 0.800	6.615 ± 0.474	4.667 ± 0.882	6.333 ± 0.882	5.833 ± 0.389	0.053
Outpatient money loss for job c1	22.720 ± 3.893	23.965 ± 2.964	21.132 ± 4.536	17.063 ± 3.613	22.596 ± 1.945	0.800
Outpatient money loss for job c2	19.746 ± 3.258	20.260 ± 2.111	23.364 ± 5.722	15.988 ± 3.435	20.346 ± 1.775	0.705
Outpatient money loss for job c3	35.027 ± NA	16.260 ± 6.056	16.510 ± NA	26.378 ± 8.649	21.867 ± 4.101	0.529
IPD number of caregiver	1.400 ± 0.062	1.281 ± 0.058	1.340 ± 0.093	1.138 ± 0.065	1.324 ± 0.036	0.159
Pr.(IPD-caregiver number 1)	0.815 ± 0.034	0.511 ± 0.038	0.635 ± 0.056	0.580 ± 0.071	0.635 ± 0.023	<0.001
Pr.(iPD-caregiver number 2)	0.274 ± 0.039	0.132 ± 0.026	0.176 ± 0.045	0.080 ± 0.039	0.178 ± 0.018	0.002
Pr.(IPD-caregiver number 3)	0.074 ± 0.023	0.023 ± 0.011	0.054 ± 0.026	0.000 ± 0.000	0.042 ± 0.010	0.056
Inpatient frequency c1	2.982 ± 0.612	3.057 ± 0.486	3.511 ± 0.640	1.655 ± 0.458	2.956 ± 0.315	0.501
Inpatient frequency c2	1.459 ± 0.221	3.870 ± 0.983	2.308 ± 0.548	1.750 ± 0.750	2.338 ± 0.344	0.023
Inpatient frequency c3	1.200 ± 0.200	2.000 ± 0.577	2.750 ± 1.750	NA	1.722 ± 0.411	0.321

Domain	Locally adv (N=135)	FL (N=174)	2L, non-PD (N=74)	2L-PD and > 2L (N=50)	Total (N=433)	Test
Inpatient duration (day) c1	9.273 ± 0.309	8.348 ± 0.340	8.149 ± 0.441	9.345 ± 0.581	8.789 ± 0.193	0.073
Inpatient duration (day) c2	9.135 ± 0.532	7.417 ± 0.715	8.231 ± 1.051	7.000 ± 1.683	8.346 ± 0.390	0.232
Inpatient duration (day) c3	9.900 ± 1.197	8.000 ± 1.414	10.250 ± 1.750	NA	9.556 ± 0.813	0.613
Inpatient money loss for job c1	19.727 ± 2.535	22.147 ± 2.646	22.934 ± 8.161	19.116 ± 5.811	20.925 ± 1.797	0.900
Inpatient money loss for job c2	21.640 ± 3.264	23.083 ± 3.897	27.419 ± 7.607	10.508 ± .	22.065 ± 2.269	0.584
Inpatient money loss for job c3	NA	17.729 ± NA	NA	NA	17.729 ± NA	

Table 56. Patient characteristics in n(%) and mean ± SE.

	Locally adv (N=141)	FL (N=210)	2L, non-PD (N=88)	2L-PD and > 2L (N=52)	Total (N=491)	Test
Sex						
Male	71 (50.4%)	113 (53.8%)	40 (45.5%)	25 (48.1%)	249 (50.7%)	0.587
Female	70 (49.6%)	97 (46.2%)	48 (54.5%)	27 (51.9%)	242 (49.3%)	
Weight (Kg)	58.86 ± 0.95	55.23 ± 0.82	54.71 ± 1.30	55.35 ± 1.60	56.19 ± 0.53	0.016
	158.44 ±	159.29 ±	158.31 ±			
Height (cm)	0.71	0.59	0.92	160.27 ± 1.43	158.97 ± 0.39	0.482
Age	67.13 ± 0.94	64.93 ± 0.73	65.48 ± 1.00	66.46 ± 1.36	65.82 ± 0.47	0.263
BMI (Kg/m^2)	23.50 ± 0.37	21.72 ± 0.28	21.73 ± 0.42	21.49 ± 0.51	22.21 ± 0.19	<0.001
BSA (m^2)	1.60 ± 0.01	1.56 ± 0.01	1.54 ± 0.02	1.56 ± 0.03	1.57 ± 0.01	0.064

Table 57. n(%) of EQ5D domains and mean ± SE of utility.

Variable	Locally adv (N=135)	FL (N=174)	2L, non-PD (N=74)	2L-PD and > 2L (N=50)	Total (N=433)	Test
Move						
1	80 (59.3%)	73 (42.0%)	35 (47.3%)	19 (38.0%)	207 (47.8%)	0.019
2	42 (31.1%)	69 (39.7%)	23 (31.1%)	15 (30.0%)	149 (34.4%)	
3	6 (4.4%)	18 (10.3%)	9 (12.2%)	6 (12.0%)	39 (9.0%)	
4	5 (3.7%)	8 (4.6%)	6 (8.1%)	7 (14.0%)	26 (6.0%)	
5	2 (1.5%)	6 (3.4%)	1 (1.4%)	3 (6.0%)	12 (2.8%)	
Self care						
1	109 (80.7%)	112 (64.4%)	49 (66.2%)	29 (58.0%)	299 (69.1%)	0.057
2	20 (14.8%)	41 (23.6%)	17 (23.0%)	11 (22.0%)	89 (20.6%)	
3	4 (3.0%)	13 (7.5%)	3 (4.1%)	6 (12.0%)	26 (6.0%)	
4	1 (0.7%)	4 (2.3%)	4 (5.4%)	2 (4.0%)	11 (2.5%)	
5	1 (0.7%)	4 (2.3%)	1 (1.4%)	2 (4.0%)	8 (1.8%)	
Activity						
1	101 (74.8%)	99 (56.9%)	40 (54.1%)	25 (50.0%)	265 (61.2%)	0.029
2	27 (20.0%)	54 (31.0%)	22 (29.7%)	14 (28.0%)	117 (27.0%)	
3	5 (3.7%)	12 (6.9%)	7 (9.5%)	5 (10.0%)	29 (6.7%)	
4	2 (1.5%)	6 (3.4%)	4 (5.4%)	4 (8.0%)	16 (3.7%)	
5	0 (0.0%)	3 (1.7%)	1 (1.4%)	2 (4.0%)	6 (1.4%)	
Pain						
1	80 (59.3%)	81 (46.6%)	32 (43.2%)	19 (38.0%)	212 (49.0%)	0.061
2	49 (36.3%)	72 (41.4%)	32 (43.2%)	20 (40.0%)	173 (40.0%)	
3	6 (4.4%)	13 (7.5%)	7 (9.5%)	8 (16.0%)	34 (7.9%)	

Variable	Locally adv (N=135)	FL (N=174)	2L, non-PD (N=74)	2L-PD and > 2L (N=50)	Total (N=433)	Test
4	0 (0.0%)	5 (2.9%)	2 (2.7%)	1 (2.0%)	8 (1.8%)	
5	0 (0.0%)	3 (1.7%)	1 (1.4%)	2 (4.0%)	6 (1.4%)	
Fear/anxiety						
1	76 (56.3%)	81 (46.6%)	46 (62.2%)	19 (38.0%)	222 (51.3%)	0.003
2	47 (34.8%)	61 (35.1%)	18 (24.3%)	17 (34.0%)	143 (33.0%)	
3	7 (5.2%)	24 (13.8%)	3 (4.1%)	9 (18.0%)	43 (9.9%)	
4	3 (2.2%)	5 (2.9%)	7 (9.5%)	5 (10.0%)	20 (4.6%)	
5	2 (1.5%)	3 (1.7%)	0 (0.0%)	0 (0.0%)	5 (1.2%)	
Utility from EQ5D5L	0.897 ± 0.012	0.823 ± 0.018	0.822 ± 0.028	0.748 ± 0.042	0.837 ± 0.011	<0.001

Table 58. Travel cost for the economic evaluation of ICI (Mean ± SE).

Variable	Locally adv (N=134)	FL (N=175)	2L, non-PD (N=74)	2L-PD and > 2L (N=50)	Total (N=433)	Test
Number of OPD visit/month	0.421 ± 0.066	1.135 ± 0.044	1.105 ± 0.063	1.043 ± 0.067	0.904 ± 0.034	<0.001
Travel cost for OPD visit	31.066 ± 2.033	39.813 ± 2.380	31.467 ± 2.962	40.939 ± 5.292	35.810 ± 1.408	0.019
Extra cost for meal per OPD visit	13.424 ± 1.091	19.963 ± 1.924	16.119 ± 2.615	18.859 ± 3.404	17.155 ± 1.041	0.060
OPD-Accommodation cost	1.963 ± 0.498	2.826 ± 0.595	3.073 ± 0.860	2.200 ± 0.803	2.529 ± 0.334	0.622
IPD travel cost	38.021 ± 2.929	41.441 ± 6.510	32.253 ± 6.808	28.097 ± 5.531	37.272 ± 3.083	0.527
Number of admission/year	1.136 ± 0.042	1.034 ± 0.019	1.043 ± 0.043	1.000 ± 0.000	1.073 ± 0.020	0.059

Table 59. AE Cost from real-world data adjusted for 28 days (mean ± SE).

Type	anemia (N=3)	fn (N=8)	hyponatermia (N=7)	infection (N=163)	nausea (N=10)	neutropenia (N=13)	pneumonia (N=48)	Total (N=252)	Test
Total charge	5438.3 ± 3088.0	9904.6 ± 2721.1	4744.3 ± 873.7	8909.0 ± 652.4	7757.2 ± 1795.6	7716.0 ± 1828.6	7539.7 ± 1053.1	8417.7 ± 492.3	0.717
Total Cost	3078.1 ± 1550.9	8445.4 ± 2348.1	4543.0 ± 895.0	8035.1 ± 591.7	6975.1 ± 1713.8	6737.4 ± 1556.4	7043.9 ± 1017.4	7595.5 ± 449.8	0.708
DRG charge	2635.7 ± 1361.5	7773.9 ± 2401.0	4307.3 ± 886.5	7130.1 ± 559.2	6482.8 ± 1705.0	6193.2 ± 1572.7	6372.4 ± 944.5	6800.6 ± 425.3	0.812
Reimburse	4408.3 ± 2845.3	6395.0 ± 2729.5	2960.0 ± 860.8	7337.5 ± 748.5	3404.4 ± 1099.8	4881.5 ± 1729.2	5857.0 ± 757.3	6596.0 ± 528.0	0.537

Table 60: Actual AE Cost from real-world data (mean ± SE).

Type	anemia (N=3)	fn (N=8)	hyponatermia (N=7)	infection (N=163)	nausea (N=10)	neutropenia (N=13)	pneumonia (N=48)	Total (N=252)	Test
Total charge	656.2 ± 351.9	2604.0 ± 1027.3	615.8 ± 128.7	3647.7 ± 443.1	1803.9 ± 580.0	2073.3 ± 651.1	2547.6 ± 456.4	3130.8 ± 307.2	0.362
Total cost	455.5 ± 315.1	2315.5 ± 974.6	595.1 ± 131.3	2954.8 ± 281.1	1550.0 ± 465.6	1875.3 ± 611.7	2341.9 ± 396.4	2611.0 ± 205.0	0.242
DRG charge	404.7 ± 293.0	1994.1 ± 831.8	561.1 ± 126.2	2470.5 ± 218.0	1376.5 ± 388.4	1643.5 ± 520.9	2008.0 ± 272.3	2203.6 ± 157.6	0.202
Reimburse	778.2 ± 657.3	1015.6 ± 268.1	338.2 ± 66.4	1889.3 ± 132.5	739.7 ± 278.9	896.6 ± 175.1	1522.8 ± 166.8	1638.6 ± 96.5	0.004
Dur admit	3.0 ± 1.5	11.0 ± 3.1	3.9 ± 0.6	12.9 ± 1.7	8.3 ± 3.0	10.0 ± 2.0	9.7 ± 1.1	11.5 ± 1.1	0.680

Table 61. Post-Progression Cost from real-world data (mean ± SE).

	DOCETAXEL	GEMCITABINE	PEMETREXED DISODIUM	Total	Test
	(N=189)	(N=45)	(N=76)	(N=310)	
Total_cost	2635.201 ± 727.296	1516.367 ± 384.562	3.2e+04 ± 8772.553	9677.443 ± 2303.028	<0.001
Cumulative duration	113.603 ± 9.478	148.267 ± 23.532	254.855 ± 35.323	153.265 ± 11.416	<0.001
Cost/day	13.102 ± 2.113	18.182 ± 1.510	132.912 ± 15.717	43.212 ± 4.987	<0.001
Cost/wk	91.716 ± 14.790	127.274 ± 10.570	930.385 ± 110.017	302.487 ± 34.908	<0.001

+

Table 62. Demographic Cost Data (Arithmetic mean) in USD.

| Variable	UCS (N=197)	CSMBS (N=217)	SSS (N=23)	Total (N=437)	Test
Annual extra-medical cost for OPD	3787.3 ± 16086.4	948.1 ± 6743.6	3021.9 ± 7967.8	2337.1 ± 11999.9	0.053
Annual extra-medical cost OPD visit other hospital	289.1 ± 2365.9	43.6 ± 348.1	70.4 ± 251.5	155.7 ± 1610.7	0.292
Annual drug cost outside hospital	17.0 ± 78.8	26.2 ± 128.7	26.5 ± 43.2	22.1 ± 105.4	0.659
Annual herb cost	23.4 ± 158.4	62.7 ± 336.4	50.9 ± 221.9	44.4 ± 264.9	0.319
Annual supplement cost	523.5 ± 602.8	809.9 ± 1122.7	416.3 ± 616.2	660.1 ± 910.9	0.002
Annual extra-medical cost IPD	281.9 ± 744.3	558.6 ± 1768.3	218.5 ± 229.3	428.9 ± 1392.3	0.244
Annual OOP for medical cost	4800.4 ± 16547.3	2271.5 ± 7280.8	3709.4 ± 8080.1	3487.2 ± 12416.3	0.117
Annual non-medical cost of OPD visit at study hospital	797.8 ± 1114.0	714.2 ± 1535.9	1055.8 ± 1786.7	769.8 ± 1376.2	0.491
Annual food cost OPD visit at study hospital	227.0 ± 478.2	173.4 ± 296.7	240.8 ± 291.3	200.1 ± 387.5	0.349
Annual stay cost OPD visit at study hospital	216.9 ± 710.9	187.1 ± 840.8	547.4 ± 1175.1	216.7 ± 805.9	0.175
Annual IPD cost	38.7 ± 71.7	38.3 ± 58.9	21.2 ± 26.3	37.6 ± 63.9	0.448
Annual house improvement and facility cost	195.3 ± 833.5	220.6 ± 699.9	67.2 ± 231.8	201.1 ± 747.6	0.640
Annual cost of formal caregiver	143.8 ± 900.8	206.1 ± 1052.7	36.5 ± 175.3	169.1 ± 957.8	0.638
Annual OOP for non-medical	1175.6 ± 1856.9	1179.2 ± 2021.4	1180.7 ± 1899.4	1177.6 ± 1938.2	1.000
Total annual OOP	5976.0 ± 17005.9	3450.7 ± 7567.1	4890.1 ± 8125.0	4664.9 ± 12775.7	0.132
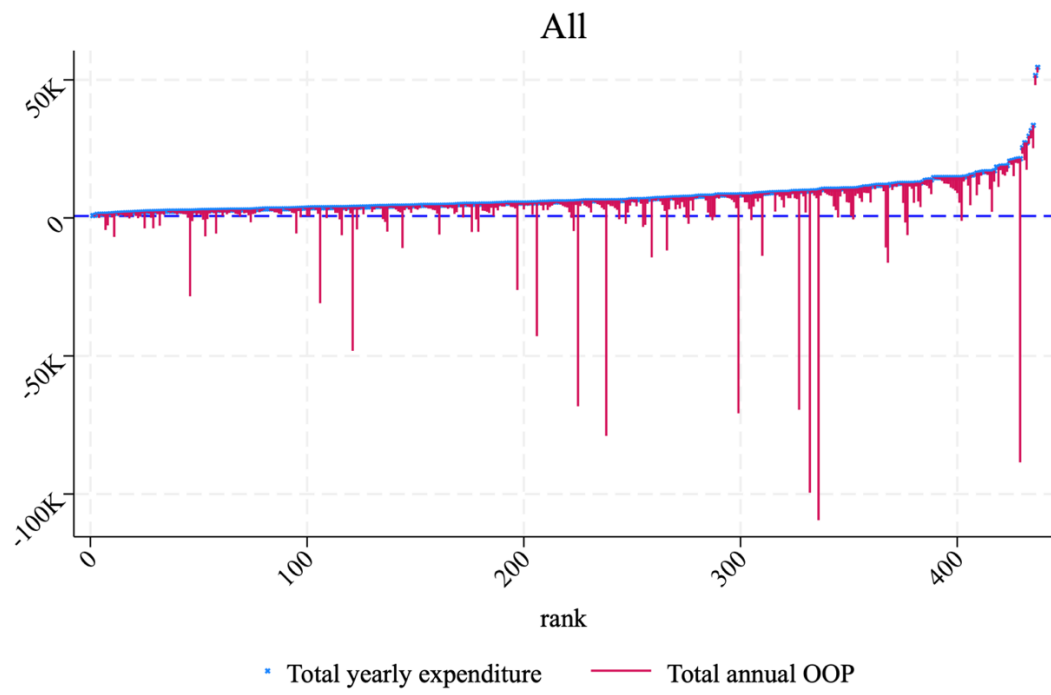
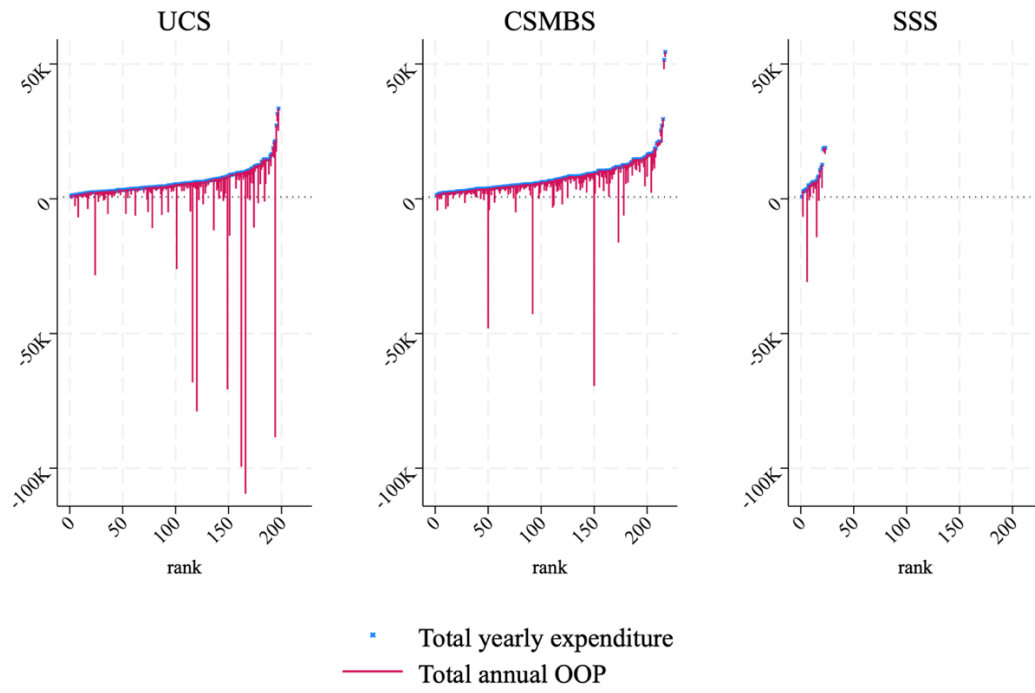*Figure 52. Yearly expenditure and annual OOP for health.*

Figure 53. Yearly expenditure and annual OOP for health schemes.

Appendix F

Publication

Original Article

Catastrophic and Socioeconomic Disparities Across Different Payment Schemes in Lung Cancer Treatment: A Cross-Sectional Single-Centre Analysis from Thailand

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Abstract:

Objective: To identify the magnitude of catastrophic health expenditure (CHE) and medical impoverishment across three payment schemes and compare the within-scheme financial disparity.

Material and Methods: A cross-sectional analysis of CHE and medical impoverishment among lung cancer patients was conducted at a university hospital in Thailand. A total of 367 lung cancer patients drawn from three payment schemes were included. The clinical data were collected from the hospital's Electronic Medical Records, while the socioeconomic data, including cost details, were collected via an interview-based questionnaire from November 2020 to June 2022. Economic analyses were performed using concentration curves and logistic regression modeling.

Results: There were 38%, 21% and 27% impoverished patients belonging to the Universal Coverage Scheme (UCS), Social Security Scheme (SSS) and Civil Servant Medical Benefit Scheme (CSMBS), respectively, and approximately further 30% in each scheme became impoverished owing to medical-related expenses. Socioeconomic disparities in CHE; concentration index; CI=-0.36 UCS, -0.59 CSMBS and -0.47 UCS, and medical impoverishment; CI=0.16 UCS, -0.15 CSMBS and 0.10 UCS, were evident in all schemes. These inequities were more pronounced among CSMBS patients. Moreover, if not impoverished already, the probability of medical impoverishment in all payment schemes peaked in the middle quintile and declined thereafter.

Conclusion: Across all payment schemes, CHE and medical impoverishment occurred at rates of around 60% and 30%, respectively, among lung cancer patients in Thailand. The gradient of CHE probability was more prominent among CSMBS patients.

Keywords: non-small cell lung cancer, catastrophic health expenditure, disparity

Introduction

Cancers cause significant health burdens, and lung cancer ranks as one of the leading causes of health burden in males and one of the top five cancers in females worldwide. Lung cancer–related deaths account for one-fifth of total cancer–related deaths and bring a huge financial burden to patients and their families, the healthcare system, and society. These financial toxicities are not only due to direct medication/non-medication costs but also from indirect costs[1]. Cancer treatment costs can result in household impoverishment or catastrophic health expenditure (CHE) despite wide coverage of social health insurance, especially among patients who are elderly, with low education, living in a rural area and with low household income[2,3].

Sun et al. reported high percentages of CHE from lung cancer treatment in China—about 73–84%, depending on the type of compensation[4].

Cancer treatment costs can result in household impoverishment or CHE despite wide coverage of social health insurance especially among patients who are elderly, with low education, living in a rural area, and with low household income[3,5–7].

Since 2002, the Thai Government has established the Universal Coverage Scheme (UCS) Act applying to all Thai citizens not otherwise covered. It aims to improve the quality of life, health security, equity, and universal access to healthcare of the citizen of the country[8].

However, there are three main payment schemes in Thailand. First, the Civil Servant Medical Benefit Scheme (CSMBS) covers government officers and their dependents and pays healthcare facilities on a fee-for-service basis. Second, the Universal Coverage Scheme (UCS) covers the majority of the Thai population. Finally, the Social Security Scheme (SSS) covers the working-age people employed by private companies. Together, these form the expanded health insurance system in Thailand.

Based on the payment scheme, patients in Thailand could be classified into three groups. Patients belonging to the CSMBS group, which comprise 4.4–4.5 million people working for the government and their parents and immediate family; they can access the new standard treatments via the well-established Oncology Prior Authorization Program (OCPA) even though the regimens are not listed in the Thai National Drug List. The payment methods are fee-for-service for out-patient costs and diagnostic-related groups with multiple cost bands for in-patient costs.[8,9] Patients in the UCS group, the largest group comprising 48–60 million people, can be reimbursed for the cost of treatment only for the regimens/treatments on the National Drug List. Otherwise, they must pay by themselves (out-of-pocket, OOP). Reimbursed payment methods for patients in UCS are based on capitation for out-patient costs and diagnostic-related groups with a global budget with free schedule for specific high-cost procedures for in-patient costs[8,9]. Patients in the SSS group, consisting of mostly people working for a private company and accounting for 8.2–10.6 million people, are younger than the patients in CSMBS and UCS groups. The treatment options for patients in this group are almost the same as for those in the UCS

group. For the SSS group, the capitation for reimbursed costs is implemented for in-patients and diagnostic-related groups with a global budget applied for out-patients[8,9].

By rationale, the poorest patients in each scheme have a higher chance of getting financial problems related to healthcare compared with more wealthy patients.

We hypothesized that the expanded health insurance system improves the financial protection for cancer patients in Thailand. However, in clinical practice, there are cases of financial limitation or inability to pay for drug/treatment costs on the part of patients under these health coverage schemes, which may lead to substandard treatment for some patients. These patients, especially those in the lowest QTE, tend to face a severe financial burden after treatments, which may have multiple sequelae for the patients, their relatives, and the society at large.

In Thailand, a few studies have examined the healthcare disparities among people with chronic diseases such as hypertension, cardiovascular diseases, chronic obstructive pulmonary disease, and chronic kidney disease. However, there is limited evidence regarding the socioeconomic disparities in treatment and financial protection among lung cancer patients following Thailand's health system reform in 2002.

The primary research question was whether there is any difference in financial burden among these three payment schemes and their QTE.

This study aimed to: (1) identify the magnitude of financial toxicities, defined as CHE and medical impoverishment, across the three payment schemes, and (2) compare the within-scheme financial toxicity across the three payment schemes. We hope our findings will be found helpful by the scientific community, policymakers, and healthcare providers.

Material and Methods

Data source

Data were extracted from the Hospital Information System (HIS) of Songklanagarind Hospital and face-to-face questionnaires were administered during interviews of all pathologically-proven lung cancer patients, who visited the oncology clinic from November 9, 2020 to June 6, 2022. The data from HIS comprised clinical information as well as data concerning height, weight, performance status, treatment options, histology, treatment regimen, and clinical response. The questionnaires covered the following domains: demographics, health status and functioning, healthcare scheme, income and consumption, and work loss of patients and their relatives. Together, the data provided information on the patients' tertiary healthcare center utilization, which included information related to the demographics, and the clinical, social, and economic status of persons with lung cancer, and also related to healthcare service utilization and costs.

Indicators

Medical expenditure information was collected during the interviews; it included total expenditure, reimbursement, and out-of-pocket expenditures for out-patient visits in the previous month and in-patient visits during the previous year. For the analysis of economic-related disparity, the annual household consumption expenditure, which included the domains of food, entertainment, education, and traveling, was used as a proxy to indicate the household economic status.

To measure the degree of financial risk, we used the CHE, which was defined as annual household health payments exceeding 40% of the capacity-to-pay (CTP), defined as non-food household costs, and medical

impoverishment, which was defined as total spending less than the computed subsistence expenditure plus the total out-of-pocket payments (OOP) health payments and not meeting the criteria for being poor.

According to previous studies, there are two types of CHE measurement OOP over 40% of the household's capacity to pay, or over 10% of total household expenditure. In this study, we defined CHE using the OOP/capacity-to-pay method[10]. Furthermore, the household's capacity to pay (denominator) was defined as the household's expenditure on non-food consumption, and the OOP expenditure (numerator) was defined as the sum of the respondents' and their spouses' medical OOP expenditure for out-patient and in-patient care over the previous year. CHE was coded as "yes" if the proportion was over 40% and "no" if it was not. The factors of age, sex, healthcare scheme, current and initial stage of lung cancer, type of current treatment, and the quintile of economic status were included as covariates.

Statistical analysis

Categorical data are presented in numbers (%). All of the cost data, discounted by the inflation adjustment factor (IAF) to be values in the year 2022, are presented as geometric means (S.D.) because of their right skewness property. QTE were created using ranking within each payment scheme. Chi-square tests were used to analyze the socio-demographic differences in treatment type, health service use, CHE, and medical impoverishment among our lung cancer participants. Concentration curves (CC) and concentration indexes (CI) were used to assess economic-related disparities among the health coverage schemes. The farther the CC lied from the equality line (45-degree line), the greater the degree of disparities in healthcare and expenditure were understood to be. The extension of the concentration index was simplified to the Erreygers index, which was used as an indicator of the degree of disparity[11,12].

Various logistic regression models were used to evaluate the effect of the QTE on the outcomes, including CHE and medical impoverishment. Firstly, the determinants of interest, QTE and payment schemes, were included in the model. Then, the interaction of QTE and payment schemes was added. Finally, other variables potentially associated with the outcomes were added and selectively removed using a backward stepwise procedure. Only for the medical impoverished outcome, the quadratic effect of QTE was added in the final two models. AIC, BIC, and AUC of logistic-ROC were used as an indicator of model performance.

Multivariable logistic regression models were applied to estimate the impacts of cancer treatment on CHE and medical impoverishment among the quintiles of total expenditure in each of the three main payment schemes after controlling for potential predictors of the outcomes. The probability of outcomes is presented graphically using the Delta-Margins method from the adjusted logistic regression. All statistical analyses were conducted using STATA 17.0. p-values of less than 0.05 were considered statistically significant.

Endnotes

US dollar was used as the currency of this study, and the exchange rate on June 7, 2022 was: 1 USD=30.72 THB.

Data sharing

Data sharing is applicable; please contact the author for data requests. Please note that all personal information such as the participants' names, addresses, ID numbers, and telephone numbers have been removed from the dataset.

Ethics approval and consent to participate

Ethical approval was obtained from the Human

Research Ethics Committee (HREC), Prince of Songkla University. The research protocol was reviewed, approved, and then implemented strictly throughout the study. The private information of patients, including name, address, ID number, and phone number, were removed from the dataset, and the participants' confidentiality was protected according to HIPPA criterea (Health Insurance Portability and Accountability Act of 1996).

Results

Sample characteristics

A total of 367 lung cancer patients were enrolled; their demographic characteristics are shown in Table 1. In total, 51% of patients were male, the median age of 65 years, and 56% were undergoing active treatment. The current medication regimens were chemotherapy (44%) and targeted/immune-oncotherapy [TKI/IO] (31%). The others were not receiving any medical treatment. Fifty-five percent initially presented as stage IV lung cancer. The histological subtypes were adenocarcinoma, squamous cell carcinoma and small cell carcinoma (86%, 8% and 3%, respectively). Fifty-five percent had no/unknown driver mutation, and 38% of the patients had the EGFR mutation. Paclitaxel-carboplatin (Pac/Cb) was the most commonly prescribed first-line treatment comprising 38% of cases, followed by 18% gefitinib and 15% erlotinib. Forty-four percent of patients were treated with docetaxel in the second-line setting.

Expenditure data

The total annual OOP payment comprised drug costs that were not reimbursed, non-medical costs, food costs, supplements costs, accommodation costs, transportation costs, in-patient costs, house improvement/facility costs, and caregiver costs (Table 2). The geometric means (geometric standard deviation, GSD) of the total annual costs were 1513 (4.6), 1674 (3.0), and 1252 (7.1) in UCS, CSMBS, and SSS, respectively. Most costs were not statistically different between the payment schemes except for supplements costs and extra-medical costs for hospitalized patients, which were highest in the CSMBS group.

CHE and medical impoverishment

CHE was experienced by 64%, 66% and 59% in UCS, CSMBS and SSS, respectively. Among patients under UCS, 38% were already impoverished, and a further 28% became impoverished owing to medical-related expenses. The corresponding values among CSMBS patients were 21% and 28%, and among SSS patients, they were 27% and 32%.

One-fourth (28.4%) of the patients met the criteria for being poor before incurring healthcare costs, and about 90% of the lowest quintiles were also in the poor group. Medical impoverishment was experienced by 9.6% in the lowest quintile groups; the proportion of such patients rose to 42.7% and 41.3% in the second and third quintiles, respectively. After that, the percentages of medical impoverishment decreased to 31.7% and 16.4% in the highest two quintiles (Table 3).

Concentration curve and concentration index

The inequity related to CHE (Figure 1A) and medical impoverishment (Figure 1B) are presented as concentration curves. In CHE, the upper-left shift of concentration curves from the line of equity (diagonal line) in all payment schemes indicated that CHE occurred more frequently in less wealthy patients. The concentration curve for CHE in the CSMBS group was far from the line of equity, meaning that there was more inequity in the CSMBS group. The concentration indices were −0.36, −0.59, and −0.47 in UCS, CSMBS, and SSS, respectively. The difference in the CI among payment schemes was statistically significant only between UCS and CSMBS groups (diff.=−0.226, p-value 0.037).

Table 1 Demographic data

Variable	UCS (n=158)	CSMBS (n=187)	SSS (n=22)	Total (N=367)	p-value
Stage of treatment, n=367					0.371
Early	56 (35.4)	56 (29.9)	7 (31.8)	119 (32.4)	
First-line	71 (44.9)	78 (41.7)	11 (50.0)	160 (43.6)	
Second-line or more	31 (19.6)	53 (28.3)	4 (18.2)	88 (24.0)	
Current status, n=367					0.680
Active Rx	85 (53.8)	109 (58.3)	13 (59.1)	207 (56.4)	
Complete Rx	73 (46.2)	78 (41.7)	9 (40.9)	160 (43.6)	
Current Rx type, n=367					0.507
No	40 (25.3)	44 (23.5)	6 (27.3)	90 (24.5)	
CMT	76 (48.1)	78 (41.7)	8 (36.4)	162 (44.1)	
Tki/IO	42 (26.6)	65 (34.8)	8 (36.4)	115 (31.3)	
Sex, n=367					0.306
Male	76 (48.1)	102 (54.5)	9 (40.9)	187 (51.0)	
Female	82 (51.9)	85 (45.5)	13 (59.1)	180 (49.0)	
Initial stage, n=367					0.647
1A	27 (17.1)	29 (15.5)	4 (18.2)	60 (16.3)	
1B	6 (3.8)	16 (8.6)	3 (13.6)	25 (6.8)	
2A	2 (1.3)	6 (3.2)	1 (4.5)	9 (2.5)	
2B	10 (6.3)	6 (3.2)	1 (4.5)	17 (4.6)	
3A	11 (7.0)	14 (7.5)	2 (9.1)	27 (7.4)	
3B	9 (5.7)	13 (7.0)	0 (0.0)	22 (6.0)	
3C	3 (1.9)	2 (1.1)	0 (0.0)	5 (1.4)	
4A	55 (34.8)	51 (27.3)	7 (31.8)	113 (30.8)	
4B	35 (22.2)	50 (26.7)	4 (18.2)	89 (24.3)	
T stage, n=367					0.485
1a	5 (3.2)	3 (1.6)	0 (0.0)	8 (2.2)	
1b	15 (9.5)	22 (11.8)	1 (4.5)	38 (10.4)	
1c	28 (17.7)	34 (18.2)	7 (31.8)	69 (18.8)	
2a	21 (13.3)	28 (15.0)	7 (31.8)	56 (15.3)	
2b	18 (11.4)	21 (11.2)	1 (4.5)	40 (10.9)	
3	29 (18.4)	32 (17.1)	2 (9.1)	63 (17.2)	
4	42 (26.6)	47 (25.1)	4 (18.2)	93 (25.3)	
N stage, n=367					0.458
0	71 (44.9)	83 (44.4)	10 (45.5)	164 (44.7)	
1	12 (7.6)	15 (8.0)	1 (4.5)	28 (7.6)	
2	33 (20.9)	51 (27.3)	3 (13.6)	87 (23.7)	
3	42 (26.6)	38 (20.3)	8 (36.4)	88 (24.0)	
M stage, n=367					0.902
0	71 (44.9)	86 (46.0)	11 (50.0)	168 (45.8)	
1	87 (55.1)	101 (54.0)	11 (50.0)	199 (54.2)	
Pathology, n=367					0.242
Adenocarcinoma	128 (81.0)	165 (88.2)	22 (100.0)	315 (85.8)	
Squamous cell CA	16 (10.1)	15 (8.0)	0 (0.0)	31 (8.4)	
SCLC	6 (3.8)	6 (3.2)	0 (0.0)	12 (3.3)	
NSCLC NOS	3 (1.9)	0 (0.0)	0 (0.0)	3 (0.8)	
Adenosquamous CA	3 (1.9)	1 (0.5)	0 (0.0)	4 (1.1)	
LCNET	2 (1.3)	0 (0.0)	0 (0.0)	2 (0.5)	
Biomarker, n=367					0.646
NOS/unknown	95 (60.1)	93 (49.7)	13 (59.1)	201 (54.8)	
EGFR	55 (34.8)	78 (41.7)	7 (31.8)	140 (38.1)	
ALK	8 (5.1)	14 (7.5)	2 (9.1)	24 (6.5)	
MET14	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	
ROS1	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)	

Table 1 (continued)

Variable	UCS (n=158)	CSMBS (n=187)	SSS (n=22)	Total (N=367)	p-value
Definite surgery, n=367					0.115
No	112 (70.9)	121 (64.7)	11 (50.0)	244 (66.5)	
Sx	46 (29.1)	66 (35.3)	11 (50.0)	123 (33.5)	
Curative XRT, n=367					0.540
No	151 (95.6)	181 (96.8)	22 (100.0)	354 (96.5)	
Curative XRT	7 (4.4)	6 (3.2)	0 (0.0)	13 (3.5)	
Adjuvant CMT, n=367					0.437
No	139 (88.0)	169 (90.4)	18 (81.8)	326 (88.8)	
Adj CMT	19 (12.0)	18 (9.6)	4 (18.2)	41 (11.2)	
CCRT, n=367					0.218
No	141 (89.2)	172 (92.0)	22 (100.0)	335 (91.3)	
CCRT	17 (10.8)	15 (8.0)	0 (0.0)	32 (8.7)	
First-line, n=244					0.107
Afatinib	13 (12.9)	6 (4.7)	2 (13.3)	21 (8.6)	
Alectinib	0 (0.0)	2 (1.6)	1 (6.7)	3 (1.2)	
Atezo Tirago	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	
Atezolizumab	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	
Brigatinib	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	
CAV	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)	
Carbo_Eto	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	
Ceritinib	4 (4.0)	7 (5.5)	1 (6.7)	12 (4.9)	
Cis Eto	3 (3.0)	2 (1.6)	0 (0.0)	5 (2.0)	
Crizotinib	1 (1.0)	3 (2.3)	0 (0.0)	4 (1.6)	
Docetaxel	2 (2.0)	1 (0.8)	0 (0.0)	3 (1.2)	
Durvalumab	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)	
Erlotinib	20 (19.8)	13 (10.2)	4 (26.7)	37 (15.2)	
Eto Cb	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	
Gefitinib	4 (4.0)	39 (30.5)	0 (0.0)	43 (17.6)	
Gemcitabine	2 (2.0)	1 (0.8)	0 (0.0)	3 (1.2)	
MEDI5752	1 (1.0)	1 (0.8)	0 (0.0)	2 (0.8)	
Osimertinib	2 (2.0)	2 (1.6)	0 (0.0)	4 (1.6)	
Pac Cb	43 (42.6)	44 (34.4)	7 (46.7)	94 (38.5)	
Pac Cb Beva	1 (1.0)	1 (0.8)	0 (0.0)	2 (0.8)	
Pac Cb Pemb	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)	
Pem Cb	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.4)	
Pem Cb Osimer	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)	
Pem Cb Pemb ACZ	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)	
Second-line, n=86					0.076
Afatinib	3 (10.3)	0 (0.0)	0 (0.0)	3 (3.5)	
Ceritinib	0 (0.0)	2 (3.8)	0 (0.0)	2 (2.3)	
Docetaxel	12 (41.4)	13 (24.5)	1 (25.0)	26 (30.2)	
Erlotinib	1 (3.4)	1 (1.9)	0 (0.0)	2 (2.3)	
Gefitinib	0 (0.0)	5 (9.4)	2 (50.0)	7 (8.1)	
Osimertinib	1 (3.4)	8 (15.1)	0 (0.0)	9 (10.5)	
Pac_Cb	12 (41.4)	22 (41.5)	1 (25.0)	35 (40.7)	
Pem Cb	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.2)	
Pem Cis	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.2)	

Table 1 (continued)

Variable	UCS (n=158)	CSMBS (n=187)	SSS (n=22)	Total (N=367)	p-value
Third-line, n=25					0.220
Afatinib	1 (25.0)	0 (0.0)	0 (0.0)	1 (4.0)	
Atezolizumab	1 (25.0)	1 (5.6)	1 (33.3)	3 (12.0)	
Docetaxel	1 (25.0)	9 (50.0)	1 (33.3)	11 (44.0)	
Erlotinib	1 (25.0)	1 (5.6)	0 (0.0)	2 (8.0)	
Gefitinib	0 (0.0)	3 (16.7)	0 (0.0)	3 (12.0)	
Gemcitabine	0 (0.0)	0 (0.0)	1 (33.3)	1 (4.0)	
Osimertinib	0 (0.0)	1 (5.6)	0 (0.0)	1 (4.0)	
Pac Cb	0 (0.0)	1 (5.6)	0 (0.0)	1 (4.0)	
Pemetrexed	0 (0.0)	2 (11.1)	0 (0.0)	2 (8.0)	

UCS=Universal Coverage Scheme, CSMBS=Civil Servant Medical Benefit Scheme, SSS=Social Security Scheme, Rx=treatment, CMT= chemotherapy, CA= carcinoma, SCLC=small cell lung cancer, NSCLC=non-small cell lung cancer, NOS=not, LCNET=large cell neuroendocrine tumor, EGFR=epidermal growth factor receptor, ALK=anaplastic lymphoma kinase, MET14=MET exon 14 skipping mutation, ROS1=ROS 1 mutation, XRT=radiotherapy, CCRT=concurrent chemoradiotherapy, CAV=cyclophosphamide/adriamycin/vincristine, ACZ=canakinumab, Sx=surgery

Table 2 Demographic cost data in USD (geometrics mean)

| Variable	UCS (n=158)	CSMBS (n=187)	SSS (n=22)	Total (N=367)	p-value
Annual extra-medical cost for OPD, n=367	1,091.1 (22.1)	112.0 (28.9)	1,209.4 (40.5)	433.2 (30.3)	0.186
Annual extra-medical cost for OPD visit at other hospital, n=367	1,723.5 (6.2)	464.5 (4.7)	720.4 (1.8)	905.3 (5.4)	0.920
Annual drug cost outside hospital, n=367	50.5 (3.5)	58.6 (3.4)	60.8 (1.8)	55.6 (3.3)	0.527
Annual herbal supplement cost, n=367	359.4 (2.7)	236.9 (3.8)	324.7 (5.1)	267.2 (3.5)	0.524
Annual supplement cost, n=367	456.8 (2.3)	593.3 (2.7)	451.3 (2.8)	527.0 (2.5)	<0.001
Annual extra-medical cost for IPD, n=223	92.8 (6.0)	210.8 (3.9)	63.7 (9.3)	144.7 (5.2)	<0.001
Annual OOP for medical cost, n=367	686.3 (7.6)	834.1 (4.2)	776.6 (10.7)	764.5 (5.8)	0.059
Annual non-medical cost for OPD visit at study hospital, n=367	357.7 (3.6)	307.4 (3.4)	372.8 (5.7)	330.9 (3.6)	0.786
Annual food cost for OPD visit at study hospital, n=348	84.0 (3.7)	82.4 (3.2)	110.0 (3.7)	84.3 (3.4)	0.945
Annual stay cost for OPD visit at study hospital, n=348	294.9 (8.5)	675.0 (4.5)	1237.1 (3.1)	465.1 (6.5)	0.379
Annual non-medical cost for OPD visit at study hospital, n=367	357.7 (3.6)	307.4 (3.4)	372.8 (5.7)	330.9 (3.6)	0.786
Annual IPD cost, n=367	45.9 (2.1)	37.0 (2.4)	27.9 (2.3)	39.7 (2.3)	0.676
Annual house improvement and facility cost, n=367	409.8 (4.7)	475.3 (4.8)	309.3 (3.8)	439.6 (4.6)	0.798
Annual cost of formal caregiver, n=367	692.4 (4.6)	2,933.6 (2.5)	811.5*	1,486.3 (4.0)	0.992
Annual OOP for non-medical expenses, n=367	453.0 (3.9)	477.2 (3.8)	317.5 (5.7)	455.8 (3.9)	0.284
Total annual OOP, n=367	1,512.9 (4.6)	1,674.2 (3.0)	1,251.6 (7.1)	1,575.4 (3.9)	0.321

UCS=Universal Coverage Scheme, CSMBS=Civil Servant Medical Benefit Scheme, SSS=Social Security Scheme, OPD=out patient department, OOP=out-of-pocket, IPD=in patient department
*only one patient in SSS group had a formal caregiver

Table 3 Impoverishment by TE Quintile: all, n (col %)

Variable	UCS (n=158)	CSMBS (n=187)	SSS (n=22)	Total (N=367)	p-value
Pre–OOP impoverishment, n=367	60 (38.0)	39 (20.9)	6 (27.3)	105 (28.6)	0.002
Medical impoverishment, n=367	44 (27.8)	53 (28.3)	7 (31.8)	104 (28.3)	0.928
CHE, n=367	102 (64.6)	123 (65.8)	13 (59.1)	238 (64.9)	0.820

UCS=Universal Coverage Scheme, CSMBS=Civil Servant Medical Benefit Scheme, SSS=Social Security Scheme, OOP=out–of–pocket, CHE=catastrophic health expenditure
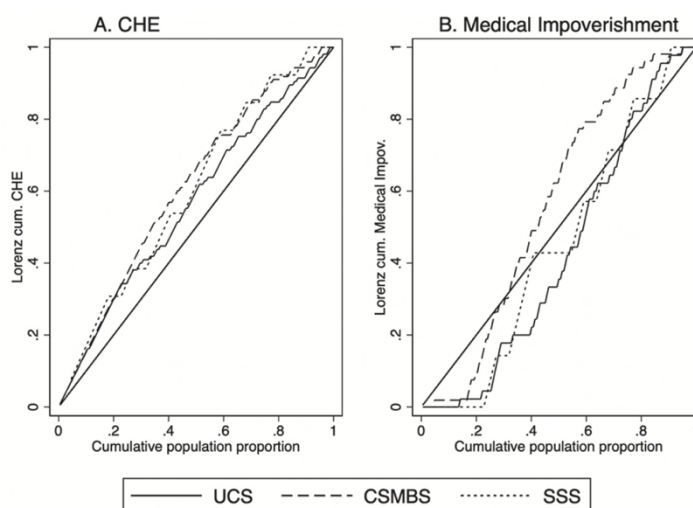
CHE=catastrophic health expenditure, UCS=Universal Coverage Scheme, CSMBS=Civil Servant Medical Benefit Scheme, SSS=Social Security Scheme

Figure 1 Concentration curves for payment schemes and cumulative proportions of catastrophic health expenditure (A) and medical impoverishment (B)

The medical impoverishment concentration curves started below the diagonal line. Then they moved closer to the line of equity only in UCS and SSS; the CI line, on the other hand, crossed above the line of equity in CSMBS. The concentration indexes for medical impoverishment were 0.16, –0.15, and 0.10 in UCS, CSMBS, and SSS, respectively. Only the CI of CSMBS showed a statistically significant difference from that of UCS (diff.=–0.310, p-value 0.005).

Logistic regression modeling

The results of the logistic regression models for CHE are shown in Table 4. The multivariable–adjusted

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interaction model had the best fit based on AIC⁄BIC and also the highest discriminating power (AUC=0.82).

Figure 2A shows the probabilities of CHE computed from the final–adjusted logistic model with the interaction of QTE and payment schemes with the adjusted covariates mentioned above. In the lowest quintile, the probability of CHE was highest in the CSMBS group (0.94 [0.89–0.98]), followed by SSS (0.84 [0.62–1.01]), and UCS (0.83 [0.75–0.92]). The probability of CHE gradually decreased as the QTE increased. In the highest quintiles, the probabilities of CHE were highest in UCS (0.42 [0.29-0.55]), but it had a value of about one–fifth in CSMBS and SSS.

The logistic regression models for medical impoverishment are illustrated in Table 5. The multivariable–adjusted interaction with a quadratic term of the QTE model showed the best fit and the highest discriminating power (AUC=0.81).

Figure 2B shows the probabilities of medical impoverishment computed from the multivariable–adjusted interaction with a quadratic term for the QTE model. The probabilities of medical impoverishment in the lowest quintile were low in all payment schemes—0.05 [0–0.11] in UCS, 0.14 [0.04–0.24] in CSMBS, and 0.12 [–0.15–0.39] in SSS. For each payment scheme, they reached the highest levels at the third quintile—0.47 [0.35–0.60] in UCS, 0.46 [0.36–0.57] in CSMBS, and 0.41 [0.12–0.70] in SSS.

Table 4 Odds ratio and 95% confidence interval for catastrophic health expenditure from various logistic models

Variable	Naive	IntAct	IntAct_Adj
QTE for each payment scheme	0.500 (0.417, 0.599)	0.620 (0.482, 0.798)	0.574 (0.435, 0.757)
CSMBS	1.039 (0.637, 1.696)	4.704 (1.200, 18.437)	4.859 (1.124, 21.006)
SSS	0.721 (0.263, 1.973)	1.106 (0.090, 13.554)	1.262 (0.092, 17.283)
CSMBS x QTE for each payment scheme		0.635 (0.433, 0.931)	0.627 (0.416, 0.944)
SSS x QTE for each payment scheme		0.882 (0.421, 1.848)	0.802 (0.361, 1.783)
Complete Rx			0.217 (0.127, 0.368)
Progression			5.679 (1.525, 21.148)
Intercept	16.308 (8.062, 32.986)	8.027 (3.314, 19.442)	20.047 (7.008, 57.342)
AIC	416	415	377
BIC	432	438	409
LROC_AUC	0.751	0.750	0.820

Naïve – the logistic model with QTE and payment schemes as determinators for catastrophic health expenditure, IntAct – the logistic model with QTE interaction with payment schemes as determinators for CHE, IntAct_Adj – the logistic model with QTE interaction with payment schemes as determinators for CHE and backward stepwise removal of other covariates, CSMBS=Civil Servant Medical Benefit Scheme, SSS=Social Security Scheme, QTE=quintile of total expenditure, AIC=akaike information criterion, BIC=Bayesian Information Criterion, LROC_AUC=area under the curve of logistic model
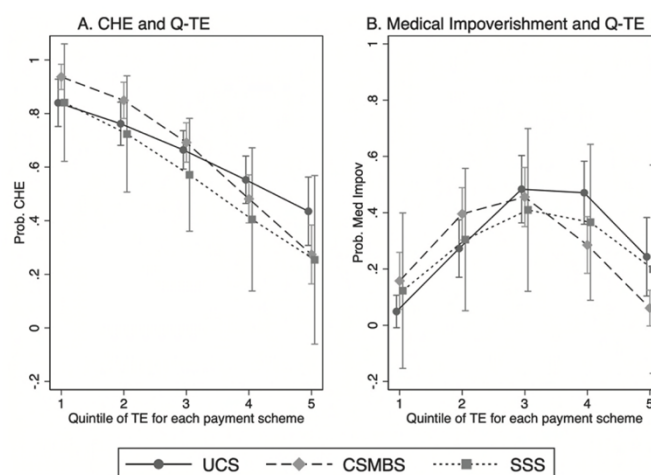
UCS=Universal Coverage Scheme, CSMBS=Civil Servant Medical Benefit Scheme, SSS=Social Security Scheme, CHE=catastrophic health expenditure, Q–TE=quintile of total expenditure

Figure 2 Delta–Margin probabilities of catastrophic health expenditure (A) and medical impoverishment (B) according to logistic regression models

Table 5 Odds ratio and 95% confidence interval for medical impoverishment according to various logistic models

Variable	Naive	Int_L_qTE_noAdj	Int_Q_qTE_noAdj	Int_qTE_Adj
QTE for each payment scheme	1.028	1.342	24.360	52.162
	(0.876, 1.207)	(1.041, 1.730)	(4.282, 138.568)	(7.707, 353.017)
CSMBS	1.026	4.702	5.735	6.214
	(0.640, 1.643)	(1.496, 14.773)	(0.222, 148.393)	(0.187, 206.350)
SSS	1.211	1.797	4.420	10.711
	(0.463, 3.171)	(0.175, 18.406)	(0.011, 1727.284)	(0.011, 1.1e+04)
CSMBS x QTE for each payment scheme		0.601	0.719	0.632
		(0.426, 0.848)	(0.076, 6.783)	(0.057, 7.045)
SSS x QTE for each payment scheme		0.886	0.530	0.236
		(0.444, 1.769)	(0.009, 33.010)	(0.002, 27.583)
QTE for each payment scheme x QTE for each payment scheme			0.632	0.565
			(0.486, 0.822)	(0.422, 0.755)
CSMBS x QTE for each payment scheme x QTE for each payment scheme			0.931	0.944
			(0.650, 1.334)	(0.642 ,1.388)
SSS x QTE for each payment scheme x QTE for each payment scheme			1.067	1.198
			(0.555, 2.053)	(0.562, 2.551)
Complete Rx				0.258
				(0.123, 0.539)
Progression				8.372
				(2.275, 30.804)

Table 5 (continued)

Variable	Naive	Int_L_qTE_noAdj	Int_Q_qTE_noAdj	Int_qTE_Adj
1B				1.458
				(0.386, 5.512)
2A				2.532
				(0.394, 16.258)
2B				1.333
				(0.302, 5.882)
3A				2.846
				(0.870, 9.316)
3B				0.908
				(0.220, 3.751)
3C				1.599
				(0.191, 13.413)
4A				1.005
				(0.386, 2.615)
4B				1.600
				(0.597, 4.289)
Equivalence of household size				0.514
				(0.278, 0.951)
EGFR				0.770
				(0.406, 1.462)
ALK				3.419
				(1.076, 10.863)
MET 14				1.000
Intercept	0.355	0.155	0.003	0.005
	(0.196, 0.643)	(0.064, 0.379)	(0.000, 0.049)	(0.000, 0.107)
AIC	445	440	408	381
BIC	461	464	443	467
LROC_AUC	0.518	0.592	0.697	0.810

Naïve – the logistic model with QTE and payment schemes as determinators for medical impoverishment, Int_L_qTE_noAdj – the logistic model with QTE interaction with payment schemes as determinators for medical impoverishment, Int_Q_qTE_noAdj – the logistic model with quadratic–QTE interaction with payment schemes as determinators for medical impoverishment, Int_qTE_Adj the logistic model with quadratic–QTE interaction with payment schemes as determinators for medical impoverishment and backward stepwise removal of other covariates CSMBS=Civil Servant Medical Benefit Scheme, SSS=Social Security Scheme, QTE=quintile of total expenditure, EGFR=Epidermal Growth Factor Receptor, ALK=anaplastic lymphoma kinase, AIC=akaike information criterion, BIC=Bayesian Information Criterion, LROC_AUC=area under the curve of logistic model

Discussion

The percentage of poverty ranked from highest to lowest in UCS, SSS and CSMBS, respectively, but there was no substantial difference in the proportion of patients becoming impoverished owing to medical expenses; in each scheme, that proportion was around 30%. Socioeconomic disparities based on CHE and medical impoverishment were evident in each payment scheme, but the gradient of CHE probability was more marked among CSMBS patients.

If not impoverished already, the probability of medical impoverishment reached a peak in all payment schemes in the middle quintile and declined thereafter.

An unexpected finding was the greater socio-economic disparity in the experience of CHE and medical impoverishment among CSMBS compared to UCS participants. One possible explanation is that CSMBS patients included the parents of people who work for the government, which was not the case for UCS patients,

and the definition of CHE is based on the ratio of the total OOP cost to the total substantial non-food expenditure, which is usually low among the elderly living alone. Another possible explanation is that the CSMBS patients, even those in the lower quintile, as a result of their sociodemographic characteristics, may tend to prefer premium services or be more willing to pay for comfort and convenience in comparison to their UCS counterparts; this entails supplementary and extra medical costs as suggested by the data presented in Table 2.

As expected, CHE in the present study occurred more frequently among the lowest quintile groups. This finding is consistent with a study from China. Leng et al.[3] studied the probability of CHE at the end-of-life period in cancer patients. Even though that study focused only on the end-of-life period, CHE occurred in 100% of the lowest three quintiles, which was much higher than the proportion found in the present study. A possible explanation for this is the severe wealth inequities in China, where the wealthiest 1% own more than 33% of the total national household wealth, while the poorest 25% own less than 2%.

Fu et al.[5] reported post-treatment impoverishment rates of 47%, 15%, 9%, 5% and 3% in cancer patients in China in quintiles one to five, respectively. These proportions include a range similar to that of the proportion of medical impoverishment in the present study but in a different pattern. In the Chinese study, the proportion decreased as the quintile increased, whereas in the present study, the proportions peaked in the middle quintiles. This is because the Chinese study included patients, who were already impoverished before experiencing medical-related expenses. In contrast, in the present study, medical impoverishment patients did not comprise patients, who were already poor.

There are two main methodological issues at play in our research. First, the present study used total expenditure as a proxy for living standard/wealth. It is still debatable whether or not it is appropriate to use expenditure instead of income to determine one's living standard/wealth. Income and expenditure data are both challenging to collect accurately. However, there are a number of people, who do not have formal work or salary, especially in developing countries; meanwhile, there are also those who may be reluctant to expose their true income. On the other hand, it is more convenient to answer a questionnaire about expenditure by referring to purchasing particular goods or services. Second, to define the QTE, the authors decided to rank the quintiles within each payment scheme as an independent variable, which is not directly translatable into real-life meaning, instead of ranking them by overall participants. However, no matter the method of ranking chosen, there are always limitations associated with it.

There are at least three limitations in this study. First, this is a single university hospital study in Thailand; therefore, the patients receiving healthcare treatment there may differ in terms economics, educational level, and expectations from those seeking treatment in private/ provincial hospitals around the country. Second, the distribution of the stages of the disease may not resemble the true incidence of the disease because of survival bias, as patients who live longer have a greater chance of being included in such a study than patients who have a shorter survival. Finally, the authors did not adjust for the participant's place of residence; distance from the health facility should affect the commute cost and time spent during the medical follow-up period.

This study employed intensive data extraction and detailed questionnaire interviewing, especially in respect to cost data. Data analyses were performed using multiple patterns of regression and the best fit model chosen.

Conclusion

In all three payment schemes for lung cancer patients in Thailand, CHE and medical impoverishment occurred in

around 60% and 30% of patients, respectively. The gradient of CHE probability was more prominent among CSMBS patients, and, if not impoverished already, the probability of medical impoverishment reached a peak in all payment schemes in the middle quintile and declined thereafter.

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Conflict of interest

Both authors declare that they have no competing interests.

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